AD NUMBER

AD099569

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies and their contractors; Administrative/Operational Use; Nov 1955. Other requests shall be referred to Air Force Aerospace Medical Research Lab., Wright-Patterson AFB, OH 45433.

AUTHORITY

Air Force Aerospace Medical Research Lab ltr dtd 11 Apr 1980

WADC TECHNICAL REPORT 55-357

STUDIES IN RESPIRATORY PHYSIOLOGY

SECOND SERIES

Chemistry, Mechanics, and Circulation of the Lung

HERMANN RAHN

WALLACE O. FENN

THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY

NOVEMBER 1955

WRIGHT AIR DEVELOPMENT CENTER

NOTICES

When Government drawings, specifications, or other data are used for any purpose other than in connection with a definitely related Government procurement operation, the United States Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

- - - - -

Qualified requesters may obtain copies of this report from the Armed Services Technical Information Agency, (ASTIA), Arlington Hall Station, Arlington 12, Virginia.

- - - - -

Copies of WADC Technical Reports and Technical Notes should not be returned to the Wright Air Development Center unless return is required by security considerations, contractual obligations, or notice on a specific document.

WADC TECHNICAL REPORT 55-357

STUDIES IN RESPIRATORY PHYSIOLOGY

SECOND SERIES

Chemistry, Mechanics, and Circulation of the Lung

HERMANN RAHN
WALLACE O. FENN

THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY

NOVEMBER 1955

AERO MEDICAL LABORATORY
CONTRACT No. AF 18(600)-17
PROJECT No. 7160

WRIGHT AIR DEVELOPMENT CENTER
AIR RESEARCH AND DEVELOPMENT COMMAND
UNITED STATES AIR FORCE
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

200 – September 1959 – 1-14

Foreword

The studies in respiratory physiology presented in this report were conducted during the period, 1951-1954 in the Department of Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York. The research was performed primarily under the provisions of contract No. AF 18(600)-17 with the Aero Medical Laboratory, Wright Air Development Center, in support of Project 7160, "Research in High Altitude Physiology." The contract was initiated by Dr. J. W. Wilson and was subsequently monitored by Dr. Wayland E. Hull and by Capt. Edwin G. Vail.

THE ANIMAL EXPERIMENTATION REPORTED HEREIN WAS PERFORMED IN ACCORDANCE WITH THE "RULES FOR ANIMAL CARE" AS ESTABLISHED BY THE AMERICAN MEDICAL ASSOCIATION.

Abstract

The scientific papers compiled in this report on the various aspects of external respiration have been divided into the following groups: Pressure Breathing, Mechanics of Breathing, Pulmonary Circulation, Changes with Acclimatization, Gas Stores of the Body, Alveolar Gas, Alveolar-Arterial Oxygen Difference, Ventilation, Behavior of Gas in Closed Body Cavities. A Summary of each of these divisions is found in the section entitled, "A Brief Summary of Investigations."

PUBLICATION REVIEW

THIS REPORT HAS BEEN REVIEWED AND IS APPROVED.

FOR THE COMMANDER:

JACK BOLLERUD
Colonel, USAF(MC)
Chief, AeroMedical Laboratory
Directorate of Research

TABLE OF CONTENTS

I. BEHAVIOR OF GAS IN CLOSED BODY CAVITIES

PREFACE

The last major report from this laboratory was issued in 1951 under the title "Studies in Respiratory Physiology-Chemistry and Mechanics of Pulmonary Ventilation" (AF Technical Report No. 6528). It consisted of some 56 individual studies carried out since 1942. This was followed by the WADC Technical Report 53-255 entitled "The Oxygen-Carbon Dioxide Diagram" which summarized general concepts of pulmonary gas exchange equations developed during the preceding years. The present report brings up-to-date our activities since 1951 and comprises a collection of some 47 individual studies in the field of respiratory physiology.

Much of this report represents further exploitation of concepts presented previously such as the pressure-volume diagrams, the gas equations on the O_2-CO_2 diagram and ventilation-perfusion ratios. In addition new areas have been explored. Those which proved most significant were the pulmonary circulation, the influence of bronchial tree structure upon gas distribution, the behavior of the gas stores in the body, the behavior of gases in closed body cavities including the synthetic gas SF_6 and methods for studying the gas exchange and altered mechanics during a developing atelectasis.

Many of our studies have been cooperative undertakings with investigators in other departments of the University of Rochester Medical Center. Without their special skills, ideas and support much of what we attempted would have been impossible to achieve. In some studies they contribute the major share of ideas and effort. It is, therefore, with deep gratitude that we express our appreciation to Drs. S. M. Tenney and R. E. Nye, Jr. (Department of Medicine), F. G. Carpenter (Department of Physiology), W. A. Dale (Department of Surgery), C. E. Tobin (Department of Anatomy), J. E. Drorbaugh (Department of Pediatrics), R. Gramiak (Department of Radiology), J. Shapiro (Department of Radiation Biology) and J. C. Mithoefer (Bassett Hospital - Cooperstown, N.Y.). In addition other investigators who were supported by special fellowships elected to contribute their time and efforts to our project. These were Drs. H. Bjurstedt and C. M. Hesser (Stockholm), P. Dejours (Paris), P. Sadoul (Nancy), H. T. Bahnson (Johns Hopkins University), and R. Ament, M. B. Sheldon, Jr., C. M. Matthews (University of Rochester School of Medicine). To them we are equally indebted. The remaining authors were supported by the contract which provided on a yearly basis the stipends for 3 graduate students, summer salaries for 1 or 2 medical student technicians and in part salaries of 2 trained investigators.

The Table of Contents lists each individual study by a serial number and abbreviated title and in the List of Papers the full title, authors and journal reference (if already published) will be found for each serial number. For permission to reproduce articles published elsewhere we are indebted to the American Journal of Physiology (Papers No. 5, 18, 26, 29, 37, 41, 45, 47), Journal of Applied Physiology (Papers No. 13, 14, 19, 23, 24, 30, 34, 38, 46), Proceedings for Experimental Biology and Medicine (Papers No. 15, 16, 17), Acta Physiolgica Scandivavica (Papers 4 and 22), and the American Journal of Physical Medicine (Paper No. 39).

Rochester, New York
January 1955

Hermann Rahn
Responsible Investigator

Wallace O. Fenn

A BRIEF SUMMARY OF INVESTIGATIONS

A. Pressure Breathing

The adaptations to a continuous or intermittent positive or negative pressure in the lung continues to challenge the physiologist. Pressure breathing in various forms has not only many practical applications but has also become a convenient tool for producing circulatory and respiratory stress in man and animals. A rather unique method of pressure breathing is voluntary pressure breathing where a subject voluntarily compresses his lung air after each inspiration. It may be viewed as an intermittent Valsalva maneuver. The mechanics, gas exchange and alteration of the mean alveolar O_2 during this maneuver are reviewed in paper (No. 1) which analyzes the benefits of so-called "grunt breathing" at various altitudes breathing air and oxygen.

As is well known, circulatory stress is produced by continuous positive pressure breathing as well as by gravity effect in the standing position. With the subject on a tilt table the effects of either or both of these factors have been studied in man, noting the changes in heart rate, ventilation and alveolar gases when the chest is unprotected and with counter pressure applied to the chest and legs (No. 2). Tilting (feet down) and positive pressure act synergistically since the reaction produced by both acting together is greater than that of either one alone. Three out of 5 subjects experienced nausea or syncope when both stresses were applied. This was prevented by counter pressure in the vest or bandaging of legs. Even in the supine position positive pressures with an unprotected chest produce hyperventilation and marked alterations in the breathing patterns studied with the pneumotachometer (No. 3). On the basis of these studies the overall effects of pressure breathing at O_2 breathing altitudes above 45,000 feet are discussed, showing how much gain in hemoglobin saturation can be attributed to the pressure gain, per se, and how much to the concomitant hyperventilation. The importance of the abdominal muscle tone in preventing venous pooling during constant positive pressure was studied in dogs (No. 4). With an open abdominal cavity the arterial pressure can no longer compensate to the usual level. By cutting the vagi, similar results are obtained and by employing both methods, the recovery of the arterial pressure during pressure breathing is either completely absent or very small. These experiments also suggest that a special reflex pathway over the vagi controls the intra-abdominal pressure and thus the venous return during pressure breathing. The effect of pressure upon the pulmonary circulation is described in a later section (No. 22).

That the vagus also exerts an influence upon the chest compliance can be demonstrated by subjecting animals to various positive or negative pressures and measuring changes in lung volume (No. 5). When the vagi are cut, the same distending pressure produces a larger volume change. Since the lung tension remains unaltered, it is believed that the muscle tone of the chest or diaphragm is partially controlled by reflexes arising in vagal receptors.

B. Mechanics of Respiration

The pressure-volume diagram of the whole chest as well as the lung provides an excellent graphic tool for the visualization of various static and dynamic mechanical events of the respiratory act. A general review has been provided with special consideration of such topics as work of breathing, pressure breathing, artificial respiration, pneumothorax and breathing at altitude (No. 6).

The structure of the broncho-tracheal tree offers many physiological problems which have received little attention in the past. The success in obtaining rather complete plastic casts of this space (No. 7) prompted a detailed analysis of its geometry (No. 8) and led to a prediction of the number of terminal bronchi supplied by any given bronchus in the lung. By assuming that each such terminal bronchus transports equal quantities of gas, a series of equations can be derived which describe the volume flow rate, the pressure gradients, the linear flow velocity and the transit time through any bronchus. Applications of these equations suggest that the overall pressure gradient to all alveoli is about the same and that the total transit time from mouth to alveolus is directly proportional to the bronchial pathway length. These differences in transit time must lead to unequal distribution of dead space gas and could also explain the shape of the CO_2 vs. time curve recorded for a single expiration since all alveoli do not contribute to the expired air simultaneously. These conclusions are based solely upon the anatomy of a rigid tube system, yet they suggest a new outlook for the interpretation of various mechanical events and problems of unequal ventilation.

The mechanics of the act of coughing has been investigated with the aid of X-ray motion picture films and synchronized pressure and airflow recordings (No. 9). These findings indicate that in man the trachea just above the carina partially collapses when the glottis opens. The narrowing of the airway thus produced must induce unusually large linear air flow velocities in this region. The possible implications of similar events during explosive decompression are discussed.

The mechanics and adjustment of ventilation during experimental atelectasis have been studied in dogs. By a new experimental procedure (No. 10) the two lungs in a dog can be separately cannulated. With this preparation various degrees of lung collapse can be produced on one side while the ventilation is recorded from the contralateral side (No. 11). The contralateral hyperventilation induced by complete unilateral collapse is only partially modified by vagus section or by occluding the blood flow through the collapsed lung. This type of preparation also provides a new method for studying the behavior of the mediastinum as well as the alteration in mechanics of the contralateral-open-lung (No. 12). When one lung is occluded, the compliance of the open lung is increased because the mediastinum now absorbs some of the volume change with each inflation. These mechanical events serve to explain some of the ventilatory changes observed during lung collapse and unilateral lung occlusion.

The problem of measuring the residual volume by a purely physical method has been re-explored with the use of rapid decompression from 2.0, 1.75 and 1.50 atmospheres (No. 13) and yields values which are the same as those obtained by a rapid gas dilution method previously described.

C. Pulmonary Circulation

Many problems of respiration, whether mechanical or chemical, are dependent on or modified by the pulmonary circulation and during the last five years some of our efforts have been directed towards exploring the reactions of the pulmonary vessels. This work first necessitated a radiographic anatomy of the heart and associated vessels in the dog in order to facilitate the catheterization procedures (No. 14). The anatomy was largely constructed from X-ray motion picture films taken after the injection of radiopaque media. From these films a pulmonary circulation time of 2.8 seconds was measured. During these experiments it was discovered that the "jamming" of the catheter into a branch of the artery suddenly opened arterio-venous shunts (No. 15). A new principle for right-sided catheterization was worked out using a completely flexible tube to the tip of which a small balloon is attached. After placing the tip in the jugular vein, the balloon is inflated with 2 ml of water and the catheter pushed toward the heart. The balloon acts as a sail and automatically guides the tip through the right heart into the pulmonary vessels. No skill and no fluoroscope are required for placement of this "self-guiding" catheter (No. 16). A permanently indwelling catheter in the pulmonary artery of dogs has also been successful and allows frequent pressure measurements in the unanesthetized dog (No. 17).

Pulmonary resistance changes induced by the effect of low O_2 are of considerable interest since this seems to be one way of modifying the pulmonary circulation. The mechanism is still uncertain. General hypoxia increases the pulmonary resistance in the anesthetized dogs but increased CO_2 has no measurable effect (No. 18). Unilateral hypoxia has a marked effect upon gas exchange in both lungs. When pure N_2 is breathed on one side, a constant O_2 excretion is recorded on that side while the contralateral side compensates for it. The alveolar gases can be measured in both lungs simultaneously and by making rather daring assumptions one may calculate the blood flow in each lung. Such calculations suggest that the blood flow in the hypoxic lung is shifted to the contralateral side (No. 19).

With the use of the self-guiding catheter it is simple to block the blood flow to parts or all of one branch of the pulmonary artery. With complete unilateral block the pulmonary artery pressure promptly rises to a new level while the cardiac output remains unaltered. The resistance of the open circuit is only slightly changed (No. 20). The distribution of blood flow to the upper and lower lobes in the supine and erect position can be ascertained by studying separately the ventilation-perfusion ratio and the relative ventilation of these lobes. While in the supine position the perfusion is approximately the same per unit volume of lung, in the erect position relatively more blood is shifted into the pendent lobe (No. 21). This

suggests that gravity can have a considerable influence upon the pulmonary vessel diameters and their resistance. The resistance changes observed during the normal respiratory cycle are explained by changes in the intramural pressures of the pulmonary vessels as they expand upon inspiration (No. 22).

D. Changes with Acclimatization

The physiological changes which occur in man with prolonged exposure to altitude continue to be a fascinating problem. A 7-day exposure at Mt. Evans, Colorado, allowed us to extend some of our earlier observations at the 14,100 feet altitude. CO_2 breathing and breath-holding experiments showed an increased sensitivity to CO_2 but not to O_2 (No. 23). Lung volumes showed an initial fall in vital capacity with an increase after the 3rd day to normal levels or higher, while the residual volume increased at first and leveled off above the sea level value. The expiratory reserve volume progressively increased (No. 25). Although little information is available regarding physiological characteristics of permanent residents at altitude in the United States, a survey indicates that considerable information can be obtained within our own border (No. 25).

Acclimatization of mice for 14 days to an equivalent altitude of 16,000-18,000 ft. makes them more tolerant to 0.25% CO than unacclimatized animals. That a considerable cross acclimatization exists has been shown by the reverse experiment where mice acclimatized for 14 days to 0.15% CO survive an acute exposure of 34,000 ft. much longer than unacclimatized animals (No. 26). The changes in hematocrit were practically the same for both groups.

Exposure of 2 subjects for 3 days to 3% CO_2 in air mixture revealed a decreased ventilatory response with time and breathholding test also indicated a greater tolerance to CO_2 (No. 27). Acute exposure of mice to 40% CO_2 but at O_2 tensions from 35 to 6000 mm indicate that maximum survival time is found at O_2 tensions between 80 and 150 mm Hg.

E. Gas Stores of the Body

Adult rats contain 1.85 ml of CO_2 per gram body weight and over 80% of this is found in the bones. While during acute changes in alveolar CO_2 this bone reservoir is not appreciably altered, prolonged reduction of the alveolar CO_2 by a 10-31 day exposure to 10% O_2 resulted in a CO_2 loss which came largely from the bone reservoir. By exposure of animals to 10% CO_2 the total CO_2 content was increased in the bone as well as soft tissues (No. 29). A chart has been designed which allows one to calculate the changes in O_2 stores and CO_2 stores of the soft tissues when either the ventilation or the cardiac output or both are changed (No. 30). This is very useful in predicting the alterations in gas exchange which occur during the unsteady state when these stores are either increased or decreased. A general model is presented for visualizing the store changes and alteration of gas transport for any change in ventilation or circulation.

F. Alveolar Gas

The alveolar gas and ventilation equations have undergone further scrutiny and graphical procedures have been developed which allow one to obtain easily gas exchange ratio lines and isoventilation lines for any desired inspired gas mixture when plotted on the O_2-CO_2 diagram (No. 31). Critical consideration is given to the practical problem of the sampling of alveolar gases (No. 32) and corrections are discussed which must be applied to the determination of dead spaces when the end-tidal sampler is used (No. 33). The gas changes during breath holding have been reinvestigated and a new procedure is presented for obtaining the mixed venous blood CO_2 tension as well as the equivalent lung volume (No. 34). An analysis of the alveolar gas changes during tilting of the body (feet down) indicates that the exchange ratio is not increased by standing in spite of a considerable hyperventilation. This paradoxical finding can be explained by the behavior of the CO_2 gas stores which remain unaltered because the cardiac output is reduced at the same time as the ventilation increases. The effect of both of these changes is such as to leave the tissue CO_2 tension unaltered (No. 35).

G. Alveolar-Arterial O_2 Difference

A theoretical analysis is presented which allows one to visualize separately the contribution of diffusion, venous admixture and distribution of the ventilation-perfusion ratio to the A-a O_2 difference when breathing various O_2 tensions (No. 36). When breathing low O_2, the A-a O_2 difference is markedly reduced in the dog while in room air the large O_2 difference is observed which is probably due to a large distribution in ventilation-perfusion ratios (No. 37). The A-a O_2 and CO_2 differences as well as the cardiac output have been investigated during various stages of anesthesia following a single injection of sodium pentobarbital. This allows one to visualize the whole O_2 and CO_2 transport and the changes which occur at any time in such a cycle (No. 38).

H. Ventilation

A new method for resuscitation has been tried on dogs. This consists of periodic insufflations of the chest with 100% O_2 after which the paralyzed animal can be left for several minutes in room air. This method has the advantage that one operator could theoretically attend several paralyzed victims in succession in case of large civilian disaster (No. 39). A method for the measurement of ventilation in unrestrained small animals or human infants has always posed a difficult problem. A barometric method has, therefore, been tried which consists essentially in measuring the minute pressure fluctuation during the respiration when the subject is in an air-tight container. Upon inspiration the pressure rises during the wetting and warming of the inspired tidal volume, while during expiration the pressure falls. This method allows one to calculate the tidal volume and has been used on newborn infants (No. 40) as well as in hamsters breathing air and CO_2-air mixtures (No. 41).

A new method for the measurement of relative ventilation in various lobes of the lung is described. This technique measures the activity of radioactive dust particles of each lobe at autopsy after the animal has breathed this aerosol for several hours (No. 21).

I. Behavior of Gases in Closed Body Cavities

The behavior of gases in closed body cavities poses many poorly understood problems. While the composition changes can be readily analyzed the volume changes have been difficult to ascertain. The discovery of a simple method for the quantitative measurement of volume changes in skin pockets of rats has provided a convenient tool for the analysis of the dynamics of this gas exchange. A theoretical treatment classifies all pockets which can occur in the body into 3 types, namely, (1) open and ventilated, (2) open and nonventilated, and (3) closed pockets. Equations are developed which predict the steady state composition of each type of pocket if the composition of the perfusing blood is assumed (No. 42). The behavior of closed skin pockets when injected with various inert gases is described as well as the effects of breathing air and 100% O_2 (No. 43). The volume and composition changes during the unsteady state have also been investigated when the gas pockets are initially injected with various O_2-CO_2-N_2 mixtures (No. 44). Atelectasis is another form of a closed pocket and the volume uptake and composition changes have been followed in the atelectatic lung while the animal was maintained by the other open lung (No. 45). Of all the naturally occurring gases N_2 is the slowest gas to diffuse. Thus for the long maintenance of a pneumothorax or pneumoperitoneum it is the most ideal gas. More recently, however, SF_6, a synthetic gas, has been employed which diffuses more slowly than N_2 and after being injected into a body cavity will actually increase in volume for a time before it is eventually absorbed. This is so because the N_2 from the surrounding tissues diffuses into the cavity faster than SF_6 can diffuse out (No. 46). This gas, when injected into a body cavity, will maintain the volume about 3 times longer than a similar initial volume of N_2. When rats with peritoneal gas pockets are subjected to 7 atmospheres of air, the CO_2 tension in these pockets is not appreciably altered, but when O_2 is substituted, the CO_2 tension will rapidly rise to values as high as 200 mm (No. 47). These changes are not believed to be due to direct interference with the CO_2 transport but rather due to secondary changes arising from acute lung damage produced by the O_2.

LIST OF PAPERS

1. A Review of Recent Work in Respiration as Applied to Voluntary Pressure Breathing

   Fenn, W. O.

   Rivista Di Medicina Aeronautica, 1955

2. The Effect of Pressure Breathing and Posture upon the Respiratory Gas Exchange and Heart Rate

   Otis, A. B., H. Rahn, and M. Suskind

3. The Effects of Positive Pressure Breathing in Man upon the Pneumotachogram, Ventilation and Alveolar Gas Pressure

   Otis, A. B., M. B. Sheldon, Jr., and H. Rahn

4. Influence of the Abdominal Muscle Tone on the Circulatory Response to Positive Pressure Breathing in Anesthetized Dogs

   Bjurstedt, H.

   Acta Physiol. Scand., 29: 145, 1953

5. Contribution of Vagus Nerve to Pressure-Volume Characteristics of Chest and Lungs in Dogs

   Van Liew, H. D.

   Am. J. Physiol., 177: 161, 1954

6. The Pressure Volume Diagram of the Breathing Mechanism

   Fenn, W. O.

   Handbook of Respiratory Physiology. W. M. Boothby, Edit. USAF School of Aviation Med., Randolph Field, Texas, 1954

7. Bronchial Tree Casts, Lobe Weights and Anatomical Dead Space Measurements in the Dog Lung

   Rahn, H. and B. B. Ross

8. The Influence of Bronchial Tree Structure on Ventilation of the Lung as Inferred from Measurements of a Plastic Cast

   Ross, B. B.

9. The Physical Dynamics of the Cough Mechanism

   Ross, B. B., R. Gramiak, and H. Rahn

10. Experimental Functional Separation of Dog Lungs

Dale, W. A. and H. Rahn

J. Thorac. Surg., 1955

11. Ventilation of the Open Lung During Unilateral Experimental Atelectasis

Dale, W. A. and H. Rahn

J. Thorac. Surg., 1955

12. Experimental Pulmonary Atelectasis: Pressure-Volume Studies of the Individual Lungs, Mediastinum and Chest Wall Related to Tidal Air and Pulmonary Volume Changes

Dale, W. A. and H. Rahn

13. Residual Volume Measurements by the Gas Expansion Method and Nitrogen Dilution Method

Dejours, P. and H. Rahn

J. Appl. Physiol., 5: 445, 1953.

14. Radiographic Anatomy of Heart and Pulmonary Vessels of the Dog with Observations of the Pulmonary Circulation Time

Rahn, H., R. C. Stroud, and H. Meier

J. Appl. Physiol., 5: 308, 1952

15. Visualization of Arterio-Venous Shunts by Cinefluorography in the Lungs of Normal Dogs

Rahn, H., R. C. Stroud, and C. E. Tobin

Proc. Soc. Exptl. Biol. and Med., 80: 239, 1952

16. A Self-Guiding Catheter for Cardiac and Pulmonary Arterial Catheterization and Occlusion

Lategola, M. and H. Rahn

Proc. Soc. Exptl. Biol. and Med., 84: 667, 1953

17. Indwelling Pulmonary Arterial and Venous Catheters in the Dog

Stroud, R. C., K. R. Stetson and H. Rahn

Proc. Soc. Exptl. Biol. and Med., 81: 246, 1952

18. Effect of O_2 and CO_2 Tensions Upon the Resistance of Pulmonary Blood Vessels

Stroud, R. C. and H. Rahn

Am. J. Physiol., 172: 211, 1953

19. Effect of Unilateral Hypoxia on Gas Exchange and Calculated Pulmonary Blood Flow in Each Lung

Rahn, H. and H. T. Bahnson

J. Appl. Physiol., 6: 105, 1953

20. The Pulmonary Hemodynamic Effect of Total and Partial Unilateral Pulmonary Artery Occlusion in the Anesthetized Dog

Lategola, M. and H. Rahn

21. The Distribution of Ventilation and Perfusion in the Lobes of the Dog's Lung in the Supine and Erect Position

Rahn, H., P. Sadoul, L. E. Farhi, and J. Shapiro

22. Effects of Lung Inflation on the Pulmonary Circulation in Anesthetized Dogs

Bjurstedt, H. and C. M. Hesser

Acta Physiol. Scand., 29: 180, 1953

23. Adaptation to High Altitude: Respiratory Response to CO_2 and O_2

Rahn, H., R. C. Stroud, S. M. Tenney, and J. C. Mithoefer

J. Appl. Physiol., 6: 158, 1953

24. Adaptation to High Altitude: Changes in Lung Volumes During the First Seven Days on Mt. Evans, Colorado

Tenney, S. M., H. Rahn, R. C. Stroud, and J. C. Mithoefer

J. Appl. Physiol., 5: 607, 1953

25. Permanent Residents at Altitude within the United States

Rahn, H.

26. Comparative Studies on Acclimatization of Mice to Carbon Monoxide and to Low Oxygen

Clark, R. T., Jr., and A. B. Otis

Am. J. Physiol., 169: 285, 1952

27. Changes in Sensitivity of the Respiratory Center in Man After Prolonged Exposure to 3% CO_2

Chapin, J. L., A. B. Otis, and H. Rahn

28. Survival of Mice in High CO_2 Environments of Varying O_2 Tensions

Chapin, J. L.

29. Changes in Carbon Dioxide Stores of Rats Due to Atmospheres Low in Oxygen or High in Carbon Dioxide

Freeman, F. H. and W. O. Fenn

Am. J. Physiol., 174: 422, 1953

30. The Gas Stores of the Body and the Unsteady State

Farhi, L. E. and H. Rahn

J. Appl. Physiol., 7: 1955

31. The Oxygen-Carbon Dioxide Diagram for Alveolar Air

Farhi, L. E. and W. O. Fenn

32. The Sampling of Alveolar Gas

Rahn, H.

Handbook of Respiratory Physiology, W. M. Boothby, Edit. USAF School of Aviation Med., Randolph Field, Texas, 1954

33. Correction of Errors Introduced by the End-Tidal Air Sampling Device into the Measurement of Ventilation and Calculation of the Dead Space

Nye, R. E., Jr. and H. Rahn

34. The Composition of the Alveolar Air During Breath Holding with and without Prior Inhalation of Oxygen and Carbon Dioxide

Fenn, W. O. and P. Dejours

J. Appl. Physiol., 7: 313, 1954

35. The Effects of Posture Upon the Gas Exchange and Alveolar Gas Composition

Rahn, H. and R. Ament

36. A Theoretical Analysis of the Alveolar-Arterial O_2 Difference with Special Reference to the Distribution Effect

Farhi, L. E. and H. Rahn

J. Appl. Physiol., 7: 1955

37. Alveolar-Arterial O_2 and CO_2 Differences in the Dog Breathing Air and Low O_2 Mixtures

Suskind, M.

Am. J. Physiol., 177: 227, 1954

38. Relationship Between Cardiac Output and Ventilation and Gas Transport, With Particular Reference to Anesthesia

Suskind, M. and H. Rahn

J. Appl. Physiol., 7: 59, 1954

39. The Accumulation of Carbon Dioxide in Apneic Dogs During Intermittent Oxygen Insufflation

Fenn, W. O., A. B. Otis, and M. Suskind

Am. J. Physical Med., 33: 299, 1954

40. A Barometric Method for Measuring Ventilation in Newborn Infants

Drorbaugh, J. E. and W. O. Fenn

41. Ventilatory Response of the Unrestrained and Unanesthetized Hamster to CO_2

Chapin, J. L.

42. The Gas Exchange in Different Types of Body Gas Pockets with Particular Reference to the Lung: Theory

Rahn, H. and H. D. Van Liew

43. Volume Changes and the Steady State Behavior of Gas Pockets within Body Cavities

Rahn, H. and R. E. Canfield

44. Volume and Gas Composition Changes of Subcutaneous Gas Pockets Immediately Following the Injection of Various Gas Mixtures

Van Liew, H. D.

45. Rate of Gas Absorption During Atelectasis

Dale, W. A. and H. Rahn

Am. J. Physiol., 170: 606, 1952

46. Gas Transfers in a Sulfur Hexafluoride Pneumoperitoneum

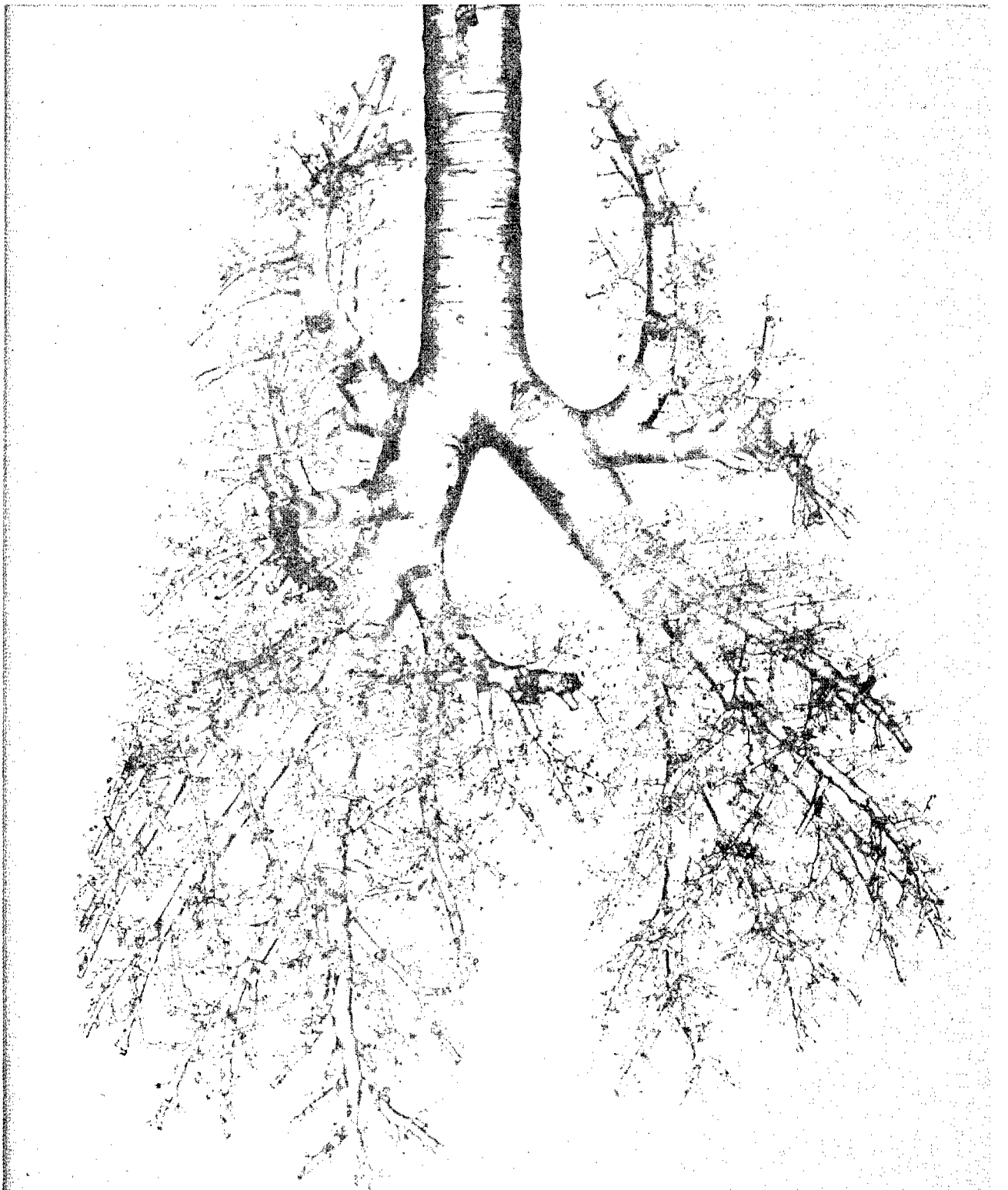
Tenney, S. M., F. G. Carpenter, and H. Rahn

J. Appl. Physiol., 6: 201, 1953

47. Blood and Tissue Gases of Animals Exposed to One and Seven Atmospheres of Oxygen and Air

Bahnson, H. T. and C. M. Matthews

Am. J. Physiol., 175: 87, 1953



BRONCHIAL TREE CAST OF DOG LUNG

A REVIEW OF RECENT WORK IN RESPIRATION AS APPLIED TO VOLUNTARY PRESSURE BREATHING

by

Wallace O. Fenn

During the last war the authors were engaged in investigations for the Air Force on the physiological problems involved in pressure breathing. In this procedure the inspired air is maintained at a pressure higher than that of the ambient atmosphere so that the chest is abnormally inflated while the alveolar Po_2 is to some extent increased. The increased oxygen tension improves the survival at altitude and apparatus for pressure breathing is now in general use in military airplanes. Toward the end of the war a system of voluntary pressure breathing was suggested by a Navy Laboratory which was supposed to provide a similar advantage without requiring any special apparatus. Having been invited to review some of our work in this article we propose to discuss the physiology of voluntary pressure breathing in the light of two fundamental concepts which developed from our war time studies. These two concepts are represented by the pressure-volume diagram and the O_2-CO_2 diagram. Both of these concepts have been widely accepted and have proved very useful for the understanding of problems of respiration. These two diagrams will be presented first after which they will be used for a discussion of voluntary pressure breathing.

The Pressure-Volume Diagram

In studying pressure breathing one of our first observations was the obvious one that when the pressure in the lungs is higher than that outside, the chest is to some degree inflated above its normal resting volume. With more pressure the degree of inflation increases. When the pressure is plotted against the inflation, one obtains the relaxation pressure curve or the passive pressure-volume diagram of the chest. To form a complete picture of this curve it was of course natural to include the amount of deflation of the chest produced by application of negative pressure to the lungs. The result is an S-shaped curve as shown in Figure 1.

Each individual has a characteristic relaxation pressure curve which summarizes in a way all the mechanical factors concerned in the inflation and the deflation of the chest. This includes the tonus of the muscles, the weight of the viscera, the stiffness of the lungs themselves and of the thoracic wall. As might be expected the relaxation pressure curve is subject to modifications as a result of changes of posture. Thus the assumption of the recumbent position moves the curve downward on the graph because the weight of the viscera against the diaphragm causes some deflation for the same alveolar pressure.

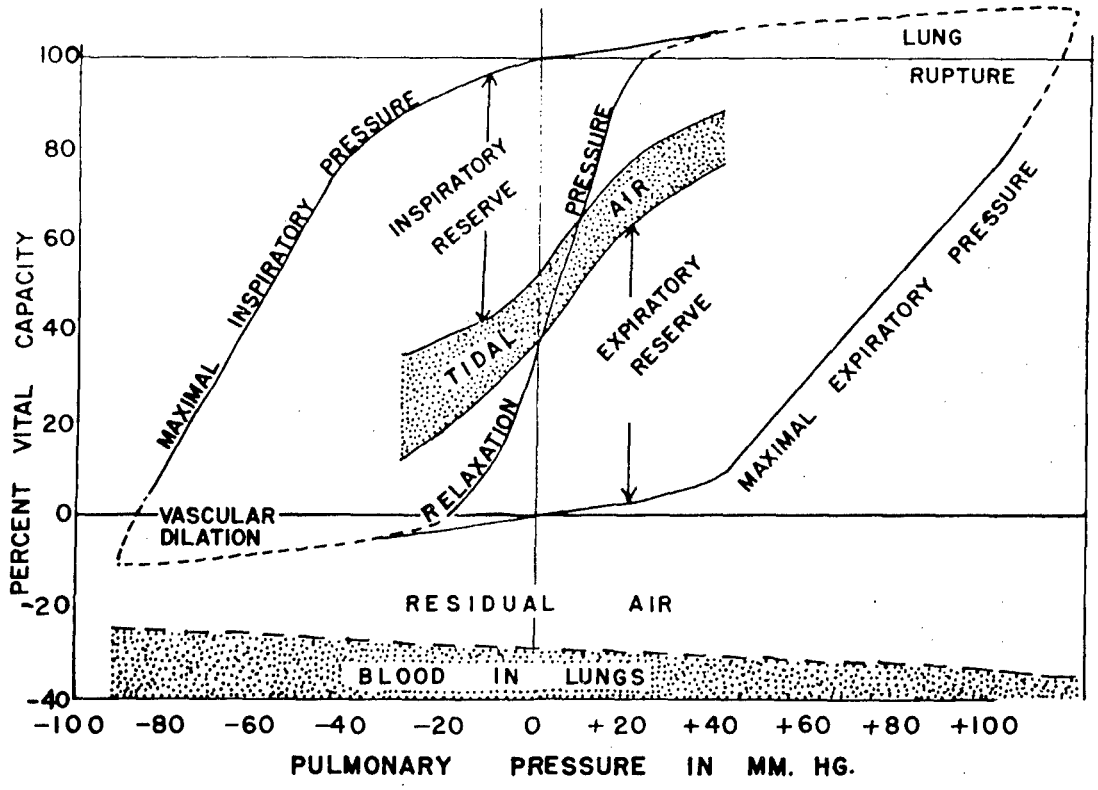


Figure 1

The pressure-volume diagram of the chest and lungs. On the ordinates 100% of vital capacity represents the height of inspiration and 0% of vital capacity represents maximal expiration, both at zero pressure or ambient pressure in the lungs. The chart shows the pressures which can be developed passively (relaxation pressure) or actively (maximal pressures) at different lung volumes.

The relaxation pressure curve is of interest from several other points of view. Thus the area between this curve and the vertical axis represents the elastic work required for inflating or deflating the lungs. The slope of the curve tells us how much tidal volume can be expected from a given change of pressure produced by an intermittent positive pressure resuscitator. Unfortunately such curves require some intelligent cooperation from the subject and they are not easy to obtain in the clinic. For this reason pathological changes in the normal relaxation pressure curves have not been published as yet, and it is impossible to say what the extreme variations may be. It is certain however, that data of this sort would be very informative.

Normal respiration can be interpreted as resulting from the modification of the relaxation pressure curve by active contraction of respiratory muscles. Enough change is produced to move the relaxation pressure curve up or down on the diagram by an amount equal to the tidal air. This is true so long as the pressure in the lung alveoli remains atmospheric.

This raises the question as to the amount by which the relaxation pressure curve can be moved by maximum effort. The pressure volume diagram (Figure 1) answers this question for it outlines the area which can be reached by inspiratory or expiratory effort. The data are obtained by making maximal inspiratory or expiratory efforts against a mercury manometer at different measured lung volumes. As might be predicted the inspiratory pressure is greatest at small lung volumes, i.e., at expiration and vice versa. All voluntary breathing procedures can be diagrammed on the pressure volume graph and the simultaneous values of pressure and volume in the lung can be represented always somewhere within the area outlined by these maximum respiratory effort curves. The diagram can also be regarded as a measure of the vital capacity at different pressures for the vertical distance between the expiratory pressure curve on the bottom and the inspiratory pressure curve on the top is obviously the vital capacity for that particular pressure. Pressures below the active area outlined by these curves represent residual air volumes which are greater on the positive pressure side because the positive pressure inhibits complete expiration. The shaded area underneath the chart represents the best estimate possible of the volume of blood in the lungs which is diminished by positive pulmonary pressure. The shaded area across the middle of the chart labeled "tidal air" represents the area instinctively used by a subject breathing naturally against different positive or negative pulmonary pressures. The vertical height of this band at any pressure indicates the tidal volume for that pressure. The top of this tidal air band represents inspiration and the bottom represents expiration. Where the relaxation pressure curve crosses the top of the band is the point where the height of inspiration is a position of relaxation. At this point therefore expiration is completely active and inspiration is passive. In the normal position along the middle of the chart where the pulmonary pressure is 0 the reverse is, of course, true.

The extreme corners of the pressure volume diagram are of some interest because they represent hazardous situations. In the upper right corner where the lung is maximally expanded and the pressure has a maximum positive value, there is danger of rupture of the lung. In the lower left corner where the blood vessels are exposed to a maximum negative pressure, there must be extreme vasodilation and danger of hemorrhage.

Further analysis of the relaxation pressure curve is possible because it is the net result of all the mechanical factors concerned in breathing. The only one of these which can be determined by itself is the elasticity of the lung proper which can be measured by intrapleural pressure determinations. If this factor is subtracted from the total relaxation pressure at every volume, the remainder curve

applies to the chest itself including the diaphragm and abdomen. This curve crosses the zero pressure line at about 70% of the vital capacity. The resting position of the chest alone, in other words, lies at a point of near-maximal inflation, and if the collapsing effect of the lungs could be suddenly eliminated, the chest would expand spontaneously to this position. This indeed occurs in emphysema where the elasticity of the lung is lost.

After completing this diagram, we found that after all it was not new but a very similar diagram had been presented some 20 years before by Rohrer (3). It had never attracted any attention, however, and had become lost in the literature. Now this diagram has been widely used and has been found extremely helpful in any consideration of the mechanics of respiration. Many of the new developments of the mechanics of breathing are now being presented against the background provided by this diagram. Highly refined and sophisticated discussions of the many problems of air flow are being presented at scientific meetings and form an impressive chapter in this expanding field of respiratory physiology.

The Oxygen-Carbon Dioxide Diagram

Perhaps the next most important new chapter in respiration concerns the mathematics of gas exchange in the lung. Simple considerations of gas mixing provides the alveolar air equation in which the oxygen tension of the lung can be expressed as a function of the alveolar CO_2 tension, the inspired gas tensions and the exchange ratio (or respiratory quotient). The minute volume of the ventilation and the ratio of gas exchange can also be incorporated into the equation. At first glance these equations are rather complicated but they become very simple when it is realized that they are really equations for straight lines on coordinates of partial pressures of CO_2 and O_2. This constitutes the Pco_2-Po_2 diagram which has also come into widespread use in predicting changes in gas pressure in the lung resulting from different maneuvers. With the use of this diagram complicated calculations can be accomplished graphically and precise thinking about the effects of many interconnecting factors, is much facilitated.

In its simplest form (Figure 2) the Pco_2-Po_2 diagram can be used to represent the problem of the aviator at high altitudes breathing pure oxygen. In this condition his lungs contain only O_2, CO_2, and H_2O vapor and the sum of the partial pressures of these three gases must always equal B, the barometric pressure. Since the P_{H_2O} is always constant in the lungs with a value at 37° C of 47 mm, it is also true that the sum of the Pco_2 and the Po_2 is always equal to B-47 mm (while breathing pure O_2). For any altitude or value of B therefore the point on the diagram representing the alveolar air must fall on one of the "altitude diagonals" at 45° angle represented on the chart. The sum of the coordinates of any point on such a line is equal to the intercept on either the Pco_2 or the Po_2 axis. In words this means that the total dry pressure of oxygen in the inspired air, the Po_2 intercept, can be divided between Po_2 and Pco_2 in the lungs or for every molecule of CO_2 added to the alveolar air one molecule of O_2 will inevitably

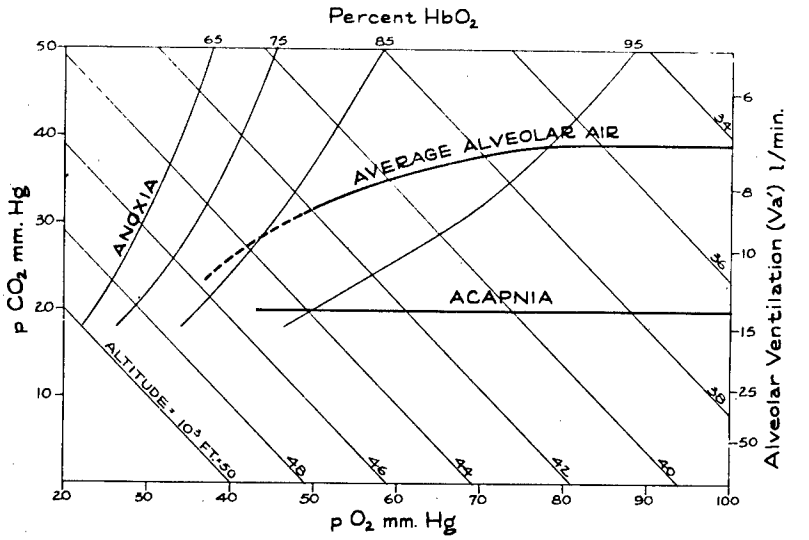


Figure 2

The O_2-CO_2 diagram for use when pure oxygen is breathed.

be lost and this will be true regardless of the exchange ratio of the individual. The uptake of O_2 in the lungs, in other words, does not diminish the Po_2 in the lungs because another molecule of O_2 will always take its place from the inspired air. If however a molecule of CO_2 enters the alveoli from the blood, O_2 will be displaced either into the blood or back through the airway. The aviator therefore can regulate his pulmonary oxygen tension by controlling the elimination of CO_2 from the lungs. He can ventilate rapidly and obtain high oxygen tension at the risk of low Pco_2 or he can risk a low Po_2 and try to maintain his Pco_2 at a level which is optimal for his neuromuscular processes. In this respect he is between the Scylla and Charybdis of acapnia and anoxia and must try to strike a happy medium position. In practice it appears that on the average aviators do instinctively assume an optimum position, but in any population of subjects there are some who overventilate and show signs of acapnia and others who underventilate and collapse prematurely from oxygen lack.

The average position of the alveolar air at different altitudes is illustrated on the chart (Figure 2) and below this there is a line which indicates the level of CO_2 tension at which symptoms of acapnia may be expected to develop. For a given rate of CO_2 output the alveolar ventilation is inversely proportional to the CO_2 concentration in the lungs and therefore it is possible to append a scale of alveolar ventilation at the right of the diagram. On the chart also are curves indicating percentage oxygen saturation of the blood equilibrated at the indicated tensions of CO_2 and O_2. To illustrate now the aviator's respiratory dilemma we may consider a subject at 42000 feet with an alveolar gas composition represented by the intersection of the average alveolar air curve and the 42000 feet diagonal. If he diminishes his ventilation to the sea level value of about 7 liters per minute, his alveolar point will move up his altitude diagonal until he develops symptoms of

anoxia with an arterial saturation of 75% or less. If on the other hand he voluntarily increases his ventilation still further, he will move down the altitude diagonal until he passes into the zone of acapnia. Somehow it appears that most subjects manage to avoid either of these extremes but in order to do so it is necessary for them to increase their ventilation when the oxygen tension falls. This tendency is indicated by the downward bend of the average normal alveolar air line in the region of high altitudes. A large number of performance tests have been carried out in our laboratory at widely varying composition of the alveoli (4). This was accomplished by varying the ventilation at different altitudes. The results of any individual test can be represented on the CO_2-O_2 diagram by a series of contour lines. Such lines from the "contrast discrimination test" are outlined in Figure 3. This is a visual test carried out in dim light and involving the legibility of letters of varying degrees of contrast. There is first a reasonably

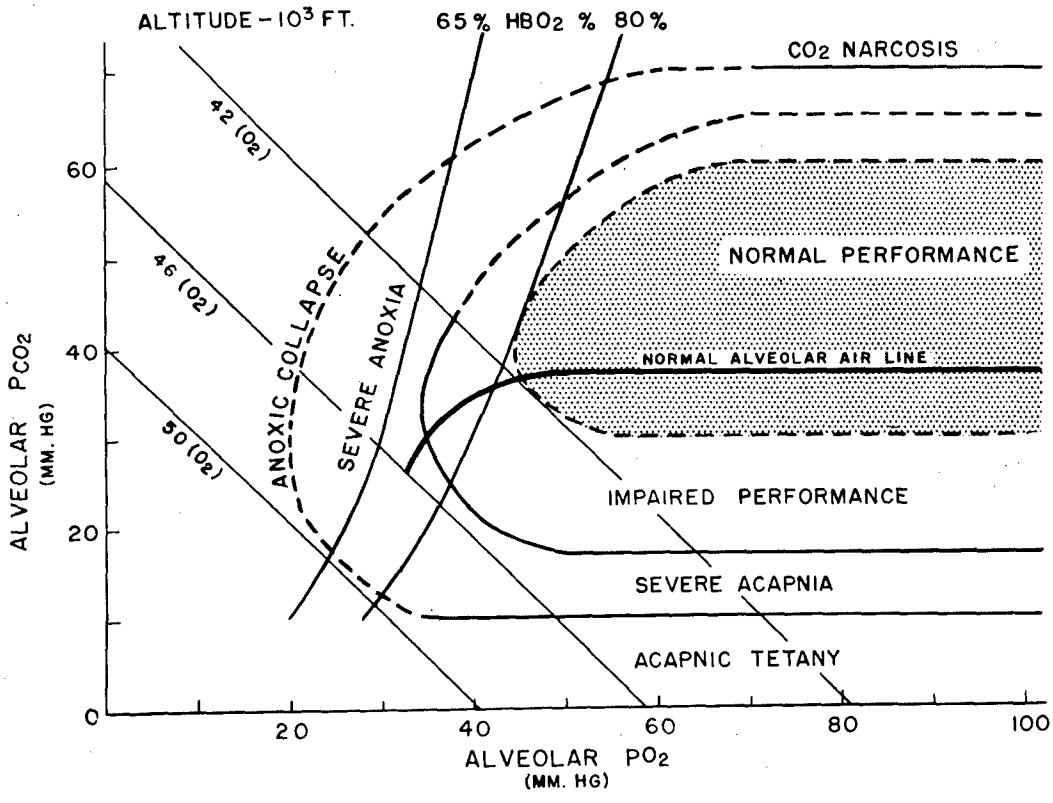


Figure 3

Areas outlined on an O_2-CO_2 diagram to represent varying degrees of impairment of performance at different compositions of the alveolar air. The 3-altitude diagonals represent 42, 46, and 50 thousand feet breathing oxygen or respectively breathing air if the R.Q. = 1.0. The performance depends only on the composition of the air in the alveoli and is independent of the altitude per se.

well-defined area of normal performance which is shaded in the diagram. Outside this area of normal performance is another zone of impaired performance and outside this the symptoms may be expected to be severe. Since the altitude diagonals are tangent to these performance boundaries at one point, it is evident that at every altitude there is a point of optimum performance and this point coincides roughly with the position of the normal alveolar air line. Similar charts are available based upon a hand steadiness test. Performance is impaired both by anoxia and by acapnia and the effects are additive. Acapnia makes anoxia less tolerable and vice versa. On the other hand by developing a mild degree of acapnia the severity of the anoxia may be relieved and vice versa. For every situation there is an optimum combination of these two hazards. Perhaps it should be considered remarkable that a man who has never previously been exposed to anoxia in his daily life will instinctively or reflexly select an optimum degree of ventilation when he finds himself in an environment dangerously low in oxygen.

Unfortunately, however, this problem is not quite so simple as it sounds and it is not exclusively a problem of respiration. The circulation is also affected by the balance between P_{O_2} and P_{CO_2}, and in this respect the cerebral circulation is particularly important. Thus if a high ventilation improves the alveolar P_{O_2} but at the same time diminishes the cardiac output, the tissue P_{O_2} will not be increased and no improvement will result. It is known that low P_{O_2} dilates and low P_{CO_2} constricts the cerebral vessels. This will tend to maintain the gas tensions constant in the brain irrespective of changes which occur in the lung. With these considerations in mind it is not surprising that this problem led to a lot of discussion between different laboratories during the war, some urging that addition of CO_2 to the inhaled oxygen will improve survival at altitude because it will avoid acapnia while others insisted that voluntary overventilation is the answer for the average man. The writer belonged to the latter school and still believes that studied hyperventilation is beneficial at altitude for most (but not all) persons. It must be admitted, however, that a severe restriction of cardiac output would nullify the respiratory advantages of increased ventilation.

Before leaving the O_2-CO_2 diagram, attention should be called to Figure 4 which represents the so-called "altitude diagonals" breathing air. When nitrogen is present in the inspired air, all possible alveolar positions can no longer be represented by a single diagonal for each altitude. Instead there is a set of diagonals for each inspired gas point depending upon the exchange ratio R. Four such families of R lines are shown in Figure 4 for four different altitudes. Since these various R lines for different altitudes intersect one another to some extent, it is evident that two subjects at different altitudes may nevertheless have exactly the same P_{O_2} and P_{CO_2} in the alveolar air provided they have different gas exchange ratios (R). The P_{N_2}, however, would be different in the two subjects and if the tensions of all three gases were known, the barometric pressure and therefore the altitude would of course be determined. The average alveolar "air" line on the chart represents the values obtained at different altitudes, but it is impossible to say what altitude corresponds to any particular point on the line

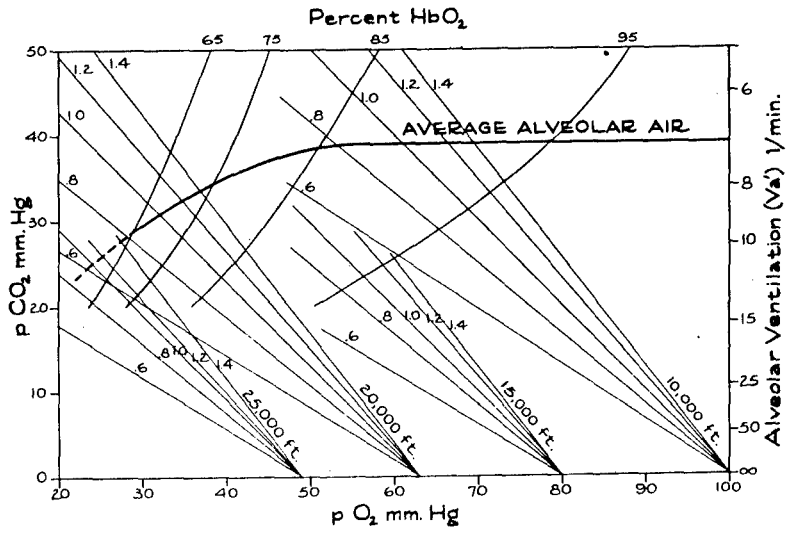


Figure 4

The O_2-CO_2 diagram when air is breathed. Every altitude is now represented by a set of diagonals for different R.Q. values. Sets of such diagonals for four different altitudes are shown. Increased ventilation moves the alveolar point down these diagonals toward the origin or inspired air point. Note that with different R.Q. values the same alveolar air composition could be obtained at two different altitudes 500 feet apart.

unless a given R of perhaps 0.85 be assumed for all subjects employed. These radiating R lines will become important for the interpretation of the problem of voluntary pressure breathing.

Voluntary Pressure Breathing

The usefulness of the pressure-volume diagram and the CO_2-O_2 diagram can perhaps be best illustrated by describing one particular application. For this purpose the problem of voluntary pressure breathing (VPB) may be selected. This was a maneuver originally proposed by the U. S. Navy for emergency survival at high altitudes. In the American vernacular it is sometimes called "grunt breathing" and was recently popularized in the Saturday Evening Post (March 13, 1954) by the dramatic escape of Lt. Comdr. Hawkins at supersonic speeds from a disabled jet plane at an altitude of 40,000 feet. After catapulting himself out through the canopy of his plane at this altitude, the pilot managed to keep himself alive and partly conscious without an O_2 tank, according to his account, by VPB

until he reached safe altitudes and opened his parachute. In our own view incidentally he derived very little advantage from VPB per se, but kept himself alive by the concomitant hyperventilation. The reasons for this will be described below.

"Grunt breathing" involves a large inspiration followed for 2 seconds by forcible expiration with the glottis closed. The pressure is then released and the air is exhaled. This is repeated every 5 seconds or more often. The mean pressure of air in the lungs is thus appreciably higher than ambient pressure so that the partial pressure of the oxygen and the arterial saturation is similarly increased. In theory this argument is valid enough but in practice the mean increment in Po_2 is so small that it does not compensate for the extra work and extra oxygen requirement which the maneuver entails.

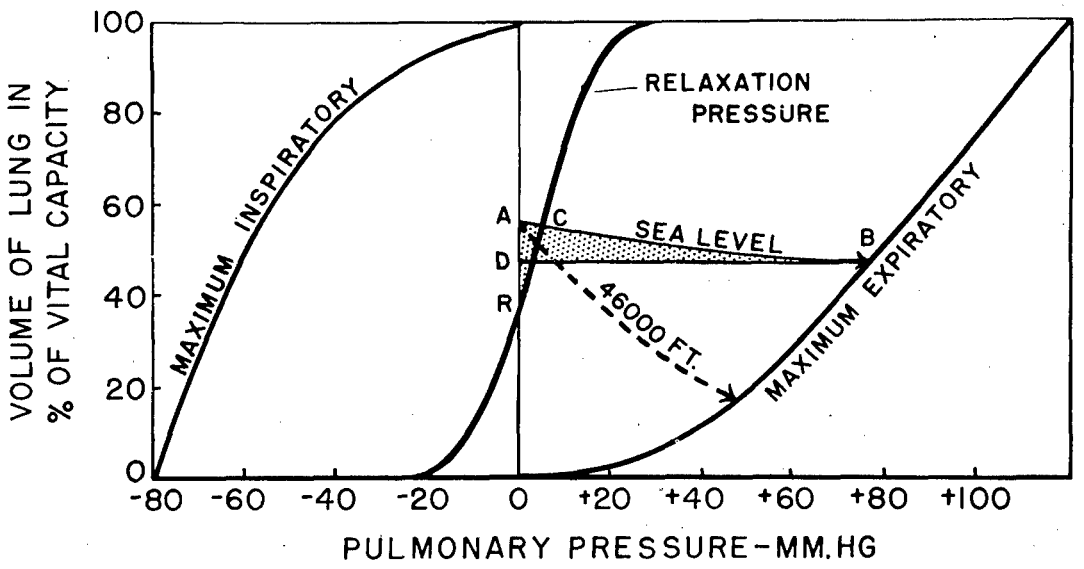


Figure 5

The maneuver of voluntary pressure breathing represented on a pressure-volume diagram. See text.

On a pressure volume diagram voluntary pressure breathing (VPB) can be represented as in Figure 5. The relaxation volume of the lungs at the end of a normal expiration is represented by point R where the pulmonary pressure is zero (or atmospheric). Inhalation is represented by the line RA representing an

abnormally large tidal volume of about 900 cc. Then the glottis is closed and maximum voluntary pressure is applied along the line AB. At sea level this involves a slight decrease in volume because the air in the lungs is compressed by the applied pressure. The higher the altitude the greater the decrease in volume resulting from the application of pressure because this depends upon the percentage increase of pressure. The dotted line, for example, shows the effect of applied pressure at 46,000 feet. Release of pressure and expiration follows the reverse pathway. In practice fatigue develops rapidly in this maneuver and the mean peak pressure developed soon fails to exceed 50 mm even though the maximum theoretical pressure indicated on the pressure volume diagram is 80 mm or more. The shaded area in the diagram represents the work involved in this maneuver. It consists of two parts. The area RAC represents the work against the elasticity of the lung and chest involved in inspiration. The area ADB represents the work of compressing the air in the lung. The overlap between these two areas is that part of the work of compressing the lung air which could be performed at the expense of the elastic potential energy stored in the elastic structures of the inflated chest during inspiration. The extra work required for moving the air is not represented in this diagram. It may be noted further that the work required to compress the lung air at 46,000 feet is much greater than at sea level because the change of volume is so much greater.

The effect of voluntary pressure breathing on the alveolar gases at altitude is illustrated on the O_2-CO_2 diagram in Figure 6. On this diagram the altitude diagonals for 50, 45, and 42 thousand feet are represented. At 45,000 feet breathing oxygen the alveolar point might be represented by point A. Survival would be difficult or impossible at this point with an alveolar partial pressure of oxygen of only 36 mm. The occasion therefore might be suitable for the initiation of VPB. If the subject succeeds for a period in maintaining an average pressure increment in his lungs of 17 mm (peak pressure = 42 mm for 2 sec. out of 5), he will have effectively transported himself to a lower altitude of about 42,000 feet where the dry inspired Po_2 is 81 instead of 64 mm. His alveolar point will then be somewhere on the 42,000 feet diagonal. If the pressure is suddenly increased by this amount, the alveolar gases at A will change their partial pressures along the line AB which is part of a straight line through the origin. When pressure is applied, it increases the partial pressures of both CO_2 and O_2 by equal percentages and therefore the alveolar point will remain on this diagonal. At point B, however, the Pco_2 is greater than before and therefore the respiratory center will presumably control the ventilation so as to bring the Pco_2 down to 30 mm as before. The result is that the Po_2 in the alveoli at C is 17 mm greater than before and all the pressure increment in the lungs is effectively applied to the O_2. If, however, in the process of VPB the alveolar ventilation is also increased 50%, then the Pco_2 will be decreased 50% (at constant CO_2 output) so that the alveolar point will move down the 42,000 ft. diagonal to point D where the Pco_2 is 20 mm instead of 30 and the Po_2 is 17 + 10 = 27 mm greater than before. When breathing pure O_2, therefore, VPB represents a real gain and, as in this case, 17/27 of the gain is due to the voluntarily applied pressure and only 10/27 due to hyperventilation.

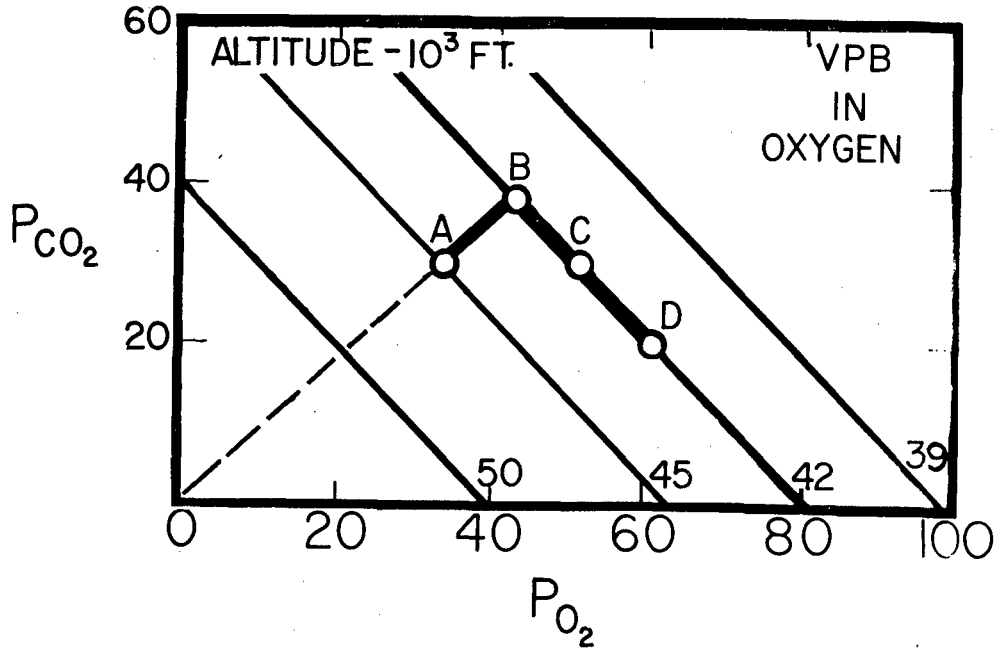


Figure 6

Voluntary pressure breathing with pure oxygen. The heavy line indicates the movements of the alveolar point as described in the text.

This provides an analysis of VPB which is unduly favorable. In stress situations and without a manometer for the subject to watch for continual guidance, the pressure developed at each pressure period is not likely to average as high as 50 mm. One doubts seriously whether Lt. Comdr. Hawkins, falling from 40,000 ft. with still unopened parachute, could have mustered strength or determination for the development of the pressure quoted. Still more important is the fact that in emergencies oxygen will not usually be available for VPB and with air the gain in partial pressure of oxygen is only one fifth as great.

Figure 7 shows the situation at an altitude of 18,500 feet breathing air. The alveolar point, A, is located on the diagonal for an R.Q. of 0.8. The alveolar partial pressures of O_2 and CO_2 in this case are exactly the same as at the alveolar point A illustrated in Figure 6 for oxygen breathing. When VPB is begun, it is assumed as before that the mean increment in pulmonary pressure is 17 mm. This increases the partial pressures of both O_2 and CO_2 along the dotted line through the origin, but the increment in Po_2 is much less than before because 17 mm is a much smaller fraction of the total pressure which is now 372 mm instead of 86 mm. Hence the alveolar point moves only to point B and the Po_2 is increased only about 3 mm. Point B lies on the 0.8 diagonal for an altitude of 17,400 feet. If the ventilation is maintained, however, at the same level as before the alveolar point moves down along the 0.8 diagonal to point C where the Po_2 is

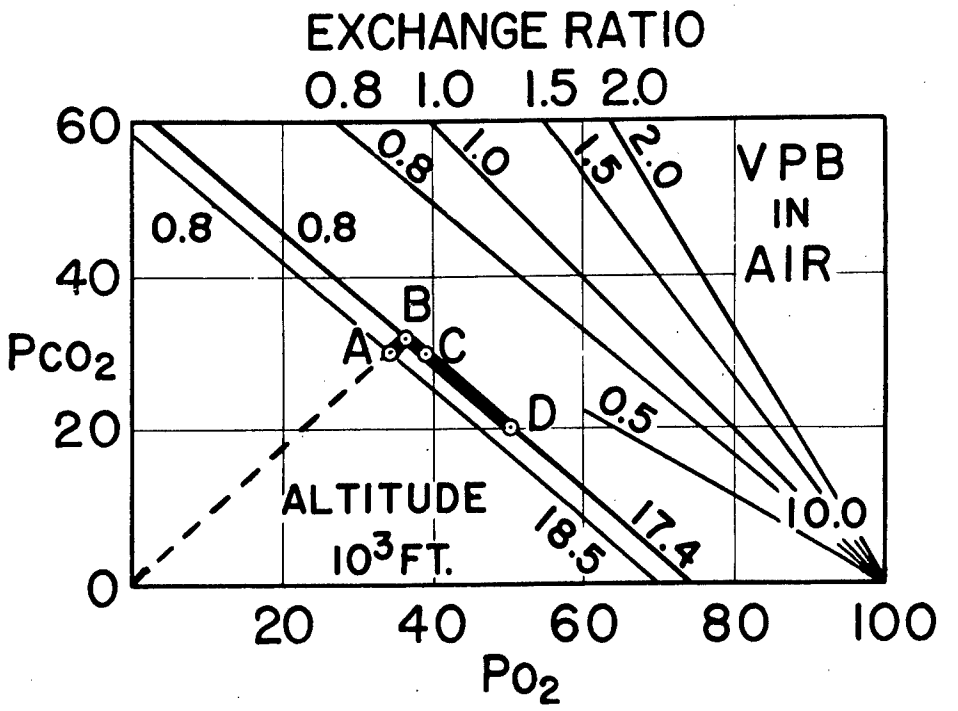


Figure 7

Voluntary pressure breathing with air illustrated on the O_2-CO_2 diagram. The heavy line indicates the movements of the alveolar point. Note that the increment in P_{O_2} in moving from left to right along this line is much less than in the corresponding diagram for pure O_2 in Figure 6.

17,400 feet. If the ventilation is maintained, however, at the same level as before, the alveolar point moves down along the 0.8 diagonal to point C where the P_{O_2} is 0.209 x 17 = 3.1 mm greater than at point A. If as before the ventilation is increased 50% by the VPB procedure, the alveolar point will move further down the 0.8 diagonal until it reaches point D. At this point the P_{O_2} is 16 mm greater than at point A, but of this amount only 3 mm is due to the pressure developed in the lungs. The same amount of hyperventilation without the effort of pressure development would have increased the P_{O_2} nearly as much (13 mm) and with a little more hyperventilation the same P_{O_2} increment could have been obtained with less effort and with only a slightly lower P_{CO_2}. When it is realized that the considerable effort of VPB increases the oxygen requirement 45%, it is evident that the increased P_{O_2} in the alveoli is scarcely enough to take care of the increased diffusion gradient needed in the lungs (45% more) and provides no reserve for the extra diffusion gradient required in the tissues.

From these considerations it is easy to understand that voluntary pressure breathing will improve survival at high altitudes in emergencies, but it is also evident that simple hyperventilation (approximately twice the normal) will accomplish at least as much and probably more. Furthermore, it may be said that without the use of this diagram, or some similar substitute, it would be very difficult to make this prediction.

There are many other applications of the O_2-CO_2 diagram which cannot be discussed at this point. These include the important ventilation-perfusion ratios, the diffusion gradients and gas tensions in the tissues, the effects of variations in cardiac output and breath holding. To facilitate the use of the diagram Dr. Hermann Rahn and the author have prepared a small book of diagrams in which is included a transparent template containing a set of R.Q. diagonals for air breathing. This template can be suitably placed on a CO_2-O_2 diagram so that the origin of the diagonals coincides with any desired inspired air point and then the alveolar point can be fixed if any two of the following are known: alveolar P_{O_2} alveolar P_{CO_2}; R.Q.; or ventilation (per unit of O_2 consumed or of CO_2 given out). For the solution of physiological problems at altitude the diagram is a great time saver and a great aid to precise thinking. It has already been utilized in publications from many laboratories and clinics and seems likely to grow in popularity as it becomes more widely known.

REFERENCES

1. Rahn, H., A. B. Otis, L. E. Chadwick and W. O. Fenn The Pressure-Volume diagram of the thorax and lung, Am. J. Physiol., 146: 161, 1946.
2. Fenn, W. O., H. Rahn and A. B. Otis A theoretical study of the composition of alveolar air at altitude, Am. J. Physiol., 146: 637, 1946.
3. Rohrer, F. Pflüger's Archiv 165: 419, 1916.
4. Margaria, R. Un trattamento quantitativo nello studio della fisiopatologia della respirazione, Recenti Progressi in Medicina, vol. 10, p. 487, 1951.
5. Otis, A. B., H. Rahn, M. A. Epstein and W. O. Fenn Performance as related to composition of alveolar air, Am. J. Physiol., 146: 207, 1946.
6. Fenn, W. O., H. Rahn, A. B. Otis and L. E. Chadwick Voluntary pressure breathing at altitude, J. Applied Physiol., 1: 752, 1949.

A STUDY OF SOME RESPIRATORY AND CIRCULATORY EFFECTS PRODUCED BY PRESSURE BREATHING AND BY POSTURAL CHANGE

by

Arthur B. Otis, Hermann Rahn and Mitzi Suskind

Both pressure breathing (1) and tilting from the supine to the vertical position (2) have been studied separately in numerous experiments as regards their respiratory and circulatory effects. However, they seem not to have been considered in a comparative fashion nor are there any reports of their action in combination. The object of the present study was to evaluate some of the effects of these two stresses both when acting singly and in combination.

EXPERIMENTAL

Five series of experiments were accomplished with the same five adult males serving as subjects throughout. The experiments were performed with the subject in a sheet metal box 18 inches high x 22 inches wide x 72 inches long, except for the head which protruded through a sponge rubber collar of the type used on the Drinker Respirator. The box was so arranged that it could be tilted quickly from its normal horizontal position to an angle of 70 degrees. A hose connection made it possible to maintain a steady positive or negative pressure within the box by attachment to a pressure line or evacuating pump. The subject breathed air at ambient pressure through a mouthpiece. Since negative pressure within the box was equivalent to positive pressure in the lungs, this condition will be referred to as positive pressure breathing, + P.B. The condition of a positive pressure within the box will be referred to as negative pressure breathing, - P.B.

The general experimental procedure was as follows: Electrodes were fastened to the chest of the subject who then entered and lay supine in the box which was in its horizontal position. The leads from the electrodes were plugged into an electrocardiotachometer. The end of the box holding the collar was clamped in place and the collar was adjusted to fit around the neck snugly but not so tightly as to be uncomfortable. The head of the subject rested on a pillow outside the box. No measurements were recorded until the heart rate and composition of the alveolar air became steady. At the end of the 10 or 15 minutes which were usually allowed for this to occur the mouthpiece and a nose clip were put in place.

Values for heart rate from the electrocardiotachometer, alveolar P_{CO_2} and P_{O_2} by the continuous method of Rahn, et al (3), and expired ventilation volume and

frequency by means of a recording gas meter, were obtained each minute for the duration of an experiment. The schedules of the several series were as follows: No subject participated in more than one series on a single day.

Series I. There were five consecutive 10-minute periods.

1. Supine.
2. Supine with 20 cm H_2O + P.B.
3. Tilted with P.B. continued.
4. P.B. removed but subject remained tilted.
5. Back in supine position.

Series II. Exactly like Series I except that the subject wore a pneumatic vest which covered the torso and which was inflated with 20 cm H_2O counterpressure during periods (2) and (3).

Series III. Like Series I except that the legs of the subject were snugly wound from the foot to high on the thigh with "Ace" bandages.

Series IV. Like Series I except that 20 cm H_2O - P.B. instead of + P.B. was applied in periods (2) and (3).

Series V. There were three consecutive 10-minute periods.

1. Supine.
2. Tilted.
3. Supine.

RESULTS AND DISCUSSION

For each series the corresponding data of all five subjects were averaged for each minute of the experiment. Figures 1 to 5 inclusive show these average values for the several measured quantities and for the calculated alveolar respiratory quotient plotted against time. To facilitate an overall comparison of the different series, the overall averages for similar measurements made during each 10-minute period are shown in Figure 6.

For purposes of discussion the heart rate changes and the respiratory alterations may be taken as a measure of the strains produced by the stresses associated with the various experimental procedures. Reference to Figure 6 shows that according to this criterion, tilting from the supine position to an angle of 20 degrees from the vertical resulted in about the same strain as did application of 20 cm H_2O + P.B. This amount of pressure breathing may be said to be

approximately equivalent to an accleratory stress of 0.94 G (i.e., G x cos 20°). Also these two stresses are approximately additive (actually the increases in heart rate, ventilation, and oxygen consumption with both stresses acting are greater than the sum of the corresponding values for the two stresses separately applied.)

Vest and bandage may be regarded as protective devices. It would appear that the vest gives somewhat better protection against + P.B. than do the bandages. Against the combined stresses of + P.B. and tilting, bandage is better as judged by heart rate and oxygen consumption, but somewhat less effective in preventing an increased ventilation. Against tilting alone (following P.B. plus tilting) the vest was not tested, but bandaging shows some reduction in heart rate and a slight increase in ventilation and oxygen consumption.

Negative pressure breathing appears to produce little circulatory strain (as judged by heart rate), but shows a marked effect in increasing ventilation and

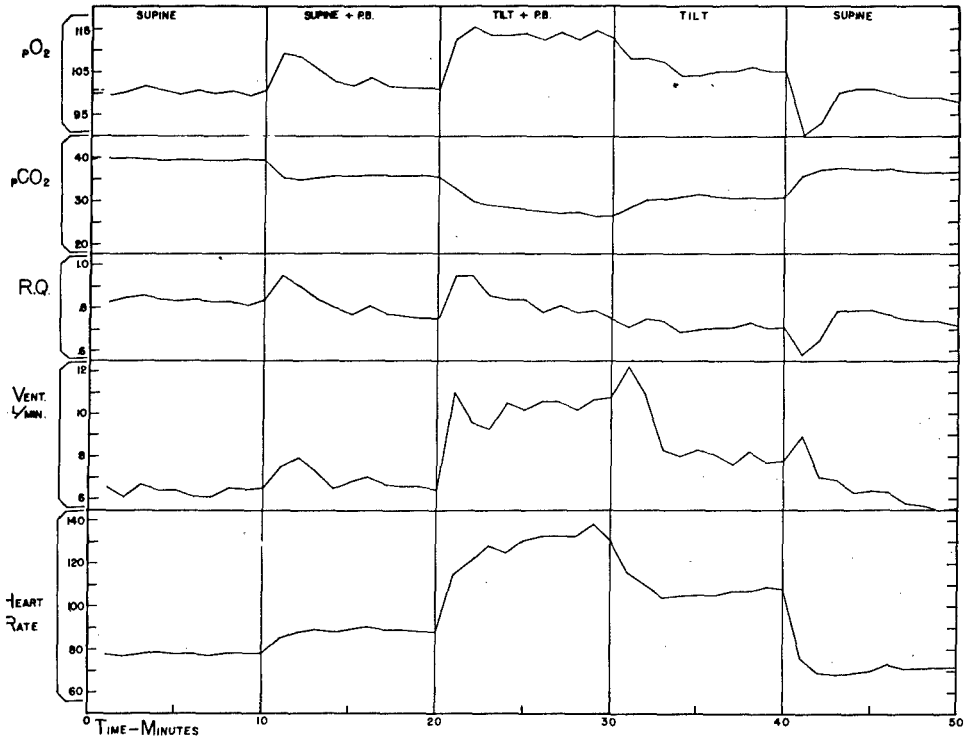


Figure 1

Averages of measurements made in Series I plotted against time. The legends at the top of the figure indicate the procedure adopted during each 10-minute period of the experiment.

oxygen consumption. When combined with tilting, - P.B. seems to exert some counter-action against the former, since the changes observed with these two stresses acting together are less than with tilting alone.

More detailed comments on some of the results will now be made by considering each series of experiments in turn.

Series I (Figure 1)

With induction of + P.B. the heart rate promptly began to rise, continued to increase during the first four or five minutes, and then remained relatively constant. Ventilation showed an increase that was more pronounced at first than later. The initial peak probably represented a period of adjustment of the breathing reflexes. The increased ventilation was also reflected in the changes that occurred in the alveolar gas tensions.

When the stress of tilting was superimposed on the + P.B., pronounced increases in both heart rate and ventilation occurred. The heart rate continued to rise, until near the end of the 10-minute period it was about 135 beats/minute. That the combined stress of + P.B. plus tilting imposed a severe strain on the body is borne out by the reports of the subjects following this experience. Blurred vision, nausea, sensation of warmth and faintness were noted. Paling was observed in all subjects and sweating in all but one.

Removal of + P.B. but with the subject still in the tilted position produced a drop in the heart rate, although a considerable tachycardia still remained. When the subject was restored to the horizontal position at the onset of the last period of the experiment, the tachycardia ceased almost immediately.

Ventilation also showed an overall decrease during the period after + P.B. was removed and again after the subject was restored to the supine position. However, the immediate effect of removal of + P.B. was a sharp transient rise in ventilation during the first minute; a similar temporary increase in ventilation during the first minute was observed after the subject assumed the supine position. These peaks in ventilation are probably due in part to the diminution of expiratory reserve volume that would be expected to occur on release of + P.B. or restoration to the supine position. It should be noted, however, that these peaks in the ventilation curve are accompanied by a dropping O_2 tension and a rising carbon dioxide tension of the alveolar air. The most likely explanation of this seems to be that both + P.B. and tilting produce a pooling of venous blood in the abdomen and in the peripheral veins, especially in the legs, and that when the P.B. is stopped or the supine position is assumed, this pooled blood, which may be presumed to be low in oxygen and high in CO_2, is suddenly put back into circulation. The respiration is stimulated and the alveolar gas composition is altered. More evidence for this will be mentioned later. Somewhat similar phenomena have also been noted elsewhere (4,6).

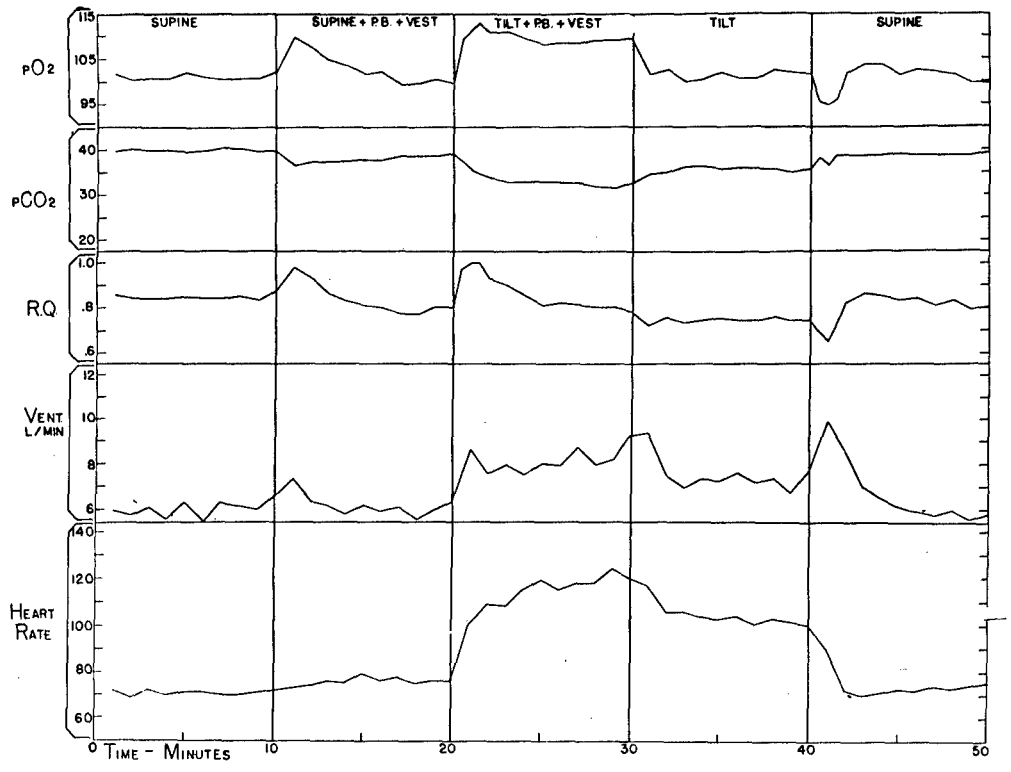


Figure 2

Average of measurements made in Series II plotted against time.

Series II (Figure 2)

With the vest in place, the application of + P.B. caused little change in any of the measured variables, except for a transient increase in ventilation at the onset. The additional changes produced by tilting were not markedly modified by the vest, however, as comparison with Figure 1 demonstrates.

The behaviour of the heart rate and ventilation during the last two periods of the experiment was similar to that in Series I except that the ventilation showed almost no transient rise when + P.B. was removed. To the extent that the presence of such a rise is an indication of the release of pooled blood, as has been suggested above, the absence of this rise may be taken to mean that there was no pooled blood to be released. The vest then appears to have been effective in preventing much of the blood pooling produced by + P.B., and since the vest covered only the chest and abdomen, it seems likely that it prevented the pooling

that ordinarily may occur in the latter area. The vest could not be expected to have any effect on pooling during tilting alone, because it fitted too loosely to offer any support except when it was inflated during pressure breathing. Consequently the transient rise in ventilation at the onset of the last period of this experiment is to be expected.

In this series of experiments the unpleasant symptoms experienced by the subjects in Series I were absent.

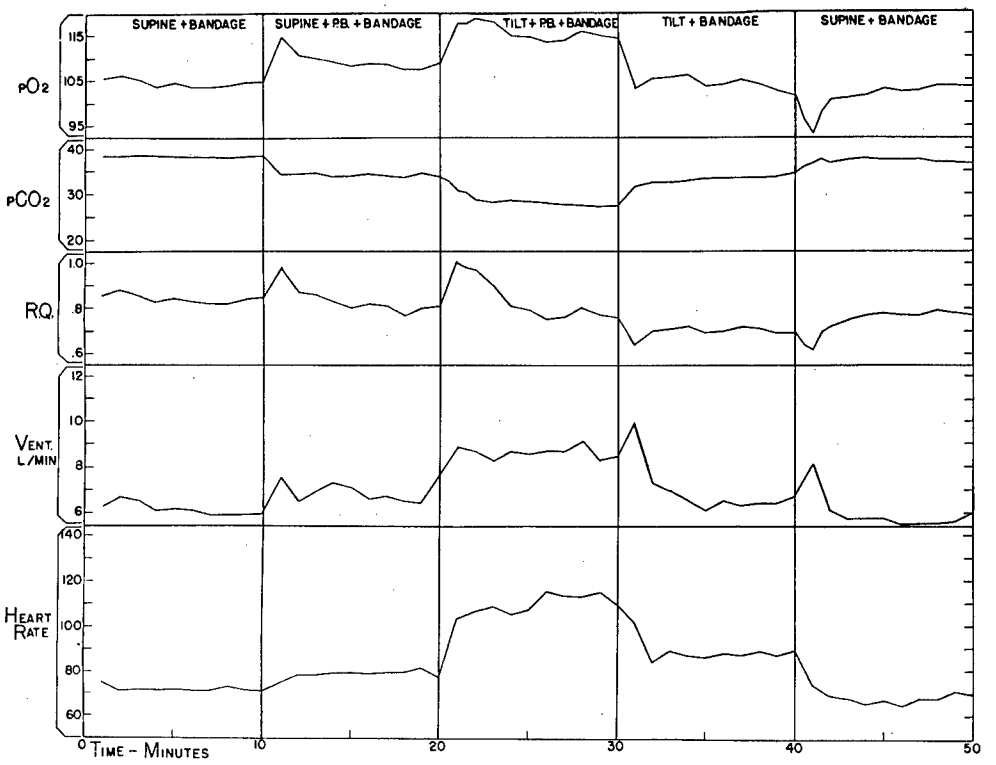


Figure 3

Averages of measurements made in Series III plotted against time.

Series III (Figure 3)

The presence of bandages did not alter qualitatively the responses to + P.B. alone or to + P.B. with tilting. The magnitude of the responses to the combined stresses is, however, appreciably less than when the bandages were absent.

(Compare Figures 1 and 3). Furthermore, with bandages, recovery following removal of the stress occurred more promptly than in the unprotected state. The lack of subjective symptoms again bore out the protective effect of the bandages. Although the bandages did not prevent the transient rise of ventilation at the onset of each of the last two periods of the experiment, the rise was less protracted, perhaps indicating a lesser amount of blood pooling during the previous periods.

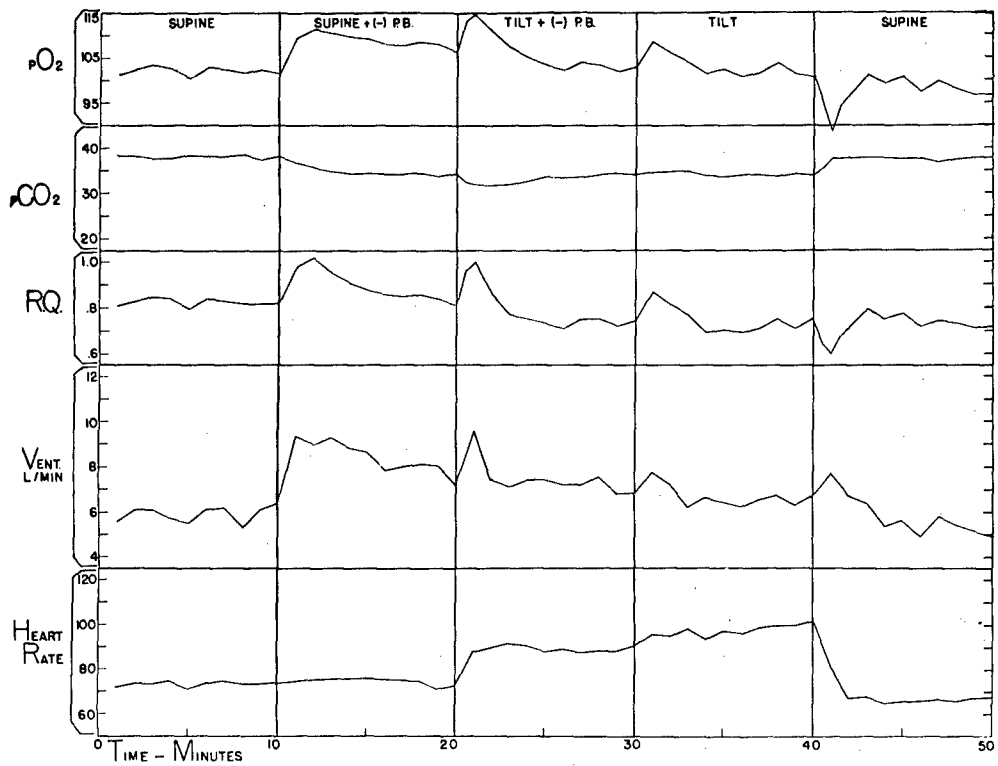


Figure 4

Averages of measurements made in Series IV plotted against time.

Series IV (Figure 4)

One point of interest in this series is that negative pressure breathing produces no significant effect on heart rate, yet at the same time increases the ventilation to a greater extent than does the equivalent amount of positive pressure. There also occurs an increase in oxygen consumption which is probably related to the fact that subjects generally find - P.B. more difficult than + P.B. Cain and Otis (5) found that added inspiratory resistance (somewhat analagous to - P.B. required more

extra oxygen consumption than did a corresponding expiratory resistance.

The addition of tilting to - P.B. produced little change in ventilation except for a transient rise at the beginning. The heart rate increased but less than in the other series. It is interesting that the oxygen consumption during the period of - P.B. with tilting is less than that during - P.B. alone.

When - P.B. is removed, there is not as pronounced a transient rise in ventilation as occurred with removal of + P.B. and furthermore the slight rise that does occur is accompanied by a rising rather than by a falling oxygen tension. During the period following removal of - P.B. the heart rate instead of falling actually increases somewhat. These facts seem to indicate a protective action of - P.B. against the stress of tilting.

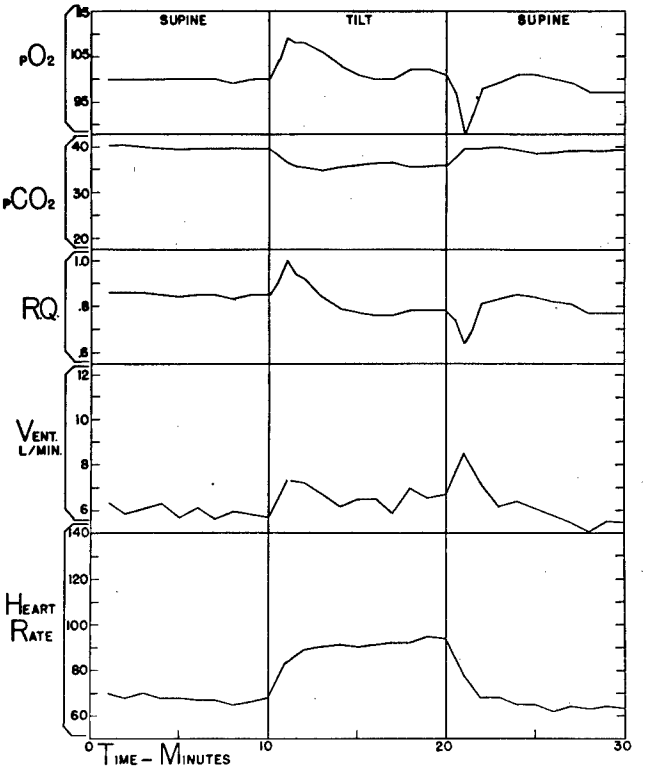


Figure 5

Averages of measurements made in Series V plotted against time.

Series V (Figure 5)

This series was performed to determine the effect of tilting alone without any previously applied stress. Comparing the second period of Series V with the fourth period of Series I, in which tilting had been preceded by + P.B., clearly shows the effect of the preceding treatment. Heart rate and ventilation are both definitely less elevated when no + P.B. occurred in the preceding period.

Comparison of tilting alone with P.B. alone indicates that the latter has a greater effect on ventilation, while the former produces the greatest displacement of heart rate.

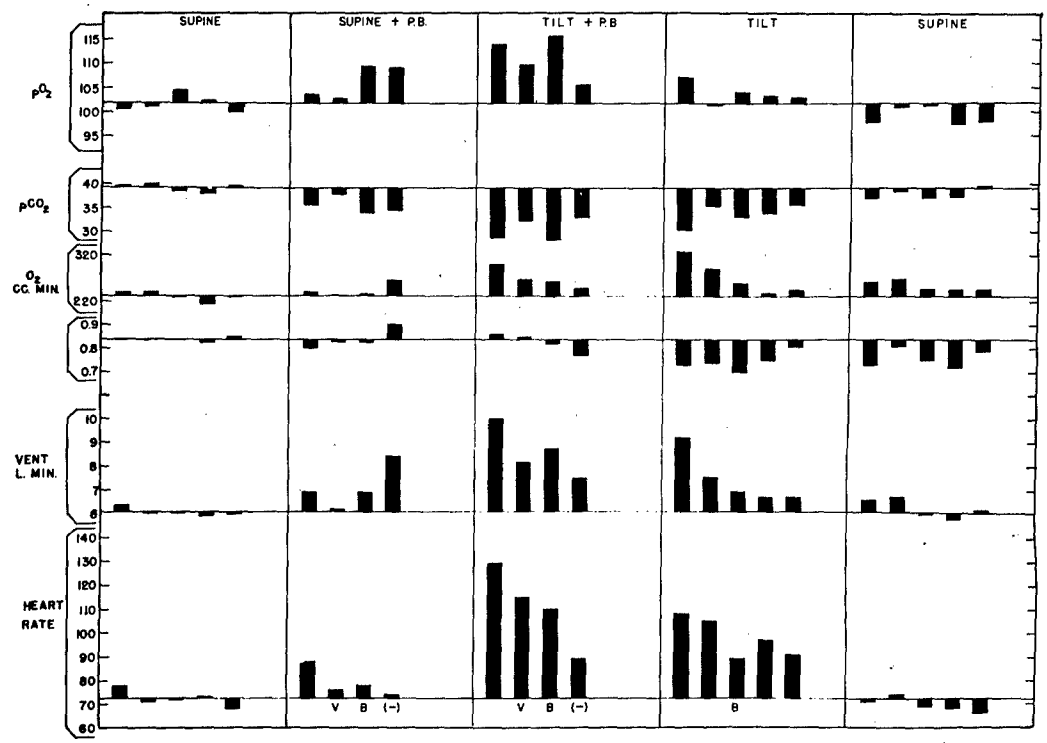


Figure 5

Each horizontal line serves as a base line to indicate the average value obtained in the first period of all experiments (i.e., with the subject supine and no applied pressure). The height or depth of each vertical bar represents the average displacement from this base line during a particular 10-minute procedure. From left to right in each group, the first bar represents Series I, the next bar Series II, and so on.

SUMMARY

Alveolar P_{CO_2} and P_{O_2}, breathing frequency and volume, and heart rate were recorded at one minute intervals on each of five subjects exposed for 10 minutes to each of the situations listed below. The average % change (without regard to sign) of all measurements is listed for each situation. (Heart rate, breathing frequency and volume, and alveolar P_{O_2} always increased and P_{CO_2} decreased.) Although such an averaging together of several diverse measurements is a questionable and inexact procedure, it is done here merely to indicate roughly the relative extent of the changes measured for the various situations.

Supine (Control)	0%
Supine, breathing 20 cm H_2O (+) pressure	10
Supine, pressure breathing, with pressure vest	5
Supine, pressure breathing, legs bandaged	10
Tilted passively to 70°	13
Tilted, breathing 20 cm H_2O (+) pressure	37
Tilted, pressure breathing, with pressure vest	32
Tilted, pressure breathing, legs bandaged	31

Tilting and positive pressure breathing act synergistically as shown by the fact that the physiological effects of both acting together are greater than the sum of the effects of each acting alone. Although the protective effects of a pressure vest or of leg bandages against the combined action of pressure breathing and tilting seem small when judged by the physiological data summarized above, they were sufficient to prevent symptoms of nausea and syncope that appeared in 3 of the 5 subjects when no protection was present. On the other hand, when negative pressure breathing alone was applied during the tilt, this maneuver seemed to offer the greatest protection, particularly as far as the circulation was concerned.

REFERENCES

1. Barach, A. L., W. O. Fenn, E. B. Ferris, and C. F. Schmidt J. Aviation Med. 18: 73, 1947.
2. Hellebrandt, F. A. and E. B. Franseen Physiol. Rev. 23: 220, 1943.
3. Rahn, H., J. Mohney, A. B. Otis and W. O. Fenn J. Aviation Med. 17: 173, 1946.
4. Otis, A. B. J. App. Physiol. 1: 743, 1949.
5. Cain, C. and A. B. Otis J. Aviation Med. 20: 149, 1949.
6. Rahn, H. and R. Ament This Report.

THE EFFECTS OF POSITIVE PRESSURE BREATHING IN MAN UPON THE PNEUMOTACHOGRAM, VENTILATION AND ALVEOLAR GAS PRESSURE

by

A. B. Otis, M. B. Sheldon, Jr. and H. Rahn

In spite of the numerous observations of the physiological effects of continuous positive pressure breathing in man (1), relatively little attention has been paid to the alteration in breathing pattern and ventilation rates. With continuous positive pressure breathing, inspiration becomes passive and expiration active - the reverse of the usual situation in normal breathing. Certain aspects of this phenomenon have been presented previously (1), but no detailed description of the alterations in the pattern of the pulmonary gas flow seem to be available. Furthermore, it is recognized that pressure breathing usually induces a hyperventilation (1,2), yet its effect upon the altered alveolar gas exchange has only been intermittently sampled (3).

While the breathing patterns are of interest in the design of masks and pressure demand regulators, the degree and persistence of spontaneous hyperventilation with pressure breathing is pertinent in the prediction of hemoglobin saturation at anoxic altitudes. Not only will the change in saturation at a particular altitude depend upon the added positive pressure, but also upon the Bohr effect induced by the lowering of the alveolar CO_2.

The following study is a detailed analysis of the breathing pattern in 4 subjects and the alveolar gas exchange in 5 subjects. The continuous positive pulmonary pressure ranged from 20 to 40 cm water. The subjects were in the supine position and the chest was not protected by counterpressure. Each part of this study is presented and discussed under its own separate heading.

THE PNEUMOTACHOGRAM

Methods:

The subject lay supine in a Drinker respirator and with a nose-clip applied breathed through a mouthpiece connected by a 35 cm length of 3/4 inch inside diameter plastic tubing to a pneumotachograph. The latter utilized a disc of 400-mesh monel gauze which offered a resistance of 1 mm H_2O at a flow velocity of 200 cc/sec. Recording of the differential pressure from this flow meter was done by means of a strain gauge pressure transmitter (Statham Laboratories) connected to a carrier wave amplifier, from which the rectified output fed into a

galvanometer of an oscillograph (Hathaway Instrument Co.) loaded with six-inch wide photographic paper. Typical records are shown in Figure 1. Calibration of the deflections on the record was accomplished at the end of each experiment by placing a Flowrater (Fischer and Porter Co.) in series with the pneumotachograph and making connection with an air line.

Pressure breathing was administered by adjusting the pump system of the respirator so that it produced a steady negative pressure within the respirator. Since this procedure made the intrapulmonary pressure positive with respect to that surrounding the body of the subject, it was mechanically equivalent to positive pulmonary pressure breathing (+ P.B.). The general procedure with each subject was to obtain a record of normal breathing and then records during the administration of 20, 30 and 40 cm H_2O + P.B. Each pressure was applied for a period of from 3 to 5 minutes, and a record was made during the last minute in each case.

The subjects studied were four healthy males between 25 and 35 years of age. Each subject was run through the test procedure twice on different days.

Results and discussion:

A series of recordings obtained on Subject R is shown in Figure 1. In the absence of pressure breathing, all four subjects showed smooth rounded inspiratory patterns, such as those illustrated in this figure, whereas expiratory patterns tended as a rule to be slightly more sharply peaked. These observations are consistent with those of Bretschger (4) on normal subjects, although his expiratory patterns were usually more markedly peaked than ours. This difference may be due in part to the fact that his subjects were sitting whereas ours were supine. With positive pressure the inspiratory curves of our subjects became markedly pointed while the expiratory pattern appeared more rectangular with a broad plateau.

With positive pressures of 30 cm H_2O or greater the expiratory pattern consistently showed an abrupt termination similar to that observed by Silverman (5) and by Cain and Otis (6), when an artificial resistance to expiration was imposed. Similar expiratory patterns were observed by Silverman in the case of four asthmatics. It appears, therefore, that an increased opposition to expiration, whether it be produced by a mechanical resistance, by positive pressure or by a pathological condition, tends to produce a plateau-like configuration of the expiratory pneumotachogram.

All subjects experienced a definite subjective desire to hyperventilate while breathing positive pressure, although actual hyperpnea was absent in some instances. This dyspnea seemed to be progressive with increases in pressure and with duration of exposure. Mild fatigue attributable to the increased expiratory effort was noted by the subjects after the tests.

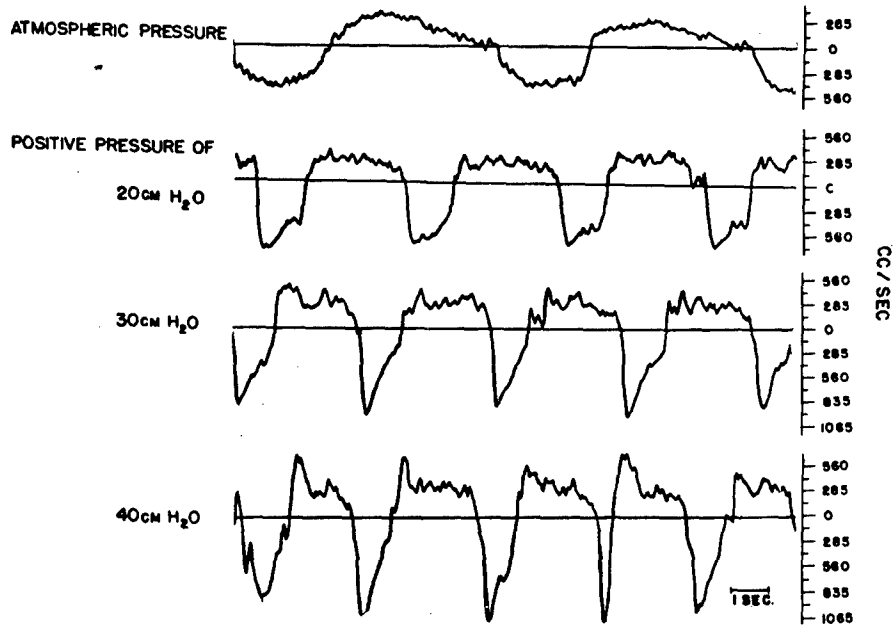


Figure 1

Pneumotachogram of normal subject (R) during breathing at atmospheric and at various positive pressures. In each recording, the curve below the reference line represents inspiration, that above the line expiration.

Quantitative information derived from the pneumotachographic records is indicated in Table I where the values shown for each subject are averages of measurements made on three to seven breathing cycles from each of the two runs. The tidal volumes were obtained by planimetric integration of the records.

These data reveal that on the average positive pressure breathing increases the ventilation and does so by an augmentation of both frequency of breathing and tidal volume. Time of inspiration and time of expiration are both decreased, as is the time required to attain peak flow in both phases of the breathing cycle. The peak flows themselves are increased.

Comparison of the separate data for the four subjects shows wide individual variations in the magnitude of the various factors and neither in any individual case nor on the average are any of the observed changes directly proportional to the applied pressure. The quantity that changes most consistently with applied pressure is the peak inspiratory flow, which in each individual increases progressively with increasing pressure, a single datum excepted. Fenn et al (3) have previously observed that during positive pressure breathing the lung volume does not increase

TABLE I

Individual averages of 2 tests

Pressure Applied cm. H_2O	Subj.	Time of Insp. secs.	Time of Exp. secs.	Cycle Time secs.	Peak Insp. Flow cc/sec	Time to Peak Insp. Flow secs.	Peak Exp. Flow cc/sec	Time to Peak Exp. Flow secs.	Mean Tidal Vol. cc.	Breaths per min.	Ventilation liters/min.
0	R.	2.77	4.61	7.38	500	1.34	368	1.09	993	8.1	8.04
+20	"	1.32	2.85	4.17	667	.34	368	.74	925	14.4	13.32
+30	"	1.22	2.47	3.69	735	.38	391	.70	663	16.3	10.81
+40	"	1.24	2.32	3.56	894	.44	504	.64	767	16.8	12.89
0	S.	3.09	4.74	7.83	460	1.42	354	.97	1008	7.7	7.76
+20	"	3.22	5.39	8.61	827	1.01	1036	.62	1864	7.0	13.05
+30	"	2.88	5.50	8.37	1314	.48	989	.51	2298	7.2	17.85
+40	"	2.73	4.96	7.69	1374	.50	988	.51	2100	7.8	16.38
0	C.	2.85	4.97	7.83	409	1.28	580	.88	955	7.7	7.35
+20	"	1.96	2.87	8.04*	515	.57	582	.78	822	7.5	6.17
+30	"	1.70	1.55	6.54*	712	.27	693	1.00	831	9.2	7.65
+40	"	1.50	1.43	8.51*	893	.30	666	1.08	823	7.0	5.76
0	B.	2.00	2.11	4.11	504	.71	595	.69	986	14.6	14.40
+20	"	1.48	1.92	3.40	687	.67	611	.51	896	17.7	15.86
+30	"	1.51	1.77	3.28	829	.55	530	.83	810	18.3	14.82
+40	"	1.70	1.94	3.64	676	.47	538	1.19	915	16.5	15.10
0	Mean	2.68	4.11	6.79	468	1.19	474	.91	986	9.5	9.39
+20	"	2.00	3.26	6.06	674	.65	649	.66	1127	11.7	12.23
+30	"	1.83	2.82	5.47	898	.42	651	.76	1151	12.8	12.78
+40	"	1.79	2.66	5.85	959	.43	674	.86	1151	12.0	12.53

* Indicates that post-inspiratory pause has been included.

as much as would be expected from the mechanical properties of the chest but that there tends to be a reflex opposition to expansion. It is probable that the large individual variations noted above are due rather more to differences in the voluntary or reflex response to P.B. rather than to differences in the mechanical properties of the chests and lungs of the subjects. Whatever their cause, the variations are so great that a large series of subjects would have to be studied before any valid quantitative generalizations could be made.

VENTILATION AND GAS EXCHANGE

Method:

The subjects were in the supine position with the continuous positive pulmonary pressure applied as in the foregoing experiment. The mouthpiece was connected to a respiratory check valve and an automatic alveolar air sampler previously described (7). The alveolar gases were continuously recorded on the Beckman oxygen tensimeter and the Cambridge thermoconductivity CO_2 analyzer. The expiration tube was connected to a 100 liter spirometer for the collection of the ventilation volume. After a period of rest the alveolar O_2 and CO_2, the breathing frequency, and ventilation volume were recorded every minute for 10 minutes. In addition the heart rate was counted by a cardiotachometer. This control period was followed by a 10-minute period of 30 cm H_2O positive pressure breathing during which the same measurements were continued. After recovery from this exposure, a 6-minute period of 40 cm H_2O pressure was applied. Five male subjects between the ages of 25 and 38 served as subjects.

Results and discussion:

The average values of all 5 subjects for each period of pressure breathing are shown in Table II. It may be seen that the hyperventilation with 30 cm H_2O pressure eventually falls off, but at the end of 10 minutes is still above the control period. The concomitant changes in alveolar Po_2, Pco_2, and exchange ratio are the result of the induced hyperventilation only and do not reflect any changes due to the positive pulmonary pressure itself. This is so because in this method the pressure of the lung gases remain always at atmospheric pressure while the rest of the body (except the head) is subjected to a pressure less than atmospheric by 30 or 40 cm H_2O as the case might be. This is equivalent to a positive pulmonary pressure of 30 or 40 cm H_2O.

The changes in ventilation and alveolar gases with 40 cm H_2O are similar but larger than those with 30 cm H_2O. This pressure is distinctly uncomfortable and was not well tolerated. The simultaneous changes which occur with time in the alveolar gases, exchange ratio (R.Q.) and alveolar ventilation may best be visualized on the O_2-CO_2 diagram of Fenn (8). These pathways are shown in Figure 2 and show the typical hyperventilation loops (7) which are induced here by positive

TABLE II

The effects of positive pressure breathing upon the gas exchange and heart rate. Average of 5 subjects breathing air in the supine position. Average barometric pressure 755 mm Hg.

Minutes	Normal Breathing	Positive Pressure Breathing															
		30 cm H_2O										40 cm H_2O					
	Average 1-10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6
Alveolar Po_2 mm Hg	102	115	115	111	110	109	109	107	104	105	107	123	121	119	117	114	112
Alveolar Pco_2 mm Hg	42	37	35	34	34	35	35	35	36	36	36	31	29	29	30	30	31
Alveolar R. Q.	.88	1.20	1.10	.90	.89	.88	.90	.82	.78	.80	.85	1.24	1.12	1.00	.93	.84	.84
Breath. Rate/min.	7.8	9	9	9	9	8	9	8	8	9	10	10	11	12	12	12	13
Vol. L/min. (B.T.P.S.)	6.3	8.6	8.0	7.6	8.8	-	6.5	5.8	6.5	7.0	7.2	9.1	10.0	-	10.0	9.3	9.8
Heart Rate/min.	70	75	78	73	79	75	77	76	75	77	73	69	70	72	70	73	77

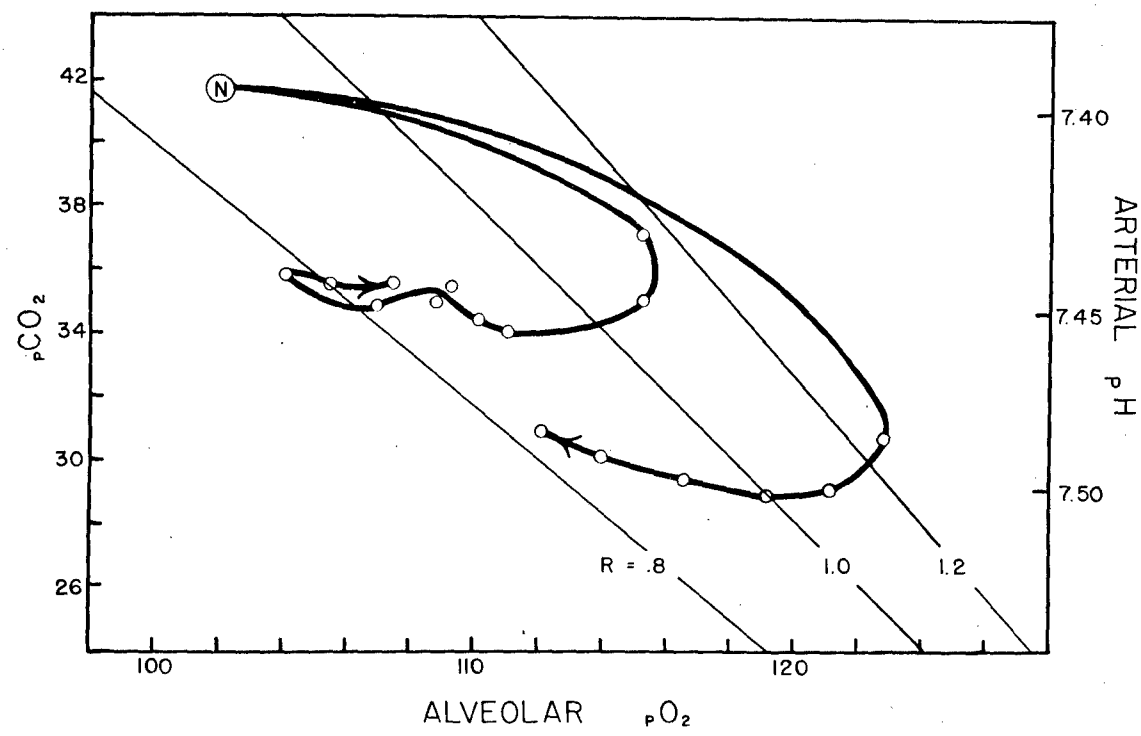


Figure 2

The progressive alveolar gas changes which follow the application of 30 and 40 cm H_2O. N is the normal control value. The points on the left pathway indicate the changes every minute with 30 cm pressure; the curve on the right, the effects of 40 cm pressure. The simultaneous changes in the exchange ratio, R, and arterial pH are indicated.

pressure breathing. If one assumes that the alveolar CO_2 is in equilibrium with the arterial CO_2, one may add the simultaneous arterial pH coordinates. These pH values have been derived from the nomogram of Dill (9).

It is of interest now to predict what blood and alveolar gas values would obtain under similar conditions of pressure breathing with oxygen at an altitude of 46,000 ft. The alveolar pathways of Figure 2 have been transferred to a similar diagram, Figure 3, where not only the positive pulmonary pressures, but also the lowering of the CO_2 are recorded. The normal control point, N, of Figure 2, is represented by Point A in Figure 3. This Point A has the same alveolar CO_2, but the alveolar O_2 is only 17 mm Hg at 46,000 ft. altitude (B = 106 mm Hg). Since only O_2 and CO_2 are present, all the gas exchange at that or any other pressure must take place along an altitude diagonal which has a negative slope of 1 and originates at the inspired gas pressure which is B-47 when 100% oxygen is breathed (8). At Point A

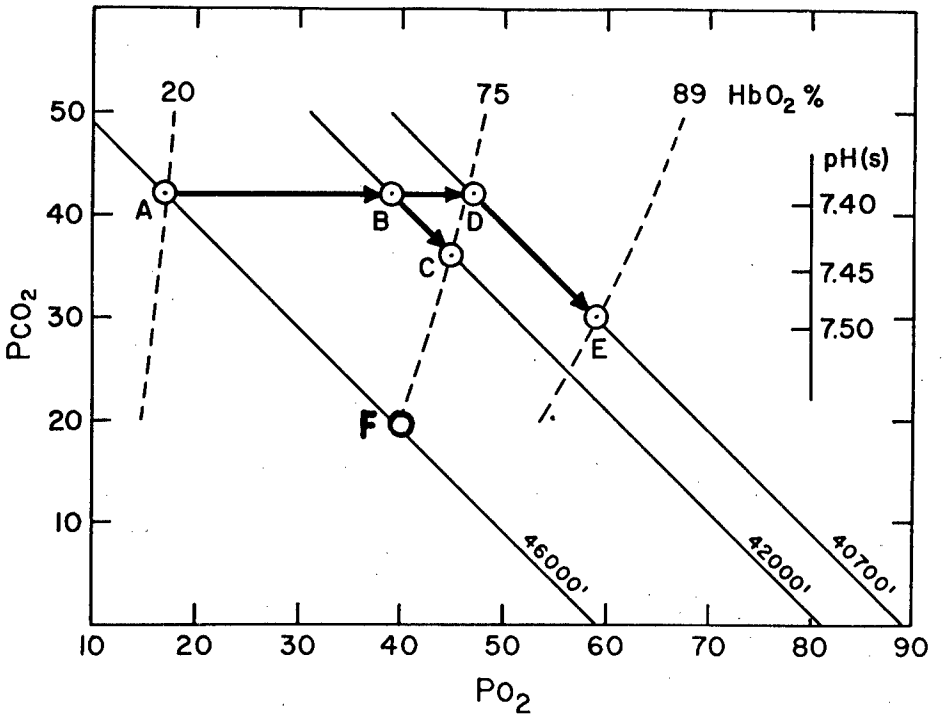


Figure 3

Theoretical application of the gas values of Figure 2 when 100% oxygen is breathed at a total pressure of 106 mm Hg (46,000 ft.). Point N of Figure 2 corresponds to Point A in this diagram; For discussion see text.

the hemoglobin saturation would be 20% if one allows for an alveolar-arterial O_2 gradient of 5 mm.

When positive pressure breathing is applied, not only does the pulmonary pressure rise, but hyperventilation ensues and the alveolar CO_2 falls. This is shown by 2 arrows for 30 cm H_2O or 22 mm Hg positive pressure breathing. The arrow from A to B represents the 22 mm Po_2 gain due to pressure, per se (if the ventilation keeps the CO_2 the same). Point B is on the 42,000 ft. diagonal and any hyperventilation must follow this line down. Point C corresponds to the CO_2 values obtained after 10 minutes of pressure breathing (Table II) and Figure 2. Point C will have a hemoglobin saturation of 75%. With 40 cm H_2O or 30 mm Hg the pressure, per se, would have attained Point D and the hyperventilation at this new altitude would have reached Point E with a saturation of nearly 90%. It is of interest to compare the Pco_2 which would have been necessary to maintain a saturation of 75% at the 3 altitudes. Even at 46,000 ft. a mere doubling of the alveolar ventilation (point F) would have given a saturation equal to that of Point C or D. It indicates again the ease with which the Hb can be loaded with more oxygen

and what important role the hyperventilation plays in continuous positive pressure breathing.

The plasma pH coordinates are indicated at the right of Figure 3 and apply strictly to only fully oxygenated blood. However, the deviations are relatively small for all but Point A. The possible loss in performance with the induced respiratory alkalosis has been discussed elsewhere (3). It is our concern here merely to indicate again that hyperventilation is a real phenomenon associated with positive pressure breathing and that, therefore, it must play an important role in the final gain of oxygen saturation which is attained with pressure breathing.

Summary:

1. Pneumotachograms were recorded on four normal subjects breathing air at atmospheric pressure and under positive pressures of 20, 30 and 40 cm H_2O. The inspiratory patterns became more peaked and the expiratory patterns more rectangular in shape. On the average, positive pressure breathing shortened the time required for inspiration and for expiration, increased the peak flow in both phases of the breathing cycle, especially in inspiration, and increased the total ventilation. Individual variations in the measured quantities were large.

2. Alveolar O_2, CO_2, ventilation, breathing rate and heart rate were recorded continuously in 5 subjects breathing air under normal conditions and under a positive pressure of 30 and 40 cm H_2O. These pressures induce a marked and persistent hyperventilation. The role of this hyperventilation in the final oxygen saturation with pressure breathing is discussed.

REFERENCES

1. Barach, A. L., W. O. Fenn, E. B. Ferris and C. F. Schmidt J. Aviat. Med. 18: 73, 1947.
2. Rahn, H., A. B. Otis, L. E. Chadwick and W. O. Fenn Am. J. Physiol. 146: 161, 1946.
3. Fenn, W. O., H. Rahn, A. B. Otis and L. E. Chadwick J. Appl. Physiol. 1: 752, 1949.
4. Bretschger, H. J. Pflügers Arch. f. d. ges. Physiol. 210: 134, 1925.
5. Silverman, L., R. C. Lee and C. K. Drinker J. Clin. Investig. 23: 907, 1944.
6. Cain, C. C. and A. B. Otis J. Aviat. Med. 20: 149, 1949.
7. Rahn, H. and A. B. Otis J. Appl. Physiol. 1: 717, 1949.
8. Fenn, W. O., H. Rahn and A. B. Otis Am. J. Physiol. 146: 637, 1946.
9. Dill, D. B., H. T. Edwards and W. V. Consolazio J. Biol. Chem. 118: 635, 1937.

Influence of the Abdominal Muscle Tone on the Circulatory Response to Positive Pressure Breathing in Anesthetized Dogs

By

H. BJURSTEDT

The effects of increased intrapulmonary pressure on the systemic arterial pressure in anesthetized animals have been described in numerous papers (for references see CARR and ESSEX 1946, DERN and FENN 1947, WERKÖ 1947). The first change to occur is a fall, the magnitude of which depends on the pressure applied in the pulmonary air-ways. After a varying period of time the arterial pressure usually shows a partial recovery, provided the intrapulmonary pressure is not kept so high as to cause a complete "tamponade" effect on the heart.

The initial fall in the arterial pressure has been explained on the basis of diminished cardiac output, caused by a blockage of the venous return to the heart by the forcibly expanded lungs. Little is known, however, as to the mechanisms responsible for the secondary recovery of the arterial pressure. Cardiovascular mechanisms of adaption have been suggested, and evidence has been presented that the arterial pressure is maintained by peripheral vasoconstriction in man (FENN, OTIS, RAHN, CHADWICK and HEGNAUER 1947, FENN and CHADWICK 1947, DELALLA 1948).

In a series of experiments designed to study vasomotor reactions and other cardiovascular components in various situations of high intrapulmonary pressure the importance of abdominal

muscular tone for the maintenance of the systemic arterial pressure became evident. The following experiments were undertaken in order to clarify the rôle of this particular mechanical component under positive pressure inflation of the lungs in anesthestized animals.

Methods.

The experiments were performed on 17 dogs under light to moderate sodium pentobarbital (Nembutal-Abbot) anesthesia. The initial dose was 25 mg/kg body weight, administered intravenously.

Continuous positive pressure breathing was obtained by connecting the tracheal tube with a large pressure chamber. The animal inspired from a bag inside the chamber, which could be filled with room air or oxygen. By previously pressurizing the chamber as needed the intrapulmonic pressure could be raised to the desired level. Air- or oxygen-breathing was used throughout the experiments.

Recordings of the intratracheal, intrathoracic, intra-abdominal and the mean pressure in the femoral artery were made on photographic paper by means of optical rubber membrane manometers. Thoracic and abdominal circumference excursions were obtained by use of pneumographs. In some instances a glass manometer and lead tubing were used to increase the fidelity of the femoral arterial pressure recordings. The intrathoracic pressure was obtained from a small rubber balloon introduced into the pleural space after inter-costal incision on the left side of the chest. Care was taken to close the wound tightly after expelling the air in the pleural cavity by application of positive intrapulmonary pressure. Likewise the intra-abdominal pressure was obtained from a balloon placed intra-abdominally by incision in the linea alba just cranial to the umbilicus.

Intrathoracic—intra-abdominal pressure differences were recorded by connecting the balloons to an optical rubber membrane differential manometer.

In some cases the heart rate was automatically and continuously recorded by means of an instantaneous cardiotachometer, operating on the impulses of the electrocardiogram (Sturm and Wood 1947)

Results.

Introductory Remarks.

Fig. 1 represents the usual course of the systemic mean arterial pressure during continuous positive pressure (20 cm H_2O) inflation of the lungs. At the onset of inflation a sharp decline is observed, which is followed by a gradual compensatory rise or recovery. On releasing the inflation pressure an additional

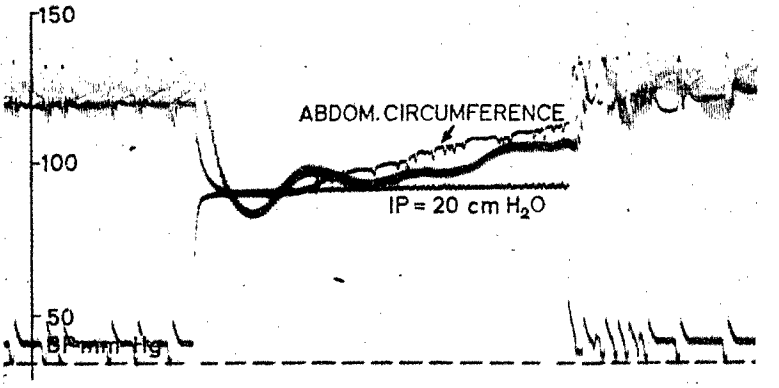


Fig. 1. Effect of increased intrapulmonic pressure on the systemic arterial pressure and the abdominal circumference. Dog, Nembutal anesthesia.

Upper tracings = arterial pressure and abdominal circumference. Increasing abdominal circumference is indicated by downward excursions.
Lower tracing = intrapulmonic pressure (IP).
Time-marking: 5 secs. between interruptions in the base-line.

increase in the arterial pressure is commonly seen, often resulting in a temporary over-shooting above the control level.

It should be pointed out that the experimental situation differed in some respects from that of positive pressure breathing in conscious human subjects. Thus one characteristic feature was that inflation of the lungs caused apnea. The duration of the apneic period seemed to depend upon the intrapulmonic pressure applied, showing an increase as the inflation pressure was raised. Furthermore, for a given intrapulmonic pressure the apnea showed a tendency to last longer, if the anesthesia was deepened by additional doses of Nembutal. This agent thus seems to join certain other barbiturates and anesthetics, under which continued inflation of the lungs have been found to produce apnea by activation of the Hering-Breuer reflex (for the mechanism cf. WATROUS, DAVIS and ANDERSON, 1950). In the present experiments the applied pressures ranged between 10 and 30 cm H_2O, and their duration between 0.5 and 2 minutes. The apneic periods often lasted as long as the duration of the intrapulmonic pressure.

The long-lasting apneic periods modified the experimental situation as compared with positive pressure breathing in conscious human subjects. Thus apnea may affect the cardiovas-

cular response in several ways, for instance by abolishing the normal action of the "lung pump" and by allowing the development of hypercapnia (cf. the early observations of GIERTZ in 1916). Probably some degree of hypoxemia is also induced, if air-breathing precedes the apneic period. In the present experiments, however, this possibility was not important, since air- and oxygen-breathing caused essentially the same respiratory and circulatory reactions under increased air-way pressure.

It was considered that the anesthetic might influence the circulatory response to positive pressure in the lungs also by direct action on the heart, vessels and/or cardiovascular reflex mechanisms. In this respect BEECHER, BENNETT and BASSETT (1943) found that the arterial pressure declines more in response to raised airway pressure when anesthesia is profound than when it is less deep. Furthermore they noted, as did also HUMPHREYS, MOORE and BARKLEY (1939), that the tolerance to pressure breathing depends on a number of other factors. Decreased blood volume, hemorrhagic shock, and exhaustion of cardiovascular reflex mechanisms lead to rapid circulatory deterioration during positive pressure breathing. The increased circulatory susceptibility to positive intrapulmonic pressure during deep barbiturate anesthesia has recently been ascribed to diminished compensatory reaction to the hypotensive state (MALONEY, AFFELDT, SARNOFF and WHITTENBERGER 1951).

As will be seen below, deepening of Nembutal anesthesia will decrease the circulatory tolerance to positive pressure breathing also by diminishing the abdominal muscular tone.

Most of the abovementioned findings of other investigators could be confirmed in the main, in a larger series of experiments. In the present selection, however, care was taken to avoid unnecessary contamination with factors, which may develop during experiments on animals under general anesthesia, such as effects of long-lasting or deep anesthesia or other shock-like conditions. The results to be described and discussed below, therefore, refer to experiments performed on dogs in the early stages of light to moderate Nembutal anesthesia, during which the animals could be assumed to be in good condition, as judged by their respiratory and cardiovascular reactions.

The abdominal circumference, always showing an initial expansion when positive intrapulmonic pressure was applied, usually diminished progressively during the rest of the apneic

period. It was observed that the course of the decrease in circumference often showed a remarkable relationship to the recovery of the systemic arterial pressure after the initial pressure drop (Fig. 1). In order to elucidate further the influence on the arterial pressure reactions of the muscular activity in the walls of the great body cavities during positive pressure breathing the following factors were studied: 1) Thoracic and abdominal circumference, 2) The effect of opening the abdominal cavity, 3) Intra-abdominal and intrathoracic pressures, and 4) Effects of sectioning of the vagi.

Thoracic and Abdominal Circumference and Relation of the Latter to the Arterial Pressure.

With small or moderate pressures (around or below 10 cm H_2O) the thoracic circumference immediately increased at the onset of inflation. Such pressures, causing short periods of apnea, allowed the thorax to contract slowly after the initial rapid expansion, revealing an active but prolonged expiration against the positive pressure. When the apnea was interrupted by a respiratory movement, the latter invariably started with a rapid inspiration, again followed by a prolonged expiration.

The onset of inflation was followed by a considerable increase of the abdominal circumference. This points to a lowering of the diaphragm and a distension of the lung tissue in the caudal direction. After its initial expansion the abdomen usually again showed a decrease in circumference during the period of prolonged expiration. Since under expiration the diaphragm itself is not active, the change of its position in the cranial direction, as evidenced by the diminishing abdominal circumference, points to abdominal muscular contraction as influencing the diaphragmatic movements under positive pressure breathing.

With higher intrapulmonary pressures (around or above 20 cm H_2O), causing prolonged periods of apnea, the thorax showed a greater expansion at the onset of inflation, and would still expand somewhat during the rest of the apneic period. A slow expiratory effort, decreasing the thoracic circumference, did not occur until during the last part of the apnea. The abdominal circumference showed a considerable increase at the onset of inflation, followed by a slow decrease, starting in some cases almost immediately after the initial expansion. The abdominal

contraction was sometimes delayed, especially under the highest intrapulmonary pressures, but always seemed to precede the thoracic expiration.

The decrease of the abdominal circumference was often sufficiently great to be clearly visible and could best be observed at intrapulmonary pressures ranging from 10 to 20 cm H_2O. The lower part of the abdomen (caudal to the umbilicus) thereby took a more rounded appearance towards the end of the apneic period.

The Effects of Opening the Abdominal Cavity.

The observed relationship between the abdominal contraction and the recovery of the arterial pressure under positive pressure breathing made it logical to study the effect of withdrawing the former factor. The response of the systemic arterial pressure to increased intrapulmonary pressure was therefore tested before and after extensive laparotomy. A long incision was made in the linea alba, from the xiphoid process to the region of the urinary bladder. The animals were kept supine on the operating table. It was found that, for a given increase of the intrapulmonary pressure, the initial arterial pressure fall became much greater after laparotomy than before (Fig. 1 and 2). The most pronounced effects on the arterial pressure were obtained if the

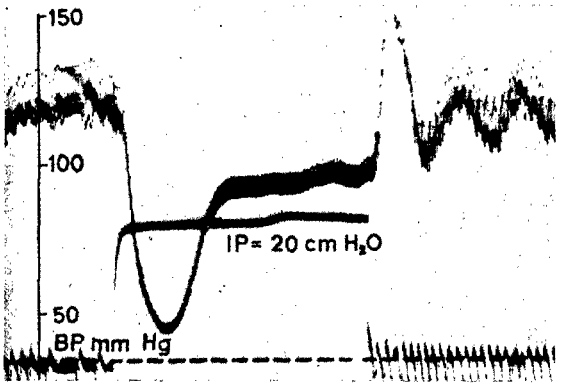


Fig. 2. Effect of extensive opening of the abdomen on the response of the arterial pressure to increased intrapulmonic pressure. Same dog as in Fig. 1.

Upper tracing = arterial pressure.
Lower tracing = intrapulmonic pressure (IP).
Time-marking: 5 secs. between interruptions in the base-line.

margins of the abdominal wound were held apart so as to partly free the muscular wall from the abdominal contents. Conversely, the pressure fall was only slightly influenced if the abdominal incision was short.

The secondary recovery normally seen during the apneic period changed somewhat in character after laparotomy. The recovery was sharper at the onset but at the same time not as complete as before laparotomy, the mean arterial pressure remaining at a lower level.

Abdominal and Intrathoracic Pressures.

For further studies of 1) the supporting action of the abdominal muscular wall in the circulatory response to positive pressure breathing and 2) the pressure distribution in the great body cavities, simultaneous recordings were made of the intra-abdominal and intrathoracic pressures as well as the intrathoracic-abdominal differential pressure.

The abdominal pressure followed the general pattern shown in Fig. 3. At the moment of pressure application in the lungs a small rise occurred, which continued progressively during the apneic period, *i.e.* during the prolonged expiratory phase. When the apnea was interrupted by an inspiratory stroke the abdominal pressure decreased temporarily. The intrathoracic pressure showed an initial rise which was always much greater than that of the abdominal, indicating that a substantial part of the former is taken up by the diaphragm and adjacent tissues. During the later part of the apneic period, the intrathoracic pressure increased at a slower rate, until a marked but short-lasting decrease was observed, which coincided with the inspiratory stroke.

From the relatively small initial rise in the abdominal pressure and the abovementioned observation that the abdominal circumference increased considerably, it can be assumed that the diaphragm moves in the caudal direction, but that its displacement is compensated for by yielding of the abdominal muscular wall, thus producing no appreciable increase in the abdominal pressure.

The immediate increase of the intrathoracic pressure over the abdominal, resulting from application of positive intrapulmonic pressure, could best be observed in the differential pressure

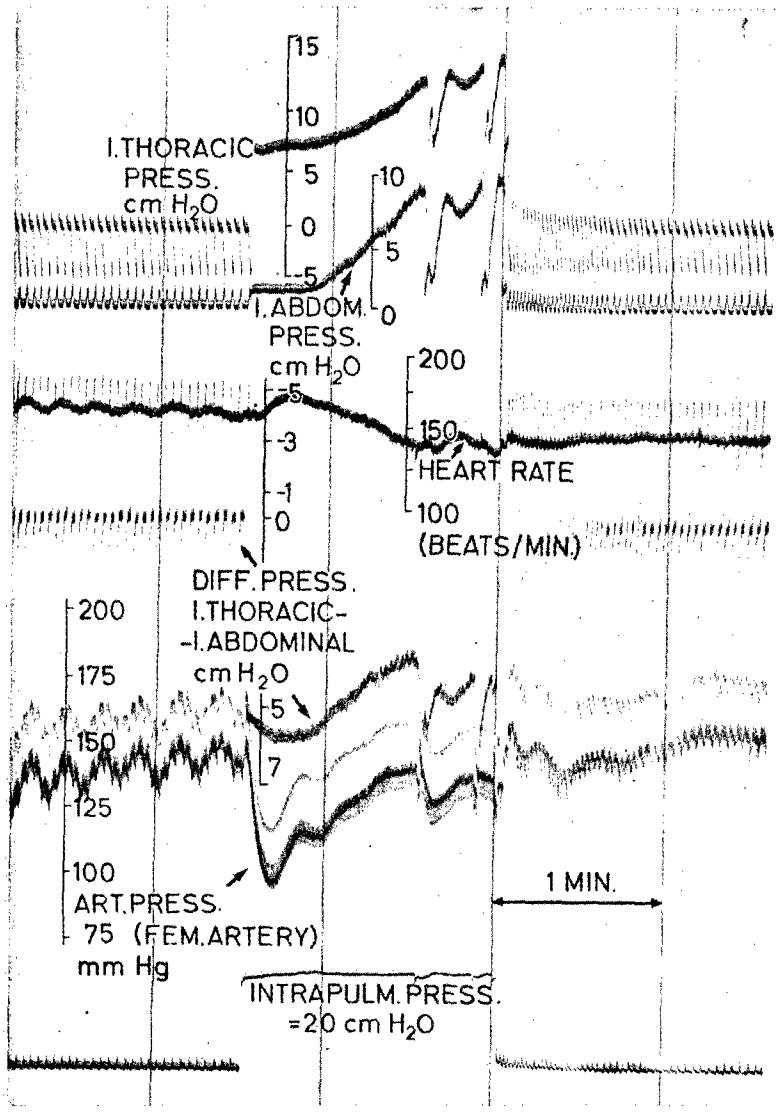


Fig. 3. Effects of increased intrapulmonic pressure on (from above downward) the intrathoracic pressure, abdominal pressure, heart rate, intrathoracic-abdominal differential pressure and arterial pressure. Note the immediate increase of the intrathoracic pressure over the abdominal at the moment of pressure application, and the secondary incomplete return of the intrathoracic-abdominal differential pressure towards normal. Dog, Nembutal anesthesia.

Time-marking: 1 minute between vertical lines.

tracings. Of special interest was the finding that, during the subsequent apnea, the differential pressure usually showed a slow return towards normal and often went strikingly parallel with the recovery of the systemic arterial pressure (Fig. 3). There is no doubt, that such return of the pressure difference in the great body cavities towards normal, even if incomplete, must have a great effect on the venous return to the heart from the abdominal region.

When apneic periods were interrupted by inspiratory strokes, there was a momentary equilibration of the abdominal and intrathoracic pressures, shown by a sudden peak upwards in the differential pressure recording (Fig. 3). The peaks observed in the arterial pressure recording immediately following the inspiratory strokes are readily explained by such pressure equilibration in the body cavities, admitting venous blood in the abdomen to enter the thorax and heart at a temporarily increased rate.

It was observed that deepening of the anesthesia caused a greater pressure difference in the body cavities for a given increase in the intrapulmonic pressure. The relative shares of the intrathoracic and abdominal pressures in this reaction have not been examined in particular but it seems likely that this finding has some bearing upon the earlier observations (cf. "Introductory remarks"), that deep anesthesia increases the circulatory susceptibility to positive pressure breathing.

Effects of Sectioning of the Vagi.

After sectioning of the vagi the application of positive intrapulmonic pressure changed the usual cardiovascular response in several respects. The initial fall in the arterial pressure was still present, but during the later period of pressure breathing the picture became somewhat complicated by the fact that respiratory movements persisted at essentially an undiminished rate. This strongly influenced the arterial pressure, which increased temporarily after each inspiratory stroke. The *average* level of the arterial pressure showed a slight tendency to rise. Little or no over-shooting occurred as the intrapulmonic pressure was released.

The action of the lung pump was studied by means of intrathoracic-abdominal differential pressure recordings. Positive pres-

sure breathing after vagotomy caused an initial increase in the pressure difference similar to that observed before vagotomy. However, following the initial increase, the differential pressure showed large fluctuations with each respiratory movement; inspiration caused an incomplete return towards normal, whereas expiration was accompanied by increased pressure difference. The excursions of the differential pressure tracing as well as those of the arterial pressure recording were greater than during vagal breathing with normal air-way pressure. The *average* level of the differential pressure showed no consistent change during the later part of the pressure breathing period.

It was observed that the large fluctuations of the pressure difference in the great body cavities were caused almost entirely by variations in the intrathoracic pressure. The abdominal pressure showed significantly smaller changes than before vagotomy. At the moment of pressure application in the lungs a small rise occurred, but no progressive increase was observed during the later course of the period. Only small fluctuations occurred as a result of the respiratory activity.

Vagotomy thus changed the pressure distribution in the body cavities during pressure breathing. The mechanism of this change was not studied in particular, but it seems evident that the cooperation of the thoracic and abdominal muscles is affected after cutting of the vagi. The participation of the abdominal muscles in the expiratory movements is apparently more or less abolished, the abdominal pressure being affected mainly by the movements of the thorax and diaphragm.

The effect of vagotomy on the arterial pressure response was also tested after extensive laparotomy. It was noted that positive pressure breathing caused an initial fall, which was not significantly influenced by the vagotomy, *i. e.* it was of the same order of magnitude as after laparotomy alone. The recovery of the arterial pressure, however, was slight if at all present. Fluctuations were commonly seen, originating from the action of the "lung pump". In a few cases the arterial pressure continued to decrease progressively after the initial fall. In these cases the animals might have become shocked by the combined effects of vagotomy and extensive laparotomy, and no clear-cut conclusions as to the mechanisms involved could be drawn. In the other cases, however, the failure of the arterial pressure to recover during positive pressure breathing may indicate, that the vagi

are of a certain importance for the recovery, not only by assisting in the preservation of the abdominal muscular tone but also by direct vasomotor influence.

Effects on the Heart Rate.

Positive intrapulmonic pressure in the intact animal usually caused only a slight acceleration of the heart following the initial decline in the arterial pressure (Fig. 3). The initial increase in the heart rate amounted to less than 15 per cent of the pre-inflation frequency, and sometimes no change at all could be observed. The increase in heart rate, if present, was always temporary and had subsided completely after 15—30 seconds. In the later part of the period of positive intrapulmonic pressure the heart rate was usually normal or showed a gradual decrease below the pre-inflation frequency. No consistent relation between the recovery of the arterial pressure and the heart rate could be observed.

Laparotomy did not cause any significant change in the response of the heart rate to increased intrapulmonic pressure. The heart rate recording usually showed the same pattern after laparotomy as in the intact animal.

After vagotomy, positive pressure breathing always caused a marked increase in the heart rate, reaching a maximum of 20—40 per cent of the original frequency after some 15—30 seconds. The tachycardia showed a tendency to persist throughout the period of pressure breathing.

Discussion.

This study was undertaken to investigate the influence of intra-abdominal pressure changes on the cardiovascular response during increased intrapulmonic pressure. It was thought that such information should be of value, considering the practical applications of the problem, for instance in the field of aviation medicine, in anesthesiology, and in certain methods of artificial respiration.

The Primary Fall of the Arterial Pressure.

The fact that positive pressure breathing causes a marked primary drop in the arterial pressure under Nembutal anesthesia

in the dog (intrapulmonic pressures = 10 to 30 cm H_2O in the present investigation) may appear somewhat puzzling in view of the reports of BARACH *et al.* (1946) and DERN and FENN (1947) that the arterial pressure tends to rise rather than to fall during positive pressure breathing in conscious human subjects. Since a primary drop in the arterial pressure has also been observed in man under barbiturate anesthesia (PRICE, CONNER, ELDER and DRIPPS 1952), it is evident that the anesthetic is responsible for this particular effect. It seems, however, that sufficient explanation has not yet been offered as to the mechanisms, through which the anesthetic exerts its action.

It is believed that part of the explanation may be derived from the present observations that 1) an exaggerated drop in the arterial pressure was produced if the abdomen was extensively opened in advance, and 2) with the abdomen intact, application of positive intrapulmonic pressure caused a considerably smaller increase in the abdominal than in the intrathoracic pressure. The reasons for this belief are presented below.

It is generally agreed that the venous return to the heart is reduced under increased intrapulmonic pressure, in man as well as in animals and irrespective of whether the subject is conscious or under general anesthesia. As to the physiological background for this effect, HENRY (1952) points out distension of the limb veins as a major factor. The distension results from the rise in peripheral venous pressure, which occurs until the new intrathoracic pressure threshold is overcome by supply of blood through capillaries and arterio-venous anastomoses. The sequestration of blood by such pooling in peripheral regions of the body will mean a reduction in the effective volume available for the circulation.

Additional pooling in the abdominal region is assumed to have played an important rôle for the arterial pressure drop in the present experiments. The significance of such pooling is borne out by the exaggerated fall in the arterial pressure, which was produced after opening of the abdomen. In this situation no external counter-pressure on the veins was present to reduce distension as the increased pressure in the abdominal portion of caval vein overcame that in the thorax. With the abdomen intact, on the other hand, a small increase was observed in the abdominal pressure, which by reducing the venous distension damped the arterial pressure fall.

The immediate effect of positive intrapulmonic pressure application depends on the resulting pressure distribution in the body cavities. The differential pressure recordings showed that the abdominal pressure increased considerably less than the intrathoracic. It can be inferrred that the observed pressure differences fairly accurately reflect the increment in the "net" (distending) pressures in the abdominal veins, which is necessary to make inflow into the thorax and right heart possible. They therefore also give an indication as to the amount of pooling, which occurs in the abdominal veins.

If this reasoning is extended to the classical Valsalva experiment and to positive pressure breathing in conscious subjects, it is interesting to note that the pressure distribution in the body cavities in these situations apparently differs from that observed in the present experiments on anesthestized animals. Thus RUSHMER (1947) observed in the Valsalva experiment and in the M-1 maneuver (used by pilots to increase the tolerance to positive radial acceleration) that the abdominal pressure increased over, or parallel with, the intrathoracic. Although no reports seem to be available as to the abdominal pressure during positive pressure breathing in conscious subjects, the similarity between the latter situation and the M-1 maneuver makes it likely that the abdominal pressure increases almost parallel with the intrathoracic. The pressure in the abdominal portion of the caval vein may therefore be expected to increase essentially parallel with the intrathoracic by direct action of the abdominal pressure on the walls of the abdominal vessels. No increase in the intravascular "net" pressure is needed for the maintenance of venous return from the abdominal region, and pooling is therefore limited to regions outside the trunk.

The rise in arterial pressure observed in the conscious state has been attributed to transmission of the rise in the intrathoracic pressure to the heart, *i. e.* the arterial pressure becomes higher simply because the initial pressure in the ventricles is higher when systole begins (HAMILTON, WOODBURY and HARPER 1936, DERN and FENN 1937, RUSHMER 1947). The mechanism thus opposes the tendency for the arterial pressure to fall, which would otherwise be produced by the diminished venous return. However, it is obvious that such action of the raised intrathoracic pressure may be masked by too extensive reduction in the venous return. A primary fall in the arterial pressure can then be ex-

pected to occur, as was the case in the present experiments. The clue to this difference evidently lies in the relaxing effect of the anesthetic on the tone of the abdominal muscular wall, causing an extension of the peripheral pooling to the abdominal region by defective increase in the abdominal pressure.

The existence of two such antagonistic mechanisms is in harmony also with the observations that 1) cyclopropane anesthesia, by producing *per se* a remarkably high pressure in the great veins of the thorax, may increase the arterial pressure under raised air-way pressure (PRICE, KING, ELDER, LIBIEN and DRIPPS 1951), whereas 2) sodium thiopental brings about a fall in the arterial pressure by diminished intrathoracic venous pressure and defective cardiac filling (PRICE, CONNER, ELDER and DRIPPS 1952).

A considerable expansion of the chest and abdomen by positive intrapulmonic pressure was shown to occur under Nembutal anesthesia. Since the primary fall in the arterial pressure persisted after vagotomy, any significant influence of stimulation of stretch receptors in the lungs can be excluded. Whether stimulation of stretch receptors elsewhere may contribute by eliciting reflex peripheral vasodilatation has not been answered by the present experiments. Other effects of distension of the lungs may be thought to occur by 1) instantaneous blockage of blood flow through the pulmonary circuit, causing a smaller supply to the left than to the right heart, 2) initial withholding of blood from the left heart by increase in the pulmonary vascular capacity at the moment of inflation. However, BJURSTEDT and HESSER (1953) found no evidence for such effects.

The Secondary Recovery of the Arterial Pressure during the Later Course of Positive Pressure Breathing.

Peripheral vasoconstriction has generally been held responsible for the tendency of mean arterial pressure to return toward the control level in anesthetized animals while the lungs remain inflated by positive pressure. However, the present experiments suggest that contraction of the abdominal muscular wall also contributes to the recovery by increasing the cardiac output. The diminishing abdominal circumference in combination with the return of the intrathoracic-abdominal differential pressure towards normal during the periods of apnea or prolonged ex-

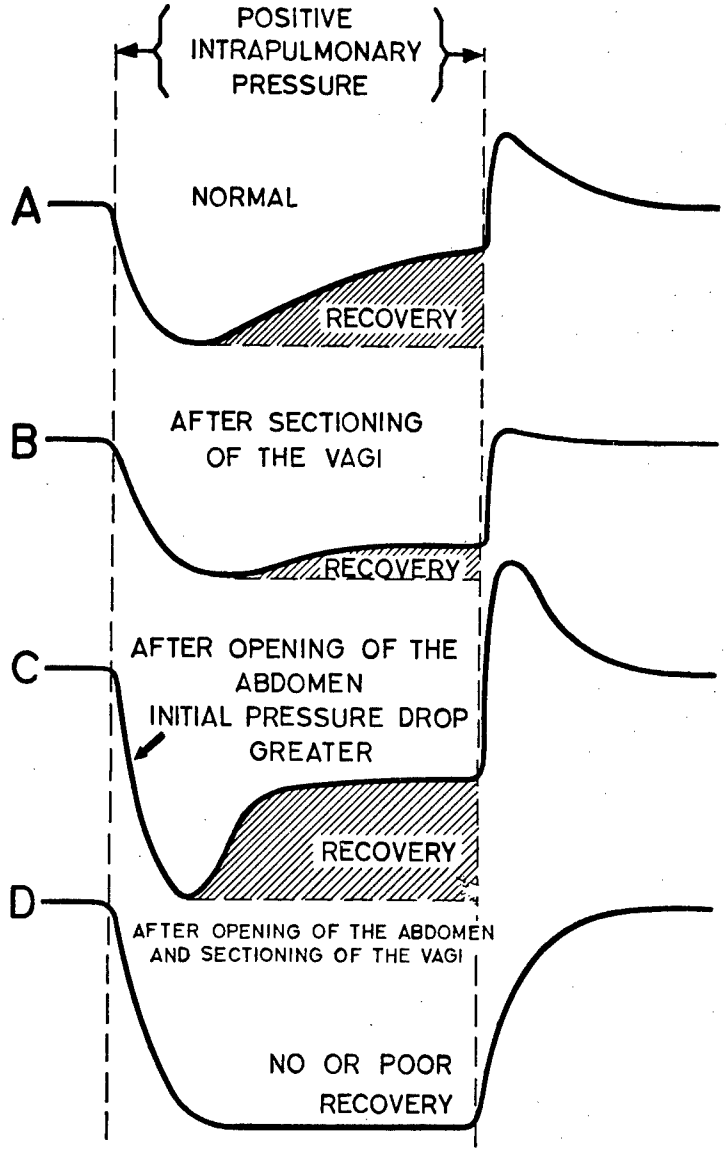


Fig. 4. Schematic representation of the primary fall and the secondary recovery of mean arterial pressure during increased intrapulmonic pressure in the dog under Nembutal anesthesia. The four situations A, B, C and D are further discussed in the text. Duration of increased intrapulmonic pressure = approximately one minute, applied pressure = 20 cm H_2O.

pirations speak in favour of an actual squeezing of venous blood from the abdominal into the thoracic region. Probably even slight increase in the tone of the abdominal muscles is sufficient to increase venous return to the heart appreciably because of the great capacity of, and the low pressure in, the abdominal venous reservoir.

Influence of Vagal Reflexes.

The effects of severing the vagi, with and without extensive opening of the abdomen, are represented schematically by Fig. 4.

It was observed that the recovery of the arterial pressure was not fully prevented by preceding vagotomy, and that further impairment was produced by additional opening of the abdomen. This is in harmony with the results of SHARPEY-SCHAFER and BAIN (1932), who demonstrated that denervation of the carotid sinuses and severing of the vagi did not prevent a partial recovery. The influence of the abdominal pressure on the recovery is in some accordance with the observation of CONKLIN (1946), that the compensatory rise in the arterial pressure, occurring in the rabbit during tipping to the head-up position, persists after sectioning of the sinus and aortic nerves, but is entirely lost if curare is given.

Since only slight cardio-acceleration followed the initial decline of the arterial pressure in the intact animal, it can be inferred that pressoceptive reflexes from the carotid sinuses and aortic regions were not active to any significant extent. A defective response of these mechanisms is in accordance with the observation that the pressor response to carotid stimulation is diminished by sodium pentobarbital (HEYMANS, BOUCKAERT and REGNIER 1933). After cutting of the vagi, however, cardio-acceleration was considerably more marked. It is therefore possible that mutually opposing influences from 1) sinus and aortic pressoceptive reflexes and 2) vagal cardiac and vasomotor reflexes from the lungs were involved in the intact animal. The latter mechanism was considered by WHITEHORN, LEIN and EDELMANN (1947) to be responsible for the bradycardia which may be caused by sudden and severe inflation of the lungs in explosive decompression.

The changes in the venous return brought about by application and release of positive intrapulmonic pressure would, indeed, be effective for arousing the BAINBRIDGE reflex (1915). No evidence

for the existence of such a reflex was obtained, however, since the response of the heart rate was usually the reverse to that which would be expected according to the original description of this reflex.

The impaired recovery of the arterial pressure after vagotomy was shown to be associated with a defective return of the average intrathoracic-abdominal differential pressure towards normal. The abdominal venous reservoir is therefore believed to be more free to dilate after vagotomy than with the vagi intact, so as to allow a more marked and persistent venous pooling. This may be due to the elimination of a special reflex, serving to regulate the mechanical pressures in the great cavities in the body. The expiratory function of the abdominal muscles seems to be coupled with an important function of preserving cardiac output in situations of increased intrapulmonic pressure. Further investigations are needed to clarify further the nervous pathways involved in this reflex and its physiological significance.

Summary.

1. Factors contributing to the initial fall and secondary recovery of systemic mean arterial pressure under positive pressure breathing have been investigated in the dog under light to moderate sodium pentobarbital anesthesia.

2. Extensive opening of the abdomen, which removes the mechanical support for the abdominal venous reservoir, causes an exaggerated fall in the arterial pressure.

3. In the intact anesthestized dog the intra-abdominal pressure increases considerably less than the intrathoracic on application of positive intrapulmonic pressure. This is believed to promote venous pooling in the abdomen, which by reducing the effective blood volume available for the circulation contributes to the initial arterial pressure drop.

4. The intrathoracic-abdominal pressure difference secondarily diminishes while the lungs remain inflated by constant positive pressure. As a result cardiac output is assumed to increase again, thereby assisting in the secondary recovery of the arterial pressure.

5. The changes observed in the heart rate do not point to any major importance of the sinus and aortic mechanisms for the secondary recovery of the arterial pressure.

6. Some evidence is presented that the vagi may afford special reflex pathways, which by controlling the intrathoracic-abdominal

differential pressure are important for the maintenance of venous return to the heart from the abdomen under increased intrapulmonic pressure.

References.

BAINBRIDGE, F. A., J. Physiol. 1915. *50*. 65.

BARACH, A. L., M. ECKMAN, E. GINSBURG, CH. C. JR. RUMSEY, I. KORR, I. ECKMAN and G. BESSON, J. Aviation Med. 1946. *17*. 290.

BEECHER, H. K., H. S. BENNETT and D. L. BASSETT, Anesthesiology 1953. *4*. 612.

BJURSTEDT, H., and C. M. HESSER, Acta Physiol. Scand. 1953. *29*. 180.

CARR, D. T., and H. E. ESSEX, Amer. Heart J. 1946. *31*. 53.

CONKLIN, R. E., Amer. J. Physiol. 1946. *147*. 661.

DELALLA, V. JR., Ibidem 1948. *152*. 122.

DERN, R. J., and W. O. FENN, J. Clin. Invest. 1947. *26*. 460.

FENN, W. O., A. B. OTIS, H. RAHN, L. E. CHADWICK and A. H. HEGNAUER, Amer. J. Physiol. 1947. *151*. 258.

FENN, W. O., and L. E. CHADWICK, Ibidem 1947. *151*. 270.

GIERTZ, K. H., Studier över tryckdifferensandning, Almqvist & Wiksells Boktryckeri A.B., Uppsala 1916.

HENRY, J. P., In WHITE, C. S. and O. O. BENSON, JR.: Physics and Medicine of the Upper Atmosphere, The University of New Mexico Press, Albuquerque 1952, p. 516.

HEYMANS, C., J. J. BOUCKAERT and P. REGNIERS, Le Sinus Carotidien. Paris. G. Doin et Cie, 1933.

HUMPHREYS, G. H., R. L. MOORE and H. BARKLEY, J. Thoracic Surg. 1939. *8*. 553.

MALONEY, J. V. JR., J. E. AFFELDT, S. J. SARNOFF and J. L. WHITTENBERGER, Surg. Gynec. Obstet. 1951. *92*. 672.

PRICE, H. L., B. D. KING, J. D. ELDER, B. H. LIBIEN and R. D. DRIPPS, J. Clin. Invest. 1951. *30*. 1243.

PRICE, H. L., E. H. CONNER, J. D. ELDER and R. D. DRIPPS, J. Appl. Physiol. 1952. *8*. 629.

RUSHMER, R. F., Amer. Heart J. 1947. *34*. 399.

SHARPEY-SCHAFER, E., and W. A. BAIN, Quart. J. Physiol. 1932. *22*. 101.

STURM, R. E., and E. H. WOOD, Rev. Sci. Instruments 1947. *18*. 771.

WATROUS, W. G., F. E. DAVIES and B. M. ANDERSON, Anesthesiology 1950. *11*. 661.

WHITEHORN, W. V., A. LEIN and A. EDELMANN, Amer. J. Physiol. 1947. *147*. 289.

Contribution of Vagus Nerves to Pressure-Volume Characteristics of Chest and Lungs in Dogs

HUGH D. VAN LIEW

STRESS-STRAIN characteristics of the chest and lungs can be measured by the application of various pressure differentials from the inside of the lungs to the outside of the chest and noting the lung volume changes that result. Pressure-volume relationships were studied in human subjects by Rahn, Otis, Chadwick and Fenn (1). The volume changes caused by different pressures when the subject relaxed voluntarily were plotted to give the relaxation-pressure curve. A considerably different curve was obtained when the subject breathed against the applied pressure instead of consciously relaxing. This was called the pressure-breathing curve and measurements for it were made at the end of expirations when there was no flow of air.

The difference between the two curves was interpreted as the effect of a continuous muscle tonus which acts when the subject breathes against pressure. It was suggested (1) that the tonus might be the effect of respiratory reflexes. If this is so, it would be expected that disturbance of some of the respiratory nervous pathways would change the tonic activity. The vagus nerves are well known to contain some of the most important respiratory afferents including fibers proven to be sensitive to inflation and deflation (2). When Culver and Rahn (3) tested the effects of negative pulmonary pressure breathing, they found a decrease in tone caused by vagus block.

This study investigates the effect of the vagus nerves on the tonic activity of the chest and lungs by measuring pressure-volume characteristics during pressure breathing in dogs before and during cervical vagus block.

METHODS

Pulmonary volume changes were produced by application of a pressure differential from the inside of the lung to the outside of the body. The induced volume changes were recorded on a spirometer and were plotted against applied pressure differential to give pressure-breathing curves which were obtained under two conditions, normal control and vagus block.

Twelve different dogs were used in 18 experiments. They were anesthetized with sodium pentobarbital with an initial intravenous injection of 28 mg/kg body weight plus additional small doses whenever necessary. The weight of the dogs ranged from 15–25 kg.

Pressure Application. The dogs were placed in a Drinker respirator with head and neck outside. A tight-fitting collar acted as a seal around the neck. With this arrangement, the pressure inside the dog's lung was always approximately atmospheric, whereas the pressure on the outside of the body (with the exception of the head) could be changed at will by varying the pressure in the box. With the cycling gear disengaged, the respirator pump could produce any desired constant pressure in the chamber from -30 to $+30$ cm H_2O, sustained for any length of time.

A negative pressure inside the box around the animal's body is the equivalent of a positive pulmonary pressure, since the effect is a pressure differential from the inside of the lungs to the outside of the chest. Similarly, a positive pressure inside the respirator box is the same as a negative pulmonary pressure. In this paper the pressure differentials are all expressed as pulmonary pressure.

The pressures were applied for short periods of time, 10–60 seconds, since the effects of vagal reflexes are most evident during the first few seconds of applied pressure. Short intervals minimize possible secondary effects of nervous adaptation and changes in the content of O_2, CO_2, and pH of the blood.

Volume Recording. After an endotracheal tube or tracheal cannula was installed, the dog breathed pure O_2 from the spirometer of an ink-recording Benedict-Roth Metabolism apparatus with a soda lime cannister for absorbing CO_2. Volume changes due to the applied pressures were read directly from the spirometer records at the end of expiration.

Chest expansion (positive pulmonary pressure) causes inhibition of respirations, and chest compression causes an increased frequency (2). During vagus block, however, the frequency of breathing is not affected by the application of pressure. Besides these

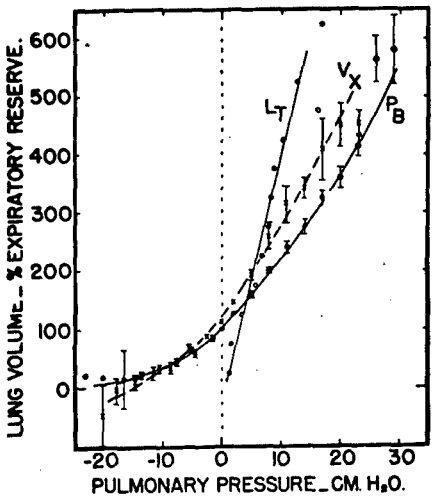


FIG. 1. Pressure-volume diagrams—averaged values for 12 dogs. The lung volume values on the ordinates are expressed as percentage of the expiratory reserve to allow comparison of different sized dogs. Abscissas are pressure differentials between the inside of the lungs and the outside of the chest expressed as cm H_2O pulmonary pressure.

Line P_B is the normal pressure-breathing curve, and *line* V_X is for pressure-breathing during cold block of the vagus nerves. The small vertical lines indicate the standard error of the points. The difference between the two curves is interpreted as a muscular tonus due to vagus conduction which is eliminated when the nerves are blocked.

Line L_T is averaged values for lung tension.

● = normal pressure breathing; × = vagus block; ○ = lung tension.

commonly reported phenomena, another interesting effect of vagus block was observed in the experiments. On application of the nerve block, often the normal base-line elevated rather quickly, indicating an increase in the resting volume of the lung.

Vagus Block. The vagus nerves were isolated in the neck and hooked over a small loop of hollow copper tubing with care to minimize trauma and stretching. When ice water was pumped through the looped tubing, conduction over the vagus was stopped in less than a minute. The block was considered complete when there was: *a*) change of breathing pattern, and *b*) cessation of reflex inhibition on lung expansion. These are the same responses which occur with actual cutting of the vagus nerves. When it was desired to rewarm the nerve, water at approximately 37°C was pumped through the system and vagus conduction was observed to resume as evidenced by the two criteria above.

Intrapleural Pressure. In order to estimate the lung tension's contribution, the static intrapleural pressure was measured in seven of the experiments between breaths during the expiratory pause.

Intrapleural pressure measurements were made by means of a rubber tube ending in a small balloon which was inserted into the dog's intrapleural space. This was accomplished by making a small incision in the skin and muscle just lateral to the sternum and puncturing through the parietal pleura in one of the rib interspaces. The balloon with its tube was passed through this opening, and after reexpansion of the lung, muscle and skin were clamped closely around the tube, sealing it in place. It was then connected to a water manometer outside the respirator.

RESULTS

The averaged values obtained from 12 dogs are plotted in figure 1. The line labeled P_B is the pressure-breathing curve, which has been defined as the volume changes due to differential pressure applied between the inside of the lung and the outside of the body, measured at the end of expiration.

To make the values from the different-sized dogs comparable the volume changes have all been converted to percentages of the dog's expiratory reserve. For this purpose, the expiratory reserve is taken as the volume of air that is displaced from the normal resting volume by a negative pulmonary pressure between 20–30 mm H_2O. The ratio of absolute expiratory reserve volume to body weight averaged 10.4 cc/kg.

During vagus block the pressure-breathing curve changes position, as indicated by the broken line V_X. Also, the upward shifts of the base-line when the vagus was first cooled averaged 14% in the expiratory reserve units. This correction was added to the vagus block values at all pressures.

The resting intrapleural pressure in this experimental set-up can be considered as positive collapse pressure of the lung (lung tension). The averaged normal lung tension is included in the figure as the line L_T.

When the lung tension points for normal conditions and during vagus block were compared on the graphs of the individual dogs, they were found to lie on the same line. No change in lung tension was observed in any of the four dogs in which intrapleural pressure values were recorded before and during vagus block. Therefore, it was concluded that the difference noted between the normal pressure-breathing curve P_B and the vagus-blocked curve V_X is not due to lung tension changes.

DISCUSSION

The forces involved in the pressure-volume relations of the lungs and chest are considered

as due to three components: *a*) the lung tension, the elastic force tending to collapse the lung; *b*) the chest and diaphragm tension, the elastic forces which tend to bring these structures to a resting position; and *c*) force exerted by activity of muscles of the chest, diaphragm and abdomen. The lung volume is determined by the net effects of these forces. If a pressure differential is applied between the inside and outside of the chest and lung, the volume will change until the additive effect of the structural forces equalizes the applied differential.

These relationships can be characterized by a modification of the equations of Rohrer (4) and Rahn *et al.* (1). At any given lung volume, $P_{PUL} = P_C + P_L + P_M$ where P_{PUL} is the pulmonary pressure, P_C is the chest and diaphragm tension, P_L is the lung tension, and P_M is pressure due to muscular activity.

In the present experiments, P_{PUL} is the known pressure applied, and the lung tension P_L was measured directly by intrapleural pressure recording. The chest and diaphragm tension, P_C, and the muscular force, P_M, are not known exactly, although their sum $P_C + P_M$ can be calculated by subtracting P_L from P_{PUL}. However, if it is true that the difference between the normal pressure-breathing curve and the curve during vagus block is due to change in muscle tonus, then the change of the P_M value can be calculated simply by subtracting the P_B and V_X values at a given volume in figure 1. This assumes that the elastic components of the lungs and chest, P_L and P_C, respectively, do not change with vagus block. This assumption was proved correct in the case of the lung tension by the intrapleural pressure measurements.

On the right side of the figure the pressure-breathing curve, P_B, is seen to lie below the vagus block curve, V_X, indicating that there is greater expiratory tonus when the vagus is intact. The change of base-line at zero pressure which resulted from cooling of the vagus in these experiments may show that there is normally an expiratory tonus acting via the vagus even when no distorting pressure is applied. The volume-increase seen on application of the block seems to be the result of removal of expiratory tonus rather than facilitation of an active inspiratory tonus, since it is difficult to envision a process of removing stimulation from the respiratory centers which would cause an active facilitation.

On the left side of the figure, the P_B and V_X curves cross at about -8 cm H_2O. Therefore, at negative pulmonary pressures greater than 8 cm H_2O the tonus is inspiratory rather than expiratory. The point at which the two curves cross is the volume and pressure at which the net effect of any inspiratory and expiratory activity due to vagal reflexes is zero.

Because figure 1 is drawn from averaged values, the left side of the graph showing the change from expiratory to inspiratory tonus is not very significant in absolute values. However, the curves drawn for each individual dog show in most cases a point on the negative pressure side beyond which the vagus-block curve lies below the normal pressure-breathing curve. Therefore, the representation of figure 1 may be regarded at least as qualitatively correct.

SUMMARY AND CONCLUSIONS

Pressure-volume characteristics of the chest and lungs were studied in anesthetized dogs. Data are presented for the normal pressure-breathing curve and the lung tension. When the cervical vagi are blocked, the pressure-volume curves are changed in such a manner that less pressure is required to produce a given volume change. Intrapleural pressure measurements indicated that during vagus block the static lung tension remained unaltered. On the basis of this finding, it is concluded that the displacement of the curve may be ascribed to change in muscular tonus that is normally present during lung distortion due to afferent impulses carried by the vagus nerves.

REFERENCES

1. Rahn, H., A. B. Otis, L. E. Chadwick and W. O. Fenn. *Am. J. Physiol.* 146: 161, 1946.
2. Breuer, J. *Sitzb. d. k. Akad. Wiss. Wien.* 58: 909, 1868.
3. Culver, G. A. and H. Rahn. *Am. J. Physiol.* 168: 686, 1952.
4. Rohrer, F. *Handbuch d. norm. u. path. Physiologie* II: 70, 1925.

THE PRESSURE VOLUME DIAGRAM OF THE BREATHING MECHANISM

Wallace O. Fenn

The muscles of respiration, like most muscles in the body, work at a considerable mechanical disadvantage. Arm muscles, for example, exert against their tendons a force which is approximately ten times as great as the force which is actually applied to the object to be moved, at the finger tips. While it is difficult or impossible to make a similar quantitative statement for the respiratory muscles, it is easy to see that in some respects at least they are not favorably disposed for the mechanical task which they have to accomplish. In most hollow organs, as in the bladder for example, the walls contain muscle fibers arranged circumferentially; when these muscles contract they develop a positive pressure inside the hollow viscus. In the thorax the external intercostal muscles are likewise arranged tangentially to the circumference but on contraction they must decrease instead of increase the pressure in the thorax to produce inspiration. This paradoxical effect is of course accomplished by the ingenious mechanism of the ribs. The internal intercostals operating on the same ribs must cause expiration. These two sets of muscles are reciprocally innervated so that when the inspiratory muscles contract, the expiratory muscles are inhibited. Similarly the diaphragm and the abdominal muscles are reciprocal in their action so that when the diaphragm contracts on inspiration the abdominal muscles must relax and vice versa. The arrangement of the diaphragm and the abdominal muscles is a little more conventional than that of the external intercostals because contraction in both cases causes a rise in pressure on the concave side. Pressure (P) is developed in accordance with the LaPlace equation $P = T/R$, where T is the tension along the circumference and R is the radius of curvature. Since the radius of curvature is large, the tension must likewise be large for a given pressure. Thus, here too the muscles work at a mechanical disadvantage.

The respiratory muscles operate with an efficiency of not more than 5 percent (1), and even lower values have been reported. This must be related to the mechanical arrangement in the body. The external intercostals, for example, pull diagonally between two adjacent ribs so that a considerable component of their force is applied in a direction longitudinal to the ribs. They must exert, in other words, too much tension for the amount of shortening which is permitted to them. According to von Ebener (2) the external intercostal muscles can shorten between one-eighth and one-fourth of their length between maximum expiration and maximum inspiration. While this appears to be sufficient to account for the total work of respiration (1), it may not be sufficient for optimum efficiency.

The overall performance of the muscles of respiration is best characterized by a determination of the pressure-volume diagram of the chest and lungs. This is readily accomplished by recording the maximum inspiratory or expiratory pressures which can be developed at every attainable lung volume (3). Data of this sort are given in figure 1. The diagram can be interpreted either as a plot of the vital capacities as ordinates with various positive or negative pulmonary pressures plotted as abscissae; or it may be read as a record of the pressures which can be developed at different volumes. The data could also be obtained experimentally by both methods but it is easier and indeed safer to choose the latter method. It would be rather dangerous, for example, to apply a pressure of 80 mm. Hg to the lungs from an external source and then to carry out the maximum possible voluntary inflation of the lungs. Such a pressure might be harmless so long as the chest volume were maintained in the normal range because the stress on the walls of the lungs depends only on their degree of inflation. For a given volume the difference of pressure across the lung wall is independent of the absolute pressure, the excess pressure not absorbed by the elasticity of the lung being simply passed along to the chest wall. Thus violent expiratory pressures are harmless but passive inflation at the same pressure might lead to a rupture of the lungs. Not a few ruptures of this sort have probably occurred in submariners practicing ascents through water from deeply submerged chambers.

If they do not allow the expanding air in the lungs to escape, the lungs may become inflated to a dangerous degree. The writer recalls also a case where, according to the newspaper, a small boy ruptured his lung when he playfully bit a hole through the herniated wall of a tightly inflated automobile inner tube!

On the negative side of the diagram the maximum inspiratory pressures are of the order of magnitude of 80 mm. Hg at the minimum lung volumes. This is also a rather dangerous region because the low pressures tend to "suck" blood into the thorax and cause extreme dilation of the blood vessels. With a single possible exception there is no well-documented record of damage actually resulting from exposures of this sort.

In a subject who can develop a maximum negative pressure on inspiration of 80 mm. Hg it can be predicted that at 13.4×80 or 108 cm. under water he would be unable to inspire. Anyone who has tried breathing while submerged, using a rigid tube reaching to the surface, will understand the terrific load of a column of water of this magnitude; it must be experienced to be appreciated. It is perhaps surprising that the load is not more noticeable when one is merely wading around in water up to the neck. Under such conditions it is probable that most of the inhalation is accomplished with the thorax rather than the abdomen. If one were lying down under water so that all parts of the body were equally far from the surface, the pressure-volume diagram would presumably be the same as in air in the same position except that the zero pressure line would be displaced to the left in proportion to the depth of the water.

When the chest is at apparent rest the pressure-volume curve is shown by the relaxation curve in figure 1. This curve is obtained by measuring the pressure exerted against a manometer at different lung volumes when all muscular activity is voluntarily suspended as far as possible (3). At large lung volumes the chest tends to collapse when the muscles are relaxed and develops a positive pressure which is a measure of the inspiratory effort previously being exerted. The reverse is true at low lung volumes. The negative pressure which develops is then a measure of the expiratory effort previously exerted by the expiratory muscles. Conversely this curve may be interpreted as a measure of the amount of positive or negative pressure which must be voluntarily exerted to produce the indicated volume changes.

This relaxation pressure curve was first obtained by Jacquet (4) in 1907 and later by Bernoulli (5) in 1911. They used the same apparatus, which was designed by Dr. Miescher in Basel according to the specifications of a "pneumatic differentiation cabinet" first built in the United States in 1885 by Dr. H. F. Williams (6), and an engineer friend of his, Mr. Ketchum. This apparatus consisted of a cabinet large enough to accommodate a subject in the sitting position breathing through a tube to the outside. At first the pressure inside the cabinet was reduced so that the subject had to exhale against a relatively positive pressure. This was supposed to be therapeutically beneficial because the subject would have to bring unused parts of the lung into play. Later the pressure in the cabinet was rhythmically changed so that the effect was substantially the same as the modern Drinker respirator. This was claimed to be even more beneficial, and many astounding "cures" were reported while the use of this cabinet was in vogue. It was even reported that four menopausal women started to menstruate again after treatment in the cabinet. Dr. Miescher unfortunately did not live long enough to make use of the American gadget which he built in Switzerland but Jacquet used it to make simultaneous measurements of the pressure changes in the cabinet and the volumes of air breathed. When the pressure is plotted against the volume a relaxation pressure curve is obtained which has the same sigmoid shape as that shown in figure 1. Thus the apparatus eventually served a real scientific purpose.

The relaxation pressure curve has only one position and can be changed only by changes in the tone of the muscles of respiration or the elasticity of the lungs. If it is regarded, however, as a *net* pressure curve, then it can be moved up and down by all artificial respiration maneuvers and even voluntary breathing may be interpreted as the result of moving the net pressure curve up and down or sideways on the pressure-volume diagram. A change in posture from the erect to the supine position causes the relaxation pressure to move to the left or upward. This can easily be demonstrated by stopping breathing at the end of a normal expiration in the erect position and then lying down with the breath still held. When

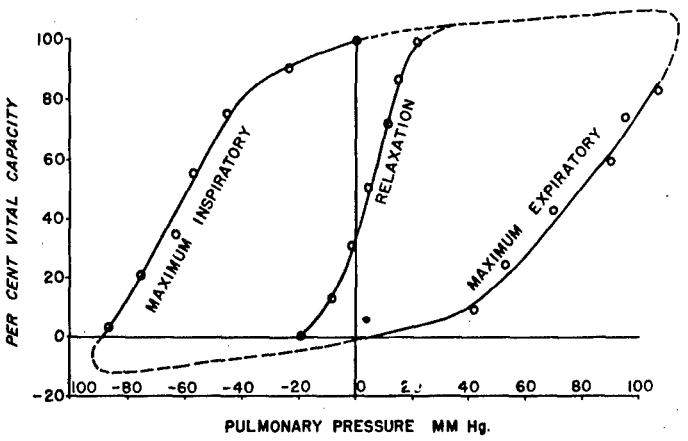


FIGURE 1

Pressure-volume diagram of the human chest and lungs, including the relaxation pressure curve.

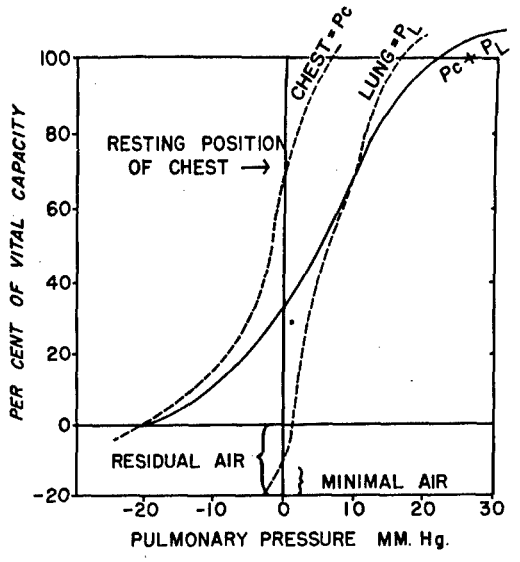


FIGURE 2

The relaxation pressure curve (solid line) of the chest and lungs ($P_C + P_L$) and its two components (broken lines), the lung elasticity (P_L) and the chest and diaphragm (P_C).

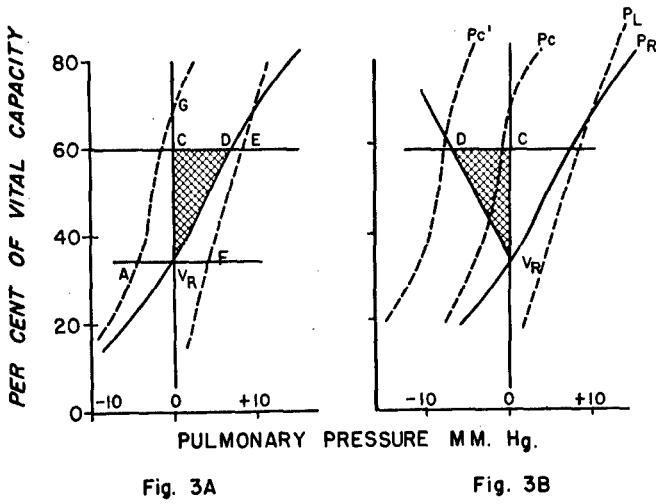


Fig. 3A Fig. 3B

FIGURE 3

Explanation of the work of breathing, using the relaxation pressure curve. Essentially similar to figure 2. Shaded area represents the elastic work of breathing.

breathing begins again the first movement is an expiration and the resting position is now at a smaller lung volume than previously. The reverse experiment also works as expected and the first movement after assuming the erect posture is an inspiration. If the breath is held for a similar length of time (5 to 10 seconds) without change of posture the first movement, of course, is an inspiration in both cases. This effect of posture is easily explained as due to the weight of the viscera and indeed the magnitude of the shift can be predicted fairly well from calculations of the pressure which would be exerted by the viscera against the diaphragm if they are regarded merely as so much fluid. The magnitude of the change in the relaxation pressure curve produced by change of posture from erect to supine has been determined as a displacement of 637 cc., or an increase of pressure of 7.5 mm. Hg (1).

The structures described by the relaxation pressure curve may be described as two elasticities, the chest and diaphragm arranged in parallel and working together in series (mechanically) with the elasticity of the lung. The pressure resisted by the chest and diaphragm is always the same but the volume change is partitioned between them in an unknown manner. Because they are in parallel it is difficult to separate the volume changes. The combined volume change of the chest and diaphragm is always equal to the volume change of the lung but the pressures are different and can readily be measured separately. The separate relaxation pressure curves for the lung and the chest (including diaphragm) are illustrated in figure 2.

At the normal relaxation volume, where the relaxation pressure curve crosses the axis, the elasticity of the lung is exactly balanced by the elasticity of the chest and both are equal in magnitude to the intrapleural pressure or 4 mm. Hg at expiration. The chest curve and the lung curve are thus represented by the two dotted lines on either side of the relaxation pressure curve.

The compliance of the whole respiratory mechanism is given by the slope of the relaxation curve and is about 98 cc. per mm. Hg. The compliance of the lung may be obtained by measurements of the intrapleural pressure at different volumes or by measurements of the venous pressure when the lungs are inflated to known degrees by different positive intrapulmonary pressures. The latter method gave a compliance for the lung of 210 cc. per mm. Hg over the volume range from 20 to 50 percent of the vital capacity. The lung curve in figure 2 has been drawn in accordance with this figure. It has, therefore, about half the slope of the relaxation pressure curve and intersects it at a volume of about 70 percent of the vital capacity. At this point the chest curve crosses the axis and all of the relaxation pressure is due to the elasticity of the lung. The lung curve is believed to have a somewhat sigmoid shape and it presumably intersects the O axis in the residual air region at a point which measures the minimal air.

The central part of figure 2 is repeated in figure 3 to illustrate the work required for breathing. The problem is to estimate the work required to increase the volume from the normal relaxation volume, V_R, to an arbitrary volume represented by point C. To expand the lung to this degree requires work equal to the area V_RFEC. In this process, however, the chest approaches its zero position at G and delivers potential energy equal to the area V_RABC. This area is equal to the area V_RFED since the widths of these two areas are equal at every volume. Hence the net work required from the inspiratory muscles is only the difference between V_RFEC and V_RFED or V_RDC, the shaded area.

In this explanation it is somewhat puzzling to find the work of inspiration represented by an area on the expiratory side of the diagram in regions of positive intrapulmonary pressure. Moreover in fact, in normal breathing the alveolar point does not deviate much from the zero axis. In the lungs there is only a slight decrease in pressure during inspiration and a slight increase in expiration due to the requirements of air flow. To meet this objection figure 3B is offered. This shows the curves P_R, P_C, and P_L as before but in addition a new chest curve, P'_C, is shown which represents the chest pressure after sufficient increase in inspiratory tone to maintain the lungs at the new volume represented by point C. In other words, the total negative chest pressure has been increased sufficiently to balance the increased relaxation pressure so that the alveolar point comes to rest at C. Now the work done is equal to the

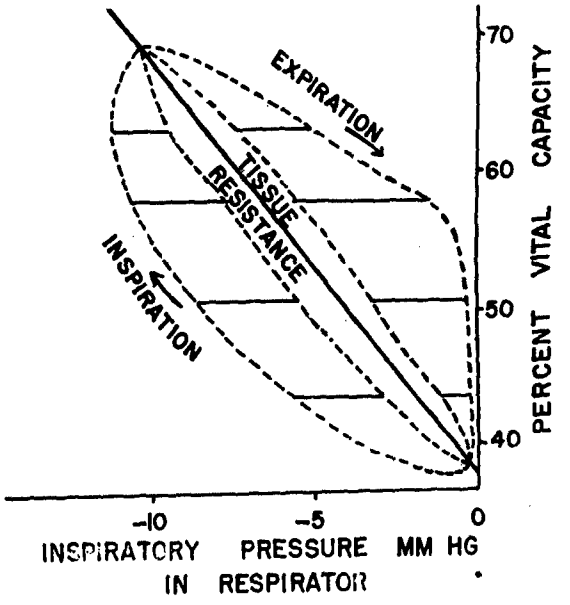


FIGURE 4

Total work of breathing including the tissue resistance and the resistance to air flow. Reproduced from Fenn (7), courtesy American Journal of Medicine.

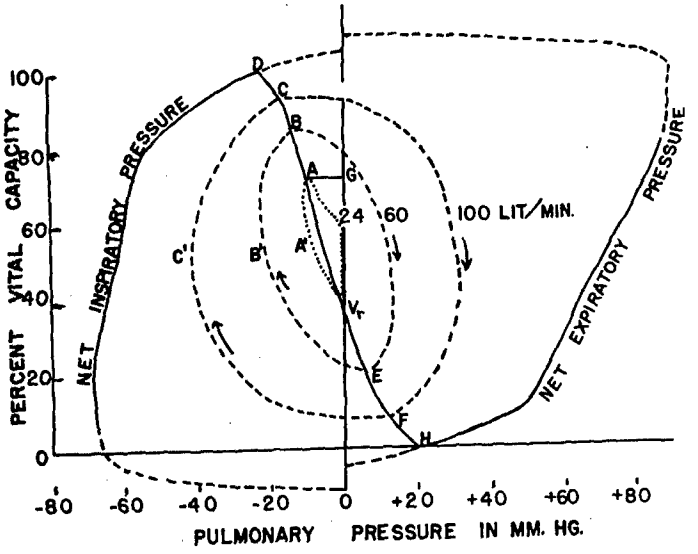


FIGURE 5

Pressure-volume diagram with work of breathing at different minute volumes. Net inspiratory pressure available at every volume plotted to the left and net expiratory pressures to the right. Expiratory muscles become necessary at high rates of ventilation. Reproduced from Fenn (7), courtesy American Journal of Medicine.

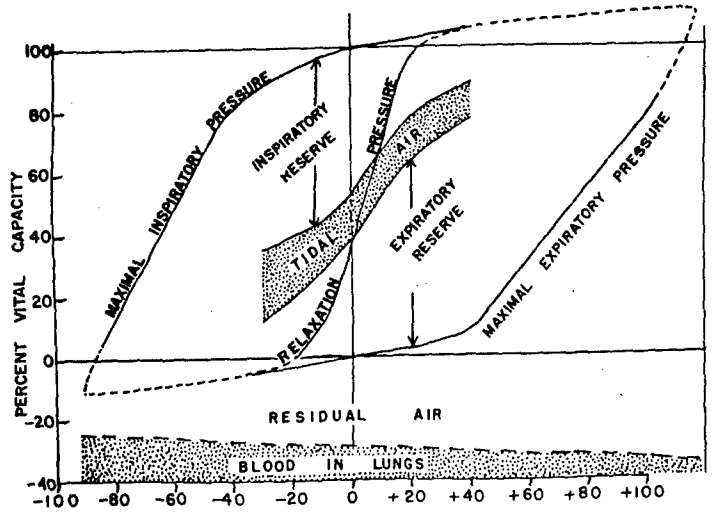


FIGURE 6

The problem of pressure breathing illustrated on a pressure-volume diagram. Modified from Fenn (7) and reproduced by courtesy of the American Journal of Medicine.

shaded area, VRDC, which is a mirror image of the shaded area in figure 3A. The line VRD represents the increments in inspiratory pressure necessary to cause inflation to the indicated volumes. It is of course the mirror image of the relaxation pressure curve of figure 3A. This explanation is really in better accord with the actual mechanism of breathing which requires a change in the inspiratory tone of the chest (including the diaphragm component) in order to produce inflation of the lungs.

The triangular shaded areas in figure 3 represent of course only the elastic work of breathing which is done during inspiration. This stores up enough potential energy to accomplish expiration except at very high speeds of air flow. The work against frictional resistance in the air stream and the tissues is represented in figure 4. The diagonal straight line is comparable to the line VRD in figure 3B and represents the relaxation pressure. The dotted lines show the actual course of the pressure-volume changes which occur during breathing. The horizontal lines represent the pressure required for movement of the air stream. In this case the expiratory loop is entirely "covered" by the elastic potential energy stored during inspiration. The central loop is due to frictional loss in the tissues themselves as distinct from the air stream.

In figure 5 we have expanded figure 3 to include the maximum net changes in inspiratory and expiratory tone which can be produced at every volume. These curves represent the differences between the maximum inspiratory and expiratory pressure curves, respectively, and the relaxation pressure curve of figure 1. The total area, therefore, is equal to the total inspiratory or expiratory work which can be done by respiratory effort. The dotted loops in figure 5 outline work areas required for ventilating the lungs at different rates as indicated, the largest area being calculated for 100 liters per minute. At 141 liters per minute it can be calculated that practically the whole area would be required (7).

1. Pressure breathing

For the purposes of this presentation we shall confine pressure breathing to the use of continuous pressure applied during both inspiration and expiration and consider the effects of intermittent pressure breathing under the heading of artificial respiration. We shall, however, include in our discussion both positive and negative continuous pressures.

The subject is best represented by figure 6. This is essentially similar to figure 1 except for the addition of a stippled band across the middle which represents the tidal volume at different pressures (3, 7). It was not considered altogether safe to continue the experiment beyond a negative pressure of 30 mm. Hg or a positive pressure of 40 mm. Hg. The vertical width of this tidal air band represents the tidal volume. The lower edge of this band crosses the zero axis at the relaxation volume where the relaxation pressure curve crosses. At this point inspiration is active and expiration is passive. Where the upper edge of the tidal air band crosses the relaxation pressure curve at about 10 mm. Hg, the condition is reversed and the resting point is at the height of inspiration. Expiration is then all active and inspiration is all passive. At higher positive pressures there is no resting point throughout the respiratory cycle but the respiratory muscles must maintain a constant expiratory pressure. At a positive pressure of 40 mm. Hg, for example, inspiration is represented by point A and expiration by point B. The pressures which must be maintained at these two points by active expiratory effort are equal to the horizontal distances from these points to the relaxation pressure curve on the left. The absolute values are about 24 and 28 mm. Hg, respectively. The rest of the 40 mm. Hg in each case is derived from the passive elastic forces of the chest as represented by the relaxation pressure curve.

This tidal air band was obtained from our experiments with nine normal male volunteers but it cannot be maintained that all subjects will follow this particular pattern and it may be that the pattern will change considerably with the experience of the subject. It would be easier to offer less resistance to the inflation and allow the tidal air band to follow the relaxation pressure curve. This, however, increases the danger of overinflating the chest and rupturing the lung. On the other hand, inexperienced subjects may resist so much that they may continue to breathe for a time at a normal degree of inflation.

One of the effects of positive pressure breathing is to displace some blood from the lungs. This is illustrated in an approximate manner in figure 6 by the stippled area at the bottom of the diagram. This shows an increase in blood with negative and a decrease with positive pressures. This change may be documented by placing a subject on a teeter board and noting the change in the center of gravity of the body when the pulmonary pressure is changed. It is also indicated by the changes in the vital capacity. With positive pressure breathing the vital capacity increases, and vice versa.

The diagram also shows that with positive pressure breathing the residual air and the expiratory reserve increase while the inspiratory reserve decreases. The reverse occurs with negative pressure breathing.

2. Artificial respiration

It has already been explained that the relaxation pressure curve may be regarded as an indication of the pressure change required in the lungs to produce a given change in the inflation of the lung. This of course oversimplifies the problem because it leaves out of consideration the dynamic aspects of artificial respiration and neglects the pressure required to cause the air column to move and the tissues to change shape. If, however, each pressure is allowed to persist until the lung reaches its equilibrium position, then the volumes can be predicted from the relaxation pressure curve for every pressure applied. The problem of resistance to air flow in the airway is essential for a thorough discussion of this subject but cannot be included here.

In manual artificial respiration of an apneic subject there is no difficulty about securing complete relaxation of all the respiratory muscles. Relaxation pressure is then the same as net pressure and movements of air may be interpreted as due to movements of the relaxation pressure curve. It has already been mentioned that in assuming the supine or prone position the relaxation pressure is displaced downward or to the right. In this position the standard Schafer method involving pressure on the lower ribs is not very effective. The relaxation pressure curve being already considerably displaced downward cannot be lowered much further by external rib pressure. For this reason it is not surprising that the hip lift method is now preferred for the effect of this maneuver is to raise the relaxation pressure curve. It allows the abdominal wall to drop and pull the diaphragm down. Like the shoulder lift, it arches the backbone (concave backwards) and so stretches the anterior aspect of the thorax. A combination of maneuvers which first raises and then lowers the relaxation pressure curve relative to the resting position is theoretically the most effective method of ventilating the lungs. This is apparently accomplished by the arm lift–back pressure method now recommended by the Department of Defense.

3. Pneumothorax

Normally the intrapleural pressure is just as much due to the elasticity of the chest wall and diaphragm pulling out as to the elasticity of the lungs pulling in. These two forces are equal and opposite at resting lung volume. The same is of course true when air is introduced into the intrapleural space except that both chest and lungs approach more closely to their equilibrium position, and the negative pressure in the intrapleural space is less. If sufficient air is introduced to permit both chest and lungs to reach their equilibrium positions (at G and H, respectively, figure 7) then the intrapleural pressure will be zero relative to atmospheric.

A more detailed analysis of this situation is shown in figure 7, which is similar to figure 2 but with a somewhat enlarged horizontal scale. At rest the volume is V_R and the lung pressure V_{RB} is equal to the negative chest pressure V_{RE}. If sufficient air is introduced to reduce the intrapleural pressure from 4 to 2 mm. Hg, the chest pressure will be V_{RD} and the chest will expand to F while the elastic recoil of the lung will be V_{RA} and the lung will collapse to a volume C. The volume of air required for this purpose is the difference in volume between F and C or 36 percent of the vital capacity. The division of this volume between chest and lungs depends upon the different compliances of the two structures. In this example they are about equal and the pneumothorax requires just as much air to expand the

chest as to collapse the lung. To bring both chest and lungs to equilibrium positions at G and H, respectively, requires a volume equal to the vertical difference between these two points, or 80 percent of the vital capacity. if more air is forced into the chest beyond this point where the intrapleural pressure is atmospheric, some pressure above atmosphere will be required. This will expand the chest beyond G and force some of the minimal air out of the lung below H.

It is interesting to note further that if air is introduced into the pleural space until the chest and lungs are at equilibrium at G and H, respectively, adequate ventilation of the lungs might still be possible by voluntary effort. The chest could still expand theoretically at least from 70 to 100 percent of the vital capacity by voluntary contraction of the inspiratory muscles. Without the opposition of the fully expanded lungs the chest could presumably be made to expand even above the 100 percent vital capacity mark. At this 100 percent level the maximum inspiratory force is equal to the relaxation pressure at that volume, or about 20 mm. Hg. To expand the chest alone from G to M requires only 7 mm. Meanwhile, however, the lung will expand (nearly) an equal volume or from -10 percent to $+20$ percent to point L where its elastic pressure is only 2.5 mm. Hg. Thus a total 9.5 mm. inspiratory pressure (out of 20 mm. available) will provide a tidal volume of 30 percent of the vital capacity. To expand the chest alone from G to M the chest curve will have to be moved from EK to E'K'. To meet the increased tension of the lung expanding from H to L will require an additional shift to E'' K''. The intrapleural pressure will now be -2.5 mm. Hg which will cause a negligible expansion of the intrapleural air of about 0.3 percent of the vital capacity.

From these considerations it seems evident that even a maximal pneumothorax is not necessarily incompatible with survival, provided the hole through which the air entered the pleural space is blocked up.

It should be noted in these discussions that we have treated the two lungs as if they were one. To what extent the relaxation pressure curves for the two lungs and the two sides of the chest differ is not known but presumably they are much alike so long as volume is plotted in percent of the vital capacity of each lung individually. With a unilateral pneumothorax the intrapleural pressure presumably differs on the two sides but the increase in inspiratory pressure on the two sides is probably nearly equal. The appropriate expansion of the two lungs can then be calculated from the diagram by the application of the principles described.

4. Breathing at altitude

Certainly the length-tension diagram of the respiratory muscles is no different at altitude from the way it is at sea level. When, however, one tries to plot out the pressure-volume diagram of the lungs by determining the maximum pressures which can be exerted at different volumes, as in figure 1, then a great difference is at once observed. One inhales, for example, to the maximum extent where the volume is certainly not grossly different from the same value at sea level. On expiring now against a manometer the volume of the lungs diminishes markedly as the pressure rises according to the equation $PV = RT$. The maximum pressure registered then on the manometer is the maximum for the final lung volume attained which at 40,000 feet may be only 50 percent of the vital capacity. Similarly on trying to develop inspiratory pressure starting at the point of maximum expiration, the lung increases rapidly in volume and the pressure finally registered is characteristic of a volume much greater than that of maximum expiration. The curves which result have been plotted on the pressure-volume diagram as dotted lines in figure 8 after Rahn et al. (3).

It is evident that at altitude the area of the pressure-volume diagram available for the work of breathing is much diminished compared to the sea-level condition. Table I shows the values of these areas measured roughly from this diagram.

This raises the question whether the maximum possible rate of ventilation is greater at sea level or at altitude. The work of moving the chest and lungs is of course just the same at altitude as it is at sea level and the muscles have the same strength. Most of the work of breathing, however, comes from the resistance to the movement of air and most of this is due to the turbulence which develops in the air stream when the velocity exceeds a critical value or where the velocity is subjected to sudden changes due to

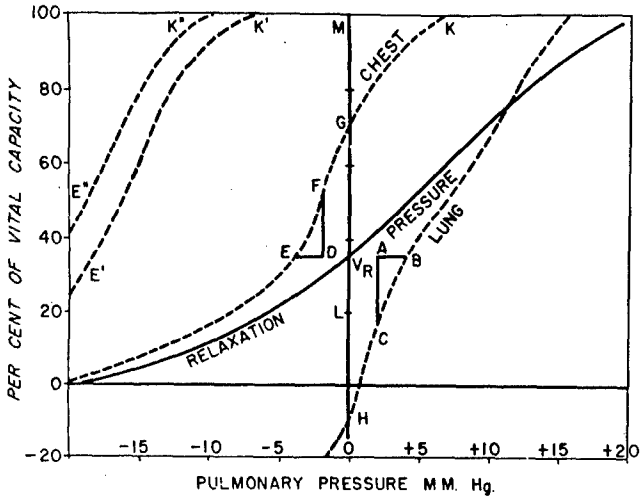


FIGURE 7

The problem of a pneumothorax illustrated on a relaxation pressure curve similar to figure 2. See text.

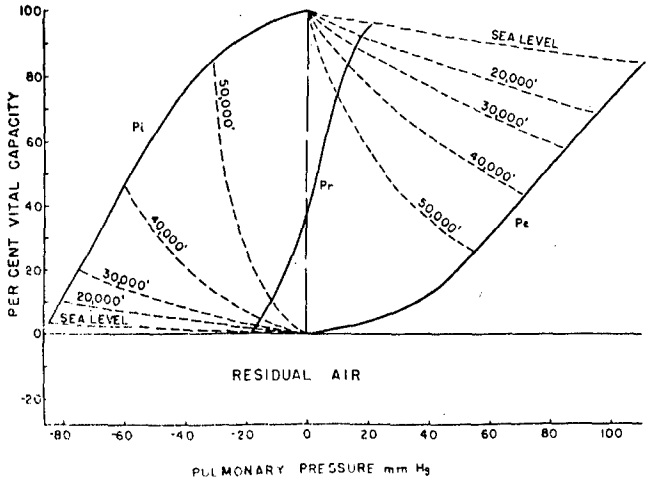


FIGURE 8

The pressure-volume diagram at different altitudes showing the diminution in available area which occurs. Reproduced from Rahn et al. (3), courtesy American Journal of Physiology.

TABLE I

Work per breath at different altitudes

Altitude (feet)	Barometric pressure (mm. Hg)	Work (kg. m.) per breath at 150 liters/min. at a frequency of 30/min.			Pressure-volume area (kg. m.)
		Linear	Turbulent	Total	
0	760	2.2	6.8	9.0	10.4
30,000	226	2.2	2.1	4.3	8.9
40,000	141	2.2	1.3	3.5	6.3
50,000	87	2.2	0.8	3.0	4.1

bifurcations of the airway or abrupt variations in diameter as in the glottis (7). The general equation for the flow of air is given by Otis and Proctor (8) as follows:

$$P = K_1V + K_2V^2$$

where V is the velocity of air flow and P is the pressure gradient. The first term is the resistance to linear or streamlined flow and the constant K_1 is independent of air density or altitude. The second term is due to turbulence and varies with the square of the velocity; its constant, K_2, was shown by Otis and Bembower (9) to be inversely proportional to the density of the air.

Now Otis et al. (1) have taken the maximum rate of breathing at sea level to be 150 liters per minute at 30 breaths per minute and have calculated that at this rate the work is equal to 9 kg. m. per breath. This is just about equal to the area of the whole pressure-volume diagram. The equation used was as follows:

$$\text{Work rate} = 1/2K' \pi^2(fV_T)^2 + 4/3K'' \pi^2(fV_T)^3.$$

Again the first term is due to streamlined flow and the second term due to turbulence. The values of the constants were found to be 61 and 0.46, respectively, when fV_T (product of frequency and tidal volume) is in liters per minute and the work comes out in gm. cm. Using 61 for K′ the first term has the value of 67 kg. m. at all altitudes. K″ is equal to $0.46 \times B/760$. Using these values the work of breathing at this maximum rate of 150 liters per minute has been calculated for several different altitudes as shown in table I. The results indicate that the work required is so much less at altitude because of the decrease in the turbulence that the diminished pressure-volume area is always adequate for the purpose. From these theoretical considerations it may be predicted that the maximum rate of ventilation would not be diminished at altitude for any purely mechanical reason and might be somewhat greater. It goes without saying that the work of breathing at less than maximal rates is less at altitude than at ground level. The effect upon the maximum rate of breathing, however, is not so obvious when one considers the data of figure 2. These predictions require, of course, experimental confirmation.

CONCLUSION

The pressure-volume diagram of the lung and chest represents the basic information which is required for the understanding of any of the mechanical events of breathing. It is not very well known in many details and the variations with age, sex, and physiological conditions have not been worked out. Many other applications are possible and the few mentioned here are only examples for the future.

REFERENCES

1. Otis, A. B., W. O. Fenn, and H. Rahn. J. Appl. Physiol. 2:592 (1950).
2. von Ebner, V. Arch. f. Anat. u. Physiol. 4:185 (1880).
3. Rahn, H., A. B. Otis, L. E. Chadwick, and W. O. Fenn. Am. J. Physiol. 146:161 (1946).
4. Jacquet, A. Arch. f. exper. Path. u. Pharmakol. Suppl. 59:309 (1908).
5. Bernoulli, E. Arch. f. exper. Path. u. Pharmakol. 66:313 (1911).
6. Williams, H. F. Medical record 27:57 (1885); J. A. M. A. 7:169 (1886).
7. Fenn, W. O. Am. J. Med. 10:77 (1951).
8. Otis, A. B., and D. F. Proctor. Am. J. Physiol. 152: 106 (1948).
9. Otis, A. B., and W. C. Bembower. J. Appl. Physiol. 2:300 (1949).

BRONCHIAL TREE CASTS, LOBE WEIGHTS AND ANATOMICAL DEAD SPACE MEASUREMENTS IN THE DOG LUNG

by

H. Rahn and B. B. Ross

Innumerable methods in the past have been suggested for making casts of the broncho-tracheal tree. The recent development of plastics has provided new casting materials and we have been fairly successful in the use of a polystyrene resin sold as "Bioplastic" which shrinks about 8% upon hardening.

Ideally one should have a material which is viscous enough when poured that it will stop short of the alveoli and alveolar sacs and ducts. If this latter region does fill, the cast becomes a large solid mass and for our purposes, useless. The material should not shrink upon hardening and have enough tensile strength to allow future handling. The problem of pouring and displacing the air ahead of the casting material was overcome by first air drying the lung under a slight positive pressure. Thus there are three major steps in the preparation of our casts: (1) air drying, (2) casting, and (3) maceration and curing of the cast.

Air drying of lung under positive pressure

Over the last 12 years we have been preserving freshly dissected lungs by simply drying them with a continuous air stream under a slight positive pressure applied to the trachea. The trachea is cannulated and attached to the compressed air outlet. The excess pressure bleeds out through the pleura and also forces out all the fluids. When the pressure is adjusted properly, the lung becomes permanently preserved upon drying, with all the lobes in their normal anatomical relationship. Such a lung is shown in Figure 1. By this exceedingly simple method we have preserved over the years nearly a hundred lungs from those of the rat which will dry in a matter of a few hours to that of the cow, which requires several days of continuous air pressure. This method has been used by Tobin (1) for studying the grosser as well as the finer structures of the human lung, and by Joffe (2) for assessing experimental pulmonary edema.

Casting procedure

Our casting efforts have been primarily directed to the bronchial tree of the dog, but equally successful results have been attained in the beaver, cat, pig, and human lung. The lungs of a 15-20 kg dog require approximately 24 hours of air drying and are then ready for casting.

The plastic is a liquid monomer of polystyrene. Polymerization is obtained by

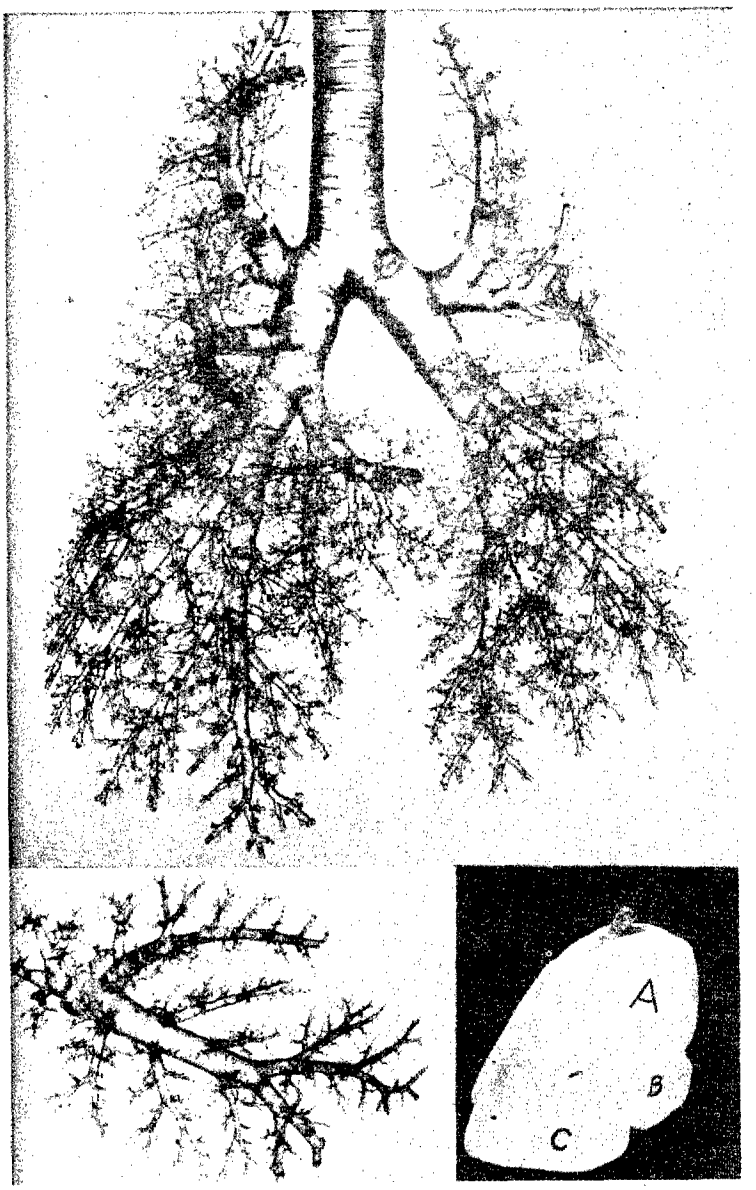


Figure 1

Trachea and bronchial tree cast of a dog lung. At the lower left hand is an enlarged portion. On the right is an air dried lung.

the addition of a catalyst and an accelerator and we have usually followed the exact proportions of these as suggested by the commercial supplier.[1] When the catalyzed plastic reaches a temperature of about 2.5-3.0° C above the room temperature of 25°, it must be poured immediately since it will polymerize about 45 seconds later. It is poured through a home-made paper funnel into the trachea and the bronchi fill by gravity. The specimen is rotated gently during this process in order to fill the various branches as evenly as possible. The success depends upon pouring the plastic during the right stage of polymerization. If one pours too early, the material is still fluid enough to fill the alveoli and the cast becomes useless. If one waits too long, the plastic will set during the actual filling and an incomplete cast is obtained. The temperature and the times of pouring recommended above vary from one batch to another and must first be empirically determined.

Curing and maceration

After polymerization is complete (several hours after pouring), the cast is hardened or cured by baking the whole lung at a temperature of 60-90° C for at least one hour or longer. The lung is then removed and placed in a bath of concentrated hydrochloric acid for at least 12 hours. The pleura is slashed with a knife to afford quicker penetration of the acid into the parenchyma. The tissues which remain after maceration are washed off by holding the specimen under running water. Should the specimen not have been completely cured at this stage, the cast can be subjected to further baking.

Casting the pulmonary vessels in addition to the bronchial tree

Here the procedure was modified. The vessels of the freshly dissected lung were cannulated and upon completion of this job the lung was inflated and kept continuously under pressure while the vessels are injected. In this case the timing is not as important since the plastic can now be injected before polymerization has proceeded to the "critical pouring point." The plastic is injected by syringe and the vessel tied off. The syringe is then immediately rinsed in acetone. Different dyes can be mixed into the plastic for the differentiation of arteries or veins. Once the plastic has been injected one must be careful to keep the lung constantly inflated while polymerization takes place, otherwise the injection mass is likely to break within the blood vessels if the lung collapses. The lung is kept under air pressure until dry and then the bronchial tree can be cast with a different color plastic as described above. By this dual injection technique excellent results can be achieved, giving the anatomical relationships between bronchi and blood vessels. Casts of the chambers of the heart as well as the coronary arteries and veins are easily prepared by this method.

---

[1] Ward's Bio-Plastic — Ward's Natural Science Establishment, Inc., 3000 Ridge Road East, Rochester 9, New York.

Note on overfilling of bronchi: It was pointed out that in casting the bronchial tree that once polymerization starts, the pouring time is rather critical. If one pours too soon, the plastic "overfills" by running into the alveolar spaces. Recent experiments have shown that this procedure can actually be used in obtaining rather perfect specimens, particularly for individual lobes.

The plastic is poured before the critical time and a deliberate "overfilling" is accomplished. However, the lung is now under cured by less intense heat before maceration of the lung tissue in HCl. This technique results in a pliable cast. After the major tissues have been removed, the "overfilled" portions representing the alveoli can easily be removed by forceps and the remaining alveoli can be easily dissolved by dipping the preparation in acetone. This procedure does not affect the small bronchi. Thereafter the cast can be cured to hardness. This "overfilling" technique has given excellent results even for complete lungs. Figure 1 shows casts obtained by this method.

Relative lung lobe weights and volumes

The air dried lungs provide excellent material for comparing the relative weights of the lobes of the lung. In Table 1 the average weights of the 7 lobes of the dog's lung are presented. They are based upon 21 mongrel dogs weighing between 15 and 20 kg. The standard error of the mean is very small, indicating a remarkable sameness from dog to dog. In order to facilitate the designation of these lobes, the arbitrary labeling of Figure 2 has been adopted. The ratio of left

TABLE 1

Relative Weights of Air Dried Lobes of the Dog Lung Expressed as Percent of the Total Weight. The Standard Error of the Mean is given Below Each Figure. The Lobes are Designated According to Figure 2.

	Right Lung				Left Lung			Left Lung
Lobe	A	B	C	M	D	E	F	
% Wt.	17.3	8.9	24.7	7.5	9.6	5.8	26.2	41.7
St. Error	.41	.22	.48	.19	.20	.13	.49	.58

to right lung is 42:58 and in good agreement with the ventilation ratio established by bronchospirometry (3). That the alveolar volume of each lobe corresponds well to its dry weight has also recently been established (4). This was done by filling in situ the lobes completely with liquid latex while the dead animal was barely submerged under water. After this hardened, each lobe could be resected and weighed.

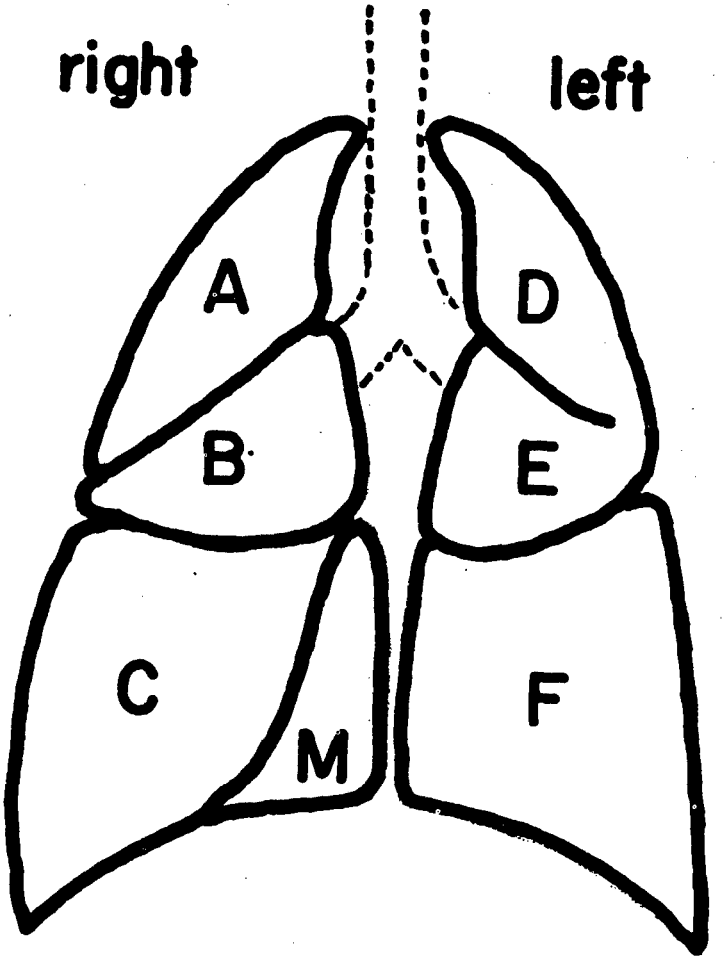


Figure 2

Schematic representation of the 7 lobes of the dog lung.

These relative weight measurements do not differ significantly from the relative dry weight measurements.

Dead space volume of individual lobes

The bronchial tree casts allow one to obtain measurements of the dead space volume in each lobe of the lung. This can be done simply by weighing the cast of each lobe. Thus in 9 dogs the individual lobes were weighed before filling and then cast. The volumes of these casts were calculated from the weight of the cast and the density of the material used. For the incomplete casts the volume was computed by assuming a direct proportionality between weight and volume for the other lungs and calculating the expected volume of the incomplete lobe cast from its dry weight. The results are shown in Figure 3. The points representing the right and left whole lung were computed by adding the volumes of the main bronchi to those of the individual lobes. The relationship between dead space and lung

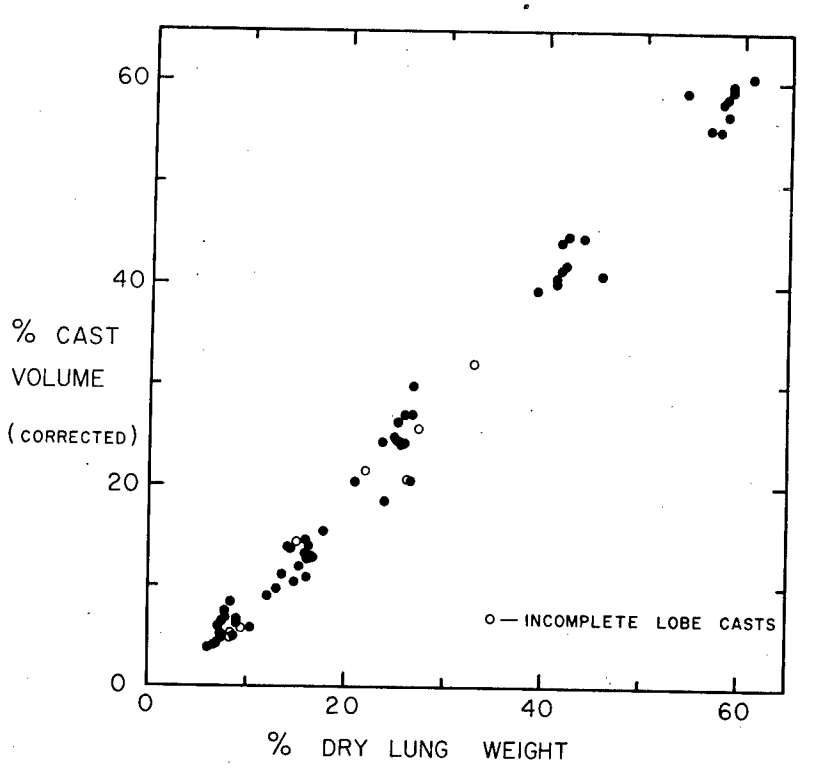


Figure 3

Percent of bronchial cast volume plotted against the percent dry weight for each of the lobes of 9 dogs. The incomplete casts were corrected as indicated in text. The upper right hand cluster represents the whole right lung, the next lower group the whole left lung.

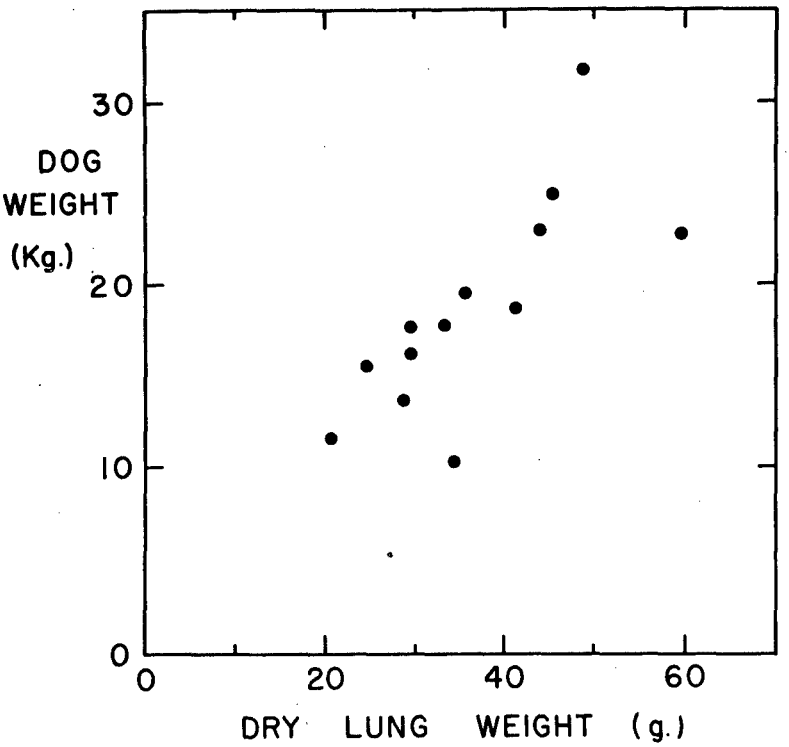


Figure 4

Total body weight of dog plotted against dry lung weight.

weight seems to be proportional over the whole range of dry weights for the dog lung. The relationship between whole body weight and dry lung weight is shown in Figure 4.

SUMMARY

1. A method for making casts of the bronchial tree using a polystyrene resin - "Bioplastic" is described. It consists first of air drying the lung under pressure and then filling the tree by gravity while the plastic polymerizes. The pulmonary vessels can also be injected, thus giving a double cast.
2. The relative weights of the individual lobes of the dog lung after air drying are presented. A linear relationship is established between the dead space volume of individual lobes and their dry weight.

REFERENCES

1. Tobin, C. E. Anat. Rec. 114: 453, 1952.
2. Joffe, M. H. Science 120: 612, 1954.
3. Rahn, H. and H. T. Bahnson J. Appl. Physiol. 6: 105, 1953.
4. Rahn, H., P. Sadoul, L. E. Farhi and J. Shapiro This Report.

THE INFLUENCE OF BRONCHIAL TREE STRUCTURE ON VENTILATION OF THE LUNG AS INFERRED FROM MEASUREMENTS OF A PLASTIC CAST

by

B. B. Ross

Various investigators have proposed models of the bronchial tree (1-4) which were considered useful in making calculations appropriate to a particular investigation. These models have generally the same limitation, namely, they are based on the supposition that the bronchi of a given order of branching are identical in size and length. Implicit in this assumption is the inference that all alveoli are supplied through identical bronchial pathways having the same number of component bronchi, of uniform caliber and length. (A bronchial pathway is here defined to be comprised of all the bronchi or parts thereof through which air must travel to get from the carina to an alveolus and vice versa.) The consequences are that all alveoli are fixed equally distant from the carina and therefore the bronchial tree structure, being uniform, has minimal influence in producing variations in the ventilation of different alveoli. It is the purpose of this investigation to derive a model of the lung tree, as true to scale as possible, and from these measurements, to determine how the structure of the bronchial tree may affect ventilation.

It should be stated immediately that the author is aware of the hazards involved in using information obtained from a rigid facsimile of the bronchial tree to describe properties of the real in vivo structure. To confound matters further, certain assumptions are made in the following presentation which may be in error and, as a consequence, the interpretations of the results presented may be incorrect. This discussion is therefore presented as a theoretical study in order to introduce a new concept of unequal ventilation and associated respiratory phenomena.

METHODS

Isolated dog lungs were prepared for casting by drying in an inflated state by means of a continuous flow of compressed air directed through the trachea for periods of 48 to 72 hours. A polystyrene plastic (Ward's Bioplastic) was used to make the cast (5). This product was used because of its small shrinkage. After adding catalyst (0.3% by volume) and accelerator (0.15% by volume), the liquid monomer was continually stirred until its temperature had risen 2° C and was then poured steadily into the trachea of the dried lung until gelling occurred (about 30-45 seconds following the time when a 2° rise is noted). Ideally, this procedure yielded a cast of the complete bronchial tree with little or no filling of alveoli. However, results were erratic because of incomplete control of the polymerization rate of the

plastic and incomplete filling of the parts of the bronchial tree, particularly in the apical lobes. After pouring, the plastic was cured by heat (70° C for 3 to 6 hours). The lung tissue was then removed by corrosion with concentrated HCl.

From one of the casts obtained in the manner described, the bronchi of the cast were measured. Measurements included the diameter of each bronchus at its base and the distance between the base of a "parent" bronchus and the base of each "daughter" bronchus. These measurements were made of all bronchi 1.5 mm diameter or larger. In addition, all daughter branches of bronchi in the range of 1.5 - 2.5 mm diameter were similarly measured. Wherever possible, when the cast was considered complete, the number of cast endings evolving from the smallest measured branches was recorded. These counted cast endings were quite uniform in size (about 0.2 mm; the error of the method of measurement was about 0.1 mm/mm) and were designated as "terminal bronchi" (Figure 1). The smallest measured bronchi gave rise to 1-3 orders of branching before terminal bronchi appeared. These branches originated from the parent in such a fashion that the length of that portion of the bronchial path from last-measured bronchus to a terminal bronchus was indeterminate. This length was approximated by measuring the linear distance between the base of the measured parent and the most distant terminal bronchus. This distance varied from 0.3 - 1.0 cm, averaging about 0.5 cm.

RESULTS

1. Statistical analysis of the measurements:

A relation was observed to exist between the cross section area of a bronchus, its position in the bronchial tree and the number of terminal bronchi ultimately arising from it. Accordingly, the data obtained from the cast was analyzed by the method of multiple regression analysis described by Quenouille (6) for evaluating parallel regressions. The data from each of the lobes of the lung yielded, by this method, a different regression constant, K. However, these constants were not significantly different from each other, so for convenience a single regression equation was derived and used in subsequent calculations. The equation obtained was:

$$N = K\, A^{1.25} / (D + 2)^{0.5} \qquad \text{-----} \qquad (1)$$

where N is the number of terminal bronchi ultimately arising from any bronchus, A is the cross section area of the bronchus at its base in mm^2 and D is the distance through the bronchial tree from the carina to the base of the bronchus in question in cm. K, the regression constant, was found to be 36.9 in the single equation for the whole lung. The correlation between the observed and predicted values of N for a randomly chosen sample from the collected data is shown in Figure 2. The value of r, the correlation coefficient, shows that the equation is in error by about 12 percent ($1 - r^2$), partly due to the use of a single equation rather than one for each lobe of the lung.

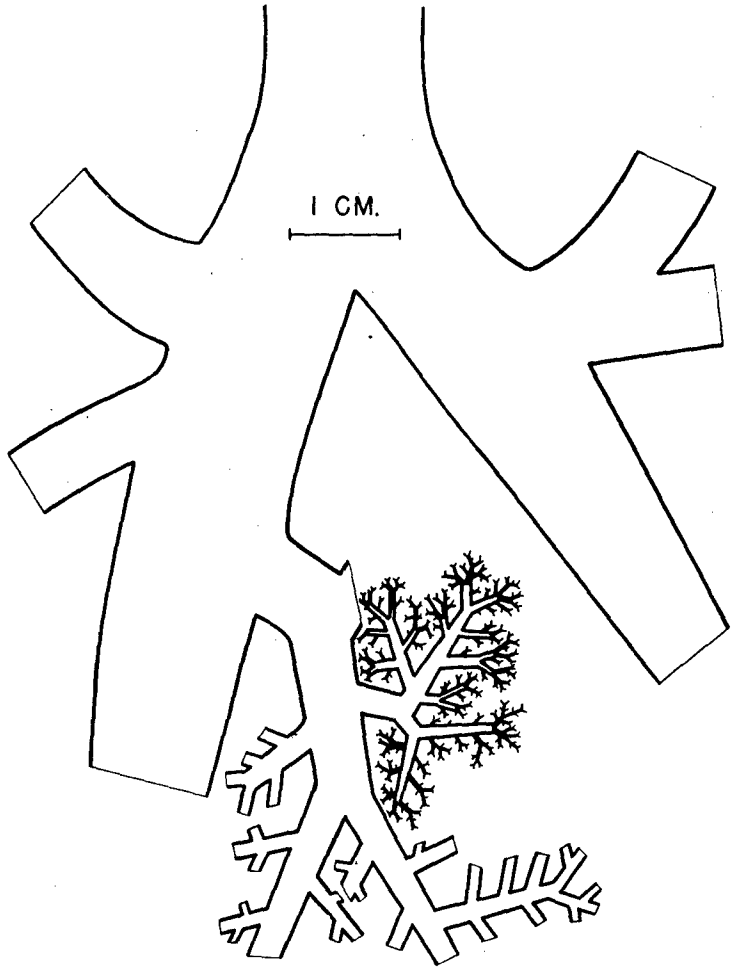


Figure 1

Scale drawing, a segment of the bronchial tree of the dog's lung, based on measurements of a cast. The bronchi shown in outline were measured. The small bronchi shown in silhouette were not measured, but the end branches ("terminal bronchi") were counted.

2. The gross structure of the bronchial tree:

The summated cross section areas of all bronchi are shown in Figure 3. Shown

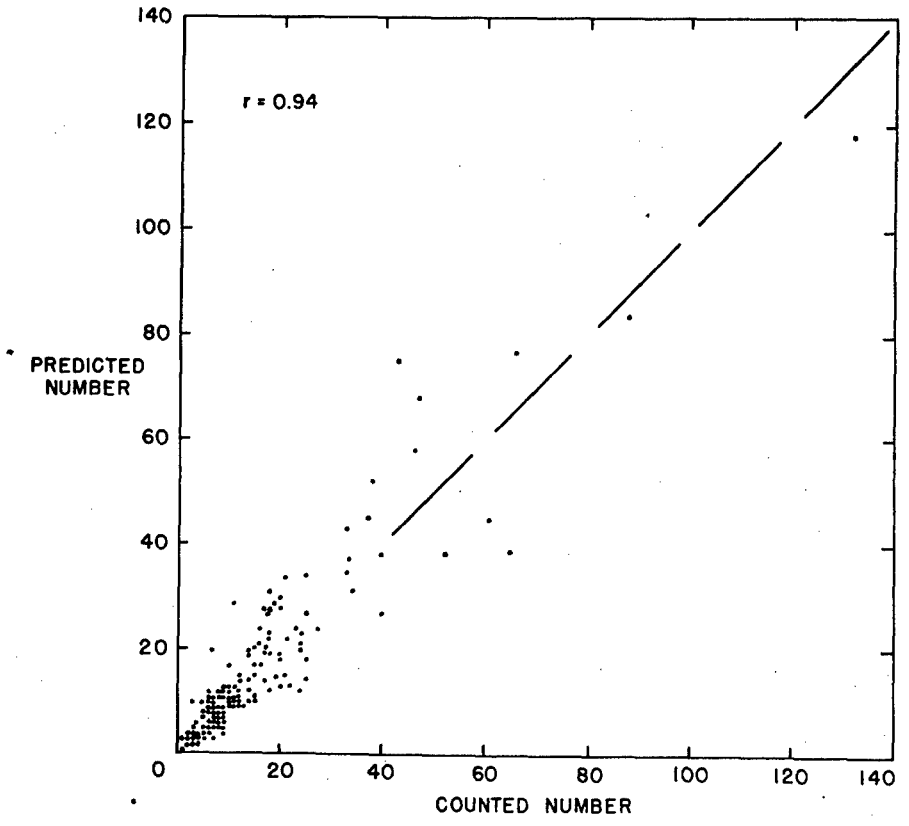


Figure 2

Relation between observed values of N (number of terminal bronchi ultimately arising from a given bronchus) and the values predicted by the empirical equation. The relation is shown for a randomly chosen sample from the collected data. The correlation between predicted and observed values indicates an error of prediction of about 12 percent ($1 - r^2$).

also in solid inked columns is the summated cross section area of the last-measured bronchi of all bronchial pathways which end in the given distance interval. It is immediately evident that bronchial pathway lengths vary over a wide range since some of the smallest measured bronchi (which are about 0.5 cm from the terminal bronchi) terminate less than 1.5 cm from the base of the lobar bronchi whereas the longest pathways may be more than 12 cm long.

3. The distribution of terminal bronchi in the lung:

The distribution of terminal bronchi in the lung was determined by calculating

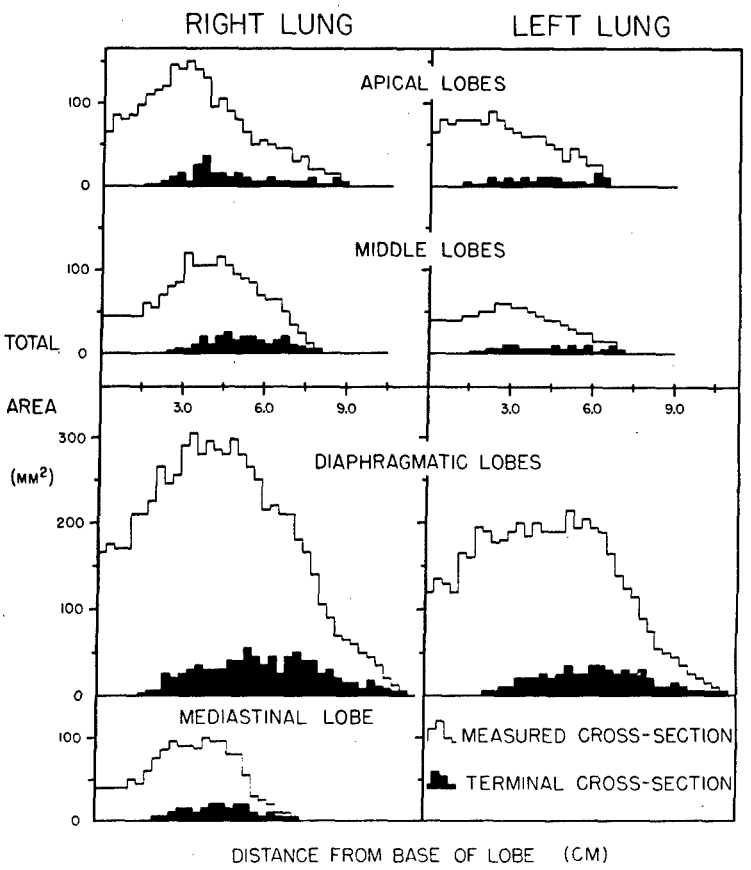


Figure 3

Summated cross section of all measured bronchi appearing or present in each lobe at given distance intervals in the lobe from the base of the lobar bronchus. The area under each histogram represents the dead space volume which was filled by plastic during casting. A solid-inked histogram for each lobe represents the summated cross section of last measured bronchi which end in a given distance interval.

N for each last measured bronchus in 3 of the lobes of the lung cast. When these "counts" of the terminal bronchi for each lobe were arranged as cumulative sums with distance into the bronchial tree, it was found that the curves obtained were best described by a Gompertz type cumulative distribution equation, viz.:

$$y = k\, a^{b^x}$$

Further investigation showed that the constants in the equation had common

characteristics and on this basis, the distributions of terminal bronchi in the remaining lobes were predicted. The predicted distributions were then tested by calculating N for the bronchi of two additional lobes and summating as was done initially. These curves compared satisfactorily with those predicted. The non-cumulative distributions were then calculated and the results plotted as in Figure 4. In Figure 4a the distributions in the lobes of the right lung are shown. Note that the mean length of the bronchial pathways, as indicated by vertical lines representing the weighted mean distance between carina and terminal bronchi, varies among the lobes. However, as shown in Figure 4b, the mean length of the bronchial pathways is the same in both right and left lungs. This observation will be discussed further in another section of this paper.

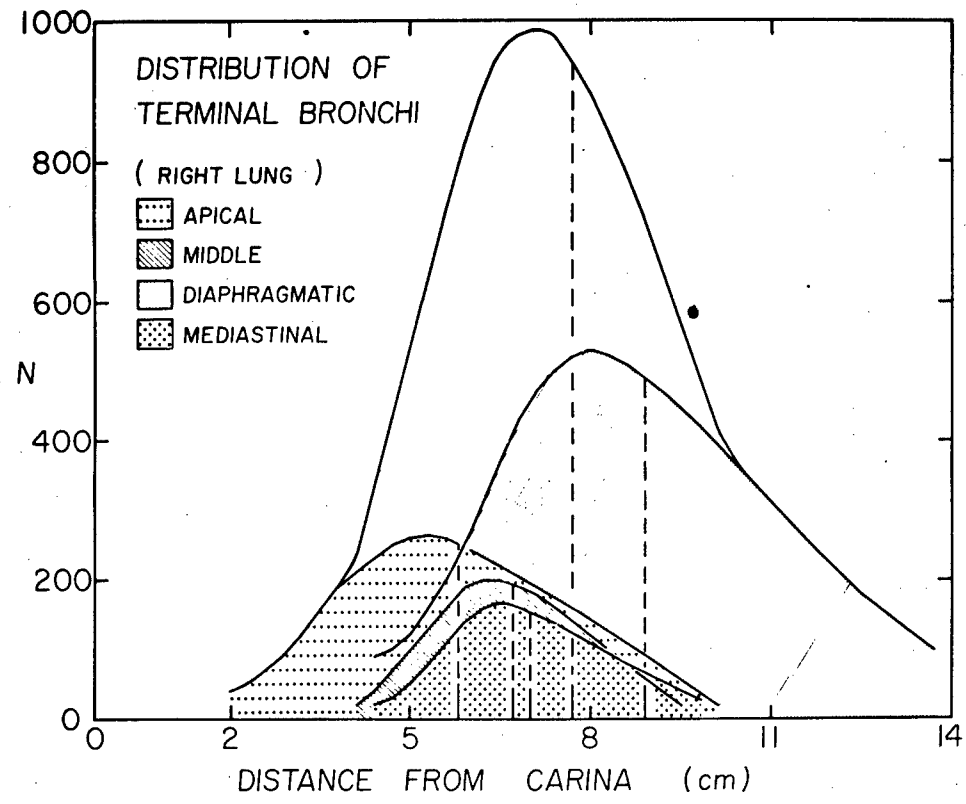


Figure 4a

Distribution of terminal bronchi in the right lung as predicted by Gompertz curves, shown in non-cumulative form. The vertical broken lines intercept the abscissa at a distance representing the weighted mean length of the bronchial pathway in each lobe and the right lung as a whole.

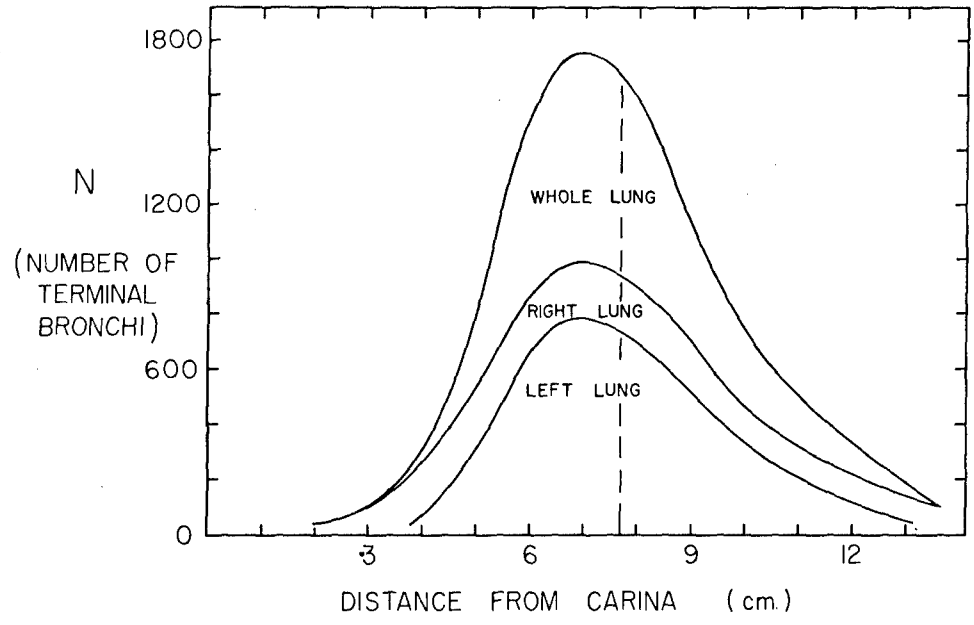


Figure 4b

Non-cumulative distribution of terminal bronchi in the right and left lungs and the lung as a whole. The mean bronchial path length is the same in each of these divisions of the lung.

4. The investigation of pressure and flow characteristics in the bronchial tree:

(a) Assumptions

Such a large variation provokes speculation concerning the nature of the changes in caliber along different bronchial pathways; whether or not the gradation of bronchial diameters is of such a sequence as to produce similar resistances, similar total pressure gradients or uniform flow rates. The investigation of this problem was made by referring to the regression equation described above (Eq. 1). The "terminal bronchus" was assumed to be the beginning of a functional alveolar unit, everywhere identical. It was further assumed that each of these units would act similarly during the respiratory cycle; i.e., each unit would receive and deliver an equal aliquot of tidal gas at an equal, simultaneous rate. Accordingly, the equation may be modified to describe the flow rate of air in any bronchus, since these assumptions have the effect of setting dV/dt, the rate of flow, proportional to N:

$$dV/dt \propto N = K A^{1.25} / (D + 2)^{0.5} \quad \text{-----} \quad (2)$$

The rate of flow in the trachea must, in consequence, be proportional to ΣN, ($(dV/dt)_T \propto N$) the total number of terminal bronchi in the lung. Therefore, the flow in any bronchus relative to that in the trachea, $\%(dV/dt)_T$, may be predicted by the equation:

$$\%(dV/dt)_T = 100\, N/\Sigma N = 100\, K\, A^{1.25} / (D + 2)^{0.5}\, \Sigma N \text{ -----} \quad (3)$$

$$= 0.12\, A^{1.25} / (D + 2)^{0.5}$$

(For the cast measured $\Sigma N = 30.5 \times 10^3$ and, therefore, $100\, K/\Sigma N = 3690/30.5 \times 10^3 = 0.12$, the constant given in the last form of the equation.)

(b) Flow velocity and transit time

The proposition stated in equation (2) may be developed along two different lines of argument. If N can be accepted as indicating flow rate, then for the first argument, the following corollary propositions may be stated:

(1) $dV/dt/A_{br} \propto N/A_{br} \propto v$; and

(2) $\dfrac{1}{dV/dt/A_{br}} \propto A_{br}/N \propto \dfrac{1}{v} \propto t/L$. These proportionalities merely state

state (1) the mean linear velocity v, in a bronchus is proportional to the flow rate, as indicated by the number of terminal bronchi, divided by the cross section of the bronchus (A_{br}) and (2) the time required for the transit of air, (t), through a unit length of the bronchus, (L), is the inverse of the velocity. For convenience, these proportions were converted by appropriate steps to provide statements of velocity and transit time in a bronchus relative to the corresponding values for tracheal flow:

$$\%v_t = 100\, K\, A^{1.25-1} A_T/\Sigma N\ (D + 2)^{0.5} \text{ -----} \quad (4)$$

$$= 20\, A^{0.25} / (D + 2)^{0.5}$$

$$\%(t/L)_T = 100\, \Sigma N\ (D + 2)^{0.5} / K\, A_T\, A^{1.25-1} \text{ -----} \quad (5)$$

$$= 500\, (D + 2)^{0.5} / A^{0.25}$$

($A_T = 165$ mm^2 for the cast measured.)

In equation (5) the transit time is expressed for a unit length of bronchus relative to a unit length of trachea. The transit time required for an aliquot of air to travel through a complete bronchial pathway (from carina to the end of a terminal bronchus, or alveolar unit) is the summated times through the individual bronchi:

$$\%(t/L)_T = 500 \Sigma L_{br}\, (D + 2)^{0.5} / A^{0.25} \text{ -----} \quad (6)$$

The total transit time through a bronchial pathway is expressed as percent of the transit time in a unit length of trachea in this equation. The total transit time through each of several bronchial pathways was calculated. It was found, as shown in Figure 5 that a surprisingly good relation existed between the total length of the bronchial pathways and the total transit time required to move an aliquot of air through it. Treating this data statistically, the following regression equation was obtained:

$$\%(t/L)_T = 530L_P - 140 \qquad \text{-----} \qquad (7)$$

showing that, as bronchial path length (L_P) increased, total transit time increased

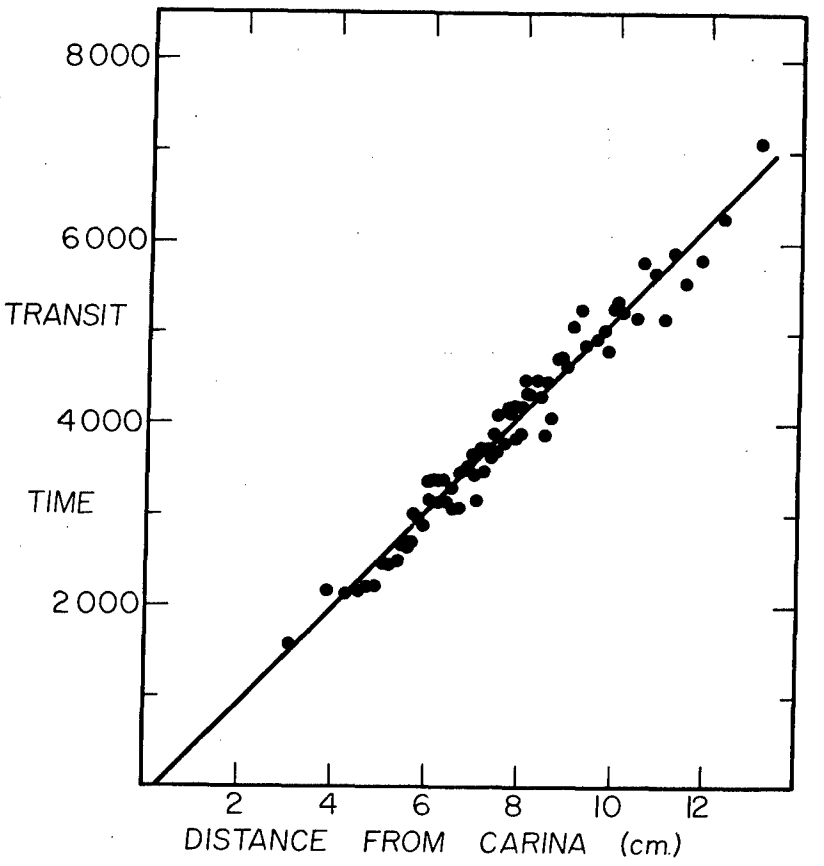


Figure 5

Total transit time (in percent of the transit time through one cm of trachea) through bronchial pathways ending at various distances from the carina. Each point is a mean of five calculations. These calculations were averaged in such a way as to retain as much of the actual scatter as possible.

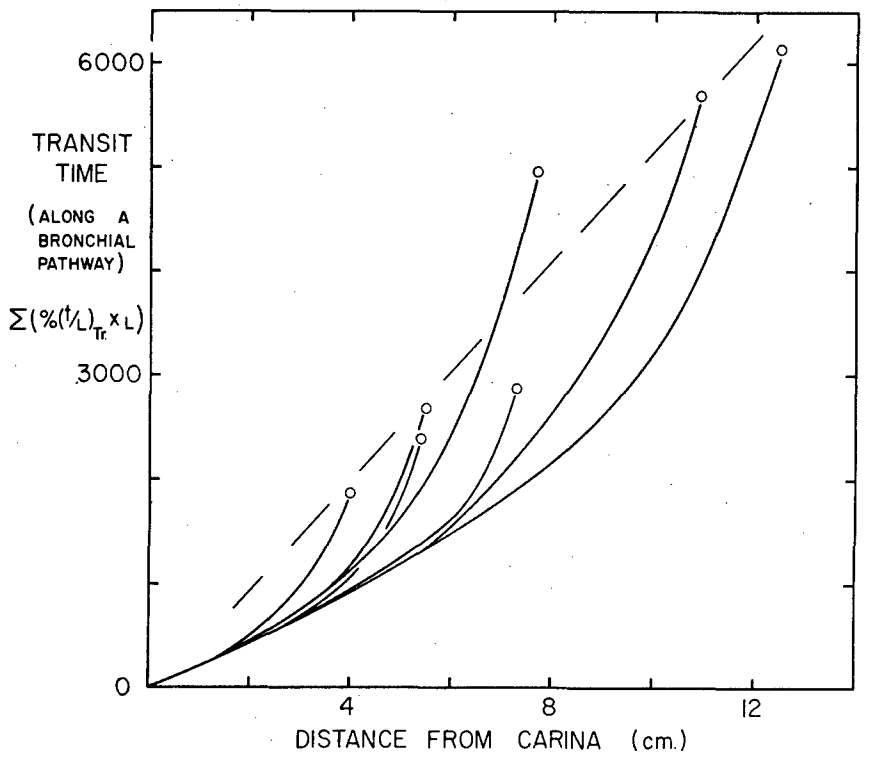


Figure 6

Cumulative increments of transit time through single bronchial pathways. Each curve shows the increase in time as air is transported through the various bronchi supplying a group of alveoli at the end of the bronchial pathway. The dashed line is the regression line shown in Figure 5.

proportionally. This is not to say that for a given increment in distance through a single pathway there is a proportional increment in the transit time. Rather, the time increment of movement along a single pathway is dependent on the size and position of the bronchus in which the air is moving. A few examples of the time increment along a bronchial pathway are shown in Figure 6. It may be seen here that the time spent in movement through the large bronchi close to the carina is relatively short and that, as the smaller bronchi in any pathway are encountered, the time required for transit increases abruptly.

(c) Pressure gradients

The second argument mentioned concerns the pressure gradients developed

along the bronchial pathways. Since the empirical equation has been equated with flow rate (equation 2), if streamline flow is assumed to occur, the empirical equivalent for flow may be substituted in Poiseuille's Law, viz.:

$$dV/dt \propto N \propto \frac{\Delta P \pi r^4}{8 L \eta} \propto K \, A^{1.25} \, / \, (D + 2)^{0.5}$$

or, rearranging

$$\left(\frac{\Delta P}{L_{br}}\right) \propto K \, / \, C \, (D + 2)^{0.5} \, A^{0.75}$$

where $C = 1/8 \pi\eta$. Proceeding as before, solving the proportion in terms of pressure gradient per unit length of a bronchus relative to the pressure gradient in a corresponding length of trachea yields:

$$\%(\Delta P/L)_T = 100 \, K \, A_T^2 \, / \, \Sigma N \, (D + 2)^{0.5} \, A^{0.75} \qquad \text{-----} \qquad (8)$$

$$= 3300 \, / \, A^{0.75} \, (D + 2)^{0.5}$$

As in the case of total transit time (equation 6) the total pressure gradient between the carina and the end of the bronchial pathway must be obtained by summation. This series of calculations was carried out for several bronchial pathways and the results obtained are shown in Figure 7. (The increment in pressure gradient along a bronchial pathway is not shown. However, it follows a trend similar to the changes in transit time demonstrated in Figure 6.) The scatter of this data, relative to that shown in Figure 5 for relative transit time, is magnified by the choice of scale. Note, however, that throughout the entire range of bronchial path lengths the total pressure gradient varies by only 1500 percent (of the pressure gradient along one cm of trachea) and shows no apparent trend with distance. In comparison, the data for total transit time varies by 5000 percent and reveals a definite trend. The conclusion was therefore made that there is no difference in the total pressure gradients to different alveoli, at least when the alveoli are chosen at random. However, if the data shown in Figure 7 are plotted as total pressure gradient vs. the length of that portion of the bronchial pathway between lobar bronchus and alveolus, as in Figure 8, the scatter of the points is reduced somewhat and indications of a trend appear. This observation may be explained if one considers that the shorter of these bronchial path segments must in general supply alveoli located in the central portion of each lobe, relative to any pleural surface, whereas the longer of the bronchial path segments more likely supply alveoli nearer the lobe surfaces. The alveoli located on the lobe surfaces should be exposed to a pressure nearly equal to the intrapleural-pressure less the component of this energy expended in stretching the pleura. As the remaining pressure is transmitted towards the center of each lobe, there is expected to be some loss of energy due to the viscous resistance of the lung tissue. Hence, the centrally located alveoli would receive a lesser proportion of the applied intrapleural pressure than would the peripheral alveoli. It appears from the calculations shown

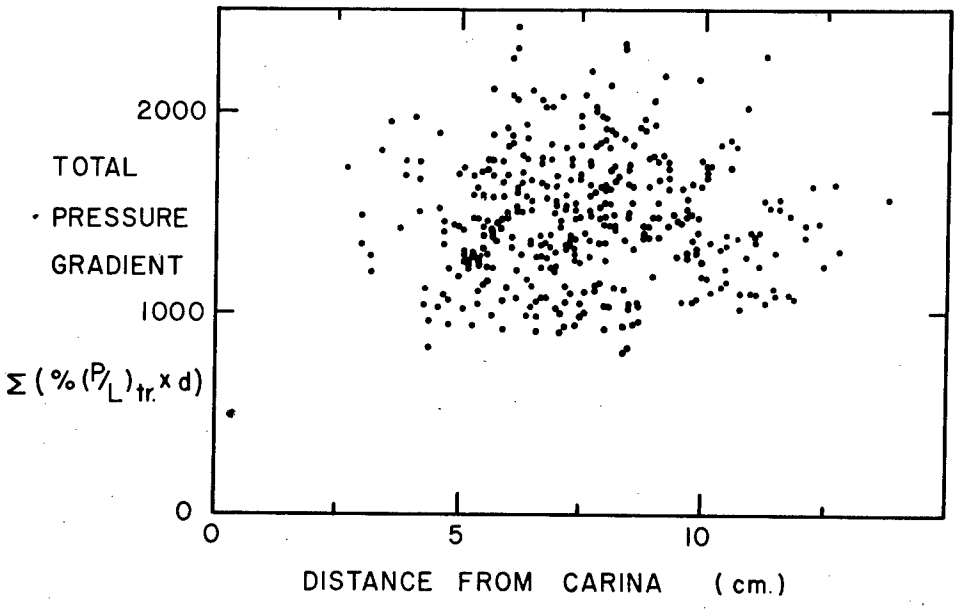


Figure 7

Total pressure gradient from carina to the end of bronchial pathways, expressed as percent of the pressure gradient along one cm of trachea.

in Figure 8 that the structure of the bronchial tree compensates for this proposed variation in pressure, allowing equal filling of all alveoli in spite of it.

If the preceding hypothesis is correct, the range of pressures observed should yield information concerning the magnitude of the viscous component of the respiratory energy expenditure. One-half of this range (750%) may be assumed to approximate the average viscous force, while the average carina-alveolar pressure is about 1750 percent. If the airway from the mouth to the carina is taken to be 30 cm (a figure obtained from other experiments), the total mouth-alveolar pressure gradient would be 4750 percent of the gradient along one cm of trachea. The ratio of viscous to alveolar pressure is, in this case, 0.16, or, the viscous force is about 16 percent of the mouth-alveolar pressure gradient. This estimate agrees remarkably well with other estimates of the magnitude of tissue viscous force (7,8).

DISCUSSION

1. Interpretation of transit time:

The most interesting finding of this investigation is that total transit time is

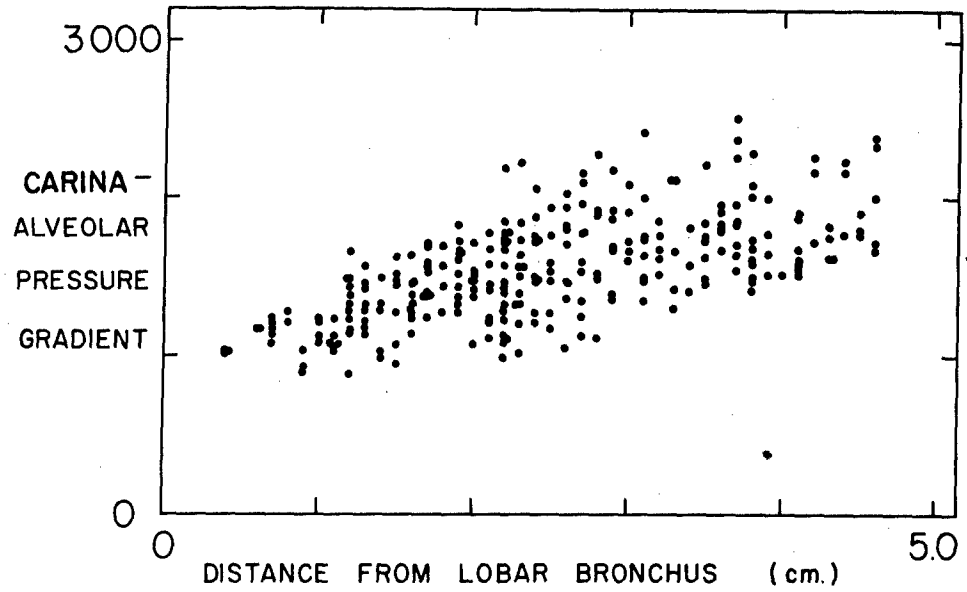


Figure 8

Total pressure gradient through a bronchial pathway vs. distance from the lobar bronchus. Bronchial pathways ending a short distance from the lobar bronchus are considered to supply centrally located alveoli in each lobe whereas bronchial pathways ending at a greater distance from the lobar bronchus are considered to lie near the periphery of each lobe.

directly proportional to total path length. Simple inspection of this property reveals that if it takes a longer time for inspired room air to reach one alveolus than it does to reach a differently placed alveolus, then the two alveoli must inspire dead space air for different periods of time. It should be remembered that this variation in transit time was found as a consequence of calculations based on the assumption that all alveolar groups simultaneously contributed the same total volume to the tidal volume. Variations in transit time must therefore cause variations in the distribution of dead space gas to alveoli during inspiration and conversely, alveolar gas from different alveoli must appear at the mouth at differing times following the onset of expiration. It follows that the variation in transit time produces unequal "alveolar" ventilation, in the presence of an equal total ventilation of each alveolus.

This concept of unequal ventilation was investigated more fully, using the

distribution of terminal bronchi described previously. To simplify matters, it was considered that transit time was the only factor affecting uniformity of ventilation; the parabolic nature of streamline flow and the possibility of mixing between dead space and alveolar gases were ignored. The upper airway (trachea, pharynx and nose-mouth) was taken to be a uniform airway 30 cm long having the same caliber as the trachea. A simplified respiratory cycle was hypothesized which was characterized by a constant flow rate during inspiration and expiration with each phase lasting an equal, finite time. Under these arbitrary conditions, the calculations pertinent to the investigation of unequal ventilation in terms of transit time are made easy. For example, the calculated transit time to an alveolus is proportional to the dead space volume inspired by that alveolus while the duration of inspiration is proportional to the total volume inspired. The ratio V_d/V_t is therefore determined by the ratio of transit time to duration of inspiration. Over any period, this ratio will remain constant so long as the same cycle is considered to occur, so that $\dot{V}d/\dot{V}t$ is also calculable. From this basic calculation, and utilizing the basic assumption underlying this entire effort that $V_t \propto N$, it is possible to analyze the ventilation of alveoli as it is influenced by transit time.

2. The influence of transit time on the composition of alveolar gas:

One factor not previously discussed which bears on the problem of how transit time affects the composition of alveolar gas is the nature of the distribution of blood to the alveolar capillary bed. At present only speculation is possible. Two obvious possibilities exist. One is that the volume flow of blood is uniform for all alveoli. The other is that the distribution of blood flow is exactly the same as is the distribution of air inspired into the alveoli from the environment. The latter alternative requires that a "well-ventilated" alveolus receive a greater volume flow of blood during the respiratory cycle. If such is the case, the influence of unequal distribution of air due to unequal transit time upon the composition of alveolar gas becomes nil since the ventilation-perfusion ratio (9) is identical for all alveoli. The first alternative is therefore chosen in order to permit the analysis of the influence of transit time alone on ventilation.

Under the stipulated conditions, two different respiratory cycles were established and investigated. To reduce the number of calculations required, the weighted mean length of the bronchial pathways in each lobe was taken to represent all bronchial pathways in the lobe. Since these lengths vary among lobes, it is reasonable to suppose that, if differences occur as a consequence of variations in path length, they could be detected at this level of subdivision of the lung. The cycles were defined as follows: 1) a 400 cc tidal at a frequency of breathing of 10/min., yielding a total ventilation of 4 liters per minute, with each phase of the cycle having a duration of one second; 2) a tidal which will produce the same total "alveolar ventilation" as in (1) when the frequency of breathing is 20/min. The analysis of these conditions of ventilation is summarized in Table 1*. Under each

* A description of the stepwise calculations required for this analysis is provided in an appendix to this paper.

condition the exchange ratio, R, and the mean alveolar gas compositions vary among the lobes of the lung. The right apical lobe is the best ventilated lobe (highest $\dot{V}_a/\dot{Q}$, R and $P_{A_{O_2}}$, lowest $P_{A_{CO_2}}$) whereas the right diaphragmatic lobe is ventilated the least. Most striking, however, is the fact that the frequency of breathing affects the distribution of alveolar ventilations as is demonstrated by comparing the values of $\dot{V}A/\dot{Q}$, R, $P_{A_{O_2}}$ and $P_{A_{CO_2}}$ for a single lobe under the two conditions defined. As the frequency of breathing is increased, the right apical lobe is burdened with an increased share of the total alveolar ventilation while the right diaphragmatic lobe is correspondingly less well ventilated.

According to the trend indicated by the calculations shown here, higher and higher frequencies of breathing would cause alterations in the distribution of alveolar ventilations such that eventually very few alveoli would be involved in maintaining the total alveolar ventilation of the whole lung. Concomitant with this increase in frequency is a decrease in depth of breathing. Consequently, a tidal volume less than the dead space volume could result in an alveolar ventilation identical with that prescribed in the above calculations provided that the frequency of breathing is high enough. Indeed this phenomenon has been seen in humans and investigated by Briscoe, et al (10). In dogs the process of panting could well provide adequate alveolar ventilation even if it is true that this act is associated with very small excursions in lung volume.

3. The distribution of alveoli along a ventilation-perfusion curve:

The variation of alveolar ventilations among lobes is sufficiently interesting to warrant investigation of the distribution of alveoli along a ventilation-perfusion curve without regard to lobes. Accordingly, calculations similar to those summarized in Table I were made using as a basis the number of terminal bronchi appearing in successive given distance intervals into the lung. The transit times to each of the alveoli supplied by the terminal bronchi was considered to be the time for transit to the middle of the distance interval. The same conditions were defined for this study as for the investigation of distributions among lobes. The results are summarized in Table II. The variation in P_{O_2} is also described graphically for the two conditions in Figure 9. In this graph a portion of a ventilation-perfusion curve is shown with a point representing the average alveolar gas composition originally defined in order to make the necessary calculations. Above this curve is shown the proportion of the total alveolar ventilation occurring in alveoli containing oxygen at a given partial pressure. The distribution curves are influenced by both the number of alveoli having a given P_{O_2} and the ventilation of each alveolus relative to the total alveolar ventilation. The area under each of the two curves shown is the same and is proportional to the oxygen consumption. The influence of frequency upon the distribution of alveoli is vividly demonstrated.

4. The instantaneous CO_2 concentration in the air expired:

The consideration of transit time provides a means of analysis in studying

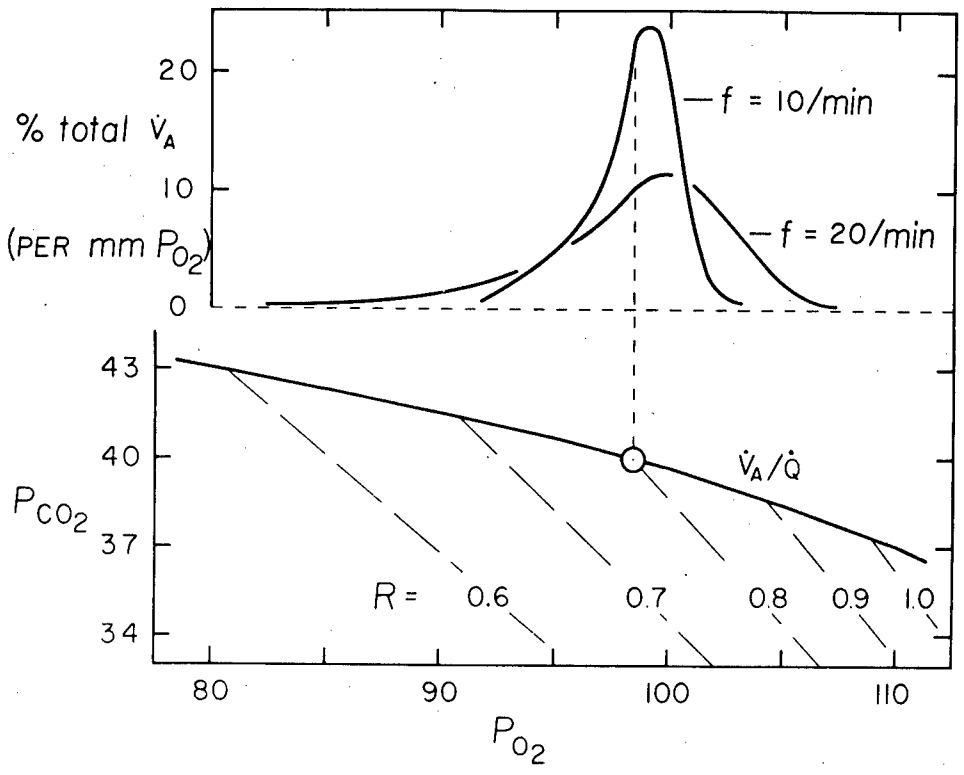


Figure 9

Distribution of alveoli along a ventilation-perfusion curve when the frequency of breathing is defined to be 10 or 20 breaths per minute. See text for further discussion.

other problems associated with the ventilation of the lungs. One of these is the nature of the curve obtained when the respiratory gas is analyzed with a fast CO_2 analyzer during the phase of expiration. This curve is characterized by a fast-rising portion and then a slow-rising portion, both preceded by a period when the expired gas contains no CO_2. It has been variously considered that mixing of dead space and alveolar gases and/or the parabolic nature of viscous flow are primarily responsible for the shape of the fast-rising portion, whereas the slow-rising portion results from continued CO_2 production occurring during expiration. It has also been suggested that a differential arrival of gas from various alveoli influences the shape of the curve, gas from well-ventilated alveoli arriving earlier in the cycle than from poorly ventilated alveoli (11). The theoretical description of transit time presented here permits a more rigorous investigation of the expired CO_2 curve, particularly with respect to the question of when

differently ventilated alveoli contribute CO_2 to the expired gas.

As a preliminary study, the expired CO_2 curve was constructed for a 400 cc tidal, as in condition (1) described previously, assuming that the CO_2 tensions in all alveoli were identical and that no CO_2 production occurred during expiration. Since total transit time is proportional to total distance, the cumulative number of terminal bronchi (alveoli) at any distance (ΣN_D) relative to the total number of terminal bronchi (ΣN) in the lung is an index of the total volume of alveolar gas arriving at the mouth relative to the total volume being expired. The instantaneous CO_2 concentration is therefore determined by the equation:

$$C_{Eco_2} = \frac{\Sigma N_D \times C_{Aco_2}}{\Sigma N}$$

The time at which this concentration can be measured at the mouth is:

$$t_D = t_T \ (35.3D - 1.4)$$

where t_D is the total transit time through the specified distance, D, for which ΣN_D occurs and t_T is the transit time through a unit length of trachea. The equation is similar to equation 7.

The calculations made for the conditions specified are summarized in Table III and are shown graphically as a solid curve in Figure 10 in order to compare these results with those obtained under the conditions about to be described. It is of interest to note that the shape of the fast-rising segment of this curve is quite similar to that obtained in actual practice under physiological conditions. As previously stated, the shape of this segment of the curve has been ascribed to mixing, the parabolic nature of viscous flow or, in a vague sense, uneven ventilation. On the basis of the results obtained here, it could well be claimed that variation in transit time, with its attendant variation in ventilation, is the major factor in determining the shape of this segment. It is also of interest to note that all alveoli are contributing alveolar gas to the expired volume when the "plateau" of the curve is measured. Therefore, it is not feasible to consider that some alveoli first contribute to the expired air only near the end of the expiration, at least using the concept of unequal ventilation being described here.

To demonstrate the effect of continuous CO_2 production upon the expired CO_2 concentration, the range of bronchial path lengths was divided into eight segments and the mean P_{Aco_2} was calculated, taking into account the ventilation-perfusion relationship previously discussed. It was assumed that continuous CO_2 production caused a total change in P_{Aco_2} of 8 mm Hg in each of these segments, that this change was linear with the change in volume throughout the respiratory cycle, and that the mean alveolar CO_2 tension occurred in the alveoli when one-fourth of the tidal was expired. Under these rather arbitrary conditions, the expired CO_2 concentration curve was reconstructed as shown in Figure 10 (lower dashed curve).

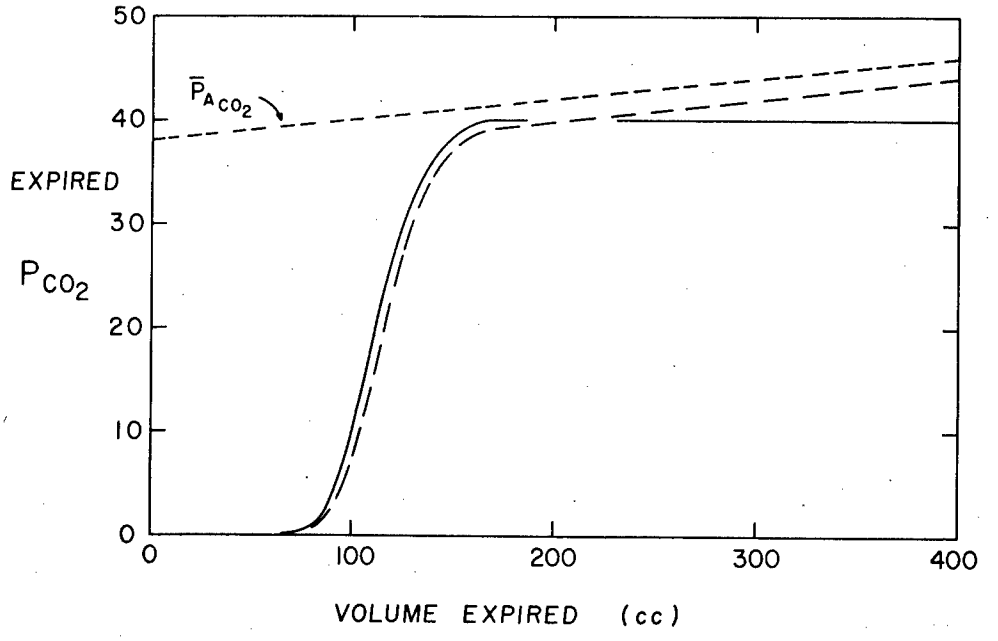


Figure 10

Expired P_{CO_2} at any instant (or volume) expired when continuous CO_2 output is not accounted for (solid line) and when it is taken into account (lower broken line). The upper broken line shows the arbitrarily defined course of the change in $P_{A_{CO_2}}$ in the alveoli during expiration. See text for further description.

The mean alveolar P_{CO_2} within all alveoli at any instant during this expiration is shown by the upper broken line. The $P_{A_{CO_2}}$ in each of the eight segments described varies around this upper line. Actually, there are three mean values of P_{CO_2} presented: the mean for all alveoli at any instant, the mean for the respiratory cycle when it occurs within the aggregate of alveoli, and the mean when it is measured at the mouth. The horizontal distance between the upper and lower broken lines is a measure of the average transit time required to move gas from all alveoli to the mouth.

The slope of the fast-rising portion of the expired CO_2 curve which takes CO_2 production into account is slightly lower than that of the curve shown which neglects CO_2 production. The shift occurs as a result of the lower tensions of CO_2 in alveoli at the onset of expiration. However, the calculable dead space volumes represented in the two curves are the same since the point of change from "fast-rise" to "plateau" occurs at the same volume and the tensions

existing at this volume are commensurate with the shift in slope. The treatment of this segment of the curves according to the method of DuBois, et al (11) yields the same value for dead space.

5. The clearance of nitrogen from the lung:

The concept of transit time has been also applied to the study of clearance. Since it has been concluded that variations in transit time induce variations in effective ventilation of alveoli under conditions of equal total ventilation, it was considered appropriate to investigate the nature of clearance curves which would be obtained under these conditions. Accordingly, the theoretical clearance of nitrogen was determined over a period of at least 30 breaths for various tidals, assuming various total functional residual volumes, and taking into account variations in nitrogen concentration which might occur as a result of differences in ventilation-perfusion. The curves were determined for each lobe of the lung and the lung as a whole, as in the investigation of ventilation-perfusion (Table I). It was found, surprisingly, that under each condition investigated the curves for both lobes and whole lung were straight lines (when the data were plotted as log of concentration vs. number of breaths) even though the slopes of these lines were all different. It was evident that the kind of "unequal ventilation" described here is not responsible for the curvilinear clearance patterns obtained from patients described as displaying evidence of "unequal ventilation". This conclusion has been supported by Otis (12) who has concluded that alinear clearance curves must result from variations in total ventilation of alveoli.

CONCLUSION

It is felt that this theoretical study has permitted the establishment of a new concept of unequal ventilation which, if accepted, necessitates the revision of currently held concepts and requires that the term itself must be more clearly defined to include the qualitative, and quantitative, differences which seem to occur between conditions stipulating equal total ventilation of alveoli and conditions stipulating unequal total ventilation of alveoli.

It is well to state again that the conclusions derived here are based on a rigid tube system representing the bronchial tree, they are tenable only on the acceptance of certain assumptions, and then they are subject to experimental verification.

SUMMARY

Casts of the bronchial tree of dogs' lungs have been made with virtually non-shrinking plastic. One of these casts has been completely measured. From the measurements obtained, an empirical equation was derived which predicted the number of terminal bronchi supplied by any given bronchus in the lung. Making the assumption that each terminal bronchus transports equal quantities of gas at

the same rate to alveoli, a series of equations was derived which described the volume flow rate, the pressure gradient, the linear flow velocity and transit time through any bronchus. Calculations based on these equations led to the following conclusions:

1. The overall pressure gradient to all alveoli is about the same, except that a slight difference may exist between alveoli located in the central part of a lobe and alveoli at the periphery of the lung.
2. The total transit time from mouth to alveolus is directly proportional to the length of the bronchial pathway supplying the alveolus.
3. Differences in transit time lead to differences in effective ventilation of alveoli, causing a distribution of alveolar ventilations similar to a calculated distribution of terminal bronchi even though the total ventilation of all alveoli is the same.
4. Differences in transit time could account for the shape of the fast-rising portion of the expired CO_2 curve obtained from a fast CO_2 analyzer, due to the fact that all alveoli do not contribute to the expired air simultaneously.
5. Differences in the relative distribution of dead space gas may cause a distribution of alveolar gas compositions along a ventilation-perfusion curve, the magnitude of which is influenced by the frequency of breathing.
6. Nitrogen clearance curves are not influenced by this type of unequal ventilation. Even though the slopes of the clearance curves are different for each lobe, the clearance of the whole lung is perfectly exponential. It is concluded that non-exponential curves require a type of unequal ventilation characterized by variations in the total ventilation of alveoli.

APPENDIX

The determination of the influence of variations of transit time of air to alveoli upon alveolar ventilation and the composition of alveolar air was made by carrying out the following calculations:

1. The magnitude of the tidal, its duration and frequency were assumed as described in the text.
2. The mean transit time to each lobe was calculated by means of a modification of equation 7 in the text, viz.:

$$\text{mean transit time} = t_T (35.3 \bar{L}_P - 1.4)$$

where t_T is the transit time through one cm of trachea and $\bar{L}_P$ is the weighted mean length of the bronchial pathways in each lobe. The transit time through one cm of trachea is determined by the ratio $A_T/dV/dt$, the cross section of the trachea divided by the stipulated flow rate.

3. The ratio of transit time to duration of inspiration is equivalent to the ratio of $\dot{V}_D/\dot{V}_T$, the ratio of dead space ventilation to total ventilation. For the defined condition, the dead space ventilation for each lobe is:

$$V_D = \frac{(\%\Sigma N)_{Lobe}}{100} \times \dot{V}_D/\dot{V}_T \times \dot{V}_{T\,Whole\ Lung}$$

where $(\%\Sigma N)_{Lobe}$ is the percent of the total number of terminal bronchi found in each lobe and $\dot{V}_T$ is the defined total ventilation of the lung.

4. $\dot{V}_T$ for each lobe was considered proportional to $(\%\Sigma N)_{Lobe}$. The alveolar ventilation was determined by subtraction of the calculated dead space ventilation from the total ventilation in each segment of the lung.

5. The following additional conditions were stipulated to define the magnitude of blood flow: The overall mean P_{Aco_2}, P_{Ao_2}, R and $C_{(a-v)\,o_2}$ were set at 40.0 mm Hg, 98.4 mm Hg, 0.80 and 5.00 vols. %, respectively. The gas inspired was considered to be air at 747 mm Hg. These conditions fixed the overall $\dot{V}_A/\dot{Q}$ ratio at 0.864 (9). Having determined the alveolar ventilation for the whole lung in step 4, the total blood flow was determined. The blood flow to each lobe was, by stipulation, proportional to $(\%\ N)_{Lobe}$. The ventilation-perfusion ratio was calculated for each lobe.

6. A ventilation-perfusion curve conforming to the above specifications was constructed on a Pco_2, Po_2 diagram. The intersections of R lines radiating from the inspired air point provided graphic information by which the numerical value of the $\dot{V}_A/\dot{Q}$ ratio could be determined at the intersections. A curve of $\dot{V}_A/\dot{Q}$ vs. R was drawn using the obtained values. The exchange ratio, R, was then determined graphically for each lobe from the calculated $\dot{V}_A/\dot{Q}$ ratio for each lobe.

7. The mean alveolar gas tensions in each lobe were then determined by plotting the appropriate R lines on the original Pco_2, Po_2 diagram. The intercepts of these new R lines with the $\dot{V}_A/\dot{Q}$ curve fixed the values of P_{Ao_2} and P_{Aco_2}.

TABLE I

Calculations of Ventilation-Perfusion Ratios and Mean Alveolar Gas Compositions in Lobes of the Lung

CONDITION I

(4 liters per minute total ventilation; 400 cc tidals @ 10 breaths per minute; inspiration and expiration each one second in duration.)

Lobe (code number)	$\%\sum N$	mean transit time (ms)	$\frac{\dot{V}_D}{\dot{V}_T}$	$\frac{\dot{V}_A}{\dot{V}_T}$	$\dot{V}_T$ ($\propto N$) $\frac{cc}{min.}$	$\dot{V}_D$ $\frac{cc}{min.}$	% Total $\dot{V}_D$
Right:							
apic.	14.1	245	0.245	0.755	564	138	12.0
mid.	7.2	265	0.265	0.735	288	76	6.6
dia.	32.8	313	0.313	0.687	1312	411	35.8
med.	5.9	271	0.271	0.729	236	64	5.6
Left:							
apic.	10.8	276	0.276	0.724	432	119	10.4
mid.	5.6	269	0.269	0.731	224	60	5.2
dia.	23.6	297	0.297	0.703	944	280	24.4
Rt. lung	60.0	287	0.287	0.713	2400	689	60.0
L. lung	40.0	287	0.287	0.713	1600	459	40.0
Total	---	287	0.287	0.713	4000	1148	---

Lobe (code number)	$\dot{V}_A$ $\frac{cc}{min.}$	% Total $\dot{V}_A$	$\dot{Q}$ ($\propto N$) $\frac{cc}{min.}$	$\frac{\dot{V}_A}{\dot{Q}}$	R	P_{Ao_2} mm Hg	P_{Aco_2} mm Hg
Right:							
apic.	426	14.9	465	0.916	0.83	100.0	39.8
mid.	212	7.4	238	0.891	0.81+	99.2	39.9
dia.	901	31.6	1083	0.832	0.78	96.9	40.4
med.	172	6.0	195	0.882	0.81	99.0	39.9
Left:							
apic.	313	11.0	356	0.879	0.81-	98.9	39.9
mid.	164	5.8	185	0.886	0.81+	99.1	39.9
dia.	664	23.3	779	0.852	0.79	97.9	40.1
Rt. lung	1711	60.0	1981	0.864	0.80	98.4	40.0
L. lung	1141	40.0	1320	0.864	0.80	98.4	40.0
Total	2852	---	3301	0.864	0.80	98.4	40.0

TABLE I

CONDITION II

(5.15 liters per minute total ventilation; 257 cc tidals @ 20 breaths per minute; inspiration and expiration each one second in duration.)

Lobe (code number)	$\%\Sigma N$	mean transit time (ms)	$\frac{\dot{V}_D}{\dot{V}_T}$	$\frac{\dot{V}_A}{\dot{V}_T}$	$\dot{V}_T$ ($\propto N$) $\frac{cc}{min.}$	$\dot{V}_D$ $\frac{cc}{min.}$	% Total $\dot{V}_D$
Right:							
apic.	14.1	380	0.380	0.620	726	276	12.0
mid.	7.2	410	0.410	0.590	371	152	6.6
dia.	32.8	486	0.487	0.513	1688	822	35.8
med.	5.9	421	0.421	0.579	304	128	5.6
Left:							
apic.	10.8	428	0.428	0.572	556	238	10.4
mid.	5.6	417	0.417	0.583	288	120	5.2
dia.	23.6	461	0.461	0.539	1215	560	24.4
Rt. lung	60.0	446	0.446	0.554	3089	1378	60.0
L. lung	40.0	446	0.446	0.554	2059	918	40.0
Total	---	446	0.446	0.554	5148	2296	---

Lobe (code number)	$\frac{\dot{V}_A}{min.}$ cc	% Total $\dot{V}_A$	$\dot{Q}$ ($\propto N$) $\frac{cc}{min.}$	$\frac{\dot{V}_A}{\dot{Q}}$	R	P_{Ao_2} mm Hg	P_{Aco_2} mm Hg
Right;							
apic.	450	15.8	465	0.968	0.86	101.6	39.5
mid.	219	7.7	238	0.920	0.83	100.1	39.8
dia.	866	30.4	1083	0.800	0.76	95.7	40.7
med.	176	6.2	195	0.903	0.82	99.5	39.9
Left:							
apic.	318	11.2	356	0.893	0.82-	99.4	39.8
mid.	168	5.9	185	0.908	0.82+	99.7	39.9
dia.	655	23.0	779	0.841	0.79	97.4	40.3
Rt. lung	1711	60.0	1981	0.864	0.80	98.4	40.0
L. lung	1141	40.0	1320	0.864	0.80	98.4	40.0
Total	2852	---	3301	0.864	0.80	98.4	40.0

TABLE II

Distribution of Alveolar Gas Compositions along a Ventilation-Perfusion Curve

CONDITION I

Dist. from carina	$\frac{\dot{V}_D}{\dot{V}_T}$	$\dot{V}_T$ ($\propto$N)	$\dot{V}_D$	$\dot{V}_A$	$\dot{Q}$ ($\propto$N)	$\frac{\dot{V}_A}{\dot{Q}}$	R	P_{Ao_2}	P_{Aco_2}
(cm)		cc min.	cc min.	cc min.	cc min.			mm Hg	mm Hg
2.0	0.162	5.2	0.8	4.4	4.3	1.016	0.882	103.2	39.1
2.3	0.168	6.4	1.1	5.3	5.3	1.008	0.878	102.9	39.1
2.6	0.175	9.2	1.6	7.6	7.6	1.000	0.873	102.6	39.2
2.9	0.181	12.0	2.2	9.8	9.9	0.993	0.869	102.3	39.3
3.2	0.188	15.6	2.9	12.7	12.9	0.984	0.864	102.1	39.3
3.5	0.194	20.8	4.0	16.8	17.2	0.977	0.861	101.9	39.4
3.8	0.201	30.0	6.0	24.0	24.8	0.968	0.856	101.6	39.5
4.1	0.208	40.8	8.5	32.3	33.7	0.960	0.852	101.4	39.5
4.4	0.214	68.0	14.6	53.4	56.1	0.953	0.848	101.1	39.6
4.7	0.221	88.0	19.4	68.6	72.6	0.944	0.843	100.9	39.6
5.0	0.227	110.0	25.0	85.0	90.8	0.937	0.839	100.6	39.6
5.3	0.234	139.2	32.6	106.6	114.9	0.928	0.834	100.3	39.7
5.6	0.240	165.2	39.6	125.6	136.3	0.921	0.830	100.1	39.8
5.9	0.247	191.6	47.3	144.3	158.1	0.912	0.826	99.9	39.8
6.2	0.254	211.2	53.6	157.6	174.3	0.904	0.822	99.7	39.9
6.5	0.260	225.6	58.7	166.9	186.2	0.897	0.818	99.4	39.9
6.8	0.267	230.8	61.6	169.2	190.5	0.888	0.813	99.2	39.9
7.1	0.273	230.8	63.0	167.8	190.5	0.881	0.809	98.9	39.9
7.4	0.280	228.0	63.8	164.2	188.2	0.873	0.804	98.6	39.9
7.7	0.286	219.2	62.7	156.5	180.9	0.865	0.800	98.4	40.0
8.0	0.293	208.4	61.1	147.3	172.0	0.857	0.796	98.1	40.1
8.3	0.299	192.8	57.6	135.2	159.1	0.849	0.792	97.8	40.1
8.6	0.306	178.4	54.6	123.8	147.2	0.841	0.788	97.5	40.2
8.9	0.313	164.0	51.3	112.7	135.3	0.833	0.783	97.2	40.3
9.2	0.319	145.6	46.4	99.2	120.2	0.825	0.779	96.8	40.4
9.5	0.326	127.2	41.5	85.7	105.0	0.817	0.774	96.4	40.5
9.8	0.332	110.0	36.5	73.5	90.8	0.810	0.770	96.1	40.6
10.1	0.339	90.4	30.6	59.8	74.6	0.801	0.765	95.7	40.7
10.4	0.345	77.2	26.6	50.6	63.7	0.794	0.762	95.4	40.8
10.7	0.352	70.8	24.9	45.9	58.4	0.785	0.757	95.1	40.8
11.0	0.358	65.6	23.5	42.1	54.1	0.778	0.753	94.8	40.9
11.3	0.365	59.2	21.6	37.6	48.8	0.769	0.748	94.4	41.0
11.6	0.372	53.6	19.9	33.7	44.2	0.761	0.743	94.1	41.0
11.9	0.378	47.2	17.8	29.4	39.0	0.754	0.740	93.8	41.1
12.2	0.385	42.0	16.2	25.8	34.7	0.745	0.735	93.4	41.2
12.5	0.391	35.6	13.9	21.7	29.4	0.738	0.730	93.1	41.3
12.8	0.398	30.0	11.9	18.1	24.8	0.729	0.726	92.8	41.3
13.1	0.404	24.8	10.0	14.8	20.5	0.722	0.722	92.5	41.3
13.4	0.411	15.6	6.4	9.2	12.9	0.714	0.717	92.1	41.3
13.7	0.417	13.2	5.5	7.7	10.9	0.707	0.713	91.8	41.3

TABLE II

CONDITION II

Dist. from carina	$\frac{\dot{V}_D}{\dot{V}_T}$	$\dot{V}_T$ ($\propto$N)	$\dot{V}_D$	$\dot{V}_A$	$\dot{Q}$ ($\propto$N)	$\frac{\dot{V}_A}{\dot{Q}}$	R	P_{Ao_2}
(cm)		$\frac{cc}{min.}$	$\frac{cc}{min.}$	$\frac{cc}{min.}$	$\frac{cc}{min.}$			mm Hg
2.0	0.248	6.7	1.6	5.1	4.3	1.172	0.964	107.3
2.3	0.258	8.2	2.1	6.1	5.3	1.157	0.956	106.9
2.6	0.269	11.8	3.1	8.7	7.6	1.141	0.949	106.6
2.9	0.279	15.4	4.3	11.1	9.9	1.124	0.939	106.1
3.2	0.290	20.1	5.8	14.3	12.9	1.108	0.930	105.8
3.5	0.300	26.8	8.1	18.7	17.2	1.092	0.922	105.3
3.8	0.311	38.6	12.0	26.6	25.8	1.074	0.913	104.9
4.1	0.322	52.5	16.9	35.6	33.7	1.057	0.903	104.5
4.4	0.332	87.5	29.0	58.5	56.1	1.042	0.895	104.1
4.7	0.342	113.3	38.8	74.5	72.6	1.026	0.886	103.4
5.0	0.352	141.6	49.9	91.7	90.8	1.011	0.879	103.0
5.3	0.363	179.2	65.1	114.1	114.9	0.993	0.868	102.4
5.6	0.373	212.6	79.3	133.3	136.3	0.978	0.860	101.9
5.9	0.384	246.6	94.7	151.9	158.1	0.961	0.852	101.3
6.2	0.394	271.8	107.1	164.7	174.3	0.945	0.842	100.7
6.5	0.404	290.4	117.4	173.0	186.2	0.930	0.835	100.4
6.8	0.415	297.0	123.2	173.8	190.5	0.912	0.825	99.8
7.1	0.425	297.0	126.2	170.8	190.5	0.897	0.817	99.2
7.4	0.435	293.4	127.6	165.8	188.2	0.881	0.808	98.8
7.7	0.445	282.1	125.5	156.6	180.9	0.866	0.800	98.3
8.0	0.456	268.2	122.3	145.9	172.0	0.848	0.790	97.5
8.3	0.466	248.1	115.6	132.5	159.1	0.833	0.782	96.9
8.6	0.477	229.6	109.5	120.1	147.2	0.816	0.773	96.4
8.9	0.487	211.1	102.8	108.3	135.3	0.800	0.765	95.7
9.2	0.497	187.4	93.1	94.3	120.2	0.785	0.757	95.0
9.5	0.507	163.7	83.0	80.7	105.0	0.769	0.748	94.4
9.8	0.517	141.6	73.2	68.4	90.8	0.753	0.739	93.7
10.1	0.527	116.3	61.3	55.0	74.6	0.738	0.730	93.1
10.4	0.538	99.4	53.5	45.9	63.7	0.720	0.720	92.3
10.7	0.548	91.1	49.9	41.2	58.4	0.705	0.711	91.7
11.0	0.558	84.4	47.1	37.3	54.1	0.689	0.703	91.1
11.3	0.569	76.2	43.4	32.8	48.8	0.672	0.692	90.1
11.6	0.580	69.0	40.0	29.0	44.2	0.655	0.682	89.1
11.9	0.590	60.8	35.9	24.9	39.0	0.640	0.673	88.2
12.2	0.601	54.0	32.4	21.6	34.7	0.622	0.663	87.3
12.5	0.611	45.8	28.0	17.8	29.4	0.607	0.652	86.2
12.8	0.622	38.6	24.0	14.6	24.8	0.589	0.641	85.1
13.1	0.632	31.9	20.1	11.8	20.5	0.574	0.633	84.3
13.4	0.642	20.1	12.9	7.2	12.9	0.559	0.623	83.4
13.7	0.653	17.0	11.1	5.9	10.9	0.542	0.613	82.4

TABLE III

Instantaneous Concentration of CO_2 in the Gas Expired During a 400 cc Expiration (400 cc/sec. for one second). (Continuous CO_2 production not included in calculations.)

Expired CO_2 concentration	PE_{CO_2} (B = 747 mm Hg)	No. of Alveoli Contributing	Time of Expiration	Volume Expired
%	mm Hg	% Total	(ms)	(cc)
0.01	0.1	0.13	162	65
0.02	0.1	0.30	168	67
0.03	0.2	0.52	175	70
0.05	0.3	0.82	181	72
0.07	0.5	1.21	188	75
0.10	0.6	1.74	194	78
0.14	1.0	2.49	201	80
0.20	1.4	3.51	208	83
0.30	2.1	5.21	214	86
0.42	2.9	7.41	221	88
0.58	4.1	10.16	227	91
0.78	5.4	13.64	234	94
1.02	7.2	17.77	240	96
1.29	9.0	22.56	247	99
1.59	11.1	27.84	254	102
1.91	13.4	33.48	260	104
2.25	15.7	39.25	267	107
2.57	18.0	45.02	273	109
2.90	20.2	50.72	280	112
3.21	22.4	56.20	286	114
3.48	24.3	61.41	293	117
3.78	26.4	66.23	299	120
4.04	28.3	70.69	306	122
4.28	29.9	74.79	313	125
4.48	31.4	78.43	319	128
4.67	32.7	81.61	326	130
4.82	33.8	84.36	332	134
4.96	34.7	86.62	339	136
5.06	35.7	88.56	345	138
5.16	36.1	90.33	352	141
5.26	36.8	91.97	358	143
5.34	37.4	93.44	365	146
5.42	37.9	94.79	372	149
5.49	38.4	95.97	378	151
5.54	38.8	97.02	385	154
5.59	39.1	97.90	391	156
5.64	39.5	98.66	398	159
5.68	39.7	99.28	404	162
5.70	39.9	99.67	411	164
5.71	40.0	100.00	417	167

REFERENCES

1. Rohrer, F. Der Stromungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmässigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. Pflüger's Arch. f. d. ges. Physiol., 162: 225, 1915.

2. Findeisen, W. Über das Absetzen kleiner, in der Luft suspendierter Teilchen in der Menschlichen Lunge bei der Atmung. Pflüger's Arch. f. d. ges. Physiol., 236: 367, 1935.

3. Landahl, H. D. On the Removal of Airborne Droplets by the Human Respiratory Tract. I. The Lung. Bull. Math. Biophys., 12: 43, 1950.

4. Hilding, A. D. and D. Hilding. The Volume of the Bronchial Tree at Various Levels and its Possible Physiologic Significance. Ann. Otol. Rhin. & Laryng., 57: 324, 1948.

5. Rahn, H. and B. Ross This Report.

6. Quenouille, M. H. Associated Measurements, Academic Press, Inc., New York, 1952.

7. Veuilleumier, P. Über eine Methode zur Messung des intraalveolaren Druckes und der Strömungswiderstande in den Atemwegen des Menschen. Ztschr. f. klin. Med., 143: 698, 1944.

8. Otis, A. B., W. O. Fenn and H. Rahn Mechanics of Breathing in Man J. App. Physiol. 2: 592, 1950.

9. Rahn, H. A Concept of Mean Alveolar Air and the Ventilation-Bloodflow Relationships During Pulmonary Gas Exchange. Am. J. Physiol., 158: 21, 1949.

10. Briscoe, W. A., R. E. Forster and J. H. Comroe. Alveolar Ventilation at Very Low Tidal Volumes. J. Appl. Physiol., 7: 27, 1954.

11. DuBois, A. B., R. C. Fowler, A. Soffer and W. O. Fenn. Alveolar CO_2 Measured by Expiration into the Rapid Infrared Gas Analyzer. J. App. Physiol., 4: 526, 1952.

12. Otis, A. B. Personal Communication.

THE PHYSICAL DYNAMICS OF THE COUGH MECHANISM

by

B. B. Ross, R. Gramiak,* and H. Rahn

The cough is a singularly interesting respiratory movement in that the violent changes in intrapleural pressure and the generation of high rates of air flow during the expiratory phase are accompanied by marked changes in the lumens of the trachea and bronchi of the lungs. The changes in the bronchi have been observed both bronchoscopically by Jackson (1) and radiographically by DiRienzo (2), and must be responsible for the occurrence of the changes in resistance to flow observed by Whittenberger and Mead (3). Stutz (4) has suggested in refutation of DiRienzo's hypothesis of bronchial peristalsis during coughing (2) that the pressures developed during the cough cause the changes in lumenal size. However, to our knowledge, no attempt has been made to demonstrate the correlation between lumen size and the forces exerted during a cough. It is the purpose of this investigation to show the relationship between tracheobronchial movements and physical changes in rate of air flow, intrapleural pressure, and resistance to flow which occur during a cough and to investigate the mechanism responsible for the tracheobronchial motion.

METHODS

Three separate studies were made. In the first, recordings of esophageal pressure and air flow rate were taken from a normal subject simultaneously with a high speed cinefluorographic record of the changes in apparent diameter of the trachea during a series of coughs. In the second study, a series of tracings were made of the projections of several X-ray motion pictures of coughs taken from patients having lipiodol in the lung airways. Measurements of the changes in apparent bronchial and tracheal diameters were made along various points along the upper bronchial tree in an effort to reveal the presence or absence of wavelike motion. In the third study, a section of human trachea was suspended in a bottle which could be pressurized. The trachea was cannulated at one end and communicated to the outside while the other end was plugged. The changes in cross section of the tracheal lumen could thus be easily visualized through the cannula as they would be through a bronchoscope and allowed one to trace the area of the lumen on a glass grid while the specimen was subjected to various positive pressures applied in the bottle.

---

* Department of Radiology.

In the first study, the pressure changes in the esophagus were detected with a Hathaway blood pressure gage and amplifier system, using an esophageal balloon catheter in the manner described by Mead and Whittenberger (5). The rate of air flow was recorded using a sensitive strain gage system and a pneumotachometer. Continuous records of pressure and flow rate were obtained with a Hathaway oscillograph. The high-speed X-ray motion picture (6) exposed 60 frames per second of the chest and was synchronized with the pressure-flow record by exposing the latter to the light from a flashbulb placed inside the oscillograph and ignited by the current used to operate the X-ray tube. With this technique, the pressure-flow record was synchronized to within two frames of the motion picture (< 0.03 seconds).

RESULTS

1. Simultaneous recording of esophageal pressure, air flow and tracheal shadow.

The subject had a remarkably constant cough pattern in terms of timing and pressure-flow relationships. The inspiratory phase lasted about 0.65 seconds and resulted in an intake of about 2.5 liters of air. Following a short period of glottal closure (about 0.2 seconds), approximately the same volume was expelled within 0.5 seconds. During inspiration, the change in intrapleural pressure measured in the esophagus rarely exceeded -20 mm Hg, but during expiration, the change reached a level of from +100 to 140 mm Hg. (The use of the esophageal balloon to measure intrapleural pressure allows the recording of only the dynamic component of that pressure, namely, the change in lung tension and the pressures required to move air and tissue during the respiratory cycle. During a cough, the pressures generated are so great that the change in lung tension is only a small part of the total change in intrapleural pressure. Failing to take the change in lung tension into account results in an error of less than five percent in the pressure determinations made during the expiratory phase. During inspiration the magnitude of this error would be much greater but, for our purposes, is not sufficiently important to make necessary the extensive calculations involved in the required corrections.)

The maximum inspiratory flow rates were 3-4 liters per second and the maximum expiratory rates were 5-6.5 liters per second. The changes in pressure and flow during the cough are shown in Figure 1. These curves were constructed from measurements of the records taken simultaneously with the X-ray motion picture. Unfortunately, the peak expiratory flow rates were not recorded due to a shift of the film in the recording chamber of the oscillograph. This shift caused the recording to run off the edge of the film paper. The missing portion of the flow curve was completed by referring to a complete record made just prior to this one. The calculations of resistance for the incomplete record were made assuming that the edge of the film corresponded to a minimal flow rate. These calculated resistances are shown below the pressure and flow records. For comparison, the calculated resistances from a complete record are also shown. The difference

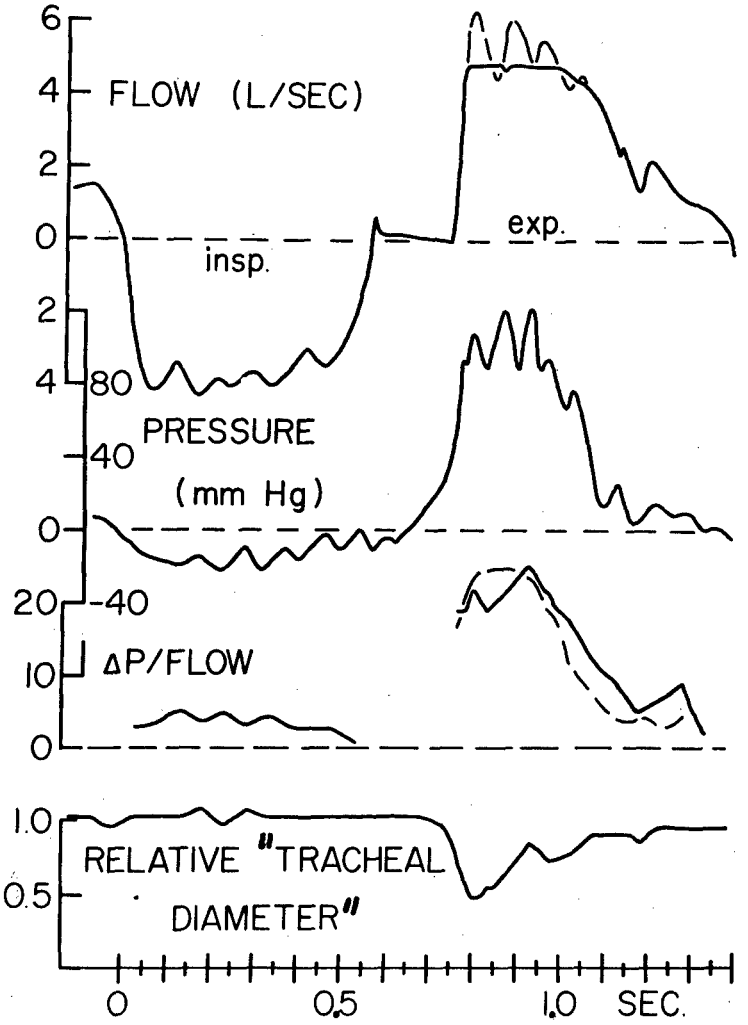


Figure 1

Measurements taken during a cough and the previous inspiration of a healthy male subject. From top to bottom: volume flow of air; esophageal pressure; resistance to air flow - Δ P/Flow; and the relative width of the tracheal shadow obtained from a cinefluorographic film. The dotted lines of graph No. 1 and 3 are explained in text.

between the two curves is not sufficient to invalidate the experiment, although the complete record shows a better example of the sequential changes in resistance during the cough.

The X-ray motion picture was examined at intervals of three frames (0.05 seconds) starting at the frame corresponding to the time of the beginning of inspiration as determined from the pneumotachogram. The projected outline of the trachea and main bronchi was traced on paper and the "apparent" diameter of the trachea was measured at a constant distance from the carina. Taking the relative sizes of the projected picture and the actual fluoroscopic projection into account, this apparent diameter measurement was made at an approximate distance of 15 cm from the carina. The tracings made of the projections of certain frames is shown in Figure 2. The time lapse from the beginning of inspiration is indicated for each frame shown. When the changes in apparent diameter were relatively abrupt, measurements were taken from the projection of every frame. These measurements were then converted to a relative scale and a curve showing the change in apparent diameter with time was constructed. This curve is also shown in Figure 1.

The synchronous nature of the changes in intrapleural pressure and apparent tracheal diameter may be further emphasized by constructing a graph of the simultaneous values of these two variables as in Figure 3. It would seem that there would be a poor correlation between these changes if they were independent of each other. The fact that there does seem to be a good correlation implies that the two variables are related and that one of them may be the cause of the other change. Simultaneous changes in resistance and intrapleural pressure also show a good correlation during expiration when the resistance changes are large.

2. Measurements of tracheal and bronchial apparent diameters.

The measurements taken at several points along the bronchial pathways of the lung provided no conclusive evidence that the reduction in diameters of the bronchi followed a sequential pattern as would be expected if a wave-like motion of the bronchial walls occurred (2). As far as it could be determined from the records analyzed, the reduction in apparent diameter occurred simultaneously in all the bronchi measured and along the whole span of the trachea included in the measurements. The return to their original diameters was also apparently simultaneous for all the bronchi and the trachea.

All of these X-ray motion pictures were taken on patients with lipiodol in the airways. The film speed was 30 frames per second and the changes in apparent diameter were relatively abrupt from frame to frame. It is possible that these records were taken at such a speed that a wave progression would not be detected by measuring the differences between successive frames. This possibility, however, is not likely, since the changes in diameter from maximum to minimum occurred over a time span in which at least three frames were exposed (0.1 second)

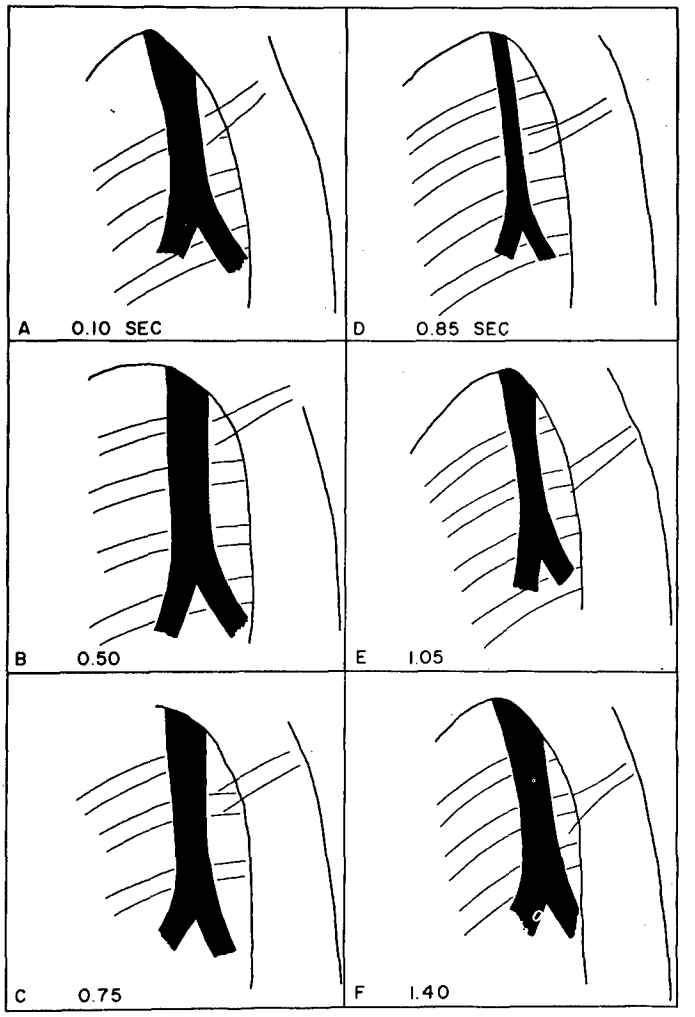


Figure 2

Changes in width of tracheal shadow before, A, B, and C, and during the cough D, E, and F. The exact times are indicated and correspond to the abscissae in Figure 1.

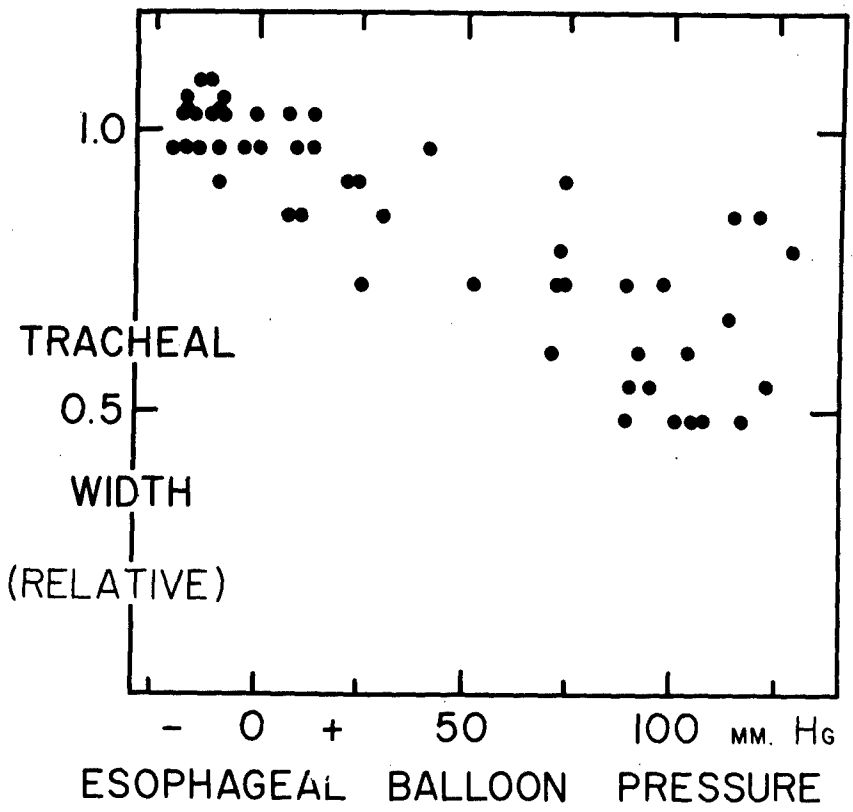


Figure 3

Relative width of tracheal shadow plotted against simultaneous esophageal balloon pressure during a cough.

and the return to original diameters occurred during a period of about 0.3 seconds in which at least 10 frames were exposed. We were, therefore, led to the conclusion that there is no wave-like progression of diameter changes, or peristalsis (2), in either direction along the bronchial tree.

3. The effect of externally applied pressure on the cross section area of the tracheal lumen

Figure 4 shows the relative changes in tracheal cross section area brought about by applying various pressures to the outer wall of the trachea. The appearance of the tracheal lumen is drawn on the right ordinate. Occlusion of this autopsy specimen was virtually complete when the applied pressure was 50-60 cm H_2O. As shown by Mead and Whittenberger (5), the resistance to air flow through

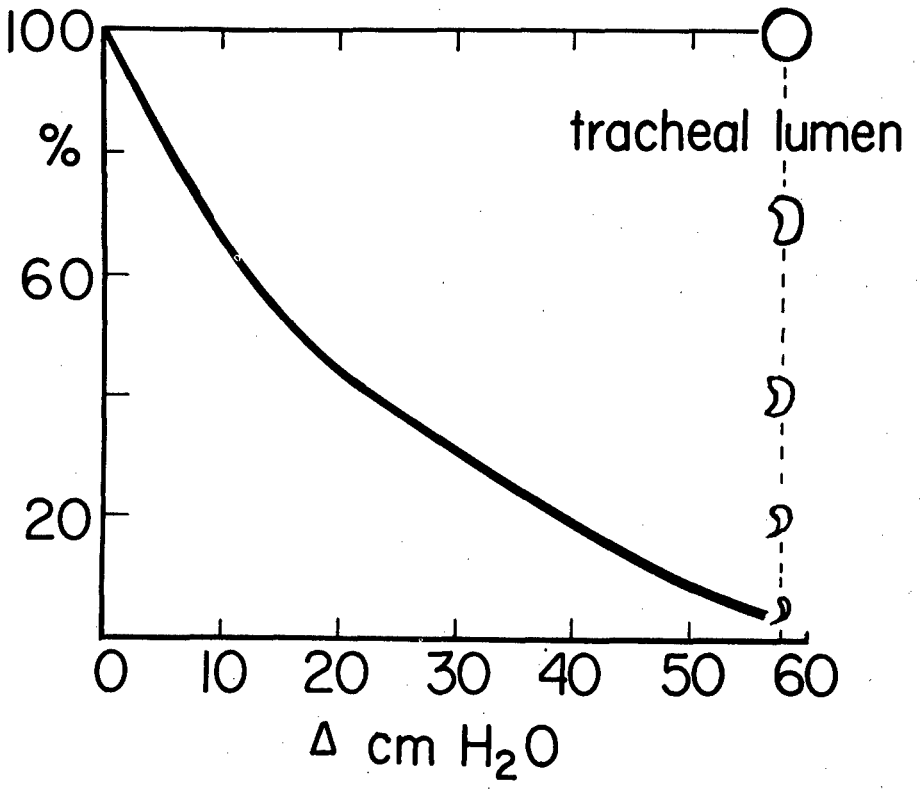


Figure 4

Percent of initial cross section of the lumen of an isolated human trachea (left ordinate) and actual lumen as observed (right ordinate) while the trachea was subjected to various differential pressures.

a section of trachea compressed in this manner increases markedly as the applied pressure is increased. Concomitant with this increased resistance to flow, there must also be a great increase in linear velocity for a given volume flow rate when the external pressure is increased. If the pressure gradient across the wall of the trachea is 40 cm H_2O, then from our figures, the linear velocity would be at least 5 times greater than the linear velocity through an unstressed section of trachea for the same volume flow rate. Since the kinetic energy of a moving air stream increases as the square of the velocity, there would be a force available to move objects in the compressed trachea which is 25 times greater than the force available in the uncompressed trachea. It would seem that the action of the high expiratory intrapleural pressures on the trachea and bronchi of the lung is as important to the objective of the cough as is the generation of high volume flow rates.

DISCUSSION

The evidence presented here does not prove that the generation of high intrapleural pressure is the only mechanism for the changes of the tracheobronchial diameters which occur during a cough. However, there is at least one other analogous situation which could give additional evidence that intrapleural pressure has an effect on the lumen size of the trachea and bronchi — explosive decompression. It has been shown that intrapleural pressure reaches a level of +100 mm Hg or more, relative to ambient pressure, during explosive decompression from 760 to 30 mm Hg ambient pressure (7). During this period, resistance to air flow in the lung airways is expected to change in a manner similar to that produced in coughing. However, a search of the literature yielded no information which could be used to determine flow resistance during explosive decompression.

The mechanical cough apparatus designed by Barach, et al (8) is essentially an explosive decompression chamber which produces sudden pressure gradients during the decompression period. Subjects placed in this device may be exposed to a sudden relative mouth-chest pressure gradient of about 40 mm Hg, causing a momentary expiration rate of upwards of 6 liters per second. This relatively low pressure gradient, compared to the actual pressure developed during a voluntary cough, taken together with the flow rates achieved suggests that the resistance to flow is not affected as much with the machine as it is during voluntary coughing. One may infer that there is not much change in the diameters of the airways of the lung and, consequently, not much increase in linear velocity, compared to a normal cough. While not intending to deny the usefulness of an artificial cough machine, it should be pointed out that the generation of high linear velocities is equally as important as the generation of high volume flow rates.

Lastly it is of interest to estimate the linear air velocities which may be achieved in the human trachea. Adult males have a diameter of 14-20 mm and females 12-16 mm. If we choose a value of 14 mm, we have a cross sectional area of 1.5 cm^2. During a normal expiration peak flow rates of 1 l/sec may be obtained. Thus the linear velocity in this trachea at this peak flow must be equal to 1000 $cm^3/sec/1.5cm^2$ = 6.65 meters/sec. (equivalent to a 15 miles/hour wind). During cough volume flow rates of 7 and more liters/sec. have been measured and if the tracheal diameter remains constant with a 7 l/sec. flow, the linear velocity will reach 7 x 6.65 or 46.5 meters/sec (equivalent to a hurricane velocity of 100 miles/hour).

If in addition we have a narrowing of the tracheal cross sectional diameter above the carina as described and these velocities are maintained during this instant of collapse, then the linear velocities must increase as an inverse function of the cross sectional area. If this area is narrowed to 1/6 the normal size, then a 7 liter/sec. flow will approach sonic speed in this particular region of the trachea.

CONCLUSIONS

The physical mechanism of the cough involves the combined effect of high intrapleural pressures on the expiratory volume flow rate and the diameters of the airways of the lungs, creating a high linear velocity air stream with a high kinetic energy available for the acceleration and displacement of any object placed in its path. It is suggested that the reduction in lumen size differentiates a cough from a forceful expiration in which flow rates equivalent to those of a cough may be easily achieved. The mechanism for the induction of these diameter changes must be the glottal closure preceding the expiratory phase of the cough which permits the generation of a high initial expiratory pressure and, once the glottis is opened, a high pressure gradient across the walls of the trachea and bronchi of the lung.

The authors are greatly indebted to Dr. Howard G. Dayman for first bringing to our attention the changes in the tracheal shadow which may be visualized fluoroscopically during a cough. It was his demonstration of this event that led us to undertake this investigation. The authors wish also to express their appreciation to Mr. S. A. Weinberg and Mr. Carl Sutter for their technical assistance in the taking of the X-ray motion pictures described above.

SUMMARY

The changes in intrapleural pressure and rate of air flow occurring during a cough were recorded simultaneously with the taking of a high-speed X-ray motion picture of the chest which permitted the visualization of the trachea. Analysis of these records showed that the changes in apparent diameter of the trachea were synchronous with the changes in intrapleural pressure, once the glottis had opened and expiratory flow had started. Analysis of several X-ray motion pictures of the bronchial tree, made visible with lipiodol, revealed no evidence of a wave-like progression of diameter changes along the bronchial tree. The effect of pressure applied to the outer wall of a section of human trachea on the cross section of the tracheal lumen was investigated. It was found that a trans-wall pressure gradient of 40 cm H_2O reduced the cross section to about 1/5 its original value. The effect of this change in cross section upon the linear velocity of the moving air stream is discussed.

REFERENCES

1. Jackson, C. J. Am. Med. A. 79: 1399, 1922.
2. Di Rienzo, S. Fortschr. Röntgenstrahlen 78: 1, 1953.
3. Whittenberger, J. L. and J. Mead Trans. Nat. Tuberc. Ass. 48: 414, 1952.
4. Stutz, E. Fortschr. Röntgenstrahlen 79: 187, 1953.
5. Mead, J. and J. L. Whittenberger J. Appl. Physiol. 5: 779, 1953.

6. Weinberg, S. A., J. S. Watson, Jr. and G. H. Ramsey Jour. Soc. Motion Pict. and Televis. Eng. 59: 577, 1952.

7. Vail, E. G. Jour. Aviat. Med. 23: 577, 1952.

8. Barach, A. L., G. J. Beck, H. A. Bickerman and H. E. Seanor Jour. Appl. Physiol. 5: 85, 1952.

EXPERIMENTAL FUNCTIONAL SEPARATION OF DOG LUNGS

by

W. Andrew Dale and Hermann Rahn

The large cross-sectional area of the tracheo-bronchial tree of the dog enables various endotracheal tubes or cannulae to be passed relatively easily into the main or smaller bronchi, either through the larynx or via tracheotomy. However, complete airway separation of the two lungs of dogs is difficult because of the short distance between the carina and upper lobe bronchi. This problem is illustrated by Figure 1 which shows the anatomic relationships of the trachea, carina, main and lobar bronchi of the dog. The drawing consists of the average dimensions of 12 dogs whose trachea and lungs were removed and dried under continuous air pressure, thereby avoiding the shrinkage which ordinarily occurs with drying. Fourteen different dimensions were measured in each preparation and the average measurements used to draw Figure 1.

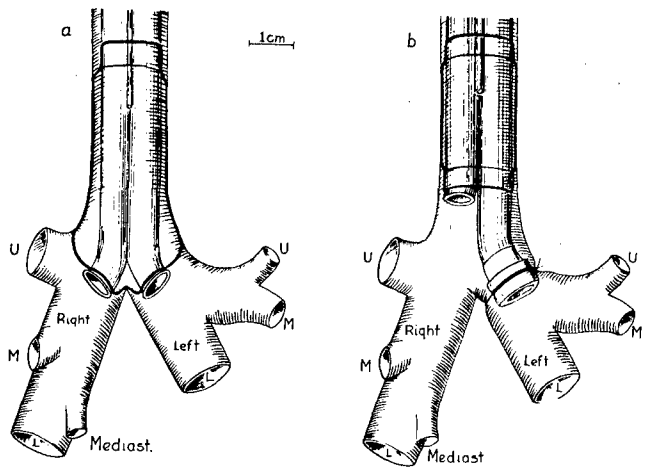


Figure 1

Scale drawing of trachea and bronchi from 14 separate measurements in each of 12 dogs. In a the Wright divider is in place, while in b the bilumen plastic catheter is tied in. Upper, middle and lower lobe bronchi are labelled respectively, U, M, and L. In addition there is the mediastinal lobe bronchus on the right side.

It is to be particularly noted that there is an extremely short distance between the carinal bifurcation and the origin of the lobar bronchi to the upper lobes. The left upper lobe bronchus originates one centimeter or less beyond the carina, while the right upper lobe bronchus originates almost opposite the carina. It is evident that effective lung separation can only be achieved by: (1) a device separating the air streams at the carina, or (2) by cannulation of the left main bronchus. The ordinary double lumen catheter used for human bronchospirometry is not satisfactory in the dog because the left main bronchus is too short for proper seating of the inflated balloon.

Several methods for lung separation have been used in this laboratory, and this experience has led to development of the devices used at present. A summary of experience with these devices follows, with a brief discussion of the advantage and disadvantages of each in our hands.

Wright tracheal divider:

This bilumen metal tube (Figure 2a) was prepared here according to the specifications of Dr. George Wright of Saranac, New York. It essentially consists of two thin-walled brass tubes soldered together with distal ends flared so that these ends just enter the main bronchi beyond the carina. A smaller metal tube soldered into the groove between the two main tubes conducts air pressure to a carefully molded balloon which encircles the distal end of the apparatus. This balloon is designed to press tightly against the tracheal walls as well as the carina, thus separating the gas flow of the lungs. The divider is maintained in position by rubber bands stretched between the proximal side vent tubes and the animal's canine teeth to force the tubes and balloon continually caudad to insure a tight seal. The entire divider is therefore passed through the larynx and impinges upon the carina, obviating tracheotomy.

Figure 1a shows this divider in place in the scale drawing of the average dog. It may be seen that the right upper lobe bronchus lies just beyond the balloon, even proximal to the metal tip, so that it may become obstructed. This and slipping of the tight carinal seal necessitate careful adjustment of position of the divider initially as well as proper maintenance of position during an experimental procedure. It is important to obtain proper oxygen consumption values for each lung prior to and after any experiment which assumes the divider is properly in place.

Further disadvantages include difficulty in making and properly fitting the balloon, frequent balloon leaks and the necessity to replace the balloon after a few experiments. However, with experience it was possible to place the divider rapidly and maintain separation of the lungs so long as there was no large pressure difference between the lungs. In certain experiments (1,2) the Wright tracheal divider has been very satisfactory and is still used routinely in this laboratory for certain types of experiments. It has the advantage that animals

are not harmed by the procedure and can be used as often as twice weekly. Analysis of the relative oxygen consumption and ventilation of the two lungs using this device indicated close correlation with the fractions of the weights of the two lungs, namely: 60% for the right, and 40% for the left lung.

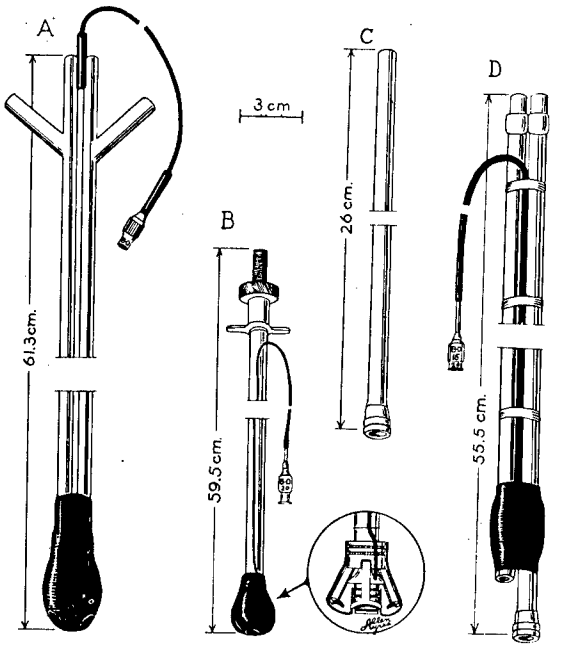


Figure 2

Devices used to separate lungs: a - Wright tracheal divider; b - Van Allen dilatable endobronchial cannula; c - transthoracically placed endobronchial cannula; d - bilumen plastic cannula.

Van Allen dilatable cannula:

Attempting to use a method which would be gas tight under pressure, a cannula was made according to the design of Van Allen (3). Figure 2b shows the apparatus constructed according to that design. The long brass tube has umbrella-like vanes at its distal end which may be expanded within the bronchus by means of a screw mechanism actuated from the proximal end protruding from the animal's mouth. It was difficult to place this and maintain it within the left main bronchus, although this could be done in a lobar bronchus. Addition of an inflatable balloon did not serve to anchor the device properly in the main bronchus, and with continued failure at this site, attempts were ended.

Transthoracically placed endobronchial cannula:

A small series of animals were prepared by tying a large lumen plastic cannula (Figure 2c) within the left main bronchus after severing it from the trachea within the chest and closing the tracheal defect. With care the trachea could be made air tight. The cannula was then led out the chest wall, in various positions,

both anterior to and posterior to the aorta or its arch. Invariably the cannula tip impinged against the left pulmonary artery, either entirely or partially blocking its blood flow (determined either by inspection or by oxygen consumption study). The device was therefore discarded.

Bilumen plastic endotracheal cannula tied within left main bronchus:

This method was eventually devised and in our experience surpassed previous ones in most respects. The cannula was easily made of two Tygon plastic tubes whose distal ends were bound together with adhesive tape over a Lucite form lying between. A metal tip protruded from within the end of the longer side (Figure 2d) with a groove to permit a ligature to lie in place. A balloon about the distal end could be inflated by means of pressure via a small polyethylene tube. Figure 1b shows this device in place in the scale drawing of the average dog, the longer tube projecting into the left main bronchus where it is tied securely, the shorter tube lying in the trachea and serving the right lung.

This bilumen plastic cannula was placed through a tracheotomy and the balloon inflated to allow intermittent pressure during the ensuing thoracotomy. The animal was then placed left side up and the left thorax entered through a high intercostal incision. After opening the mediastinal pleura anterior to the aorta and posterior to the left vagus nerve, the left main bronchus was bluntly dissected up out of the mediastinum and the tube pushed down into it. A heavy silk suture was tied about the metal tip lying in the left main bronchus to retain the tube exactly as placed. Prior to closure of the chest the left tube was temporarily disconnected from the pressure source to ascertain that the upper lobe bronchus was not obstructed and that the lobe would collapse as pressure was removed. Occasionally the tube was changed to a more proximal position when this occurred. The chest was then closed in layers about a catheter in the pleural space which was used to remove pneumothorax air at conclusion.

After some experience with this method the preparation could be made in an average of 30 minutes, often in less time. The animals survived in good condition under anesthesia until sacrifice as long as eight hours later. There was no instance of mucus plugging of the tubes. Once the tube slipped out of the ligature, and was replaced successfully by reopening the chest. Once in place the animals could be moved or turned as desired with assurance that the lungs were separated not only from each other but also from the outer air. In 12 instances data were obtained for the right and left lung tidal volumes and oxygen consumptions. The averages are indicated in Table 1, with comparative figures obtained by the Wright tracheal divider method in 19 animals by Rahn and Bahnson (2). Both series were obtained in this laboratory and our evaluation indicates that they are comparable within statistical limits for small series.

The chief disadvantage of the bilumen plastic tube method is the necessity for sacrifice at termination of experiment, since non-sterile conditions were

TABLE 1

FRACTIONS OF TOTAL TIDAL VENTILATION AND TOTAL O_2 CONSUMPTIONS OF THE RIGHT LUNGS OF DOGS USING TWO LUNG SEPARATING DEVICES

Series	Number	% tidal right	% O_2 cons. right
Bilumen plastic cannula	12	50.3	56.1
Wright divider (Rahn, Bahnson) (2)	19	57.5	58.4

always used. With additional time and care it is thought that the animals would survive placement and later removal. A survey of the relative costs indicated sacrifice to be as economical when after care of a surviving animal was considered.

CONCLUSIONS

1. Experience with methods of functional separation of dogs lungs is summarized. A bilumen plastic cannula with one tube tied within the left main bronchus and the other lying in the trachea is at present our method of choice for lung separation experiments where differential pressures are to be maintained between two lungs. This method allows easy preparation, effective seal and division of air-ways, and allows observations in any position for many hours without mucus obstruction. It is the only one of the devices available which allows one lung to be maintained at very high positive or negative pressures in relation to the other.
2. The ventilation and oxygen consumption fractions of the two lungs by this method compares favorably with those previously obtained by other methods.
3. A scale drawing of the tracheo-bronchial measurements of 12 dogs is presented, indicating the large lumen but small interbifurcation lengths of the dog bronchi. These anatomical features are important considerations in the design of cannulas for dog lungs.

REFERENCES

1. Dale, W. A., Rahn, H. "Rate of gas absorption during atelectasis," Am. Jour. Physiol. 170: 606, 1952.

2. Rahn, H., Bahnson, H. T. "Effect of unilateral hypoxia on gas exchange and calculated pulmonary blood flow in each lung," Jour. Appl. Physiol. 6: 105, 1953.

3. Van Allen, C. M. "A dilatable bronchial catheter," Yale Jour. Biol. and Med. 2: 295, 1930.

VENTILATION OF THE OPEN LUNG DURING UNILATERAL EXPERIMENTAL ATELECTASIS

by

W. Andrew Dale and Hermann Rahn

Previous studies in this laboratory have reported our findings concerning the principles governing gas absorption from the blocked off lung in the early phase of atelectasis (1), the evolution of more satisfactory methods for separation of dog lungs to allow individual lung function experiments (2), and the effects of atelectasis of one lung upon the volume and the pressure-volume relationship of the contralateral lung (3).

The present study was done to evaluate the causes which precipitate rapid changes in the frequency of breathing and contralateral tidal volume increase whenever unilateral atelectasis is produced experimentally. Similar changes may be observed in humans with sudden atelectasis (particularly when this is of major degree).

EXPERIMENTAL DESIGN

Directly following a major degree of atelectasis such as that of an entire lung, the pulmonary tissue available for gas exchange is markedly decreased. One would assume that adjustments in ventilation would follow, probably in the direction of increased ventilation of the open lung. Observations of experimental animals indicates that such does occur and can be measured in terms of increased rate of respiration, increased tidal volume and a larger minute volume of the open lung. In fact the minute volume of the one open lung now becomes larger than the total minute volume of both lungs prior to atelectasis.

This increase in total pulmonary ventilation might be attributed to various mechanisms acting alone or together. First, previous experimental data have indicated an immediate contralateral tidal volume increase following unilateral atelectasis, due to the "mechanical effect" of blocking one bronchus (3). The mechanical increase does not, however, explain all the increase in contralateral tidal volume that occurs. It has been apparent that besides this immediate change which follows upon bronchial occlusion, that there is a slow increase in total volume to approximately twice that of the control level. Thus, all of the tidal increase is not due to the "mechanical effect." Further, the mechanical effect cannot explain the increase in rate of respiration.

Two other factors may be considered, namely, reflex changes probably mediated over the vagus nerves and blood chemical changes acting on the respiratory center. Experiments were therefore designed to test the effect of unilateral atelectasis with vagi intact and blocked (or cut), and others to learn the results of atelectasis when the blood flow through the pulmonary artery bed in the atelectatic lung (resulting in a shunt of high CO_2 and low O_2 blood from venous to arterial circulation) was blocked.

It was also thought that the increased work of ventilation (respiratory and cardiac components) during atelectasis might be measured in terms of total oxygen consumption. This was therefore measured before, during, and after unilateral atelectasis.

METHODS

Mongrel dogs were anesthetized with intravenous nembutal (.026 gram/kilogram) mixed with .0003 gram atropine sulfate, with subsequent injections given as necessary to maintain the proper plane of anesthesia. Non-sterile operative technic was used and each animal was sacrificed at the conclusion of the experiment. Each animal was prepared for individual lung study by a method described previously (2). Briefly this consisted of tying the long end of a double lumen endotracheal plastic tube into the left main bronchus during open thoracotomy, so that this lumen of the tube carried air to the left lung, while the other lumen lay in the trachea above and furnished ventilation to the right lung. After thoracotomy closure, pneumothorax was aspirated by a tube which was then removed. Further preparation varied with the plan of the individual experiment.

(1) Vagus nerve block was obtained when desired by cooling both nerves after their cervical exposure. Each vagus nerve was dissected gently and laid in a copper tube coil through which ice water could be pumped from a reservoir as desired. Rapid cooling and resultant nerve block occurred within a minute as evidenced by loss of Hering-Breuer reflex when the chest was compressed, or by the absence of respiratory changes when the nerves were cut while being cooled. Rapid reversal of cooling was effected by passage of water at 40° C through the system.

(2) pH determinations of the arterial blood were obtained from continuous flow through a blood electrode assembly (Beckman model 290-31) immersed in a constant temperature water bath at 38° C. The electrode was connected on one side by a polyethylene catheter to the femoral artery and on the other side to the femoral vein. The animal thus pumped blood continuously through the electrode chamber immersed in the warm bath, clotting being prevented by heparinization (200 milligram initial dose plus 100 milligrams every two hours). Prior to each experiment the pH meter was standardized against a pH 7.00 standard at 38° C. pH sensitivity was attested by the minute galvanometer needle fluctuations which

occurred with each respiratory cycle. By this method pH data were obtained easily for as long as five hours and in these experiments were recorded every two minutes.

(3) Unilateral pulmonary arterial blockade was obtained in one of two ways. Initially an indwelling catheter with attached balloon connected to a side lumen was passed through the jugular vein, right heart and left in place in the left main pulmonary artery (5). Position was checked fluoroscopically. By inflating the balloon the left pulmonary artery could be blocked. Since there was possibility that the balloon might slip down into a distal branch of the pulmonary artery, a second method was used later, by which the whole artery could definitely be blocked and released. A heavy silk tie was placed loosely about the left main pulmonary artery and tied into the posterior thoracic wall tissue. Several long silk ligatures were then passed about the artery and led out the chest wall. When pulmonary artery occlusion was desired, a long ligature was pulled up tight and clamped outside the chest wall. Release was accomplished by cutting and pulling out the suture. Subsequent arterial block was effected by repeating this maneuver with a second long suture and so forth.

(4) Atelectasis was obtained either by blocking the left lung cannula or by rapidly aspirating all gas from the left main bronchus cannula lumen and clamping the end. At conclusion further unsuccessful attempts to remove gas insured that no leak had occurred.

(5) Standard metabolism machines containing CO_2 absorber could be connected to either one or both lumens of the bronchial cannula to allow measurement of O_2 absorption, rate, tidal volumes, and minute volumes.

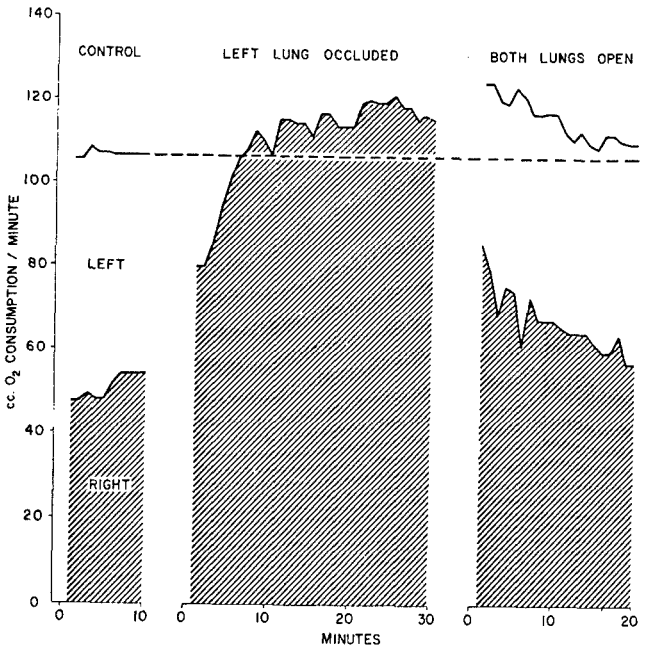
RESULTS

Fifty-eight experiments were done on 40 animals. The results may be divided into two groups.

(1) Complete O_2 consumption data were obtained during the development of atelectasis in nine experiments on 7 animals. Initially both lungs were connected to spirometers and the O_2 consumption of each lung measured over a minimum period of 10 minutes. The final 10-minute period before initiation of atelectasis served as a control. Left lung atelectasis was begun by bronchial occlusion and right lung O_2 consumption determined for a minimum period of 30 minutes. Left lung atelectasis was then reversed simply by removing the clamp from the left main bronchial cannula and allowing the left lung to resume function and to reaerate. O_2 consumption in both lungs was measured then for a minimum period of 20 minutes. Figure 1 illustrates the averaged findings. During the latter part of the control period the right lung O_2 consumption was about 50% of the total. When left atelectasis was initiated by clamping the left lung cannula, the right O_2

Figure 1

Average data of nine experiments on 7 dogs showing the O_2 consumption of the right lung before, during, and after total airway occlusion of the left lung. Shaded portion indicates right O_2 consumption and clear portion between lines that of left lung. Dotted line shows projection of control total O_2 consumption.



consumption as indicated by the graph rapidly increased about 50% of its control value, then over a six-minute period reached the control total O_2 consumption value and thereafter exceeded this by about 6%.

When the left lung was allowed to re-expand, the right O_2 consumption rapidly at first and more slowly later returned to approximately pre-atelectasis values. The total O_2 consumption likewise returned to the control value which is indicated by the broken line on the graph.

(2) Forty-nine experiments on 33 animals were done to evaluate the vagal reflex and blood chemical control of respiration during unilateral atelectasis. The summary of these data (averaged) are indicated in Figure 3 as five types of experiments. The respiratory rates and tidal volumes of the right (open) lung as well as the total (calculated) ventilation and pH values were measured and are shown as an average value during one set of conditions contrasted with the average value when a new factor was added. Since in many cases the differences in measurements between two experimental procedures were not statistically significant only the average values have been given. These indicate qualitatively the trends as observed.

DISCUSSION

O_2 consumption of the open lung during unilateral atelectasis:

Immediately upon left lung cannula occlusion (and initiation of atelectasis in the left lung) the right lung O_2 consumption sharply increased. At the end of approximately six minutes the right lung O_2 consumption reached a level equal to the previous control total O_2 consumption. During the initial period of rapid increase in the right lung value, the remaining difference between right lung and previous total level is assumed to equal about half the left lung O_2 consumption, which rapidly declines toward zero.

Figure 2 diagrammatically represents an enlarged portion of Figure 1, whose lower portion has been omitted. The shaded region represents the average oxygen consumption measured by the spirometer connected to the right lung before and

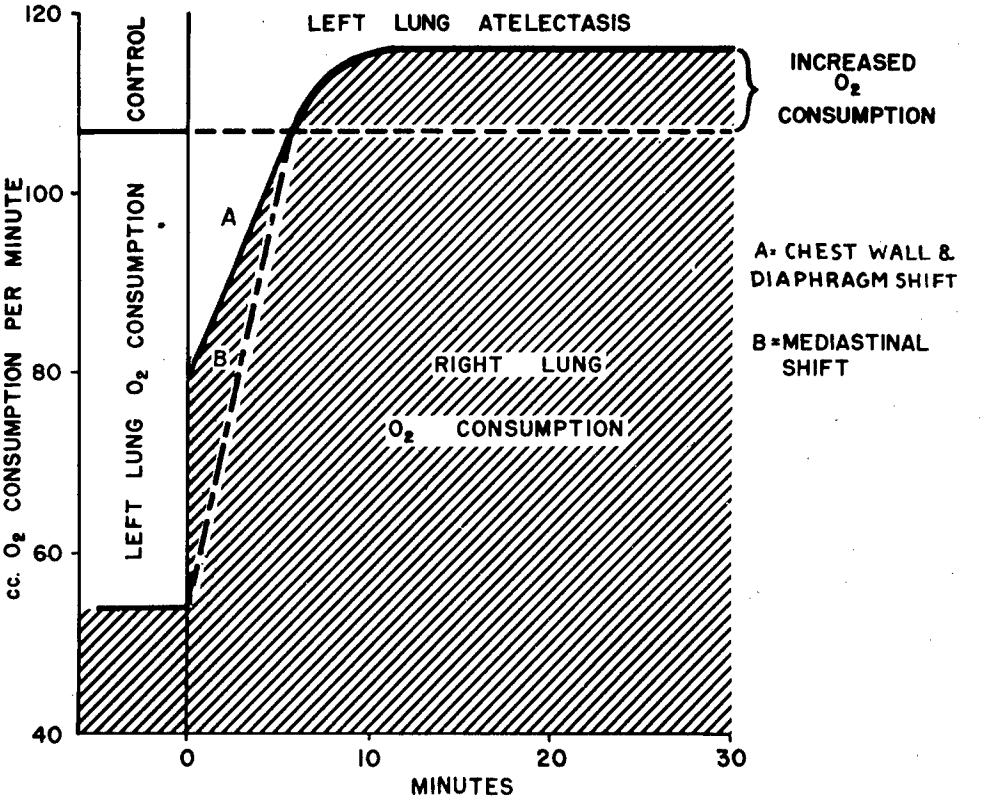


Figure 2

Diagrammatic form of Figure 1 showing O_2 consumption study before, during, and after left lung occlusion. See text.

after atelectasis was induced on the left side by clamping the inlet tube. The horizontal broken line indicates the total oxygen consumption during the control period. The unshaded area represents the oxygen uptake of the left lung before occlusion. It is about 50 cc/min. Immediately upon occlusion it is apparently reduced to 25 cc/min. and 6 minutes later is reduced to zero as indicated by area A.

However, analysis of the events accompanying lung collapse under these conditions provides a different picture and indicates that the spirometer attached to the open right lung is now not only measuring right lung O_2 consumption but also is indicating about 50% of left lung O_2 consumption. It has been shown elsewhere (3) that when gas is removed from the left lung by aspiration that about 50% of the volume decrease can be accounted for by increase in open right lung volume due to a mediastinal shift. It has been assumed that the remaining 50% volume change is accounted for by inward movement of the chest wall and cephalad movement of the diaphragm. Figure 4 illustrates these shifts diagrammatically.

Therefore the sudden apparent increase of 25 cc/min. right lung O_2 consumption in Figure 2 represents not only the true right O_2 consumption, but 50% of the left O_2 consumption (since this continues until O_2 is completely absorbed from the left lung.) Area B in Figure 2 thus represents overdistension of right lung and mediastinal shift, while area A is the chest wall (including diaphragm) shift, and A and B are approximately equal. The ascending broken line of Figure 2 thus marks the true right lung O_2 consumption. At 6 minutes after left lung airway occlusion the right lung carries the total O_2 consumption and the left lung must be collapsed. This is ample time if one assumes that the blood flow to the collapsing lung is maintained. The functional resting volume of our dogs is approximately 150 cc and the left lung circulation normally removed about 50 cc/min. in our control run.

Figure 2 also allows one to compute the total volume of the left lung from areas A and B. Initially the O_2 uptake was 50 cc/min. and was reduced to zero at 6 minutes after occlusion. The integration of this triangle A and B is (50 cc x 6/2) or 150 cc which would represent on the average the resting lung volume of left lung of our dogs at the time of occlusion.

After 6 minutes of left lung atelectasis the total O_2 consumption as measured on the right lung averaged about 6% greater than during the control pre-atelectasis period. The experimental curve in Figure 1 shows that after atelectasis the total O_2 consumption returned almost to a pre-atelectasis level. This is strong evidence for an actual increase in total O_2 consumption during the atelectasis, probably due to increased respiratory and cardiac work.

Vagal and blood chemical influences during unilateral atelectasis:

The data summarized in Figure 3 indicate that total atelectasis of one lung (produced by aspiration) is associated with increased contralateral ventilation in

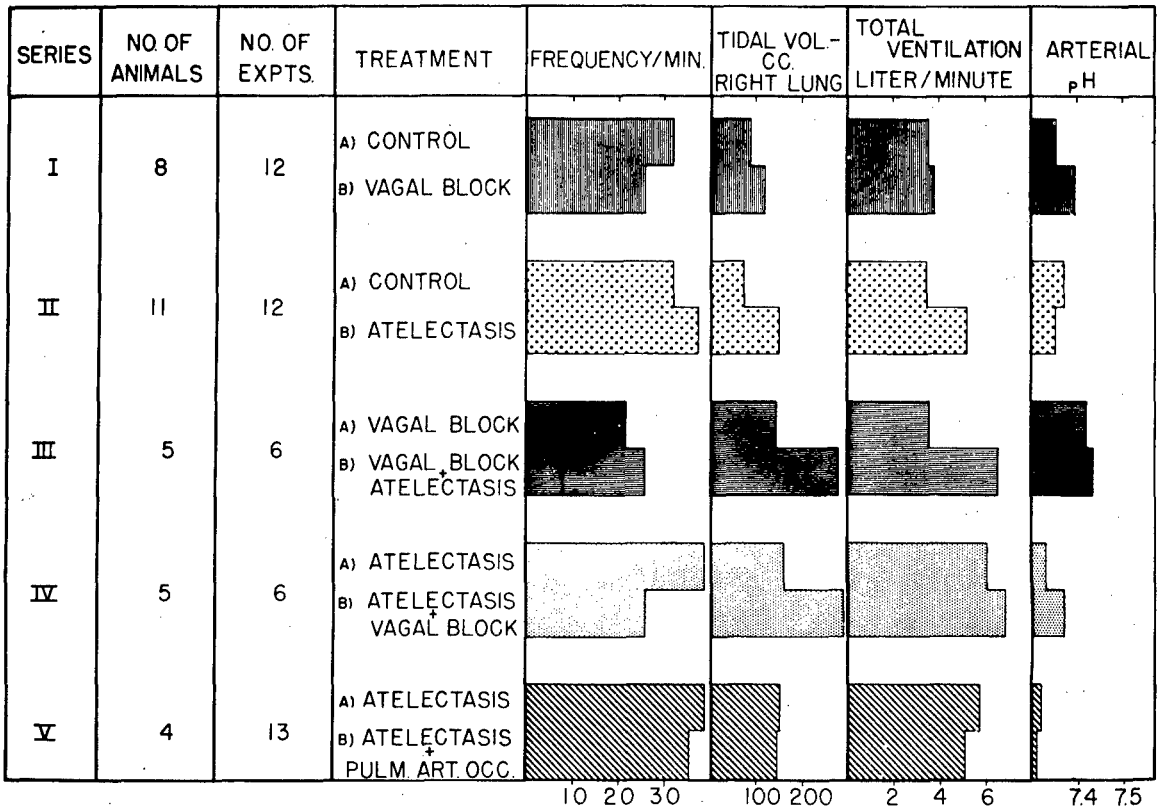


Figure 3

Average data of forty-nine experiments on 33 dogs to assess the differences in open lung ventilation between two sets of conditions as indicated.

terms of tidal volume, rate, minute volume, and in total ventilation of the animal. The increased open lung ventilation might be due to O_2 deprivation, inability to clear the blood of CO_2, or to a reflex effect.

Since the total ventilation (the minute volume of the right lung alone during atelectasis, contrasted with the minute volume of both lungs when both were open) increased from an average of 3465 cc control to 5180 cc during atelectasis, the ventilatory efficiency must be much lower during atelectasis. Both lungs exchanged 3465 cc of air prior to atelectasis to obtain almost the same amount of oxygen for the blood which was obtained during left atelectasis by the right lung from 5180 cc air. The total dead space has meanwhile been decreased by approximately 50%. Yet the increase in both rate and tidal volume of the right lung are unable to compensate completely since the P_{CO_2} rises as judged by the

fall in pH. The increase in overall O_2 uptake would likewise require a 6% increase in alveolar ventilation to account for the greater air exchange for this O_2 consumption.

Chemical factors:

The function of one lung can be eliminated either by acutely cutting off the pulmonary artery blood flow and permitting the ineffective ventilation to continue or by acutely stopping the ventilation (atelectasis) and permitting the ineffective pulmonary blood flow to continue. In either case the contralateral open lung must take over the entire function of gas exchange by approximately doubling the alveolar ventilation if the carbon dioxide tension or pH of the arterial blood is to remain as before. If, however, the blood flow through the atelectatic lung is not stopped completely (6), then only the CO_2 level of the arterial blood can be compensated for by hyperventilation while O_2 desaturation cannot. The mixed arterial O_2 level (breathing O_2 or air) must fall in proportion to the magnitude of the shunt since the hyperventilation would not appreciably increase the arterial O_2 content on the contralateral side.

Observations of the ventilation after sudden occlusion of the left pulmonary artery in dogs shows that the ventilation is increased and partially compensated (4) while with atelectasis (Figure 3 series II) likewise partial compensation is observed. In either case one would not expect full compensation since this would remove the chemical stimulus necessary for hyperventilation. A compromise must be reached between a lowered arterial pH and a considerable degree of hyperventilation. By occluding the left pulmonary artery during atelectasis the created A-V shunt is abolished, thus removing in part the chemical stimulation produced by hemoglobin unsaturation and the venous CO_2 contribution to the mixed arterial blood. Series V indicates that this has a slight effect on reducing the frequency of breathing and the total ventilation. The observed changes in pH are not significant.

Vagal factors:

The fact that even a slight decrease in the resting volume of the lung produces an immediate increase in the frequency of breathing has been appreciated for a long time. Although the tidal volume in such cases is reduced, the effective ventilation in the dog is usually increased and it would seem that a good share of the observed hyperventilation during unilateral atelectasis could be attributed to this Hering-Breuer reflex mediated over the vagus nerve. On the other hand a less well appreciated fact is that simply the blocking of the vagi also produces an increased alveolar ventilation and this is well illustrated in Series I where it can be seen that in spite of the reduced breathing frequency the arterial pH is increased. The latter observation would suggest a normal inhibitory action of the vagi on the chemical drive of the respiratory center and must be kept in mind during the following discussion. In other words, by blocking the vagus nerve during atelectasis

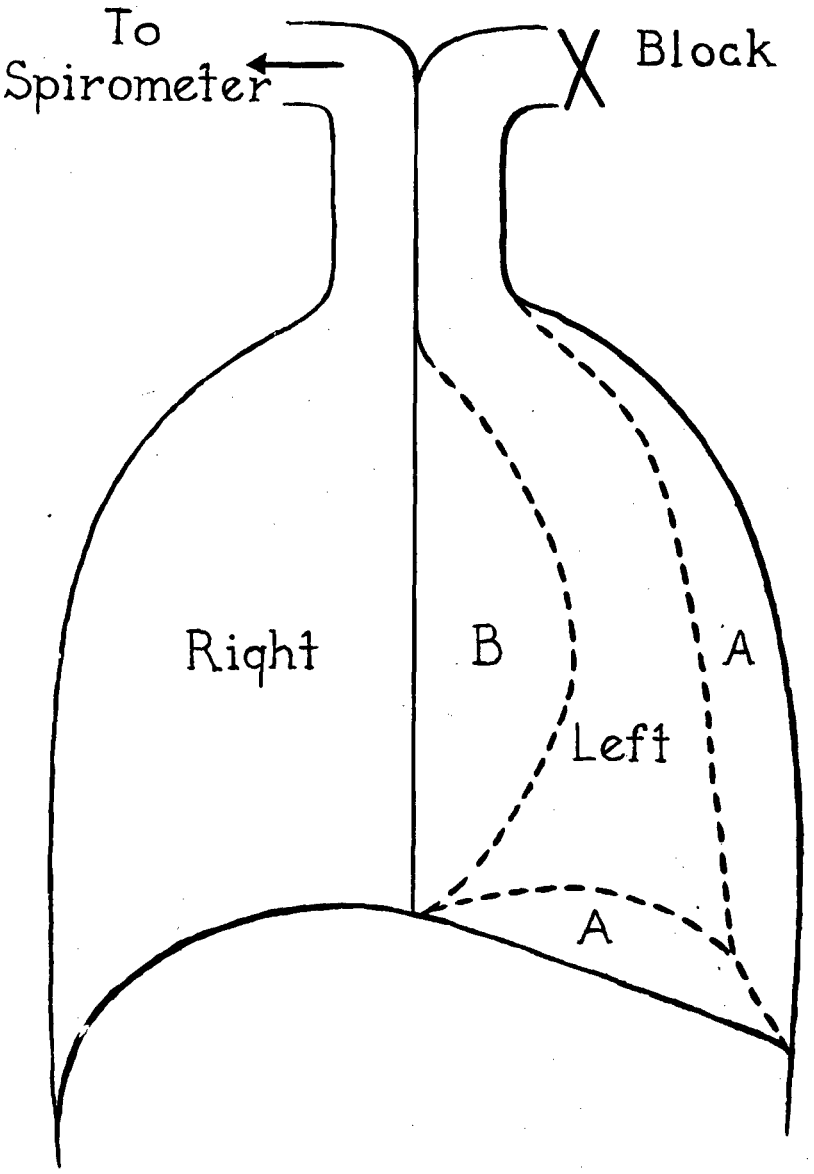


Figure 4

Schematic representation of partial collapse of left lung based on findings to be reported elsewhere (3). B represents the volume displacement of the mediastinum by overdistension of right lung. A represents the displacement of diaphragm and rib cage as the left lung collapses. The total volumes of areas A are nearly equal to the volume of area B.

one does not only remove the newly added stimuli produced by collapse of one lung, but also interferes with the normal chemical regulation.

The typical response to atelectasis is seen in Series II. When the vagi are blocked after atelectasis has been induced (Series IV) the response is qualitatively similar to that seen in the normal animal when vagi are blocked (Series I), namely, an increased tidal and minute volume but a reduced breathing frequency. Thus the elimination of the excitatory response from the collapsed lung by vagal block still evokes a hyperventilation. This could be attributed to the normal inhibitory action of the vagus upon the chemical respiratory drive discussed above. Series III represents the effect of atelectasis superimposed upon a vagotomized animal. Qualitatively this response is similar to that of the normal animal, Series II. Atelectasis induces in both cases a hyperventilation which must be credited to chemical stimulation. These various observations would seem to minimize the importance of the vagal afferents in producing the observed increased minute volume.

From these considerations one may conclude that the vagal afferents contribute relatively little to the overall ventilation during collapse of the left lung in dogs, but may be important in regulating the frequency of breathing. The main stimulus is probably CO_2 and pH acting on the respiratory center and O_2 lack contributed by the left lung shunt acting through the chemoreceptors. By occluding the shunt only a minor reduction in ventilation is achieved. The overall ventilatory increase can therefore be visualized as partial compensation for the chemical stimuli. Complete respiratory compensation is not possible since the hyperventilation stimulus would then be removed.

An interesting point may here be raised in connection with oxygen therapy used in the presence of dyspnea during clinical atelectasis. O_2 therapy alone cannot be expected to either completely saturate the arterial blood or to lower the arterial Pco_2 since both are due to shunt through non-ventilated lung. The indicated therapy is re-aeration of the atelectatic lung. Also, as noted previously, if pulmonary tissue is blocked off containing oxygen, or if oxygen ventilation has allowed N_2 to be blown off, a new atelectasis would proceed more rapidly (1).

CONCLUSIONS

1. The contralateral (open) lung ventilation was studied during unilateral atelectasis in dogs.
2. A small increase in total O_2 consumption during atelectasis is probably due to increased cardiac and respiratory work.
3. O_2 consumption data corroborate our previous observations that approximately 50% of the atelectatic lung volume change is reflected by overdistension of the open lung and mediastinal shift and 50% by chest wall and diaphragm shift.

4. The factors effecting the immediate increase in contralateral open lung ventilation during unilateral atelectasis were evaluated. To the previously determined "mechanical effect" of bronchial occlusion is added ventilatory stimulation due to blood chemical changes (arterial O_2 desaturation and increased CO_2). Vagal afferents seem to contribute little to the compensatory ventilation volume.

5. The effects of the pulmonary blood shunt during atelectasis and the changes due to its abolition are described.

REFERENCES

1. Dale, W. A. and H. Rahn "Rate of Gas Absorption During Atelectasis," Am. J. Physiol. 170: 606, Sept., 1952.

2. Dale, W. A. and H. Rahn "Experimental Functional Separation of Dog Lungs," (see this report).

3. Dale, W. A. and H. Rahn "Lung and Chest Volume Changes During Experimental Atelectasis," (to be published).

4. Lategola, M. Personal communication.

5. Lategola, M. and H. Rahn "A Self-guiding Catheter for Cardiac and Pulmonary Arterial Catheterization and Occlusion," Proc. Soc. Exper. Biol. and Med. 84: 667, 1953.

6. Peters, R. M. and A. Roos "The Effects of Atelectasis on Pulmonary Blood Flow in the Dog," J. Thor. Surg. 24: 389, Oct., 1952.

EXPERIMENTAL PULMONARY ATELECTASIS: PRESSURE-VOLUME STUDIES OF THE INDIVIDUAL LUNGS, MEDIASTINUM AND CHEST WALL RELATED TO TIDAL AIR AND PULMONARY VOLUME CHANGES

by

W. Andrew Dale[1] and Hermann Rahn

In our previous studies (1,2,3) a dog preparation with airways to the two lungs divided has been employed in order to study certain problems of atelectasis. By such a method atelectasis may be induced in one lung while the other remains expanded and maintains the animal. It was observed that when one airway was suddenly occluded or when one lung was suddenly deflated by aspiration, the contralateral open lung at once showed an increased tidal volume. Furthermore, if a certain volume of air was suddenly added to or removed from one lung, the functional residual volume of the contralateral lung was changed in the opposite direction. This contralateral volume change, however, was not exactly equal to the volume added or removed in the blocked lung and a considerable volume was unaccounted for. It appears that these changes can be accounted for on a mechanical basis. They have been investigated by a study of the pressure volume relationships of dogs' lungs.

METHODS

Mongrel dogs were anesthetized with .026 gm/kg. Nembutal mixed with .0003 gm. atropine sulfate and subsequent injections given as needed to maintain a proper plane of anesthesia. Each animal was prepared for individual lung function study using the double plastic cannula described previously (1). The left lung was always the one blocked or rendered atelectatic while observations were made on the right lung.

Tidal volume data were recorded on a basal metabolism machine with the animal obtaining O_2 from the spirometer where CO_2 was also absorbed.

Vagus nerve block was obtained bilaterally when desired by cooling both nerves with ice water circulating through brass coils in which the cervical portions of the vagus nerves lay. Rapid cooling with resultant cervical vagal nerve block uniformly occurred within a minute as evidenced by loss of the Hering-Breuer reflex effects when the chest was squeezed, or by the absence of changes in experimental data when the nerves were actually cut after being cooled. Rapid reversal of cooling was effected by passage of 40° C water through the system.

---

[1] Department of Surgery

A Drinker respirator was used for certain experiments to produce an artificial respiration. This could be easily set at any desired tidal volume level and at any desired rate. The respirator could also be changed to a constant positive or negative pressure. Lung volume changes were recorded on the spirometer during these periods to enable construction of single lung pressure-volume curves.

Volume changes were produced in the left lung by rapidly aspirating or injecting a measured volume of air by a syringe attached directly to the cannula leading to the left lung. When it was desired to maintain a given volume change, the cannula leading to that lung was blocked with a clamp.

RESULTS

Table 1 summarizes the experimental data regarding contralateral tidal volume increase following sudden occlusion of the left main bronchus cannula. Quantitative data were obtained from 13 animals, although similar changes were observed in many others. A minimum of three trials constituted each experiment and the table shows the average of all. The tidal volume of the single respirations just preceding and following sudden left lung block were measured. Five of the animals were studied just after Nembutal sacrifice by producing an artificial Drinker respirator tidal exchange.

Figure 10 consists of data taken from eight experiments to determine the relation between volume change of the blocked left lung and open right lung. Left lung volume changes (by means of sudden removal or addition of air) were plotted against the right lung volume changes which at once appeared on the spirometric record. The heavy line represents an average of the points. The broken line represents the predicted curve taken from pressure-volume diagrams discussed below. The inset diagram is discussed later.

PRESSURE-VOLUME RELATIONSHIPS

If the above observations have a mechanical explanation, it is necessary to focus upon the elastic forces of the thorax and how they are altered by the sudden occlusion of one lung or by the addition and withdrawal of gas from one lung.

The lung volume at any moment is determined by 2 elastic forces which oppose each other over a considerable lung volume range, namely, the tendency of the lung to collapse, P_L, and the tendency of the chest wall and diaphragm to expand, P_C. Their algebraic sum determines the intrapulmonary pressure if all the muscles are relaxed and has been called the relaxation pressure, P_R. This relationship can be expressed —

$$P_R = P_C + P_L$$

These components have been reported previously from this laboratory for both man (7) and dog (8).

TABLE 1

The tidal volume (ml) of right lung before and after sudden occlusion of the left airway. The left airway was blocked either at the end of expiration or inspiration. % Indicates the percent increase in tidal volume.

Animal	Expiratory Block			Inspiratory Block			Vagi cut Expiratory Block			Dead Expiratory Block			Dead Inspiratory Block		
	Before	After	%	Before	After	%	Before	After	%	Before	After	%	Before	After	%
1	131.8	171.0	27.5	136.0	193.8	42.4									
2	100.3	149.1	48.8	98.2	161.5	64.5									
3	111.3	144.3	29.7	103.0	144.3	40.1									
4	87.2	96.9	9.9	87.2	98.2	12.6	184.7	220.1	19.2						
5	132.5	172.7	30.3				179.3	207.9	15.9						
6	85.3	124.6	46.1				218.5	260.0	19.0						
7	80.9	94.9	17.3	77.7	96.5	24.2	177.3	221.4	24.8	111.3	125.4	12.7	83.9	94.1	12.2
8	63.3	81.0	28.0	61.8	85.9	39.0				229.0	250.0	9.0	229.0	258.0	12.7
9	130.5	174.5	33.7	158.3	199.2	25.9				124.7	142.7	14.4	113.4	119.4	5.3
10	79.1	93.4	18.1							137.0	149.9	9.4	123.6	144.3	14.3
11	83.8	101.5	21.1							185.1	198.7	7.3			
12	130.4	184.9	41.8												
13	103.0	149.8	45.4												
Average	101.5	133.7	30.6	103.2	139.9	35.5	190.0	227.4	19.7	157.4	173.3	10.6	137.5	154.0	11.1

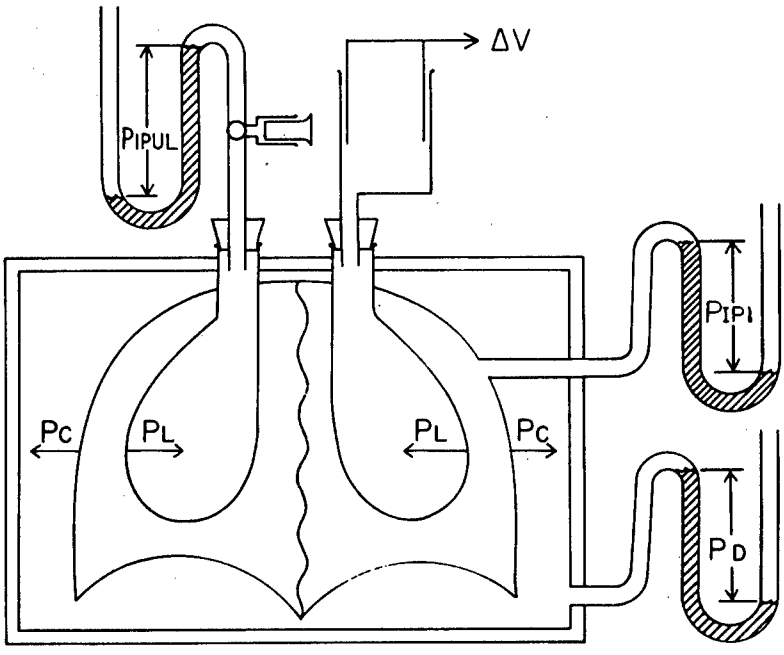


Figure 1

Apparatus to determine pressure-volume curves for functionally separated dog lungs. Box represents Drinker respirator with manometer measuring its pressure, P_D. Right lung is shown "open," i.e., attached to spirometer. Catheter within pleural cavity measures intrapleural pressure, P_{ipl}. Left lung is shown "blocked," connected to manometer to measure intrapulmonary pressure, P_{ipul}. Syringe used to remove or add gas. Arrows indicate direction of pressure of lung, P_L, and chest wall, P_C. Formulae are in text.

Figure 1 (the right side) illustrates the method used for measuring these elastic forces at different lung volumes when the right lung is open and connected to a spirometer. The left side of the diagram indicates the similar measurements for the occluded left lung.

The animal's body is enclosed in a Drinker respirator box with the cycling gear disconnected. The pressure within the box (P_D) can be maintained at any desired negative or positive constant pressure measured by a water manometer. The pressure within the intrapleural space (P_{ipl}) is also measured on a water manometer by connection to a balloon tipped plastic cannula in the pleural cavity. The manometer is outside the box and read only during the expiratory pause. Thus only the elastic component of the lung is measured uninfluenced by the viscous component during active respiration.

When the pressure within the respirator is made negative (i.e., 100 mm H_2O), the pressure within the open (right) lung remains essentially atmospheric. But the pressure around the animal is subatmospheric and thus we have the equivalent of a positive pulmonary pressure of +100 mm H_2O with a lung volume increase of ΔV measured on the spirometer. The chest wall including the diaphragm is now held relatively rigidly (in relation to the open right lung). The collapse tendency of the right lung is measured by the intrapleural pressure when we change the sign of the reading. Thus the negative intrapleural pressure is equivalent to $+P_L$ and the negative pressure in the respirator equals $+P_R$* (as shown for right lung side of Figure 1). From equation 1, P_C can be determined and all these values plotted against the change in lung volume, ΔV, as is indicated in Figure 2 which represents the average values for 6 dogs for the left lung and the right lung. These values have been determined for each lung separately. This, however, is actually not necessary since the only difference between them will be difference in ΔV for a given change in pressure (see discussion of Figure 3).

From previous studies it had been ascertained that not only the tidal volumes but also the lung weights of the right and left lung have a ratio of approximately 60:40 in the dog (1). Thus, for a given pressure increment it is to be expected that volume change, ΔV, will also bear a similar relationship. This was actually confirmed by studying each lung separately in these six dogs. The volume change for a given change in P_L or P_R measured averaged out to a ratio of 59.4:40.6. It is thus possible to describe the pressure volume diagram for both lungs on the same graph having a different volume scale for the right and left lung (Figure 3).

P - V relationship with one lung blocked. Figure 1 shows on the left side the measurements as made when the left lung is blocked. The intrapleural pressure (P_{ipl}) in this instance indicates the chest wall component (P_C) because with the

---

* Actually, as pointed out previously (7,8) P_R represents relaxation pressure and theoretically can only be measured if no muscle tone or force exists. In practice the measurements on living man or dogs must include some element of muscle tone or force. Therefore the values obtained by us as P_R actually include this factor. These authors have referred to the experimentally determined curves as P_B curves (pressure breathing curves). We recognize this concept but refer to our curves as P_R curves for simplicity.

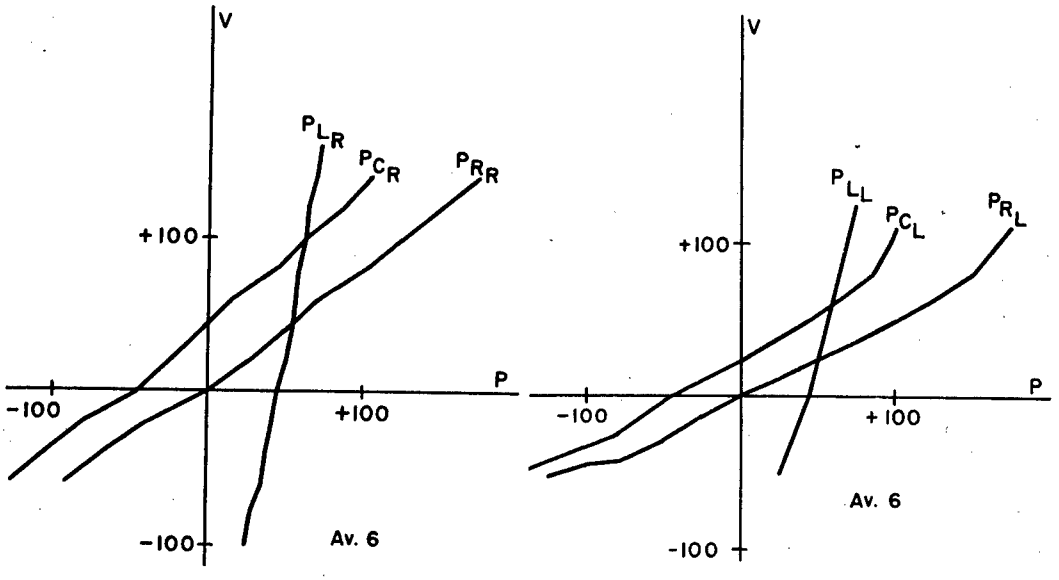


Figure 2

Average individual pressure-volume curves from 6 dogs. P_R = relaxation pressure, P_L = lung pressure, P_C = chest wall pressure. Subtended letters indicate left and right lungs. Volume change in cc; pressure in mm H_2O.

lung blocked it becomes fixed, while the chest wall pulls away from it. Note this difference from the right (open) lung. Also, with the left lung blocked, the relaxation pressure curve (P_R) is obtained by subtracting the Drinker pressure (P_D) from the measured left intra-pulmonary pressure (P_{ipul}).

Experiments have shown that when the left lung is blocked at the end of expiration the pressure-volume relationships of the contralateral (right open) lung are immediately altered. Figure 4 indicates this shift which has been averaged for 3 dogs. In each instance the right lung volume change and intrapleural pressure was determined for a given P_R with the left lung open. After a brief return to normal respiration, the same data were recorded at the same P_R but with the left lung blocked at the end of a normal expiration. Thus data for the two conditions at the same P_R points were obtained alternately.

Figure 4 indicates that the P_L curve is essentially unchanged. Since P_L represents lung tissue tension, it is not expected that it will be altered. On the other hand, the P_R curve shifted so that with left lung blocked, the right lung volume change is greater per unit change of pressure P_R than when the left lung was open. This indicates a shift of the same magnitude in the P_C curve by calculation. Hence, with left lung blocked, there is greater right volume change per unit change of pressure. The shift of the P_C curve denotes change in the compliance of the chest wall upon occlusion of the left lung.

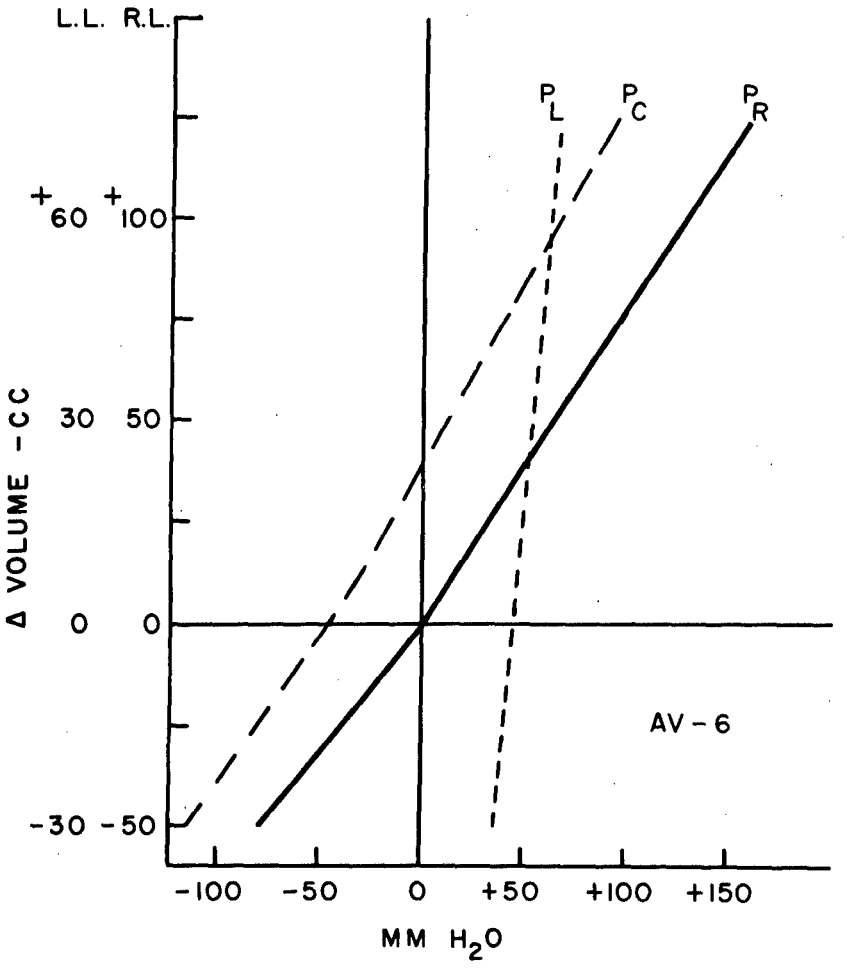


Figure 3

Replot of Figure 2 to show both right and left lung curves on same diagram. Note right and left lung scales are different in a 63:37 ratio. This approximates the ratio of right to left lung weight, volume, tidal air and O_2 consumption (1).

From Figure 4 it appears that the P_L curve is not affected by occlusion of one main bronchus. Accordingly the shift of P_C varies with the shift of P_R. Further study of characteristics of the P_R curve should allow prediction of similar behavior of the P_C curve, without actually measuring P_L. This is desirable since determination of both P_R and P_L curves simultaneously necessitates a complicated recording apparatus.

The characteristics of the P - V diagram of the open lung when the other was

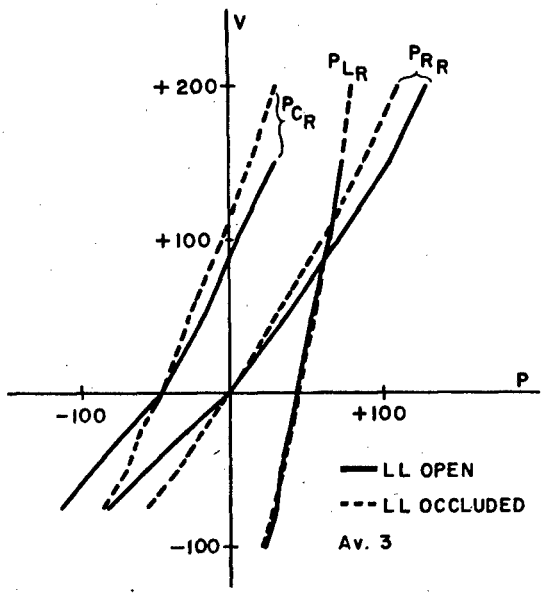


Figure 4

Average right P - V curves for 3 dogs to compare results with left lung open and blocked. P_L (lung tension) curve does not shift, while P_R (relaxation pressure) and P_C (chest wall pressure) curves change to a steeper slope.

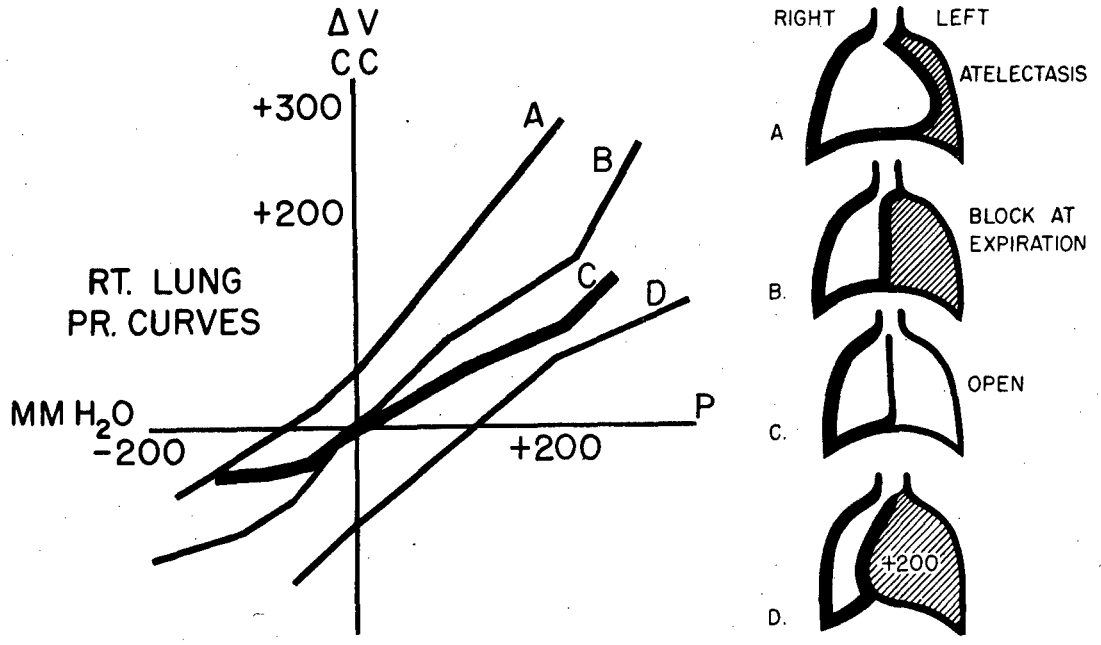


Figure 5

Right lung P_R curves in an experiment to compare effect of blocking left lung at complete atelectasis A, end of expiration B, normal open control C, and blocked left lung with 200 cc gas added D.

blocked at different volumes was now investigated by determining P_R curves for three such animals. Figure 5 is the plot of one such experiment where right P_R curves were obtained when left lung was blocked at five different volumes (only three and "normal" are shown in Figure 5). This figure on the right has a diagram of both lungs for each curve. The A curve represents complete left lung atelectasis, with diaphragm pulled over and right lung over distended. The B curve shows left lung blocked at the end of expiration without initial volume change or initial mediastinal shift. The C curve (heavy line) is the normal control, and D represents left lung blocked after 200 cc air had been pumped into it.

The area transmitting muscle force to the right lung is in each instance shown as a heavy outline. Note that in the normal open C diagram this is only chest wall and diaphragm and not mediastinum. However, in A, B, and D the mediastinum is represented by a heavy line (whose position varies). When left lung is blocked, it acts to transmit the force of left chest wall-diaphragm to mediastinum with each inspiration.

Figure 5 and similar experiments on 2 other dogs indicate that the P_R curves produced when left lung is blocked are essentially parallel, showing that the P_C curves will also be parallel. This parallelism of the curves has been further tested by cutting both vagi in the neck of one dog which alters the chest wall characteristics and therefore the P_R curves as shown by Van Liew (8).

Figure 6 represents an experiment where right P_R curves were obtained first with both vagi intact. The solid lines show the control right P_R curve (left lung open) and the slightly differently sloped right P_R curves when left lung was atelectatic ("ATEL") and when left lung was blocked after 200 cc air had been pumped in ("+200"). The broken lines show the same curves after the vagi were cut. Again the "atelectasis" and "+200" curves are roughly parallel and different in slope from control. This experiment indicates that despite bilateral vagal section (which itself alters chest wall compliance as seen in the different "control" P_R curve), blocking the left bronchus still produces a parallel group of P_R curves of different slope from the control. To avoid further complicating this figure, the curves obtained when left lung was blocked at end of expiration have been omitted.

DISCUSSION

Contralateral tidal increase and "mechanical" changes after pulmonary occlusion.

Many random observations here have indicated that simple unilateral lung occlusion in the dog is at once followed by an increase in the contralateral open lung tidal volume. Pump (4) has recently summarized experimental (6) and clinical (5) studies regarding this. In broncho-spirometric studies of 23 men, he evaluated the changes in respiration of the open lung when the other was occluded and enumerated three features of this ventilation, namely, (1) increase in functional residual capacity, (2) increase in tidal volume in cases where the first was marked, and (3) increase in respiratory rate.

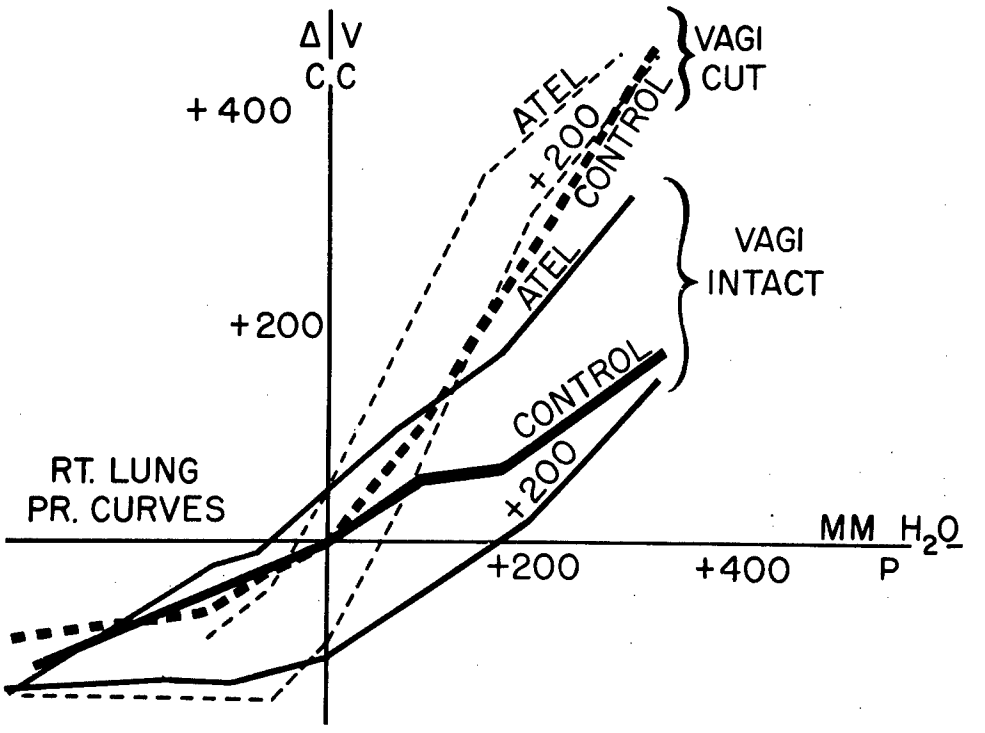


Figure 6

Right lung P_R curves to show effect of cutting both vagus nerves in neck with open left lung (control) and blocked left lung. The left lung was blocked after aspiration of its air content (atelectasis) or after adding 200 ml of air (+200).

Examination of his published records indicates to us that the phenomena herein reported are the same with which this paper is concerned. In the animals studied by us, it was possible to standardize conditions or vary them at will, accounting for some differences between our findings and those of Pump. For instance, while it is agreed that the tidal volume of the open lung at once increases, our experiments indicate that the functional residual capacity only changes when the other lung is blocked at the height of inspiration and not when it is blocked at the expiratory pause. The reason for this difference is discussed below. Figure 7 illustrates this point and parallels the two records which Moore (6) published in 1925. Also our animals clearly show initially the Hering-Breuer reflex effect when the left lung is blocked at inspiration as shown by a decrease in rate in Figure 7.

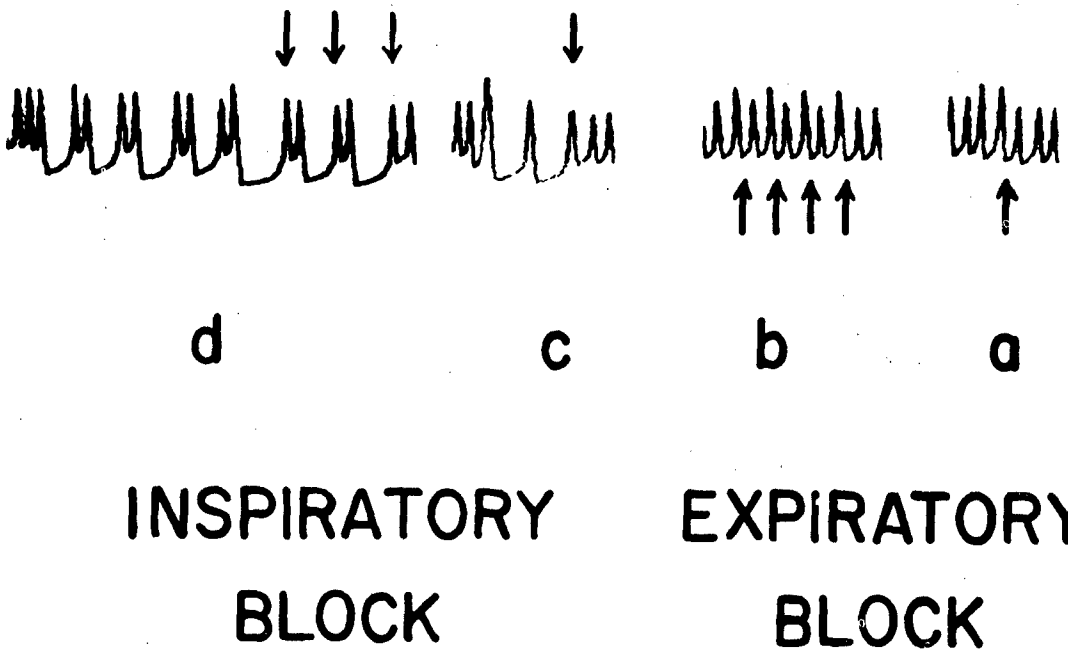


Figure 7

Spirographic tracing of right lung, reading right to left. Arrow indicates points at which left lung was occluded, in **a** and **b** at end of expiration, in **c** and **d** at height of inspiration. **b** and **d** show effect of alternate left bronchial block and release. Note reflex rate change in **c** and **d**.

Consideration of the pressure-volume diagrams of dog lungs allows certain explanations of the increase in contralateral tidal volume when one lung was blocked. Reference to Figure 5 and the discussion of that figure recalls that the P-V diagram of the open lung changes following contralateral block. However, one must distinguish between an occlusion made at the end of a normal expiration and one made at the end of a normal inspiration. Figure 7a shows the spirographic tracings of 7 successive tidal volumes reading from right to left. Inspiration is upward. The first 3 on the right are normal tidal volumes. At the end of the 3rd expiration (arrow) the contralateral lung was occluded and kept occluded for the next two respirations. These 2 tidal volumes show an increase in tidal volume of approximately 30%. Upon release of occlusion the original tidal volume resumes.

In Figure 7b the contralateral lung was blocked at the end of expiration of every other breath which resulted in an alternating large and normal tidal volume. These responses are typical and have never failed to appear. When the left lung is blocked on expiration, there is no right lung base line shift, indicating no change in functional resting volume. However, when the left lung is blocked on inspiration, the base line (functional resting volume) shifts (Figure 7c and 7d).

Three possible causes for this phenomenon might be considered, namely, (1) reflex origin, (2) chemical stimulation, and (3) mechanical origin. Chemical stimulation would seem least likely since the increased CO_2 tension or decreased O_2 tension of the blood during the occlusion would not have time to reach the nearest known chemo-receptor before the completion of the first inspiration. Reflexes arising from the stretch receptors can be ruled out as sole origin since bilateral cooling of the vagus nerve does not prevent this phenomenon. Chest wall reflexes cannot be solely responsible since with paralysis of the skeletal muscles by succinylcholine and even in post-mortem animals we were able to show a distinct if lessened increase in tidal volume upon contralateral occlusion during rhythmical ventilation in the Drinker respirator. (For details of observed changes see Table 1). These considerations would suggest that part or all of this observed response is attributable to altered mechanics of the chest.

Figure 8 represents the average P_R curves of the right lung of 5 animals. Alternate points were obtained with left lung open, and blocked. The solid curve represents the right P_R when left lung was open. The broken line curve represents right P_R when left lung was blocked at expiration. The shift of P_R (previously seen in Figure 4) is present as expected. Point Y denotes the average control tidal value of the 13 control animals in Table 1 (101.5 cc). Upon blocking the left lung when the right is at the zero point (end of expiration) it may be predicted that the right lung will follow the broken line P_R closed curve now. Thus if the same pressure occurs on the following respiration, one may predict volume at the top of the arrow in Figure 8. This proves to be 137 cc, which compares well with the experimental average of 133.7 cc in Table 1. Thus the increase in open lung tidal volume may be predicted by knowledge of the shift in its P_R curve resulting from the change of chest wall compliance when the other lung was blocked.

This allows then the hypothesis that when one part of the total pulmonary tree is blocked suddenly, there is at once an increase in tidal volume of the remaining open part because the same work is done by the muscles of the chest wall and diaphragm, but practically all the work is now directed toward the open portion of the lung. This immediate shift of muscular effect to the open portion of lung is termed mechanical effect and is associated with changed chest wall compliance. The diagrams of Figure 5 illustrate our concept of this. When the left lung is blocked at any volume, it no longer changes volume appreciably* with respiration,

---

* That the blocked lung volume does not appreciably change during inspiration can be shown as follows: In an experiment the left lung was blocked by attaching its

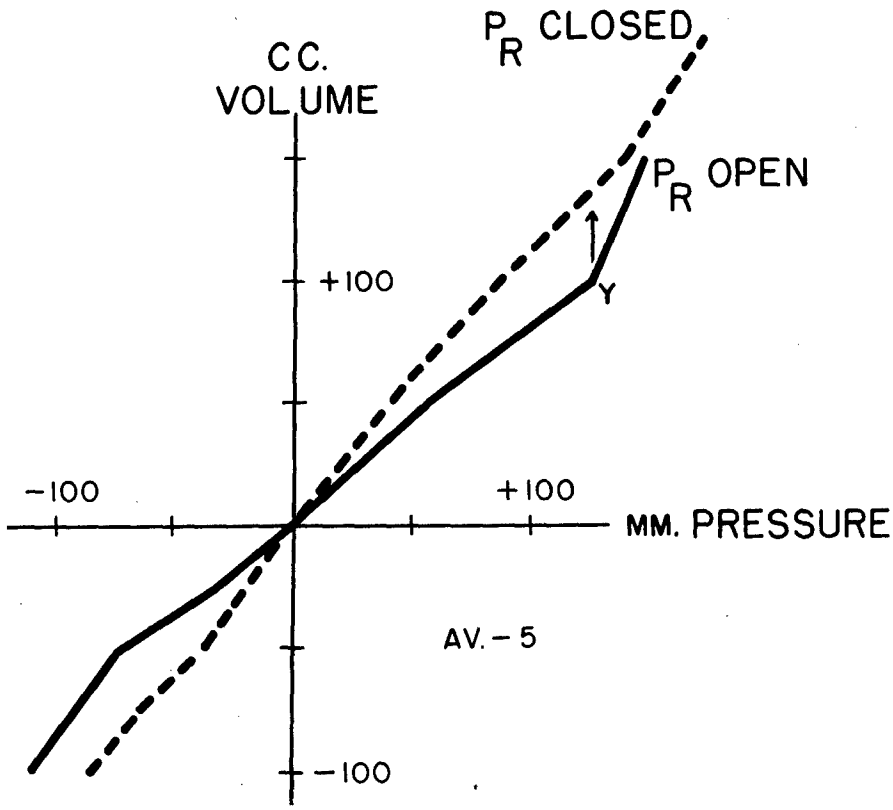


Figure 8

Average right lung P_R in 5 dogs to show shift occurring upon left bronchial occlusion.

but simply acts to transmit chest wall-diaphragm force to the mediastinum. Inspection of records indicates the tidal volume increases more after the initial change in the living animal, which may be due to reflex or blood chemical changes. That the initial change is not solely on a reflex or chemical basis is indicated by the occurrence of the increase in contralateral open lung tidal volume even though the vagus be blocked or the animal be dead (Table 1). Further, in one experiment,

---

* (Continued) cannula to a manometer, so that the intrapulmonary pressure could be determined during large respirator induced inspiratory attempts. When the Drinker pressure was made -288 mm, 680 cc of gas entered the open right lung. At the same time the left lung intrapulmonary pressure became -120 mm H_2O. The volume change of the left lung may be calculated from $V_2 = V_1 (P_1/P_2)$. If the left blocked lung volume was 200 ml, it would expand by (760 + (120/13))/760 to a volume of 202 ml.

the tidal volume increase occurred not only under the mentioned conditions of vagal section but also after intravenous succinylcholine had negated neuromuscular effector mechanisms. These experiments therefore suggest that chest wall compliance change following bronchial occlusion is due to a change in the role of the mediastinum from a passive membrane separating the two lungs to an active force transmitting chest wall-diaphragm pressure to the open lung. The experiments typified by Figures 5 and 6 seem to show that the chest wall compliance change is the same (P_R curves tend to be parallel) with left main bronchial occlusion despite varied contained gas volumes of the left lung.

It seems likely therefore that the chest wall compliance change may be a function of the amount of blocked off lung tissue rather than a function of the volume of gas contained within that tissue at the time of block. This final point has yet to be studied.

Experimental measurements of contralateral tidal changes

The average contralateral tidal volume increase when the left lung was blocked at the height of inspiration was 35.5% in 7 animals, while the general average for 13 animals blocked on expiration was 30.6%. However, the average on expiration for the same 7 animals studied by inspiratory block was 27.8% increase. Thus, there was a slightly greater average tidal increase upon inspiratory block (35.5%) than upon expiratory block (27.8%) for the 7 dogs studied both ways.

Following left lung occlusion at the height of inspiration, the right (open) lung will not only empty its usual tidal volume, but also a certain additional amount which is equal to approximately 50% of the tidal volume of the left lung. The additional 50% of left lung tidal volume results from mediastinal shift associated with occlusion of the left lung in a condition where volume has been added. (See below.)

Table 1 shows the average right tidal volume before inspiratory block to be 103.2 cc. If we assume a 60:40 ratio between right and left lung tidal volumes, we may estimate the left tidal volume was approximately 68.8 cc of which 50% is 34.4 cc. If this 50% estimated left tidal be added to measured right tidal:-

Measured right tidal	= 103.2 cc
50% Estimated left tidal	= 34.4 cc
Expected post-block right tidal	= 137.6 cc

The calculated right tidal volume of 137.6 cc after block now compares well to the experimental average of 139.9 cc. Thus when the left lung is blocked on inspiration, the immediate increase in right tidal volume may be predicted as a function of the mediastinal shift occurring on expiration. The right lung volume now dips below the 0 point on the graph and functional residual volume decreases (see base line shift of Figure 7).

This should also be predictable from the P-V curves. In Figure 5 a study of the right lung P_R curves obtained by blocking the left lung with different enclosed volumes of gas showed that the new P_R curves lay on a different slope but were essentially parallel. Further analysis showed that they each crossed the 0 pressure axis at a volume which differed from 0 volume by about 50% of the gas added to the left lung. For instance in Figure 5 when 200 cc were added to the left lung, the right P_R curve at 0 pressure lies at 91 cc. As discussed later this is because about 50% of the volume change in a blocked lung is reflected in mediastinal shift and open lung volume change.

Figure 9 is a diagrammatic form of Figure 5, and shows right lung P_R curve

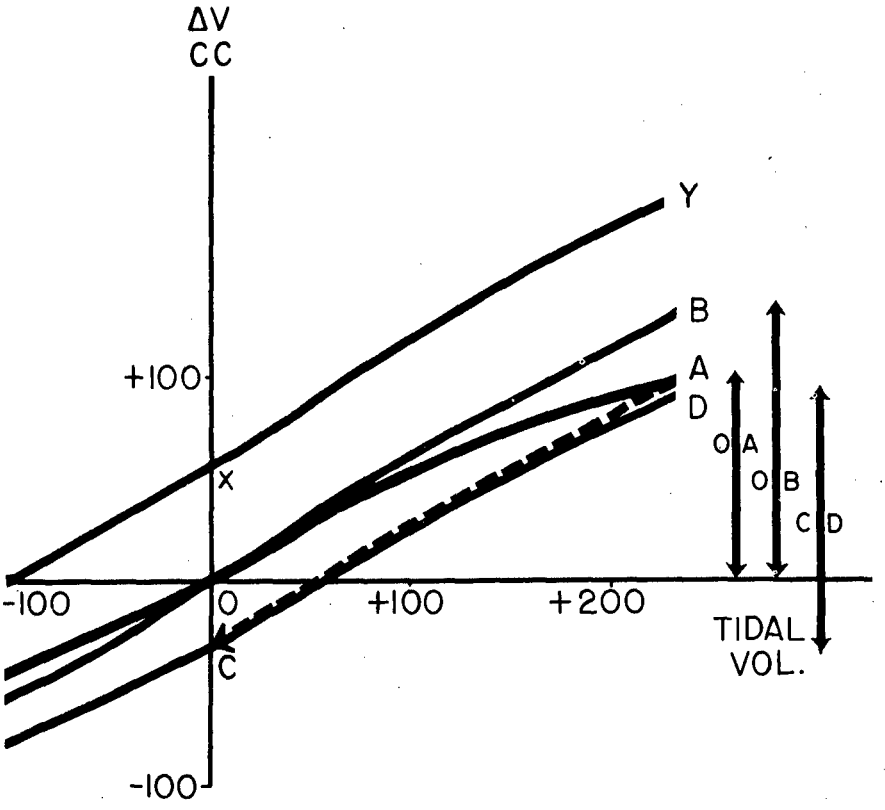


Figure 9

Diagrammatic replot of Figure 5 to explain right tidal volume increase when left lung is blocked. O is zero point, OA is normal right P_R curve, OB, CD and XY are parallel right P_R curves produced by blocking left lung at different volumes (at end of expiration for OB, at height of inspiration for CD and at complete atelectasis for XY). Vertical arrows represent right tidal volumes associated with each curve if inspiratory pressure is unchanged.

(OA) when left lung is open and (XY, OB and CD) when left lung is blocked containing 3 different gas volumes. The XY, OB and CD curves are shown as parallel. The difference in slopes from the normal P_R line OA is similar to the experimental difference.

If the left lung be blocked at end of expiration (O point), the right lung is expected to increase its volume along the new P_R curve OB so that if the same inspiratory pressure develops there will be increase in right tidal from 101 cc at A to 134 cc at B.

If on the other hand the left lung be blocked on inspiration (when the right lung is at A on the P_R curve, at the succeeding expiration approximately 50% of the volume trapped within the left lung (69 cc) will be reflected as change in right lung functional residual capacity to point C at 34.5 cc below the O point at C. The right lung now is expected to operate along the new P_R curve CD. The figure indicates that the functional residual capacity of the right lung has decreased (to C). If the same inspiratory pressure occurs, the right lung is expected to operate along CD. Because the OB and CD curves appear to be parallel, the right tidal volume increase should be the same whether the left lung is blocked on inspiration or expiration.

Experimentally this equality of right tidal increase was not completely realized. Left expiratory block caused 27.8% tidal increase while inspiratory block caused 35.5% (for the 7 animals tested both ways in Table 1). This may be simply experimental variation. However, we are more inclined to think that reflex effects are more prominent when the lung is blocked upon inspiration than upon expiration and that this may account for the difference. A reflex effect upon rate is easily seen in Figure 7c In dead animals (Table 1) no difference was observed between block on inspiration (11.1%) and expiration (10.6%). Hence it may be stated that this phenomenon can be demonstrated in the absence of reflexes but that it is quite likely that reflexes do modify this response in the living animal.

Contralateral lung volume and chest volume changes

When a portion of the total pulmonary volume becomes atelectatic, the total gas contained within the lungs is decreased. If the collapse occurs in the left lung, there is at the same time increase in the open right lung volume although the total of both is less. Random observations indicated that volume changes in one lung were not quantitatively reflected by a reverse change in the other. Figure 10 shows a heavy line connecting the average data of 8 experiments where known volume changes were induced in the left lung and plotted against the spirometrically measured volume change in the open right lung. If there were 100% reflection of the volume change of left lung by right lung, a straight line with a slope of 1 should occur on the graph. This line is indicated in the inset diagram as a diagonal from lower left to upper right. In the inset diagram the experimental average is also

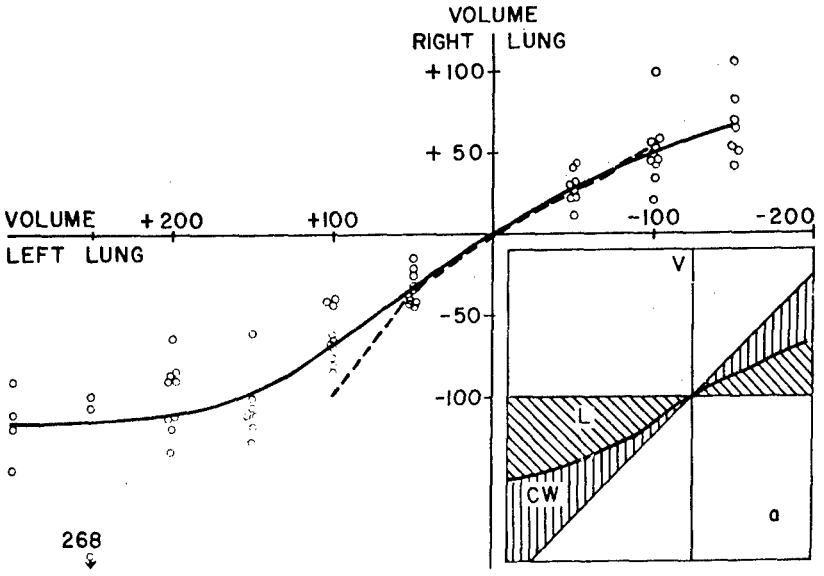


Figure 10

Average data from 8 dog experiments showing on the solid curved line the relationship of the volume change of the open right lung to that produced experimentally in the blocked left lung. Inset shows the straight diagonal line which would be produced if same volume change occurred in both lungs. The curved line reproduces the experimental data. The shaded area L marks the lung volume change, while CW marks the change in the chest wall and diaphragm. The broken line is discussed in the text.

indicated as the heavy line. The overall average experimental curve indicates that approximately 50% of the left lung volume change is reflected as the reverse volume change in the right lung up to the point where the curve flattens.

If 175 cc of gas be removed from the left lung while it is blocked, the mediastinum shifts toward the left, and the open right lung increases its resting (functional residual) volume by approximately 87.5 cc. The remaining unaccounted for 87.5 cc must then represent decrease in total chest volume as the chest wall (including diaphragm) moves in toward the lung. The shaded portion of the inset diagram of Figure 10 marked "L" represents the change accounted for in the open lung as it overexpands and the mediastinum shifts. The shaded portion marked "CW" accounts for the remainder of the volume and represents diminution in chest volume due to shift inward of the chest wall (including the diaphragm). By this method the mediastinal and chest wall-diaphragm components may be separated.

O_2 consumption studies (3) also indicated that approximately 50% of the volume

change is matched by reverse contralateral lung volume change while the remainder is matched by chest wall and diaphragm shift. Further indication was obtained by plotting pressure-volume curves of the mediastinum as well as of the chest wall and diaphragm. Figure 11 was derived from the average data of 8 dogs. The solid line shows the average volume change of the right lung plotted against the measured pressure within the left lung when air was added or subtracted to or from the left lung. In other words, if enough air was added to the left lung to raise its intrapulmonary pressure to +100 mm H_2O, 82 cc of gas were pushed out of the right lung. The heavy line thus represents the mediastinal* pressure volume curve. The broken line shows that at the same time, there was 60 cc of gas added to the left lung and not accounted for by the measured amount pushed out of the right lung. This broken line represents volume change of the left chest wall and diaphragm.

Inspection of Figure 11 indicates that the mediastinal volume change for a given pressure was always slightly greater than ipsilateral chest wall-diaphragm shift and accounted for as much as 57% of total volume change.

The three approaches, however, all indicate that about half the volume change of the blocked lung is reflected by the contralateral open lung's volume change in the opposite direction, while approximately half the volume change occurs in the chest wall and diaphragm.

Again recourse was had to the individual lung pressure-volume curves in order to explain the experimental findings. Inspection of Figure 2 shows that the measured intrapleural pressure on the side of the blocked (left) lung indicates the chest wall pressure, P_C. On the side of the open (right) lung the measured intrapleural pressure indicates the lung tension, P_L, with sign reversed.

Due to the areolar character of the mediastinal tissue separating the pleural spaces of the dog there is equalization of the intrapleural pressure of the two sides except at extremes of either negative or positive pressure, as noted from simultaneous measurements in the dog with one lung blocked and subjected to a range of pressures in the Drinker respirator. Within the range of pressure under consideration here, the two intrapleural pressures may be assumed equal. Therefore measurement of either intrapleural pressure will indicate both the chest wall tension of the blocked left lung P_{C_L} and the lung tension P_{L_R} curve of the open lung. If the curves for these P_{C_L} and P_{L_R} be known, one may use such a diagram to estimate volume changes in each lung associated with a given P_{C_L} or P_{L_R} pressure change. Since the curves are different, there is a different volume in open and closed lung.

---

* Actually the line represents not only mediastinal shift, but also any change which occurs in right chest wall and diaphragm, since if these components change, it will effect the right lung volume. We have been as yet unable to measure this.

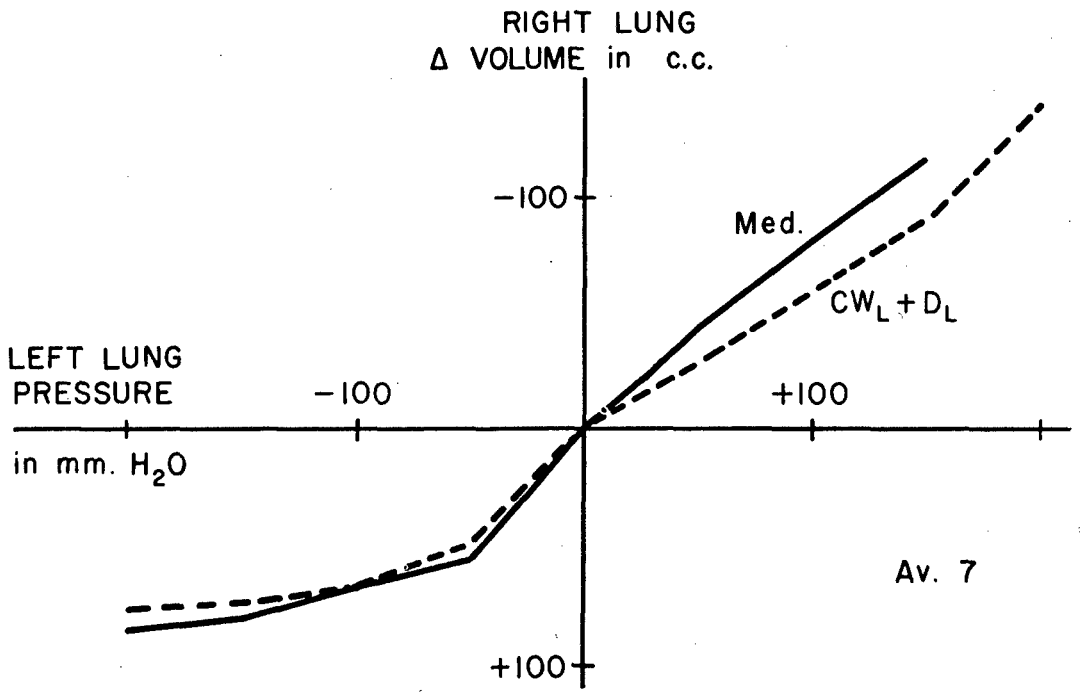


Figure 11

Pressure-volume curve of the mediastinum (solid line) and chest wall-diaphragm component (broken line) as the average of 8 dog experiments recalculated from Figure 10.

Average P_{C_L} and P_{L_R} curves were drawn for 5 animals by measuring the intrapleural pressures and by determining the right lung volume changes when a given volume change was made in the left lung. From these curves the expected change in pressure of the P_{C_L} curve associated with a given change in left lung volume was found. The expected right lung volume associated with a similar pressure change in the P_{L_R} curve in the opposite direction was then also calculated. From these calculations an expected curve was drawn in Figure 10 as the broken line. The diagram from which this prediction was made shows by inspection that the difference of slope of the P_{C_L} curve is approximately 50%.

It appears, therefore, that the relative proportion of open lung volume change and mediastinal shift as well as the chest wall-diaphragm volume change and shift

is predictable by consideration of the curves for blocked lung side chest wall pressure and open lung side lung tension. This approximates 50%.

SUMMARY AND CONCLUSIONS

Sudden occlusion of one lung of a dog uniformly produces an immediate tidal volume increase in the contralateral open lung. This occurs after inspiratory as well as after expiratory block, whether or not the vagus nerves be intact or severed, after a paralyzing dose of succinylcholine, and in the dead animal (using a mechanical respirator).

Relaxation pressure-volume curves of the individual lungs of dogs have been plotted and show an increased compliance of the open lung following contralateral lung occlusion. If the same inspiratory pressure is exerted following occlusion, the increased compliance is just large enough to explain the observed increase in tidal volume. Since the blocked lung becomes essentially immobilized, the mediastinum moves on each inspiration and accounts for the increased compliance of the open lung volume. This immediate shift of forces in the open lung is termed the mechanical effect of sudden bronchial occlusion. Certain findings indicate an additional reflex effect under some conditions.

Pressure-volume diagrams for the mediastinum and for the chest wall-diaphragm components, as well as measurements of contralateral lung reflection of volume changes in the other lung, and O_2 consumption studies (the latter reported elsewhere) indicate that volume changes in a blocked lung are associated with volume changes in both the contralateral open lung and movements of the chest wall and diaphragm. Volume change in an occluded lung causes a mediastinal shift which results in the contralateral open lung volume reversely reflecting approximately 50% of the blocked lung volume change. The remaining 50% volume shift must then be due to movements of the chest wall and diaphragm surrounding the blocked lung. In other words, if 180 ml of gas is aspirated from the left lung and occluded in its collapsed state, the mediastinum pulls over, and the open lung becomes overdistended by a functional residual or resting volume increase of about 90 ml. The other 90 ml volume change is reflected by a movement of the left chest wall and diaphragm toward the collapsed lung. These changes may be explained on the basis of individual lung pressure-volume curves.

The observations and explanations elucidate mechanisms involved in pulmonary occlusion such as atelectasis as well as overdistension occurring behind ball-valve blocks.

REFERENCES

1. Dale, W. A., and H. Rahn "Experimental Functional Separation of Dog Lungs," Jour. Thor. Surg. (In press).

2. Dale, W. A. and H. Rahn "Rate of Gas Absorption During Atelectasis," Am. J. Physiol. 170: 606, 1952.

3. Dale, W. A. and H. Rahn "Ventilation of the Open Lung During Unilateral Experimental Atelectasis," Jour. Thor. Surg. (In press).

4. Pump, K. K. "The Effect on Respiration of the Occlusion of a Bronchus in Man During Bronchospirometry," J. Clin. Invest. 33: 611, Apr. 1954.

5. Jacobaeus, H. C. and T. Bruce "A Bronchospirometric Study of the Ability of the Human Lungs to Substitute for One Another," Acta Med. Scand. 105: 193, 1940.

6. Moore, R. L. "A Study of the Hering-Breuer Reflex," J. Exp. Med. 46: 819, 1927.

7. Rahn, H., A. B . Otis, L. E..Chadwick and W. O. Fenn "The Pressure Volume Diagram of the Thorax and Lungs," Am. J. Physiol. 146; 161, 1946.

8. Van Liew, H. "Pressure-Volume Characteristics of the Chest and Lungs of Dogs and the Contribution of the Vagus Nerves," Am. J. Physiol. 177: 161, 1954.

Residual Volume Measurements by the Gas Expansion Method and Nitrogen Dilution Method

PIERRE DEJOURS[1] AND HERMANN RAHN

THE COMMON PROCEDURES for the determination of the residual lung volume are essentially chemical methods which depend upon a gas analysis before and after dilution with a gas of known volume. Such methods assume that the mixing has been complete. Whether or not homogeneous mixing is obtained may be questioned in those procedures where the subject rebreathes only a few times in a closed system as described by Lundsgaard and Van Slyke (1) and its modification (2) employed in these studies where only three breaths are required. The object of this study was to compare this latter method with a physical method which would not depend upon homogeneous mixing of gases but upon measuring the expansion of the lung gas volume when man is quickly decompressed from one pressure to another.

This expansion method was first used by Pflüger in 1882 (3) and has more recently been tried by Willmon and Behnke (4) who rapidly decompressed their subjects from 4 to 1 atmospheres. Our procedure employed a much smaller pressure difference of .5, .75 or 1 atmosphere and can be done repeatedly and easily without fatigue or danger to the healthy subject.

METHODS

Gas Expansion Method. The procedure is similar to that employed by Willmon and Behnke (4). The subject is seated in a compression chamber and the pressure is raised from atmospheric pressure, P_B, to a higher pressure, P_C. In these studies P_C was 1.5, 1.75 or 2.0 atmosphere. At this new pressure the subject expires completely, closes his glottis and gives the signal for decompression. The lung volume at this instance is the residual volume, V_R, at a pressure of P_C. As the pressure in the chamber is released V_R expands and at the end of 14 seconds (usual time for decompression) has increased by a volume, V_I, at the ambient pressure, P_B. A maximal expiration into a spirometer at this time allows one to measure V_I. The temperature of the spirometer is read. Applying the Law of Mariotte-Boyle where $PV = P'V'$ and making corrections for water vapor in order to change all volumes to B.T.P.S., we have:

$$V_R \times (P_C - 47) = (V_R + V_I)(P_B - 47) \text{ and } V_R = V_I \frac{P_B - 47}{P_C - P_B}.$$

The determination of V_R depends upon the accuracy with which V_I can be measured in the spirometer. The larger the pressure drop the larger is V_I. In these experiments a mean pressure difference of 0.5, 0.75, or 1.0 atmosphere was used.

[1] Fellow of the French Government; on leave of absence, Faculté de Médecine de Paris.

Lung Gas Mixing Method. This method has been previously described (2) and utilizes the N_2 dilution after rebreathing three times a known volume of pure oxygen. After a complete expiration the seated subject inhales and exhales once every 3 seconds the full contents of a bag containing 2 liters of pure oxygen. After the third expiration a sample of the mixed gases is analyzed in duplicate with a 0.5 cc. Scholander analyzer. From the observed dilution of the normal alveolar N_2 concentration the residual volume can then be calculated.

TABLE 1. COMPARISON OF RESIDUAL VOLUMES, V_R, OBTAINED BY EXPANSION AND MIXING METHODS. ALL VOLUMES ARE EXPRESSED IN CC. AT B.T.P.S.

SUBJECT		B. R.	P. S.	P. D.	F. C.	H. R.	GRAND MEAN
		Residual volume by expansion method:					
$\frac{P_C - P_B}{}$							
.5 atm.	n	8	8	9	6	11	
	V_R	1939	2014	1487	1182	2430	
	S.E.	122	217	68	96	72	
.75 atm.	n	6	7	8	5	8	
	V_R	1724	1623	1349	1173	2399	
	S.E.	52	197	53	66	48	
1.0 atm.	n	7	7	8	7	8	
	V_R	1975	1520	1358	1190	2250	
	S.E.	146	91	63	64	50	
Mean	n	21	22	25	18	27	
	V_R	1890	1732	1402	1182	2367	1715
	S.E.	70	112	37	42	36	
		Residual volume by mixing method:					
	n	6	6	6	7	6	
	V_R	1709	1387	1590	1611	2010	1661
	S.E.	88	22	94	38	40	
$\frac{V_R\text{-expansion method} \times 100}{V_R\text{-mixing method}}$		110.5	124.5	94.0	73.5	117.8	103
Vital capacity		4971	5145	4832	5380	6225	5311

RESULTS AND DISCUSSION

For each pressure difference of 0.5, 0.75 and 1.0 atmospheres, five to nine determinations of V_R were obtained in each of five healthy subjects. All lung volumes are expressed at B.T.P.S. The results are given in table 1 and may be compared in each subject with those obtained by the gas mixing method. A statistical treatment indicates that the values calculated at pressure differences of .5, .75 and 1.0 atmosphere in any one subject are not significantly different. The same conclusion applies when the mean values of all subjects are compared at these three pressure differences. This would suggest that all of these pressures are equally reliable and produce homogeneous results. Of course it does not attest to the accuracy for the determination of residual air volumes.

When the results obtained by the mixing method are compared with the mean values obtained by the expansion method one finds no significant difference (Student —Fisher *t* test) in three subjects. In *subject F. C.* the mixing method yields a significantly higher lung volume and in *subject H. R.* a significantly lower lung volume. A priori, one cannot ascribe these differences to the failure of one or the other technique employed.

It was the original purpose of this study to demonstrate the possibility of unequal mixing by the N_2 dilution technique employed here. A consistently higher V_R by the expansion method, which does not require mixing, would have suggested this. The present finding, however, indicates a fairly good agreement between these two methods. Willmon and Behnke (4) reached similar conclusions comparing the volume expansion method with two other N_2 washout methods. In their study they decompressed their subjects from 4 atmospheres to 1 atmosphere. Although they did not observe any signs of air emboli, they did observe fatigue in repeated daily determinations. Decompression of .5 to 1.0 atmosphere, however, is easily tolerated and could be repeated several times in succession.

TABLE 2. ALVEOLAR CO_2 FRACTION AT 2 ATMOSPHERES AND IMMEDIATELY AFTER DECOMPRESSION TO 1 ATMOSPHERE. TIME FOR DECOMPRESSION WAS 14 SECONDS

	P MM. HG	% ALVEOLAR CO_2 IN SUBJECT			MEAN
		F. C.	P. D.	H. R.	
Before compression	747	5.4 5.8 5.5	5.4 5.0 5.0	5.6 5.7	5.4
At 2 atmospheres	1510	2.5 2.2 2.2	2.4 2.3	2.2 2.3 2.4	2.3
Immediately after decompression from 2 to 1 atmospheres	747	6.0	5.5	5.8	5.8

Although the expansion method is free from the criticism of unequal mixing, there are other factors which can alter the accurate determination of V_R by this method. In the first place there must be an excess removal of nitrogen from the circulation during the 14 seconds of decompression. This amount can be calculated (2) and would not exceed 12 cc. Probably of greater consequence is the excess CO_2 elimination during the decompression. In order to evaluate this factor the alveolar CO_2 was determined at 2 atmospheres just before and immediately after decompression in three subjects. The values are found in table 2. Had no CO_2 entered the lung during this 14-second interval, then the average lung volume of these three subjects would have contained 1740 cc. $\times$ 2 $\times$ 2.39 per cent CO_2 or 80 cc. CO_2. However, the alveolar CO_2 after decompression had attained a value of 5.8 per cent and the total amount of CO_2 was 3480 cc. $\times$ .058 or 200 cc. (In this example the small correction for water vapor has been omitted.) Therefore, the volume increment, V_I, recorded in the spirometer was augmented by (200 — 80) or 120 cc. and the determination of V_R would be larger by the same amount.

On the other hand one may assume that the oxygen uptake of the blood proceeds at the normal rate during this breath holding maneuver of 14 seconds (5) Thus with a resting oxygen uptake of 300 cc/min. one may expect a volume reduction

equal to 14/60 × 300 or 70 cc. Thus the net effect of the CO_2 and O_2 exchange would result in a net increase of (120 − 70) or 50 cc.

This increase in volume may possibly be offset by a mechanical factor which inadvertently comes up in the maneuver of holding the glottis closed during decompression. The subject is so intent upon trying to prevent any gas escape that he may not allow his chest to relax sufficiently while the lung gases expand during the decompression. Thus a positive pulmonary pressure is developed as in a Valsalva maneuver. It has been shown recently (6, 7) that even with a slight positive pulmonary pressure of 10–40 mm. Hg, the vital capacity can be increased up to 2 per cent in the sitting position. This effect has been linked with a reduction of the pulmonary blood volume, thus making more room for air. If similar factors operated during the decompression, the measured volume increment would be reduced by approximately (.02 × 5000) or 100 cc. and would offset the CO_2 increment described above.

Summary

In the gas expansion method for the determination of residual lung volume five subjects, after a complete expiration, were rapidly decompressed from 1.5, 1.75 or 2.0 atmospheres to 1 atmosphere. The resulting volume increment from the remaining lung volume was measured in a spirometer and the residual volume calculated. When these results were compared with values obtained by a N_2 dilution method (2) no systematic differences could be established. The various factors which may contribute to the errors of the expansion technique are discussed.

REFERENCES

1. Lundsgaard, C. and D. D. Van Slyke. *J. Exper. Med.* 27: 65, 1918.
2. Rahn, H., W. O. Fenn and A. B. Otis. *J. Applied Physiol.* 1: 725, 1949.
3. Pflüger, E. *Pflüger's Arch. f. d. ges. Physiol.* 29: 244, 1882.
4. Willmon, T. L. and A. R. Behnke. *Am. J. Physiol.* 153: 138, 1948.
5. DuBois, A. B. *J. Applied Physiol.* 5: 1, 1952.
6. Bahnson, H. T. *J. Applied Physiol.* 5: 273, 1952.
7. Fowler, R. C., M. Guillet and H. Rahn. *Air Force Tech. Report* 6528: 522, 1951.

Radiographic Anatomy of Heart and Pulmonary Vessels of the Dog with Observations of the Pulmonary Circulation Time[1]

H. RAHN, R. C. STROUD AND H. MEIER

DURING THE LAST FEW YEARS the dog has become increasingly useful for various types of cardiac and pulmonary vessel catheterization. Although good angiocardiographic studies are available for guiding catheterization in man, similar studies of the dog heart were not found in the literature. Of particular interest is the fluoroscopic anatomy of the lateral aspect of the wedge-shaped chest of the dog since this view provides less density than the A.P. projection and in our hands provides the easiest approach to catheterization. This study presents a brief fluoroscopic anatomy of the dog's heart and pulmonary vessels. The angiocardiograms were recorded on a large number of cinefluorographic films prepared for us through the courtesy of the Department of Radiology. This technique has been described elsewhere (1). The actual procedure for catheterizing the pulmonary artery and pulmonary vein in the dog has been described recently in some detail (2).

METHOD

Dogs weighing approximately 20 kg. were anesthetized with sodium pentobarbital. A Bard X-ray catheter, size no. 11, or a no. 10 polyethelene tube was inserted into the external jugular vein. The catheter tip was placed either into the inferior vena cava, right atrium, ventricle, coronary sinus or various regions of the pulmonary artery. Twenty cubic centimeters of Thorotrast (24–26% ThO_2 by vol.) were then injected within 2 to 3 seconds. Just prior to the injection the moving picture camera was started, exposing 15 or 30 frames per second for a period of 10 to 15 seconds. A continuous film strip, double printed, allows one to visualize the whole progression of the radio-opaque material through the heart and lung. Detailed studies of the anatomy were done by tracing projections of individual frames.

RESULTS

The lateral aspect of the dog's chest provides generally the clearest picture and all figures given present this aspect. The cinefluorography was done with the dog in the supine position and all the drawings (figs. 1, 3 and 5) were made in this position. The X-ray photographs showing the positions of no. 10 catheters (figs. 2, 4 and 6) were reproduced from still pictures with the dog lying on its side. This will shift the heart and vessels to some extent and therefore the drawings and X-ray photographs are not necessarily superimposable. The line drawings represent the average contours obtained from some 12 movie films.

[1] The authors are greatly indebted to Dr. J. S. Watson and Mr. S. A. Weinberg of the Department of Radiology for their generous aid in the cinefluorography.

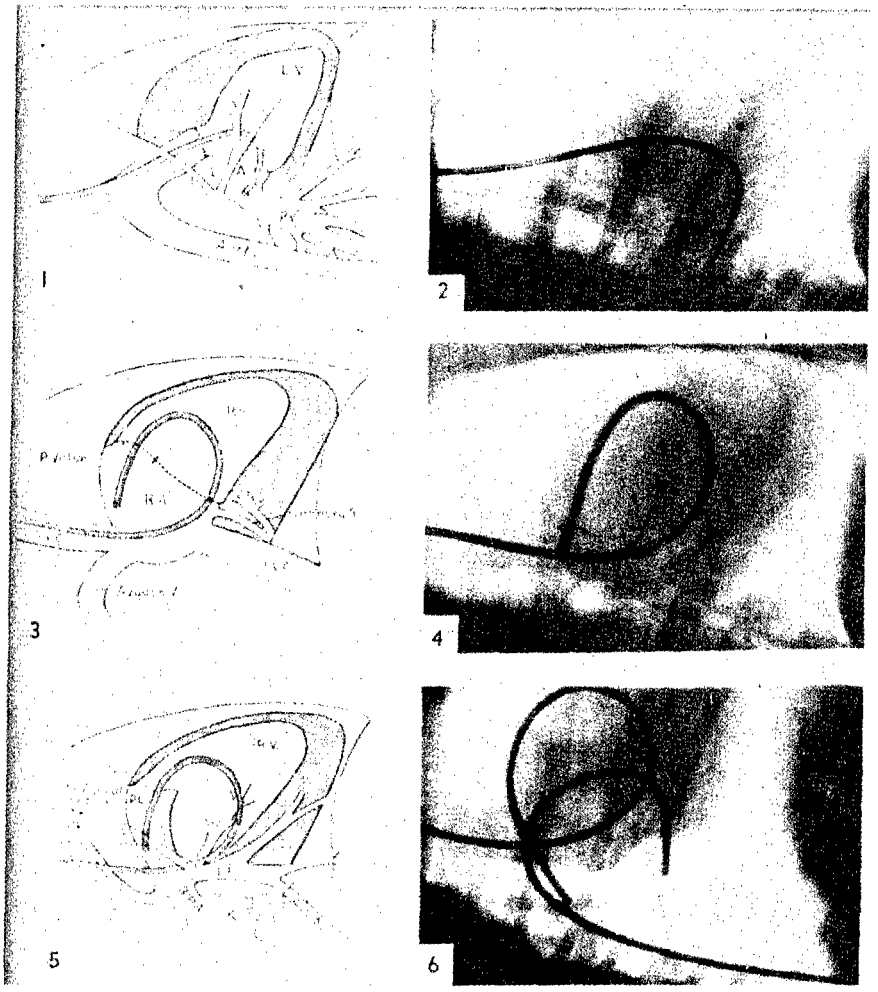


Fig. 1. LEFT VENTRICLE, *L. V.*; left auricle, *L. A.*; and confluence of the pulmonary veins, *P. V.* The two anterior veins drain the apical and middle lobe, the remaining branches drain the diaphragmatic lobe. It can be seen that the catheter in this position is apt to occlude against the wall of the atrium when it is advanced since its natural curvature does not easily follow the contours of the thin-walled veins.

Fig. 2. X-RAY PICTURE corresponding with figure 1 showing a no. 10 catheter advanced retrogradely from the common carotid to the confluence of the pulmonary veins.

Fig. 3. LATERAL ASPECT OF THE MAJOR VEINS leading to the right heart. *Dotted line* indicates the location of the A-V valve and pulmonic valve. Superior and inferior vena cava, *S. V. C.* and *I. V. C.*; right atrium, *R. A.*; right ventricle, *R. V.*

Fig. 4. X-RAY PICTURE corresponding to figure 3 showing the tip of the catheter in the common pulmonary artery.

Fig. 5. MAJOR BRANCHES OF THE PULMONARY ARTERY (slightly oblique aspect). The areas occupied by the letters *L. P. A.* and *R. P. A.* (left and right pulmonary artery) are actually the upper regions of the diaphragmatic branches. Just anteriorly one can see the branches to the medial and apical lobes.

Fig. 6. X-RAY PICTURE with catheters ending in the pulmonary artery—diaphragmatic branch (*left*) and the pulmonary vein (*right*). The latter has been introduced through the femoral artery. The pulmonary artery catheter is similar to figures 3 and 4.

TABLE 1. CIRCULATION TIME OF THE DOG FROM THE PULMONARY CONUS TO THE ARRIVAL AT THE LEFT ATRIUM

Film	1	2	3	4	5	6	7	8	9	Mean
Seconds	2.7	2.5	2.4	2.0	2.4	2.9	4.2	4.0	2.1	2.8

CIRCULATION TIME OF PULMONARY CIRCUIT

In nine films the circulation time was determined by counting the frames between the first appearance of the radio-opaque dye in the pulmonary conus and its first arrival in the left atrium. Table 1 gives the values obtained in dogs weighing 20.5 to 23.6 kg. (except *dog 9*—11.4 kg.). On the assumption that the average of 2.8 seconds is close to the mean circulation time and the volume flow of blood is 55 cc/sec. (average cardiac output obtained on dogs of similar weight in this laboratory), the average circulating volume in the pulmonary vessels is 55 × 2.8 or 154 cc. This is approximately equal to 9 per cent of the total blood volume.

REFERENCES

1. RAMSEY, G. H. S., J. S. WATSON, T. B. STEINHAUSEN, J. J. THOMPSON, F. DREISINGER AND S. A. WEINBERG. *Radiology* 52: 684, 1949.
2. HADDY, F. J., G. S. CAMPBELL, W. L. ADAMS AND M. B. VISSCHER. *Am. J. Physiol.* 158: 89, 1949.

Visualization of Arterio-Venous Shunts by Cinefluorography in the Lungs of Normal Dogs.*

HERMANN RAHN,† ROBERT C. STROUD, AND CHARLES E. TOBIN.‡

Catheterization of the pulmonary vessels in man and animals is currently a common procedure for experimental and diagnostic purposes. Frequently the catheters are advanced peripherally in branches of the pulmonary artery until they occlude the vessel in order to record "pulmonary capillary" pressure or to obtain arterialized blood samples by retrograde flow. In view of this technic and the many descriptions of arterio-venous shunts in

* This study was supported in part by funds from the Air Materiel Command, Wright Field,† and by a grant from the National Heart Institute of the U. S. Public Health Service.‡

the lungs of mammals it is of interest to report that following the occlusion or "jamming" of the pulmonary artery by a catheter, large A-V shunts can be visualized by cinefluorography. Since Prinzmetal *et al.*(1) have shown that glass spheres, many times the diameter of capillaries, will pass through the pulmonary vessels of the dog, cat, and rabbit, the presence of arterio-venous (A-V) shunts in mammalian lungs have received attention for their role in blood gas analyses(2), the passage of parasites through the lung(3) and the formation of arterio-venous aneurysms(4-7). Although A-V shunts were not observed in isolated human lungs by some investigators(8,9), they have more recently been demonstrated within the lobules and visceral pleura(10) by the use of the glass sphere technic of Prinzmetal *et al.*(1) followed by the injection of radiopaque media, vinyl acetate or liquid latex.

Method. Four dogs, with body weights of 40-55 lb, were anesthetized with Veterinary Nembutal (1 cc/5 lb). A Bard x-ray, whistle tip catheter, size No. 11, with openings at the tip and at 1 and 2 cm proximal to the tip, was passed into the jugular vein, right atrium and ventricle, and into the pulmonary artery. The progress and final position of the catheter were determined by fluoroscopic examination. During each cinefluorographic study, 20 cc of Thorotrast (24-26% ThO_2 by vol.) was injected in 2 to 3 seconds and 15 or 30 frames of 35 mm film per second were exposed for a period of 10 to 15 seconds.

Results. With the tip of the catheter in the pulmonary conus, the contrast medium passed into and through the pulmonary artery and veins, the left chambers of the heart and the aorta. But if the catheter was later advanced further (about 4 cm for dogs No. 1, 3, and 4) or retracted and then reinserted (No. 3) until "jammed" into the pulmonary artery of the left lower lobe, there was little filling of the branches of the pulmonary artery; most of the Thorotrast passed from one of the proximal openings in the catheter via an A-V shunt into the left chambers of the heart. In another instance (the second injection of dog No. 4) when an attempt was made to withdraw the catheter, arterial spasm held its distal end firmly but after several forceful trials, the catheter was dislodged and withdrawn until its tip was in the pulmonary conus. The injected Thorotrast in this case refluxly filled both major branches of the pulmonary artery and its smaller branches. Although the shunt could not be visualized with certainty, the left atrium contained some radiopaque medium before the remainder had traversed the pulmonary veins, indicating that the shunt must have remained open even though the catheter was removed from the pulmonary artery.

In one dog (No. 2) no evidence of A-V shunts was noted. The Thorotrast coursed normally through the pulmonary vessels of this animal both when the catheter tip was 4.5 cm out from the pulmonary conus and one-half hour later, when it was advanced about 2.2 cm still further.

Additional confirmation of the A-V shunt was obtained in dog No. 1 when one catheter was inserted into the pulmonary conus and another passed retrogradely through the femoral artery into the aorta, until the tip of the latter was just above the semilunar valves (dog No. 1). While this dog was breathing 30% O_2, several hundred glass spheres, 200 $\pm$ 25 μ in diameter, in saline were injected via the catheter into the pulmonary artery. Three seconds after introducing the spheres, 10 cc of arterial blood was withdrawn as rapidly as possible from the aortic catheter and one glass sphere was recovered. Repeating this procedure, but with the animal breathing 10% O_2, 2 spheres were recovered. This dog was killed and the heart and lungs removed as a unit. The pulmonary arteries were injected with red, and the veins, with blue vinyl acetate, respectively. The casts of the pulmonary vessels were obtained according to the technic of Tobin and Zariquiey(10) and revealed the presence of an A-V shunt in the inferior lobe of the left lung.

Discussion. In a routine study of the anatomy of pulmonary vessels of dogs by cinefluorography it was discovered that A-V shunts in the lung could be readily visualized when the catheter was advanced until it "jammed" in the pulmonary artery. In 12 dogs with the catheter tip in the right atrium,

ventricle, pulmonary conus or the proximal part of the pulmonary artery, no evidence of A-V shunts was ever seen with the injection of Thorotrast. However, with deliberate "jamming" of the catheter into a branch of the pulmonary artery, A-V shunts were seen in 3 of 4 dogs. It is suggested that the irritation produced by the catheter may cause the pulmonary vessels to constrict around the catheter as well as peripherally and thus force the injection material through A-V shunts. Another explanation is that this irritation may cause the A-V shunts to open without need of greater filling pressure.

Summary. A shunt between the pulmonary artery and vein was demonstrated in 3 of 4 dogs by injecting Thorotrast into a catheter inserted tightly into the pulmonary artery and following the circulation by cinefluorography. In one of these dogs the passage of glass spheres 200 $\pm$ 25 μ in diameter, through a cannula in the pulmonary artery, to and through a cannula in the aorta, together with the location of the shunt from plastic casts of the pulmonary vessels, help to confirm the presence of the shunt.

The authors are greatly indebted to Dr. J. S. Watson and Mr. S. A. Weinberg of the Department of Radiology, for their aid in the cinefluorography. This technic has been previously described(11).

1. Prinzmetal, M., Ornitz, E. M., Jr., Simkin, B., and Bergman, H. C., *Am. J. Physiol.,* 1948, v152, 48.

2. Riley, R. L., and Cournand, A., *J. Applied Physiol.,* 1949, v1, 825.

3. Brink, A. J., *Quart. J. Med.,* 1950, N.S., v19, 239.

4. Yater, W. M., Finnegan, J., and Griffin, H. M., *J.A.M.A.,* 1949, v141, 581.

5. Carswell, J., Jr., *J. Thoracic Surg.,* 1950, v19, 789.

6. Lawrence, E. A., and Rumel, W. R., *J. Thoracic Surg.,* 1950, v20, 142.

7. Lindskog, G. E., Liebow, A., Kausel, H., and Janzen, A., *Ann. Surg.,* 1950, v132, 591.

8. Miller, W. S., *The Lung,* Charles C Thomas, Springfield, Ill., 1950.

9. Liebow, A. A., Hales, M. R., Harrison, W., Bloomer, W., and Lindskog, G. E., *Yale J. Biol. and Med.,* 1950, v22, 637.

10. Tobin, C. E., and Zariquiey, M. O., PROC. SOC. EXP. BIOL. AND MED., 1951, v75, 827

11. Ramsey, G. H. S., Watson, J. S., Steinhausen, T. B., Thompson, J. J., Dreisinger, F., and Weinberg, S. A., *Radiology,* 1949, v52, 684.

A Self-Guiding Catheter for Cardiac and Pulmonary Arterial Catheterization and Occlusion.

M. LATEGOLA AND H. RAHN

In closed-chest dog preparations, catheterizations of the right heart and pulmonary arteries are usually accomplished with radiopaque catheters which are placed by manipulation with fluoroscopic visualization(1). The catheter described below enjoys certain advantages in that it can be placed quite rapidly without apparent trauma to the heart and vessels, it can be easily constructed and above all, it does not require a fluoroscope for placement. It is particularly suited to experimental procedures where pressure recording and blood sampling are desired. Furthermore, it may also be used to block the blood flow at some particular site.

This catheter has been used routinely in this laboratory for two years. Its success is due mainly to its large degree of flexibility whereby a small inflatable balloon located at its tip is able to guide the catheter automatically in the direction of the blood flow from the veins through the right heart and into the pulmonary artery.

Construction of Catheter. The catheter (Fig. 1) is approximately 3 feet long and consists of 2 tubes. The outer tube, through which pressures are recorded or blood samples are withdrawn, consists of polyvinyl† (O.D. 3.2 mm; I.D. 2.4mm). The other tube consists of polyethylene‡ (O.D. 1.27 mm; I.D. 0.86 mm) and is placed inside. It emerges through the wall of the larger tube at each end where it is secured by thread as indicated in the figure. This tube serves to inflate the balloon which consists of the tip of a rubber "finger-cot", likewise fastened by thread after first flame-flanging the polyethylene tip. The thread-covered areas are coated with liquid latex and are vulcanized by a 20-second exposure to the vapors of sulfur monochloride. A No. 13 gauge needle is fitted into the lumen of the larger tube and a No. 20 gauge needle serves the smaller tube for attachment to a three-way stop cock and syringe, respectively.

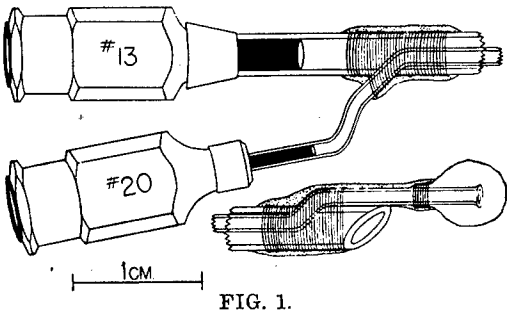


FIG. 1.
Detailed construction of a self-guiding catheter.

Placement procedure. The above catheter size serves adequately for dogs of 20 kg or more. The larger tube is filled with saline and connected to either a gravity-feed, heparinized-saline drip or a saline manometer by means of a 3-way stop cock. The smaller tube is attached to a 10 cc syringe which also contains saline. The catheter is introduced into the jugular vein with a balloon in a deflated state. The 3-way stop cock is then turned to record pressure in the manometer via the larger tube. The manometer is set to zero with reference to venous pressure in the vicinity of the heart. One cc or more of saline is then injected into the balloon. As the catheter is slowly advanced into the jugular vein, the partially inflated balloon, acting like a sail, is swept into the right heart by the blood flow. The entrance of the balloon into the right ventricle is signalled on the manometer by a rise in pressure from zero to that of mean right ventricular pressure. This is usually about 10 cm H_2O. With the balloon still inflated, further slow admittance of the catheter allows the balloon to be swept into the pul-

† No. 12 transflex extmold plastic tubing—Irvington Varnish and Insulation Co., Irvington, N. J.

‡ Tubing PE-90-Clay-Adams Co. Inc., 141 E. 25th St., New York City.

monary arterial system. This event is signalled by a further rise in pressure to approximately double that of the mean right ventricular pressure. The balloon can now be deflated and the three-way stop cock turned from the manometer to the saline drip to prevent clotting. The entire catheterization procedure takes approximately 5 minutes. The maximum time of passage through the right heart is usually no more than a few seconds.

For acute occlusion of the pulmonary arteries or the chambers of the right heart, the balloon may be reexpanded. Right or left pulmonary artery occlusion is usually obtained with 5-7 cc of saline. If specific placement of the balloon is required, this system may be filled with a radio-opaque liquid instead of saline and placed by means of fluoroscopy.

Discussion. The success with which these catheters are placed is due mainly to their complete flexibility. In contrast to the usual stiff radio-opaque catheters, these cannot be "guided" at all and depend entirely for their directional movement on the flow of blood pushing the partially inflated balloon through the chambers of the heart—hence "self-guiding". It should therefore be emphasized that the much more flexible polyvinyl plastic is necessary and that substitution of the stiffer polyethylene plastic for the outside tube is not recommended.

If the catheter is truly self-guiding, no skill should be necessary for its placement once it has been inserted into the jugular vein. This has been repeatedly verified by asking medical students and other staff members to place this catheter into the pulmonary artery merely by watching the pressure rise in the saline manometer as they slowly advance the catheter into the jugular vein. The branching of the two main pulmonary arteries is such that this catheter will in most instances enter the left pulmonary artery.

One disadvantage of this catheter is the clots which frequently develop along the folds of the balloon. These, however, are minimal in size and number and have not interfered with the experimental procedures.

Summary. 1. A self-guiding catheter has been described for placement in the right heart or pulmonary arteries of dogs. 2. This technic does not require a fluoroscope and localization is determined from the pressure recording 3. The same catheter has likewise been used routinely for occlusion of the left pulmonary artery.

1. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF. and Richards, D. W., Jr., *J. Clin. Invest.* 1945, v24, 106.

Indwelling Pulmonary Arterial and Venous Catheters in the Dog

R. C. Stroud, K. R. Stetson, and H. Rahn.

In order to obtain pressure measurements or blood samples from the pulmonary vessels of unanesthetized animals over a long period of time, investigators have usually resorted to externalizing the blood vessels to the chest wall by various types of cannulas. This requires major surgery. The following method describes a relatively simple procedure for placing and securing polyethylene tubes in the pulmonary artery or vein without resort to major surgery. They are introduced through the external jugular vein and common carotid artery, respectively. Catheters in the pulmonary artery have been retained in dogs up to two months. Such animals seem to keep in perfect health.

Placing the catheter into the pulmonary artery. Polyethelene tubes having an inside diameter of 1.27 mm (Clay-Adams cat. No.

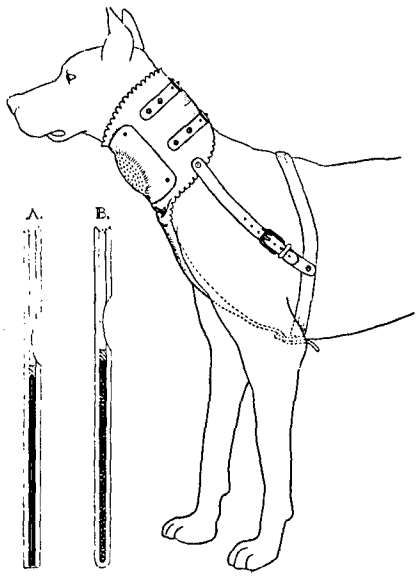


FIG. 1. A collar designed to protect the free ends of the indwelling tubes leading to the pulmonary artery and vein. A perforated metal plate bulges outward over the area of the incision. For fluoroscopic visualization the polyethelene tips were provided either with a nail (A) or mercury (B). (See text.)

PE 90) were cut to 100 cm lengths. In order to visualize the tip under the fluoroscope, our original method was to push a small, tight fitting nail into the end of the tube, after first removing its point and head. The metal piece was then sealed in place with glyptal and a smooth edged hole cut in the tube just behind the nail. More recently we have sealed off one end by heat and filled the tube with mercury for a distance of about two centimeters. A small hole is cut just above the level of the mercury which is sealed in place with glyptal. This latter method has the advantage of supplying a flexible catheter tip which is less likely to cause tissue damage. Longitudinal sections of each type of catheter tip are shown in Fig. 1.

The dogs were anesthetized with nembutal, and their necks shaved and cleaned. A section of jugular vein was exposed through a small incision, tied off distally, and the tube inserted through a small cut in the vein. A slow saline drip was started. With the dog lying on its side, the catheter tip was visualized under the fluoroscope and advanced into the right ventricle. In order to move the tip beyond this point, it was necessary to remove the saline drip and insert a stiff, flexible wire to within about 2 cm of the opening. With this extra support the tip of the catheter could now be moved along the inside curvature of the ventricle towards the pulmonary artery. This was most readily accomplished by advancing the tube a few centimeters, withdrawing the wire a few centimeters, advancing the tube, etc., until the tip was headed towards the artery. The wire was then withdrawn and the tip brought to the desired position in the artery, usually the diaphragmatic branch. After the saline drip had been started again, the loose ends of a tight ligature securing the catheter to the vein were sewn through the skin and tied. In order to permit drainage, no other stitching was done. The tube was then filled with heparin solution (50 mg/ml), and plugged, folded in loops, and taped to the neck with thin strips of adhesive tape. 600000 units of procain-penicillin were injected intramuscularly. A collar was designed to protect the free end of the catheter and yet allow free access of air to the incision. It consists of a wide piece of leather which covers the whole neck. A section of perforated sheet metal bulges outward over the area of the incision, allowing air to reach the wound. The collar is fastened with buckles and straps. To prevent twisting of the collar, a leather strap is fastened around the body just behind the forelegs and three straps connect it to the collar, 2 near the shoulder and one between the legs. The collar, as it appears on the dog, is illustrated in Fig. 1.

Placement of catheter into the pulmonary vein. The polyethelene tubes were prepared similar to those described above except that they are about 200 cm in length. A section of the common carotid artery was exposed through a small incision and tied off distally. A No. 10 radio-opaque cardiac catheter was inserted into the artery with a pressurized saline drip. After the catheter had been advanced in a retrograde manner into the low pressure system of the pulmonary vein, the saline drip was discontinued and the polyethelene tube threaded through the catheter until its tip was visible under the fluoroscope. By careful manipulation the regular cardiac

catheter could be withdrawn leaving the polyethelene tube in place. Two fine wire ligatures were tied around the carotid artery to secure the tubing and stitched through either side of the incision in such a way as to externalize the cut end of the artery.

Results. Wound healing was found to occur within about 10 days provided penicillin was infiltrated in the incision during the operation. Seven dogs were prepared with indwelling catheters in the pulmonary artery and lived in apparent health and good spirits. Three of these animals retained these tubes for 41, 50 and 56 days, respectively. No clotting occurred in the tubes provided the heparin was changed at least once or twice a week. Blood samples could be withdrawn at any time and the pressures measured. At various times after successful healing in of the pulmonary arterial tubes, the catheterizations of the pulmonary veins were made. Contrary to the successful results on the pulmonary arterial side apparently considerable trauma is caused by the pulmonary venous catheters. In spite of all possible therapeutic measures wound healing was slow. The dogs lost their spirit and usually succumbed within 10 days unless the catheter was withdrawn. Autopsies revealed interlacing antemortem clots, raised hard plaques lining the vessel walls and inflammation of heart valves. The evidence strongly indicates that death was a consequence of the placing of the pulmonary venous catheter.

Summary. A method is described for placing permanent polyethelene catheters into the pulmonary artery and vein of dogs through the jugular vein and common carotid artery, respectively. The pulmonary artery catheter seems to cause little trouble to the animals and has been kept in place up to 56 days for sampling blood and measuring pressures. The pulmonary vein catheters, however, cause considerable trauma and animals succumb within 10 days after placement of the tube.

Effect of O_2 and CO_2 Tensions Upon the Resistance of Pulmonary Blood Vessels

ROBERT C. STROUD AND HERMANN RAHN

In very recent years attention has been focused upon the effect of lowering the oxygen tension of the inspired air and the concomitant rise in pulmonary arterial pressure, as first reported by v. Euler and Liljestrand (1). This response was interpreted by them as evidence for vasoconstriction, although the possible contribution of an increased blood flow to this pressure rise was not determined.

More recent studies attempting to confirm or deny the conclusions of v. Euler and Liljestrand have employed one of three types of experiments: *1*) the isolated lung or heart-lung preparation (2–9), *2*) the divided lung preparation (10–15) and *3*) cardiac catheterization of the human (16–19). Although, in general, these experiments have shown evidence for hypoxic pulmonary vasoconstriction, the results obtained with the isolated lung preparation are open to criticism on technical grounds (7); those obtained with the divided lung preparation depend upon indirect estimation of the blood flow through each lung, while catheterization studies with the human have not permitted direct measurement of the pulmonary venous pressures.

It is the purpose of this study to provide more concrete evidence for the concept of pulmonary vasomotion in the dog, induced by alterations of the inspired O_2 tensions. In order to do so, two simultaneous measurements are necessary, *1*) the pressure drop across the pulmonary vessels and *2*) the volume flow of blood through the lungs. This allows one to calculate, according to Poiseuille's law, any quantitative changes which occur in the resistance to flow through the pulmonary vessels, as well as to estimate the direction of changes in vessel caliber. The results of this study (20) are essentially in agreement with those of Lewis and Gorlin (21) reported recently.

Experimental Procedure

Dogs weighing 20 to 25 kg. were anesthetized with intravenous Nembutal (28 mg/kg.). A No. 8 single lumen Cournand cardiac catheter was placed with the tip in the main pulmonary artery and a no. 10 catheter was placed with the tip at the confluence of the pulmonary veins. The larger size catheter was used in the latter case in order to facilitate the drawing of blood samples. The exact positions required for the catheter tips had previously been determined by numerous studies of cinefluoroscopic films to be described elsewhere.

Pressure measurements were obtained through these catheters by means of

saline manometers and then, during the time that simultaneous blood samples were being withdrawn slowly from the two catheters into syringes containing just enough heparin (50 mg/ml.) to fill the dead space, a timed volume of expired air was collected in a Tissot spirometer. Thus, both blood and gas samples were obtained during the same period of time which averaged about 1 minute in length.

The oxygen and carbon dioxide content of the blood samples were usually determined in duplicate by the Van Slyke manometric technique. However, in other instances the oxygen saturation of the blood was determined instantaneously by means of the Waters-Conley absolute reading oximeter cuvette. The oxygen content was then calculated from the hemoglobin concentration as determined by the recently revised copper sulfate gravity method (22). A correction factor for dog's blood was empirically determined in this laboratory.

TABLE 1. SUMMARY OF AVERAGES FOR CALCULATING PULMONARY BLOOD FLOW RESISTANCES BREATHING VARIOUS GAS MIXTURES

BREATHING	NO. OF EXPER.	$\dot{V}_E$	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}/\dot{V}_{O_2}$	$(A-V)_{O_2}$	$\dot{Q}$	PA	PV	ΔP	R
21% O_2	16	3.08± .31	109± 7	.83±.03	3.6±.2	3.23±.27	17.5±1.2	4.4± .5	13.1±1.1	4.06±.23
8% O_2	16	6.50± .55	114± 7	1.04±.06	3.2±.2	3.78±.30	26.3±1.2	3.8± .5	22.7±1.1	6.01±.45
% of air values		211	104	125	89	117	150	86	173	148
21% O_2	8	3.35± .27	117± 9	.78±.03	3.8±.2	3.13±.29	15.1±1.0	4.6± .9	10.5± .4	3.35±.35
15% O_2	8	4.14± .42	122±14	.89±.12	3.6±.5	3.45±.26	18.7±1.2	4.2± .9	14.5±1.6	4.20±.67
% of air values		124	104	114	95	110	124	91	138	125
21% O_2	6	3.37± .09	113± 7	.81±.03	3.3±.1	3.62±.22	21.6±2.8	5.8± .4	15.8±2.5	4.36±.87
30% O_2	6	3.34± .30	107± 8	.87±.03	3.0±.2	3.65±.55	18.9±1.6	4.8± .7	14.1±1.8	3.87±.77
% of air values		99	95	107	91	101	88	83	89	89
21% O_2	5	3.12± .58	120±17	.74±.04	4.1±.5	3.12±.28	26.9±3.8	4.3±1.0	22.4±1.7	8.49±.38
5% CO_2–25% O_2	5	6.25±1.50	121±17	.68±.03	4.0±.5	3.32±.30	27.4±3.4	5.5±1.1	23.0±1.6	8.32±.37
% of air values		200	101	92	103	106	102	129	103	98

Standard errors of the means are indicated after each value. $\dot{V}_E$ = Volume expired, liters/min. STPD. $\dot{V}_{O_2}$ = Oxygen consumption, ml/min. STPD. $\dot{V}_{CO_2}/\dot{V}_{O_2}$ = Respiratory exchange ratio. $(A-V)_{O_2}$ = Arterial-venous oxygen difference, volumes per cent. $\dot{Q}$ = Cardiac output, liters/min. PA = Pulmonary arterial pressure, cm. H_2O. PV = Pulmonary venous pressure, cm. H_2O. $\Delta P = PA - PV$. R = Resistance = $\Delta P/\dot{Q}$.

The oxygen and carbon dioxide content of the expired air samples were determined in duplicate by the Scholander 0.5 ml. analyzer. The oxygen consumption could then be calculated and the volume flow of blood through the lungs determined by the Fick equation.

This procedure was followed for each gas mixture to which the dog was exposed. Five different mixtures varying in O_2 and CO_2 content were tested. These were 8, 15, 21, and 30 per cent O_2 in N_2 and 5 per cent CO_2 to 25 per cent O_2 in N_2. For any one experiment, two or more mixtures were compared. Ten to fifteen minutes were allowed on any gas before the measurements were begun and after their completion the animal was returned to room air before the next mixture was given.

At the conclusion of the experiment, the catheters were withdrawn and the blood vessels tied off. Procaine-penicillin was injected intramuscularly and complete recovery usually followed in 4 to 5 days, after which the dog could be used again.

A second series of experiments was undertaken in a preliminary effort to investi-

gate the mechanism of hypoxic pulmonary vasoconstriction. Control measurements of the pressure-flow relationships breathing air and 8 per cent oxygen were obtained, as described above, for three dogs. After recovery, these dogs were subjected to a two-stage transthoracic sympathectomy with removal of the sympathetic chain from the level of the middle cervical through the ninth thoracic ganglia.* In order to observe the effects of sympathectomy upon the resistance to pulmonary blood flow, the experiments were repeated 29, 26 and 28 days after completion of the second stage operation for *dogs 11*, *13* and *15*, respectively.

In a final series of experiments, measurements of total ventilation volume, breathing rate, pulse rate, pulmonary arterial pressure and systemic arterial pressure were obtained from seven dogs while breathing air and also each of the other gas mixtures, with the exception of 15 per cent oxygen in nitrogen. Catheterization of the pulmonary artery was accomplished as described above. *Pulmonary arterial pressure* was measured with the saline manometer. *Systemic arterial pressure* was

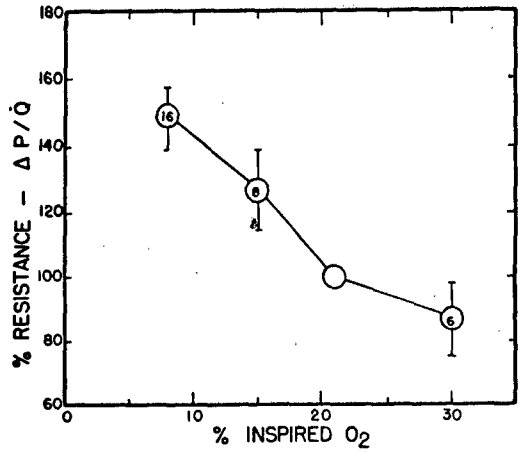


Fig. 1. AVERAGE CHANGES in calculated resistance of pulmonary vessels when various oxygen mixtures were breathed. The calculated resistance breathing air is expressed as 100 per cent. *Numerals* in *circles* indicate the number of dogs. *Vertical lines* indicate the standard deviation of the means. ΔP = Pressure drop between the pulmonary artery and vein. $\dot{Q}$ = Cardiac output.

obtained by passing a no. 10 cardiac catheter through the femoral artery until the tip was located about 10 cm. below the aortic arch. Measurements were made with a mercury manometer attached to the arterial catheter. *Pulse rate* was obtained by counting the heart beats as reflected in the manometer. Ventilation was obtained by collecting a timed sample of expired air in a spirometer. Breathing rate was measured by counting the number of respiratory cycles during the gas collection. Every dog breathed each of the three gas mixtures for 10 minutes before measurements were taken. Control values on room air were obtained 10 minutes before and after each set of experimental determinations.

RESULTS

Normal Dogs. The relationship between pulmonary blood flow and pulmonary blood pressures are summarized in table 1. For each experiment, the pulmonary blood flow and the pulmonary arterial and venous pressures are recorded for a control period breathing air and for the special gas mixtures. From these values, the vascular resistance (R) can be calculated as equal to the pressure drop between the pulmonary artery (PA) and the pulmonary vein (PV) divided by the blood flow ($\dot{Q}$).

* Dr. A. Dale of the Department of Surgery was kind enough to perform the operations.

In general, it may be noted that as the inspired oxygen decreases, the calculated resistance increases. These changes are shown graphically in figure 1 on a percentage basis, with reference to the resistance on air. It should be pointed out that neither the differences in cardiac output nor in pulmonary venous pressure with the different gas mixtures are highly significant. Moreover, no significant alteration in resistance occurs when 30 per cent oxygen is breathed instead of air. Due primarily to changes occurring in the pulmonary arterial pressure, a significant increase occurs in the calculated resistance (R) when either 8 or 15 per cent oxygen is breathed instead of air. This analysis is summarized in the table of P values as calculated by Fisher's t test (table 2).

Sympathectomized Dogs. The resistance changes occurring in the sympathectomized dogs breathing 8 per cent oxygen are shown in table 3. Although each dog showed an increase in resistance before denervation, all three failed to show such a response after the operation.

Ventilation and Blood Pressure Measurements. The results of a separate series of ventilatory and blood pressure measurements are summarized in table 4. It appears that under the condition of the experiments the pulse rate is essentially unaffected by altering the inspired gas, while a significant increase in systemic arterial pressure occurs only when 8 per cent oxygen is breathed.

TABLE 2. PROBABILITY VALUES CALCULATED FOR DIFFERENCES BETWEEN GROUPS BREATHING VARIOUS GAS MIXTURES (SYMBOLS AS IN TABLE 1)

GAS MIXTURES COMPARED	PA	PV	$\dot{Q}$	R
8% O_2–15% O_2	<.001	.693	.745	.002
8% O_2–21% O_2	<.001	.121	.173	<.001
15% O_2–21% O_2	.005	.130	.722	.005
21% O_2–30% O_2	.419	.238	.961	.683
5% CO_2–21% O_2	.923	.604	.631	.757

DISCUSSION

Measurements During the Unsteady State. As the CO_2/O_2 exchange ratios (table 1) indicate, all measurements were made during the unsteady state. When an animal or man is suddenly subjected to a lower oxygen tension at least three factors may be recognized which contribute to this imbalance of gas exchange. The first is the pulmonary washout period with the new gas mixture and is completed in less than 1 minute. The second feature is the temporary reduction in oxygen uptake of the lung which in man lasts about 10 minutes (23). During this period the total oxyhemoglobin and tissue oxygen level is slowly reduced to a new value. This serves as a temporary oxygen source and thus reduces the uptake from the lung. This fact by itself would increase the exchange ratio measured in the expired air. A small increase in exchange ratio is also expected from the temporary nitrogen uptake by the blood when the inspired N_2 pressure is increased as a consequence of lowering the inspired O_2 pressure. Finally, the hypoxic stimulus induces a hyperventilation which lowers the CO_2 level of the blood and tissues. Thus CO_2 stores are liberated and produce high exchange ratios which may not return to normal for 30 to 40 minutes in man (24).

In our experiment at least 10 minutes were allowed before measurements were begun after changing to a new gas mixture. Whether or not a normal CO_2/O_2 exchange ratio (R.Q.) is necessary for describing reactions to an acute oxygen decrease is open to question. The additional release of CO_2 from the body stores (high ex-

change ratio) tells one that the gas exchange has not reached a steady state, yet it does not disclose anything about the steady state of other processes. Furthermore, our so-called normal, anesthetized animals are never in a steady state of gas exchange when breathing air. They undergo a continuous modification in the exchange ratio (25).

Mechanical Factors and Pressure Changes. Judging from the unchanging pulmonary venous pressures in all experiments (see also fig. 2), it would seem that no valvular insufficiency of the left heart was produced by the left heart catheterization. Alteration of the ventilation per se seems to have little effect upon the pulmonary arterial pressure (26, 27). Furthermore, it may be seen that greatly increased ventilation was observed with 8 per cent O_2 as well as with 5 per cent CO_2, yet only with the former gas could a significant rise in pulmonary arterial pressure be demonstrated.

TABLE 3. PULMONARY BLOOD FLOW RESISTANCE MEASUREMENTS BEFORE AND AFTER SYMPATHECTOMY (SYMBOLS AS IN TABLE 1)

	DOG NO.	BREATHING 21% O_2						DOG NO.	BREATHING 8% O_2				
		$\dot{Q}$	PA	PV	ΔP	R			$\dot{Q}$	PA	PV	ΔP	R
Before symp.	*11*	2.37	13.3	2.7	10.6	4.47	Before symp.	*11*	3.50	22.8	2.4	20.4	5.82
	13	3.36	17.4	6.7	10.7	3.19		*13*	3.33	30.0	4.0	26.0	7.55
	15	3.65	29.8	5.7	24.1	6.52		*15*	3.55	33.8	5.0	28.8	8.12
	Mean	3.13	20.2	5.0	15.2	4.72		Mean	3.12	28.9	3.8	25.1	7.17
After symp.	*11*	3.48	22.2	5.6	16.6	4.78	After symp.	*11*	4.32	23.7	4.7	19.0	4.30
	13	3.08	22.6	4.4	18.2	5.90		*13*	4.00	26.1	3.5	22.6	5.65
	15	2.95	20.3	5.3	15.0	5.08		*15*	3.15	22.9	6.6	16.3	5.18
	Mean	3.17	21.7	5.1	16.6	5.25		Mean	3.82	24.2	4.9	19.3	5.04

Interpretation of Resistance Changes. It is evident from Poiseuille's law that in a nonrigid tube the resistance will remain constant at different rates of flow only if the length and radius of the tube, as well as the viscosity of the liquid, remain constant. However, various investigators have shown that, as flow increases, not only do the dimensions of blood vessels become passively altered but also the apparent viscosity of the blood decreases (28–32). Although previous investigations of this problem have been confined to other parts of the circulatory system, Edwards (33) has recently determined the pressure-flow curve for the right diaphragmatic lobe of the dog's lung *in situ*. Curves were obtained with the lungs in the 'inflated' and 'deflated' position, as produced by both positive and negative pressure.

These data of Edwards' may be used to calculate an approximate pressure-flow curve for the total blood flow through both lungs, if one assumes that the flow through any one lobe of the lung is proportional to the weight of that lobe. Measurements recently obtained in this laboratory show that the average weight of a dog's right diaphragmatic lobe is 25 per cent of the total weight of both lungs. Since the pressure in the artery leading to any lobe must be about equal to that in the main pulmonary artery, we may obtain an approximate pressure-flow curve for the total lung circulation if we multiply by four the flows measured at various pressures by Edwards.

The curve thus obtained represents the relationship between the volume flow of blood through the whole lung and the pressure drop between the pulmonary artery and vein, in the absence of vasomotion. In the range of our blood flow and pressure

measurements the pressure-flow relationships are nearly linear. They have been transferred to a relative scale in figure 3 and are indicated by a *solid line*. The *broken line* in this diagram connects the average flows and pressures presented in table 1. In each particular O_2 and CO_2 series the values obtained on air (21%) have been reduced to unity or 100 per cent. The estimated pressure-flow curve also goes through this point. It can be seen that with the low O_2 mixtures the average points lie to the right of the control curve calculated from Edward's data and suggest increasing vasoconstriction as the inspired O_2 tension falls.

By a similar argument, it may be concluded that the average point obtained with 30 per cent oxygen would indicate a vasodilatation while that for the dogs breathing 5 per cent carbon dioxide indicates the absence of vasomotion.

TABLE 4. AVERAGE VENTILATORY AND BLOOD PRESSURE MEASUREMENTS OF SEVEN DOGS BREATHING VARIOUS GAS MIXTURES

BREATHING	f	$\dot{V}_E$	V_T	PA	SP	PR
21% O_2	19 ± 4	4.33 ± .83	217 ± 25	24.9 ± .8	145 ± 5	145 ± 1
8% O_2	35 ± 4	8.94 ± .92	255 ± 14	34.1 ± 2.0	159 ± 6	148 ± 4
% of air values	184	207	118	137	110	102
21% O_2	16 ± 4	3.13 ± .49	196 ± 20	26.4 ± 1.4	139 ± 5	145 ± 4
30% O_2	18 ± 4	4.40 ± .68	244 ± 23	25.5 ± 1.7	144 ± 6	149 ± 3
% of air values	112	141	124	97	104	103
21% O_2	19 ± 3	4.32 ± .91	227 ± 21	26.0 ± 1.4	142 ± 3	147 ± 4
5% CO_2–25% O_2	27 ± 5	11.20 ± 2.3	415 ± 38	25.1 ± .9	143 ± 4	141 ± 2
% of air values	142	260	183	97	100	96

Standard error of the means are indicated after each value. f = Respiratory frequency per min. V_T = Tidal volume, STPD. SP = Systemic arterial pressure, mm. Hg. PR = Pulse rate. Other symbols as in table 1.

Effects of Nembutal Upon the Hypoxic Vasoconstriction. The large variability of the response to breathing the various oxygen mixtures may be due to the depth of the Nembutal anesthesia at the time the measurements were undertaken. Each dog was given the same dose per kilogram of body weight but variations in the amount and distribution of fat, size of the bones etc., as well as variations in individual sensitivity may have resulted in unequal depth of anesthesia for all animals. Thus, one of the dogs failed to show significant vasoconstriction when breathing 8 per cent oxygen and two of the dogs failed to show this response while breathing 15 per cent oxygen. Moreover, during the experiments to determine the ventilatory and systemic cardiovascular responses to low oxygen, it was noted in several cases that the pulmonary arterial pressure did not increase at the first trial but only later after the animal was less deeply anesthetized. One dog failed to show a significantly increased pressure at any time while under anesthesia. A few weeks later, while awake, he showed a large increase in pulmonary arterial pressure as measured through an indwelling catheter (34) while breathing 8 per cent oxygen through a mask.

It is, indeed, recognized that barbiturates can depress the vasomotor center and, moreover, cause dilatation of the smaller blood vessels by direct action upon their walls. With regard to the pulmonary vascular system, Dale (35) observed that the vasoconstrictor effect of stimulating either the vagi or the stellate ganglia was

usually abolished by Nembutal anesthesia in the guinea pig. Woodbury (36) noted with dogs that although the usual response to histamine was an increased pulmonary arterial pressure, deep anesthesia of morphine plus Nembutal would abolish this response.

It would appear, therefore, that Nembutal probably desensitizes the cardiovascular and vasomotor reflexes to some extent. This may not only explain the rather large scatter of results with the various gas mixtures but also may explain why the pulmonary arterial pressure shows a considerably larger increase for the *unanesthetized* dogs breathing 8 per cent oxygen than for those under anesthesia (table 5). Whether this difference is due to a larger increase in cardiac output or to more intense pulmonary vasoconstriction cannot be stated with certainty. However, it seems likely that without anesthesia each dog would display about the same degree of vasoconstriction and unlikely, in view of the probable shape of the pressure-flow curve, that the cardiac output increased enough to account for the pressure change observed.

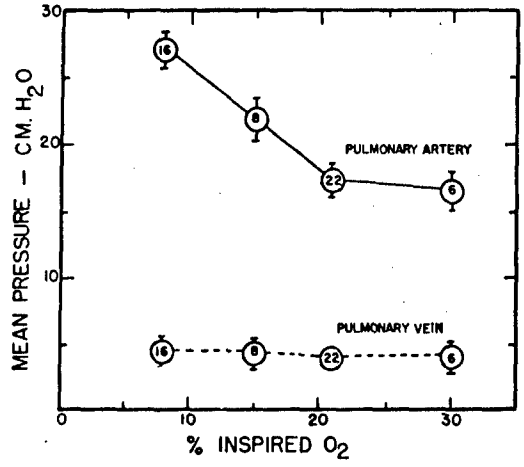


Fig. 2. AVERAGE PRESSURE CHANGES occurring in the pulmonary arteries and veins of normal anesthetized dogs as the inspired percentage oxygen is altered. *Numerals* in the *circles* indicate the number of animals represented. *Vertical lines* indicate the standard deviations of the means.

Sympathetic System in Hypoxic Pulmonary Vasoconstriction. Although the evidence of previous investigators concerning the effects of parasympathetic stimulation is not clear (12, 35, 38–42), we may conclude that sympathetic stimulation causes them to contract (35, 37, 43, 44). As a result of our sympathectomy experiments, we may further tentatively conclude that pulmonary vasomotion, resulting from alterations in the blood or alveolar oxygen tensions, is to some degree dependent upon the sympathetic innervation. Thus, in figure 3 the point labeled 8 per cent-*S* represents the average pressure-flow values obtained when these dogs breathed 8 per cent oxygen. In spite of the fact that the calculated resistance did not change (table 3), a slight vasoconstriction is indicated if we accept the estimated pressure-flow curve. However, this constriction is relatively insignificant when compared with the average changes of the normal dogs.

This conclusion appears to be contradictory to the reports of v. Euler (1) and Dirken (13). The former found that extirpation of the stellate ganglia in the cat had no effect upon the increase in pulmonary arterial pressure observed when a low oxygen mixture was breathed. Since v. Euler did not measure blood flow in his experiments, it is difficult to conclude whether or not vasoconstriction occurred. Dirken

and Heemstra (13) observed with the rabbit that bilateral sympathectomy with removal of the sympathetic chain from the superior cervical ganglia down through the third thoracic had no effect upon the shunting of blood away from the nitrogen breathing lung. The oxygen uptake of the oxygen breathing lung, however, was observed to increase over the presympathectomy level. Dirken points out that even as extensive a sympathectomy as he performed may leave some intact axons in the pulmonary vascular bed. It is also noteworthy that the mechanism of pulmonary vasoconstriction may be of a different nature in the rabbit than in the dog since several hours of breathing low oxygen are necessary in order to demonstrate this response in the former species.

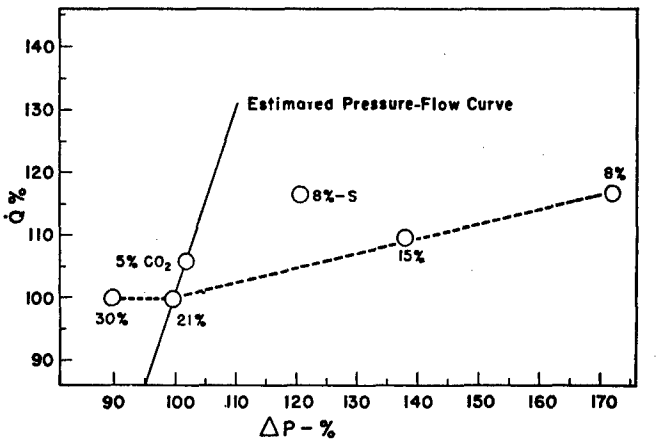


Fig. 3. AVERAGE CHANGES of flow ($\dot{Q}$) and of the pressure drop between the pulmonary artery and vein (ΔP) as the percentage of inspired oxygen or carbon dioxide is altered. All values are expressed as percentages of the values obtained while the animals were breathing room air. The *solid line is* extrapolated from the pressure-flow data of Edwards (1951) as explained in the text. Any point to the *right* of this line indicates vasoconstriction. Any point to the *left* indicates vasodilatation.

Function and Mechanism of Hypoxic Pulmonary Vasoconstriction. At present we may only speculate concerning the physiological purpose, if any, of pulmonary vasoconstriction in response to low oxygen tensions. However, three possibilities have been suggested by various investigators and deserve consideration here. These are protection of the capillary bed from excess pressures (1), regulation of the pulmonary blood pool (39) and distribution of blood to the better ventilated parts of the lung (1, 5, 11).

With regard to the protection of the pulmonary capillary bed, increased arteriolar or arterial resistance would not lower the capillary pressure unless blood flow were thereby reduced. Therefore, increased pulmonary arterial resistance would serve only to increase the pressure which must be developed in the right ventricle in order to maintain the necessary flow.

Similar considerations may be applied to the theory which envisages hypoxic vasoconstriction as a means of altering the pulmonary blood pool. In this case it is conceivable that an increase of resistance to flow through the lungs may result in either an increase or decrease of pulmonary blood volume, dependent upon whether the constriction takes place on the venous or arterial side of the capillary bed. To what extent changes in pulmonary blood pool are effected by such a mechanism is not possible to predict from the available evidence.

It seems, however, quite possible that hypoxic vasoconstriction may be a mechanism serving to shunt blood to the better ventilated parts of the lung. If this is so, it implies that the mechanism must be local in nature. The oxygen content of the blood which enters the veins draining one part must determine, at least partially, the tone of the arterioles leading to that part. This would also be indicated by the divided lung experiments showing that blood is shunted from a nitrogen breathing to an oxygen breathing lung (11, 14, 15).

It is difficult to conceive of a unilateral central reflex mechanism having this degree of selectivity. Thus, it seems reasonable to postulate the action of axon reflexes, the afferent limbs originating on the venous side of the capillary bed. When low oxygen mixtures are breathed, the oxygen tension of the blood from all parts of the lungs becomes reduced and a general arteriolar vasoconstriction occurs.

The possibility of a physiological limit to this reaction has recently been suggested by dog experiments similar to those reported here (21, 45). It was observed that if the arterial oxygen saturation did not fall below 55 per cent, no significant increase in cardiac output occurred and the resistance to flow ($\Delta P/\dot{Q}$) became greater. This is in agreement with the data reported here. However, in extreme hypoxemia with arterial oxygen saturation below 55 per cent, the cardiac output increased 40 to 300 per cent and the resistance did not change. These interesting observations suggest that the vasomotor effects of oxygen are confined to concentrations which

TABLE 5. PULMONARY ARTERIAL PRESSURES IN UNANESTHETIZED DOGS BREATHING 21 AND 8 PER CENT O_2 THROUGH A MASK

DOG NO.	STATE	*PA* (21% O_2)	*PA* (8% O_2)	% OF AIR VALUE
12	Normal	25.2	50.1	199
24	Normal	23.2	49.0	211
13	Sympathectomized	27.8	40.0	144

do not endanger the oxygen supply at the tissue level. Thus, above O_2 saturations of 60 per cent the local action of hypoxic vasoconstriction may serve as a homeostatic mechanism to adjust the ventilation-perfusion ratio in the smaller units of the lung. As long as this ratio is constant in all parts of the lung the pO_2, pCO_2 and pH must be the same (46). For example, normally perfused but underventilated regions have a lower O_2 and higher CO_2 tensions than other parts of the lung supplied by a normal ventilation-perfusion ratio. Should, in such a case, the lower O_2 tensions reduce the local blood flow sufficiently, the ventilation-perfusion ratio and consequently the O_2 and CO_2 tensions would be restored to normal. Complete compensation, however, is not possible for it would remove the necessary stimulus.

When the general O_2 tensions fall below a certain level which may endanger the tissues of the body, this local selective mechanism for shunting blood is discarded in favor of getting all possible oxygen with the least burden on the right heart (45).

SUMMARY

Pulmonary arterial and venous pressures were obtained from anesthetized dogs by the technique of cardiac catheterization. Blood flow was measured by the Fick method. The calculated resistance to the flow through the pulmonary circuit was determined while the animals were breathing 8, 15, 21 and 30 per cent O_2 in N_2, or a mixture containing 5 per cent CO_2, 25 per cent O_2 and 70 per cent N_2. It was found that the resistance increased 25 and 48 per cent as the inspired oxygen tension decreased from 21 to 15 and 8 per cent, respectively, but did not change when the

carbon dioxide tension of the inspired air was raised. An attempt was made to relate these changes to actual alterations in the relative caliber of the pulmonary vessels. It appears that these changes in resistance are produced by actual vasomotion. Three dogs subjected to a two-stage transthoracic sympathectomy failed to show an increased resistance postoperatively when breathing 8 per cent oxygen-nitrogen mixture. The possible significance of these results is discussed.

REFERENCES

1. V. EULER, U. S. AND G. LILJESTRAND. *Acta physiol. scandinav.* 12: 301, 1946.
2. HEBB, C. O. AND R. H. NIMMO-SMITH. *Quart. J. Exper. Physiol.* 34: 159, 1947–8.
3. NISELL, O. *Acta physiol. scandinav.* 16: 121, 1948–9.
4. NISELL, O. *Acta physiol. scandinav.* Suppl. 73: 21, 1950.
5. NISELL, O. *Acta physiol. scandinav.* 23: 85, 1951.
6. NISELL, O. *Acta physiol. scandinav.* 23: 352, 1951.
7. NISELL, O. *Act physiol. scandinav.* 23: 301, 1951.
8. DUKE, H. *Quaart. J. Exper. Physiol.* 35: 25, 1949.
9. DUKE, H. *J. Physiol.* 111: 17P, 1950.
10. JACOBAEUS, H. C. AND T. BRUCE. *Acta med. scandinav.* 105: 211, 1940.
11. DIRKEN, M. N. J. AND H. HEEMSTRA. *Quart. J. Exper. Physiol.* 34: 193, 1947–8.
12. DIRKEN, M. N. J. AND H. HEEMSTRA. *Quart. J. Exper. Physiol.* 34: 213, 1947–8.
13. DIRKEN, M. N. J. AND H. HEEMSTRA. *Quart. J. Exper. Physiol.* 34: 227, 1947–8.
14. RAHN, H. AND H. T. BAHNSON. *Federation Proc.* 9: 102, 1950.
15. ATWELL, R. J., J. B. HICKMAN, W. W. PRYOR AND E. B. PAGE. *Am. J. Physiol.* 166: 37, 1951.
16. MOTLEY, H. L., A. COURNAND, L. WERKO, A. HIMMELSTEIN AND D. DRESDALE. *Am. J. Physiol.* 150: 315, 1947.
17. COURNAND, A. *Circulation* 2: 641, 1950.
18. DOYLE, J. T., S. S. WILSON AND J. V. WARREN. *Federation Proc.* 10: 37, 1951.
19. WESTCOTT, R. N., N. O. FOWLER, R. C. SCOTT, V. D. HAVENSTEIN AND J. MCGUIRE, *J. Clin. Investigation* 30: 957, 1951.
20. STROUD, R. C. AND RAHN, H. *Federation Proc.* 11: 56, 1952.
21. LEWIS, B. M. AND R. GORLIN. *Federation Proc.* 11: 93, 1952.
22. PHILLIPS, R. A., D. D. VAN SLYKE, P. B. HAMILTON, V. P. DOLE, K. EMERSON AND R. M. ARCHIBALD. *J. Biol. Chem.* 183: 305, 1950.
23. SCHAEFER, K. E. AND H. J. ALVIS. *Med. Res. Lab.*, U. S. Naval Submarine Base, New London. 10: 76, 1951.
24. RAHN, H. AND A. B. OTIS. *Am. J. Physiol.* 150: 202, 1947.
25. AMENT, R., M. SUSKIND AND H. RAHN. *Proc. Soc. Exper. Biol. & Med.* 70: 401, 1949.
26. KUNO, Y. *J. Physiol.* 50: 140, 1915.
27. LOGARAS, G. *Acta physiol. scandinav.* 14: 120, 1947.
28. WHITTAKER, S. R. F. AND F. R. WINTON, *J. Physiol.* 78: 339, 1933.
29. PAPPENHEIMER, J. R. AND J. P. MAES. *Am. J. Physiol.* 137: 187, 1942.
30. BINGHAM, E. C. AND R. R. ROEPKE. *J. Gen. Physiol.* 28: 79, 1944.
31. GREEN, H. D., R. N. LEWIS, N. D. NICKERSON AND A. L. HELLER. *Am. J. Physiol.* 141: 518, 1944.
32. LAMPORT, H. *Federation Proc.* 6: 146, 1947.
33. EDWARDS, W. S. *Am. J. Physiol.* 167: 756, 1951.
34. STROUD, R. C., K. STETSON AND H. RAHN. To be published.
35. DALE, A. S. AND B. NARAYNA. *Quart. J. Exper. Physiol.* 25: 85, 1935.
36. WOODBURY, R. A. AND W. F. HAMILTON. *J. Pharmacol. & Exper. Therap.* 71: 293, 1941.
37. DALY, I. DE B. AND U. S. V. EULER. *Proc. Roy. Soc., London, s. B.* 110: 94, 1932.
38. GADDUM, J. H. AND P. HOLTZ, *J. Physiol.* 47: 286, 1913.
39. V. EULER, U. S. *J. Physiol.* 74: 271, 1932.
40. ALCOCK, P., J. L. BERRY AND I. DE B. DALY. *Quart. J. Exper. Physiol.* 25: 369, 1935.
41. JOHNSON, V., W. F. HAMILTON, L. N. KATZ AND W. WEINSTEIN. *Am. J. Physiol.* 120: 624, 1937.
42. BEAN, J. W., W. P. MAYO, F. O'DONNELL AND G. W. GRAY. *Am. J. Physiol.* 166: 723, 1951.
43. DALY, I. DE B. AND C. O. HEBB. *Quart. J. Exper. Physiol.* 31: 211, 1941–2.
44. DALY, I. DE B., H. DUKE, C. O. HEBB AND J. WEATHERALL. *Quart. J. Exper. Physiol.* 34: 285, 1947–8.
45. GORLIN, R. AND B. M. LEWIS. *Federation Proc.* 11: 57, 1952.
46. RAHN, H. *Am. J. Physiol.* 158: 21, 1949.

Effect of Unilateral Hypoxia on Gas Exchange and Calculated Pulmonary Blood Flow in Each Lung[1]

H. RAHN AND H. T. BAHNSON.[2]

IN RECENT YEARS numerous studies have demonstrated a relationship between the level of alveolar oxygenation and pulmonary vascular resistance Discussion of these observations can be found in recent reports by Stroud and Rahn (1) and Lewis and Gorlin (2). Of particular interest are the observations of Dirken and Heemstra (3) who first demonstrated that in the rabbit hypoxia in one lung causes local vasoconstriction which shunts blood to the other oxygenated lung. Since that time similar results have been reported in the dog (4, 5). This study enlarges upon observations on the dog which have previously been briefly reported (6); it includes information on gas exchange as well as an attempt to calculate blood flow in each lung during unilateral hypoxia and hypercarbia.

METHODS

Six dogs weighing about 20 kg were repeatedly used in this study. Premedication consisting of 16 mg of morphine sulphate and 0.4 mg atropine sulphate was given subcutaneously prior to general anesthesia with intravenous pentobarbital (approximately 36 mg/kg). A rigid tracheal divider patterned from a design of George Wright was used to separate gas exchange of the two lungs. When inflated a dipped latex balloon at the end of the double lumen tube effectively sealed the two main bronchi at the carina. Figure 1*A* shows the tracheal divider with inflated balloon in position at the tracheal bifurcation. In order to test the effectiveness of separation each lung was connected to a recording spirometer filled with oxygen. When a leak was present, it could be readily demonstrated by a transfer of gas from one spirometer to the other by application of pressure to one system. Thereafter each lung was connected to an alveolar air sampler of small dimensions and deadspace but similar to that previously described (7). From this device alveolar gases were continuously aspirated into a Pauling oxygen tensimeter and a Cambridge Thermal-Conductivity CO_2 meter (fig. 1*B*). Two sets of meters allowed continuous and simultaneous analysis of alveolar O_2 and CO_2 from each lung. At definite intervals the expired air was collected in balanced 6-liter spirometers and analyzed on the same meters for the determination of oxygen uptake, CO_2 output and the exchange ratio (R.Q.).[3]

[1] This study was supported by the Air Research and Development Command, Wright Field.

[2] National Research Council Fellow in the Medical Sciences. Present address: Department of Surgery, The Johns Hopkins Hospital, Baltimore, Md.

[3] When the two lungs breathe different O_2–N_2 mixtures, an error is introduced into the usual method of calculation of gas exchange from analysis of expired air. This is due to the excretion of nitrogen into the lung breathing the higher oxygen mixture and nitrogen uptake from the other lung. The error is small and was ignored in these studies.

The experiment thus consisted of simultaneous measurement in each lung of alveolar pO_2 and pCO_2, oxygen uptake and CO_2 output. During a control period both lungs breathed 30% O_2. Thereafter the right lung continued on this mixture to assure a high alveolar pO_2 while the left lung was given 21, 15, 11 or 0% oxygen in nitrogen mixtures. Readings were made at intervals after exposure of the left lung to test gases for periods ranging from 5–110 min.

In the experiments with CO_2 the left lung was exposed to 5 and 7% CO_2 in air mixtures. During the preceding control period both lungs breathed room air. In these particular studies the dogs were placed in a Drinker respirator which assisted

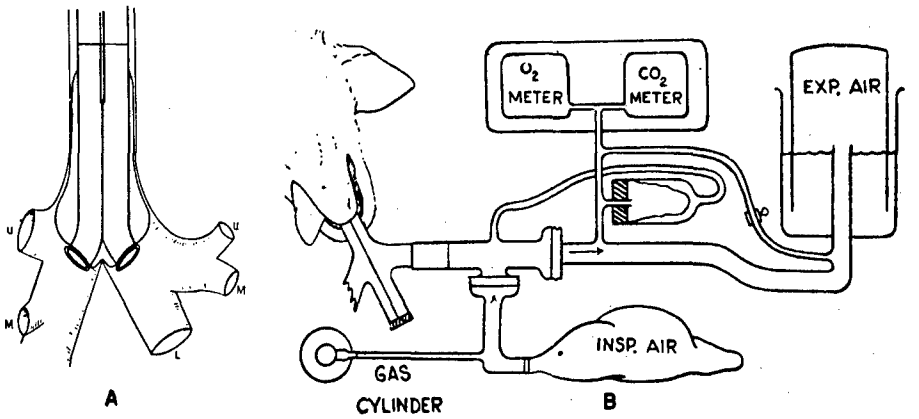


FIG. 1*A*. Scale drawing showing the position of the G. Wright tracheal divider with inflated balloon (*shaded region*) lodged against the carina. *U* = upper, *M* = middle, *L* = lower lobe bronchi. Left lung on the right side. *B*. Arrangement for the collection and analysis of alveolar and expired gas from each lung separately. The apparatus shown was duplicated for the other lung in order that simultaneous sampling from both lungs could be accomplished.

their ventilation and allowed regulation of alveolar pCO_2 of the right lung within a physiological range.

RESULTS AND DISCUSSION

Gas Exchange in Each Lung. It may be seen that normally about 40% of the total pulmonary function was performed by the left lung during control periods (table 1). The relative ventilation of the two lungs remained essentially unaltered throughout control and test periods. As might be expected the greatest changes were observed in relative O_2 uptake. When both lungs were on 30% O_2 or air (*columns 1, 6*) 41 and 42% respectively of the total O_2 was taken up on the left side. As the inspired oxygen tension in the left lung was lowered (*columns 1–5*), the uptake was progressively reduced while it correspondingly increased in the well-oxygenated right lung. The total oxygen uptake remained approximately constant even when oxygen was excreted in the nitrogen breathing left lung. With both lungs on the same gas mixture the CO_2 output of the left side was likewise about 42% of the total (*column 6*). In *column 1* for some unexplained reason this value is only 37%; the difference in R.Q. between the two lungs suggests an error in these data but the explanation is not apparent. With the reduction of alveolar pO_2 on the left side (*columns 2–5*) the relative CO_2 output was reduced. In the N_2 breathing lung the CO_2 output is only 28% of the total. These changes in O_2 and CO_2 exchange

account for unusual exchange ratios which were encountered in each lung with unilateral hypoxia. The over-all CO_2 output was only slightly increased with the hyperventilation of hypoxia.

When both lungs breathed the same gas mixture (*columns 1, 6*) similar gas tensions would be expected in both lungs if their ventilation perfusion ratios remain identical. This was usually the case in many unpublished observations but again in *column 1* we have an exception in the CO_2 tension without evident explanation. With unilateral hypoxia the O_2 tension fell on the left side and reached a value of 25 mm when N_2 was breathed. This alveolar pO_2 was maintained by O_2 excretion into the N_2 breathing lung. A steady state was usually achieved after 5-min. exposure and persisted for periods up to 110 min. Of even greater interest is the difference in

TABLE 1

	Rt. Lung on 30% Oxygen					Rt. Lung on Air		
	1	2	3	4	5	6	7	8
Test gas to lt. lung	30% O_2 in N_2	Air	15% O_2 in N_2	11% O_2 in N_2	N_2	Air	5% CO_2 in Air	7% CO_2 in Air
No. of exper.	8	8	6	13	7	11	17	22
pO_2, mm Hg —L	155±15.1	102±6.7	80±3.2	64±3.3	25±5.4	86±6.3	103±8.8	106±5.7
R	155±14.2	158±10.5	162±2.0	148±11.6	148±10.7	86±6.1	108±6.5	111±5.3
pCO_2, mm Hg —L	55±9.7	50±7.7	42±9.1	39±10.0	33±8.9	53±6.0	52±4.4	59±3.7
R	64±10.1	58±8.9	54±8.9	54±8.4	55±9.6	55±6.7	39±6.2	40±6.3
V_{O_2}, ml/min. —L	39±13.4	23±6.2	17±7.3	9±7.4	−22±3.9	49±9.3	43±14.1	39±6.3
R	57±9.5	64±8.4	88±15.4	96±22.8	131±41.8	67±11.7	61±14.7	57±15.5
Exch. ratio —L	.72±.12	1.15±.13	1.83±.48	3.32±1.34	−1.08±.10	.79±.06	.40±.10	.08±.17
R	.85±.11	.73±.07	.63±.06	.54±.05	.48±.09	.80±.06	1.09±.17	1.23±.26
Q_l/Q_t, %	40±6.1	29±6.0	20±5.7	16±8.3	11±3.0	42±4.9	42±13.4	40±14.0
Total vent., l/min.	1.48±.34	1.65±.51	2.04±.56	2.04±.65	2.28±1.09	1.90±.52	2.85±.57	3.18±.88
V_l/V_t, %	39±4.7	40±2.5	36±4.0	42±5.1	40±2.5	45±3.3	43±4.7	45±5.5

All values are given as means with standard deviations of the mean.

V_{O_2} = O_2 uptake; during N_2 breathing in left lung O_2 excretion. Exchange ratio = V_{CO_2}/V_{O_2}. Q_l/Q_t = fraction of cardiac output perfusing left lung. V_l/V_t = fraction of total ventilation performed by left lung. Average barometer = 747 mm Hg.

L = left. R = right.

the pCO_2 between the left and right lung with increasing unilateral hypoxia. While the pCO_2 in the oxygenated lung remains relatively constant, that in the left side fell progressively. This relationship is shown graphically in figure 2. This difference we believe is in part explained by the Haldane effect, i.e. the role of O_2 upon the loading and unloading of CO_2 (8). Actually in 1892 Werigo (9) demonstrated this effect *in vivo* by the difference in alveolar CO_2 concentration of two lungs, one breathing O_2 and the other H_2. He observed a 2–3% greater CO_2 concentration in the O_2 lung and held the low O_2 tension in the H_2 lung responsible for the reduced unloading of CO_2. Bohr (10) originally did not accept this interpretation. However, it can be shown with the aid of our present knowledge of the dissociation curves that if ventilation as well as perfusion is maintained at normal values in each lung, the alveolar pCO_2 in the hypoxic lung must be lower than in the oxygenated contralateral lung.

Another factor which would contribute to the CO_2 difference between the two lungs is the possible vasoconstriction of the hypoxic lung shunting blood to the oxygenated lung. That such a local action is possible was first shown by Dirken and Heemstra in the rabbit (3). More recently Atwell *et al.* (4) and Peters and Roos (5) have demonstrated such action in the dog where the response is comparatively rapid.

On the basis of certain assumptions one can calculate the blood flow through each lung in these experiments.

Calculation of Blood Flow Through Each Lung. This method is based on the Fick equation, but requires unequal gas tension in the two lungs. Briefly, the oxygen uptake is measured for each lung, and the arterial blood gas content[4] leaving each lung is estimated from the alveolar gas concentration. The mixed venous blood is common to both lungs and its content can be calculated provided that the exchange ratio (R.Q.) and the arterial gas content for each lung are known.

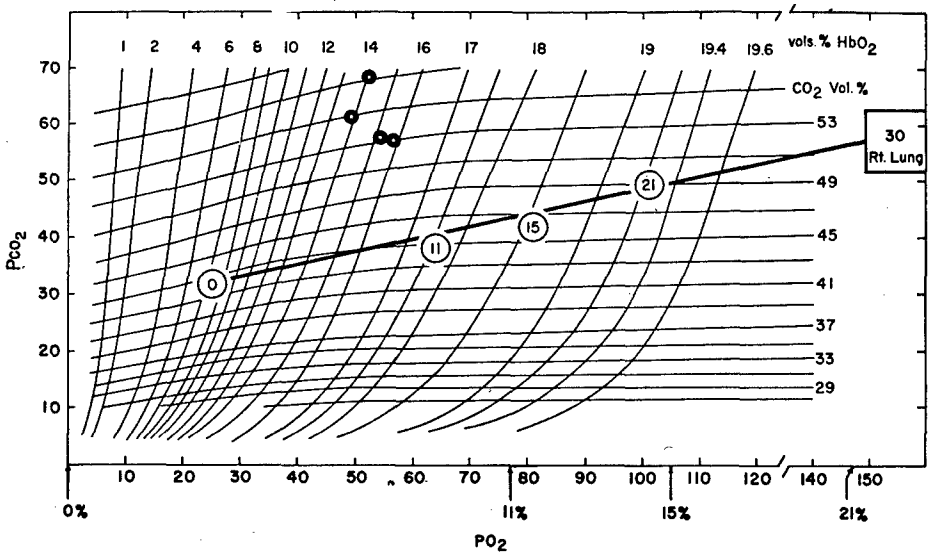


FIG. 2. Isopleths for HbO_2 content and total CO_2 content of dog blood plotted against pCO and pO_2 coordinates. The curvature of the isopleths for HbO_2 is due to the Bohr effect (10) while that for the CO_2 content lines is due to the Haldane effect (8). *Open circles* represent average alveolar gas values found in the left lung breathing 0, 11, 15, and 21% O_2. The *open square* on the right indicates the range of alveolar gas values found in the right control lung breathing 30% O_2. *Solid circles* represent calculated gas contents of mixed venous blood. From the top towards the bottom they are, respectively, the values when the left lung breathed 21, 15, 11 and 0% oxygen. It can be readily appreciated that as the O_2 tension of the left lung is reduced, the alveolar CO_2 values in this lung become progressively smaller while the alveolar CO_2 in the oxygenated right lung remains high.

As an example of the method, data from table 1 have been selected in which the left lung breathed 11% and the right lung 30% O_2. Analysis of the alveolar air showed a pO_2 of 64 and a pCO_2 of 39 mm Hg in the left lung. Assuming for the moment no terminal alveolar-arterial gradient this corresponds to a gas content of 17.6 vol. % of O_2 and 45.1 vol. % of CO_2 (fig. 2). The left lung took up 9 ml of oxygen per minute with an exchange ratio of 3.32 (table 1, *column 4*). The right lung had a pO_2 of 148 and a pCO_2 of 54 mm Hg which corresponds to a content of 20 vol. % O_2 (in this example the physically dissolved O_2 has been ignored) and 50.6 vol. % of CO_2. The oxygen consumption of the right lung was 96 ml/min. and the exchange ratio .54. The values for the two different arterial bloods are then plotted on coordinates expressed in terms of gas content (fig. 3). The venous point

[4] Throughout this discussion 'arterial blood' refers to pulmonary venous blood, while 'mixed venous blood' is the blood in the pulmonary artery.

for each lung must lie somewhere on a line having a slope corresponding to the exchange ratio of that lung. The point at which the two lines intersect is common to both lungs and represents mixed venous blood. Obviously this method can be used only when arterial points and exchange ratios of the two lungs differ.

The mixed venous point may also be determined by equations which solve separately for the venous O_2 and CO_2 contents. Thus

$$V_o = (R_l A_{ol} - R_r A_{or} + A_{cl} - A_{cr})/(R_l - R_r); \quad \text{and}$$

$$V_c = (R_l R_r (A_{or} - A_{ol}) + R_l A_{cr} - R_r A_{cl})/(R_l - R_r)$$

where R, V and A are exchange ratio, mixed venous and arterial blood contents, respectively; subscripts o and c are O_2 and CO_2; and l and r refer to left and right

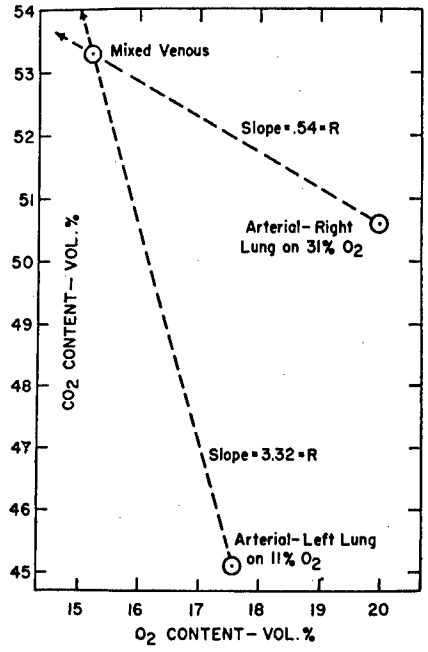


FIG. 3. Graphic method for determination of gas content of mixed venous blood. The arterial gas content for each lung is originally estimated from the alveolar gas composition and the combined O_2 and CO_2 dissociation curves of fig. 2. From each arterial point a straight line is drawn having a slope equal to the measured exchange ratio. The intersection of the two lines represents the gas content of mixed venous blood. (See text.)

lung. These equations are derived from the relationship $R = (V_c - A_c)/(A_o - V_o)$. V_o and V_c are the same for both lungs. The two equations defining V_o and V_c for each lung are equated and solved for V_c and V_o, respectively. When N_2 is breathed in one lung, both O_2 and CO_2 are excreted and the exchange ratio becomes negative. To solve the above equation in this instance, the R of the N_2 lung which is excreting both O_2 and CO_2 carries a negative sign.

Limitations of Method. The greatest source of possible error lies in the estimation of the arterial gas content in each lung. For this determination several important assumptions have to be made. The first is in regard to the relationship of the gas tension of alveolar air and arterial blood. Suskind (11) has shown in the dog that the alveolar sampler gives mean pCO_2 values which do not differ from simultaneously determined mean arterial pCO_2. During hypoxic hyperventilation the alveolar-arterial O_2 gradient is approximately 5 mm Hg. In the oxygenated control lung the alveolar-arterial oxygen gradient is expected to be considerably

larger (11) but fortunately is not so important for the estimation of the O_2 content. In these experiments various gradients up to 10 mm Hg in the hypoxic lung were assumed. The calculated values of relative blood flow did not vary significantly from those when no gradient was assumed.

In addition to the determination of the partial pressures of arterial blood the dissociation curve for O_2 and CO_2 may be a source of error. As has been pointed out by Dill *et al.* (12), the characteristics of dog blood are similar to those of man. The dissociation curves (fig. 2) were established by blood tonometry, various O_2 and CO_2 mixtures being used and followed by analysis of the blood gas content on the manometric Van Slyke apparatus. Our data for the oxygen contents were confined primarily to the upper parts of the dissociation curve and combined with data of

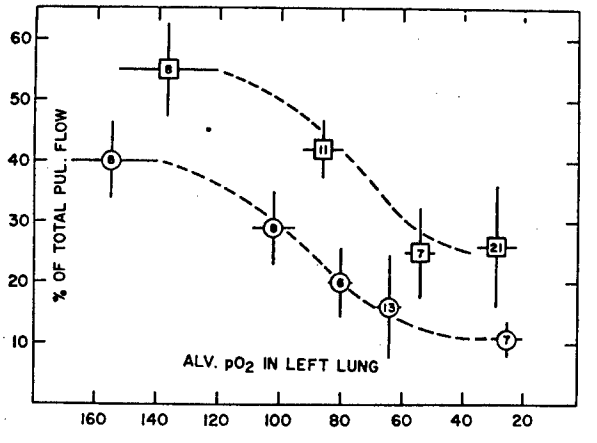


FIG. 4. Percentage of cardiac output perfusing the left lung when it breathed various O_2–N_2 mixtures which altered its alveolar oxygen tension. *Circles* represent experiments in which the right lung breathed 30% oxygen and the alveolar pO_2 in the right lung was thus kept above 150 mm Hg. *Squares* represent experiments in which the right lung breathed air. Normally 40-42% of the cardiac output perfuses the left lung when both lungs breathe the same gas, for example 30% O_2 represented by 1st point on *lower curve* and 21% O_2 represented by 2nd point on *upper curve*. *Numbers* within the circles and squares refer to number of experiments and the *lines* from these represent one standard deviation of the mean.

Bohr, Hasselbalch and Krogh (9). The O_2 capacity of our dogs averaged 20 vol. %. The CO_2 dissociation curves were determined at various O_2 tensions. By interpolation and extrapolation smoothed curves for both dissociation curves were established and entered as isopleths of O_2 and CO_2 content on the O_2 and CO_2 diagram (fig. 2).

Estimated Perfusion of Each Lung With Unilateral Hypoxia or Hypercarbia. With this method blood flow was determined separately for each individual experiment and is expressed as the fraction of the cardiac output perfusing the left lung. The mean values for each series of conditions are given in table 1. It can be seen that when both lungs were subjected to the same gas (*column 1* and *6*) the blood flow through the left lung was 40–42% of the total. This fraction is similar to the ventilation and thus indicates equal ventilation perfusion ratios in each lung. With increasing hypoxia in the left lung the flow was progressively reduced to 11% when N_2 was breathed. The changes in blood flow which occurred in the left lung are plotted against the alveolar pO_2 of the left lung in the *lower curve* of figure 4. It may be seen that the greatest vasoconstriction occurred in the range between 60 and 120 mm Hg and thus the phenomenon is most active over the normal range of alveolar pO_2. Maximal vasoconstriction was obtained with N_2 breathing. Calculations of blood flow were made at intervals of from 5–110 min. after exposure of the

left lung to N_2; during this period the fraction of flow through the left lung did not vary.

The flow through each lung is dependent upon the resistance offered by the other lung. The above observations suggest that with a normal alveolar pO_2 breathing air there is some vasoconstriction. (Compare estimated blood flow of left lung with pO_2 of 100 and pO_2 of 158.) Hence a smaller shift in relative blood flow would be expected in the hypoxic left lung when the right lung breathes air than when it breathes 30% O_2. Forty seven experiments were carried out in which the right lung was supplied with 30, 21, 11 and 0% O_2. These data are not given in table 1, but the calculated flows and alveolar pO_2 are shown in figure 4 (*upper curve*). These suggest that by increasing vasoconstriction in the control lung less blood is shifted out of the hypoxic lung. For example, with N_2 in the left lung the flow is reduced to only 26% of the total wnen the right lung breathes air while in the former experiments it was reduced to 11%. On the other hand, if the experimental left lung is given a higher fraction of O_2 to breathe than the control more blood will flow through it. A reduced resistance to blood flow for the whole dog's lung when changing the inspired gas from air to 30% O_2 has recently been suggested by Stroud and Rahn (1). There seems to be maximal vasodilatation when alveolar pO_2 is around 150 mm Hg (fig. 4).

If one can accept these calculated flow values as approximately correct, we have here a demonstration of an independent regulation of blood flow through a lung. This regulation is dependent upon: *a*) the local alveolar-arterial O_2 tension, and *b*) the flow resistance on the contralateral lung. The mechanism by which this shunting is accomplished is unknown; the various suggested mechanisms have recently been reviewed (1–6). The general conclusions of local regulation are in agreement with those of Dirken and Heemstra (3) who were first to demonstrate clearly this phenomenon in the rabbit. Atwell *et al.* (4) have demonstrated a similar mechanism in the dog and more recently Peters and Roos (5) determined the reduction of flow in the N_2 breathing lung by blood analysis from direct cannulation of the pulmonary veins of each lung. The values of Atwell and associates and Peters and Roos are in fairly good agreement with those suggested in this study.

The effects of changing only the CO_2 tensions in one lung (table 1, *columns 7* and *8*) indicate no evidence for a change in flow. This is in agreement with recent determinations where no flow resistance changes were observed when both lungs were exposed to increased CO_2 tension (1).

Summary

A method has been described for separation of gas exchange of the two lungs and simultaneous measurement in each of alveolar pO_2 and pCO_2, O_2 uptake and CO_2 output. Using this method the left lung of the dog has been subjected to various mixtures of O_2 in N_2. The changes in gas exchange with unilateral hypoxia have been presented and discussed.

On the basis of certain assumptions, using data obtained in these experiments and blood dissociation curves for O_2 and CO_2, the blood flow through each lung has been estimated. When the right lung is maintained on 30% O_2 and the left lung is made hypoxic there is a local vasoconstriction in the latter which varies with the degree of unilateral hypoxia. With the left lung breathing N_2, 11% of the pulmonary flow goes through this lung, in contrast to control values of 40%. If on the other

hand, the right lung is maintained on air, the hypoxic left lung will constrict less for a given alveolar pO_2.

REFERENCES

1. STROUD, R. C. AND H. RAHN. *Am. J. Physiol.* 172: 211, 1953.
2. LEWIS, B. M. AND R. GORLIN. *Am. J. Physiol.* 170: 574, 1952.
3. DIRKEN, M. N. J. AND H. HEEMSTRA. *Quart. J. Exper. Physiol.* 34: 193, 213, 1948.
4. ATWELL, R. J., J. B. HICKAM, W. W. PRYOR AND E. B. PAGE. *Am. J. Physiol.* 166: 37, 1951.
5. PETERS, R. M. AND A. ROOS. *Am. J. Physiol.* 171: 250, 1952.
6. RAHN, H. AND H. T. BAHNSON. *Federation Proc.* 9: 102, 1950 and Abstr., XVIII Internat. Physiol. Congress, Copenhagen 401, 1950.
7. RAHN, H. AND A. B. OTIS. *J. Applied Physiol.* 1: 717, 1949.
8. CHRISTIANSEN, J., C. G. DOUGLAS AND J. S. HALDANE. *J. Physiol.* 48: 244, 1914.
9. WERIGO, B. *Pflügers Arch. f. d. ges. Physiol.* 51: 321, 1892.
10. BOHR, C., K. HASSELBALCH AND A. KROGH. *Skandinav. Arch. f. Physiol.* 16: 402, 1904.
11. SUSKIND, M. Unpublished.
12. DILL, D. B., H. T. EDWARDS, M. FLORKIN AND R. W. CAMPBELL. *J. Biol. Chem.* 95: 143, 1932.

THE PULMONARY HEMODYNAMIC EFFECTS OF TOTAL AND PARTIAL UNILATERAL PULMONARY ARTERIAL OCCLUSIONS IN ANESTHETIZED DOGS

M. Lategola and H. Rahn

In recent years concomitant advances in the techniques of cardiac catheterization and bronchospirometry have made possible a closer scrutiny of certain pulmonary hemodynamic functions once thought to be physiologically inaccessible. The use of these two techniques in combination with a "closed chest" preparation approaches to a great extent an "ideal" physiological preparation.

In 1951 Dotter and Lucas (1) reported that complete unilateral pulmonary arterial occlusion in dogs produced pulmonary arterial pressure (PAP) rises of about 200-300% and that this rise was usually followed by right heart failure within 3 minutes. Severe systemic arterial pressure (SAP) drops and marked tachypnea were reported as concomitant findings. The establishment of complete unilateral occlusion was based on fluoroscopic criteria. Pulmonary blood flow ($\dot{Q}$) was not measured.

Also in 1951 Carlens, et al (2) reported that in a few trial experiments on dogs, a slight increase in PAP was registered in immediate association with occlusion of one of the main branches of the pulmonary artery (PA). This report established the valuable criterion of complete unilateral PA occlusion as the reduction of the spirometrically measured oxygen consumption ($\dot{V}o_2$) in the ipsilateral lung to zero. It was further reported that in complete unilateral PA occlusions in sedated humans, one case resulted in a PAP rise from 17 to 22 cm H_2O with a return to the initial level after 10 minutes of occlusion and in a second case the occlusion was followed by no PAP rise at all. $\dot{Q}$ was not measured.

It is felt that a more complete study of this type is warranted especially since present available techniques make such a study quite feasible. Concomitant measurements of $\dot{Q}$ and the pressure drop (ΔP) across the pulmonary vessels along with the use of Poiseuille's Law should permit quantitative estimation of changes in pulmonary vascular resistance (R) accompanying the redistribution of blood flow from the occluded vascular segment.

This report consists of 5 sets of experiments. The first deals with the effects of complete unilateral PA occlusion. The second, third and fourth are control experiments. The fifth set deals with the effects of graded unilateral PA occlusions.

METHODS

The experimental methods for the first set of experiments will be described in detail since they will remain essentially the same in the remaining experiments. Only those modifications peculiar to each consequent set will be described.

(Set I) - Six dogs weighing about 20 kg each were used for a total of eight experiments. Each dog was anesthetized with intravenously injected pentobarbital (approximately 36 mg/kg) in which 0.43 mg atropine-sulfate had previously been dissolved. Either the left or right jugular vein was surgically exposed. A special bi-lumened catheter was then introduced into the left PA via the jugular and right heart and externally connected by way of a three-way stop cock to a saline manometer as described in a previous paper (3). In this manner the heart rate and PAP could be determined and a mixed-venous blood sample could be withdrawn. The blood samples were anaerobically collected in pre-heparinized 10 cc syringes and stored at about zero degrees centigrade until completion of the experiment, whereupon they were analyzed by means of the Van Slyke manometric technique for their O_2 and CO_2 contents. Either the left or right femoral artery was surgically exposed and a No. 10 Cournand Catheter was introduced and positioned in the aorta about 10 cm below the heart. This catheter was externally connected to a mercury manometer via a three-way stop cock. SAP measurements were made and arterial blood sampled by means of this catheter. A rigid tracheal divider patterned from a design of George Wright was used to separate the gas exchange of the two lungs. The construction and placement of this divider and a test for the effectiveness of respiratory separation of one lung from the other has been described (4). Each lung was then connected to a 5-liter, oxygen-filled Benedict-Roth metabolism spirometer so that the $\dot{V}o_2$ of each lung could be recorded continuously. The unilateral reduction of $\dot{V}o_2$ from a finite value to zero (Figure 1) has been described elsewhere (2) as a criterion of complete unilateral PA occlusion. Figure 1 depicts the experimental apparatus.

During a control period simultaneous measurements of heart rate, PAP and SAP were recorded until a reasonable degree of constancy was observed. Simultaneous arterial and mixed-venous blood samples were then slowly drawn. Immediately after this the pulmonary-catheter balloon was inflated in order to completely occlude the $\dot{Q}$ to the left lung. As in the control period, PAP, SAP and heart rate determinations were made at definite intervals during this occlusion period. Two additional simultaneous A-V blood samples were drawn at the 10th and 28th minute of this period. At the 30th minute the PA occlusion was released by deflation of the catheter balloon. Measurements were continued until such time (usually quite rapidly) as the animal returned to the control level, whereupon the experiment was terminated. The $\dot{Q}$ through each lung was calculated from the A-V oxygen difference $(A\text{-}V)_{O_2}$ and concomitant $\dot{V}o_2$ according to the Fick equation. The vascular resistance (R) of each lung was calculated from the previously determined $\dot{Q}$ and the ΔP, as obtained from the difference between the manometrically observed PAP and an assumed pulmonary venous pressure (PVP)

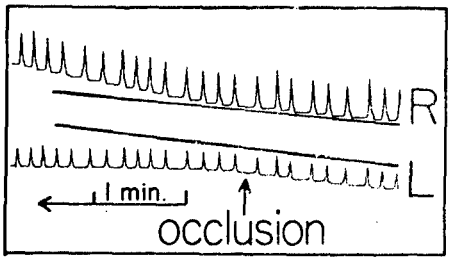
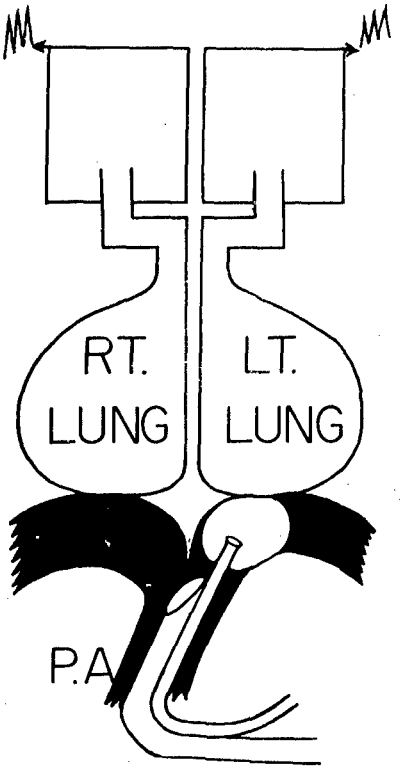


Figure 1

The upper portion shows a typical spirometric tracing obtained in complete unilateral PA occlusion. The lower portion diagrammatically depicts the experimental set up, including the position of the occluding balloon in the left pulmonary artery.



of 5 cm H_2O (5). Respiratory rates (f) and tidal volumes were obtained from the spirometer tracings. The dogs breathed 100% O_2 during the entire experiment.

(Set II) - The effect of anesthetic agent on the response to complete unilateral PA occlusion: Seven experiments were performed on 2 dogs substituting chloralose for sodium barbital. The only modifications in procedure were the duration of the occlusion (10 minutes) and the omission of $\dot{Q}$ measurements.

(Set III) - The effect of atropine sulfate on the response to complete unilateral PA occlusion: Since atropine was used routinely to suppress bronchial mucous secretion and because of its parasympatholithic properties, control experiments were deemed necessary. In one experiment it was omitted entirely and in a second, it was administered in our standard dose during the occlusion. $\dot{Q}$ measurements were omitted. Both occlusions were maintained in excess of 30 minutes.

(Set IV) - In situ anatomical location of the occluding balloon: Since fluoroscopic visualization was not employed in our experiments and since protrusion of the occluding balloon into the main PA might cause an artificial rise in PAP, it was necessary to perform two experiments in which complete unilateral PA occlusion was effected, the dogs sacrificed by rapid intravenous injection of concentrated KCl and the in situ position of the inflated occluding balloon determined by careful dissection. No measurements were taken other than those needed to establish the completeness of the unilateral PA occlusion.

(Set V) - The effects of graded unilateral PA occlusions: Thirty-six random graded (partial to complete unilateral) PA occlusions were performed on 10 nembutalized dogs. The occlusions were maintained for 10-minute durations. Since a mathematical relation (which is derived in a later section) allowed the calculation of $\dot{Q}$ changes in terms of corresponding $\dot{V}o_2$ changes, direct Fick $\dot{Q}$ determinations were omitted. For reasons reported later, SAP measurements were also omitted.

RESULTS

(Set I) - Table I presents a summary of the measured and calculated data obtained in the first set of experiments. All the averages, except those starred, are based on 8 experimental values. Left lung averages may be obtained by simple subtraction.

Table II presents a summary of the average %-changes from pre-occlusion control levels for the same set of experiments. In general, it may be noted that the increased $\dot{Q}$ to the right lung as a result of complete left PA occlusion resulted in a significant PAP rise which was maintained during the entire occlusion period. This same order of maintained PAP rise was observed in a separate experimental occlusion lasting 73 minutes. It should also be noted that the total pulmonary blood flow ($\dot{Q}$-$_T$) seems to remain constant during the entire experiment. There is a decrease in R of the right lung (R-$_{Rt}$) which does not seem to be significant according to the related "P" values. This will be discussed later.

The SAP seemed to remain significantly constant, the values after 10 and 28 minutes of occlusion being -0.01% (P = 0.992) and -2.8% (P = 0.450). A seemingly significant slight rise of 5 - 7% in heart rate was observed (P = 0.030). The $(A\text{-}V)_{O_2}$ did not appear to change significantly during occlusion, the values at 10 and 28 minutes being +4.9% (P = 0.694) and +13.7% (P = 0.473). The "f" seemed significantly increased, the values at 10 and 28 minutes being +36.2% (P = 0.014) and +44.2% (P = 0.021). The right lung ventilation ($\dot{V}e$-$_{Rt}$) seemed significantly increased, the 10 and 28 minute values being +42.4% (P = 0.004) and +55.4% (P = 0.005). The total ventilation ($\dot{V}e$-$_T$) also seemed significantly increased, the 10 and 28 minute values being +33.9% (P = 0.013) and +45.7% (P = 0.012). Figure 2 presents a graphical summary of the effects of complete unilateral PA occlusion on the more pertinent hemodynamic parameters involved.

TABLE I

Summary of observations made on 8 dogs during complete occlusion of the left pulmonary artery

Time	P.A.P.	†S.A.P.	H.R.	$\dot{V}o_{2-T}$	$\dot{V}o_{2-Rt.}$	$(A-V)_{O_2}$	Q_{-T}
Pre-occ.	21.2 (1.9)	119.6 (7.7)	139 (8)	102.3 (6.3)	44.0 (4.7)	4.19 (0.47)	2.807 (0.545)
Occ + 10 min.	34.9 (2.6)	118.8 (5.9)	146 (8)	106.5 (8.9)	106.5 (8.9)	4.19 (0.21)	2.741 (0.355)
Occ + 28 min.	33.2 (2.3)	115.2 (4.6)	149 (9)	103.6 (9.8)	103.6 (9.8)	4.37 (0.51)	2.500 (0.267)
Post Release	20.5 (1.8)	114.5 (6.7)	149 (8)	105.7 (9.2)	48.8 (6.3)	*4.11 (0.26)	*2.635 (0.351)

Time	$\dot{Q}_{-R}$	$\Delta P_{-P.A.P.}$	R_{-T}	$R_{-Rt.}$	$\dot{V}e_{-T}$	$\dot{V}e_{-Rt.}$	f
Pre-occ.	1.237 (0.296)	16.2 (1.9)	7.0 (1.2)	18.3 (4.6)	3875 (698)	2131 (363)	14.7 (5.2)
Occ + 10 min.	2.741 (0.355)	29.9 (2.6)	12.6 (2.3)	12.6 (2.3)	4930 (810)	2872 (383)	18.9 (6.7)
Occ + 28 min.	2.500 (0.267)	28.2 (2.3)	13.0 (2.6)	13.0 (2.6)	5549 (1197)	3237 (629)	20.7 (7.1)
Post Release	*1.296 (0.180)	15.5 (1.8)	* 5.1 (0.6)	*10.8 (0.9)	5418 (1128)	3116 (639)	22.3 (7.3)

Standard errors of the means are indicated after each value. P.A.P. = Pulmonary arterial pressure, cm H_2O. S.A.P. = Systemic arterial pressure, mm Hg. H.R. = Heart rate, beats/min. $\dot{V}o_{2-T}$ = Total O_2 consumption, ml/min. STPD. $\dot{V}o_{2-Rt.}$ = O_2 consumption of right lung, ml/min. STPD. $(A-V)_{O_2}$ = Arterial-venous O_2 difference, volumes percent. $\dot{Q}_T$ = Total pulmonary blood flow, liters/min. $\dot{Q}_{-R}$ = Blood flow through right lung, liters/min. $\Delta P_{-P.A.P.}$ = Pulmonary arterial pressure head (P.A.P.-P.V.P.), cm H_2O. R_{-T} = Total pulmonary resistance, $\Delta P/\dot{Q}$. $R_{-Rt.}$ = Pulmonary resistance, right lung, $\Delta P/\dot{Q}_{-Rt.}$ Ve_{-T} = Total ventilation, ml/min. Ve_{-R} = Ventilation, right lung, ml/min. f = Respiratory frequency, breaths/min. † = Only measured in 6 of the 8 experiments. * = Measured in only 4 of the 8 experiments.

TABLE II

Summary of average percent changes from pre-occlusion control levels for the eight experiments performed and their "P" values

	P.A.P.	$\dot{V}o_2$-R_t.	$\dot{V}o_2$-Total	$\dot{Q}$-R_t.	$\dot{Q}$-T	P	R-R_t.
Occ. + 10 min.	+66.0 (<.001)	+155.9 (<.001)	+3.2 (0.299)	+162.3 (.005)	+4.7 (.626)	+89.1 (<.001)	-15.6 (.259)
Occ. + 28 min.	+58.7 (<.001)	+146.3 (<.001)	-1.1 (0.832)	+145.7 (.007)	+1.9 (.908)	+79.7 (<.001)	-13.0 (.398)
Post Release	- 3.1 (.273)	+ 11.5 (.175)	+5.2 (0.095)			- 4.2 (.287)	

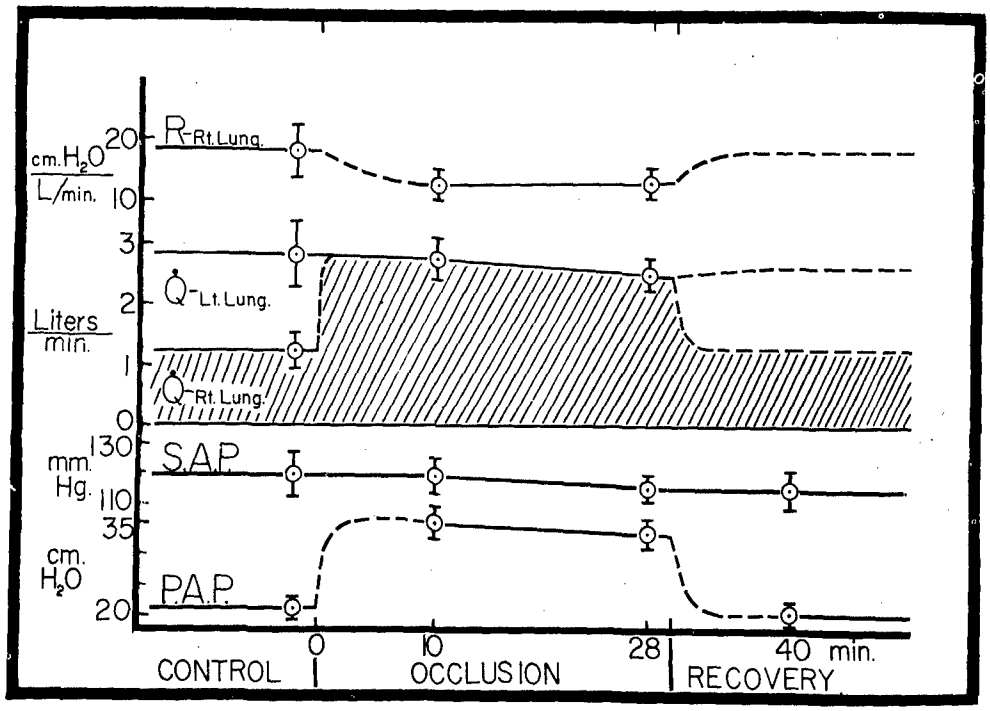


Figure 2

The time course of complete unilateral PA occlusion. R = pulmonary vascular resistance; $\dot{Q}$ = pulmonary blood flow; SAP = systemic arterial pressure and PAP = pulmonary arterial pressure.

(Set II) - The results obtained using chloralose in place of sodium barbital were essentially the same. The PAP rise observed was maintained, as before, for the duration of the occlusion. Complete unilateral PA occlusion produced an average PAP rise of 81.1% (S.E. = 8.1) while the average $\dot{V}o_2$ of the unoccluded right lung ($\dot{V}o_{2\text{-}Rt}$) increased 178.4% (S.E. = 37.6).

(Set III) - The omission of atropine entirely or its administration in our standard dose (0.43 mg) seemed to cause no apparent deviation from the PAP response obtained in the first set of experiments.

(Set IV) - In both dogs sacrificed while complete unilateral PA occlusion was in effect, careful dissection revealed that the proximal rim of the still inflated balloon was located 1 to 1.5 cm distal to the junction with the main PA. Furthermore, in the living animal with a PAP of about 30 cm H_2O (during occlusion), the balloon would tend to be pushed further away from rather than towards the junction with the main PA. The flexibility of the catheter used would also seem to discourage partial blockage of the main PA. In addition, partial unilateral occlusions

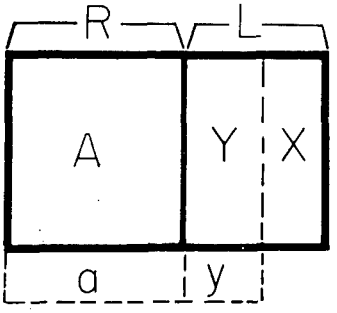
leave little doubt that any PAP rise observed could have been due to an artifactual partial obstruction of the main PA.

(Set V) - The first 4 and last 3 columns in Table III present a summary of the measured data obtained in the graded unilateral PA occlusion experiments. It should be noted that in every case a maintained PAP rise was obtained. The SAP was not measured since it was previously shown that it remained constant during complete unilateral PA occlusion.

The mathematical relation which allowed us to calculate the changes in $\dot{Q}$, in terms of the corresponding changes in $\dot{V}o_2$ for the "Effective Segment, E.S." (that segment of total lung which remains open to circulation during partial unilateral PA occlusion) will now be derived.

Let us assume that: 1) the total oxygen consumption ($\dot{V}o_{2-T}$) is not altered by partial unilateral PA occlusion (Table II), and 2) the $\dot{V}o_2$ previously occurring in the occluded segment is redistributed proportionately to the E.S. remaining open.

In order to calculate the % increase in $\dot{V}o_{2-ES}$ resulting from occlusion, we must first mathematically define "Effective Segment" in terms of the formula to be derived. A simple diagram will expedite this matter.



Let: A = $\dot{V}o_2$ rt. lung, pre-occlusion

B = $\dot{V}o_2$ lt. lung, pre-occlusion = (Y + X)

X = Pre-occlusion $\dot{V}o_2$ of the segment of lt. lung to be occluded. This amount of $\dot{V}o_2$, (X), is equal to (a+y) which is assumed to be redistributed proportionately in the segment of total lung remaining open during occlusion.

C = $\dot{V}o_2$ rt. lung during occlusion = (A + a)

D = $\dot{V}o_2$ lt. lung during occlusion = (Y + y)

TABLE III

Summary of Experimental Data of Partial Unilateral PA Occlusions

	$\dot{V}o_2$-Control Period		$\dot{V}o_2$-Occ. + 10 min		$\dot{V}o_2$-Effective Segment			P.A.P.		
	Rt.	Lt.	Rt.	Lt.	Control Period	Occ + 10 min	% Increase	Control Period	Occ + 10 min	% Increase
Dog	A	B	C	D	E	F	G	H	I	J
1	62.1	27.7	73.2	19.2	76.2	92.4	21.3	16.8	19.7	17.3
1	57.4	**29.7**	**69.2**	**19.2**	72.2	88.4	22.4	16.3	19.3	18.4
1	56.0	26.7	69.8	21.3	66.4	91.1	37.2	16.5	20.7	25.4
1	55.2	35.8	72.6	22.4	69.2	95.0	37.3	15.2	18.9	24.3
7	50.5	27.3	71.7	0.0	50.5	71.7	42.0	15.3	26.4	72.6
1	50.9	38.2	70.3	22.4	64.5	92.7	43.7	16.3	20.0	22.7
4	46.9	39.9	72.9	8.7	55.8	81.6	46.2	14.5	19.8	36.5
4	50.3	42.0	77.1	12.1	60.2	89.2	48.2	17.0	22.8	34.1
1	60.6	34.3	92.5	0.0	60.6	92.5	52.6	18.8	25.0	33.0
2	45.6	44.6	27.0	67.2	59.9	94.2	57.3	21.7	25.7	18.4
2	65.7	33.1	96.1	10.8	67.6	106.9	58.1	20.5	27.0	31.7
2	47.6	44.3	26.3	68.6	59.3	94.9	60.0	19.0	23.9	25.8
2	59.0	34.7	25.3	60.7	53.6	86.0	60.4	14.8	20.5	38.5
2	52.7	32.3	29.2	54.7	50.2	83.9	67.1	17.5	24.0	37.1
2	56.7	34.7	96.4	0.0	56.7	96.4	70.2	18.1	24.4	34.8
4	57.0	42.4	97.2	0.0	57.0	97.2	70.6	17.3	27.9	61.3
5	51.4	48.0	96.1	0.0	51.4	96.1	87.1	19.1	30.6	60.2
3	48.1	46.8	92.9	0.0	48.1	92.9	93.1	20.1	30.8	53.2
2	58.2	38.9	12.6	80.2	47.1	92.8	97.0	15.1	23.0	52.3
3	61.0	57.6	128.9	0.0	61.0	128.9	111.3	22.0	37.2	69.2
2	55.6	34.4	33.1	67.4	45.9	100.5	119.0	15.5	23.9	54.2
5	68.7	69.8	153.1	0.0	68.7	153.1	122.8	21.7	35.7	64.5
2	48.9	36.4	29.7	71.9	43.2	101.6	135.2	14.5	22.0	51.7
1	56.4	32.1	19.6	72.6	39.1	92.2	135.8	15.9	26.0	63.5
2	58.2	38.9	0.0	92.0	38.9	92.0	136.5	15.1	25.5	68.9
1	49.6	33.1	19.6	73.6	37.2	93.2	150.5	15.8	23.0	45.6
9	35.6	61.2	92.4	0.0	35.6	92.4	159.5	22.0	38.5	75.0
8	35.9	57.6	94.9	0.0	35.9	94.9	164.2	29.4	41.0	39.5
1	48.7	28.7	19.6	67.5	32.9	87.1	164.7	15.5	23.5	51.6
2	42.2	31.3	0.0	85.2	31.3	85.2	172.2	14.2	25.5	79.6
2	55.6	31.6	0.0	87.0	31.6	87.0	175.3	16.2	25.9	59.9
10	44.6	68.3	128.4	0.0	44.6	128.4	187.8	14.4	25.1	74.3
6	39.8	63.9	114.9	0.0	39.8	114.9	188.6	20.3	35.4	74.4
2	67.4	30.4	0.0	92.7	30.4	92.7	204.8	17.2	31.0	80.2
2	68.0	19.0	0.0	74.8	19.0	74.8	293.5	16.8	39.5	135.0
8	25.4	70.1	100.2	0.0	25.4	100.2	294.2	27.6	46.2	67.4

Legend: $\dot{V}o_2$ = cc/min. STPD. P.A.P. = cm H_2O. Utilizing column-heading letters, $\dot{V}o_2$-Effective Segment = $A + \frac{A(A+B-C)}{C}$. Effective Segment = that segment of total lung remaining open during occlusion.

Only A, B, C and D are directly measurable. In order to calculate the increase in $\dot{V}o_{2}\text{-}_{ES}$ resulting from a partial unilateral occlusion, we must first know the $\dot{V}o_{2}$ of this same segment prior to occlusion. According to the diagram, the $\dot{V}o_{2}\text{-}_{ES}$ pre-occlusion is equal to A + Y. A can be experimentally measured, but Y has to be calculated. If, as assumed, $\dot{V}o_{2}\text{-}_{T}$ remains constant, it follows that:

$$A + B = C + D = (A + a) + (Y + y) \quad \text{-----} \quad (1)$$

and $$X = (a + y) \quad \text{-----} \quad (2)$$

Assuming proportional redistribution of occluded $\dot{V}o_{2}$:

$$\therefore \quad A/a = Y/y \quad \text{-----} \quad (3)$$

Since $a = C-A$; $X = B - Y$ and $\therefore$ $y = B - Y - C + A$

Substituting for a and y in equation (3) and solving:

$$Y = \frac{A\,(A+B-C)}{C} \quad \text{-----} \quad (4)$$

Since A, B and C are experimentally measurable, this enables us to calculate Y. The $\dot{V}o_{2}\text{-}_{ES}$ pre-occlusion (A + Y) may be found in column E and $\dot{V}o_{2}\text{-}_{ES}$ at occlusion +10 minutes (C + D) in column F of Table III. The % increase in $\dot{V}o_{2}\text{-}_{ES}$ above control level may be found in column G of the same table. Corresponding formulae may be derived for partial occlusions of the right PA.

According to the Fick equation for blood flow:

$$\dot{Q} = \dot{V}o_{2} / (A\text{-}V)_{O2}$$

In the first set of experiments in which direct Fick $\dot{Q}$ determinations were made, it was found that the $(A\text{-}V)_{O2}$ seemed to remain significantly unchanged as a result of unilateral PA occlusion. If we therefore assume that the $(A\text{-}V)_{O2}$ does remain constant and also that it is the same in all parts of the lung when the animal is breathing 100% O_2, we may rewrite the previous equation as follows:

$$\dot{Q} = K\ \dot{V}o_{2} \quad \text{where } K = 1/(A - V)_{O2}$$

In this manner any increase in $\dot{Q}\text{-}_{ES}$ is reflected by a proportional increase in $\dot{V}o_{2}$ of the same segment. Therefore, the % increase in $\dot{Q}\text{-}_{ES}$ (in terms of the corresponding $\dot{V}o_{2}\text{-}_{ES}$) is graphically plotted against the % increase in PAP in Figure 3.

DISCUSSION

The literature to date reveals two rather divergent observations concerning the effects of complete unilateral PA occlusion. As previously mentioned the

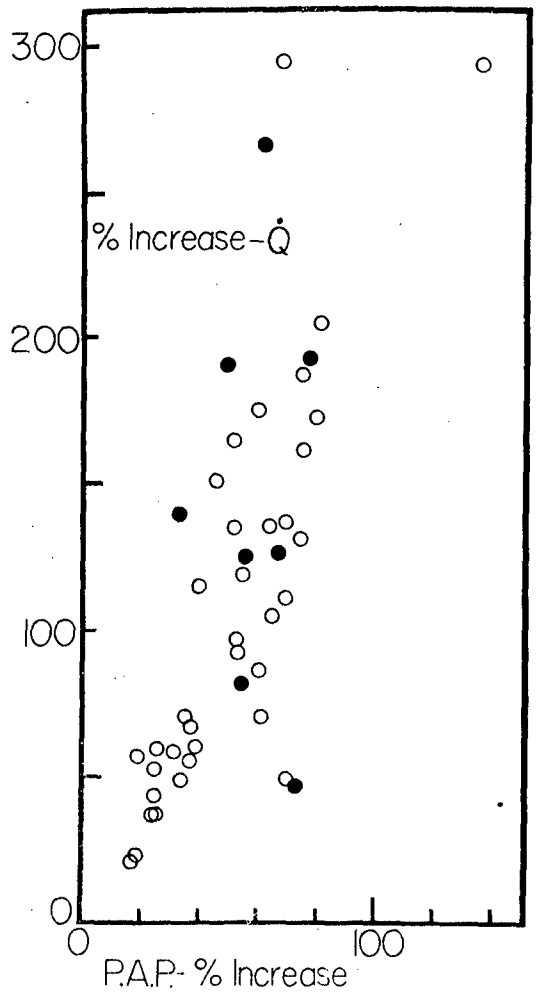


Figure 3

$\dot{Q}$ = blood flow through the "Effective Segment" (that segment of total lung which remains open during graded unilateral PA occlusion), and P.A.P. = pulmonary arterial pressure.

results of Dotter and Lucas (1) seem to indicate a picture of acute, intolerable, traumatic stress under which the animal is not likely to survive.

Contrariwise, a quite different response was observed by Carlens, Hansen and Nordenstrom (2) which was recently resummarized by Nordenstrom (6) as follows: "The experiments showed that it was possible to perform unilateral occlusion of the PA in the dog under narcosis by means of a small rubber balloon applied to the tip of a cardiac catheter. No alterations in the heart or breathing frequency, or in the general conditions of the dogs could be observed on occlusion of the artery, nor was there any increase in pressure in the main trunk of the PA, except in one case where, after a slight initial rise, the pressure soon returned to its original value. The oxygen absorption of each lung was measured by bronchospirometry and no absorption could be measured in the occluded lung."

Our experiments of complete unilateral PA occlusion were as uneventful as those of Dotter and Lucas were traumatic. Figure 1 and Table I both attest to the lack of severe acute traumatic response. In order to position the occluding balloon for a complete unilateral PA occlusion, in our experiments, one sometimes accidentally occluded the main PA. When this occurred, all the observations of Dotter and Lucas were closely duplicated. If such an occlusion was not released immediately, the animal succumbed.

While our observations are in many respects similar to those of Carlens, et al (2), they differ in some essential features, notably the changes in PAP. Our experiments reveal a definite, maintained PAP rise as a result of complete unilateral PA occlusion in contrast to no pressure rise as reported by them. Their observations of no change in PAP resulting from occlusion would suggest that 1) either the $\dot{Q}$ through the open lung remained the same (i.e., the total cardiac output decreased proportionately with no change in the R of the open lung) or 2) the R decreased in order to comply with the increased $\dot{Q}$ in the open lung or 3) a combination of both occurred. In any case, the changes which must occur would have to be regulated in such a way as to leave the PAP unaltered. Our observations (Tables I and II) indicate no significant alteration in the total pulmonary blood flow ($\dot{Q}\text{-}_T$), but a highly significant rise in PAP which was maintained for the entire 30 minute occlusion period. PVP was not measured. Since $\dot{Q}\text{-}_T$ remained constant and no significant changes in SAP could be demonstrated, it is believed that the PVP did not change in any significant manner. A PVP of 5 cm H_2O was assumed on the basis of previous direct measurements obtained in this laboratory (5). Utilizing this assumed figure, the change in ΔP can be estimated and a value for the change in R (of the open lung) can be calculated whenever the related measured $\dot{Q}$ increases. The average results indicate a slight decrease in R offered by the open PA. The seeming non-significance (P = approximately 0.3) of this resistance decrease is discussed below.

Because of the anatomical location of the right PA directly over the tracheal carina, inadvertant accidental leverage sometimes caused the tip of the rigid "Wright" tracheal divider to press upwards and partially occlude this main branch of the pulmonary circulation. It was on this account that we sometimes obtained the initially surprising picture of a control period average right:left ventilation ratio of 57:43 (which is in good agreement with previous data from this laboratory) along with a reversed $\dot{Q}$ ratio between these two lungs of 44:56. The average % change in $R\text{-}_{Rt}$, at occlusion +10 minutes, for 3 of the 8 experiments (when $\dot{Q}\text{-}_{Rt} > \dot{Q}\text{-}_{Lt}$ pre-occlusion) was +21% (P = 0.235) and for the remaining 5 experiments (when $\dot{Q}\text{-}_{Rt} < \dot{Q}\text{-}_{Lt}$ pre-occlusion) the corresponding value was -37.5% (P = 0.015). The 28 minute values were similar. It is felt that the apparent difference between these two figures is a relative rather than an absolute one and that it will be resolved on the basis that the amount of $\dot{Q}$ which is shifted by the occlusion may not necessarily correspond to the gross anatomical amount of lung that has been occluded. However, on the basis of the average value for the 8 experiments combined, we may not state that the decrease in R observed was significant.

Because of a statistical paucity in the number of points on the graph in Figure 3, a calculated regression line would have no real quantitative validity. A few general extrapolations might nevertheless be speculatively made from this graph. The resistance does not seem to remain constant but rather seems to decrease with increasing $\dot{Q}$. As previously stated the decrease in R does not seem to be the only factor involved in the response to increased $\dot{Q}$ since the PAP seems to increase substantially above control level during occlusion.

The scatter of points on the graph seems to suggest a concave upward paraboloid distribution. This type of curve is not uncommon to elastic vessel systems similar to the one encountered here. In such a system if the constituent number of vessels remained constant, one would in general expect a three-phase response. In the first phase (starting with a finite flow) the decrease in resistance per unit increment in flow, $\Delta R/\dot{Q}$, would tend to be small (Law of LaPlace). Then a transition would follow from this into a second phase in which the $\Delta R/\dot{Q}$ reaches a maximum. Then, if the system does not burst, a transition into the third phase should take place in which the $\Delta R/\dot{Q}$ approaches zero as R approaches a constant value at which time the vessels would become essentially "rigid" tubes and thereafter the pressure should vary directly with the flow. It is felt that our experiments may correspond generally to the latter part of the first phase and a substantial portion of the second phase. The extent of the second phase should depend on the maximum capacity of the constituent number of vessels involved. If, however, the number of vessels were augmented during this phase by more vessels opening up in parallel, the maximum capacity of these added vessels would be added to that of the others and the range of the second phase extended commensurately. There is some evidence that this type of capacity increase may occur in the pulmonary circulation in response to exercise (7,8).

In the range studied the interesting possibilities may, therefore, exist that, in response to increased flow, 1) the range of maximal $\Delta R/\dot{Q}$ will be limited by the capacity of a constant number of vessels, or 2) the opening up of additional vessels in parallel will extend this range in accordance with the related increase in capacity, or 3) a combination of both.

Since the diffusion capacity of oxygen (Do_2) is dependent upon the area of diffusion involved, an increase or constancy in the number of vessels participating in the range studied should be reflected in a measure of this function.

A graphical plot of ΔDo_2 versus Δ PAP, corresponding to Figure 3, may yield the information needed for the correct interpretation of the resistance behavior in the range of $\dot{Q}$ increase studied. Preparations for such a study are under way at present.

In March of 1954 Nordenstrom (9) reported that the effect of complete unilateral PA occlusion decreased the pulmonary circulation time (C.T.) on the average 33%. Assuming a pre-occlusion right:left $\dot{Q}$ ratio of 60:40 and a constant

$\dot{Q}$-$_T$, the % increase in pulmonary blood volume (PBV) in the open lung was calculated from his average values of ΔC.T. for left and right PA occlusions. An average increase in PBV of 11.9% was calculated for the left PA occlusions and 89.3% for the right PA occlusions. Nordenstrom reported in 1954 (6) that complete unilateral PA occlusions (as measured by radiographic densitometry) did increase the PBV of the open lung, but no average figures were given in quantitative estimation of the increase.

A parallel study of the effect of graded unilateral PA occlusions on Do_2 should be undertaken in man, for, if no PAP rise results from such occlusions as reported by Carlens, et al (2), then a very interesting species difference between man and dog in pulmonary circulatory regulation may be revealed.

SUMMARY

1. Eight complete left PA occlusions of 30 minutes' duration were performed on 6 pentobarbital anesthetized dogs.
2. None of the experiments produced acute "Cor Pulmonale".
3. The occlusions always resulted in a large significant PAP rise which was maintained for the duration of the occlusion.
4. Both the total pulmonary blood flow and the systemic arterial blood pressure remained significantly unaltered.
5. The average pulmonary resistance of the "open" lung decreased approximately 15% (P+0.300). The significance of this decrease is discussed.
6. In a second group of experiments, 10 pentobarbitalized dogs were used for a total of 36 random, graded unilateral PA occlusions.
7. A derived mathematical relation allowed the calculation of blood flow changes resulting from occlusion in terms of corresponding measurements of oxygen consumption.
8. A graphical plot of increase in blood flow of the open lung versus related PAP increase is presented. It suggests that increased blood flow results in a partial reduction in resistance and a measurable increase in PAP. Possible explanations for the observed vessel behavior are discussed and a method outlined to ascertain, in future experiments, which of the alternatives may be correct.

REFERENCES

1. Dotter, C. T. and D. S. Lucas Am. J. Physiol., 164: 254, 1951.
2. Carlens, E., H. E. Hansen and B. Nordenstrom J. Thor. Surg., 22: 527, 1951.

3. Lategola, M. and H. Rahn Proc. Soc. Exper. Biol. & Med., 84: 667, 1953.

4. Rahn, H. and H. T. Bahnson J. Appl. Physiol., 6: 105, 1953.

5. Stroud, R. C. and H. Rahn Am. J. Physiol., 172: 211, 1953.

6. Nordenstrom, B. Acta Radiol., Suppl., 108: 7, 1954.

7. Cournand, A., R. L. Riley, A. Himmelstein and R. Austrian Jour. Thor. Surg., 19: 80, 1950.

8. Riley, R. L., A. Himmelstein, H. L. Motley, H. M. Weiner and A. Cournand Am. J. Physiol., 152: 372, 1948.

9. B. Nordenstrom Acta Radiol., 41: 209, 1954.

THE DISTRIBUTION OF VENTILATION AND PERFUSION IN THE VARIOUS LOBES OF THE DOG LUNG

by

H. Rahn, P. Sadoul[1], L. E. Farhi[2], and J. Shapiro[3]

Many studies over the recent years have indicated that the ventilation may not be evenly distributed throughout the lung. By inhaling a foreign gas one can show by continuous gas analysis of the succeeding expirations that this gas must have mixed better in some areas than in others (1). However, these areas are not well defined geographically and furthermore they do not yield information concerning the distribution of blood flow. This study is an attempt to explore possible differences between ventilation and blood flow on a regional basis. The first part deals with ventilation/perfusion ratio differences in different lobes of the dog's lung while the second part is an attempt to study only the relative ventilation in the different lobes by measurement of their radio-activity after breathing labeled dust particles. The combined observations of these studies allow one, furthermore, to draw some conclusions concerning the distribution of blood flow.

I. Ventilation/Perfusion Differences in Different Lobes.

For any given mixed venous blood and inspired gas concentration it is possible to predict all the gas concentrations which could theoretically exist in the alveoli of the lung. These concentrations vary from alveolus to alveolus depending upon the ventilation/perfusion ratio. Furthermore, any particular ventilation/perfusion ratio is associated with a definite gas exchange ratio (2). Figure 1 plots the relationship between $\dot{V}_A/\dot{Q}$ ratio and exchange ratio, R. It is not important here to define the exact conditions in the mixed venous blood and inspired gas from which this particular curve has been derived. It merely serves to indicate that the higher R is the larger is the $\dot{V}_A/\dot{Q}$ ratio and that if at any given moment one can demonstrate that the R in any 2 regions of the lung are not the same, the $\dot{V}_A/\dot{Q}$ in these 2 regions must also be different. It is further of interest to note that in order to determine R it is not necessary to obtain an alveolar gas sample, but that this value can be obtained from the expired gas or any mixture of dead space and alveolar gas. Thus in these experiments gas samples were drawn simultaneously

---

1 On leave of absence from Faculté de Médicine, Nancy, France.
2 On leave of absence from Hadassah-Hebrew University, Jerusalem, Israel.
3 Department of Radiation Biology

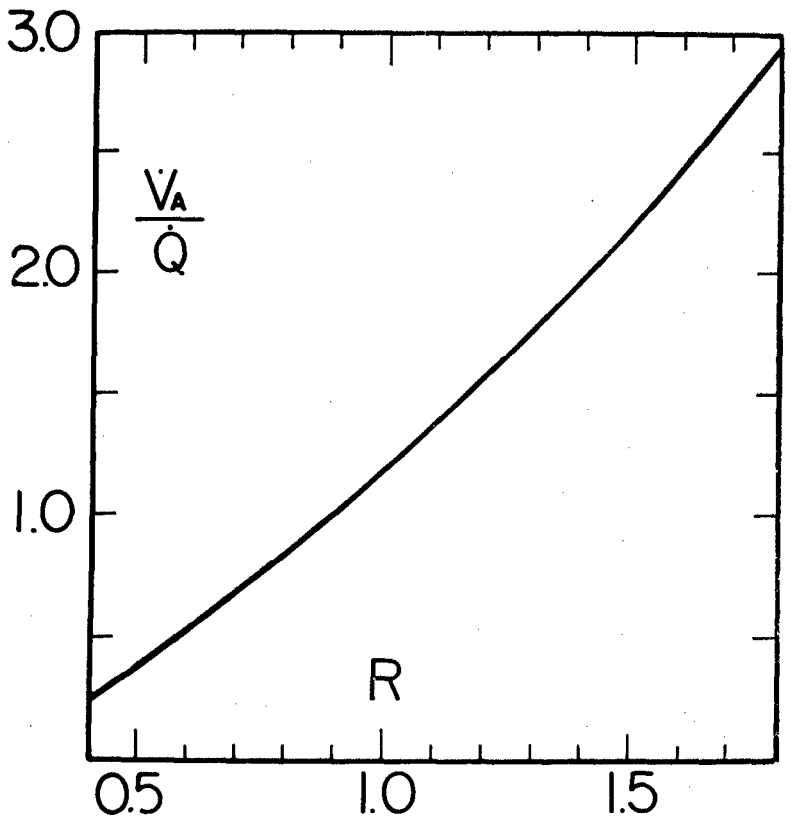


Figure 1

Relationship between the ventilation/perfusion ratio of an alveolus or larger lung unit and the corresponding exchange ratio, R. This curve is computed for a particular mixed venous and inspired gas tension.

from small catheters placed in the bronchi of 2 or more lobes and the R determined from the gas analysis.

METHOD

Large dogs weighing more than 20 kg were anesthetized with sodium pentobarbital. A bronchoscope (12 mm diameter) was inserted and polyethylene tubes PE-90 (1.27 mm diameter) were inserted and placed under direct vision, usually in the upper and lower lobe bronchus of the left or right lung.

Since these tubes are quite flexible they cannot be inserted directly but are first threaded through a long 2 mm diameter brass tube with the catheter tip just barely projecting at the end. These brass tubes may thus be advanced through the bronchoscope to the orifice of the lobar bronchus. The final placement was done fluoroscopically by visualizing the radio-opaque tip of the polyethylene catheter as it was advanced beyond the brass tube about 2 cm into a particular lobar bronchus. The brass rod was then carefully withdrawn leaving the polyethylene tube in place. In order to place catheters into the upper lobes a 2 cm flexible, curved tip was soldered to the brass tube using a tube of spiral spring material. With this U-shaped tip one can guide the polyethylene catheter into the bronchi of the upper lobes. The tips of the catheter were sealed and filled with mercury which provided a radio-opaque, but flexible tip. Gas was aspirated from a whistle-tip opening just proximal to the sealed off mercury. The detailed construction has been described previously (3).

The exact placement of the catheters required a knowledge of the fluorographic anatomy of the dog's lung not available in the literature. For this reason considerable effort was spent in securing a large series of bronchographs[1]. With the aid of these as well as plastic casts of the bronchial tree we were able to work out a fluoroscopic anatomy which gave us considerable assurance concerning the exact position of the catheters. Figure 2 is an AP view showing the location of the major bronchi. The end of the shade region marks approximately the location of the catheters when gas samples were collected.

The gas sampling was done in the following manner. Since we felt it unnecessary to obtain alveolar samples, the gas from 2 or more of these major bronchi was simultaneously and continuously aspirated into Haldane mercury gas sampling reservoirs. The polyethylene tubes were connected to the mercury filled sampling tubes which were permanently mounted. The open mercury reservoirs were mounted on a large bar which could be gradually lowered by turning a long worm screw. Thus one is able to aspirate the gas at any desired rate. We collected our samples at the rate from 5-7 ml/min. The collected samples were then analyzed in duplicate on the Scholander 0.5 cc gas analyzer and the exchange ratio, R, computed. After sampling, the position of the catheter tips was again checked by the fluoroscope.

RESULTS

A large number of simultaneous gas samples were obtained from 2 or more of the 7 distinct lobes of the dog's lung. Only those comparisons are given here which were done simultaneously in the upper and lower lobes of the right or left lung. Furthermore, the O_2 and CO_2 analyses for each sample have also been omitted and

---

[1] We are greatly indebted to Dr. W. Strain of the Department of Radiology whose help and experience allowed us to obtain excellent pictures.

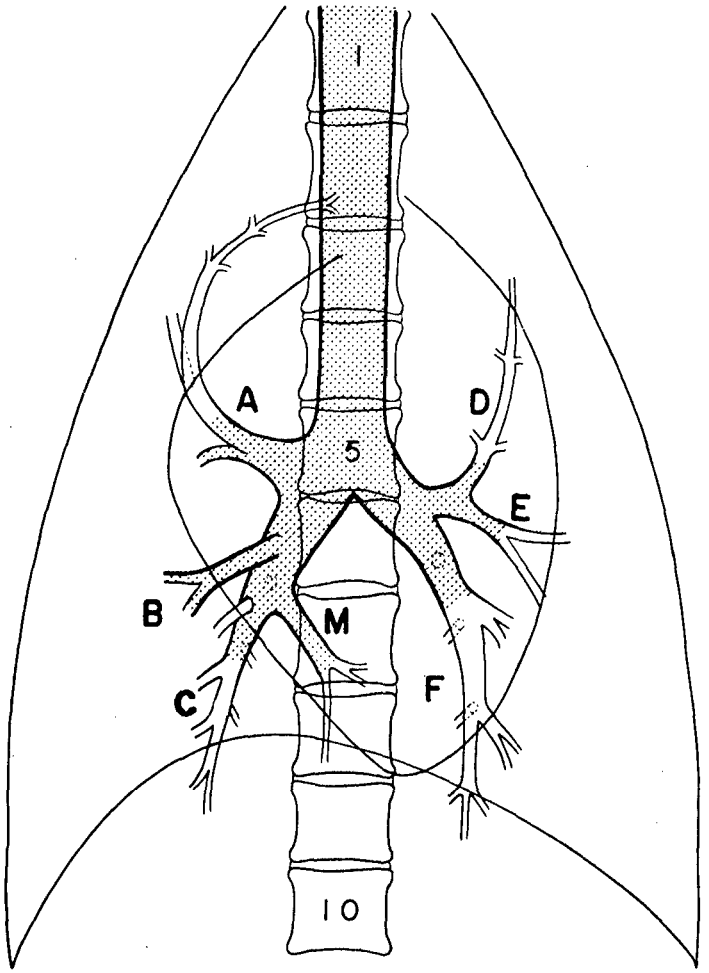


Figure 2

Fluoroscopic anatomy of the broncho-tracheal tree of the dog in the supine position. The shaded region shows the major bronchi and the letters indicate the respective lobes which they supply and correspond to those labeled in Figure 5. The numbers designate the corresponding thoracic vertebrae.

only the computed gas exchange ratio, R, for each lobe has been recorded in Table 1 for the supine position and for the upright position (30° from the vertical axis).

TABLE 1

The exchange ratio, R, between upper, D, and lower lobe, F, of the left lung and upper, A, and lower lobe, C, of the right lung in the supine and erect position.

	Supine			Erect			Supine			Erect		
Lobe	D	F	Δ	D	F	Δ	A	C	Δ	A	C	Δ
	.75	.65	.10	1.38	.79	.59	.83	.79	.04	.95	.85	.10
	.89	.79	.10	1.48	.84	.64	.82	.59	.23	.95	.74	.21
	.70	.66	.04	.88	.70	.18	.70	.64	.06	.80	.71	.09
	.78	.67	.11	.95	.79	.16	.83	.77	.06	.67	.69	-.02
	.76	.73	.03	.91	.75	.16	.79	.73	.06	.66	.67	-.01
	.74	.72	.02	.64	.63	.01	.87	.90	-.03	1.23	1.04	.19
	.88	.88	.00	1.24	1.04	.20	.82	.65	.17			
	.73	.62	.11	.56	.55	.01	.86	.81	.05			
	.82	.77	.05	.73	.74	-.01	.80	.60	.20			
	.63	.64	-.01	.83	.82	.01	.90	.84	.06			
	.70	.73	-.03	.80	.73	.07	.90	.85	.05			
	.68	.64	.04									
	.88	.84	.04									
	.60	.59	.01									
	.95	.93	.02									
Mean			.04			.18			.09			.09
St. Error			.011			.068			.025			.037
P			$<.01$			$<.03$			$<.01$			$<.06$

It will be noted that the exchange ratio is almost invariably higher in the upper lobe when compared to the lower lobe, in the right lung as well as in the left lung. This difference seems to be highly significant. In the experiments on the left lung the R difference is exaggerated upon tilting into the erect position. Not enough experiments are available to show a similar trend on the right side.

II. Ventilation Differences in Different Lobes

A simple, direct method for recording the undisturbed ventilation of a lobe of a lung has yet to be developed. Fowler (4) has recently suggested an indirect method employing the principle of gas dilution.

Our search was directed toward selecting a substance for inhalation which ideally would have the following characteristics: It should be (1) insoluble and not affected by circulation, (2) deposited only in the alveolar portion, and (3) chemically or physically detectable after deposition. Ideally the concentration of such a substance in each lobe at autopsy would reveal its relative ventilation.

In brief, we selected for these experiments aerosols consisting of radio-active daughter products of radon gas deposited on naturally occurring or artificially produced dust particles. These dust particles accumulate in the deeper portions of the lung and are only slowly removed by the circulation. The soluble radon gas which is also inhaled and radioactive does not interfere in these determinations since it does not accumulate and the activity of its daughter products, as counted, is less than 1% of that of the accumulated daughter products (5). After this aerosol was inhaled for 2 hours, the animals were autopsied and each lobe counted and its dry weight determined.

METHOD

Production of the radioactive aerosol

The aerosol in the exposure chamber was made radioactive by inserting radon gas into the chamber. Radon is an inert gas, and, in general, the radon molecules would not be expected to stick to any of the dust in the air. Radon, however, decays to a series of short-lived radioactive daughters. These daughter products are radioactive isotopes of polonium, lead, and bismuth, and when produced in air, they become attached to particulate or other matter in the environment. It is for this reason that investigators who first studied their characteristics called them the "active deposit" of radon. The decay scheme of radon is shown in Figure 3. Only those daughter products which are responsible for the radioactivity measured in our experiments are included.

When air containing radon gas is inserted into a chamber whose walls do not adsorb radon, the radon molecules soon become distributed uniformly throughout the chamber. Since radon has a half-life of 3.8 days, its radioactivity remains constant during the few hours required for the completion of the experiment. The radon daughter products attain essentially radioactive equilibrium with the radon in the air about three hours after the radon is inserted. If the concentration of particulate matter in the air of the chamber is high enough, practically all of the daughter products will be deposited on dust particles, making the dust particles radioactive. These dust particles emit very penetrating gamma radiation as well

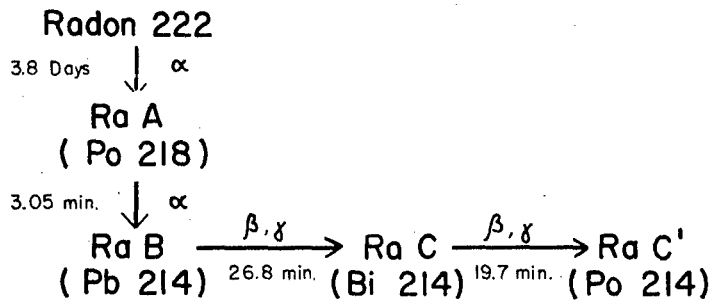


Figure 3

The radioactive decay scheme of Radon. The gamma rays of Radium B and C were counted in these experiments.

as the readily absorbed alpha and beta radiation. Only the gamma radiation was detected in these experiments.

The radon gas was obtained from a 50 microcurie radium chloride source. The chamber had a capacity of 1800 liters. The gamma activity of the particulate matter per liter of chamber air was found to be of the order of 5500 counts per minute when counted in the same counter in which the dogs' lungs were counted. The activity was determined by passing a liter of the chamber air through a millipore filter paper which removed all of the particulate matter from the air passing through it, and then counting the filter paper.

The aerosol used in the first few experiments consisted of the dust in ordinary atmospheric air, blown into the chamber from the out-of-doors by a fan placed in a window in the laboratory. The experiments were performed just a few hours after the air had been blown into the chamber and mixed with radon. In later experiments the aerosol was produced by the sparking of a blower motor in the chamber. The blower motor was turned on for about fifteen minutes on the day preceding the experiment and thus, the particulate matter it produced had been suspended in the chamber air and undergoing coagulation for at least 15 hours prior to the commencement of the experiment. Measurements on this aerosol indicated that it had a particle size of about 0.1 micron. This particle size was larger than that measured for aerosol obtained from the out-of-doors. Particles of these dimensions are deposited mainly by diffusion to the walls of the airways and alveoli and were chosen because of the ease with which they were obtained. Further information on the properties and measurement of radon daughter product aerosols is given elsewhere (5).

Buildup of radioactivity in the dogs' lungs

The high levels of radioactivity attained in the dogs' lungs was caused by the removal in the lung of the radioactive particulate matter carried by the inspired air. The radioactivity produced by the radon gas itself was small compared to the radioactivity produced by the deposition of the inspired radioactive matter. Because radon is an inert gas, its concentration in the lung passageways and in the lung tissue could not exceed the concentration in the inspired air. On the other hand, the activity of the radioactive matter deposited in the lungs increased until the radioactive matter decayed at the same rate at which it was deposited. In independent rat experiments, it has been shown that the lung radioactivity produced from radon alone is less than one percent of the radioactivity produced from the deposition of the radon daughter products when the daughter products are essentially in radioactive equilibrium with their parent, radon (6).

Measurement of radioactivity in the dogs' lungs

The dogs were exposed in the chamber until the radioactivity of their lungs attained over 90% of the maximum level which could be attained at a constant breathing rate. The exposure period was approximately two hours. At the end of the exposure period, the lobes were quickly removed and inserted into test tubes for measurement in the Texaco well-type Geiger counter, Type GR, manufactured by Welch-Allyn Inc. Since the half-life of the daughter products in the lungs, once the lungs were removed from the source of radioactivity, was less than 40 minutes, the measurements on the 7 lobes had to be made rapidly. The counting times for each lobe were so adjusted as to give approximately the same number of total counts per lobe. After exploratory experiments had indicated rough estimates of the relative counting rates of the different lobes, the lobes were counted in such an order as to keep the counting time a minimum. Approximately 6000 counts were accumulated per lobe which gives a standard deviation in the counts of approximately 1.3%.

The seven lobes were counted at least twice and the activities plotted on graph paper. A template of the theoretical decay curve was used to draw the theoretical decay curve through the first determination. The falling of the second determination on the theoretical decay curve served as a check on the stability of the counting system. In only a very few cases was the departure from the theoretical decay curve other than what one would expect on purely statistical grounds. If the two points did not seem to fall on the same decay curve, a third reading was taken. Since more counts were collected for the first reading, its reading was taken as the activity of the lung, if the second reading did not differ significantly from it. A typical count of the lobes of one lung is shown in Figure 4.

Relative activities of the different lobes of the lungs were read for a fixed decay time from graphs such as the one shown in Figure 4. It was necessary to apply small corrections to these values because the different-sized lobes occupied

different volumes in the test tubes. The geometry correction factors, which were determined by independent calibration experiments, were applied to the measured activities. They were never greater than 5%. Because of the low resolving time of the counter, it was not necessary to make dead time corrections for the range of activities that was measured.

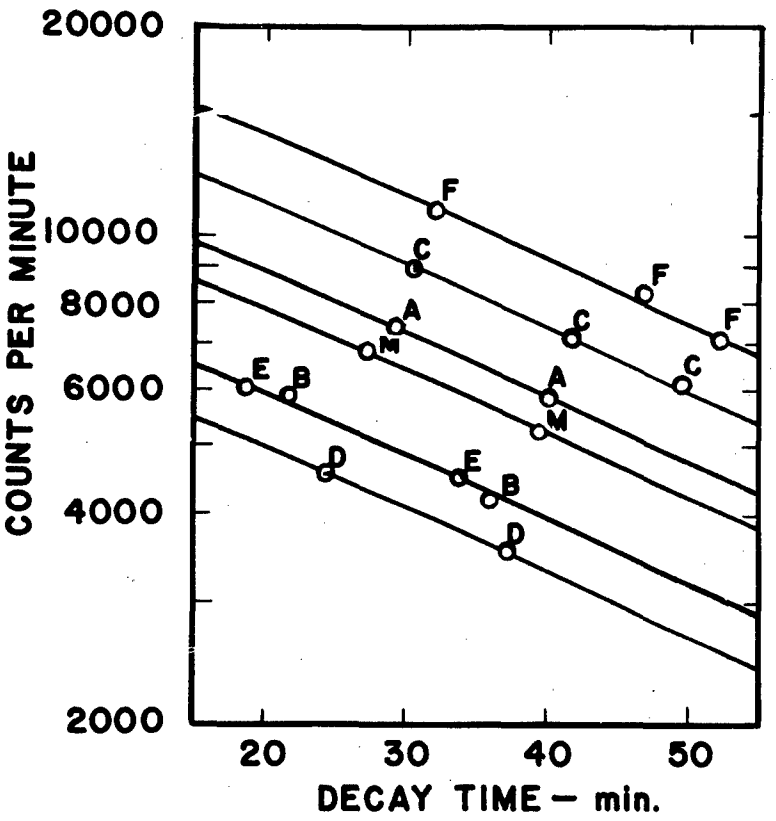


Figure 4

Log of activity against time for a typical count of the seven lobes of the lung after aerosol exposure.

The effect of the pulmonary circulation upon the aerosol activity

In order that the radioactivity measured in the dogs' lungs be a function of the respiration only, it is important that the retention of the aerosol in the lung should

not be significantly affected by the circulation. Some experimental results have been reported on the extent to which the deposited radon daughter product aerosol remains in the respiratory tract of rats (7). Here it was found that about 17 percent of the deposited aerosol was removed from the respiratory tract by some means other than physical decay. The biological half-life of the material in the respiratory tract was calculated to be 3 hours. It is not known what portion of the removed material was carried away by the circulation.

Even if all of it were removed by the circulation, it would not introduce large errors unless ventilation/perfusion ratio differed markedly from lobe to lobe. Since our previous discussion (Part I) suggests only small differences in this ratio, we feel that this rate of uptake does not interfere with these relatively gross measurements and that we can interpret the radioactive count of a lobe as being approximately proportional to the ventilation. Whether or not this ventilation index represents total or alveolar ventilation is difficult to say. When the larger airways (trachea and major bronchi) were tested separately, they showed relatively low activity compared to the deeper parts of the lung.

We are fully aware that this approach leaves many questions unanswered, particularly in regard to the translation of the radioactive count into the equivalent of ventilation which a lobe received. Our results are presented with such reservations in mind.

The relation of lung volume to lung weight

After obtaining the relative count in each lobe at the end of the aerosol exposure the lobes were dried and weighed. Thus one could obtain a ratio of the relative count/relative weight for each lobe. It was felt that it would be preferable to have the relative lung volume instead of the weight and that this relationship should be established. In order to measure the relative lung volumes of the lobes in the dog the technique previously described by Tobin was adapted (8).

The trachea of the anesthetized dog was cannulated and a catheter placed in or near the right heart. The dog was then killed with an overdose of nembutal and the dog ventilated artificially for 5 - 10 minutes with pure CO_2. After all the alveolar gas was displaced by CO_2, the cannula was connected to a reservoir filled with liquid latex (which is quite alkaline). The liquid rapidly filled all the lung spaces by absorbing the CO_2 in about 2 minutes. In order to avoid the hydrostatic pressure of the latex from distorting the lung and chest wall, the latex filling procedure was carried out with the dog barely submerged under water. In this fashion the hydrostatic pressure of the latex was counterbalanced by the pressure of the water.

After filling the lungs, small amounts of dilute acetic acid were injected through the venous catheter in order to hasten the coagulation of the latex. After a few hours the dog was removed from the water, the chest opened and the lungs excised. Each lobe was weighed and its relative weight (% of total weight)

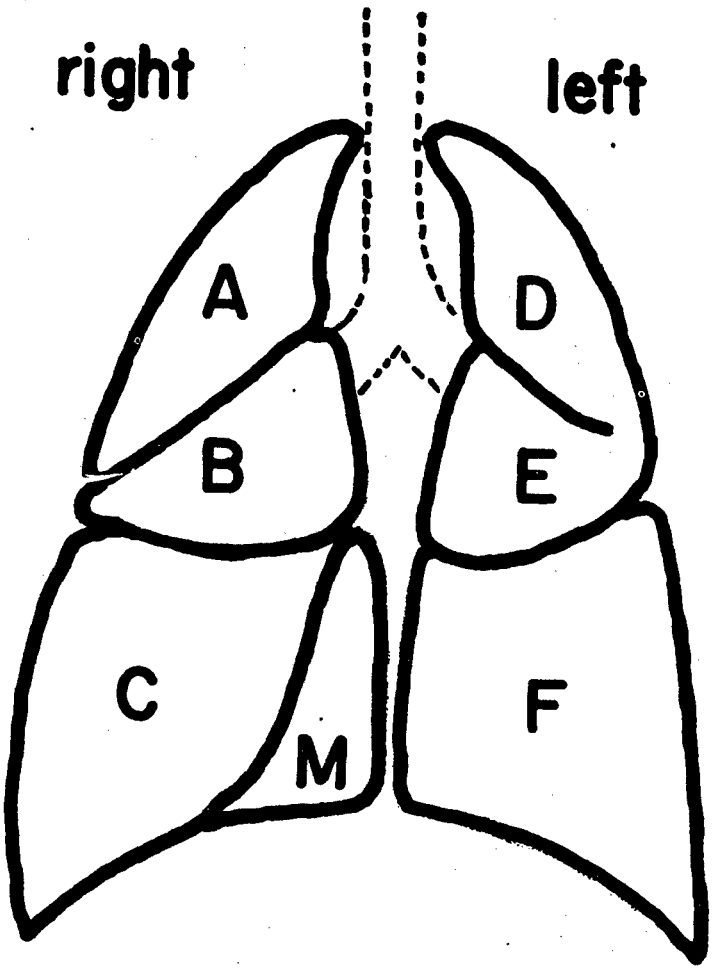


Figure 5

Schematic representation of the 7 lobes of the dog lung. M represents the mediastinal lobe.

recorded. The average values of 5 dogs are given in Table 2. Each lobe has been designated by letters as shown in Figure 5. Since the weight of the latex-filled lobe is about 100 times greater than the weight of the dried lobe, it represents percentagewise the volume of each lobe. Furthermore, the average latex weights are not statistically different from the average dry weight of the similar lobes, obtained in 21 dogs (9). The only exception is lobe E. This is probably due to an artefact caused by the artificial separation of lobe E and D which are partially fused. When lobes D + E are compared for each group in Table 2 this difference

disappears. As the dead space of each lobe is proportional to its dry weight (9), the latex weights or the dried weights may therefore be taken to represent either the total lobe volume, or the alveolar lobe volume.

TABLE 2

Percent relative weights of dog lungs (1) dried by air inflation (21 lungs), and (2) filled with Latex (5 lungs). P = probability that they belong to same universe.

Lobe	A	B	C	M	D	E	F	D+E	Rt. Lung
(1)	17.3	8.9	24.7	7.5	9.6	5.8	26.2	15.4	58.3
S.E.	.41	.22	.48	.19	.20	.13	.49	.23	.57
(2)	17.2	9.3	24.4	7.7	9.7	6.6	25.7	16.3	58.3
S.E.	.31	.43	.59	.33	.62	.45	.84	.59	.59
P	$>.5$	$>.4$	$>.5$	$>.5$	$>.5$	$<.04$	$>.5$	$>.4$	$>.5$

RESULTS

Supine dogs

Nine dogs in the supine position inhaled the radioactive aerosol for approximately 2 hours. The tracheal cannula was directly connected with the 1800 liter gas chamber. In order to facilitate the designation of each of the seven lobes of the dog's lung, the scheme of Figure 5 was employed. These designations are used in Tables 1 - 3. It should be noted that lobe D and E are usually fused for about a quarter of their adjoining surfaces and are tabulated separately as well as a single unit in Tables 2 and 3.

Table 2, Row 1 gives the count of each lobe as % of the total lung count, while Row 2 is the ratio (% count of total count)/(% dry weight of total weight). If we accept the values of Table 2 showing no statistical difference between relative lobe volume and relative lobe weight, then Row 2 indicates that lobe C and F have a significantly smaller deposit in relation to their respective volumes. In other words to have in each lobe a deposit proportional to its lobe volume the ratio should have been 100%. Thus the two lower lobes received significantly less radioactive aerosol and the upper lobes A and D more than their share. However, the values for the upper lobes is not significantly different from 100 or exact proportionality.

Erect dogs

Six dogs in this series had lobe counts as indicated in Row 4. Here we see a reversal of the aerosol distribution. The upper lobes received less percentagewise and the lower lobes more. There is a significant difference in this distribution based upon the counts alone between Row 1 and Row 4.

The ratio of (% counts)/(% weight) in Row 6 also indicates a significantly smaller deposit in the upper lobes A and D, while the lower lobes now receive an increased deposit. The difference between Row 2 and 6 is expressed by the P values in Row 8.

In summary we can say that in the supine position the lower lobes contain aerosol in significantly smaller concentration than would be expected on the basis of their relative volumes or weight. In the erect position this situation is reversed and the upper lobes now have a significantly lower concentration than would be predicted.

DISCUSSION

The exchange ratio differences between the upper and lower lobes (Table 1) in the supine position are very small but highly significant in both lungs and tend to be increased upon tilting. Similar observations have been reported by Martin et al (10) in man who sampled alveolar gas simultaneously from the upper and lower lobe. They obtained significant differences only in the upright position and later findings (11) suggest that these differences are in no way correlated with changes in resting lung volumes.

Figure 1 indicates the various exchange ratios, R, which one would predict for alveoli or larger lung units having different alveolar ventilation/perfusion ratios. The particular curve drawn is for a definite mixed venous blood gas and inspired gas tension. In our dog experiments we did not know the mixed venous blood gas tensions at the time of gas sampling and were unable to construct the precise curve. For this reason we are unable to assign precise $\dot{V}_A/\dot{Q}$ ratio to our experimentally obtainable R values. Nevertheless, we can definitely say that a lobe with a relatively lower R has a lower $\dot{V}_A/\dot{Q}$ than a simultaneously sampled lobe with a higher R value.

Thus the findings of Table 1 allow us to say that in the supine as well as the erect position the R was higher in the upper lobes compared to the lower lobes and that therefore the $\dot{V}_A/\dot{Q}$ ratios were higher in the upper lobes than in the lower lobes. One may also make an approximate guess from the average R values and Figure 1 that the $\dot{V}_A/\dot{Q}$ ratio in the upper lobes is somewheres in the neighborhood of 0.9 and in the lower lobes 0.75.

Even if we knew the absolute $\dot{V}_A/\dot{Q}$ ratio differences between the 2 lobes, one

TABLE 3

Percent relative count and ratio of % Count/% Dry Weight of lobes after inhaling particles in the supine (9 dogs) and erect position (6 dogs).

		Lobes of Right Lung				Lobes of Left Lung				Rt. Lung
Supine		A	B	C	M	D	E	F	D+E	
1.	Count	18.0	10.1	22.3	10.1	8.3	8.7	22.4	17.1	60.4
	S.E.	1.0	.72	.89	.89	.57	.59	.72	.60	.94
2.	C/Wt.	109	110	89	121	96	134	87	112	103
	S.E.	6	7	3	8	8	6	3	3	2
3.	P	.17	.19	$<.01$	.03	.47	$<.01$	$<.01$	$<.01$	.17
Erect										
4.	Count	12.8	9.7	28.0	7.5	5.5	7.0	28.2	13.0	58.0
	S.E.	.56	.71	.84	.59	.66	.63	1.10	1.17	1.02
5.	P	$<.01$	$>.5$	$<.01$	$<.04$	$<.01$	$<.05$	$<.01$	$<.02$	$>.5$
6.	C/Wt.	75	115	110	113	64	107	116	81	99
	S.E.	4	6	4	10	2	9	12	7	8
7.	P	$<.01$	.04	.04	.23	$<.01$	.46	.23	.03	.9
8.	P	$<.01$	$>.5$	$<.01$	$>.5$	$<.03$	$<.08$	$<.01$	$<.01$	$>.2$

S.E. = the Standard Error of the Mean of the figures above it.
Row 1. % Count of Lobe = (Count of Lobe x 100)/Count of Whole Lung.
Row 2. C/Wt. = (% Count of Lobe x 100)/(% of Dry Weight).
Row 3. P = Probability that Row 2 is the same as 100%.
Row 4. Same as Row 1 but in erect position.
Row 5. P = Probability that the % Count in erect dogs (Row 4) is the same as the % Count in supine dogs (Row 1).
Row 6. Same as Row 2 but in erect position.
Row 7. P = Probability that Row 6 is the same as 100%.
Row 8. P = Probability that Row 6 is the same as Row 2.

would not be very much farther ahead since we are dealing here with a ratio. In other words the reason that the upper lobe has a relatively higher $\dot{V}_A/\dot{Q}$ ratio could mean (1) that the perfusion was normal (i.e., proportional to its lobe volume) but that the ventilation was proportionally larger than one would predict from its lung volume, or (2) that the ventilation was normal but the lobe was relatively underperfused. This distinction is important and therefore necessitates the separate measurement of either the ventilation or the perfusion. It is for this reason that we undertook the second part of this study which attempts to measure the relative ventilation of lung lobes in the supine and erect position.

The hazards connected with interpreting the relative radioactivity of each lobe at autopsy as the relative ventilation which such a lobe has received has been discussed above. The overall particle retention is of the order of 20% (5) and this figure as well as the particle size of approximately 0.1 micron suggests that the deposition is primarily in the deeper parts of the lung and not the upper airways (furthermore, counts of the isolated trachea and main bronchi show very low activity compared to the lobes). These particles are largely deposited by diffusion and it is possible that the altered geometry of the alveolar regions before and after tilting may affect the diffusion pathways and thus contribute to the deposition which is independent of the ventilation. Nevertheless, we feel that the radioactive count is an approximate index of the relative alveolar ventilation and the further discussion is based upon this assumption.

Thus Table 3 (Row 2) indicates that in the supine position the lower lobes (C and F) receive proportionally less ventilation than the upper lobes (A and D) while in the erect position this situation is completely reversed (Row 6). On the other hand we have evidence from Table 1 that the upper lobes have a higher $\dot{V}_A/\dot{Q}$ ratio than the lower lobes regardless of the position.

It is now possible to arrive at qualitative predictions for changes in the distribution of blood flow to these lobes when the dog is tilted from the supine to the erect position. (If the $\dot{V}_A/\dot{Q}$ ratios could be determined accurately, a quantitative approach would be possible). Let us assume that the values of Figure 1 apply to our dogs in the supine as well as the erect position. Then lobe A in supine position has an R of .83 and a $\dot{V}_A/\dot{Q}$ of .90, while the simultaneously sampled lobe C has an R of .74 and a $\dot{V}_A/\dot{Q}$ of .75. From Table 3 (Row 2) we find that A receives a ventilation of 109% or 9% more ventilation than would be expected from its weight or volume and C receives a ventilation of 89%. We can now calculate Q, the relative perfusion. For A, V_A is equivalent to 109% and $\dot{V}_A/\dot{Q} = .90$. Thus $\dot{Q} = \dot{V}_A/.9$ and substituting the value for V_A we obtain $Q = 109/.9 = 121$. For lobe C the value for Q is practically the same, 119. These values for Q are only relative to the observed ventilation. They indicate that in the supine position lobes A and C receive the same perfusion per unit volume and that, therefore, the relative lower ventilation of the lower lobe, C, is responsible for lower $\dot{V}_A/\dot{Q}$ ratio and lower R value.

If we now turn to lobes A and C in the erect position, the R values and therefore the $\dot{V}_A/\dot{Q}$ ratios are again lower in the lower lobe, but the relative ventilation is now larger and very much reduced in the upper lobe. This can only be interpreted as more blood per unit volume of lung flowing through the lower lobe than through the upper lobe and that the ventilation, although increased in the lower lobe, is not enough to make the R or $\dot{V}_A/\dot{Q}$ ratio equal to or higher than in the upper lobe.

It is of interest to compare this increased distribution of blood to the dependent portions of the lung in the erect position to that which occurs in the lateral decubitus position. In this case we can compare the relative ventilation and blood flow of the right and left lung in the supine with that in the lateral position. Two such studies have recently been made on man which are summarized in Table 4. Eight cases of uncomplicated T.B. were selected from the data of Rothstein, et al (12) and Inada, et al (13) reports experiments on 10 healthy medical students. In both instances the O_2 uptake and ventilation were recorded by bronchospirometry in the supine and right lateral decubitus position. Their findings are almost identical.

The ventilation (percent of the total) of the right lung in the down position was insignificantly increased, but the O_2 uptake of the down lung became considerably larger. This can only be interpreted as relatively more blood being shifted into the down lung. Here we see a trend similar to that observed in our animal experiments, namely that the pendent portions of the lung obtain a relatively greater perfusion.

TABLE 4

Ventilation and O_2 uptake of the right and left lungs in the supine and right lateral position in man, expressed as percent of the total.

	Supine		R. Lateral		Supine		R. Lateral	
	R.	L.	R.	L.	R.	L.	R.	L.
% Ventilation	52	48	54	46	52	48	53	47
% Vo_2	50	50	61	39	49	51	63	37
	Average of 10 medical students - Inada, et al (13)				Average of 8 patients Rothstein, et al (12)			

Thus gravity has a definite influence in shifting the relative perfusion of the lung whether the lung is rotated around its longitudinal axis when in the supine position or as in our animal experiments when the lung is rotated from the horizontal to the vertical position. The ventilation of the pendent lung is also increased thus tending to keep the $\dot{V}_A/\dot{Q}$ ratio constant. In the bronchospirometry experiments of man this increased ventilation of the pendent side is very small indeed, but might have been considerably larger if the ribcage of the down side could be freed from the supporting bed.

The possible consequences of such perfusion distribution in upright man and in animals upon the early formation of pulmonary tuberculosis lesions has recently been discussed by Dock (14). If the level of the alveolar O_2 tension of an alveolus or lobe is an important factor in the early localization of such an infection, then the perfusion distribution itself is not as important as the ventilation/perfusion ratio of a particular segment. It is this ratio which determines the precise O_2 and CO_2 tension. The relation between $\dot{V}_A/\dot{Q}$ and the alveolar P_{O_2} is somewhat similar to the relationship of $\dot{V}_A/\dot{Q}$ to R shown in Figure 2. As $\dot{V}_A/\dot{Q}$ increases the P_{O_2} increases from the mixed venous O_2 tension when $\dot{V}_A/\dot{Q} = 0$ to the inspired O_2 tension when $\dot{V}_A/\dot{Q} = \infty$.

Finally, it is of interest to compare our results with those of Stockinger, et al (15) on the relative retention of uranium dust in various lobes of the rat lung. These authors exposed 10 rats for 6 hours to UO_2 dust of a mass-medium diameter of 0.45 micron. The animals were sacrificed 20 hours later for determination of the UO_2 concentration in each lobe and its wet weight. There are 4 lobes in the right lung similar to that found in the dog (Figure 5) while those of the left lung are fused. If we express their findings the way our data were expressed in Table 3, namely, each lobe as the ratio of (% of total concentration to % of total wet lung weight) x 100, we obtain the following results: The total right lung as well as total left lung is equal to 100%, indicating exact correspondence between retention and lung weight. However, the individual lobes of the right lung give values of 128% for upper lobe A, 92% for B, 95% for lobe C and 94% for lobe M. Thus the upper lobe received relatively more dust than all the other lobes. To what extent these values were modified by the dust elimination processes during the next 20 hours after exposure is difficult to say. Nevertheless, here is another example which suggests uneven air distribution to the lobes of the rat lung.

APPENDIX

The gas sampling technique as well as the large scatter of R values requires some further explanations.

Relationship of catheter size to ventilatory obstruction

The introduction of a catheter into a bronchus will reduce the effective cross

sectional area and thus reduce the relative ventilation of this particular lobe. If one assumes that the alveolar pressures are the same before and after introduction of the catheter and that the gas flow is essentially linear, one can calculate the change in ventilation by the application of Poiseuille's Law. Thus, if A_0 is the cross sectional area of a bronchus before, and A_1 the effective area after catheterization, then the ventilation before, V_0, will be reduced to V_1 by the relationship where $(A_0)^2/(A_1)^2 = V_0/V_1$ and $(V_0-V_1)/V_0 = v$, where v is the relative reduction of ventilation (expressed as %) to be expected after introducing the catheter. The v values are numerically equal to nearly 2 x a, where "a" is the % reduction of the effective cross sectional area (for "a" values less than 10%). Thus a 1% reduction in area will reduce the ventilation 2%. For a values greater than 10%, the factor 2 becomes progressively smaller.

Table 5 shows the absolute diameters and cross sectional areas of the main bronchi in the dog. These values were obtained from six tracheal-bronchial casts of dogs weighing approximately 20 kg. It will be seen that with the catheter used in these experiments, Polyethylene PE-90, the percent reduction in area "a", does not exceed 3.5% and this only in the smallest bronchus, and that the v values will be 2 x a. For our purposes of comparison of two or more lobes, however, we are not concerned with v for an individual lobe but rather with the difference between v values for these lobes. Table 5 indicates these differences for any two lobes which are to be compared.

Artifact produced by continuous sampling

Once the catheters were in place gas samples were aspirated at a slow rate of 5 - 7 cc/min. in order to avoid possible contamination with gas from other lobes. During expiration only gas from a particular lobe is removed but during the first phase of inspiration the mixed alveolar gas from all portions of the lung is present in the dead space and this aliquot would now enter each catheter wherever located. Thus with continuous aspiration a slight contamination is introduced with each inspiration which does not represent gas which necessarily comes from that particular lobe. The ultimate effect of this artifact is to reduce the differences which exist between any lobes. Thus whatever differences are determined between 2 lobes, they are apt to be actually larger than their analyses would indicate.

The large scatter of R values

Table 1 indicates a large range of R values for a particular lobe from one dog to the next. This is due to the fact that the anesthesia will initially depress the total ventilation and thus the exchange ratio while later on these values will increase and often rise above .85. In the erect position hyperventilation frequently ensues thus producing R values which may seem abnormally high. Thus the R values are a function of the depth of anesthesia at the moment of sampling while in the erect position this is further influenced by the posture-induced hyperventilation.

TABLE 5

Diameter and cross sectional areas of the main bronchi based upon measurements of casts of the broncho-tracheal tree of six dogs weighing approximately 20 kg. From these data the percent reduction of the effective area by a PE-90 catheter, (a), has been calculated as well as the percent reduction of the relative ventilation (v). The differences in relative ventilation reduction between any two or more lobes which are sampled may then be calculated.

	Mean Diameter mm	Area mm^2	% Area Occluded (a)	% Ventil. Reduced (v)	Differences in Reduction of Ventilation between any 2 Lobes with a Catheter						
					A	B	C	M	D	E	F
Lobe A	11.8	111	1.1	2.2	-	2	0	3	2	5	0
B	8.3	54	2.3	4.6		-	3	1	1	2	3
C	13.8	150	0.8	1.6			-	4	2	5	0
M	7.5	45	2.8	5.6				-	2	1	4
D	9.1	65	1.9	3.8					-	3	2
E	6.7	36	3.5	7.0						-	5
F	12.8	129	1.0	2.0							-
Cath. PE-90	1.27	1.25									

SUMMARY

This is an attempt to analyze the distribution of blood flow and ventilation to the different lobes of the dog's lung in the supine and erect position.

The first study consists of the simultaneous sampling of expired air from 2 or more lobes. From the gas analyses the exchange ratio, R, and the approximate $\dot{V}_A/\dot{Q}$ ratio of each lobe can be computed. The $\dot{V}_A/\dot{Q}$ ratio of the upper lobes is nearly always greater than that of the lower lobes in the supine as well as the erect position.

The second study is an attempt to estimate the relative ventilation of the lobes by counting the radioactivity of individual lobes after they had been exposed for 2 hours to an aerosol consisting of daughter products of radon gas deposited on dust

particles of approximately 0.1 micron size. These findings indicated that in the supine position less activity per unit lung is found in the lower lobes than in the upper lobe. In the erect position this situation is reversed.

On the assumption that the radioactive count is proportional to the ventilation one can substitute such ventilation figures into the $\dot{V}_A/\dot{Q}$ ratios determined in the first study and arrive at approximate values of the relative blood flow to each lobe. This analysis shows that the perfusion per unit lung is nearly the same for both lobes in the supine position. In the erect position the perfusion per unit lung of the lower lobe is greater than that for the upper lobe.

From these studies and bronchospirometry studies of man in the lateral decumbent position, it appears that gravity produces an uneven distribution of blood flow favoring the pendent portions of the lung. The relative ventilation in the lobes of the dog is also effected by posture and is markedly reduced in the upper lobes when tilted from the supine to the upright position.

REFERENCES

1. Fowler, W. S. Physiol. Rev. 32: 1, 1952.
2. Rahn, H. Amer. J. Physiol. 158: 21, 1949.
3. Stroud, R. C., K. R. Stetson and H. Rahn Proc. Soc. Exptl. Biol. Med. 81: 246, 1952.
4. Fowler, W. S. Federation Proc. 13: 47, 1954.
5. Shapiro, J. Univ. Rochester Atomic Energy Project Report, UR-298, 1954.
6. Cohn, S. H., R. K. Skow, and J. K. Gong A.M.A. Arch. Ind. Hyg. 7: 508, 1953.
7. Bale, W. F. and J. Shapiro (to be published).
8. Tobin, C. E. and M. O. Zariquieh Med. Radiogr. and Photogr. 26: 38, 1950.
9. Rahn, H. and B. B. Ross This Report.
10. Martin, C. J., F. Cline, Jr. and H. Marshall J. Clin. Invest. 32: 617, 1953.
11. Martin, C. J., H. Marshall and F. Cline, Jr. J. Appl. Physiol. 6: 209, 1953.
12. Rothstein, E., F. B. Landis and B. G. Navodick J. Thorac. Surg. 19: 821, 1950.
13. Inada, K., S. Kishimoto, A. Sato and T. Watanabe J. Thorac. Surg. 27: 173, 1954.
14. Dock, W. Arch. Int. Med. 94: 700, 1954.
15. Stockinger, H. E., L. T. Steadman, H. B. Wilson, G. E. Sylvester, S. Dziuba and C. W. La Belle A.M.A. Arch. Ind. Hyg. 4: 346, 1951.

Effects of Lung Inflation on the Pulmonary Circulation in Anesthetized Dogs.

By

H. BJURSTEDT and C. M. HESSER.

The question how the vascular resistance in the pulmonary circulation is altered during inflation and deflation of the lungs in normal respiration, as well as in abnormal or artificial situations, has for a long time been under discussion and is still a controversial point.

Pressure fluctuations in the pulmonary circuit may be accurately measured in different ways. However, many difficulties have arisen from attempts to interpret results based on recordings from the isolated lung, and by manometers balanced against a constant atmospheric pressure. HAMILTON, WOODBURY and VOGT (1939) have pointed out the advantages of measuring the pressures in the heart and pulmonary circuit relative to the intrathoracic pressure. Only by such measurements correct conclusions can be drawn as to the changes in the effective or "net" (distending) pressures within the heart and pulmonary vascular bed, when these organs are submitted to changing intrathoracic pressure.

It is now generally agreed that the effective pulmonary arterial pressure increases during inspiration. As to the cause of this increase, however, opinion is divided. According to one view it is caused by an increased output from the right heart being largely accommodated by a concomitant decrease in the pulmonary resistance. Another view is that increased pulmonary resistance is the causative factor (for a more comprehensive review see WIGGERS 1949). With OPDYKE and BRECHER (1950) it may be said

that no compromise is possible between such diametrically opposed opinions.

The present investigation, being a contribution to the current discussion, is partly based on measurements and recordings of effective pressures in the right auricle and pulmonary artery, during normal breathing and positive pressure inflation of the ungs in the anesthetized dog.

Methods.

Nine dogs weighing 15—28 kg were used, in moderately deep sodium pentobarbital anesthesia (Nembutal Abbott, initial dose 25 mg per kg intravenously).

A general scheme of the experimental arrangement is shown in Fig. 1. The systemic arterial pressure was recorded from the right femoral artery, and the peripheral venous pressure from a distal subcutaneous vein in the left hind leg. A glass or plastic T tube was inserted in the vein to allow a free blood flow. Right auricle and pulmonary arterial pressures were obtained by use of the catheterization technique. Curved-tip, terminal-opening cardiac catheters were introduced into the right femoral and external jugular vein respectively and put in position under fluoroscopic control. To prevent clotting heparin was given intravenously, and, in addition, the catheters were occasionally flushed with saline-heparin solution. The intrathoracic pressure was obtained from a small rubber balloon introduced into the pleural space after inter-costal incision on the left side of the chest. After expelling the air in the pleural cavity by application of positive pressure in the airways, the wound was sealed by inflating a rubber cuff around the tube leading from the balloon.

All pressures were recorded on photographic paper by means of optical rubber membrane manometers. In some cases they were read directly on water or mercury manometers.

The pressures in the right auricle and the pulmonary artery were usually measured or recorded as differential pressures ("net" or effective pressures), the reference level being the intrathoracic pressure. This was done by connecting the intrapleural balloon to the free end of the water manometers or to the air chamber of optical rubber membrane differential manometers. All connections between the vascular systems and the manometers were filled with saline-heparin solution. At the end of each experiment the membrane manometers were calibrated against mercury or water manometers. The horizontal plane through the right auricle was used as reference zero level for all vascular pressures.

In a preliminary series of experiments positive inflation of the lungs was accomplished by a demand regulator of the continuous pressure type. However, in order to obtain a more constant intrapulmonic pressure and a more rapid pressure build-up another method was also used. The animal was placed outside a pressure chamber and connected

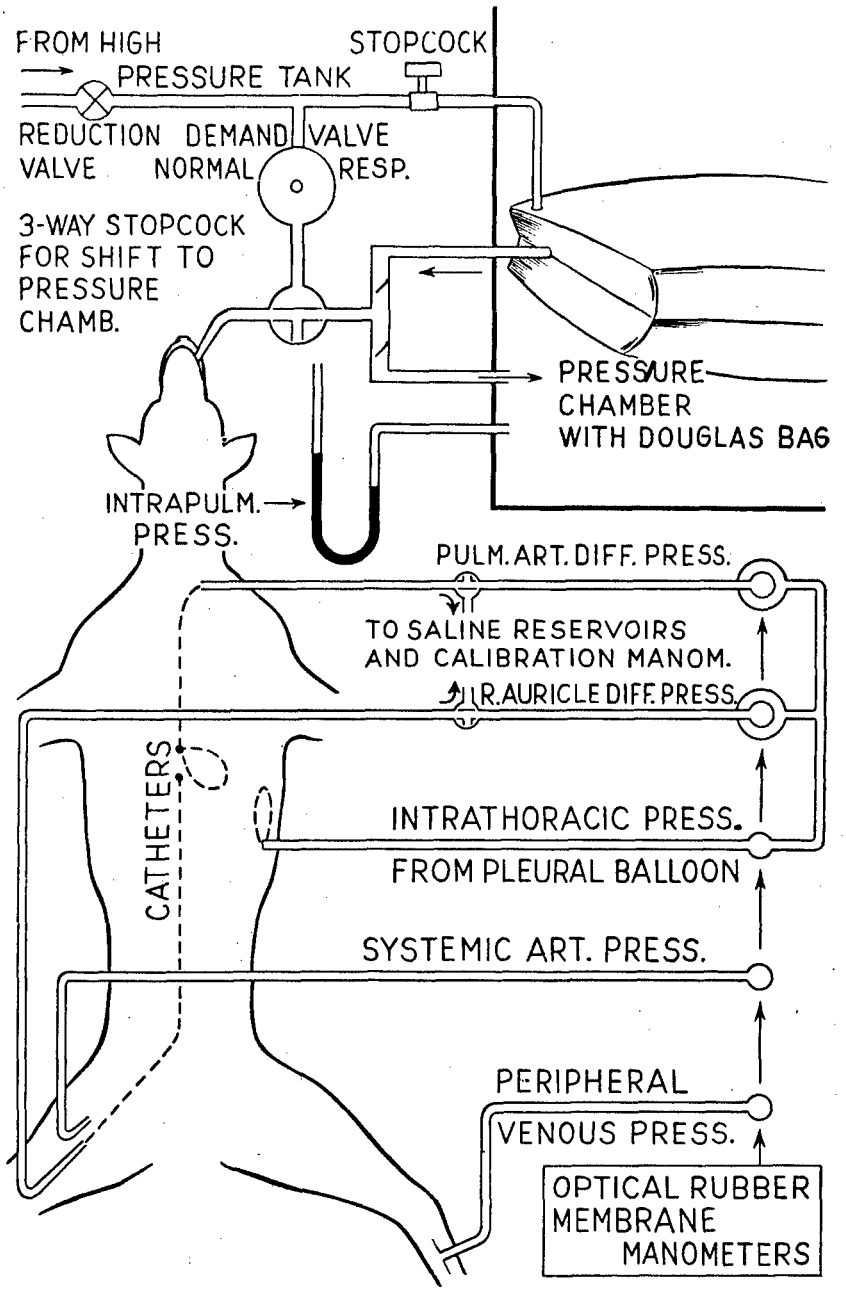


Fig. 1. Schematic representation of general experimental arrangement.

to the inside via an endotracheal tube and a Lovén respiratory valve. By means of a 3-way stop-cock the pressure in the air-ways could rapidly be changed to the pressure prevailing in the chamber. The latter pressure was pre-set as desired, and controlled by means of a water manometer.

In the experiments to be described in this paper, pure oxygen breathing was used throughout. When using the pressure chamber oxygen was supplied from a bag inside the chamber, connected to the inspiratory side of the Lovén valve. The bag was filled in advance with oxygen from a high pressure cylinder outside the chamber (Fig. 1). Under normal breathing oxygen was delivered from the cylinder by means of an ordinary demand regulator.

The applied pressure usually amounted to 15—30 mm Hg. The duration of the period of increased pressure was kept around one minute.

Results.

Effects of Elevated Air-Way Pressure on the Intrapleural Pressure and the "Transmural" Pressure in the Lungs.

When the lungs were inflated by positive pressure exceeding 10—15 mm Hg, a tendency for a long-lasting apnea to occur was invariably observed. The intrapleural pressure could therefore be measured during "steady state" at different intrapulmonic pressures. It was noted that, with increasing intrapulmonic pressures (up to 30 mm Hg), the intrapleural pressure showed an approximately linear increase. About 60 per cent of the applied pressure was passed on to the intrapleural space, the remaining part thus being absorbed in the elastic walls of the lungs.

Deepening of the anesthesia caused a tendency for the intrapleural pressure to decrease for a given intrapulmonic pressure. This is probably due to increased expansion of the lungs following diminished tone of the thoracic and abdominal muscles, leading to an increased absorption of the intrapulmonic pressure in the lung tissue.

During the periods of elevated, constant air-way pressure the intrapleural pressure usually showed a slow additional increase (cf. Fig. 2). The cause of the small gradual increase has not been investigated in particular. Evidence that a diminished lung volume plays a rôle may be found in the observation of BJURSTEDT (1953), that a slow contraction of the abdominal muscular wall occurs during the period of raised air-way pressure in anesthetized dogs, pushing the diaphragm in the cranial direction. Changes in the elastic properties of the lung, or alterations in the ac-

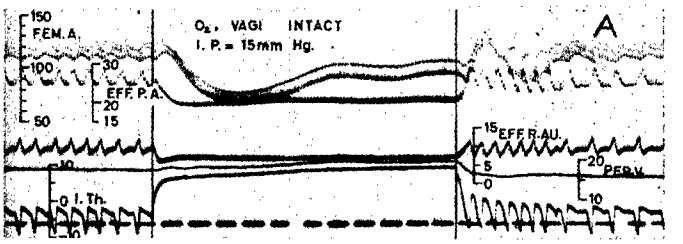


Fig. 2 A.

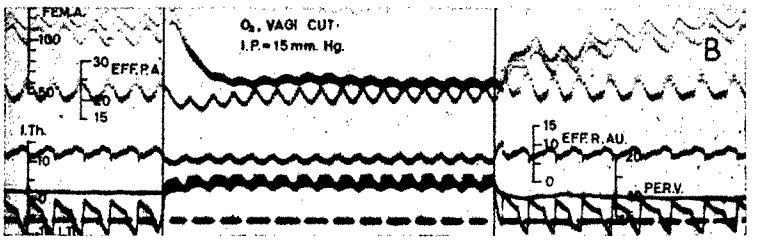


Fig. 2 B.

Fig. 2. Dog, Nembutal anesthesia. Effects of normal and increased intrapulmonic pressure on systemic arterial (fem.a.), effective pulmonary arterial (eff.p.a.), effective right auricular (eff.r.au.), peripheral venous (per.v.) and intrathoracic (i.th.) pressures. Oxygen breathing. The intrapulmonic pressure (i.p.) is elevated 15 mm Hg between vertical lines. All pressures in mm Hg. Time: 5 secs. between interruptions in base line.

A: Before vagotomy.
B: After vagotomy.

commodated volume of blood in the thoracic cavity, may, however, also have been a contributing factor.

The difference between the intrapulmonic and intrapleural pressures is in the following referred to as the "transmural" pressure in the lungs. This pressure is in the main determined by the elasticity of the lung tissue. Hence, the transmural pressure is a function of the volume of the lungs and not of the intrapulmonic or intrapleural pressures *per se* (see further Discussion).

Systemic and Effective Pulmonary Arterial Pressures.

In normal breathing the effective pulmonary arterial pressure showed an increase during inspiration and a decrease during expiration. The pressure variations were relatively large, amounting up to 20 per cent of the mean pulmonary arterial pressure (Fig. 2).

Rapid elevation of the intrapulmonic pressure was followed by a fall both in the systemic and the effective pulmonary arterial pressures. Certain striking details in the recordings were observed. Thus the pulmonary arterial pressure decreased almost immediately, whereas the fall in the systemic pressure appeared only after a delay of 2—3 seconds. Also on release of the air-way pressure, causing a sharp rise in both the systemic and pulmonary arterial pressures, a similar delay was observed in the response of the systemic pressure (Fig. 2).

It is generally agreed that the fall in the systemic arterial pressure is caused by a decrease in the venous return occurring as a result of peripheral venous pooling and a concomitant reduction of the effective blood volume available for the circulation.

During the period of raised air-way pressure a marked secondary recovery in the systemic pressure was always seen. This has been explained on the basis of a compensatory peripheral vasoconstriction. Evidence that a secondary increase in cardiac output contributes to the arterial pressure recovery in anesthetized dogs has been presented by BJURSTEDT (1953). In the present experiments such increase in cardiac output could often be clearly observed as a gradual increment in the pulse pressure. In contrast to the secondary recovery occurring in the systemic arterial pressure, little or no secondary increase could be observed in the effective pulmonary arterial pressure. The significance of this difference is discussed below.

Effective Right Auricular and Peripheral Venous Pressures.

In normal breathing the effective right auricular pressure increased during inspiration (Fig. 2). Conversely, on rapid inflation by application of positive intrapulmonic pressure an instantaneous decrease was regularly observed. Release of the pressure caused an instantaneous return of the auricular pressure towards normal.

The peripheral venous pressure showed only very slight fluctuations during normal breathing. On rapid elevation of the intrapulmonic pressure a slow increase could be observed, reaching its maximum after a varying period of time.

Effects of Vagotomy.

Bilateral vagotomy caused no significant changes in the response of the mean right auricular and pulmonary arterial pres-

sures, when the air-way pressure was elevated. Since no apnea occurred, respiratory fluctuations appeared in the records (Fig. 2 B). However, the secondary recovery of the systemic arterial pressure was impaired, which is in accordance with recent observations (BJURSTEDT 1953).

Discussion.

The results of the present experiments confirm the general conception that normal inspiration causes an increase in the filling pressure of the right heart, and is at variance with the opinion of DUOMARCO, ESTABLE, RIMINI, DE BONNEVAUX and GIAMBRUNO (1946) that inspiration has no effect in altering venous return or effective right auricular pressure.

The fact that the effective pulmonary arterial pressure showed an increase during normal inspiration is in accordance with the results of HAMILTON, WOODBURY and VOGT (1939). As to the cause of this effect an increased output from the right heart would seem near at hand. According to LAUSON, BLOOMFIELD and COURNAND (1946) an increase in the effective right auricular pressure causes an increase in the right ventricular stroke volume, demonstrating the validity of Starling's law of the heart in the case of the right ventricle. However, JOHNSON, HAMILTON, KATZ and WEINSTEIN (1937) have demonstrated that in anesthetized animals a two to three fold increase in the total blood flow can be accommodated with very small changes in pulmonary arterial pressure. Likewise EULER and LILJESTRAND (1946) reported that occlusion of the arteries to one lung in the anesthetized cat causes only a moderate rise in the pulmonary arterial pressure, amounting to approximately 20 per cent. The great distensibility of the pulmonary vascular bed was thus demonstrated. Furthermore EDWARDS (1951) showed that alterations in pulmonary arterial pressure and flow in the isolated lung lobe are accompanied by passive changes in pulmonary vascular resistance opposite in direction to that of the pressure changes.

It therefore seems unlikely that the relatively large pressure increase during inspiration (up to 20 per cent of the total mean pressure in the present experiments) can be fully explained by an increased blood flow. This is further borne out by the experiments, in which the air-way pressure was elevated. Little or no secondary increase in the pulmonary arterial pressure was observed, although a marked recovery was seen in the systemic

arterial pressure. Evidence has been presented that the recovery is accompanied by a secondary increase in the cardiac output (BJURSTEDT 1953). It may thus be inferred that the blood flow through the lungs increased without any significant rise in the pulmonary arterial pressure.

Considering the observations described above, it seems logical to assume that also during inspiration the pulmonary vascular bed is *passively* dilated by the increased pulmonary flow. We believe, however, that this passive dilatation is more or less counteracted by a concomitant increase in the "intramural pressure" of the lungs, *i. e.* the pressure within the lung tissue as referred to the pericardial pressure. With this definition the intramural pressure is always positive in the intact body and represents a fraction of the pressure acting on the exterior of the *intrapulmonic* vessels. The intramural pressure increases during inflation of the lungs, irrespective of whether the inflation is caused by inspiration ("negative" inflation) or by increased pressure in the air-ways ("positive" inflation). As the intramural pressure increases, it tends to diminish the caliber of the vessels and therefore appears in the hemodynamic picture as a contribution to peripheral resistance against outflow from the right heart. During inspiration the total resistance thus does not decrease as much as would otherwise be the case as a result of the increased right ventricular output. This reasoning seems to explain the substantial rise in the effective pulmonary arterial pressure.

Other hemodynamic events observed in the present investigation may also be accounted for by application of the theoretical considerations outlined above. Thus the delay in the systemic arterial pressure fall when the lungs were inflated by positive pressure may be explained as resulting from "squeezing" of blood from the pulmonary vascular bed due to increased intramural pressure. On release of the positive inflation the intramural pressure decreases, and the passive dilatation of the vascular bed following the increased flow from the right heart is thus facilitated by decreasing external pressure. The result will be an accommodation of blood in the lungs and a delay in the rise of the systemic arterial pressure as observed in the present experiments.

The decrease in the effective pulmonary arterial pressure during positive pressure inflation is caused by defective filling

of the right heart. Also in this case the resistance against outflow can be assumed to increase, but any effect thereof is masked by the decrease in right ventricular output.

For a given lung volume the average intramural pressure may roughly be estimated as amounting to half the transmural pressure, *i. e.* half of the intrapulmonic-intrapleural pressure difference. During positive inflation the transmural pressure increased by about 40 per cent of the intrapulmonic, and consequently the average intramural pressure increased by about 20 per cent.

It is of special interest to note that also in heart-lung preparations the intramural pressure is positive, when the lungs are inflated either by 1) positive pressure, or 2) negative external pressure and the heart is included in the negative pressure system. The only case in which the intramural pressure is negative is when only the lungs are exposed to negative external pressure. In the last-mentioned situation the intramural pressure tends to dilate the intrapulmonic vessels, thus decreasing the vascular resistance.

Summary.

1. The changes in the intrathoracic, the systemic arterial and the effective ("net") right auricular and pulmonary arterial pressures, occurring during oxygen breathing in normal respiration and during positive pressure inflation of the lungs in dogs under moderately deep sodium pentobarbital anesthesia, have been measured and simultaneously recorded.

2. The concept, that the net right auricular and pulmonary arterial pressures increase during normal inspiration but decrease during positive pressure inflation of the lungs, is confirmed.

3. To account for the hemodynamic reactions observed, some theoretical considerations are presented. It is postulated that in the intact body any kind of inflation of the lungs, whether voluntarily or artificially induced, causes an increase in the resistance to outflow from the right heart. This concept is based on the fact that the "intramural pressure" of the lungs, that is the pressure within the lung tissue as referred to the pericardial pressure, 1) is always positive, 2) increases with both positive and negative inflation of the lungs and 3) represents a fraction of the pressure acting on the exterior of the intrapulmonic vessels.

4. The average intramural pressure increased by about 20 per cent of the applied intrapulmonic pressure (up to 30 mm Hg), due to expansion of the lungs.

5. On the basis of the theoretical considerations it is believed that the increase in the effective pulmonary arterial pressure during normal inspiration is partly due to increased right ventricular output, and partly to increased intramural pressure opposing the tendency of the intrapulmonic vessels to dilate passively. On the other hand the decrease in pulmonary arterial pressure, following positive pressure inflation of the lungs, is primarily ascribed to defective filling of the right heart.

6. Sectioning of the vagi did not cause any significant effect on the pulmonary hemodynamics in normal breathing or during positive pressure inflation of the lungs.

References.

BJURSTEDT, H., Acta Physiol. Scand. 1953. *29*. 145.

DUOMARCO, J., J. J. ESTABLE, R. RIMINI, S. C. DE BONNEVAUX and C. E. GIAMBRUNO, Rev. Argent. Cardiol. 1946. *13*. 139.

EDWARDS, W. S., Amer. J. Physiol. 1951. *167*. 756.

EULER, U. S. v. and G. LILJESTRAND, Acta Physiol. Scand. 1946. *12*. 301.

HAMILTON, W. F., R. A. WOODBURY and E. VOGT, Amer. J. Physiol. 1939. *125*. 130.

JOHNSON, V., W. F. HAMILTON, L. N. KATZ and W. WEINSTEIN, Ibidem 1937. *120*. 624.

LAUSON, H. D., R. A. BLOOMFIELD and A. COURNAND, Amer. J. Med., 1946. *1*. 315.

OPDYKE, D. F. and G. A. BRECHER, Amer. J. Physiol. 1950. *160*. 556.

WIGGERS, C. J., Physiology in Health and Disease, 5th Edition, 1949. Lea & Febiger, Philadelphia.

Adaptation to High Altitude: Respiratory Response to CO_2 and O_2[1]

H. RAHN, R. C. STROUD, S. M. TENNEY AND J. C. MITHOEFER.[2]

THE AIM OF THIS STUDY is a further attempt to measure the response of the respiratory system in man after a 5–6 day residence at an altitude of 14,100 feet. In terms of alveolar or arterial gas tensions, residence at this altitude means an adjustment to a CO_2 level of approximately 28 mm Hg instead of 40, and an O_2 tension one half of the normal sea level value. With such an adaptation one may expect to find altered sensitivities as well as thresholds to such factors as CO_2, O_2 and H ions. These problems were explored *a*) by testing the ventilatory response to mixtures of CO_2 in oxygen, and *b*) by determination of alveolar gas concentrations at the breaking point of breath holding after breathing various O_2 concentrations higher than 21% in N_2. This last test was designed to detect changes in threshold and sensitivity toward O_2 with altitude acclimatization. These experiments were carried out in 4 male subjects during the summer of 1952 at the Inter-University High Altitude Laboratory situated on Mt. Evans, Colorado, at an altitude of 14,100 feet (4300 m) and a barometric pressure of 456 mm Hg.

The control tests were made in Rochester, New York, approximately 2 weeks before establishing residence at Mt. Evans. The expedition came directly from sea level to an altitude of 10,500 feet and stayed at this level for 2 days before going to the top. The altitude tests reported here were carried out 5–7 days after continued residence on Mt. Evans.

Respiratory Response to CO_2 in the Inspired Gas. The inspired gas mixtures used at the two altitudes are shown in table 1. The gas was inhaled from a Douglas bag and expired through a large capacity gas meter. The meter drum made an electrical contact for every 400 cc expired and these contacts were added on an impulse counter. A tambour arrangement activated by the mask pressure recorded in similar fashion the respiratory frequency on another counter. Each gas was breathed for 15 minutes with the exception of the 7.9% CO_2 mixture, which was breathed for 10 minutes. At the conclusion of each period an end-expiratory Haldene-Priestley alveolar gas sample was delivered and analyzed on the Scholander gas analyzer. The Rochester breathing tests were carried out twice, the altitude tests once on each person. The overall ventilation averages for the last 5 minutes on each gas mixture are given in table 1. It was assumed that the dead space remained constant (1) and the alveolar ventilation was computed by subtracting (150 cc × frequency)

[1] This study was supported in part by the Air Research and Development Command, Wright Field, a grant from the National Heart Institute of the National Institutes of Health and the American Heart Association.

[2] From the Mary Imogene Bassett Hospital, Cooperstown, N. Y.

from the total ventilation. The alveolar ventilation was then expressed as the alveolar ventilation ratio (VaR) with the normal alveolar ventilation at Rochester being equal to 1.00.

Breath-Holding Tests. These tests were simply a voluntary apnea until the maximal breath-holding time was reached. At this point the subject expired forcefully all of the remaining expiratory reserve volume through a 3-way stopcock into a large rubber tube and closed the cock for sampling of the alveolar air. A spirometer connected to the distal end of the tube recorded the total expired volume at the breaking point. Mithoefer (2) has recently shown that the absolute lung volume is an additional factor which determines the gas concentrations which can be tolerated at the breaking point. Consequently, the lung volume at the beginning of a breath-holding test was adjusted for each subject in such a way that approximately the same

TABLE 1. EFFECTS OF BREATHING CO_2 IN O_2 MIXTURES ON VENTILATION AT ROCHESTER, N. Y., AND AFTER 7 DAYS ON MT. EVANS. AVERAGES OF 4 SUBJECTS

	Inspired Gas Mixt. CO_2-O_2%	Inspired CO_2, mm Hg	Ventilation, l/min. (B.T.P.S.)	Frequency, per min.	Alveolar CO_2, mm Hg	Alveolar Vent. Ratio
Rochester, N. Y.	0. -100	0	8.0	12	40.1	1.00
P_B = 743	3.5- 96.5	24	13.8	13	42.2	1.88
	5.0- 95.0	34.8	20.4	14	45.2	2.91
Mt. Evans	0. -100	0	8.0	14	30.5	0.94
P_B = 456	5.2-94.8	24.2	19.7	16	34.4	2.75
	7.9-82.1	35.0	33.0	18	38.1	4.81

* For calculation of Alveolar Ventilation Ratio see text.

TABLE 2. ALVEOLAR CO_2 VALUES AFTER BREATHING O_2 AT REST AND AT THE BREAKING POINT

	Resting	Alveolar pCO_2 Breaking point	Δ	VaR at Breaking Point
Rochester, N. Y. 550 feet	39	63	24	10
Wyoming 9500 feet	32	50	18	9
Mt. Evans 14,100 feet	30	43	13	7

Overall averages of three expeditions, Wyoming 1946 (3), Mt. Evans 1949 (15), and Mt. Evans 1952. The VaR of breaking point is computed by Gray's equation using the slope constants derived in fig. 1.

lung volume existed at the breaking point, regardless of the time of apnea. Table 2 shows that the average lung volume at the breaking point ranged from .58 to 1.2 liters. Various O_2-N_2 mixtures were breathed from a demand regulator for 5 minutes before the breath-holding test started. The breath-holding times and the alveolar concentrations at the breaking point are given in table 2.

RESULTS AND DISCUSSION

CO_2 Breathing Tests. All tests were carried out with CO_2 mixture in oxygen in order to eliminate O_2 as a separate factor. The average response of the four subjects is given in table 1 and the calculated alveolar ventilation ratio, VaR, is plotted against the alveolar pCO_2 in figure 1. It can be seen that the Mt. Evans slope is steeper than the one obtained near sea level.

In addition, the average ventilatory response curve for three subjects after adaptation to 9,500 feet (B = 537 mm Hg) has been added. These were obtained from a previous expedition to Wyoming (3). In these older experiments, 4.5 and 7.0% CO_2 in air was breathed and the alveolar pO_2 was 83 and 91 mm, respectively. If one assumes that these oxygen tensions exerted little effect per se upon the ventilation response (4, 5) then we can make these conditions comparable to the experimental conditions on Mt. Evans, where CO_2 in oxygen was the breathing mixture. Figure 1 shows that the Wyoming response curve fell intermediate between the other two.

If one now takes the data obtained at the three altitudes and assumes a linear relationship between VaR and pCO_2, one finds that they fit very well Gray's (4, 5) general alveolar ventilation equation where $VaR = K \times pCO_2 - 15$. K represents the slope of the lines in figure 1 or the ventilatory response for a given CO_2 increment. The slope constants, K, are .40, .485 and .521, respectively, for 550, 9,500 and 14,100 feet altitude.

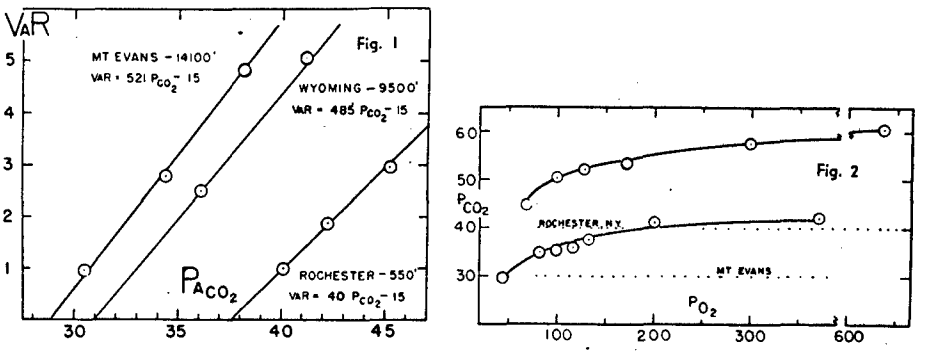


FIG. 1. Changes in alveolar ventilation ratio, *VaR*, breathing oxygen and CO_2 in oxygen mixtures at Rochester, N. Y., and after 5–6 days' residence on Mt. Evans, plotted against alveolar pCO_2. For data on the 9500-foot altitude, see text. Constants for Gray's equation have been determined for each of the three altitudes and are represented by the lines.

FIG. 2. Alveolar pCO_2 and O_2 at the breath holding breaking point after breathing various O_2-N_2 mixtures at Rochester, N. Y., and after 5–6 days' residence on Mt. Evans. *Broken horizontal lines* indicate the general resting alveolar CO_2 level at the beginning of each particular breath holding test at these two localities.

If we accept this relationship where the intercept of -15 remains constant it is simple to predict the change in sensitivity at any altitude. Since the resting alveolar pCO_2 and the relative ventilation ratios after adaptation to altitudes up to 24,000 feet are fairly well established—for a compilation see (3)—one can simply substitute these values into Gray's equation and solve for K when the intercept is kept constant. Thus, at 20,000 feet where the alveolar pCO_2 is 20 and resting alveolar ventilation ratio is 2.0, $K = (2 + 15)/20$, or .85. At this altitude one would expect, therefore, little more than twice the ventilation response for the same increment in alveolar CO_2.

Furthermore, it is of interest that at any altitude the increased ventilatory response is so nearly balanced by the expected decrease in plasma $BHCO_3$ that one can say that for a given change in VaR at any altitude the change in pH will be the same. On the other hand, with continued residence beyond the period experienced by our party the gradual increase in hemoglobin will increase the overall buffering capacity of the blood to CO_2 (6). It is in this return of the buffering capacity that we

might find a clue to the recent observation of Chiodi (7) that with increased residence at 14,700 feet (4515 m) beyond a week, the newly acquired sensitivity to CO_2 decreases and after several months or years returns to sea level values (8).

The first demonstration of these sensitivity changes with altitude adaptation was provided by Nielsen (9) who studied the CO_2 response in two subjects who lived for 7 days in a low pressure chamber at an equivalent altitude between 12,500 feet and 14,500 feet. The sensitivity changes which he observed were, however, very much greater than those described by us. More recently Nielsen and Smith (10) have provided a detailed discussion of the possible mechanisms by which these changes may be accomplished, and have furthermore provided evidence that the sensitivity of the respiratory system to CO_2 is likewise increased upon acute exposure to low oxygen tensions. On the other hand, Brown *et al.* (11) have shown that a greater respiratory response to CO_2 can also be obtained when the alveolar CO_2 is lowered by passive

TABLE 3. ALVEOLAR O_2 AND CO_2 TENSION AFTER MAXIMUM BREATH HOLDING FOLLOWING 5 MIN. OF BREATHING VARIOUS O_2 IN N_2 MIXTURES AT ROCHESTER, N. Y., AND AFTER 5 DAYS ON MT. EVANS. AVERAGE OF 4 SUBJECTS

	Breathing Mixture O_2% in N_2	Lung Vol-l at Breaking Point	Breath Holding Time, sec.	Alveolar Gas at Breaking Point pCO_2	Alveolar Gas at Breaking Point pO_2
Rochester, N. Y.	20.9			40.1*	96.7*
P_B = 745	20.9	.58	34	44.8	68.5
	31.1	.86	69	50.5	101.3
	35.1	.92	70	52.2	128
	46.7	.79	92	53.4	173
	66.8	.80	130	57.6	299
	100.0	.67	157	60.5	637†
Mt. Evans	20.9			27.8*	44.6*
P_B = 456	20.9	.86	14	29.7	44.8
	39.1	1.21	22	35.2	82.6
	44.2	1.04	30	35.5	100.6
	49.0	1.12	37	35.9	116.6
	57.1	1.11	53	37.7	132.3
	100.0	.83	89	41.8	371†

* Normal, resting alveolar air samples. † Obtained by difference.

ventilation for 24 hours in a respirator and where the alveolar oxygen remains effectively unaltered.

Breath-Holding Tests. The breath-holding test can be treated in a similar fashion. The breaking point must be ventilation urge equivalent to a finite VaR. According to the CO_2 breathing response curves in figure 1, a given breaking point, VaR, will be reached sooner and with a smaller change in alveolar pCO_2 after adaptation to altitude. This is indeed the case, and absolute differences in these values are averaged for three expeditions in table 2. However, the reductions in pCO_2 observed are actually greater than those theoretically necessary for the maintenance of a VaR of 10. This suggests that the actual VaR of the breaking point is gradually reduced after adaptation to altitude (see table 2).

O_2 Sensitivity and Threshold. An oxygen threshold of ventilation may be defined as that value beyond which an increase in arterial or alveolar pO_2 causes no change in ventilation. For the resting ventilation in man acclimatized at sea level this value lies at an alveolar pO_2 of approximately 60 mm Hg (3). However, when a

breaking point curve for various inspired O_2 mixtures is plotted out on the O_2/CO_2 diagram, it appears now that this curve does not flatten out at 100 mm pO_2 at all, as had formerly been indicated (12), but slowly rises without ever reaching a plateau (figure 2). This suggests that under the stress of acute respiratory acidosis the O_2 threshold (where the breath-holding breaking point becomes entirely dependent upon the CO_2 pressure) is displaced considerably above 100 mm Hg. A similar shift is suggested during moderate exercise, where the same work performance yields increasingly higher alveolar CO_2 and inversely smaller ventilations when 15, 21 and 100% O_2 are inspired (13). At rest these three gases have very slight effects, if any, upon the ventilation. With the adjustment at altitude from a normal alveolar pO_2 of 97 to 45, the breaking point curve again indicates a shape similar to that obtained at sea level. A finite plateau is not demonstrated, and one may conclude that the oxygen threshold (as thus defined), if any, for the state of maximal breath-holding effort is not altered with acclimatization. Furthermore, the ratio of ΔpCO_2 at Rochester/ΔpCO_2 at Mt. Evans is constant for any given pO_2 value between the range of 80–370 mm in figure 2. (ΔpCO_2 is the vertical distance between resting CO_2, the dotted line, and the breaking point line.) Thus one may conclude that with acclimatization there has been no demonstrable change in sensitivity to pO_2. However, this does not preclude changes in sensitivity to O_2 at very low concentrations indicated by the studies of Luft (14).

Summary

After a residence of 5–6 days on Mt. Evans, Colorado, at an altitude of 14,100 feet, CO_2 breathing and breath-holding tests with oxygen were compared with those obtained 2 weeks previously at Rochester, New York (altitude 550 feet). All the subjects demonstrated an increased sensitivity to CO_2 after adaptation to altitude. Breath-holding studies were also carried out after breathing various O_2-N_2 gas mixtures. Under these conditions of acute respiratory acidosis a definite oxygen threshold cannot be established. With adaptation to altitude this lack of a definite threshold persists. The analysis of these breath-holding tests, furthermore, suggests that no change in sensitivity of the respiratory system to O_2 has taken place.

REFERENCES

1. Pappenheimer, J. R., A. P. Fishman and L. M. Borrero. *J. Appl. Physiol.* 4: 855, 1952.
2. Mithoefer, J. C. Personal communication.
3. Rahn, H. and A. B. Otis. *Am. J. Physiol.* 157: 445, 1949.
4. Gray, J. S. *Science* 103: 739, 1946.
5. Gray, J. S. *Pulmonary Ventilation and its Physiological Regulation.* Springfield, Ill: Thomas, 1950.
6. Dill, D. B., J. H. Talbott and W. V. Consolazio. *J. Biol. Chem.* 118: 649, 1937.
7. Chiodi, H. Personal communication.
8. Chiodi, H., L. O. Calderon and J. R. Suárez: *Ciencia e invest.* (*Buenos Aires*) 8: 465, 1952.
9. Nielsen, M. *Skandinav. Arch. f. Physiol.* 74: Suppl. 10, 83, 1936.
10. Nielsen, M. and H. Smith. *Acta. physiol. scandinav.* 24: 293, 1951.
11. Brown, E. B., Jr., G. S. Campbell, M. N. Johnson, A. Hemingway and M. B. Visscher. *J. Appl. Physiol.* 1: 333, 1948.
12. Otis, A. B., H. Rahn and W. O. Fenn. *Am. J. Physiol.* 152: 674, 1948.
13. Rahn, H. and A. B. Otis. *J. Appl. Physiol.* 1: 717, 1949.
14. Luft, U. C. *Ergebn. d. Physiol.* 44: 256, 1941.
15. Rahn, H., H. T. Bahnson, J. F. Muxworthy, Jr. and J. M. Hagen. *J. Appl. Physiol.* 6: 154, 1953.

Adaption to High Altitude: Changes in Lung Volumes During the First Seven Days at Mt. Evans, Colorado[1]

S. M. TENNEY, H. RAHN, R. C. STROUD AND J. C. MITHOEFER.[2]

IT HAS BEEN WELL KNOWN for many years that part of the process of accommodation to high altitude involves changes in the various volumes of the lung. Most extensively recorded have been the changes in vital capacity which have uniformly shown a decrease; however, the order of magnitude of this reduction appears extremely variable ranging from 0 to 14 per cent for acute exposure and from 2 to 50 per cent with prolonged exposure to high altitude. These data have been summarized by Rahn and Hammond (1) who point out that lack of correction for temperature and tension of water vapor accounts in large part for the excessive reductions recorded. Their study of vital capacity during a 7-day sojourn to 14,250 feet would indicate that, with the proper corrections, the vital capacity diminishes about 4 per cent on the 3rd day and then promptly recovers, even to exceed sea level values by the end of 7 days.

Changes in the residual air have been less frequently noted. An acute exposure in a low pressure chamber to a simulated altitude of 16,400 feet was made by Hurtado, Kaltreider and McCann (2). These authors demonstrated an increase in the residual air concomitant with the fall in vital capacity, but do not state whether the volumes were corrected to any particular conditions for control with sea level values. Barcroft (3), in the Cerro de Pasco expedition of 1923, measured the residual air of his colleagues after some 2 weeks at altitude and showed no significant change over control values at sea level. He states that proper corrections were made, but again we do not know for what particular conditions.

Observations on the lung volumes of native residents at high altitude reveal what Hurtado has called a 'physiological emphysema.' In general, this altitude-acclimatized population has larger total lung volumes than sea level residents of similar stature. Both the vital capacity and residual air tend to be excessive by sea level standards (4).

Because the literature appears to contain few data on the changes of the various compartments of the lung volume, other than vital capacity, after ascent to high altitude, and the results that have been recorded are at variance for acute (2), subacute (3) and chronic (4) exposure, it has seemed worth while to investigate this problem during the early period of altitude adaptation. Estimates of the functional

Received for publication November 10, 1952.

[1] This study was carried out at the InterUniversity High Altitude Laboratory, Mt. Evans, Col., and was supported in part by a research grant of the National Heart Institute of the National Institutes of Health, the Air Research and Development Command, Wright Field and the American Heart Association.

[2] From the Mary Imogene Bassett Hospital, Cooperstown, N. Y.

residual capacity would allow evaluation of the 'third form of respiratory regulation to high altitude' emphasized by Verzar (5), i.e. increase in lung surface area. Measurements of the expiratory reserve were also made in order to further evaluate the apparent increase in inspiratory muscle tonus which has been reported to occur (6).

METHODS

Control values for the four subjects were made daily for 5 days at Rochester, New York, elevation 600 feet, during the last week in June. The evening of July 9 the party reached an altitude of 10,500 feet. The day and night of July 10 were spent at this altitude, and on July 11 party reached the summit of Mt. Evans, Colorado, at 14,250 feet. On this and each of the following 6 days lung volume measurements were recorded in the same manner as during the control period. Vital capacity measurements only were made on the 8th day. Vital capacities were blown from the sitting position into a standard 6-liter spirometer. The largest of three values was chosen as the vital capacity for a given subject on that day. The residual air was measured from the same sitting position using the modification of the method of Lundsgaard and Van Slyke (7) as described by Rahn, Fenn and Otis (8). The N_2 in the gas samples was determined by the Scholander method (9). The expiratory reserve volume was recorded from the supine position in order to minimize day to day posture effects. A minimum of 5 and occasionally as many as 10 values were recorded for each subject daily, and the mean was taken as that day's expiratory reserve volume.

All volumes recorded were corrected to the volume they would occupy at body temperature, ambient barometric pressure and fully saturated with water vapor, BTPS. Thus, $V_{BTPS} = V_{Obs} \cdot [(273 + 37)/(273 + t)] \cdot [(B - pH_2O)/(B - 47)]$, where t is the temperature of the spirometer, B is the prevailing atmospheric pressure, pH_2O is the tension of aqueous vapor at temperature t, and 47 is the tension of aqueous vapor at body temperature, 37°C.

RESULTS AND DISCUSSION

The control values for the group at Rochester are shown in the first column of table 1. All are within the normal range for each subject and show a rather small daily variation. The temperatures during this period ranged from 24 to 28.5°C. and the barometric pressure between 739 and 748 mm. Hg. The values obtained at altitude are summarized in table 1. The temperature in the laboratory at the top of Mt. Evans ranged from 15° to 22°C., and the barometric pressure was 457 mm. Hg with a variation of less than 1 mm. Hg during the stay. Though the individual response tended to be variable, certain trends are indicated.

Vital Capacity. The vital capacity in all subjects showed a pronounced fall on the 1st day. This trend continued in the downward direction and reached its lowest value on the 3rd day for all but one subject, *M. T.*, whose vital capacity began to increase after the 1st day and from the 3rd day on remained at a value higher than at sea level. The other three subjects, after reaching the slump on the 3rd day, all began progressively to increase the vital capacity. By the 7th day, *J. M.* had reached sea level value and on the 8th day exceeded it. The other two subjects had still not reached the control values though a continued but slow increase is noted. These changes are summarized graphically in figure *1a*.

Breathing 100 per cent oxygen for 3 minutes was tried in all subjects for the first 4 days and caused no increase in the vital capacity. Two subjects, *H. R.* and

M. T., tested short trials of continuous positive pulmonary pressure breathing but were unable to effect a significant change in the vital capacity.

The greatest changes in vital capacity occurred on the 3rd day of exposure, a finding in agreement with the data of others (1, 10). However, the magnitude of change is considerably greater, even twice as great, for *subject H. R.* who was also a subject in the earlier experiments (1).

The fact that 3 minutes of breathing 100 per cent oxygen failed to raise significantly the vital capacity of any subject suggests that hypoxia alone is unlikely as the final mechanism causing the decrease, though it may well act as the stimulus to secondary changes which cannot be reversed in 3 minutes. Continuous positive pres-

TABLE 1. LUNG VOLUME MEASUREMENTS AT ROCHESTER, N. Y. AND ON MT. EVANS

	ROCHESTER, N. Y.		DAYS ON MT. EVANS							
	Mean ± S.D.	*n*	1	2	3	4	5	6	7	8
Vital capacity										
MT	4808 ± 76	5	4730	4760	4900	4870	4850	4800	4850	4840
HR	6161 ± 43	5	5950	5650	5540	5800	5900	5820	5850	5960
RS	5328 ± 77	5	5000	5050	5000	5200	5100	5200	5140	5160
JM	5210 ± 49	5	4950	5050	4680	5050	5020	5160	5220	5260
Group mean	5376		5157	5127	5030	5230	5217	5245	5265	5305
Residual volume										
MT	1205 ± 74	7	1315	1220	1210	1420	1360	1310	1355	
HR	1996 ± 65	5	2540	2080	2170	1960	1900	2080	2010	
RS	1508 ± 99	6	1690	1590	1775	1510	1410	1540	1485	
JM	1377 ±104	6	1890	1710	1700	1560	1680	1750	1635	
Group mean	1522		1859	1650	1714	1613	1588	1670	1621	
Expiratory reserve										
MT	687 ± 43	16	740	700	790	865	870	905	878	
HR	923 ± 45	24	1020	900	980	1020	965	1015	880	
RS	684 ±110	25	596	648	724	765	730	800	610	
JM	484 ± 26	21	508	570	650		600	575	600	
Group mean	695		716	705	786	883	791	824	742	

S.D. = standard deviation, *n* = no. of observations.

sure breathing was attempted in order to 'squeeze out' any excess blood that might be engorging the pulmonary vessels and thus encroach upon respiratory air space (11). Again no significant change was noted, and if such a procedure constitutes a valid test (12), then engorgement of the lung vessels with blood is not a major cause for the reduction in vital capacity. Fatigue, diminished muscular efficiency, or perhaps unwillingness to blow a maximal sample due to general malaise are all factors difficult to evaluate but believed not to be significant. The increased inspiratory muscle tonus which is believed to play a part in accommodation (6, 13) might interfere with complete emptying and thus lower the vital capacity.

Residual Air. The residual air changes are summarized in figure 1*d* and again show a definite trend. All subjects were well above sea level values on the 1st day at high altitude, in good agreement with the acute experiments of Hurtado *et al.* (2). The values decreased progressively, more rapidly in some than others. *Subjects J. M.* and *M. T.* began to level off at about the 5th day at values considerably in

excess of their sea level values. *Subjects R. S.* and *H. R.* had residual air volumes on the 5th day less than at sea level, but they promptly recovered, and by the 7th day were at and above sea level values, respectively. This general trend towards normal or even supranormal values within a week's time indicates that the change with acute exposure (2) is only transitory. It will be recalled that in Barcroft's

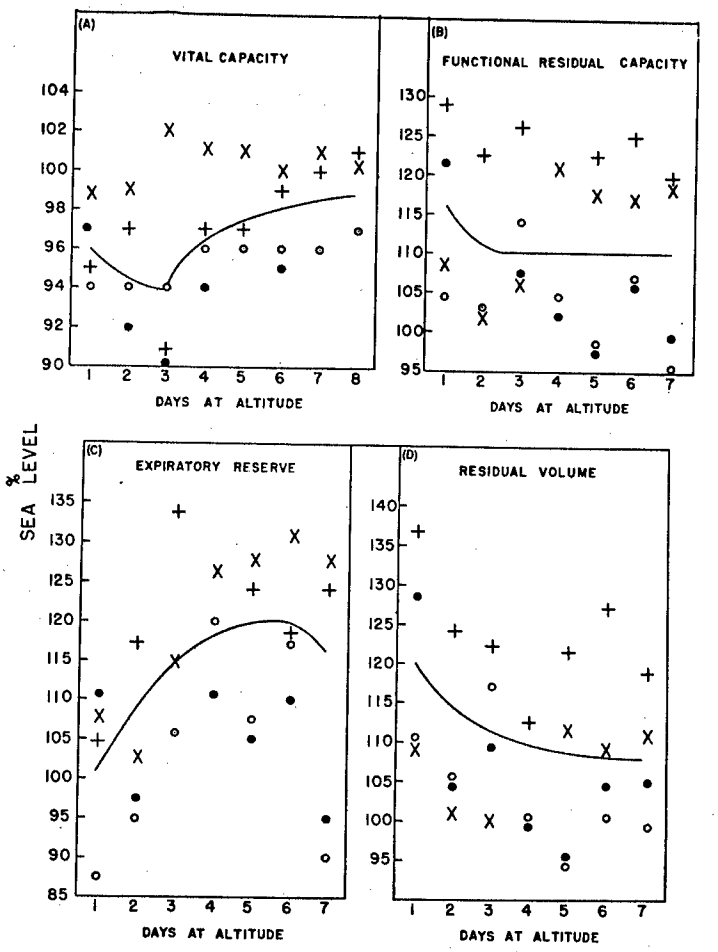


Fig. 1. LUNG VOLUMES as percentage of sea level value. The best mean value line is indicated on each. *Subject M.T.* = ×, *H.R.* = ●, *R.S.* = ○ and *J.M.* = +.

group (3) all the residual air volumes at the end of 2 weeks differed insignificantly from control. If acclimatization proceeds to the point occupied by the Peruvian Indians (4), then the lung volume response must be a diphasic one, initial increase, fall within 1 to 2 weeks to near normal or below and then a rise to a high value after perhaps months' or even years' residence at high altitude.

Total Lung Volumes. All subjects but *R. S.* had a larger total lung volume than normal on the 1st day, this being due to a residual air value which increased proportionally more than the vital capacity fell. On the 3rd day the total lung volumes of

all subjects, except *M. T.*, were below normal because the vital capacity had fallen to an exceedingly low value and could not be matched by the residual air. From the 3rd day on, *J. M.* and *M. T.* had total lung volumes greater than normal due both to a large residual air volume, and also because the vital capacity was increasing. *Subjects R. S.* and *H. R.* from the 3rd day on, to the contrary, maintained total lung volumes below normal in spite of near normal residual air volumes, because their vital capacities remained low. The mean values for the total lung volume for the group show slight change since half increased about as much as the other half decreased.

That the total lung volume increases in size initially is in good agreement again with the acute experiments of Hurtado *et al.* (2). However, during the 2nd and 3rd day the vital capacity and residual air both fell; hence the acute increase (2) in total lung volume is also a transient phenomenon which may return again late in the process of acclimatization. At the end of the week two subjects, *M. T.* and *J. M.*, showed enlarged vital capacities, residual air and total volumes, while the other two showed the same trend upward, but more slowly, and still had subnormal total lung volumes by the end of 1 week. It is interesting that the two subjects who showed the more prompt approach to what may be considered acclimatized lung volumes were the younger of the four subjects, though it would be hazardous to assume that age factors alone may have been operative.

Expiratory Reserve. The expiratory reserve volume showed a surprisingly consistent trend for the whole group. Whereas the other changes noted have been most marked on the 1st day on the mountain top and gradually returned to control values, the expiratory reserve appears progressively to increase up to the 6th day. This is shown in figure 1*c*. Breathing 100 per cent oxygen caused no change in expiratory reserve. The cause for this increase in expiratory reserve volume may be an increase in the inspiratory tonus of the voluntary muscles of respiration (13), though it is odd that other skeletal muscles show a decrease in tonus after initial increase for the first 2 days (14).

Functional Residual Capacity. An estimate of the functional residual capacity can be made by taking the sum of the residual volume and expiratory reserve. In this situation all such estimates will represent minimal values because the expiratory reserve, which was expelled in the supine posture, is less than when made sitting upright, as were all the other volumes. Figure 1*b* illustrates the trend in this minimal mid-capacity estimate. It is marked again as an initial high on the 1st day paralleling the increase in size of the thorax as a whole when animal or man is subjected to an hypoxic stimulus (15, 16). Immediately thereafter it falls but remains above the control values. It seems unlikely that such an increase in functional residual air could be of much benefit to the organism (5) in spite of an increase in effective surface area across which gas transfer may occur. Indeed, one may calculate the change of the internal surface area of the lung (17) for a mean increase in chest circumference of 22 mm. (5). At best this would be about plus 3 per cent.

Relationship of Air Volume to Pulmonary Blood Volume. If one could assume that the maximal volume of the thorax were constant, then the sum of lung air volume and lung blood volume must be constant, and these two volumes would bear inverse relations to one another. Some useful information concerning the important and controversial question as to whether hypoxia changes the pulmonary blood volume might thus be obtained. As already noted, the results on total air volume are not consistent for the group and show on the 4th day the extremes of a gain of 5

per cent for one individual and a loss of 5 per cent for another. If the thorax volume were constant, this might mean as much as an excess of 350 cc. pulmonary blood volume for one individual and a diminution of 350 cc. for another in the two extremes. However, there may be a change in the total volume of the thorax, thus changing the assumed constant which would compensate for these differences, e.g. by changing the position of the diaphragm or costal muscles.

The inverse relationship between pulmonary blood and air volumes which was suggested for the position of maximal inspiration should hold for any thorax position as long as it could be reproduced. Verzar, first using the whole body plethysmograph and later the 'thorakometer' (18), has been able to record the volume changes in the thorax following acute exposure to hypoxic air mixtures. This 'thorax volume' change, which is recorded externally, uses as its base line the position at end expiration; therefore, changes in functional residual capacity may be compared in the same manner as was total lung volume in order to estimate lung blood volume changes, but now the change in size of the thorax at this new position may be estimated from Verzar's data. Schweizer (16) in Verzar's laboratory, gives the mean increase in thorax volume with acute exposure to low oxygen tension as 300 cc. With this information one knows that, for the mean, the new value for the constant sum, c, which was measured under control conditions, is $c + 300$ under the stress of hypoxia. There is considerable individual variation in this response, and the variable response in lung volume for the present group is striking. If we assume that the changes in thorax volume observed acutely by Schweizer are those operating at the time our lung volume measurements were made the 1st day on the peak of Mt. Evans, the mean increase in external thorax volume almost matches the mean increase in air volume. Our mean increase in functional residual capacity was 358 cc., an insignificant difference from the 300 cc. increase in thorax volume. Further, following a drop after the 1st day (fig. 1*b*), the functional residual capacity remains fairly constant throughout the week and suggests that the acute change in thorax volume measured by Verzar also persists. If such assumptions are justified, there appears to be no significant change in the pulmonary blood volume under the conditions of hypoxia studied.

The earlier animal experiments which demonstrated pulmonary edema (19) and vascular engorgement (2) with hypoxia have recently been ascribed to the added result of heart failure superimposed on the hypoxic stress (20). In instances where the 'pulmonary blood volume' has been measured in man during a short time exposure to hypoxia no change has been recorded (21), but in the experimental animal pulmonary hypertension with anoxia has been interpreted on the basis of excessive pulmonary blood volume (22).

SUMMARY

The lung volumes of four subjects during a 7-day stay at 14,250 feet have been studied, and the following trends observed. The vital capacity decreased during the first 3 days, then progressively increased in all subjects and exceeded sea level values in two subjects. The residual volume increased the 1st day, then fell during the next 4 days and had leveled off by the end of the week so that three subjects were above control values, and one subject was just at sea level value. The total capacities were high initially, but by the end of the week two subjects had total volumes above those at sea level and two below. The expiratory reserve volume increased progressively in all subjects over the first 6 days. Breathing oxygen in all four subjects and con-

tinuous positive pressure breathing in two subjects failed to increase the vital capacity. Certain implications of the lung volume changes, particularly as concerns pulmonary blood volume changes, are discussed.

REFERENCES

1. RAHN, H. AND D. HAMMOND. *J. Applied Physiol.* 4: 715, 1952.
2. HURTADO, A., N. L. KALTREIDER AND W. S. MCCANN. *Am. J. Physiol.* 109: 626, 1934.
3. BARCROFT, J., C. A. BINGER, A. V. BOCK, J. H. DOGGART, H. S. FORBES, G. A. HARROP, J. C. MEAKINS AND A. C. REDFIELD. *Phil. Tr.* Roy. Soc. s. B. 211: 351, 1923.
4. HURTADO, A. *Am. J. Phys. Anthropol.* 17: 137, 1932.
5. VERZAR, F. *Bull. schweiz. Akad. med. Wissensch.* 7: 201, 1951.
6. VISCHER, A. *Pflüger's Arch. ges. Physiol.* 234: 394, 1934.
7. LUNDSGAARD, C. AND D. D. VAN SLYKE. *J. Exper. Med.* 27: 65, 1918.
8. RAHN, H., W. O. FENN AND A. B. OTIS. *J. Applied Physiol.* 1: 725, 1949.
9. SCHOLANDER, P. F. AND F. J. W. ROUGHTON. *J. Biol. Chem.* 167: 235, 1947.
10. VERZAR, F. *Höhenklima Forsch. d. Basler Physiol. Inst.* Basel, Switzerland: Schwabe, p. 93, 1945.
11. FENN, W. O., A. B. OTIS, H. RAHN AND L. E. CHADWICK. *Am. J. Physiol.* 151: 258, 1947.
12. BAHNSON, H. T. *J. Applied Physiol.* In Press.
13. HARRIS, A. S. *Am. J. Physiol.* 143: 140, 1945.
14. FLEISCH, A. AND E. GRANDJEAN. *Klimaphysiol. Untersuch. in der Schweiz.* 2: 474, 1948.
15. PEYSER, E., A. SASS-KORTSAK AND F. VERZAR. *Am. J. Physiol.* 163: 111, 1950.
16. SCHWEIZER, W. Inaug. Dissert. Physiol. Inst. Univ. Basel, Basel, Switzerland, 1944.
17. TOMKIEFF, S. I. *Nature* 170: 117, 1952.
18. VERZAR, F. *Höhenklima Forsch. d. Basler Physiol. Inst.* Basel, Switzerland: Schwabe, 1945, p. 77.
19. WARREN, M. F. AND C. K. DRINKER. *Am. J. Physiol.* 136: 207, 1942.
20. HEMINGWAY, A. *J. Applied Physiol.* 4: 868, 1952.
21. DOYLE, J. T., J. S. WILSON AND J. V. WARREN. *Circulation* 5: 263, 1952.
22. AVIADO, D., D. M. AVIADO, JR., A. CERLETTI, J. ALANIS, P. H. BULLE AND C. F. SCHMIDT. *Am. J. Physiol.* 169: 460, 1952.

PERMANENT RESIDENTS AT ALTITUDE WITHIN THE UNITED STATES

by

H. Rahn

Little systematic effort has been directed toward measuring the effects of reduced barometric pressures upon the physiological response of the population contained within the United States of America. Miss Fitzgerald from England was possibly the first to make a systematic effort toward recording the alveolar CO_2 and hemoglobin of native residents of the Colorado Mountains (1). While she wandered from one lonely mining camp to another collecting and analyzing, Haldane and his group carried out their famed experiments on Pike's Peak. Much of the research on permanent residents since that time has come from other countries, particularly the Andes where an estimated 10 million people live above 7000 feet.

It is of interest here to point out that much information can still be gathered within our own country since the altitude effect actually starts as soon as one leaves sea level. The estimated population residing at various levels is really quite large and many of our Universities are located at considerable altitude. The University of Wyoming is probably the highest at an elevation of over 7000 feet.

Figure 1 indicates very roughly the main altitude levels within the U.S., while Table 1 tabulates very approximately the number of residents within each area. Table 2 attempts to predict various physiological constants which one would expect at such altitudes. These were obtained by interpolation between sea level and altitudes for which published data are available. Some of it may have to be revised eventually but, nevertheless, it serves to indicate what one may expect and may serve to stimulate further work of altitude acclimatization within the United States.

The blood gas values have been adapted from the recent investigations of Hurtado and Aste-Salazar (2) who made their determination in the Peruvian Andes. The other values are based upon our own experiments and those recorded in the literature (3,4).

For example, according to Table 2 the population of Colorado Springs, Colorado which lies close to 6000 feet, have a 12% greater alveolar ventilation than people at sea level. Their alveolar CO_2 is 34 mm and their blood O_2 saturation 93%. The alkali reserve is 7% lower and they are able to hold their breath in air only 60% as long as they could at sea level. One would not predict that they would ever set an underwater swimming record at this altitude.

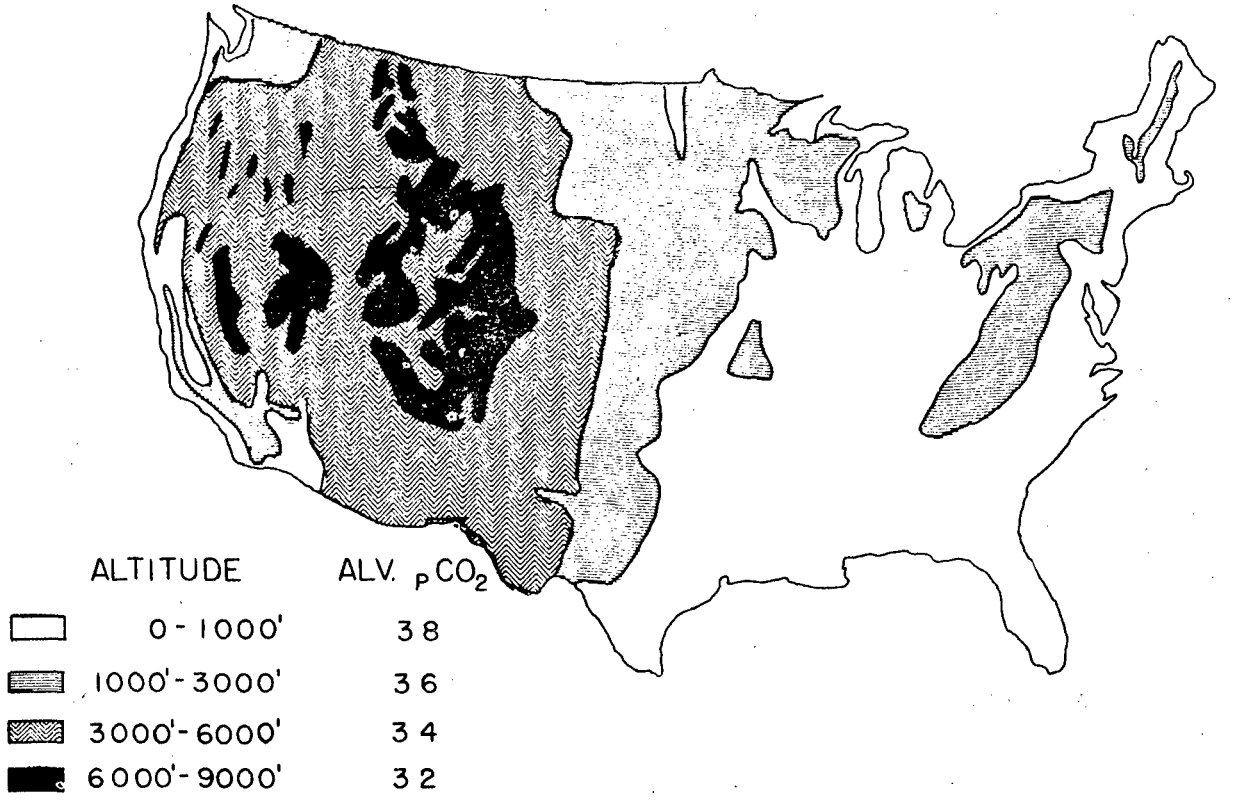


Figure 1

TABLE 1

	0-1000'	1000'-3000'	3000'-6000'	6000'-9000'
No. of People in the U. S. x million	94	32	4	1

TABLE 2

		Sea Level	3000'	6000'	9000'
Barometric Press. mm		760	681	609	543
Alveolar	Po_2	103	89	77	66
	Pco_2	38	36	34	32
Alveol. Ventil. Ratio		1.00	1.05	1.12	1.18
Breath Holding Time - %		100	78	60	50
HbO_2 - % Saturation		96.1	94.5	93.0	91.5
O_2 Capacity - %		100	102	104	108
Plasma CO_2 - T_{40} - %		100	96	93	90

REFERENCES

1. Fitzgerald, M. P. Trans. Roy. Soc. London, B. 203: 351, 1913.
2. Hurtado, A. and H. Aste-Salazar J. Appl. Physiol. 1: 304, 1948.
3. Rahn, H. and A. B. Otis Am. J. Physiol. 157: 445, 1949.
4. Rahn, H., H. T. Bahnson, J. F. Muxworthy and J. M. Hagen J. Appl. Physiol. 6: 154, 1953.

Comparative Studies on Acclimatization of Mice to Carbon Monoxide and to Low Oxygen

ROBERT T. CLARK, JR. AND ARTHUR B. OTIS

Various investigators (1–5) have mentioned the close resemblance of the effects of anoxia produced by low oxygen to that caused by carbon monoxide. However, certain differences have been noted which suggest that anoxia caused by the two methods, even when showing comparable HbO_2 values, may not bring about identical physiological responses. Only one investigator (1) has compared experimentally an animal that has been acclimatized to CO with one that has been acclimatized to low O_2.

In the present investigation an attempt has been made to determine whether animals acclimatized to carbon monoxide are also acclimatized to low oxygen. If the physiological responses are the same, animals acclimatized to CO should be more resistant to low O_2, and, conversely, animals adjusted to low O_2 should be equally resistant to CO. Comparisons have also been made of oxygen capacities, hematocrits, and CO_2 capacities in the studies of changes in the blood system during acclimatization. In the studies reported below, the experimental animals used were male white mice about 5 weeks of age (CFCW strain obtained from Carworth Farms).

Tolerance to Low O_2 of Mice Previously Exposed to CO

Methods. Acclimatization of mice to CO was carried out in a 12.5-liter desiccator charged with soda lime and connected to a spirometer containing pure oxygen. At the beginning of an experiment the desiccator contained an atmosphere of air plus the desired amount of CO, which was obtained from a commercially supplied tank. A valve in the line connecting the desiccator and spirometer permitted automatic replacement of oxygen used by the animals but prevented any back flow of gas from the desiccator. The details of this method have been described previously (6).

The animals were exposed to gradually increasing concentrations of CO over a period of 14 days. Approximately 0.04 per cent was added the first day and the amount was increased by this percentage every fourth day until a concentration of 0.12 per cent CO was reached. The concentration was held at this level for the remainder of the exposure period. Every fourth day the mice were removed and weighed, and fresh supplies of soda lime and food were added to the desiccator. A gas sample was also taken from the desiccator at this time and analyzed for CO by the Roughton and Root (7) technique.

Both the control and experimental groups were placed in a constant temperature

room at 23° ± 1°C. during the experiments. Sufficient food was withheld from the control group to produce a weight loss about equal to that of the experimental animals. An adequate supply of water was provided for each group. At the end of the exposure period, the mice were placed in room air for 3 hours and then returned to the desiccator for the tolerance test at altitude. To carry out this test, the desiccator was attached to a vacuum pump and evacuated to a simulated altitude of 34,000 feet as determined by a mercury manometer attached to the container. A screw-clamp on a piece of rubber tubing connected in parallel with the mercury manometer permitted sufficient air to be 'bled into' the system so as to maintain the desired altitude and at the same time allowed the vacuum pump to run continuously. The survival times, that is the times until death, were recorded from the time the animals reached 34,000 feet. Approximately 2 minutes were required to reach this altitude. Mice that survived the tolerance test for 1 hour were removed from the desiccator

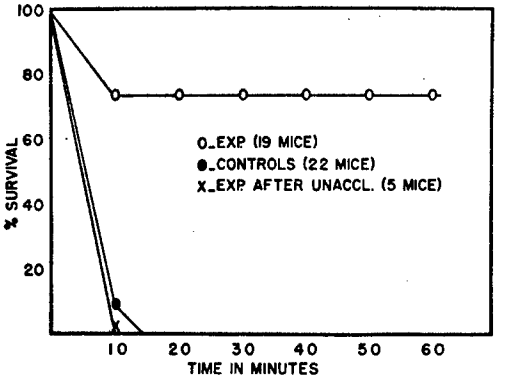


Fig. 1. Survival times, in minutes, of mice at a simulated altitude of 34,000 feet after an exposure period of 14 days to an atmosphere containing up to 0.14 per cent CO.

and placed in room air for a 14-day period of retro-acclimatization. This group of retro-acclimatized mice was then taken back to 34,000 feet and the survival times recorded

Results. The results of the experiment are summarized in figure 1, which shows that of the experimental mice (mice previously exposed to CO) 70 per cent (14 out of a total of 19 animals tested) survived the 60-minute tolerance test at a simulated altitude of 34,000 feet, whereas none of the controls or those retro-acclimatized survived more than 14 minutes of the test peroid. The average survival time for the controls was 4.7 minutes and those retro-acclimatized, 4.6 minutes.

Survival Times in CO of Mice Previously Exposed to Low O_2

Methods. The apparatus used for this experiment was the same as for the experiments on acclimatization to CO. The mice were exposed to a simulated altitude of 16,000 feet for the first 8 days, and 18,000 feet from the eighth day to the end of the experimental period on the fourteenth day. The experiments were carried out in a constant temperature room at 23° ± 1°C.

In order to simulate the desired altitude, the desiccator, containing an atmosphere of air and charged with soda lime, was attached to a vacuum pump, which was connected in parallel with a mercury manometer. When the pressure corresponding to the desired altitude was reached, the vacuum pump was removed and a cylinder containing pure nitrogen was attached. Nitrogen was added until the mercury ma-

nometer indicated that the atmospheric pressure had returned to ambient conditions. The desiccator was then connected with an oxygen filled spirometer in the manner described previously. A gas sample was removed every fourth day for measurement of oxygen content.

The control mice were kept in the constant temperature room during the experiment. Food was rationed to maintain their weight similar to that of the experimentals. At the end of the fourteenth day the experimental mice were placed in room air for 3 hours, after which both the experimentals and controls were put back into the desiccator. A CO concentration of 0.25 per cent was added and the survival times of both groups noted. Animals that did not survive were removed at the end of each day and the others were placed immediately back into the same concentration of CO. All animals surviving at the end of nine days were returned to room air.

Results. The results are presented in figure 2, which shows that 88 per cent of the experimental mice (mice previously exposed to low O_2) survived 1 day in 0.25 per cent CO, and 62 per cent survived for 9 days. Of the control group, 14 per cent

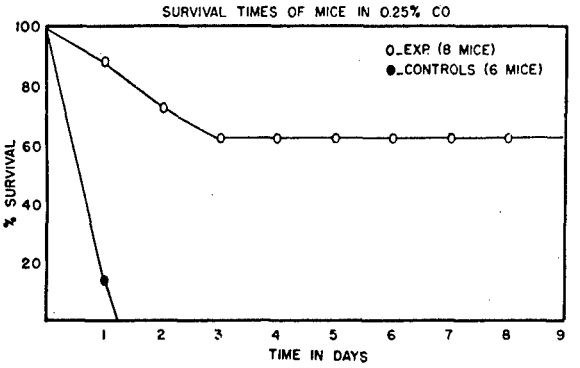


Fig. 2. SURVIVAL TIMES, in days, of mice in 0.25 per cent CO after an exposure period of 14 days to a simulated altitude of 16,000 to 18,000 feet.

survived 1 day and none survived longer than $1\frac{1}{2}$ days. The survival times for the controls ranged from 0.1 to 26 hours, with an average of 11.6 hours for the six mice. The survival times for the mice previously exposed to low O_2 averaged 45 hours for three of the mice and the remaining five survived the 9-day test period.

BLOOD STUDIES OF MICE ACCLIMATIZED TO CO AND LOW O_2

Determination of O_2 and CO_2 Capacities. *Methods.* A total of 12 male white mice averaging 24 gm. each were exposed to gradually increasing concentrations of CO for 14 days until a CO concentration of 0.15 per cent was reached. For the experiment with low O_2, 10 mice were exposed to an altitude of 18,000 feet for 14 days. The methods used during the exposure periods were the same as previously described.

In order to collect blood, the mice were decapitated and the blood allowed to drop into a small beaker containing dry heparin. To obtain a sufficient volume for equilibration and subsequent analysis it was necessary to pool the blood from two mice. This gave about 1.5 to 2.5 cc. of blood, depending on whether the mice used were controls or experimentals; more blood could always be obtained from the latter than from the former. The blood was pulled from the beaker into a 30-cc. syringe to which was attached a 24-gauge needle. The plunger of the syringe was lubrictaed with mineral oil in order to prevent leakage during the equilibration period. The equilibration mixture, 5 per cent CO_2 and 95 per cent O_2, was introduced by insert-

ing the needle into a rubber tube through which the gas was flowing and then withdrawing the plunger to the 30-cc. mark. The needle was then withdrawn from the tube and immediately inserted into a solid rubber stopper. The syringe was equilibrated on a mechanical rotator in a water bath set at 37° for 5 minutes. The gas was then expelled and replaced by a fresh mixture. This procedure was followed for two additional equilibrations of 10 minutes each. At the end of the last equilibration period, the needle of the syringe was inserted into a 0.2-cc. pipette and the gas mixture expelled through the capillary of the pipette, followed by 0.2 cc. of the blood. The sample was then transferred to the Van Slyke manometric apparatus for determination of the CO_2 and O_2 capacities according to the conventional method described by Peters and Van Slyke (8). The remainder of the blood was transferred under oil into hematocrit tubes and centrifuged for 30 minutes at 3400 revolutions per minute. After the hematocrit value was determined, the plasma was drawn off into a 0.2-cc. pipette for transfer to the Van Slyke apparatus.

Results. The results for mice acclimatized to CO are given in table 1 and show that the CO_2 capacity of the true plasma of mice exposed to CO is slightly higher than

TABLE 1. BLOOD STUDY OF MICE AFTER ACCLIMATIZATION TO CO

NO. OF ANIMALS	CO_2 CAPACITIES PLASMA[1]		CO_2 CAPACITIES WHOLE BLOOD[1]		O_2 CAPACITIES[1]		HEMATOCRIT	
	Control	CO	Control	CO	Control	CO	Control	CO
2	42.14	50.59	38.00	32.90	21.00	30.70	36.0	63.7
2	42.82	48.00	37.67	31.80	20.50	29.76	36.0	64.0
2	42.40	44.40	37.75	31.69	20.00	30.15	35.8	63.7
2	43.10	44.90	37.95	32.00				
Av.	42.62	46.97	37.84	32.10	20.50	30.20	36.0	63.8

[1] Volumes per cent. The gas mixture for equilibration was 95 per cent O_2, 5 per cent CO_2.

that of the controls. On the other hand, the CO_2 capacity of whole blood is lower than that for the controls, a finding explained in part by the larger hematocrit of the mice exposed to CO (see table 3). Exposure of mice to CO produced an increase in hematocrit of 80 per cent and an increase in oxygen capacity of 50 per cent of the control values.

Table 2 gives the results obtained with the group exposed to low oxygen. The figures show that the CO_2 capacity of the plasma as well as of whole blood was markedly reduced in the mice exposed to low oxygen. An 80 per cent increase in hematocrit and 50 per cent increase in oxygen capacity was obtained after the mice were exposed to low oxygen for 14 days.

An average of the results from tables 1 and 2 is presented in the first three rows of table 3, together with other data calculated from these results. The pH values in *column 7* were calculated by the Henderson-Hasselbach equation. The values given in *columns 2, 4* and *5* were calculated from the experimental data shown in *columns 1, 3* and *6*. An illustrative calculation involving the data for the control animals will now be given.

Plasma CO_2 capacity = 42.72 vol. %.
Whole blood CO_2 capacity = 38.20 vol. %.
% cells = 36.
% plasma = 64.

Of the CO_2 contained in 100 cc. of whole blood, 0.64 × 42.72 = 27.34 cc. is in plasma and 38.20 − 27.34 = 10.86 cc. is in cells.
The concentration of CO_2 in cells is 10.86/36 × 100 = 30.17 vol. per cent.

The two lower rows of figures in table 3 were estimated from the nomogram of Dill, Talbott and Consolazio (9) for a pCO_2 = 35 mm. and are included for comparison with our data for mice.

A comparison of the results obtained from mice in low oxygen with those from miners who habitually live at high altitude shows that the same order of change has occurred in the blood although the values are all higher for the human subjects, both at sea level and at high altitude.

The ratio of (HCO_3^-) in cells to (HCO_3^-) in plasma is not significantly changed by acclimatization to altitude in either man or mouse. For mice acclimatized to CO, however, there seems to be an appreciable lowering of this ratio. This is a point which requires further investigation for if confirmed it would suggest the possibility that prolonged exposure to CO alters the hemoglobin molecule in some fashion.

TABLE 2. BLOOD STUDY OF MICE AFTER ACCLIMATIZATION TO LOW O_2

NO. OF ANIMALS	CO_2 CAPACITY PLASMA[1]		CO_2 CAPACITY WHOLE BLOOD[1]		O_2 CAPACITIES[1]		HEMATOCRIT	
	Control	Low O_2	Control	Low O_2	Control	Low O_2	Control	Low O_2
2	42.01	29.74	38.74	23.78	19.33	28.39	36.0	64.10
2	43.66	29.90	39.05	24.00	19.00	29.00	35.8	63.30
Av.	42.83	29.82	38.89	23.89	19.17	28.70	35.9	63.70

[1] Volumes per cent. The gas mixture for equilibration was 95 per cent O_2, 5 per cent CO_2.

Determination of Alkali Reserve by Measurement of the pH. In order to obtain confirmatory information as to the behavior of the alkali reserve of animals exposed to low O_2 and to CO the following experiment was performed.

Methods. A group of 10 mice was exposed for 14 days in the usual manner to gradually increasing concentrations of CO until a concentration of 0.10 per cent was reached. Blood was obtained immediately upon removal of the animals to room air and was equilibrated in a 30-cc. syringe as before. A mixture of 5.35 per cent CO_2 in oxygen was used for the equilibration.

Three of the mice that had been exposed for the 14-day period to CO and one control that had remained in room air were placed in a desiccator and taken to a simulated altitude of 18,000 feet for 3 days before removal for pH determination of the blood. The pH was measured on the blood of each mouse instead of pooling the blood of two as before.

The pH measurements were made on the Beckman pH meter by means of a microelectrode. The blood was delivered directly from the syringe into the capillary of the microelectrode through a small-bore flexible plastic connecting tube. Calculations for the CO_2 capacity were determined from the Henderson-Hasselbach equation.

Results. The results are shown in table 4. A comparison of the average CO_2 capacities in table 4 with those in table 3 shows that the method of pH measurement gives results similar to those obtained by the van Slyke method and confirms the conclusion reached above that the CO_2 capacity of plasma is lowered during exposure to low O_2 but is slightly elevated during exposure to CO.

Time Course of Changes in Hematocrit Values and Body Weight During Acclimatization and Retro-Acclimatization to CO and Low O_2

Methods. A group of 11 mice was exposed to a simulated altitude of 18,000 feet for 12 days. The methods used were the same as described above. The mice were removed from the desiccator every few days for weighing, and at the time of each removal one mouse from the group was killed for hematocrit ratio determination. After 12 days of exposure to altitude, the remaining mice were placed in room air for a similar period of retro-acclimatization during which hematocrit readings and weight determinations were made at regular intervals.

A parallel group of 11 mice was exposed to gradually increasing concentrations of CO for 13 days according to the method previously described in this paper. Hematocrit values and body weight were measured during both the acclimatization and retro-acclimatization periods in the same manner as for the mice exposed to low O_2.

Table 3. Blood study of mice acclimatized to CO and low O_2 compared with human subjects at high altitude

	(HCO_3^-) content at pCO_2 = 35 mm.			Partition of (HCO_3^-) between plasma and cells in 100 ml. whole blood				
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Plasma[1]	Cells[1]	Whole blood[1]	Plasma	Cells	% Cells	Plasma pH	O_2 capacity
Controls	42.72	30.17	38.20	27.34	10.86	36.00	7.36	18.00
Carbon monoxide	46.97	23.70	32.10	17.00	15.10	63.80	7.40	30.20
Low oxygen	29.82	20.50	23.89	10.80	13.09	63.70	7.20	29.50
Sea level[2]	53.00	36.70	45.70	29.30	16.40	44.70	7.45	20.10
Miners[2]	39.90	28.70	32.30	13.00	19.30	67.40	7.33	30.00

[1] Volumes per cent. The gas mixture used for equilibration was 95 per cent O_2 and 5 per cent CO_2. [2] Data calculated from nomogram of Dill, Talbott and Consolazio (9) for human subjects at sea level and miners who live at altitudes between 15,000 to 18,000 feet.

Results. Results for both CO exposure and low O_2 are summarized in figure 3, which indicates the similarity of the effects of these two forms of anoxia on body weight and on hematocrit values. Both treatments produced a progressive weight loss, which at the end of 12 days' exposure amounted to about 35 per cent of the initial weight. On return to the normal environment the animals gained weight steadily and after 8 days had fully recovered their initial weight.

Except for an initial delay in the case of the mice exposed to CO, both groups showed a similar steady rise in hematocrit ratio during the exposure period. On return to the normal environment, the hematocrit ratios of both groups remained elevated at an approximately constant value for the next 8 days and then during the next few days fell rapidly back to normal.

Oxygen Consumption Measurements on Mice During Acclimatization to CO and Low O_2

Methods. All oxygen consumptions were determined from spirometer readings taken during the exposure periods to CO and low O_2. The readings were made at intervals of from 6 to 12 hours at which time the barometric pressure and temperature were also recorded. The volumes as read from the spirometer were converted

to S.T.P. and then the cubic centimeters of oxygen used per gram of body weight per hour were calculated, using the average of weights taken at the beginning and the end of a period.

Results. Table 5 gives the rates of oxygen consumption for mice during acclimatization to low O_2 and to CO, and shows that the rate of oxygen consumption was about the same for the groups in CO, low O_2 and air. The average rate for mice in low O_2 was 3.1 cc/gm/hr.; for mice in CO, 3.0 cc/gm/hr.; and for mice in room air, 3.2 cc/gm/hr.

Discussion

In the experiments with mice it has been shown, by means of acute tolerance tests, that mice which have been acclimatized to CO for 2 weeks can survive considerably longer at a simulated altitude of 34,000 feet than controls. Conversely, mice which have been acclimatized to low oxygen for a similar length of time can survive

Table 4. The pH of blood of mice at 37 mm. Hg-CO_2 tension

CO		low O_2	
pH	true plasma CO_2 capacity[1]	pH	true plasma CO_2 capacity[1]
7.38	45.12	7.22	30.40
7.37	44.05	7.22	30.40
7.41	48.50	7.20	28.90
7.42	49.70	7.24[2]	31.10
Av. 7.40	46.84	7.22	30.20

[1] Volumes per cent. Gas mixture used for equilibration was 95 per cent O_2 and 5 per cent CO_2.
[2] Blood from mouse not previously exposed to CO.

much longer in a high concentration of CO than controls. On the basis of the results, it would appear that at least some of the factors responsible for acclimatization to the two types of anoxia are similar.

Our results for the hematocrit values and oxygen capacities during acclimatization to CO and low O_2 indicate similar responses of the two groups of animals. In both cases there was a 70 per cent increase in hematocrit ratio and 50 per cent increase in oxygen capacity. Moreover the time course of the increase was almost identical for both conditions.

The initial rise in the hematocrit was perhaps due to the combined results of release or mobilization of stored blood and a process of hemoconcentration, as has been suggested by Douglas, Haldane, Henderson and Schneider (10). Barcroft (11) has stated that the spleen can contract to half its own volume under anoxic conditions and might in this way add as much as 5 per cent of red cells to the circulation. The continued increase in hematocrit was probably the result of erythropoietic activity of the bone marrow. Evidence that this response occurs during chronic exposure to anoxia has been observed by numerous investigators on subjects at high altitude (10–13) and on animals in CO (14, 15). There was more of a lag in the red cell increase for the mice in CO. However, this probably would be expected since the experiments on the mice in CO were started at a very low concentration which was gradually increased during the course of the experiment. The percentage of red cells at the end of the experiment was the same as for the experiment in low oxygen.

The CO_2 capacities of mice after exposure to CO and low O_2 show that in the former case the alkali reserve was somewhat increased, whereas in the latter group

there was a marked drop. The fall in bicarbonate as a result of exposure to high altitude has been shown by many investigators (10–12, 16) to be associated with hyperventilation, which produces a drop in alveolar CO_2 tension, thereby causing a loss of H_2CO_3 from the blood. In response to the alkalosis thus produced the kidney secretes bicarbonate, thereby lowering the alkali reserve. The net result is that the animal is in a state of compensated respiratory alkalosis. Thus the drop in alkali reserve recorded in our experiments with mice in low oxygen would seem to indicate that the animals were hyperventilating. The alkali reserve of the mice exposed to CO is higher than that of the controls, indicating that these animals almost certainly were not hyperventilating and were probably underventilating in spite of the severe anoxia. Our inference that the animals in CO were not hyperventilating is in agreement with

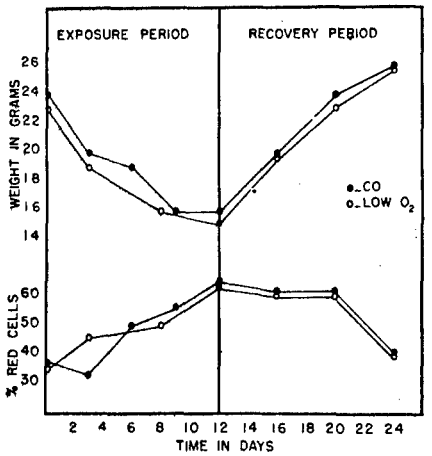


Fig. 3. HEMATOCRIT and weight changes for mice during exposure to an atmosphere containing CO or low O_2, followed by a recovery period in room air. Eleven mice were used in each experiment.

the findings of Chiodi, Dill, Consolazio and Horvath (17), and of Dahlstrom, Obreschkow and Sjostrand (5) for acute exposure of human subjects to CO. On the other hand, Haldane noted hyperventilation in the mouse (18) and on himself (19) during acute exposure. Likewise, Haggard and Henderson (20), and Von Oettingen, Donahue, Välaer and Miller (21) obtained evidence for hyperventilation on dogs during acute exposures. The stimulus to anoxic hyperventilation is believed by Asmussen and Chiodi (4) and Comroe and Schmidt (22) to be a reduction in oxygen tension (acting on the carotid bodies) rather than to a reduction in oxygen content of the blood. Since CO does not appreciably affect the tension of O_2 in the arterial blood (23, 24), it then follows that the carotid body should not be stimulated even at relatively high concentrations of CO. This point has been demonstrated by Comroe and Schmidt (22), who have shown by perfusion experiments that the carotid body was not stimulated sufficiently to cause hyperventilation as long as the oxygen tension was high even though the amount of oxygen present was negligible. Underventilation as a result of continued exposure to CO could perhaps be brought about by action on the respiratory center, inasmuch as a number of investigators have demonstrated toxic effects of CO on nervous tissue (25–31) although the mechanisms which operate are not defined.

Oxygen dissociation curves for blood partially saturated with CO show two features, a reduction of oxygen capacity and a transformation from the characteristic S shape to a more hyperbolic form (23). In relation to the present experiments, these changes in the dissociation curve would require a lower venous oxygen pressure for the release of a given amount of oxygen to the tissues, and the fall in oxygen capacity

would limit the amount of oxygen available. Hyperventilation would not alleviate either of these conditions because the effects of the increased alveolar oxygen pressure would be on the upper (or flat) portion of the curve.

In low oxygen, on the other hand, the shape of the dissociation curve is not altered but the arterial point is shifted to the steep portion of the curve. Therefore, in order to unload the usual amount of oxygen to the tissues the venous point would have to move down the curve, thereby lowering the unloading pressure of oxygen to the tissues. In both CO and low O_2, then, the first effect on the oxygen dissociation curve would be to lower the unloading tension of oxygen to the tissues. In the case of animals in CO, hyperventilation would not change this unloading tension, but for animals in low O_2, the increased alveolar oxygen pressure produced by hyperventilation would cause the arterial point to move up the steep portion of the dissociation curve, thereby allowing the same amount of oxygen to be unloaded to the tissues at a higher pressure of oxygen.

TABLE 5. OXYGEN CONSUMPTION OF MICE DURING ACCLIMATIZATION TO DIFFERENT CONCENTRATIONS OF O_2 AND CO

	NO. OF MICE	DAYS	GAS[1] IN NITROGEN	O_2/GM./HR.		NO. OF MICE	DAYS	GAS[1] IN AIR	O_2/GM./HR.
			%	*cc.*				%	*cc.*
Mice in low O_2	10	3	9.4	3.2	Mice in CO	10	3	0.06	2.9
	10	3	9.3	2.8		10	4	0.09	3.2
	10	3	8.4	3.1		10	3	0.10	3.2
	10	3	8.2	3.2		10	3	0.14	2.8
					Controls in air	10	5	Air	3.2

[1] Gas used is given in the first column.

If an increase in the unloading pressure of oxygen to the tissues is an important factor in acclimatization to anoxia, then on the basis of our experimental observations, this could have been accomplished to a certain degree for the mice in low oxygen by an increase in oxygen capacity and by hyperventilation. For the mice in CO an increase in O_2 capacity was the only observation which was noted that would raise the oxygen unloading pressure to the tissues. However, the mice that had been exposed to CO seemed to be just as resistant to low O_2 as did the animals which had been acclimatized to the latter environment.

Killick (32), in her experiment with the human subject, found evidence that acclimatization to CO took place even though there was no increase in O_2 capacity of the blood. She concluded that the acclimatized subject was able to secrete CO from the blood stream into the lungs. Our experiments neither substantiate nor refute this possibility, which although an interesting one, is bound to be received with scepticism until more amply confirmed.

SUMMARY

Mice which have been acclimatized to concentrations of CO up to 0.15 per cent for 14 days can survive an acute exposure to 34,000 feet considerably longer than mice unacclimatized to CO. Mice which have been exposed to low O_2 for 14 days can survive in an atmosphere containing 0.25 per cent CO considerably longer than mice unacclimatized to low O_2. The oxygen capacity and hematocrit increased to about the same extent for the mice acclimatized to CO and low O_2. The oxygen capac-

ity increased about 50 per cent above the controls, and the hematocrit 85 per cent. The CO_2 capacity of the plasma was found to decrease for the mice acclimatized to low O_2. Mice acclimatized to CO showed a higher CO_2 capacity than unacclimatized mice. The decrease in CO_2 capacity of the mice acclimatized to low O_2 was of the same magnitude as the decrease that other investigators have observed for human residents at high altitude. Hematocrit ratios and weight changes were measured during acclimatization and retro-acclimatization to CO and low O_2. The changes noted for the mice in CO and low O_2 were the same. The hematocrit values increased steadily during the acclimatization period. During the retro-acclimatization period the hematocrit remained at about the same high value for the first 8 days and then dropped rapidly to the normal level. The weights of the mice during acclimatization decreased rapidly during the first few days and then more slowly. About 35 per cent of the body weight was lost during the acclimatization period. During the retro-acclimatization period the weights rose rapidly for the first few days and reached the control level about the eighth day.

The average rate of oxygen consumption during the acclimatization period for mice in low O_2 was 3.1 cc/gm/hr.; for mice in CO, 3.0 cc/gm/hr.; and for mice in room air, 3.2 cc/gm/hr.

REFERENCES

1. CAMPBELL, J. *J. Physiol.* 68: 81, 1929.
2. CAMPBELL, J. *Brit. J. Exper. Path.* 10: 304, 1929.
3. YANT, W., J. CHORNYAK, H. SCHRENK, F. PATTY AND R. SAYERS. *Pub. Health Bull.* no. 211, 1934.
4. ASMUSSEN, E. AND H. CHIODI. *Am. J. Physiol.* 132: 426, 1941.
5. DAHLSTRÖM, H., G. OBRESCHKOW AND T. SJÖSTRAND. *Acta pharmacol. et toxicol.* 3: 105, 1947.
6. CLARK, R. T. *Am. J. Physiol.* 162: 560, 1950.
7. ROUGHTON, F. AND W. ROOT. *J. Biol. Chem.* 160: 135, 1945.
8. PETERS, J. P. AND D. VAN SLYKE. *Quantitative Clinical Chemistry, Methods*, Vol. 2. Baltimore: Williams & Wilkins, 1932.
9. DILL, D., J. TALBOTT AND W. CONSOLAZIO. *J. Biol. Chem.* 118: 649, 1937.
10. DOUGLAS, C. G., J. S. HALDANE, Y. HENDERSON AND E. C. SCHNEIDER. *Phil. Tr. Roy. Soc. London* B203: 185, 1913.
11. BARCROFT, J. *The Respiratory Function of the Blood.* Part I. Lessons from High Altitudes. London: Cambridge Univ. Press, 1925.
12. FITZGERALD, J. *Phil. Tr. Roy. Soc. London* B203: 351, 1913.
13. HURTADO, A., C. MERINO AND E. DELGADO. *Arch. Int. Med.* 75: 284, 1945.
14. NASMITH, G. AND D. A. GRAHAM. *J. Physiol.* 35: 32, 1906–07.
15. KILLICK, E. *J. Physiol.* 91: 279, 1937–38.
16. HOUSTON, C. AND R. RILEY. *Am. J. Physiol.* 149: 565, 1947.
17. CHIODI, H., D. DILL, F. CONSOLAZIO AND S. M. HORVATH. *Am. J. Physiol.* 134: 683, 1941.
18. HALDANE, J. *J. Physiol.* 18: 201, 1895.
19. HALDANE, J. *J. Physiol.* 18: 430, 1895.
20. HAGGARD, H. AND Y. HENDERSON. *J. Biol. Chem.* 47: 421, 1921.
21. VON OETTINGEN, W., D. DONAHUE, P. VALAER AND J. MILLER. *Pub. Health Bull.* no. 274, 1941.
22. COMROE, J. AND C. SCHMIDT. *Am. J. Physiol.* 121: 75, 1938.
23. ROUGHTON, F. AND R. DARLING. *Am. J. Physiol.* 141: 17, 1944.
24. MCFARLAND, R., F. ROUGHTON, M. HALPERIN AND J. NIVEN. *J. Aviation Med.* 15: 381, 1944.
25. CHORNYAK, J. AND R. SAYERS. *Pub. Health Rep.* 46: 1523, 1931.
26. EROS, G. AND G. PRIESTMAN. *J. Neuropath. & Exper. Neurol.* 1: 158, 1942.
27. FORBES, H., S. COBB AND F. FREMONT-SMITH. *Arch. Neurol. & Psychiat.* 11: 264, 1924.
28. NICHOLS, I. C. AND M. KELLER. *Am. J. Psychiat.* 93: 1063, 1937.
29. SHILLITO, F., C. DRINKER AND T. SHAUGHNESSY. *J. A. M. A.* 106: 669, 1936.
30. SJÖSTRAND, T. *Acta physiol. Scandinav.* 15: 351, 1948.
31. STEWART, R. M. *J. Neurol. & Psychopath.* 1: 105, 1920.
32. KILLICK, E. *J. Physiol.* 107: 27, 1948.

CHANGES IN THE SENSITIVITY OF THE RESPIRATORY CENTER IN MAN AFTER PROLONGED EXPOSURE TO 3% CO_2

by

John L. Chapin, Arthur B. Otis and Hermann Rahn

Several investigators have studied physiological changes following prolonged exposure to CO_2 (1-4). Schaefer, et al (5) found that ventilation was slightly decreased and the alveolar Pco_2 was elevated following exposure of men to 4% CO_2 for six days.

The present study completed in February 1947 has attempted to discover whether the sensitivity of the respiratory center could be reduced by prolonged exposure to CO_2. If such a reduction occurred as a result of exposure to a high CO_2 environment, it is assumed here that the organism has "adapted" or "acclimatized" to some degree to that environment.

METHOD

Two healthy male subjects were exposed to 3% CO_2 for 78 hours in an air tight room. Minute volume, frequency of respiration, alveolar and expiratory gases, breath holding time, and the composition of alveolar gases at the breaking point were measured before, during, and after the exposure.

The gas composition of the room was measured periodically using continuous CO_2 and O_2 gas analyzers and was adjusted to 3% CO_2 and 21% O_2 by admitting the appropriate gases from cylinders.

Ventilation volume was measured in a 100 L spirometer, respiratory frequency by an aneroid and recording tape. Alveolar gas was sampled by a device described by Rahn and Otis (6) and was measured by continuous gas analyzers described by Rahn, et al (7). All volumes were converted to the condition body temperature, saturated (BTPS).

Each subject kept a partial log of his own reactions and of his impressions of the other subject. A stationary bicycle ergometer was provided on which the subjects could exercise.

RESULTS

The mean alveolar Pco_2 values before and at the end of breath holding are

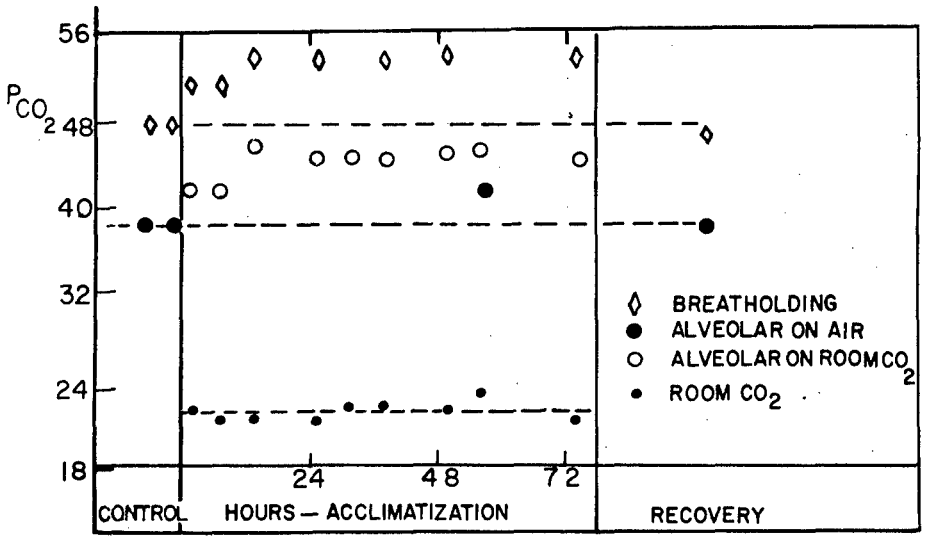


Figure 1

depicted in Figure 1 for the course of the experiment. Increased breath holding P_{CO_2} values at the second and eighth hours suggest that some quick acclimatization may have occurred. However, more than 8 but less than 13 hours were required for both resting and breath holding P_{ACO_2} to attain maximum values. Twenty hours after the exposure both of these had returned to their original values.

At approximately the 55th hour of exposure each subject breathed air for about 15 minutes. The mean P_{ACO_2} was somewhat reduced by this procedure but failed by 3.6 mm to fall to unacclimatized values. The room gas could not be maintained constant but fluctuated slightly. These values while measurements were being made are depicted in Figure 1.

Figure 2 shows the average total ventilatory response to CO_2 both acclimatized and unacclimatized. If alveolar ventilations are calculated from respiratory frequencies and an assumed average dead space of 160 ml, both curves are lowered but their relative positions remain about the same. (The total unacclimatized ventilatory response to 5.66% CO_2 was 43.3 L/m of which 40.6 L was alveolar ventilation. The acclimatized ventilatory response to 5.92% CO_2 was 32.7 L of which 30.5 L was alveolar ventilation. The unacclimatized and acclimatized total ventilatory responses to 3% CO_2 were 15.05 and 12.9 L/min. The corresponding alveolar ventilations were 13.1 and 11.1 L, respectively.) The unacclimatized ventilatory response data to 5.66% CO_2 were gathered two days before the start of the acclimatization experiment. The comparable acclimatized

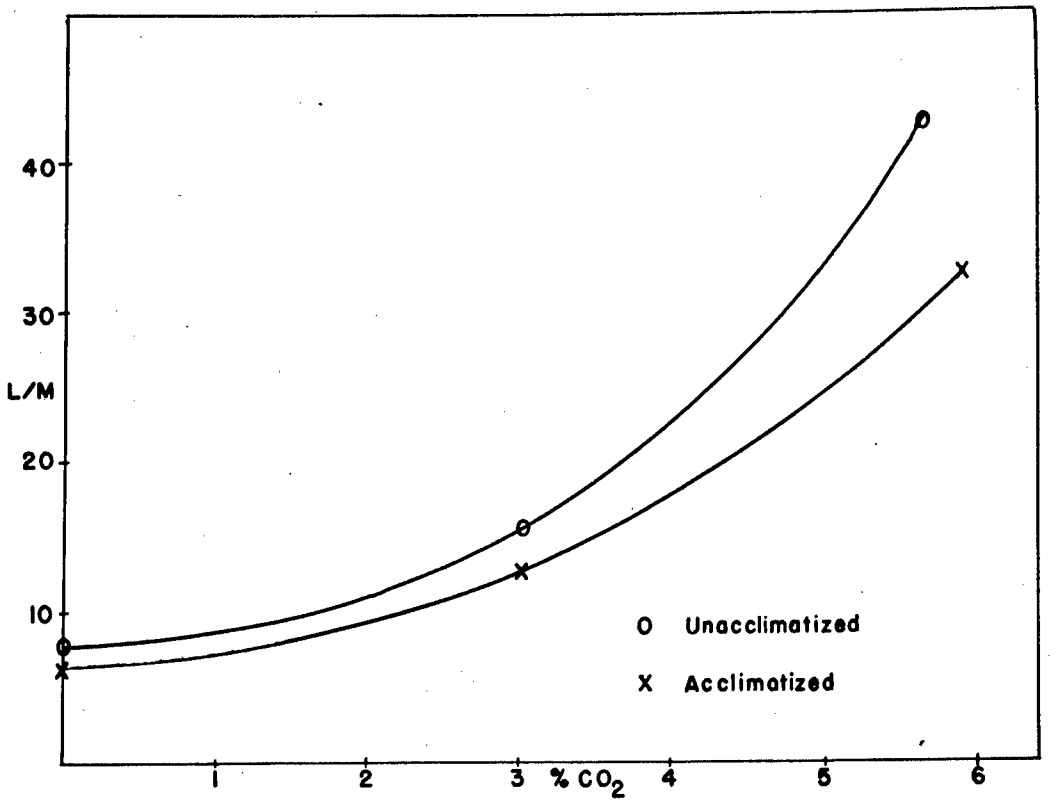


Figure 2

data were gathered at the end of the acclimatization experiment before the subjects breathed room air. The ventilatory responses to 3% CO_2 are values taken early and late in the acclimatization experiment.

Both subjects kept extensive logs the first day. They felt keen mentally, made the necessary computation on the accumulated data, and spent considerable time exercising on the bicycle. The second day the logs were brief. The subjects felt mentally depressed. The bicycle was used little and work on computation lagged. On the third and fourth days the logs were even briefer. The bicycle was not used. Appetite failed. Mental cloudiness and apathy were present. These results are in general accord with those of Schaefer, et al (5).

After leaving the acclimatization room at the end of the experiment, each subject had a dull headache and each observed that the outside air smelled of ammonia. No other person could smell it. Consolazio, et al (3) reported the same reaction.

DISCUSSION

Insofar as sensitivity of the respiratory center to CO_2 is an index of acclimatization, the two subjects of these experiments acclimatized. They tolerated higher P_{ACO_2} values during: 1) air breathing; 2) CO_2 breathing; and 3) breath holding and the ventilatory response to CO_2 was lowered.

These experiments suggest that by these criteria CO_2 acclimatization may be accomplished in a fairly short time. Measurements made at about the thirteenth hour of exposure show that both resting and breath holding P_{ACO_2} values have reached the plateau which was maintained for the next three days. Acclimatization is apparently lost within 20 hours. In view of this short period, one might speculate that sleep with its attendant high CO_2 may involve some CO_2 acclimatization. The experiments of Rahn, et al (8) on Mt. Evans, on the other hand, suggest that acclimatization to low CO_2 is not quick. When they left the mountain at the end of 7 days, there was no indication that their falling P_{ACO_2} values had stabilized.

One might inquire whether CO_2 acclimatization involves an upward extension of the tolerable range of CO_2 or whether it represents a shift in this range whereby both upper and lower limits of tolerance are shifted upward. Experiments of Barbour and Seevers (2) in which rats acclimatized to 23% CO_2 convulsed when removed to air, suggest a range shift.

SUMMARY

Two healthy male subjects spent 78 hours in a room containing 3% CO_2 in air. Measurements were made before, during, and after this exposure, of alveolar CO_2 tensions at rest and at the end of breath holding. Ventilation was also measured.

Using the criterion of reduced sensitivity of the respiratory center to CO_2, these subjects acclimatized in that: 1) their breath holding breaking points showed increased tolerance to high CO_2; 2) resting alveolar P_{CO_2} was higher when breathing air or CO_2; 3) ventilatory response to increased P_{ACO_2} was reduced.

Using these criteria, acclimatization appears to have occurred within 13 hours and to have been lost within 20 hours.

REFERENCES

1. Miller, A. T., Jr. Am. J. Physiol., 129: 529, 1940.

2. Barbour, J. H. and M. H. Seevers J. Pharmacol., 18: 11, 1943.

3. Consolazio, W. V., M. B. Fisher, N. Pace, L. J. Pecora, G. C. Pitts and A. R. Behnke Am. J. Physiol., 151: 479, 1947.

4. Otis, A. B. Proc. Soc. Expt. Biol., 9: 96, 1950.

5. Schaefer, K. E. (Ed.) Symposium on Submarine Medicine. Fleet Naval Forces Germany, Technical Section (Medical), pp. 836.

6. Rahn, H. and A. B. Otis J. Appl. Physiol., 1: 717, 1949.

7. Rahn, H., J. Mohney, A. B. Otis and W. O. Fenn J. Av. Med., 17: 173, 1946.

8. Rahn, H., H. T. Bahnson, J. F. Muxworthy and J. M. Hagen J. Appl. Physiol., 6: 154, 1953.

SURVIVAL OF MICE IN HIGH CO_2 ENVIRONMENTS AT VARYING O_2 TENSIONS

by

John L. Chapin

Seevers (1) found that most rats survive acute exposures up to 15% CO_2. He also found that with gradual acclimatization they could survive 23% CO_2. Several investigators have found that narcosis and eventually death occur with acute exposure to 30% CO_2 and higher (1-3). The relative toxicity of CO_2 concentrations higher than 30% and the role varying oxygen concentrations may play have been neglected.

METHOD

Mice were exposed to prepared gas mixtures by confining them in vessels which were closed except for ports which permitted circulation of test gases. When higher than atmospheric pressures were required, a pressure bomb with a transparent window was used.

The first set of experiments consisted of exposing 138 mice to 7 different CO_2 concentrations (32.5 to 77.5%) each in 20% oxygen and nitrogen. In the second set of experiments 10 mice each were exposed to the sea level equivalents of 4.7, 6.5, 12, 20, 60, 380 and 800% oxygen in 40% CO_2 and nitrogen.

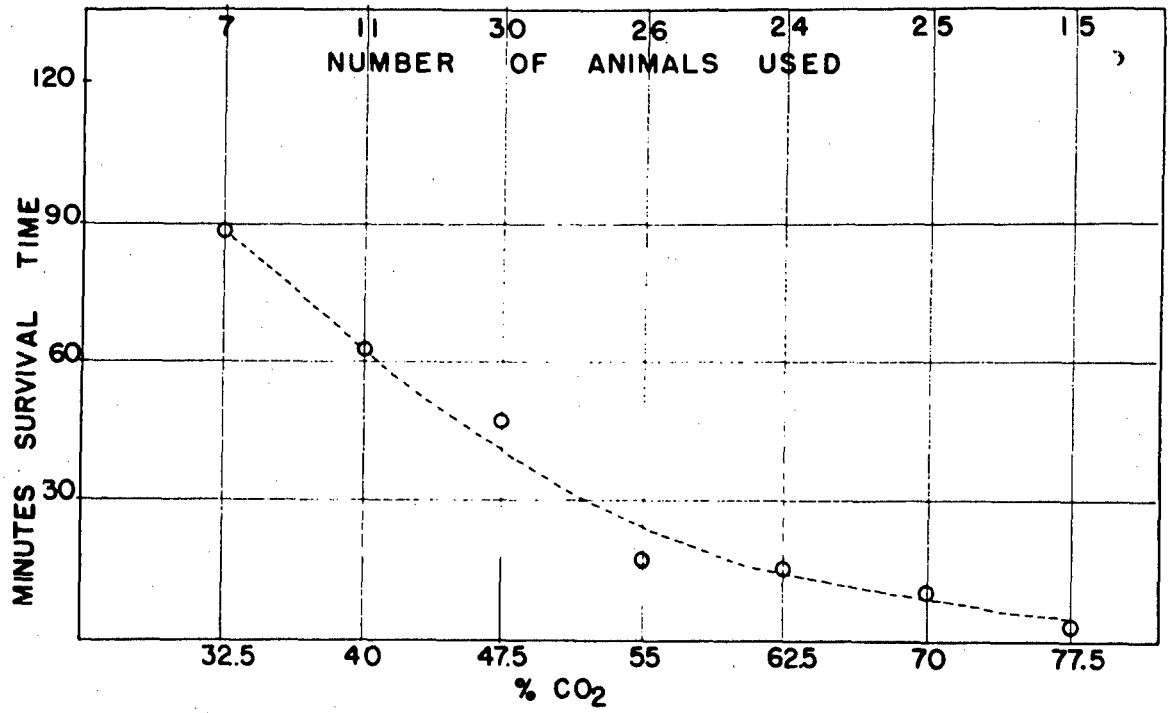
The test gas in each case was passed rapidly into the chamber assuring CO_2 anesthesia in a short time. Thereafter the gas flow was cut but maintained at a high enough level to maintain the test gas concentration.

Respiratory arrest was taken as the end point, and the time from the onset of exposure until respiratory arrest was the survival time.

The first set of experiments used adult albino mice from many sources and of both sexes. The second set used only young adult male C_3H mice.

RESULTS

The mean survival times for mice used in the first set of experiments are shown in Figure 1. As might be expected, the shortest mean survival time of 4.4 minutes (median 2.5 minutes) occurred when the mice were exposed to the highest



MEAN SURVIVAL TIMES OF MICE EXPOSED TO VARYING CO_2 CONCENTRATIONS IN 20% O_2

Figure 1

concentrations of CO_2. The second series (Figure 2) shows the longest survival time when the oxygen was 12%.

In a few cases mice were autopsied immediately after respiratory arrest. In some, but not all of these, the hearts were still beating. In no case, however, was it possible to revive animals which had undergone respiratory arrest.

DISCUSSION

A short series of experiments on 26 rats similar to the first set of experiments on mice suggests no essential difference between rats and mice in CO_2 tolerance. However, another series of similar exposures using three cats suggests a much lower tolerance to CO_2 in cats.

An additional short series on mice and rats in which rectal temperature was recorded showed a precipitous temperature drop. In its initial stages this drop

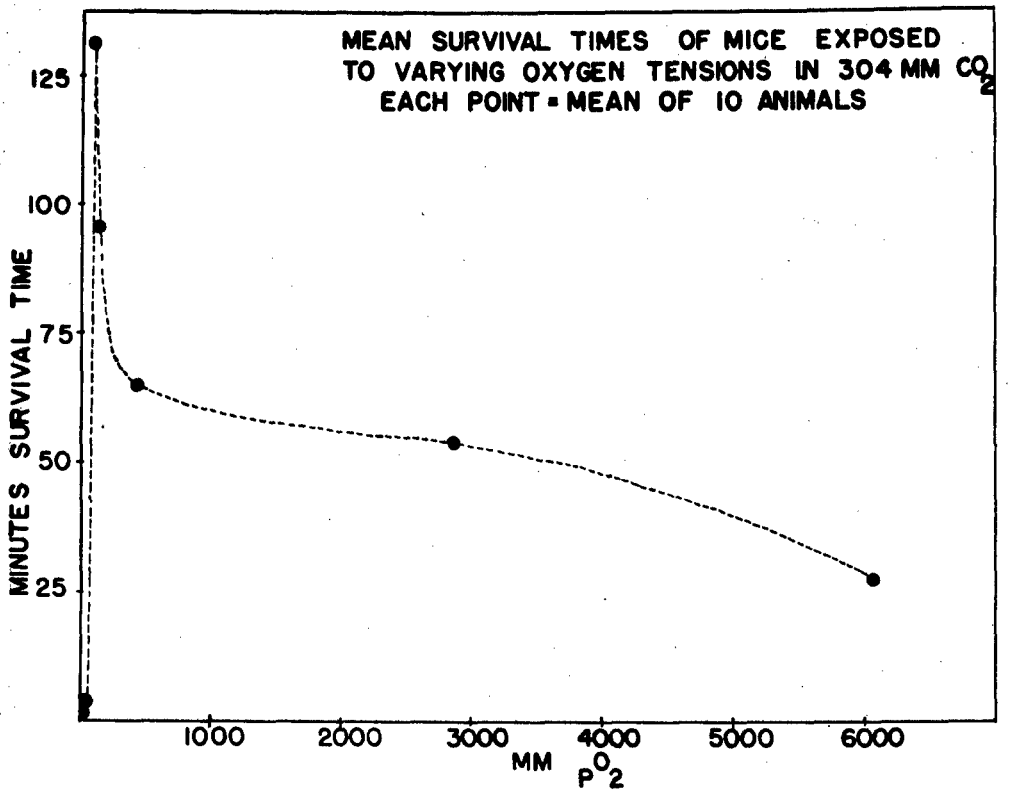


Figure 2

was faster than that of freshly killed animals. Since these animals were confined, however, it is not known whether the drop was due to CO_2 or to the effect of confinement per se as described by Bartlett, et al (4).

SUMMARY

1. Survival times of mice exposed to high CO_2 and varying oxygen concentrations were measured.
2. Longer survival times were encountered when the CO_2 was lowest and with 40% CO_2 when the oxygen concentration was between 12 - 20%.
3. OHP failed to produce convulsions in the presence of high CO_2.

REFERENCES

1. Seevers, M. H. N. Y. State J. Med., 44: 597, 1944.
2. Plavec, W. Pflüger's Arch., 79: 195, 1900.
3. Hill, L. and M. Flack J. Physiol., 37: 77, 1908.
4. Bartlett, R. G., Jr., R. H. Helmandack, and V. C. Bohr Proc. Soc. Biol. and Med., 83: 4, 1953.

Changes in Carbon Dioxide Stores of Rats Due to Atmospheres Low in Oxygen or High in Carbon Dioxide

FLORENCE HERBER FREEMAN AND WALLACE O. FENN

IT WAS SHOWN by Ferguson, Irving and Plewes (1) that overventilation of an eviscerated cat led to a loss of CO_2 from the body, of which only a fraction could be accounted for by measured losses from blood and the soft tissues. The remainder was suspected to come from the bones but due to the small amount this could not be demonstrated by direct analyses of the bones with their very large CO_2 content. The purpose of this paper is to report some analyses of bone carbonate which demonstrate that the bones can supply expired CO_2 in the overventilation of anoxia and can take up CO_2 when the inspired air contains a high percentage of CO_2. By analyzing the whole bodies of rats for CO_2 we have been able to provide additional data concerning the total CO_2 stores of the body and have arrived at a sort of CO_2 dissociation curve of the whole body and of bone in particular. This may serve in an imperfect way as a guide in estimating the CO_2 storage capacity of the bones when the alveolar CO_2 tension undergoes changes. Changes in bone carbonate in acidosis and other dietary conditions are well known and many such references are given by Huggins (2) in his review of the subject.

Plan of Experiments. Rats were maintained for various periods of time in low oxygen or high CO_2 gas mixtures and were then killed and analyzed for CO_2 contents of the whole body or separate parts of the body. Six different experiments are described. The first 3 experiments involved the effects of approximately 10% oxygen for periods up to 31 days. *Experiments 4* and *5* tested the effects of approximately 10% CO_2 for periods up to 4 weeks. *Experiment 6* was a short 6-hour experiment on rats in 7% oxygen. Details of these experiments are listed in table 1.

METHODS

Gas Mixtures. In *experiments 1–5* the rats were kept in a 60-liter aquarium, the gas content of which was adjusted by one of two different methods. In *experiments 1*, *2* and *6*, CO_2 was absorbed and the original air mixture was diluted with nitrogen until the desired oxygen percentage was obtained. Thereafter, as O_2 was used up, more O_2 was taken in from a spirometer by way of a check valve so that the pO_2 remained at the original level. In *experiment 3*, the CO_2 was absorbed and nitrogen was added until the pO_2 reached the desired level of about 10%. Thereafter it was maintained at that level by a steady inflow of air at a suitably-adjusted rate. In *experiments 4* and *5*, the CO_2 was not absorbed but was maintained at about 10% by a steady adjusted inflow of a mixture of 30–35% O_2 in N_2. The high oxygen prevented any fall in the pO_2. *Experiment 6* was similar to *experiment 1* except for the use of a desiccator in place of an aquarium to hold the rats. In all cases frequent samples of the gas were withdrawn, sometimes 4–7 times daily, and analyzed on a Fry gas analyzer (3) for CO_2 or O_2 as required. The average composition and the range of the variation found are shown in table 1.

All rats were males. Control rats were litter-mates of the experimental rats and were kept in an adjacent aquarium in air. The temperature was that of the room (about 27°C.). In *experiments 3–5*, the aquaria were kept in a thermostat-controlled room at 28 ± 1°C. In all experiments rats were taken out at intervals, beginning some days after the start of the experiment, as indicated in table 1. One experimental and one control rat were killed each day or on alternate days until the supply was exhausted and the experiment terminated. Each rat was killed by a stunning blow on the head and the neck was incised for the collection of blood where needed. Cages were open momentarily for cleaning once a day and removal of rats for sampling. Water was provided ad libitum. Control rats were given

only as much food as that consumed by their mates in the experimental group (i.e. 'pair-fed').

Total Body CO_2. Within 2 minutes after removal from the aquarium the dead rat was inserted into a quart fruit jar containing 200 cc of water and sealed tight with a cover containing three tubes. CO_2-free air entered via a water trap through one of these tubes (reaching to the bottom) and bubbled through the solution in the jar. The air emerged through a second tube and passed through a H_2SO_4 trap and condenser and was bubbled through 50 cc of 0.7 N NaOH in a 13-mm diameter glass tube for the absorption of CO_2. After testing for leaks, the CO_2 in the rat was liberated by introducing 200 cc of 4 N HCl through the third tube in the cover of the fruit jar. The jar was partially immersed in a glycerin bath and brought to a boil for 3 hours at which time the contents were thick and oily without solid particles. The NaOH containing the absorbed CO_2 was transferred quantitatively to a 200-cc volumetric flask and the CO_2 content determined in 0.5-cc aliquots by the Van Slyke and Neill (4) manometric method. In a series of five experiments using known Na_2CO_3 solutions in place of the rat a 96.9% recovery was obtained.

Muscle CO_2 Content. Samples of biceps femoris muscles weighing approximately 1 gm were placed quickly in weighing bottles containing FeF_3 solution and analyzed by the method of Danielson and Hastings (5). To test the method six pairs of muscles were analyzed, one muscle of each pair after storage for 16–20 hours in the cold room and the other muscle of the pair after storage for an equal period at room temperature. No significant differences were found, the averages in cc/100 gm being 28.2 ± 4.5 and 29.7 ± 4.6 respectively ($P = 0.5$).

Blood Analyses. Blood was collected from the incised neck in a beaker in which 0.2 cc of 6.5% liquaemin (heparin preparation) had been dried. This was promptly transferred to a 50-cc syringe and stored in the icebox until analyzed (within 2 hours). The syringe was filled with the proper gas mixture and the blood was equilibrated by rotation in a water bath at 37°C. before analysis by the Van Slyke manometric method. Whole blood values were converted to plasma CO_2 by the Van Slyke-Sendroy nomogram (6) and an hematocrit determination (4000 rpm for 20 minutes in 0.5 cc in a capillary tube).

Bone CO_2. Bones were dissected as cleanly as possible and were weighed and stored in tared stoppered combustion tubes in the cold room for analysis within 24 hours of the time the rat was killed. The bones were analyzed by the method of Van Slyke and Folch (7) as modified by Sobel *et al.* (8). Errors in the uniformity of the dissection were determined by preparing paired femurs. The average difference in weight was found to be 1.64 ± 1.30% of the weight of one femur. It was found that exposure of the bones to air for 2–4 hours after dissection did not alter their CO_2 content, for paired bones stored for a similar period in an atmosphere of 5% CO_2 contained only 0.18% more CO_2 than their mates in air ($P = 0.5$). The bone marrow was usually analyzed along with the bones. The marrow

TABLE 1. GENERAL DESCRIPTION OF EXPERIMENTS

Exper. No.	Composition of Gas Mixture		No. of Rats		Av. Wt. of Rats		Time of killing Rats	Age of Rats*	Temp.	Analyses	Results, Table No.
	CO_2	O_2	C	E	C	E					
	%	%			*gm*	*gm*	*days*	*days*	*°C*		
1	0	10.0±0.08 (8.2–11.8)	7	8	174.7 (±10.3)	187.6 (±10.0)	11–19	111–118	27±0.5	Total body CO_2	Text
2	0	9.9±0.8 (7.9–11.9)	10	10	150.5 (±5.4)	195.9 (±11.5)	11–31	86–92	27±	CO_2 of blood, muscle, bone	2 and 3
3	0	11.0±0.9 (8.9–14.2)	7	8	174.5 (±18.1)	170.6 (±11.5)	6–15	61–69	28±1	CO_2 of blood, muscle; pO_2, pCO_2 of tissues	4
4	10.3±0.9	23.2	10	10	163.7 (±10.4)	178.8 (±10.2)	7–16	61–69	28±1	Total body CO_2	Text
5	10.3±0.7 (8.8–11.7)	23.1	10	10	182.1 (±14.4)	183.1 (±14.0)	6–28	62–68	28±1	CO_2 of blood, muscle, bone; pCO_2, pO_2 of tissues	5 and 6
6	0	7.0	4	3			6 hr.			Plasma, muscle, bone CO_2	Text

* At the beginning of the experiment.

accounts for approximately 13% of the weight of the bone but contains only 0.5% of the total CO_2 (determined by analysis with and without marrow). Thus a change of 20% in the CO_2 content of the marrow would cause only a 0.1% change in the CO_2 content of the whole bone. Differences between bones cannot therefore be attributed to changes in the CO_2 content of the marrow.

Bone Ca and P. The acid bone digests remaining at the end of the CO_2 analyses were filtered under suction and transferred quantitatively to 25-cc volumetric flasks. Aliquots were analyzed for Ca by the method of Kochakian and Fox (9) and for P by the method of Fiske and Subbarow (10). The reliability of the Ca method was in some doubt because of the possible presence of oxidizing or reducing substances in the digest. Some aliquots were therefore ashed prior to analysis. The mean Ca content for duplicate analyses of eight ashed bone aliquots (expressed in percentage of wet bone weight) was 15.67 ± 0.64% as compared to 15.54 ± 0.85 for nonashed aliquots of the same bones. All interfering substances had apparently been removed in the boiling process.

TABLE 2. EXP. 2. 11–31 DAYS IN 9.9% O_2. BLOOD AND MUSCLE DATA

	Muscle CO_2, cc/100 gm	Red Cell, Vol. %	Plasma CO_2 at 2.8% CO_2 Vol. %	Plasma CO_2 at 4.6% CO_2 Vol. %
Control	29.6	39.6	39.4	51.6
σ (η)	3.6(20)	3.7(9)	(1)	2.6(7)
9.9% O_2	23.4	69.9	28.9	43.2
σ (η)	3.8(19)	1.7(9)	1.3(3)	3.2(8)

RESULTS

Experiment 1 (10% O_2). The animals in 10% O_2 lay prostrate for the first 24 hours with the hind legs stretched out behind and moving only rarely. Very little if any food and water were consumed during the first day but subsequently gradually increasing amounts were utilized. The mean body weight accordingly decreased markedly at first and later became constant for a time at about 89% of the starting weight. Eventually the weight returned nearly to its initial value. The activity of the rats also increased noticeably. Their irritability also increased particularly when they were in room air for the daily period of ½–1 hour required for cleaning the cages.

Analyses for total body CO_2 gave the following results in cc of CO_2/gm of rat: control rats, 1.85 ± 0.07 (7).[3] 10% O_2 rats, 1.51 ± 0.08 (8). (*P* of difference 0.01.)

[3] Standard deviations are used throughout this paper with the number of determinations in parentheses.

Experiment 2 (9.9% O_2). This experiment was similar to the first except that analyses were made for bone, muscle, and plasma CO_2 and red cell volume (hematocrit). Table 2 gives the average blood and muscle data while the more critical bone data are given in table 3 for

TABLE 3. BONE WEIGHTS AND CO_2, Ca, P CONTENT—EXPERIMENT 2

Rat No.	Bone Wt., gm	CO_2, %	Ca, %	P, %
		Controls		
21 R	0.538	2.45	16.21	8.25
L	0.522	2.49	16.59	8.29
20	0.525	2.52	16.98	8.76
	0.526	2.43	16.74	8.29
29	0.483	2.59	16.41	8.45
	0.496	2.46	15.83	8.26
25	0.478	2.57	17.29	8.65
	0.483	2.58	16.40	8.41
28	0.516	2.55	16.69	8.65
	0.506	2.61	18.00	9.53
22	0.423	2.63	16.68	8.91
	0.430	2.62	16.80	8.76
26	0.441	2.52	16.81	8.90
	0.425	2.61	17.35	8.58
27	0.518	2.56	17.82	9.13
	0.522	2.61	17.46	8.98
24	0.502	2.63		
	0.501	2.66	18.29	9.61
Mean	0.491	2.56	17.08	8.78
	±0.039	±0.07	±0.67	±0.42
		Experimentals		
32 R	0.544	2.25	15.99	8.09
L	0.554	2.28	15.40	7.85
36	0.586	2.26	16.08	8.09
	0.590	2.28	15.50	8.16
34	0.554	2.14	15.88	8.26
	0.539	2.27	15.65	8.27
33	0.532	2.34	16.34	8.45
	0.542	2.37	16.70	8.43
30	0.568	2.27	15.76	8.13
	0.572	2.26	15.95	7.91
35	0.542	2.33	15.97	8.69
	0.568	2.33	16.38	8.63
38	0.540	2.29	16.31	8.49
	0.539	2.32	16.00	8.47
37	0.531	2.26	15.95	8.62
	0.521	2.26	16.08	8.74
39	0.511	2.40	17.07	8.66
	0.514	2.38	17.20	8.67
31	0.508		16.34	8.65
	0.511	2.30	16.60	9.03
Mean	0.543	2.29	16.16	8.41
	±0.024	±0.06	±0.47	±0.31

Ca, P and CO_2 are expressed as gm/100 gm of wet bone weight. Each figure for Ca and P is an average of duplicate analysse.

the individual animals. These figures show that acclimatization to low oxygen causes a decrease in the muscle CO_2 content, a decrease in the plasma buffer base and a remarkable increase in the hematocrit ratio. The data of table 3 show that the weights of the femurs were not significantly different in the control and anoxic series. The bone Ca and CO_2 were both significantly decreased ($P < 0.01$) while the bone phosphorus was slightly decreased but perhaps not significantly ($P = 0.3$–0.4).

Experiment 3 (11.0% O_2). This experiment was similar to the previous experiments except that an attempt was made to determine the tensions of gases in the tissues. For this purpose 50 cc of air were injected intraperitoneally into lower than was intended. This may account for the more acute symptoms observed in this experiment.

The average results of these determinations are shown in table 4*A*. The figures indicate that the effect of the low oxygen was to decrease both the CO_2 and the O_2 tensions in the intraperitoneal gas bubble, and to decrease the bicarbonate of the plasma about 9 vol.% at three different partial pressures of CO_2. The muscle CO_2 was also significantly decreased from 22.6 to 19.4 cc/100 gm ($P = 0.01$), while the hematocrit, the oxygen capacity and the hemoglobin content of the blood were all increased 10–13% in accordance with expectations.

TABLE 4. BLOOD AND MUSCLE CHANGES IN RATS ACCLIMATIZED TO LOW O_2 AND TO HIGH CO_2

	Peritoneal Gas		Plasma CO_2 at CO_2 conc. of				Cell Vol.	O_2 Cap.	Hb	Muscle CO_2
	pCO_2	pO_2	2.27%	4.54%	4.77%	7.96%				
	mm Hg		*vol. %*				*%*	*vol. %*	*gm/100 cc*	*cc/100 gm*
A. Exper. 3, 5–15 days in 11% O_2										
Control	33.4	50.2	36.6		50.2	69.7	50.0	22.7	16.8	22.6
σ (n)	1.4(7)	3.1(7)	6.2(4)		2.3(3)	1.8(2)	6.1(6)	6.9(6)	3.9(6)	4.2(12)
11% O_2	21.2	32.1	27.9		44.1	57.3	56.6	25.0	18.5	19.4
σ (n)	2.0(8)	5.7(8)	2.6(5)		2.7(4)	3.3(3)	6.1(7)	1.8(7)	1.2(7)	2.6(14)
B. Exper. 5, 6–28 days at 10% CO_2										
Control	41.6	50.0		54.5		62.9	45.1	19.6	14.6	20.0
σ (n)	4.5(10)	4.8(10)		5.6(9)		2.4(3)	10.1(9)	2.9(9)	2.1(9)	2.9(18)
10% CO_2	93.6	64.4		87.3		92.9	33.1	16.8	12.5	44.7
σ (n)	5.0(5)	11.9(5)		3.1(8)		3.7(4)	4.4(8)	2.6(8)	1.9(8)	3.6(13)

each rat 3 days before it was to be killed (cf. Campbell, 11). Samples (5 cc) were then removed at desired intervals for CO_2 and O_2 analyses on the Fry analyzer. Equilibration with intraperitoneal tissues was complete in 24 hours as shown by analyses in 5 cases after 1, 2 and 3 days. Only the 24-hour results are reported here.

In this experiment all the experimental rats continued to lose weight throughout the experiment until approximately 29% of the starting weight was lost. The irritability of the experimental rats was greater than in the previous two experiments. Many animals reacted suddenly and very violently to the slightest stimuli and were very difficult to handle. It was found that 10% O_2 is very close to the minimum tolerable oxygen content and it is possible that the O_2 tensions in the initial period of this experiment were somewhat

Experiment 4 (10.3% CO_2). The normal activity of the experimental rats appeared only slightly diminished during the first few days of exposure. Rate and especially depth of respiration appeared markedly increased over the control level. After a few days the breathing seemed to be much more effortless, though the tidal volumes were obviously increased. Normal activity reappeared and continued throughout the experiment. During the first 3–5 days the mean body weight of the animals decreased 3–5%, then increased to the starting level and became constant at that point.

It was found that the exposure to this high CO_2 atmosphere increased the total body CO_2 from 1.34 ± .06 cc/gm in 10 control rats to 1.68 ± .07 cc/gm in 10 experimental rats.

Experiment 5 (10.3% CO_2). The general responses of the rats to acclimatization were exactly the same as in the last experiment.

Analyses were made for CO_2 in bone, blood and muscle and for intraperitoneal gas tensions. The average results of the analyses are shown in table 4*B*. Averages alone do not seem sufficient for the more critical bone analyses and table 5 gives individual analyses for bone CO_2, Ca and P together with the averages. The exposure to high CO_2 produced no significant difference in the weights of the femurs of the two sets of rats ($P = 0.5$). The CO_2 content was increased significantly ($P < 0.01$) by exposure to high CO_2 from 2.31 to 2.48%; the phosphorus content was decreased from 8.37 to 8.17 ($P = 0.5$–0.1); while Ca remained substantially unchanged ($P = 0.4$).

TABLE 5. BONE WEIGHTS AND CO_2, Ca, P CONTENTS—EXPER. 5

Rat No.	Bone Wt., gm	CO_2, %	Ca, %	P, %
		Controls		
78 R	0.466	2.18	15.42	8.48
L	0.469	2.27	15.48	8.58
77	0.458	2.17	15.91	8.11
	0.458	2.18	15.51	8.78
80	0.493	2.23	15.22	8.53
	0.500	2.23	15.19	8.36
79	0.443	2.22	15.61	8.03
	0.442	2.18	15.00	8.30
84	0.422	2,26	14.96	7.68
	0.416	2.42	14.87	8.04
76	0.422	2.38	15.31	8.08
	0.433	2.36		
83	0.463	2.36	15.86	8.61
	0.464	2.42	16.10	8.40
75	0.461	2.45	16.96	8.80
	0.468	2.52	16.30	8.60
81	0.457	2.37	15.99	8.62
	0.463	2.36	15.32	8.60
Mean	0.455	2.31	15.54	8.37
	±0.022	±0.11	±0.55	±0.31
		Experimentals		
86 R	0.495	2.52	15.30	8.56
L	0.480	2.44	15.52	8.62
85	0.433	2.32	15.17	8.47
	0.438	2.43	14.74	8.32
91	0.432	2.65	16.71	8.49
	0.451	2.61	16.68	8.36
94	0.427	2.36	15.17	7.87
	0.416	2.34	15.15	7.72
90	0.376	2.47	15.43	8.32
	0.378	2.59	15.31	7.89
88	0.408	2.35	14.60	8.08
	0.404	2.37	15.38	8.13
93	0.438	2.50	15.03	7.94
	0.449	2.64	15.62	8.35
89	0.447	2.53	14.99	7.80
	0.450	2.53	15.00	7.87
Mean	0.433	2.48	15.36	8.17
	±0.032	±0.11	±0.58	±0.30

Ca and P values are each averages of duplicate analyses which differed from each other by a mean of 0.11 ± 0.07% and 0.14 ± 0.11% respectively.

CO_2, Ca, and P are all expressed in gm/100 gm of bone.

It will be seen further from table 4*B* that high CO_2 acclimatization more than doubled the muscle CO_2 content, increased the buffer base of the plasma over 50% and decreased the hematocrit 26.5%, and the O_2 capacity and hemoglobin content both 14.5%. The changes in the CO_2 and O_2 tensions in the intraperitoneal gas bubble reflected the changes in the inspired air, both being higher in the experimental animals.

On autopsy no differences were noted grossly between the control and experimental series. Microscopic findings in liver, kidney, spleen, heart and lung were also negative.

Experiment 6 (7% O_2). Exposures of three male white rats to 7% O_2 for 6 hours in a 7.5-liter desiccator were carried out principally to determine whether alterations in bone CO_2 content occur within that short time. At such low O_2 tensions, equivalent to 27,000 feet altitude, the rats were very limp; they crouched with their eyes shut and rarely moved. They did not eat or drink and only rarely responded to tapping of the desiccator. Urination and defecation were marked and the rats became smeared with waste products.

After the 6-hour exposure period, the mean plasma CO_2 capacity of the experimental rats was found to be approximately 25% lower than that of the control animals. Control muscles contained 32% more CO_2 than those of the experimental animals. No change was detected in bone CO_2 content between control and experimental rats. Values were 2.06 ± .04% CO_2 in 5 analyses of bones of 3 control rats and 2.05 ± .05% in 4 analyses of bones of 2 experimental rats.

DISCUSSION

In no single experiment are all the necessary data available for the construction of the CO_2 dissociation curve of the whole body of the rat but by certain reasonable assumptions it is possible to combine the data of different experiments so that such a curve can be constructed as shown in figure 1. The values of

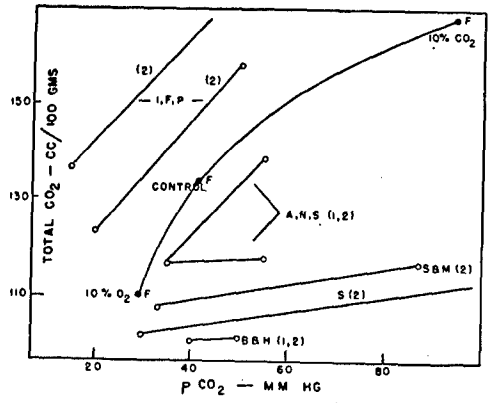


FIG. 1. Carbon dioxide dissociation curve, *F*, of the whole body of rats based on an interpretation of experimental data. Other data from the literature are plotted with the proper slope and pCO_2 range but at an arbitrary vertical level. *1* = eliminative and *2* = accumulative method. *Letters on lines* refer to authors, as follows: *B & H*, Brocklehurst and Henderson (15); *ANS*, Adolph *et al.* (16); *S*, Shaw, (13); *S & M*, Shaw and Messer (14), *IFP*, Irving *et al.* (12); *F*, this paper.

lowance of sufficient time for participation of the bones. Similar values were obtained by Irving *et al.* (12) (*IFP*) in cats for a 2.5-hour period. Shaw's values (13, 14) (*S* and *S & M*) obtained on cats in 30–90 minutes were only 0.16 cc/100 gm mm. The figures of Brockelhurst and Henderson (15) (*B & H*), 0.04 cc/100 gm mm were obviously due to incomplete equilibration in man in 2.5 minutes. The values of Adolph *et al.* (16) applied to man after 30 minutes and were both high and low for unknown reasons.

The sum of the CO_2 contents of the various 'compartments' of the animal body should equal the CO_2 content determined on the whole rat. The classical body weight percentages of the compartments blood, muscle, bone and 'remainder' (by difference) considered in this thesis are cited by Donaldson (17), from the data of Jackson and Lowrey and Hatai. Using these mean absolute weights

TABLE 6. SUMMARY OF DATA

	Body Wt.	10% O_2		10% CO_2		Av. CO_2 Normal	Loss in 10% O_2	Gain in 10% CO_2
		Con.	Exp.	Con.	Exp.			
	%	*cc CO_2 in 200-gm rat*				%	*cc/200 gm*	*cc/200 gm*
Blood	5.5	5.6	3.3	5.6	9.3	1.7	2.3	3.7
Muscle	42.6	25.2	19.9	17.1	38.1	6.3	5.3	17.0
Skeleton	11.5	298.0	266.3	269.0	289.0	83.3	32.0	20.0
Other tissues	40.4*	29.6	24.6	29.6	49.5	8.7	5.0	19.9
Sum	100	358.4	314.0	321.3	386.0	100	44.6	60.6
Direct analysis	cc/200 gm	370	302	268	336		68	68
Direct analysis	cc/gm	1.85	1.51	1.34	1.68		.34	.34
	σ (n)	.07(7)	.08(8)	.06(10)	.07(10)			

* By difference.

pCO_2 are those obtained in the intraperitoneal gases. The normal control point was taken as 1.34 cc/gm at 41.6 mm Hg as found in *experiment 4*. Higher values such as 1.85 cc/gm in *experiment 1* and 2.8 cc/gm reported by Ferguson *et al.* (1) for mice were presumably due to the use of older animals. In figure 1 are also included data from the literature, the slope of each line representing the slope of a CO_2 dissociation curve of the whole organism. Some of these data were obtained by measuring the amount of CO_2 accumulated as the pCO_2 rose and some by measuring the amount eliminated as the pCO_2 fell. The larger slopes like our own value of 1.16 cc CO_2/100 gm mm were presumably due to al-

of tissues for a typical 200-gm rat, and the CO_2 contents of each tissue, as determined in these experiments, it is possible to sum the CO_2 contents of the four compartments. This has been done in table 6. The values taken for the CO_2 contents of the various tissues were the averages of the values in tables 2, 3, 4*B* and 5. The CO_2 content of blood was calculated for the appropriate arterial pCO_2 values (black dots) in figure 2. The CO_2 content of 'other tissues' was based on the average value obtained from analyses of the following tissues: liver, 36.3 ± 4.7 (2); kidney, 31.3 ± 1.1 (3); spleen, 39.0 ± 1.8 (2); skin 39.7 ± 4.1 (4). The average value is 36.6. The values for low O_2 and high CO_2 were obtained by sub-

tracting from or adding to 36.6 the appropriate losses and gains observed in muscles. The calculations in table 6 show that the skeleton represents 11.5% of the weight of the body but contains 83% of the total CO_2.

Subtracting the 10% oxygen values from the corresponding control values the volumes of CO_2 lost from each of the four compartments of the body are found as indicated in table 6. Similarly the last column gives the CO_2 gained in 10% CO_2. Thus it may be concluded that the whole normal rat contains an average of 339 cc of CO_2, of which 44.6 cc are lost in 10% oxygen, while 60.6 cc are gained in 10% CO_2.

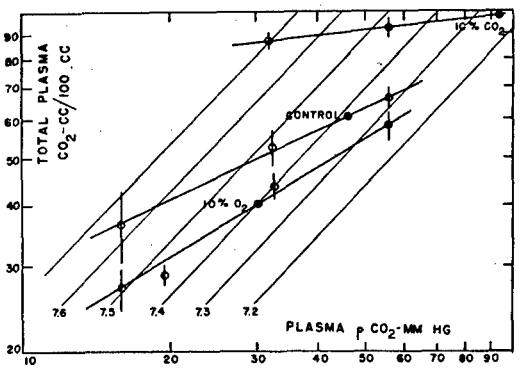


FIG. 2. Plasma CO_2 dissociation lines. Logs of plasma pCO_2 in mm Hg are plotted against logs of plasma CO_2 content in cc/100 cc; pH lines are parallel, at equal distances, and at 45° angles with the x axis. *Open* or *partially open circles* indicate mean plasma CO_2 capacity values, and *solid lines*, their standard deviations. *Solid circles* indicate *in vivo* arterial plasma points of control and experimental rats.

As a check on the validity of these results the values obtained in *experiments 1* and *4* for whole body CO_2 are given in table 6 together with the differences between the control and experimental values. These figures show a loss of 68 cc in 10% O_2 and a gain of an equal amount in 10% CO_2. The total CO_2 contents thus determined by direct analysis agree fairly well with the values obtained by summation of the separate compartments except in the 10% CO_2 series where the direct analysis figures are too low. These low values can be accounted for by supposing that the skeleton in these younger rats represents about 9.3% instead of 11.5% of the body weight reported by Donaldson (17) and used in calculating the results. On account of the high CO_2 content of bone a small error in the percentage bone weight makes a large difference in the final summary. Unfortunately, however, the weight of the skeleton decreases in weight relative to age so that an even lower figure would have to be assumed for the rats of *experiments 1* and *2*. Presumably the discrepancy is due to uncontrolled differences between the rats used in the different experiments. While, therefore, the exact amounts lost from the different body compartments remain in some doubt the general conclusion is clear that a large fraction (30–70%) of the gains or losses of CO_2 observed in these experiments are due to bone changes. These changes are relatively slow, however, since the data of *experiment 6* showed no changes in 6 hours of extreme anoxia.

The mean plasma CO_2 content and pCO_2 values of *experiments 2*, *3* and *5* are plotted in terms of their logarithms in figure 2. Mean values are shown as *open* or *partially open circles*, and the σ values as *solid vertical lines*.

A control and two experimental (10% O_2 and 10% CO_2) CO_2 dissociation lines have been calculated according to the method of least squares. All the available data from all the experiments were employed. With one exception, these lines fall well within the standard deviation range of each experimentally-determined point.

Probable arterial points are indicated by the *solid circles*. The normal value is based upon an arterial pH of 7.38 (18) and gives a pCO_2 which agrees well with our value of 41.6 mm (*exper. 5*). The low O_2 arterial value is based on the assumption that the arterial pH returned closely to the normal value after acclimatization. The decrease of 17% in the plasma $BHCO_3$ at low O_2 tensions is in accord with expectations. The arterial point at 10% CO_2 is based on an intraperitoneal pCO_2 value of 93.6 mm. This gives an arterial pH of 7.25 and indicates an uncompensated acidosis in agreement with data of Barbour and Seevers (19) on rats and Consolazio *et al.* (20) on human subjects. The data indicate a remarkable increase of 62% in the plasma $BHCO_3$. Otis (21) reported a 26% increase in mice in 7 days in 10% CO_2 and Schafer (22) found 30% increase in guinea pigs in 12% CO_2 in

9 days (after an early transient decrease). A similar increase was reported by Henderson and Haggard (23), while Miller (24) and Gesell *et al.* (25) reported a decrease. There are apparently different phases to the response under different conditions as Schafer (22) found.

In accordance with numerous other reports an increase in hematocrit ratio was found in the low oxygen experiments. This increase amounted to 76.5% in *experiment 2* and only 13% in *experiment 3*. This corresponds perhaps to other differences between the behavior of the rats in these two experiments. In high CO_2 the hematocrit ratio and hemoglobin content decreased 27 and 14%, respectively. A similar decrease was found by Schafer (22) but others have found either no change (19) or a marked increase in the number of cells (24–27).

Our data and those of Irving and Chute (28) indicate that the CO_2 combining power of normal rat muscle is higher than that of dog muscle (29) at any given tension. The wide scatter of our muscle data is due largely to a lack of precise muscle pCO_2 measurements. The figures indicate for low O_2 rats a 15–25% decrease in CO_2 content as compared to 33% found by Irving *et al.* (12) and for high CO_2 rats a 125% increase as compared to 55% (in 6–9% CO_2) found by Irving *et al.* (12).

On the basis of x-ray diffraction measurements and evidence for the lability of bone carbonates, the inorganic structure of bone may be considered a multiple apatite of the general formula $Ca_6(PO_4)_4 \cdot CaX_2$ (30, 31). In this structure, X may indicate OH_2, F_2, SO_4, or CO_3, according to the classical view (HCO_3, according to Neuman *et al.* (32)). The best evidence for the surface position of CO_2 in the apatite crystal is that found by Bale (33) in x-ray studies. Recent evidence has indicated that OH, F, and HCO_3 compete equally for the X positions on the surface of the crystal (32).

We can now outline a virtual CO_2 dissociation curve for bone (fig. 3) plotting bone CO_2 content in cc/100 gm against *in vivo* arterial pCO_2 (*solid line*) or against plasma HCO_3 content (*broken line*). This CO_2 dissociation curve suggests that only small decreases in plasma pCO_2 would be necessary to bring about a further decrease in bone CO_2 content, whereas in the higher pCO_2 ranges of our 10% CO_2 experiments, we were apparently working in the upper limits of possible bone CO_2 content for these animals.

We can calculate from the bone chemistry data of *experiment 2* that approximately 1 mEq of HCO_3 and 6 of PO_4 were lost for every 8 of Ca under those conditions. The data of Irving and Chute (28) indicate a loss of 1 mEq of HCO_3 and 11 mEq of PO_4 for each 8 mEq of Ca in rats fed 5 cc of 1N HCl for 3–48 days. In our experiments, anions and cations lost are approximately equivalent, but not so in those of Irving and Chute (28). Our data, as well as those of Irving and Chute (28), however, support the evidence that the lability of Ca, P and CO_2 is not in proportion to

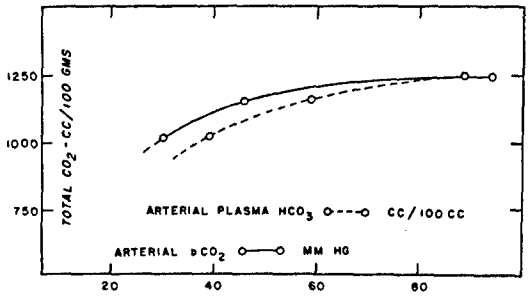


FIG. 3. Carbon dioxide dissociation curve of bone. *Solid line* indicates relation of total bone CO_2 content to arterial pCO_2. *Broken line* indicates relation of total bone CO_2 to arterial plasma HCO_3 content.

their presence in control bones, and that CO_2 is the most labile component of the three.

Apparently in conditions of high plasma HCO_3 inorganic constituents of bones do not respond in an exactly opposite manner to their method of response in low plasma HCO_3. In high CO_2 atmospheres, the bones of our rats had a statistically significant increase in CO_2 percentage, no change in Ca and possibly a slight decrease in P, as noted previously, Similar changes were noted by Marek *et al.* (34) in bone ash of swine. The X-positions in the apatite molecule become occupied by more HCO_3 linkages, according to Neuman *et al.* (32), but the mechanism of possible changes in P remains obscure.

SUMMARY

Rats 67–93 days old contain 1.34 ± 0.06 cc of CO_2/gm of body weight. Older rats

(121–138 days) contain more (1:85 ± 0.07) chiefly due to increasing CO_2 in the bones.

Twenty-six rats were acclimatized to 10% O_2 in N_2 for 10–31 days and 20 rats to 10% CO_2 in air for 6–28 days. Analyses were made at intervals for CO_2 in muscle, bone, blood and the whole body as well as hematocrit and blood O_2 capacity. Results were compared with similar analyses in pair-fed controls.

On the average a 200-gm rat lost 68 cc of CO_2 on acclimatization to 10% O_2 and gained an equal amount of CO_2 on acclimatization to 10% CO_2. Of this amount 55 cc came from the skeleton in low O_2 while 21.7 cc was gained by the skeleton in high CO_2. The skeleton normally contains 83.5% of the total 319 cc contained in a 200-gm rat. Bones lost 11% of their normal CO_2 in 10% O_2 and gained 7% in 10% CO_2.

The losses and gains of CO_2 determined by analysis of the whole body were closely equal to the losses and gains determined by calculation from the contents of the individual tissues and their relative weights.

The *in vivo* arterial plasma HCO_3 content (in cc/100 cc) was 39 in 10% O_2, 59 normal and 89 in 10% CO_2. The arterial pCO_2 values were 30 mm in low O_2, 47 mm normal and 94 mm in high CO_2. The hematocrit ratio was increased from 39.6 to 69.9% by low O_2 and decreased from 45.1 to 33.1% in high CO_2.

During acclimatization to 10% O_2 bones lost 6 mEq of PO_4 and 1 mEq of HCO_3 for every 8 mEq of Ca. In 10% CO_2 there was a gain in CO_2 in the bones, but no change in Ca or PO_4. Acute exposure to 7% O_2 for 5–6 hours did not cause any measurable changes in the bone CO_2, but over longer periods the skeleton represents an important storage depot for CO_2.

Muscle CO_2 was increased from 20 to 44.7 cc/100 gm by acclimatization to 10% CO_2 and was decreased from 51.6 to 43.2 cc/100 gm by acclimatization to 10% O_2.

REFERENCES

1. Ferguson, J. K. W., L. Irving and F. B. Plewes. *J. Physiol.* 68: 265, 1929–30.
2. Huggins, C. *Physiol. Rev.* 17: 119, 1937.
3. Fry, F. E. J. Report No. 1, Clin. Invest. Unit 18-3, Project No. A-78, (R.C.A.F.), Apr. 22, 1942.
4. Van Slyke, D. D. and J. M. Neill. *J. Biol. Chem.* 61: 523, 1924.
5. Danielson, I. S. and A. B. Hastings. *J. Biol. Chem.* 130: 349, 1939.
6. Van Slyke, D. D. and J. Sendroy, Jr. *J. Biol. Chem.* 79: 781, 1928.
7. Van Slyke, D. D. and J. Folch. *J. Biol. Chem.* 136: 509, 1940.
8. Sobel, A. E., M. Rockenmacker and B. Kramer. *J. Biol. Chem.* 152: 255, 1944.
9. Kochakian, C. D. and P. Fox. *J. Ind. and Eng. Chem., Anal. Ed.* 16: 762, 1944.
10. Fiske, C. H. and Y. Subbarow. *J. Biol. Chem.* 66: 375, 1925.
11. Campbell, J. A. *J. Physiol.* 59: 1, 1924–25.
12. Irving, L., J. K. W. Ferguson and F. B. Plewes. *J. Physiol.* 69: 113, 1930.
13. Shaw, L. A. *Am. J. Physiol.* 85: 158, 1928.
14. Shaw, L. A. and A. C. Messer. *Am. J. Physiol.* 100: 122, 1932.
15. Brocklehurst, R. J. and Y. Henderson. *J. Biol. Chem.* 72: 665, 1927.
16. Adolph, E. F., F. D. Nance and M. S. Shiling. *Am. J. Physiol.* 87: 532, 1929.
17. Donaldson, H. H. *The Rat.* Philadelphia: Wistar Inst., 1924.
18. Christiansen, W. R. and A. B. Hastings. *J. Aviation Med.* 20: 221, 1949.
19. Barbour, J. H. and M. H. Seevers. *J. Pharmacol. & Exper. Therap.* 78: 11, 1943.
20. Consolazio, W. V., M. B. Fisher, N. Pace, L. J. Pecora, G. C. Pitts and A. R. Behnke. *Am. J. Physiol.* 151: 479, 1947.
21. Otis, A. B. *Federation Proc.* 9: 96, 1950.
22. Schafer, K. E., G. Maloney, P. Pointer, C. Habisch, H. Storr, K. Scheer and H. Meessen. *U. S. Navy Translation of German Submarine Research,* 1949.
23. Henderson, Y. and H. W. Haggard. *J. Biol. Chem.* 33: 333, 1918.
24. Miller, A. T. *Am. J. Physiol.* 129: 524, 1940
25. Gesell, R., H. Krueger, G. Gorham and T. Bernthal. *Am. J. Physiol.* 94: 402, 1930.
26. Dufton, D. J. *J. Physiol.* 51: 5, 1917.
27. Dallwig, H. C., A. C. Kolls and A. S. Loevenhart. *Am. J. Physiol.* 39: 77, 1915–16.
28. Irving, L. and A. L. Chute. *J. Cell. & Comp. Physiol.* 2: 159, 1933.
29. Irving, L., H. C. Foster and J. K. W. Ferguson. *J. Biol. Chem.* 95: 95, 1932.
30. DeJong, W. F. *Rec. Trav. Chim. Pays-bas* 45: 445, 1926.
31. Taylor, N. W. and Sheard, C. *J. Biol. Chem.* 81: 479, 1929.
32. Neuman, W. F., M. W. Neuman, E. R. Main, J. O'Leary and F. A. Smith. *J. Biol. Chem.* 187: 635, 1950.
33. Bale, W. F. *Am. J. Roentgenol.* 43: 735, 1940.
34. Marek, J., O. Wellman and L. Urbanyi. *Ztschr. Physiol. Chem.* 226: 3, 1934.

THE GAS STORES OF THE BODY AND THE UNSTEADY STATE

by

L. E. Farhi[1] and H. Rahn

Whenever the oxygen uptake and carbon dioxide output measured in the expired air is equal to the metabolic gas exchange of the tissue we have by classical definition a "steady state". This state is ordinarily recognized by the attainment of a gas exchange ratio, R, which is equal to the ratio one would predict for the combustion of a mixture of certain foodstuffs. Under these conditions one is unaware of a body gas store which in man (excluding the lung gases) consists of about 1 liter of N_2, 1 liter of O_2, 17 liters of CO_2 (soft tissues) and about 100 liters CO_2 (bone). These gases are either physically dissolved or chemically bound and may under appropriate conditions increase or decrease thus contributing in a negative or positive way to the normal metabolic gas exchange. Under such conditions we have an "unsteady state" and the pulmonary exchange ratio is not that in the tissues. In addition the N_2 balance will be altered with a decrease or increase in N_2 store. We may therefore define the "steady state" in another way, namely, that state where there is no change in the gas stores of the body. Although these concepts have long been well appreciated we have found in the literature no systematic effort to evaluate quantitatively the various factors which will alter the gas stores and only a limited number of observations which have attempted measurements of the magnitude of the gas stores. This study concerns itself with the calculation of gas stores and prediction of changes in gas stores for any changes in ventilation, cardiac output and inspired gas tensions. This required new information concerning the CO_2 stores of the soft tissues for which data are presented. A second part concerns itself with the rate of changes of CO_2 and O_2 stores during certain conditions of changes in cardiac output alone and ventilation alone. Finally, a generalized model is presented which provides a quantitative estimation of the changes of gas stores when one or more parameter is altered.

GAS STORES OF THE BODY

Oxygen stores:

By far the greatest quantity of body oxygen is present in the blood. Blood volume constitutes 7.7% of total body weight (1). This in turn can be divided into two compartments. The oxygenated blood which is present in the last part of the pulmonary capillaries, pulmonary venous system, left heart, systemic arteries and arterioles, and the first part of the systemic capillaries. This will be designated as arterial blood and has been assumed to constitute 25% of the total blood volume, or 19.2 cc/kg body weight. The remaining 75% or 57.8 cc/kg make up the venous blood.

---

[1] On leave of absence from Hadassah-Hebrew University, Jerusalem, Israel.

The water content of the human body averages 70% (1) allowing for 640 cc of water per kg outside the blood volume. Here, oxygen is present in the physical solution with an assumed α of .024. Furthermore, we have assumed equality of oxygen tensions in the tissues and in the mixed venous blood, but even the presence of a relatively large venous-tissue oxygen tension difference would not result in an appreciable change in the oxygen content of the body.

An appreciable quantity of O_2 is stored in myohemoglobin, $MHbO_2$, and its role as an O_2 store has been investigated by Millikan (2). During tetanic contraction of muscle this reservoir is immediately depleted but also immediately restored upon relaxation. A net change in O_2 store, therefore, would not occur unless the muscle O_2 tension is permanently lowered. The hyperbolic saturation curve of $MHbO_2$ is shifted to the extreme left and a muscle tissue Po_2 of 10 and 3 mm are required to unload 25 and 50% of the O_2 store, respectively (2). During exercise and low O_2 breathing a lowering of the muscle Po_2 to such level can conceivably occur and would have to be taken into consideration. The myoglobin O_2 stores can be approximately estimated as 5 gms/kg of wet muscle saturated at 90% at normal tissue tension or 5 x 1.34 cc O_2 x .90 = 6 cc O_2/kg wet muscle. In our further discussion the myohemoglobin stores have not been considered.

Carbon dioxide stores:

CO_2 stores can also be divided into arterial, venous and tissue CO_2. However, as opposed to the oxygen stores, the tissue compartment is here the most important, and knowledge of the CO_2 content of the tissues (or of the whole body) is necessary in order to determine the CO_2 store.

Experimental determination of CO_2 dissociation curve of the whole body:

Partial CO_2 dissociation curves of the tissues are to be found in the literature. However, most of them are based on two points (3,4,5,6) and none of them has more than three (7,8). It was the need for additional data regarding this curve which prompted us to reinvestigate the matter.

Twenty-three experiments were conducted on nine dogs. The animals were anesthetized with sodium pentobarbital and placed in a Drinker respirator. An intravenous drip of succinylcholine (Anectine) provided muscular paralysis of such a degree that the ventilation of the dog was entirely controlled by the respirator. An intratracheal tube was placed and connected to an alveolar air sampler (9). Alveolar gas was analyzed simultaneously on a Pauling oxygen meter and a Cambridge CO_2 analyzer.

In order to obtain an initial steady state the animal was ventilated at a particular machine setting until the alveolar gases did not change more than 1 mm for 15 minutes. This was usually attained within 40-50 minutes. After recording

this initial alveolar gas tension, the respirator tank pressure was changed abruptly and maintained at its new level for the duration of the experiment. In some experiments, instead of changing the tank pressure, the inspiratory valve was connected to a CO_2 mixture (3.45% of CO_2 in room air).

The expired CO_2 was obtained by measuring and sampling the expired gas or by integrating the changing alveolar CO_2 concentrations over the alveolar ventilation. Alveolar ventilation was calculated from the minute volume, (measured a number of times during the unsteady state) and the alveolar and expired carbon dioxide tensions at the end of the experiment. It is assumed that the ratio of alveolar ventilation to total ventilation did not change throughout the procedure. Both methods gave identical results.

When a new steady state was reached in about 45 minutes, the alveolar gas tensions were recorded and the basic CO_2 output was measured. The difference between the total CO_2 output (S.T.P.D.) during the experiment and the basic CO_2 output calculated for the same period of time, divided by the weight of the animal, gave the body CO_2 stores changes per kg (Table I). The blood volume of dogs is 10% of their bodyweight (10). If the venous-arterial CO_2 difference was the same at the beginning and at the end of the experiment, the contribution of the blood CO_2 changes to the stores change per Kg could be calculated to be equal to the difference in content that would exist in 100 cc of arterial blood at the initial and terminal state. This was obtained from the alveolar CO_2 tensions and the CO_2 dissociation curve of the dog blood (11). The difference between the total stores changes and the blood changes was termed tissue stores change.

The tissues CO_2 tension was assumed to be that of the mixed venous blood during the steady state. Such an assumption had already been made by Krogh (12) and Irving (13). This in turn was obtained from the alveolar (or arterial) CO_2 tension, postulating a venous-arterial difference of 4 vol. percent.

The ratio of the tissues CO_2 stores change to the change in tissues CO_2 tension represents the slope of the tissues CO_2 dissociation curve at this CO_2 tension. The mean slope of all 23 experiments was taken as the best available estimate and is 1.02 cc/kg/mm Pco_2 ± S.E. 0.07 cc. It is lower than the values given by Irving, et al. (13).

If the slope of the whole body CO_2 dissociation curve is calculated by dividing the total store change by the difference between the initial alveolar tension and the final alveolar tension, an average slope of 1.5 cc/kg body weight/mm Pco_2 is obtained. This agrees fairly well with Shaw's figures on cats (4,6) where the slope was 1.6 cc/kg/mm Pco_2, but falls below values obtained by Irving, et al. and Freeman and Fenn in experiments of long duration.

The CO_2 dissociation curve of the tissues in the physiological range can therefore be represented by the equation content $Tco_2 = K + 1.02\ P_{Tco_2}$, where K is the

TABLE I

CO_2 DISSOCIATION CONSTANT OF THE TISSUES IN THE DOG

Expt.	P_{Aco_2} I	P_{Aco_2} F	Change in CO_2 Stores cc/kg (S.T.P.D.)			P_{Vco_2}	Tissue constant cc CO_2/kg/mm
			Total	Blood	Tissue		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1	38.5	14.3	-78.0	16.6	61.4	28.5	2.15
2	41.5	26.2	-33.0	8.9	24.1	18.0	1.34
3	26.2	11.7	-21.9	11.4	10.5	16.5	.64
4	30.1	18.8	-19.5	7.8	11.7	13.0	.86
5	18.8	11.2	-11.0	7.1	3.9	9.0	.43
6	47.5	37.2	-15.5	5.0	10.5	10.0	1.05
7	30.5	26.3	- 6.3	2.9	3.4	5.5	.62
8	24.0	14.8	-12.4	7.1	5.3	11.2	.47
9	52.5	40.6	-15.7	6.1	9.6	12.5	.77
10	42.5	21.2	-34.9	12.7	22.2	24.5	.91
11	51.5	45.0	-11.4	3.1	8.3	7.0	1.19
12	43.0	11.0	-55.5	21.6	33.9	37.0	.95
13	14.6	26.4	+20.5	8.8	11.7	13.5	.84
14	15.5	38.5	+37.2	15.5	21.7	17.5	1.30
15	12.0	16.5	+ 8.0	3.5	4.5	5.0	.90
16	17.3	24.6	+13.1	5.6	7.5	8.0	.94
17	24.6	28.6	+ 8.6	2.8	5.6	5.0	1.12
18	51.0	59.1	+14.6	3.9	10.7	10.5	1.02
19	59.1	67.0	+16.8	3.1	13.7	8.5	1.61
20	11.0	27.0	+31.3	11.7	19.6	18.0	1.09
21	38.0	57.5	+18.4	8.9	9.5	22.0	.43
22	27.0	53.0	+59.4	13.9	45.5	28.5	1.60
23	63.0	38.0	-41.6	11.9	29.7	20.0	1.48
						Grand Mean	1.02
						± S.E.	0.07

(1) All experiments with controlled ventilation. Expts. 1-12 - hyperventilation; Expts. 13-20 - hypoventilation; Expts. 21-22 - breathing 3.4% CO_2 in air; Expt. 23 - CO_2 discontinued.

(2) P_{Aco_2} I - initial alveolar CO_2 value in steady state.

(3) $P_{Aco_{2_F}}$ - final alveolar CO_2 value of new steady state.

(4) Differences between total CO_2 output and metabolic CO_2 output. + denotes store gain; - store loss.

(5) Calculated store derived from the blood.

(6) Difference between Column 4 and 5.

(7) Change in venous Pco_2 assuming a constant venous-arterial CO_2 content difference of 4 vols. percent.

(8) Slope of tissue CO_2 dissociation curve expressed in cc CO_2 (S.T.P.D.)/kg body weight/1 mm CO_2 difference obtained by dividing Column 6 by 7. The assumption is made that the tissue CO_2 tension varies as the venous tension.

content at Pco_2 of zero. Obviously K is not known to us, but if all the tissues behave like muscle, using Irving's figures (5), this would be 152 . Our lack of knowledge of K does not allow us to calculate the absolute CO_2 stores, but would introduce no difficulty in calculating differences in body CO_2 between two different conditions.

It is not postulated that the curve we have obtained represents the true dissociation curve of the tissues. In fact, the contrary is probably true, since one cannot expect the bone CO_2 to have reached its new equilibrium during such short experiments. These bone CO_2 changes are known to be several times greater than those of the rest of the body (8). The equation represents, however, the "acute experiment CO_2 dissociation curve of the tissues", for experiments of less than one hour.

Nitrogen stores:

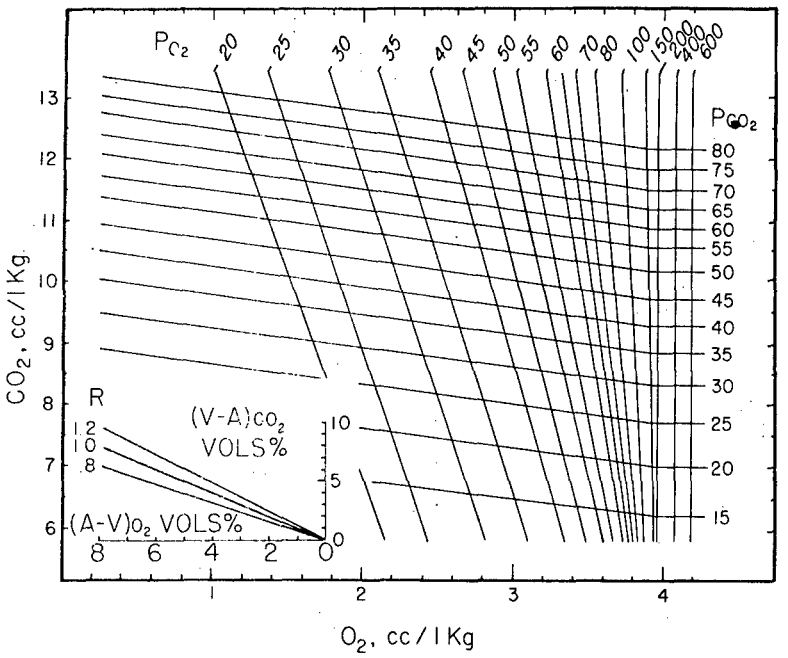
The nitrogen stores of the body have received considerable attention during the last decade, since the knowledge of their total value as well as accumulation and elimination rates is of great practical importance in the prevention of caisson disease or bends occuring at high altitude or deep sea diving operations (14). With an N_2 solubility of 12 cc/kg in fat-free tissue and 60 cc/kg in fat, a 70 kg man with 10 kg of fat, would contain approximately 865 cc. The amount of nitrogen in the lungs will be twice as much.

Combined stores of the body:

Figure 1 presents a diagram for the calculation of total O_2 and CO_2 store changes during acute experiments, provided the arterial and mixed venous blood tensions are known or assumed for the beginning and the end of the experiment.

Figure 1

Chart for the determination of body gas stores. The arterial and mixed venous points are plotted with the aid of the isobars of Pco_2 and Po_2. With these two points the total gas stores can be computed (for details see text).



This diagram plots on linear coordinates the total O_2 content of 100 cc of blood against the total CO_2 content with the addition of isobars for CO_2 and O_2 tensions obtained from Dill, et al. (15). The dimensions of the ordinates were then changed from volumes percent to cc present in the arterial blood of one kg body weight by multiplying the ordinates by .192 since the arterialized blood volume constitutes 19.2 cc/kg. Thus, if the O_2 and CO_2 tensions of the arterial blood are known, the coordinates in Figure 1 express the total O_2 and CO_2 volumes, in cc, STPD, which will be found on the average in the arterialized blood volume of one kg body weight. The usefulness of these dimensions will become apparent in the calculation of the total gas stores of the body.

When calculating the body stores, we have excluded the alveolar gas, but they can be easily computed from the alveolar gas tensions if the lung volume is known.

To calculate the stores an arterial point is plotted at the intersection of the isobars corresponding to the arterial blood gas tensions, and a venous point at the intersection of the venous tensions isobars. If the venous tensions are not known, they can be easily obtained from the A-V volume % differences with the aid of the insert in Figure 1. The A-V O_2 difference is plotted on the abscissa of the insert, and this distance transferred directly to the left of the arterial point, along the horizontal axis. From this point, a similar vertical plotting of the V-A CO_2 distance, permits plotting on the diagram of the venous point.

Calculation of the oxygen stores:

1. The quantity of oxygen in the arterial blood is read directly below the arterial point on the O_2 axis.

2. To obtain the venous oxygen, the oxygen content of the venous point is multiplied by three, since the quantity of venous blood is three times the quantity of arterial blood.

3. In addition to this a certain amount of oxygen is present in the tissues, assumed to be equal to the mixed venous blood tension. With 640 cc of water in one kilogram of tissue, and α O_2 being .024, the following table is set up as an approximate guide:

If the $P_{\bar{V}O_2}$ in mm Hg is:	25	25-35	35-45	45-55	55-65	65-75,
then the tissue O_2, cc/kg is:	.35	.58	.77	.96	1.15	1.35

The sum of these three components gives the total oxygen stores for 1 kilogram body weight.

Calculation of the CO_2 stores:

1. The arterial CO_2 content in the arterial blood of 1 kg body weight is read on the CO_2 axis, opposite the arterial point.

2. The venous content is obtained by multiplying by three the CO_2 reading of the venous point.

3. The tissue CO_2 is calculated from the venous CO_2 tension, and is equal to $K + 1.02\ P_{\bar{V}CO_2}$.

As an example, the following calculations have been made: If the P_{AO_2} is 100, the P_{ACO_2} 40, the $P_{\bar{V}O_2}$ 40, and $P_{\bar{V}CO_2}$ 46, the stores are:

Store	O_2 cc/kg	CO_2 cc/kg
Arterial	3.8	9.3
Venous	3 x 2.8 = 8.4	3 x 10.1 = 30.3
Tissue	.8	K + 1.02 x 46 = K + 47.6
Total	13.0	K + 87.2

Gas stores under different conditions:

From these calculations it can be seen that stores changes can be obtained by varying either the arterial or venous tensions or both. Figure 2 indicates the position of the normal arterial and venous points on the stores diagram.

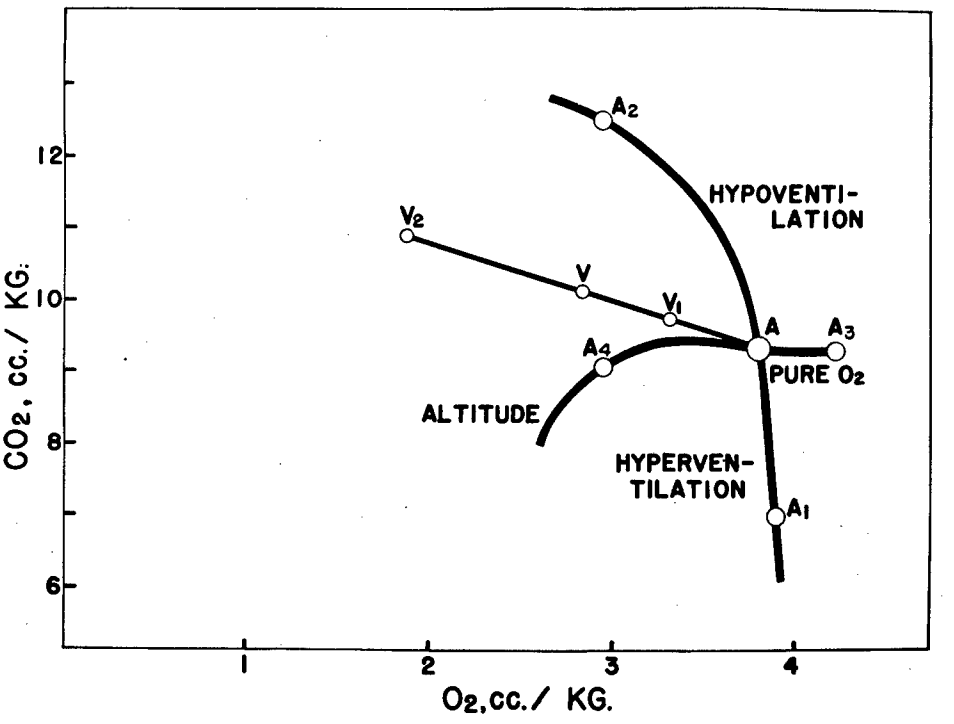


Figure 2 .

The solid lines represent the arterial point as it would travel from the normal point, A, during increasing hyperventilation, or hypoventilation, during acute exposure to increasing altitudes and with increasing fraction of O_2 in the inspired air. A_1 is the arterial point after the ventilation is doubled, A_2 when it is 50% of normal, A_3 when 100% O_2 is breathed and A_4 at an altitude of 18,000'. When the cardiac output only is changed, then the arterial point remains fixed at A but the normal venous point, V, moves to V_1 when the cardiac output doubles and to V_2 when it is reduced 50%.

Changes in cardiac output alone will result in changes in position of the venous point, the arterial point remaining fixed. Doubling the cardiac output brings the venous point nearer to the arterial and the O_2 stores of a 70 kg man would be increased by 100 cc, while his CO_2 stores would be decreased by 300 cc. Conversely, a decrease in cardiac output of 50% would decrease the O_2 stores by 220 cc and increase the CO_2 stores by 610 cc.

By changing the ventilation or inspired O_2 tension both arterial and venous must change, if we assume that the arterial-venous difference remains constant. In this case, a 70 kg man doubling his alveolar ventilation would increase the O_2 store by 20 cc and decrease the CO_2 store by 1600 cc. A 50% decrease in alveolar ventilation would decrease the oxygen by 260 cc, increasing the CO_2 by 4000 cc. By breathing pure oxygen, the same man could increase his oxygen store by 210 cc with an increase in CO_2 stores of 70 cc due to the Haldane effect. On acute ascent to an altitude of 18,000 ft. breathing air (or breathing 10% O_2 in nitrogen), he would lose 350 cc of O_2 and 1150 cc of CO_2.

DYNAMIC CHANGES OF GAS STORES - THE UNSTEADY STATE

Having considered the overall stores changes it is of interest now to consider the rates of stores adjustment. This brings us to the period of unsteady state, where in addition to normal gas exchange we have the additional influence of the gas stores exchange and we have the additional influence of the gas stores adjustment. While elimination of excess CO_2 from the stores will manifest itself in an additional release of CO_2 beyond the metabolic CO_2 output, excess O_2 stores are not released externally but are utilized by metabolism and reflected by a reduced external O_2 uptake. The reverse holds true for filling O_2 or CO_2 stores. Filling O_2 stores is shown by an apparent increase in O_2 metabolism, while filling the CO_2 stores reduces the CO_2 output.

It can be appreciated that if we consider the exchange ratio of the stores only, this will be a function of the relative magnitude of the adjustment of the two stores at any time. This R can be positive or negative and have values from 0 to infinity. Thus the overall gas exchange ratio, as measured either in the alveolar gas or in the expired gas, will be the result of the metabolic R (R_M) and the stores R (RS). The relationship of these three R values will be considered below.

The changes in O_2 and CO_2 tensions and stores during hyperventilation:

The simultaneous changes in alveolar O_2 and CO_2 following an abrupt increase in ventilation can conveniently be analyzed with the help of Figure 3. P_{A_I} represents the initial alveolar concentration plotted on the conventional O_2-CO_2 diagram. This value was obtained in an anesthetized dog following a controlled ventilation period of at least 30 minutes when the alveolar gas concentrations were no longer changing. This was assumed to represent a steady state with a R_M slightly above 0.8. With a sudden and constant increase in ventilation (ventilation being thereafter kept constant for the duration of the experiment), the alveolar point moves to the right along the pathway indicated. Each circle represents an interval of one minute for the first 7 minutes. The alveolar point then moves slowly down the line marked ∞ and finally comes to rest on the initial R_M line after forty minutes. At this final point, P_{A_F}, the new steady state has been achieved.

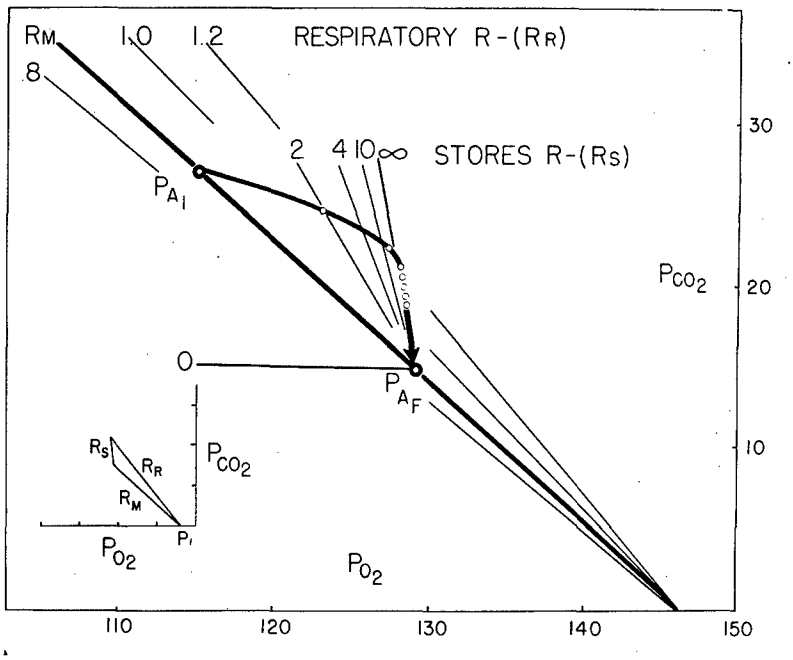


Figure 3

Changes in alveolar gas tensions during hyperventilation. P_{A_I} represents the initial gas point, P_{A_F} the final gas point, R_M is the metabolic gas exchange ratio, and R_S the stores gas exchange ratio. Each open dot represents a one-minute interval. Insert: interrelations between the metabolic gas exchange ratio, the stores gas exchange ratio, and the overall respiratory gas exchange ratio. For explanation, see text.

The overall R values at any time are indicated at the intersection of the family of R lines originating at the inspired air point. A very similar loop has been obtained when man suddenly hyperventilates at a constant rate (9).

It is now of interest to consider the stores changes independently of the metabolic gas exchange. During the whole unsteady state period, CO_2 was released from the stores and a very much smaller amount of O_2 was taken up by the stores. At the final alveolar point, P_{A_F}, this store exchange stopped. If there had been no stores whatsoever in the body, this point P_{A_F} would have been reached immediately upon the initiation of hyperventilation or at least within a few breaths as soon as the gases in the lung had readjusted.

If metabolism remains constant during the whole experiment, it can be stated that the difference between the final alveolar point, P_{A_F}, and the experimental alveolar point at any time is due to the stores exchange at that time. Given the final oxygen tension and the oxygen tension at a particular instant, one can calculate

the oxygen store exchange at that moment by applying the alveolar air equation (16), considering the final alveolar point as a relative "inspired gas point" for the stores. Similarly, the CO_2 stores exchange can be calculated, using the alveolar air equation and the CO_2 tensions.

Furthermore, the fact that the final alveolar gas composition serves as an "inspired gas point" for the stores, a grid of R lines can be drawn from that point, these representing the stores gas exchange ratio, R_S. These are indicated as R_S in Figure 3. It can be seen that after one minute of hyperventilation, the stores R is 2.0 and thereafter rapidly approaches ∞ . At this point the O_2 stores are satisfied, and only CO_2 stores are still exchanging.

In the insert of Figure 3 the relationships between the metabolic R, the stores R and the overall R has been shown. It can be seen that the overall R is the resultant of the interaction of R_S and R_M, being equal to the metabolic R, when there is no stores gas exchange. An equation for the interrelation has been derived but will not be presented here.

O_2 and CO_2 changes with time:

The gas stores of the body can be visualized as reservoirs the heights of which represent the partial gas pressure and the cross sections represent the slopes of the body dissociation curves. (For details see Figure 6 and the discussion). The CO_2 reservoir, for example, has a hole in the bottom, through which CO_2 escapes exactly at the rate at which it is supplied by the metabolism in the steady state. If this hole is enlarged (hyperventilation), the stored CO_2 should escape in a simple exponential fashion until the new steady state is reached. Changes in oxygen stores would also follow a similar exponential curve, as long as the walls of the reservoir are essentially parallel over the range considered.

If we now plot the experimental changes in alveolar gas tensions as percent of the difference between initial tension and final tension, on a log scale against time, the O_2 values group themselves along a straight line with a very steep slope, and the CO_2 values along another straight line with a lesser slope. This is independent of the magnitude and direction (hyperventilation, CO_2 inhalation, etc.) of the change.

Figure 4 gives the average curves for 17 experiments. The half time store change for CO_2 is 4.2 minutes with a standard error of .24 min., while the half time change for O_2 is 0.5 minute with a standard error of 0.3 minute. These lines correspond to the following equations when we assume 4.0 instead of 4.2 minutes for the half time CO_2 store in order to simplify the calculation. At any time, T, when I and F as subscripts represent the initial and final gas concentration, one can write

$$P_{Aco_{2_T}} - P_{Aco_{2_F}} = (P_{Aco_{2_I}} - P_{Aco_{2_F}}) \times 0.5^{\,T/4} \quad \text{-----} \quad (1)$$

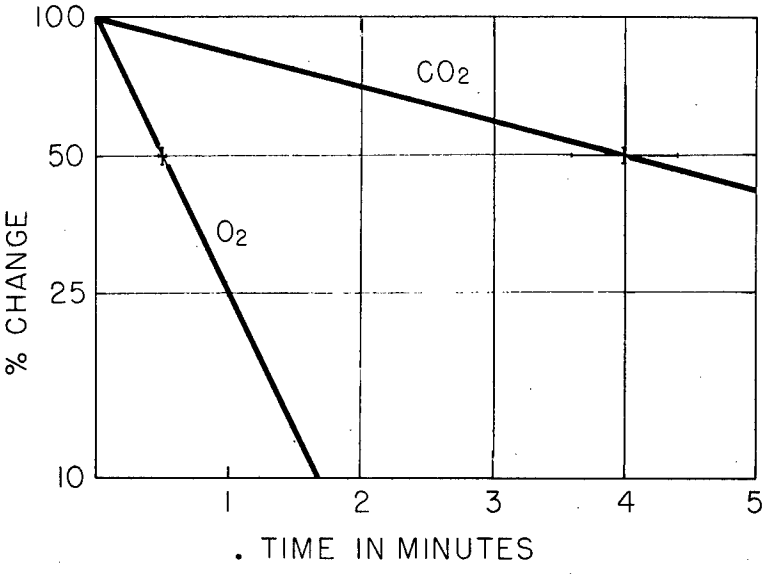


Figure 4

The percent change of dog gas stores is plotted on a logarithmic scale versus time. Gas store changes are induced by an acute change in ventilation. The horizontal and vertical bars represent 2 x standard error at 50% change.

$$\text{and } P_{Ao_{2_F}} - P_{Ao_{2_T}} = (P_{Ao_{2_F}} - P_{Ao_{2_I}}) \times 0.5^{\frac{2T}{}} \quad \text{-----} \quad (2)$$

By combining these two equations the relative rate changes in O_2 and CO_2 tension can be compared at any time as the stores approach their new equilibrium.

$$\left[\frac{P_{Aco_{2_T}} - P_{Aco_{2_F}}}{P_{Aco_{2_I}} - P_{Aco_{2_F}}}\right]^8 = \frac{P_{Ao_{2_F}} - P_{Ao_{2_T}}}{P_{Ao_{2_F}} - P_{Ao_{2_I}}} \quad \text{-----} \quad (3)$$

The CO_2 stores which are being eliminated at any time are equal to the total rate of CO_2 output, $\dot{V}co_{2_T}$, minus the rate of metabolic CO_2 output, $\dot{V}co_{2_M}$. At constant alveolar ventilation, $\dot{V}_A$, the $\dot{V}co_{2_T} = \dot{V}_A \times F_{Aco_{2_T}}$ and $\dot{V}co_{2_M} = \dot{V}_A \times F_{Aco_{2_F}}$, then

$$\dot{V}co_2 \text{ stores } T = \dot{V}_A \times (P_{Aco_{2_T}} - P_{Aco_{2_F}}) \times \frac{1}{B-47} \quad \text{-----} \quad (4)$$

and similarly

$$\dot{V}o_2 \text{ stores } T = \dot{V}_A \times (P_{Ao_{2_F}} - P_{Ao_{2_T}}) \times \frac{1}{B-47} \quad \text{-----} \quad (5)$$

and the stores exchange ratio is then at any time

$$R \text{ stores } T = \frac{P_{Aco_{2_T}} - P_{Aco_{2_F}}}{P_{Ao_{2_F}} - P_{Ao_{2_T}}} \quad \text{-----} \quad (6)$$

(For simplification the slight volume corrections for R have been omitted.) Equation 6, for example, indicates that as soon as the alveolar O_2 tension approaches its final values (after 2 minutes in experiment of Figure 3), the stores R approaches infinity.

Changes in O_2 and CO_2 tension and stores with increased cardiac output:

If the ventilation and metabolic rates are kept constant, then a change in cardiac output must alter the gas stores, since the venous and tissue reservoirs will change. Thus with an increase in blood flow, the O_2 stores will increase and the CO_2 stores decrease, since the venous blood is now nearer the arterial blood composition. The direction of the changes is similar to that found with hyperventilation, yet the relative difference between O_2 and CO_2 store changes is smaller than when ventilation only is altered (see Figure 2). Besides, since the alveolar ventilation is maintained constant, the initial and final steady state alveolar concentration must be identical.

In our experiments, an increase in cardiac output was obtained in dogs by the injection of 2×10^{-6} to 1×10^{-5} gm of epinephrin, injected through a venous drip. The ventilation was maintained constant throughout the experiment. A typical response curve is shown in Figure 5. There is a rapid drop of the alveolar oxygen tension associated with a slight rise in the carbon dioxide tension. After one to two minutes, the oxygen tension starts to rise and reaches its original level in about 5 minutes. The carbon dioxide continues to rise, reaching a maximum after four to five minutes, and then decreases very slowly, until the alveolar tensions are restored to what they were initially.

The two elements in this loop - temporary drop in oxygen tension and temporary rise in carbon dioxide tension - merely reflect the fact that the oxygen uptake and carbon dioxide output are increased at constant alveolar ventilation. Actually, during the very first part of the experiment, the venous blood composition remains unchanged, and the first part of the horizontal portion of the loop is due to shift of the alveolar point along the ventilation-perfusion line.

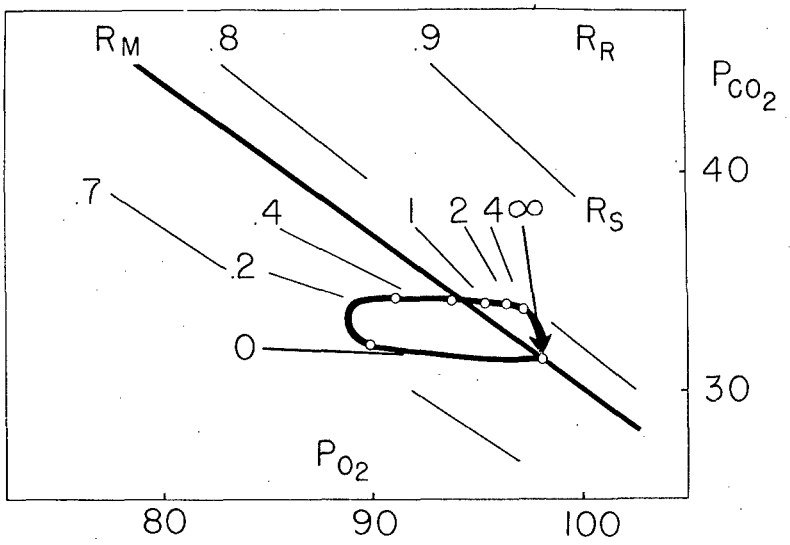


Figure 5

Changes in alveolar gas tensions during increase in cardiac output. R_M represents the metabolic gas exchange ratio, R_R the respiratory gas exchange ratio, and R_S the stores gas exchange ratio. For explanation, see text.

This simple analysis assumes that the increase in cardiac output is maintained throughout the experiment and that the metabolic Vo_2 is constant. There are, however, good reasons to doubt the validity of the first assumption. Return of the cardiac output to its initial value would restore the stores to their initial level, thereby decreasing the oxygen uptake and the carbon dioxide output. This should be reflected by a shift of the alveolar point downward and to the right (contributing to a faster return of the alveolar point to the initial value). If the decrease in cardiac output is gradual, the stores changes will be spread over a relatively long time and the influence on the alveolar gas composition will be too small to be detectable.

Changes in nitrogen stores:

Rahn and Fenn (17) have studied the changes in alveolar nitrogen tension during hyperventilation, hypoventilation and subsequent recovery. It is apparent from their data that when passing from one steady state to another the alveolar nitrogen tension must be permanently altered, and during the unsteady state differences of 30 mm can be temporarily obtained. This tension difference between alveoli and blood causes nitrogen to pass from one compartment to another. All gas exchange equations are based on the assumption that the number of molecules

of nitrogen inspired is equal to the number expired, and this is not true until the tissues have reached an equilibrium with the new alveolar nitrogen tension. The maximum transfer across the alveolar membrane can be computed from the solubility coefficient of N_2. With a cardiac output of 6 1/min., and a Δ Pn_2 of 40 mm., 4 cc/min. of N_2 can exchange. This volume is inconsequential in the total alveolar minute ventilation. When a subject is changed from room air to a mixture of 10% O_2 in N_2, the initial Δ Pn_2 is 70 mm., and a maximum transfer of 7 cc N_2 min. can be temporarily expected. In a 7 1/min. alveolar ventilation this concentration would be .1% and of little consequence. However, when changing from air to pure O_2, the initial N_2 elimination can be of considerable consequence as has been pointed out by others.

DISCUSSION

The foregoing analyses allow us to visualize the various gas stores of the body as individual fluid reservoirs of various cross-sectional dimensions filled with O_2 or CO_2 to different levels. These compartments are connected in series by pipes which transport the O_2 and CO_2 to their respective destinations (Figure 6). The shape of each reservoir is determined by the gas dissociation curve of the particular tissue while the height of fluid level in each reservoir is determined by the volume flow through the pipe (the O_2 uptake or CO_2 output) and the resistance offered by the pipe or by the pressure. It seems pertinent to discuss this model in more detail since it demonstrates in a simple manner all the aspects of the foregoing studies and provides a basis for the construction of simple working models.

In the upper left hand corner of Figure 6 we have an infinite reservoir of O_2 filled to a height of 150 mm Hg, the $P_{I_{O_2}}$ in air. This represents the maximum available pressure head of O_2. The tissue metabolism is represented at the right hand side by a pump (labelled metabolism) which withdraws this O_2 at a constant rate, the $\dot{V}o_2$. The flow through the interconnecting pipe is therefore equal to $\dot{V}o_2$. The tissue metabolism at the same time discharges $\dot{V}co_2$ (equal to $\dot{V}o_2 \times R_M$) into the tissue CO_2 stores reservoir filled to a height of 50 mm Hg. From there it finds its way eventually to the room air. We thus have 2 pipes one having a flow of $\dot{V}o_2$, the other a flow of $\dot{V}co_2$ and each communicating along its way with O_2 and CO_2 reservoirs, respectively.

When the $\dot{V}o_2$ entering the pipe on the left is equal to the $\dot{V}o_2$ entering the metabolic pump and the $\dot{V}co_2$ leaving it equals the $\dot{V}co_2$ outflow on the left, the levels of all the stores must be constant and we have a "steady state". One may easily appreciate that by changing any one of the resistances the stores level will be altered and on "unsteady state" will prevail until a new permanent level has been attained to compensate for the altered resistance - the "new steady state."

In this model (Figure 6) it will be seen that the major resistance is offered by the ventilation (R_1,R_6) and by the cardiac output (R_2,R_5) and that they essentially control the volumes of the gas stores. Changes in the ventilation will affect all the

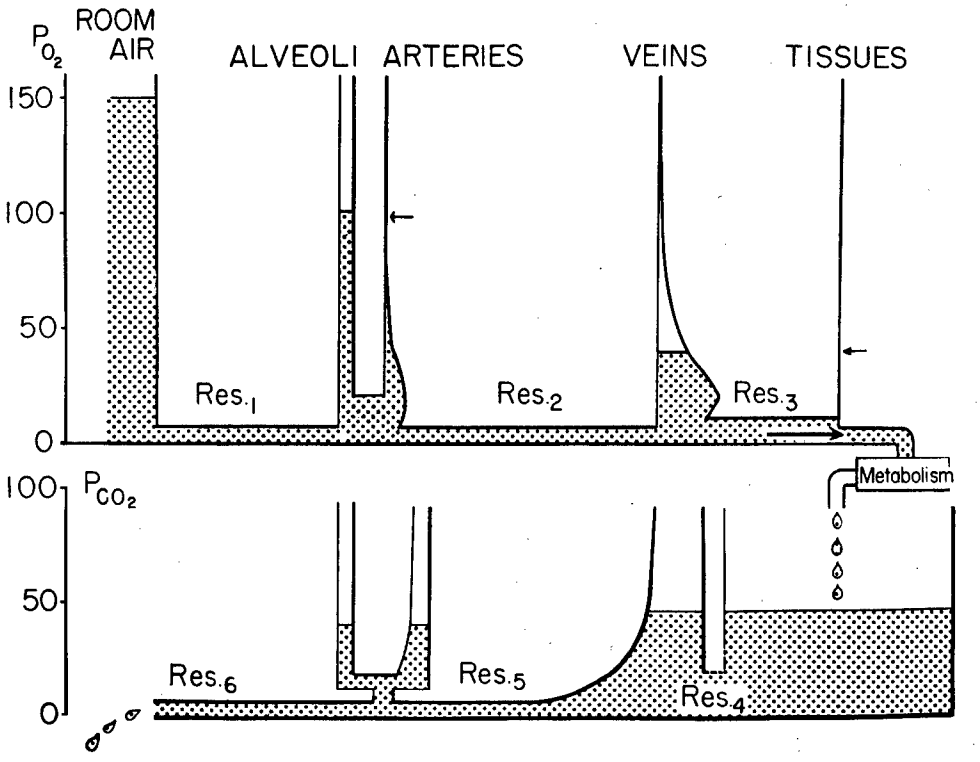


Figure 6

Model illustrating the different compartments of the body gas stores. Upper half is O_2 model, lower half CO_2 model. Scale on the left represents tensions, in mm Hg (for details, see text).

reservoirs while changes in cardiac output will permanently affect only the venous and tissue reservoirs. If the chief aim of the gas transport system is to provide an adequate O_2 or CO_2 tension at tissues or venous level, then the sum of the resistance to O_2 flow and CO_2 flow is important and the cardiac output and alveolar ventilation can adjust themselves in various ways to meet this goal. The relative importance of each in altering the resistances to O_2 and CO_2 flow is discussed below.

The shape of the gas reservoirs:

The relative size of the O_2 and CO_2 stores can be readily appreciated in Figure 6. The tissue CO_2 store is the largest and the tissue O_2 store the smallest. The muscle myoglobin O_2 store has been omitted. The width of the reservoirs has been calculated from the slope of the dissociation curve and represents cc of gas which will be found in the amount of blood or tissue present in 1 kg body weight/mm pressure change at a particular partial pressure. For example, between a Po_2 of

40 and 41 mm the slope of the O_2 dissociation curve is 0.22 cc/100 cc blood/mm. Since 1 kg body weight contains 59 cc of venous blood, the calculated width of the reservoir at the Po_2 of 40 is (0.22 x .58) or 0.13 cc O_2/kg body weight/mm. The integrated surface area of such reservoir (as drawn) thus represents the total gas store. The tissue O_2 store (omitting the myoglobin) is a straight cylinder having only dissolved O_2. The tissue CO_2 store cylinder has also been drawn with parallel sides over the Pco_2 range of 20-50 since our experimental data was insufficient to differentiate a change in the slope of the tissue dissociation curve. The alveolar gas stores have a constant slope of .05 cc/mm/kg body weight at atmospheric pressure, assuming an alveolar volume of 3000 cc for a 70 kg man.

The resistance between reservoirs:

With a constant flow, $\dot{V}o_2$, through the pipe the resistance to the O_2 flow is $\Delta P/\dot{V}o_2$ and the resistance to the CO_2 flow will be $\Delta P/\dot{V}co_2$. One can now substitute the equations for alveolar ventilation and cardiac output and arrive at general resistance equations which express for this type of volume model the resistance as inverse functions of ventilation and blood flow. This has been done in Table II. The absolute values for normal conditions have also been calculated when for O_2 the $P_I = 150$, P_A and $P_a = 100$, $P_{\bar{V}} = 40$; for CO_2, $P_{\bar{V}} = 45$, P_a and $P_A = 40$; $\dot{V}o_2 = 300$; $\dot{V}co_2 = 240$; and $\dot{V}_A = 5.2$. These resistances are most conveniently expressed as the pressure drop in mm Hg/100 cc of O_2 (or CO_2) flow/ minute.

This model is unphysiological in the sense that it sidesteps the diffusion resistance encountered at the capillary bed of the lesser and greater circulation ($R_{3,4}$). This resistance can be defined as $\dot{V}o_2$/mean (alveolar-capillary) O_2 difference for the lesser circulation, for example, as developed by Fenn (18). In this volume model, however, where the venous blood does not return to the lung, only the final end-capillary O_2 difference is of consequence and this has been assumed to be negligible. Similarly, for the greater circulation it is assumed that the tissuesequilibrate with the venous gas tension. Thus, we are left with only 2 major resistances, the ventilation and the cardiac output which control the volume of the various gas stores in the body.

Table II indicates that the resistance offered by the ventilation is the same for the O_2 and CO_2 flow. (Actually the O_2 resistance differs very slightly if the proper corrections for P_{Io_2} is made in the original formula). The ventilatory resistance in our case is 16.7 mm, i.e., for a $\dot{V}o_2$ of 300 cc, the pressure drop would be 16.7 x 3 or 50 mm between the inspired and alveolar O_2 and 16.7 x 2.4 or 40 mm for the CO_2 differences. By doubling the ventilation (V_A x 2, Table II) the resistance would be halved to 8.4.

Although the cardiac output is the same for the transport of both gases, the resistance offered to the O_2 is 10 x greater than that for the CO_2 transport. This is due to the slope constant, S, which for O_2 is 10 x smaller and therefore increases the resistance 10 fold. If one considers the total resistance for both

TABLE II

Derivation of equations for the resistance to gas flow. On the right absolute values have been derived for normal conditions and when either the alveolar ventilation or the cardiac output is doubled.

V_A = 1/min. (B.T.P.S.); Q = cardiac output 1/min; S_{O_2} and S_{CO_2} designate the mean slopes, respectively, of the O_2 and CO_2 dissociation curves between $P_{\bar{V}}$ and P_a expressed as cc of gas / liter blood / 1 mm pressure difference.

Basic Equation for Derivation of Resistance	General Resistance Equation	Normal Values	Hyper-ventilation V_A x 2	Increased Blood Flow Q x 2
O_2 Transport				
Res. 1 $V_A = \frac{V_{O_2} \cdot .864}{P_{I_{O_2}} - P_{A_{O_2}}}$	$R = \frac{.864}{V_A} \times 100$	16.7	8.4	16.7
Res. 2 $Q = \frac{V_{O_2}}{(Pa_{O_2} - P\bar{v}_{O_2})\, S_{O_2}}$	$R = \frac{1}{Q \cdot S_{O_2}} \times 100$	20.0	30.0	16.0
Total Res.		36.7	38.4	32.7
CO_2 Transport				
Res. 6 $V_A = \frac{V_{CO_2} \cdot .864}{P_{A_{CO_2}} - P_{I_{CO_2}}}$	$R = \frac{.864}{V_A} \times 100$	16.7	8.4	16.7
Res. 5 $Q = \frac{V_{CO_2}}{P\bar{v}_{CO_2} - Pa_{CO_2}}$	$R = \frac{1}{Q \cdot S_{CO_2}} \times 100$	2.1	1.3	1.3
Total Res.		18.8	9.7	17.0

gases (Table II), it can be seen that ventilation offers 90% of the resistance to the CO_2 flow but only 45% of the total resistance to the O_2 flow. By doubling the ventilation (V_A x 2, Table II) the total CO_2 resistance is halved, but the total resistance to O_2 is nearly unaltered or actually increases. The reason the O_2 resistance remains constant is due to the decrease in the slope constant which compensates for the reduced ventilation resistance. This reemphasizes the importance of ventilation in the regulation of venous-tissue Pco_2 and pH.

On the other hand the most effective way to reduce the resistance to O_2 flow is to increase the cardiac output. By doubling it, however, (Q x 2, Table II) only a small reduction can be achieved. The increased cardiac output has practically no effect on the total CO_2 resistance. Thus under these various conditions breathing air it will be seen that the venous Po_2 remains relatively stable but that the venous Pco_2 is primarily influenced by the ventilation and little affected by the blood flow rate. Similar deductions have recently been presented elsewhere (19).

The changes in gas stores:

So far we have dealt with the detailed dimension of a model which with certain reservations allows us to duplicate the in vivo conditions. It is obvious that we may now vary the conditions in Figure 6 in many ways in order to vary the gas store content. There are four principal methods, namely: (1) decreasing the level of the inspired O_2 reservoir, i.e., anoxia; (2) increasing the inspired CO_2 level by building up a CO_2 reservoir at the expired end, i.e., CO_2 breathing; (3) changing Res. 1 and 6 by altering the alveolar ventilation and altering Res. 2 and 5 by changing the cardiac output.

Although any one method is sufficient, all of them would come into play, for example, if a low O_2-CO_2 mixture were inspired. Each condition has its special effect and for each condition its effect must be evaluated. It is of interest here only to consider 3 particular conditions to serve as examples.

Hyperventilation:

In such a case the alveolar Po_2 and arterial Po_2 will increase, for example, 20 mm, but the store effect is very small. The venous O_2 reservoir will not increase in volume any more than the arterial reservoir if the cardiac output remains constant. The overall increase in O_2 store is therefore negligible. The CO_2 stores on the other hand will all fall about 20 mm and release a considerable amount of CO_2.

Increasing the cardiac output:

This is comparable to decreasing Res. 2 and Res. 5. If we double the flow, the Po_2 in the venous and tissue O_2 reservoir will rise about 15 mm and lower the arterial and alveolar reservoir temporarily since the ventilation (or Res. 1) has been kept constant. When the venous reservoir has been filled, the alveolar-

arterial reservoirs will return to their former level. On the CO_2 model the venous-tissue reservoir will only fall 3 mm and produce a temporary rise in the arterial-alveolar CO_2 reservoir.

Breath holding:

B^v sudden occlusion of the inlet and outlet to the model (infinite resistance of Res. 1 and 6) the metabolism pump will drain quickly the alveolar and arterial O_2 reservoir while the alveolar-arterial CO_2 reservoir will rise comparatively little since most of the metabolic CO_2 is absorbed by the large tissue-venous reservoir. These large discrepancies between O_2 and CO_2 changes in the alveoli during breath holding are well established in the literature.

A simple working model for CO_2 stores:

The CO_2 stores model of Figure 6 can be much simplified for practical demonstration purposes. Only 2 cylinders are needed which have a relative diameter of 3:1. The larger cylinder represents the combined venous-tissue stores since the resistance between them is negligible. The parallel walls of the cylinder represent the theoretical shape fairly well when the level in the reservoir is maintained above 25 mm. The smaller cylinder represents the combined arterial-alveolar CO_2 stores. Water flows into the large cylinder at a constant rate, the $\dot{V}co_2$, and leaves at the opposite end at the same rate. By adjusting the resistances of the interconnecting tubes one can simulate various rates of alveolar ventilation and cardiac output. The effects of inspiring CO_2 can be simply accomplished by raising the outflow tube to the height of the inspired CO_2 tension. With this model all the various CO_2 stores changes can be easily demonstrated.

General conclusion:

The combined O_2-CO_2 stores model is at best a simplification of the overall gas transport of the body. The interest of this model resides principally in a single demonstration of the resistances offered to the transport of gas to and from the tissues and how they control the total gas stores in various compartments. By varying the environmental gas tensions or any of the resistances one will necessarily alter the gas stores which in turn upset the normal O_2 and CO_2 flow when measured by conventional methods. The relative magnitude of the store changes in the various compartments can be readily visualized for any given new condition and the qualitative changes and direction the overall exchange ratio will assume during the unsteady state can be predicted.

It is of interest to point out that the alveolar or arterial gas tensions can be considered essentially as a manometer interposed between two major resistances. The O_2 manometer gives us relatively little information concerning the tissue-venous O_2 tensions since the resistance offered by the cardiac output is at least 50% or more of the total resistance of the O_2 transport system (breathing air or

higher O_2 concentrations). On the other hand the CO_2 manometer serves as a rather reliable index of the tissue-venous CO_2 and pH since more than 85% of the total resistance to CO_2 flow occurs as a function of the alveolar ventilation.

SUMMARY

In order to predict the changes in the respiratory gas exchange during the unsteady state it becomes necessary to know how the ventilation and the cardiac output control the O_2 and CO_2 stores of the body. The changes in body CO_2 stores were obtained experimentally in dogs and are 1.5 cc/kg/mm CO_2 change. Of this 1.02 cc comes from the tissues to the exclusion of blood. Readjustments of the O_2 stores are faster than that for the CO_2 stores. With changes in alveolar ventilation these readjustments proceed at an exponential fashion, 50% change being obtained in .5 minute for O_2 stores and 4 minutes for CO_2 stores.

From these data overall changes in body stores between different steady states can be calculated as well as their effect on the respiratory gas exchange during the unsteady state. The influence of stores readjustment on the respiratory gas exchange ratio was determined during changes in ventilation or in cardiac output.

A model based on the experimental data can be constructed and allows visualization of the integrated mechanism of gas transport as well as the different factors which influence gas transport and storage.

REFERENCES

1. Best, C. H. and N. B. Taylor Physiological Basis of Medical Practice Williams and Wilkins, publishers.
2. Millikan, G. A. Physiological Reviews 19:503, 1939.
3. Brocklehurst, R. J. and Y. Henderson J. Biol. Chem. 72: 665, 1927.
4. Shaw, L. A. Am. J. Physiol. 85: 158, 1928.
5. Irving, L., J. K. W. Ferguson and F. B. Plewes J. Physiol. 69: 113, 1930.
6. Shaw, L. A. and A. C. Moser Am. J. Physiol. 100: 122, 1932.
7. Adolph, E. F., F. D. Nance and M. S. Shiling Am. J. Physiol. 87: 532, 1929.
8. Freeman, F. H. and W. O. Fenn Am. J. Physiol. 174: 422, 1953.
9. Rahn, H. and A. B. Otis J. Appl. Physiol. 1: 717, 1949.
10. Gregersen, M. I. and W. S. Root Am. J. Physiol. 148: 1, 1947.
11. Rahn, H. and H. T. Bahnson J. Appl. Physiol. 6: 105, 1953.

12. Krogh, A. The Anatomy and Physiology of the Capillaries, New Haven, 1929.

13. Irving, L. H., C. Foster and J. K. W. Ferguson J. Biol. Chem. 95: 95, 1932.

14. Jones, H. B. Decompression Sickness, W. B; Saunders Co., Philadelphia, 1951.

15. Dill, D. B., H. T. Edwards and W. V. Consolazio J. Biol. Chem. 118: 635, 1932.

16. Fenn, W. O., H. Rahn and A. B. Otis Am. J. Physiol. 146: 637, 1946.

17. Rahn, H. and W. O. Fenn Air Force Technical Report 53-255, 1953.

18. Fenn, W. O. Personal communication.

19. Suskind, M. and H. Rahn, J. Appl. Physiol. (In press).

THE OXYGEN-CARBON DIOXIDE DIAGRAM FOR ALVEOLAR AIR

by

Leon E. Farhi and Wallace O. Fenn

The oxygen-carbon dioxide diagram was designed by Fenn, Rahn and Otis (1) for the graphic analysis of problems concerning the composition of the alveolar air. Since its publication this diagram has been rather widely used by other investigators to represent different respiratory situations. Further consideration of the theoretical basis for this diagram has indicated that the original presentation was incomplete, especially in cases where the inspired air contains some carbon dioxide. In this paper we wish, therefore, to present this diagram in a somewhat more generalized form and to indicate incidentally some short-cut methods for drawing the exchange ratio or R lines and the isoventilation lines.

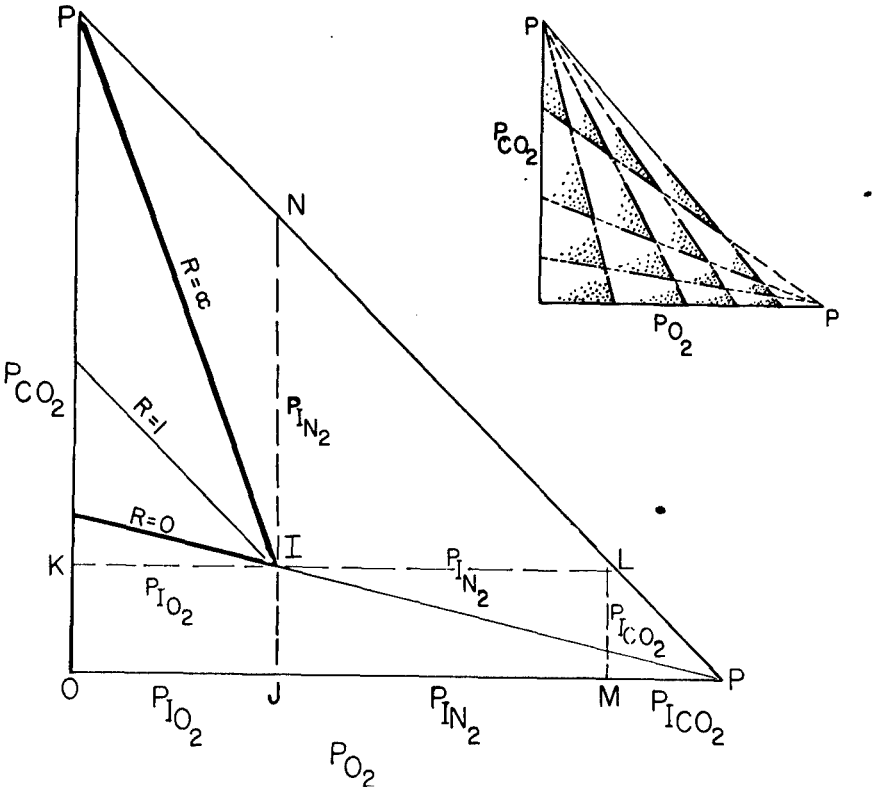


Figure 1

In the generalized diagram Po_2 is plotted horizontally against Pco_2 vertically as in Figure 1. On each axis a point P can be fixed representing P_B-47 where P_B is the barometric pressure. These two points are joined by a straight line, PP. In the triangle so formed any gas mixture, I, containing O_2, CO_2, and N_2 can be plotted by its CO_2 and O_2 tensions. Horizontal and vertical lines are drawn through I, cutting the PP line at N and L, respectively. The vertical distance from L to the O_2 axis, LM, which is equal to the CO_2 tension of the gas, is in turn equal to the distance MP. Since the distance OP represents the total tension, while OJ represents the oxygen tension, by difference one obtains $JM = P_{In_2} = IL = IN$. Thus in any plot such as Figure 1 either the vertical or the horizontal distances from any point to the PP line represent the nitrogen tension of that point. This relationship has already been pointed out by Rahn and Fenn (2) but the following method of drawing the R = O and the R = ∞ lines was not previously described in detail.

The R = O line:

When R = O the carbon dioxide output is nil and both inspired nitrogen and inspired carbon dioxide are concentrated by equal percentages as oxygen is withdrawn so that the ratio of Pco_2 to Pn_2 remains constant. The R = O line is therefore drawn from P on the O_2 axis through I. As the point I moves along this line, the ratio of IJ (or Pco_2) to IN (or Pn_2) remains constant.

The R = ∞ line:

In this case there is no oxygen uptake and the changes in gas tension are due to dilution by the added CO_2 of both oxygen and nitrogen in equal percentages. The R = ∞ line is therefore drawn from P on the CO_2 axis through I. As the point I moves along this line the ratio of IK (or Po_2) to IL (or Pn_2) remains constant. For convenience in drawing these lines on charts which do not include points P, it may be noted that the intercept of the R = O line on the CO_2 axis =

$$\frac{P \times P_{Ico_2}}{P - P_{Io_2}} = \frac{P_{Ico_2}}{1 - F_{Io_2}}$$

and the intercept of the R = ∞ line on the O_2 axis =

$$\frac{P \times P_{Io_2}}{P - P_{Ico_2}} = \frac{P_{Io_2}}{1 - F_{Ico_2}}$$

where F_I represents the fraction of the gas in the inspired air.

The R = 1 line:

The R = 1 line is drawn through I with a slope of -1 (45 degree angle) since the quantity of oxygen withdrawn is equal to the quantity of CO_2 added.

In the insert in Figure 1 is drawn a similar O_2-CO_2 diagram containing a

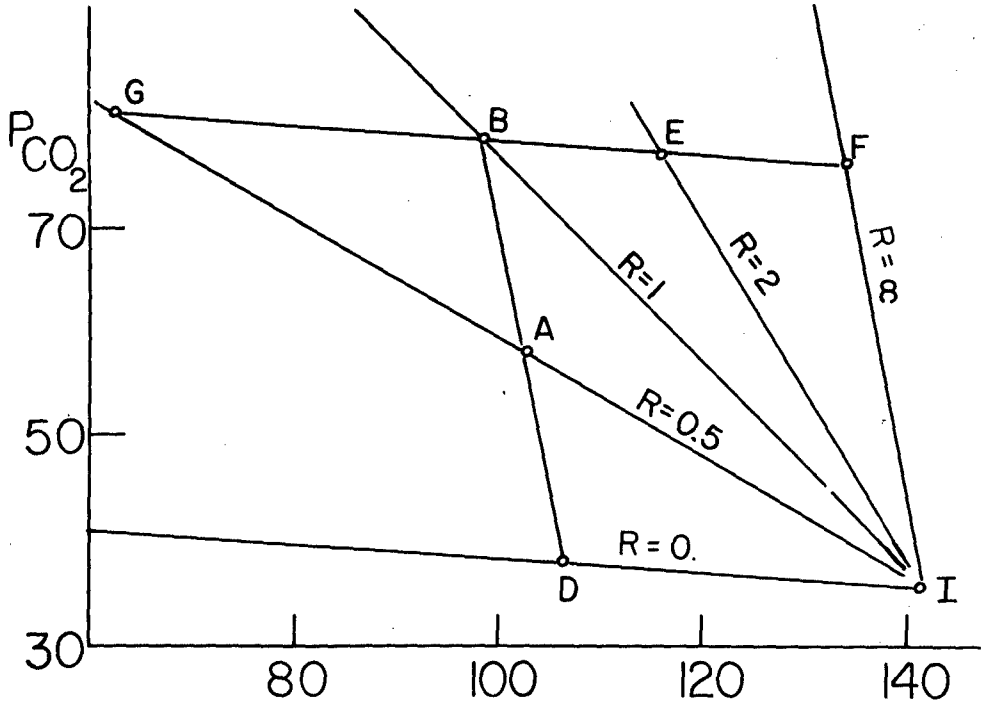


Figure 2

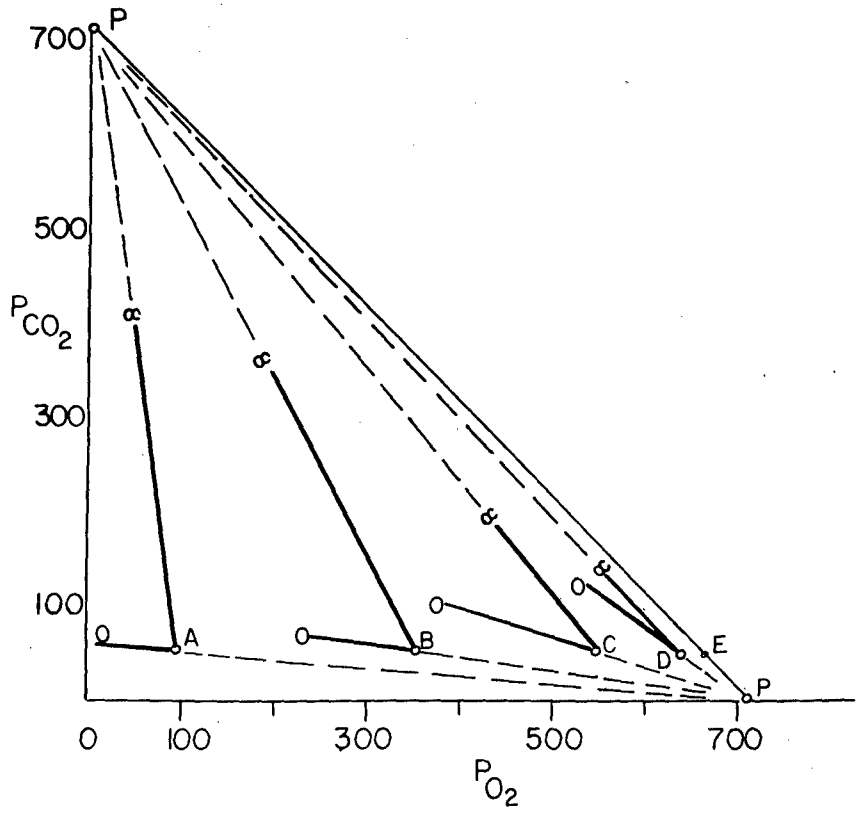


Figure 3

number of R = O and R = ∞ lines. Intersections of any two of these lines may be considered as representing a possible inspired air point. For each such point the shaded area represents the region of the diagram which would be applicable to the composition of the alveolar air. Within this shaded area the CO_2 concentration is always greater and the O_2 concentration is always less than it is at the inspired air point.

The construction of other R lines of values greater or less than 1 is best shown on Figure 2 which represents a part of Figure 1 on a larger scale. In this case the inspired air point I represents 5% CO_2 in air where P_{CO_2} = 35.6, P_{O_2} = 142., and P_B-47 = 713. The R = ∞ line is drawn to the point on the CO_2 axis where the CO_2 tension = 713 and the R = O line is drawn through I to the point on the O_2 axis where the P_{O_2} = 713. The R = 1 line is drawn through I at 45 degrees, or a slope of -1. From any point B on the R = 1 line draw BD and BF parallel, respectively, to the R = ∞ and the R = O lines. On this diagram the R = 0.5 line can be shown mathematically to pass through point A which bisects BD and to intersect the extension of BF at G where GB = BF. Likewise the R = 2 line can be shown to pass through point E which bisects BF and if extended would intersect the extension of DB at a distance above B equal to BD. Further, the R = 4 line bisects EF and the R = 0.25 line bisects AD. The R = .75 line bisects BA but the R = 1.5 line does not bisect BE. Instead it lies at a distance from equal to 1/1.5 of BF. More generally it can be said that the R = X line will intersect GF at point X such that BF/FX = R and that the R = Y line will intersect BD at point Y such that DY/DB = R.

The effect on the R lines of changing the fraction of oxygen in the inspired air is shown in Figure 3. The diagram represents the situation for a barometric pressure of 760 mm. Five inspired air points, A, B, C, D, and E, are represented at a P_{ICO_2} = 50 mm but with increasing oxygen fractions and diminishing concentrations of nitrogen. The R = O and R = ∞ lines are drawn for each inspired air point through points P on the O_2 and CO_2 axes, respectively. It is evident that as the O_2 fraction increases from A to E the two R lines approach one another until at point E, where there is no longer any nitrogen in the inspired air, all the R lines coincide with the PP line. Similarly, Fenn, Rahn and Otis (1) have shown that the R lines converge progressively as the oxygen fraction of the inspired air increases.

In theory this same diagram applies to the case where air is inhaled with a P_{CO_2} of 0.3 mm as in air, but if the P_{CO_2} of the inspired air is actually zero, the R = O line will always coincide with the O_2 axis regardless of the amount of nitrogen present. When both nitrogen and carbon dioxide are (mathematically) absent from the inspired air, the R = O line must coincide with both the PP and the OP lines simultaneously and is therefore confined to a point. This is merely another way of saying that if no CO_2 is given out in the lungs there can be none in the alveolar air if it is absent from the inspired air.

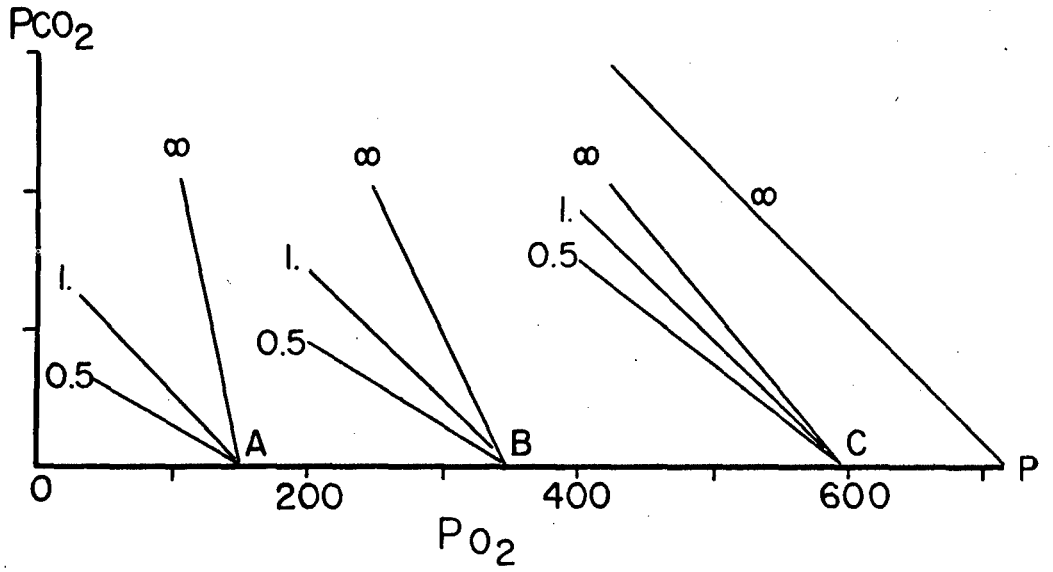


Figure 4

Similarly in Figure 4 four inspired gas points, A, B, C, and P are illustrated. Here again the fraction of oxygen in the inspired gas increases at a constant barometric pressure, but the inspired CO_2 remains zero so that the R = O line coincides always with the O_2 axis. Here, in general, it is true that the R lines tend to fold up until at P where pure oxygen is inhaled all the R lines coincide with the PP or R = 1 line. However, the angle between the R = 0.5 line and the R = O line or base line increases as the inspired air point moves toward P. Thus there is always some R value below which the angles between adjacent R lines are increasing and above which they are decreasing for the interval between R = 1 and R = O remains constant. The higher the inspired oxygen fraction, the lower the R value below which the R intervals increase with further increase in oxygen fraction.

Alveolar isoventilation lines:

Fenn, Rahn and Otis (1) described two sets of isoventilation lines which could be drawn on an O_2-CO_2 diagram, the $\dot{V}_A/\dot{V}o_2$ lines where the rate of oxygen consumption is constant and the $\dot{V}_A/\dot{V}co_2$ lines where the rate of carbon dioxide is held constant. In the original description of these lines it was stated that the ventilation lines for O_2 were always parallel to the R = CC line. The fact that the isoventilation lines for CO_2 are always parallel to the R = O line was not explicitly stated, although it is apparent from their Figure 8. It is important therefore to make a somewhat more generalized presentation of this subject.

In the paper of Fenn, et al (1) equations 18 and 22 describe the alveolar ventilation in terms of inspired and alveolar gas tensions and oxygen uptake (eq. 18) or carbon dioxide output (eq. 22). These equations are completely general and cover all cases with or without CO_2 in the inspired air. Since this presentation is largely graphic, we shall not repeat here the derivation of these equations but start with a modification of equation 13 of the former paper which expresses the $\dot{V}_A/\dot{V}_{O_2}$ ratios in terms of inspired and alveolar CO_2 tensions for the special case when R = 1

$$\frac{\dot{V}_A}{\dot{V}_{O_2}} = \frac{.864(R - F_{I_{CO_2}}(1-R))}{P_{A_{CO_2}} - P_{I_{CO_2}}} \quad \text{and (when R = 1)} = \frac{.863}{P_{A_{CO_2}} - P_{I_{CO_2}}}$$

This equation says that the ratio of alveolar ventilation ($\dot{V}_A$ in liters BTPS per min.) to O_2 intake ($\dot{V}_{O_2}$ in ml per min. STPD) is equal to 0.02 when the alveolar CO_2 tension ($P_{A_{CO_2}}$) is 43.2 mm greater than the inspired CO_2 tension ($P_{I_{CO_2}}$) and R = 1. The constant $.863 = \frac{310 \times 760}{273 \times 1000}$ and serves to express ventilation and O_2 uptake in conventional units. With this information the ventilation lines can be drawn on Figure 5 which represents a further elaboration of the case illustrated in Figure 2. For this purpose a point B is found on the R = 1 diagonal which has a

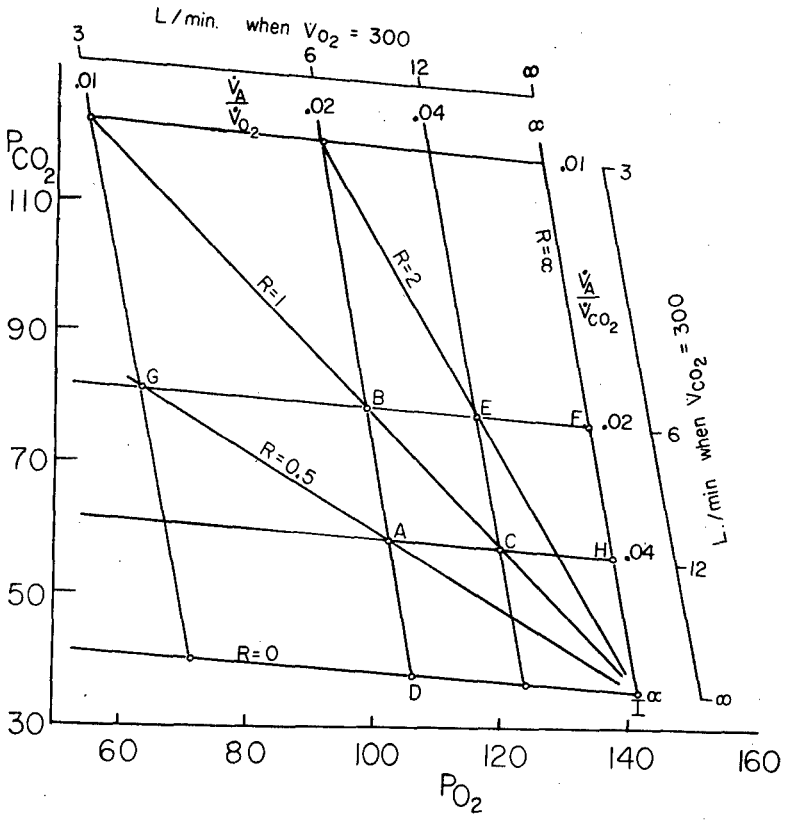


Figure 5

P_{CO_2} = 43.2 + P_{ICO_2} or 43.2 + 35.6 = 78.8 mm. A line drawn through B parallel to the R = CC line represents a $\dot{V}_A/\dot{V}_{O_2}$ ratio of 0.02 or an alveolar ventilation of 300 x 0.02 or 6 liters per minute for a rate of oxygen uptake of 300 ml per minute. To construct other isoventilation lines draw BF parallel to the R = O line. Where the R = 2 line cuts BF draw another line parallel to R = CC. This is the isoventilation line for $\dot{V}_A/\dot{V}_{O_2}$ = .02 x R = .04. In general where any R line = R' cuts BF or its extension to the CO_2 axis a ventilation line can be drawn parallel to the R = CC line which will represent a $\dot{V}_A/\dot{V}_{O_2}$ ratio = .02R' or an alveolar ventilation of 300 x .02R' = 6R' for an oxygen uptake of 300 ml per minute. If the ratio of alveolar ventilation to oxygen intake is known for a given subject, his alveolar point must lie somewhere along the appropriate $\dot{V}_A/\dot{V}_{O_2}$ line, its position on that line depending only on the exchange ratio or the rate of CO_2 output.

It is now possible to draw the isoventilation lines for CO_2 or the $\dot{V}_A/\dot{V}_{CO_2}$ lines, since $\dot{V}_{CO_2}$ = R x $\dot{V}_{O_2}$ and therefore $\dot{V}_A/\dot{V}_{CO_2}$ = $\dot{V}_A/\dot{V}_{O_2}$ divided by R. Thus at point B, $\dot{V}_A/\dot{V}_{CO_2}$ = .02/1 = .02 and at point E it is 0.04/2 = .02. Thus the line GBF is the isoventilation line for $\dot{V}_A/V_{CO_2}$ = .02 or an alveolar ventilation of 6 liters per minute for 300 ml of CO_2 output per minute. Similarly, at C where the .04 ventilation-oxygen line for .04 intersects the R = 1 line the $\dot{V}_A/\dot{V}_{CO_2}$ value is also .04 as it is at point A where .02/0.5 = .04. Thus the line AH represents the $\dot{V}_A/\dot{V}_{CO_2}$ = .04 line. By similar considerations the .01 line can be drawn. The $\dot{V}_A$ = CC line for constant CO_2 output is identical with the R = O line.

The real meaning and usefulness of the O_2-CO_2 diagram can be made clear by considering any point such as B on the diagram of Figure 2. Five different straight lines can be considered as intersecting at this point to determine its location; these are (1) the horizontal P_{CO_2} ordinates, (2) the vertical P_{O_2} abscissae, (3) the R = 1 line, (4) the $\dot{V}_A/\dot{V}_{O_2}$ ratio lines, (5) the $\dot{V}_A/\dot{V}_{CO_2}$ ratio lines. In addition we could draw two more lines through any such point, i.e., (6) the constant HbO_2 saturation lines, and (7) the constant blood CO_2 content lines. Thus it can be said that once the barometric pressure and composition of the inspired air is known any two of the seven quantities named above will determine the composition of the alveolar air and, furthermore, once this alveolar point is identified on the diagram, all the other five quantities are also known. The unique characteristic of the O_2-CO_2 diagram in this connection is that all of these lines are straight with the exception of the HbO_2 saturation lines and (at low oxygen tensions) the CO_2 content lines. Moreover, as shown in this paper all these lines are easily drawn without the use of complicated equations and calculations once the inspired point and the barometric pressure are known.

The nitrogen-carbon dioxide diagram:

Since all three of the respiratory gases can be represented on the O_2-CO_2 diagram, it is obvious that it does not matter which of the three are selected for the coordinates of the diagram. Thus in Figure 6 we have plotted P_{CO_2} vertically and P_{N_2} horizontally, the P_{O_2} values being implicit. I represents the inspired air

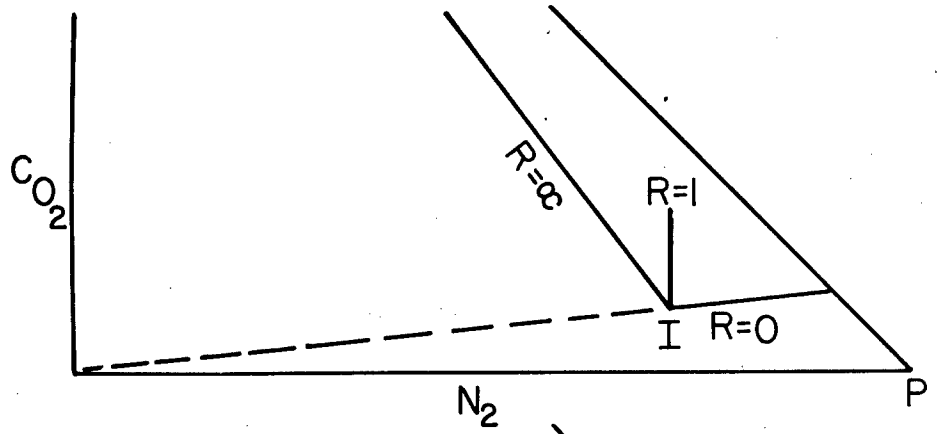


Figure 6

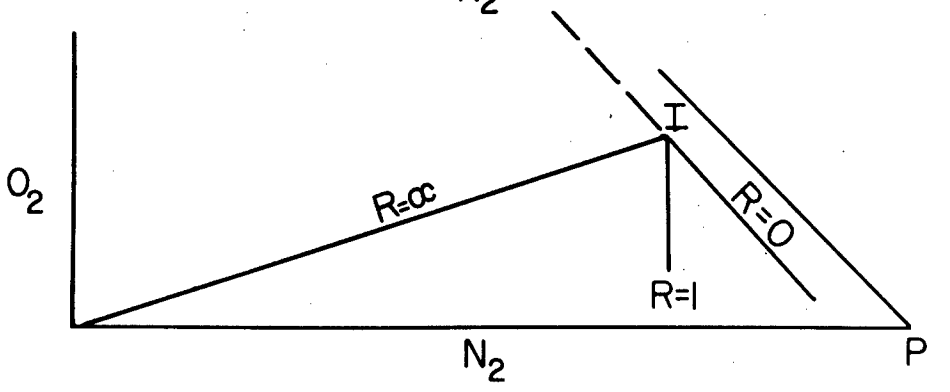


Figure 7

point where Pco_2 = 50. When R = O the withdrawal of oxygen leaves Pco_2 and Pn_2 in a constant ratio so the R = O line must be drawn from I through the origin. The R = ∞ line involves the addition of CO_2 without withdrawal of oxygen and this dilutes the N_2 and O_2 equally. The R = ∞ line is therefore drawn through I to the point P on the CO_2 axis because at every point on such a line the horizontal distances to the CO_2 axis and to the PP line (Pn_2 and Po_2, respectively) remain in a constant ratio. The R = 1 line is drawn vertically from I. The vertical distance from I to the PP line is the Po_2 and along this line the Po_2 diminishes 1 mm for every mm increase in Pco_2.

The nitrogen-oxygen diagram:

Similarly in Figure 7 we have plotted Po_2 vertically against Pn_2 horizontally. The inspired air point I is the same as that represented in Figure 5, and the three special R lines are drawn according to the same principles as before.

Intermediate R lines can be drawn on both these diagrams by the same principles as those illustrated in Figure 2. Through any point on the R = 1 line two lines are drawn parallel, respectively, to the R = O and the R = ∞ lines. The

fraction of the line between R = 1 and R = O is bisected by the R = 0.5 line and the fraction of the line between R = 1 and R = OC is bisected by the R = 2 line.

It should perhaps be added that Figures 6 and 7 are of limited physiological use because when pure oxygen is inhaled the $Pn_2 = O$ and the diagram is reduced to one dimension or a single vertical line without area.

SUMMARY

Some theoretical features of the oxygen-carbon dioxide diagram are considered which have not previously been fully appreciated. In particular, a method is described for drawing the R = O and the R = OC lines for any inspired air point. After the positions of these two lines are established, a method is described for determining graphically the positions of any other R line for the same inspired air point. After the R lines are thus established, the two sets of isoventilation lines for constant oxygen uptake and for constant carbon dioxide output are easily drawn: the former are always parallel to the R = OC line and the latter are always parallel to the R = O line. Samples of oxygen-nitrogen and nitrogen-carbon dioxide diagrams are also drawn.

REFERENCES

1. Fenn, W. O., H. Rahn and A. B. Otis "A theoretical study of the composition of the alveolar air at altitude," Am. J. Physiol. 146: 637, 1946.

2. Rahn, H. and W. O. Fenn "The oxygen-carbon dioxide diagram," Wright Air Development Center, Technical Report 53-255, Aug., 1953 (see p. 20).

THE SAMPLING OF ALVEOLAR GAS

Hermann Rahn

The alveolar gases and not the inspired gases represent the effective gaseous environment of our body. In order to appraise this effective stimulus of our gaseous environment one must be able to test the alveolar gas composition. Furthermore, the analysis of alveolar gases provides us with a relatively simple tool for "estimating" the arterial blood gas tensions as well as the arterial blood gas content. This chapter discusses some theoretical considerations of alveolar air in order to lay a foundation for a practical approach to the problem of alveolar air sampling.

At first glance the possible combinations of O_2, CO_2, and N_2 which could theoretically exist in any one of some hundreds of thousands alveoli of the lung may seem nearly infinite. Yet by the application of the ventilation/perfusion equation (1, 2) one may now limit these possible combinations to a relatively few which describe the curve in figure 1, provided the gas tensions of the mixed venous blood and the inspired gas are known. This curve, therefore, describes all the possible alveolar gas concentrations which could exist and each point is the result of a particular ventilation/perfusion ratio. This ratio is 0 at the mixed venous point and becomes infinity at the inspired air concentration. In the healthy person at rest, with a normal cardiac output and ventilation, it would appear that most of the alveoli have a ratio in the neighborhood of one; that is, each unit of alveolar ventilation is exposed to a similar volume of mixed venous blood. If all alveoli had this exact ratio it would result in a homogeneous composition of alveolar gas (pO_2 of 100 and pCO_2 of 40 mm.) as indicated by the dot in figure 1. And furthermore, if we assume that the end capillary blood gas tensions come into equilibrium with the alveolar gas tension, then the mixed arterial blood would also have the same tension as that in the alveoli. This is an ideal situation. It is of interest here to explore how closely such conditions are actually met in the healthy person and what methods should be employed to collect alveolar gases.

Unequal ventilation and perfusion

It is not likely that all the alveoli will have the same ventilation/perfusion ratio. That means that one will find different gas concentrations in various alveoli but whatever they are they will be confined to the curve in figure 1. Now if one has a distribution of some kind, one may visualize a normal variance of pO_2 and pCO_2 around a mean *or* a normal variance of a ventilation/perfusion ratio around a mean. Each type of variance would give different results after mixing all the alveolar content to obtain a mean value. A priori it would seem preferable to assume a normal variance of the ventilation/perfusion ratio since it is this ratio which actually determines the pO_2 and pCO_2.

If one now starts out with a normal distribution of the ventilation/perfusion ratio around the mean of 1.0 as in our example (figure 1) with a standard deviation of 30 percent, one will find that 99.5 percent of the alveoli will be distributed between 74 and 123 mm. pO_2 along the curve of figure 1. Those to the right of our mean point will have an increasingly greater ventilation relative to their perfusion, while those to the left decrease their V_A/Q ratio. If we now collect the alveolar gas from all these alveoli (making allowance for the fact that alveoli with low V_A/Q ratios contribute less alveolar volume than those with high ratios) and determine the mean alveolar gas concentration, we will find that the alveolar pCO_2 is about 0.6 mm. lower than 40 mm. and the pO_2 somewhat higher than 101. In general we can say that this assumed distribution yields a mean alveolar O_2 and CO_2 which differs negligibly from that expected if all alveoli had ventilation/flow ratio of 1.0. On the other hand, if we collect all the blood leaving these alveoli (making allowance for the fact that alveoli with lower V_A/Q ratios contribute relatively more blood having low O_2 tensions than alveoli with high ratios) we find that it has a pO_2 which is about 5 or 6 mm. lower than 100 but a pCO_2 which is essentially unchanged from 40. In summary then, even if the V_A/Q ratio for all the alveoli averages to a mean ratio of 1.0, one can expect to find a pO_2 difference of 5 to 6 mm.

TABLE I

Mean Differences Between Arterial Blood and End-Tidal pCO_2

	No. Samples	Arterial Minus End-Tidal pCO_2, mm Hg	S.E.	References
Man	25	0.2	1.27	Suskind, et al (8)
Dog	81	0.5	1.15	Suskind (9)
Man*	9	0.0	--	Galdston, et al (11)
Man	18	0.6	--	Saxton (10)

* The end-tidal samples were obtained by aspiration from the oral cavity.

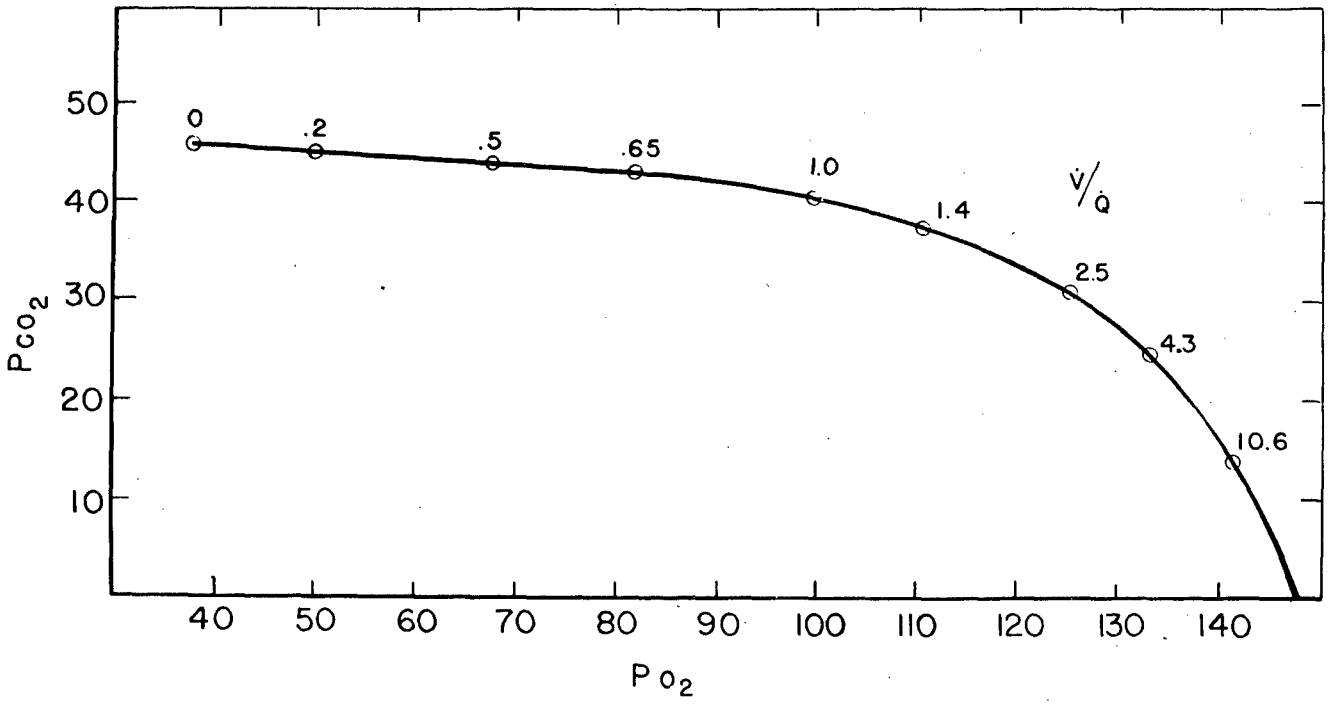


FIGURE 1

The V_A/Q curve depicting all possible combinations of alveolar or pulmonary capillary O_2 and CO_2 tension when the inspired $pO_2 = 147$ mm. and the mixed venous blood gas tensions are 38 and 46 for O_2 and CO_2, respectively. Each particular point on this curve is the result of a particular V_A/Q ratio. Some of these ratios are indicated and range from 0 at the mixed venous point where there is only perfusion to infinity at the inspired gas concentration where we have only ventilation and no perfusion.

between the mixed arterial blood and the mixed alveolar air, and a negligible, but finite CO_2 difference, if the distribution is of the magnitude indicated above.

Effects of venous admixture on the arterial blood

In the above description the lowering of the arterial pO_2 is due to the contribution of the relatively more highly perfused alveoli with their low O_2 tensions. In addition to this distribution effect we can have direct contribution of venous blood to the oxygenated blood from direct A-V shunts in the pulmonary circulation, contribution of venous blood from that part of the bronchial supply which drains directly into the pulmonary veins, as well as from part of the Thebesian vessels in the heart and the vasa vasorum. If this direct venous blood contribution is equivalent in volume to 2 percent of the cardiac output, it would also lower the arterial blood pO_2 by 5 mm., but with a negligible effect on the arterial blood pCO_2.

Assuming complete equilibrium of gases in each alveolus, we thus have two sources contributing to the difference between the mean alveolar pO_2 and the mean arterial pO_2. It is not possible to distinguish between them but the net effect as commonly measured in a healthy individual at sea level is approximately of the order of 10 mm., the so-called A-a gradient. It is important to point out that the difference in pCO_2 on the other hand is certainly less than 1 mm. in the examples cited and that the distribution effect is of greater consequence than the direct venous admixture effect. If one arbitrarily assigns one-half of the observed A-a O_2 gradient to the effect of distribution produced by variance of V_A/Q ratio and the other half to direct venous admixture, one can estimate that approximately 95 percent of the alveoli will fall on the V_A/Q line in figure 1 between 85 and 115 mm. pO_2 range and that the pCO_2 difference between the arterial blood and the mixed, mean alveolar air is negligible.

The respiratory cycle and alveolar gas

So far we have considered only the results of a static state with continuous perfusion and ventilation. We must consider the effects of the respiratory cycle. Actually ventilation is a discontinuous process with periodic dilution of the alveolar gases, a constantly changing alveolar volume to which with the beginning of each new inspiration alveolar air (dead space) is added, followed by fresh air. Expiration may be compared to breath holding with a constantly decreasing lung volume. DuBois (3, 4) has recently made a detailed analysis of the expected changes which one might encounter while breathing at the rate of fifteen times a minute with a tidal volume of 626 cc. and a mean ventilation/perfusion ratio of 1.0.

The changes in CO_2, O_2, and R are shown in figure 2 and indicate the fluctuation to be expected during a respiratory cycle. By integrating these curves a mean concentration may be determined for the alveolar gas. These would also be found in the arterial blood provided no venous admixture is encountered. Thus the mean CO_2 concentration in the lung will be found about half way through the expiration (see arrow No. 1). The mean concentration for O_2 will actually be found later (arrow No. 2) and the mean exchange ratio still later (arrow No. 3). Thus the portion of the expired tidal volume representing mean CO_2, O_2, and R would, strictly speaking, be found at definite intervals during normal expiration. Fortunately, the time differences are negligible so that the proper time for sampling one constituent is probably good enough for the other values.

The mean concentration for O_2 and CO_2 is found to exist in the lungs about midway during the expiration (figure 2). Actually this gas has to be transported from the alveoli to just beyond the mouth for sampling. At the assumed expiratory velocities this delay is approximately 0.5 second. This additional time factor should theoretically be considered in the sampling of mean alveolar air since it is assumed that the gas concentrations do not change after leaving the alveoli.

If we now return to our diagram in figure 1 we can replace each point of this curve representing the static concentration by a circle which denotes the cyclic changes encountered during a respiratory cycle. This has been done in figure 3 which combines one particular point of the curve in figures 1 and 2. Thus the instantaneous alveolar concentrations for any point along the V_A/Q line can be made analogous to a satellite spinning in phase with the respiration around the theoretical mean concentration; however, the mean concentration can never be achieved simultaneously for all its components, the CO_2, O_2, and N_2. The width of the ellipse in figure 3 has actually been somewhat exaggerated in order to convey visually the concept of a loop. The cyclic

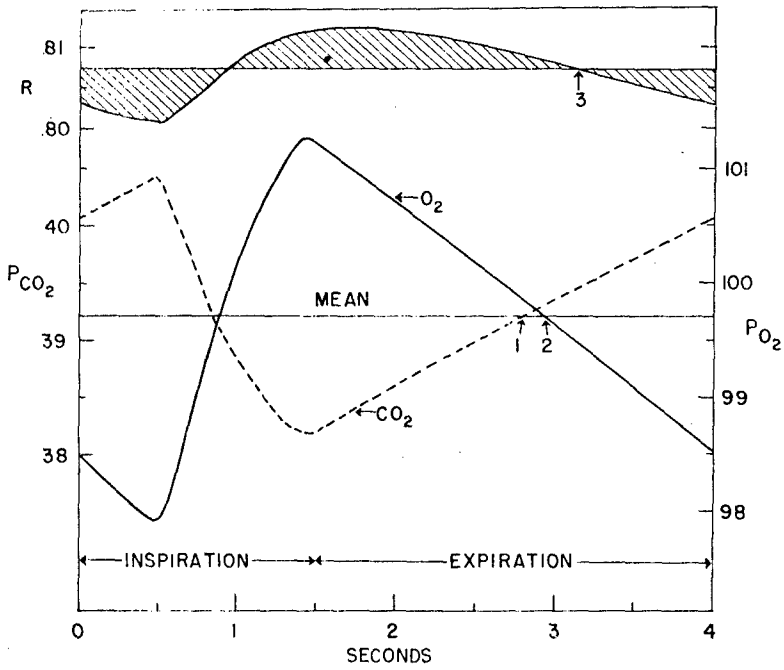


FIGURE 2

Changes in the alveolar O_2 and CO_2 tensions and the exchange ratio, R, during a single respiratory cycle. The horizontal lines represent the integrated mean values. Note that during expiration the mean values for CO_2, O_2, and R occur at different times. Modified from DuBois (3, 4).

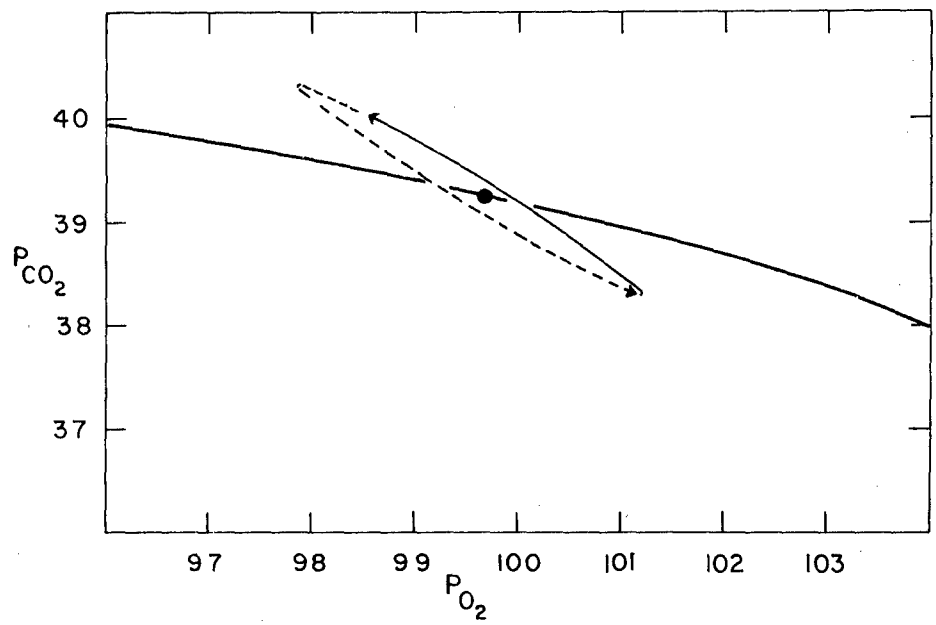


FIGURE 3

Changes occurring during a single respiration. The solid line of the ellipse represents the changes during expiration, the dotted line during the course of inspiration. The center of the ellipse indicates the mean concentration for alveoli having a mean V_A/Q ratio of 1.0. The nearly horizontal curve represents other mean points for alveoli having greater and smaller V_A/Q ratios similar to the line of figure 1. Any other mean alveolar concentration on this line would have a somewhat similar respiratory loop. Modified from DuBois (3, 4).

variation can actually be best appreciated in a model which adds inspiratory and expiratory velocities as a third dimension. The loop in figure 3 represents the predicted pathways in alveoli having a V_A/Q ratio of 1.0. One may picture slightly smaller and more horizontal loops in alveoli to the left of our mean point of the V_A/Q line. This results from the relatively larger perfusion. On the other hand, points to the right would have larger and more vertical loops because of their relatively higher ventilation and smaller perfusion.

Sampling alveolar air

From the above discussion one may conclude that the arterial pCO_2 determination is probably the best available index of the mean alveolar CO_2 composition and that the alveolar gas should be sampled ideally four-fifths of the way along a normal expiration if it is to represent a mean value. In light of these theoretical discussions it might be well to re-examine the Haldane-Priestley technique for the collection of alveolar air. This method has been the classic standard for the last half century.

If one extrapolates the curves in figure 2 to the time of sampling and considers the fast recording of the CO_2 concentrations during a Haldane-Priestley maneuver (figure 4), it can be readily appreciated that the gas sampled from the last part of the forced expiration will have a value which is too high in CO_2, too low in O_2, and too low in the exchange ratio. The reason is that in the prolonged expiration during which gas exchange still goes on we are dealing essentially with a short breath-holding response (4, 5) which becomes actually exaggerated by the continuous reduction of the lung volume. These theoretical considerations are supported by the following facts:

1. Arterial pCO_2 determinations when compared with a Haldane-Priestley sample are too low by 4 mm. (6). It is not likely that such a reverse gradient can exist and thus seems good evidence for faulty sampling.

2. Exchange ratio. Since expired air is only the alveolar gas diluted with the inspired air and since such dilution by itself will not alter the ratio, it is a reasonable assumption that the exchange ratio (R) if it represents mean alveolar air must be the same as that for the expired air. Such a comparison has previously been reported (1) and indicates that this ratio is lower for the alveolar gas than for the expired gas. Such a difference can be reasonably well predicted from the information of figures 2 and 4. During expiration this ratio falls rapidly and particularly so when the 1 to 2 seconds of breath holding begins during the forced expiration which is also accompanied by a constantly diminishing volume of the lung which allows for greater changes in the gas exchange and exchange ratio than would take place with a larger lung volume.

One consequence of these changes which occur with the forced expiration is that the O_2 is altered more than the CO_2. The ratio of these differences is approximately 2:1. Thus if the CO_2 differs from the mean alveolar concentration by 2 mm., the O_2 will differ by nearly 4 to 5 mm. This accounts for the unequal dead space when calculated separately for CO_2 and O_2 and makes the O_2 dead space larger. The dead space for these two gases can be identical only when the exchange ratio for O_2 and CO_2 are the same (1).

In spite of these drawbacks and the requirements of a trained subject who knows precisely when and how to deliver a sample, this method has still many applications when spot tests are desired or when a difference of 1 or 2 mm. CO_2 from the mean CO_2 is not of great importance, particularly in comparative studies where changes in CO_2 concentration under two or more conditions are being sought.

Description of an automatic alveolar gas sampler

Over the last forty years dozens of techniques have been described for the sampling of alveolar gases. The apparatus pictured below (figure 5) has been in steady use at this laboratory for some seven years. It is simple to install into any check valve system, its operation is entirely mechanical, and it is automatically activated by the mouth or mask pressure changes during a breathing cycle. From it a few cubic centimeters of the last part of each normal tidal can be aspirated continuously into a mercury bottle or by a pump which can deliver the gas into automatically recording O_2 and CO_2 meters. From the earlier discussion it is doubtful whether any technique can actually deliver "mean alveolar air" and for that reason it may be more correct to refer to this device as an *end-tidal sampler*. The action of this device has been previously described (7). Briefly, during inspiration the gas beyond the expiratory check valve represents the last part of the normal tidal volume. The mouth or mask pressure is negative during this phase and thus the balloon is brought into the inflated position, filling it with the alveolar air. Beginning with the expiration we encounter the hazardous phase

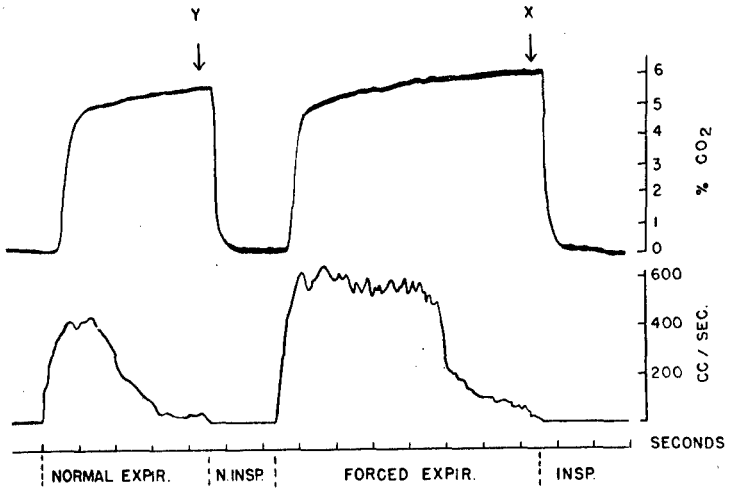


FIGURE 4

Expiratory velocities (lower curve) recorded simultaneously with the expired CO_2 concentrations on the rapid infra ed CO_2 analyzer of R. C. Fowler during a normal expiration and during a forced expiration simulating a Haldane-Priestley maneuver. The arrow at **Y** *indicates approximately the region sampled by the end-tidal sampler, while the arrow at* **X** *indicates the region sampled by the Haldane-Priestley maneuver.*

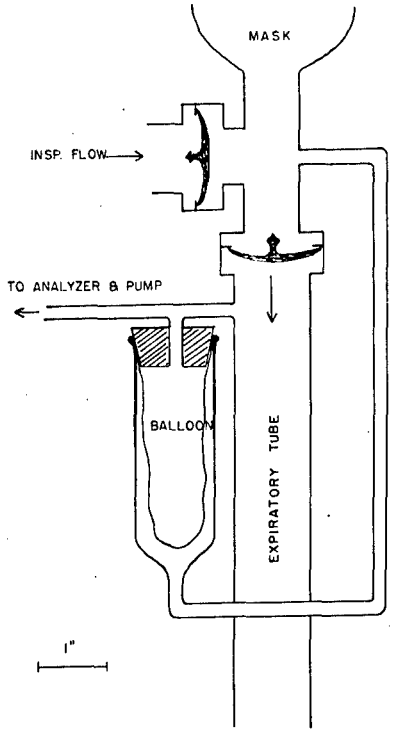


FIGURE 5

The automatic end-tidal gas sampler.

when the dead space air leaves and passes the sampling orifice just beyond the expiratory check valve and could contaminate the previously sampled alveolar portion. However, the mask pressure becomes positive during expiration; the balloon collapses faster than the end-tidal sample is being aspirated and empties most of its contents back into the main expiratory tube just as the dead space air comes by. The balloon action thus serves as a valve at just the right time to prevent the aspiration of dead space air. It should be pointed out that on some occasions the balloon tends collapse too quickly, and then the alveolar portion becomes contaminated with dead space air. In such event it is simple to constrict the tube activating the balloon with a screw clamp. It is also important that the apparatus dead space be kept minimal. Otherwise the dead space air is not completely washed out by the alveolar portion. With small tidal volumes where the dead space and alveolar volume tend to be equal in volume this method is not practical, but in dogs (see below) it has been used successfully by constructing a check valve of smaller dimensions.

Evaluation of the end-tidal alveolar gas sampler

Figure 2 would suggest that the most representative CO_2 (mean CO_2) samples can be obtained at about four-fifths of the time period of a normal expiration. During the whole period of inspiration the sample will come from the last part of the expiration. Theoretically, this will give a value for CO_2 which is actually too high but the difference from a practical standpoint may be too small. Figure 4 compares the CO_2 concentration found during a normal tidal and those following a forced expiration. The arrows indicate the parts sampled by the end-tidal sampler and the Haldane-Priestley method. The difference between these points is quite obvious. If the theoretical analysis of DuBois (figure 2) is correct, the end-tidal sampler approaches the ideal value much more closely than the Haldane-Priestley method.

Arterial CO_2 vs. end-tidal CO_2

Using the arterial pCO_2 as a yardstick for the proper evaluation of an alveolar sampling method, the comparison made by Suskind et al. (8) shows very good agreement. There the subjects' end-tidal O_2 and CO_2 were continuously recorded over long periods. When a stable value was obtained, blood was withdrawn from the radial artery for gas analysis by the Riley method. The agreement on the average is rather good (table I). Similar observations have been made in anesthetized dogs by Suskind (9) and these likewise show good agreement. In the latter case a sampler was constructed with a smaller dead space and the check valves attached directly to a tracheal intubation tube. More recently Saxton (10) has compared the end-tidal CO_2 in twenty cases with the arterial CO_2 and finds the end tidal values to average 0.6 mm. lower than the blood value. Galdston et al. (11) reported perfect agreement in nine subjects when the end-tidal sample was aspirated from the oral cavity. When CO_2 is added to the inspired gas, the ventilation is greatly increased. Under such conditions a mean difference of 0.9 mm. has been reported by Carter (19). The samples were obtained after breathing CO_2 for 40 minutes and the steady state re-established. On the other hand, Lambertsen (16) reports in thirty-two human experiments a considerably lower value for the end-tidal CO_2. The mean difference was 3.2 mm. when air was breathed. It is difficult to explain this large difference and it suggests that dead space air was aspirated in addition to alveolar air. This might have been inadvertently accomplished by a too early collapse of the balloon during the first phase of expiration.

Another approach has been to compare the automatic end-tidal sampler value with another independent means of obtaining an end-tidal sample. Thus Lundgren (12). trapped end-tidal samples from the oropharynx and compared these with gas samples collected simultaneously by automatic sampler. The means of twenty-seven samples in seven subjects show a difference of only 0.01 percent CO_2. The largest difference found in one subject was 0.8 mm. Hg. Saxton (10) aspirated a continuous fraction of gas from a subject's expired air stream through an instantaneously recording infrared CO_2 gas analyzer and compared the very last portion with that obtained by the automatic sampler. The mean difference was a 1.4 mm. higher CO_2 value by the infrared analysis; however, it should be pointed out that the infrared values were also 0.8 mm. higher than arterial CO_2 values of blood drawn simultaneously.

During exercise and voluntary hyperventilation the problem of sampling alveolar gas is even more difficult since the fluctuations during a respira-

tory cycle are considerably greater than those pictured at rest and proper timing becomes of even greater importance. The magnitude of such cyclic changes can be appreciated by inspection of the instantaneous CO_2 recordings of the expired air during exercise and voluntary hyperventilation made by DuBois et al. (17). They differ from those shown at rest in figure 4 by a very much steeper slope. If the mean alveolar concentrations under these stress conditions fall somewhere just beyond the middle of a normal expiration (as they do at rest), a sample from the end of a tidal will yield an appreciably higher CO_2 tension than the mean alveolar or arterial blood value. That this may actually be the case is indicated by the studies of Suskind et al. (8) and Filley (18) whose healthy subjects walked a 10 percent grade at 1.7 and 3.2 miles per hour, respectively. In the first case arterial CO_2 values during the first, second, third, and fourth minute of exercise were compared with simultaneous end-tidal gas analyses in each of ten subjects. In the second study of twenty-eight people a similar comparison was made between the fourth and sixth minute of exercise. In the latter case the end-tidal sample was obtained from a Henderson-Haggard modification of the Muller trap. In both cases the end-tidal CO_2 was higher than the arterial CO_2. Suskind's figures show a mean difference of 1.4 mm. The values reported by Filley are 2.2 mm. higher and highly significant. These combined studies on approximately 70 simultaneous comparisons of arterial and end-tidal CO_2 suggest strongly that during exercise these methods sample alveolar gas too late during the expiration and that a more representative mean sample can be obtained earlier during the expiration. This implies, furthermore, that a Haldane-Priestley sample taken during exercise would deviate considerably more from the mean alveolar CO_2. This was actually demonstrated by Riley et al. (6) in his comparisons between simultaneous arterial and Haldane-Priestley CO_2 during exercise.

The exchange ratio

As pointed out above, the exchange ratio of the Haldane-Priestley sample in our hands yielded a lower value than that obtained from the expired air. The exchange ratio determined from the end-tidal sampler gives values which are in agreement with those obtained simultaneously from the expired air (1). This would seem to be another requirement met by this type of sampling. This also means that the dead spaces calculated independently for O_2 and CO_2 by the Bohr equation are identical, as has been pointed out above.

Differences between absolute values derived from Haldane-Priestley and end-tidal samples

These values are shown in table II. The Haldane-Priestley samples yield values that are lower for O_2 and higher for CO_2. The discrepancy for O_2 is about two times larger than that for CO_2 (1, 13). This is to be expected if we regard the extra time consumed with the forced expiration as breath holding. With breath holding the oxygen consumption is maintained but the CO_2 output is rapidly reduced (4), giving rise to larger changes in O_2 than CO_2.

In summary the problem of sampling that portion of the alveolar gas which most closely represents the mean alveolar or arterial CO_2 is at best beset with many difficulties. From the accumulated evidence it seems almost certain that the Haldane-Priestley method yields CO_2 values which are too high and O_2 values which are too low. The automatic end-tidal sampler described above seems to meet more closely the theoretical requirements and yields values which approach rather closely the arterial pCO_2 values during rest.

The variability of alveolar gas concentrations

I would finally like to leave the concepts of how to measure alveolar gas concentrations and turn to the more general topic of the variability of alveolar gas from time to time. All too often the magic but convenient numbers of $pCO_2 = 40$ and $pO_2 = 100$ mm. Hg are used as "proper" guides. While the alveolar pO_2 (for a given CO_2 output and ventilation) is purely a function of the barometric pressure (when air is breathed), the pCO_2 is regulated by the body itself. More precisely it is determined by the ratio of CO_2 output: alveolar ventilation. The question arises as to how constant this ratio is from day to day and how much it is apt to vary from moment to moment. In male subjects one can find individuals who consistently have high or low alveolar pCO_2. This may be correlated with their alkali reserve level. On the other hand considerable evidence in recent years has shown that in females the pCO_2 fluctuates with changing hormone levels of the

TABLE II

Mean Differences Between Haldane-Priestley and End-Tidal Samples

	No. Samples	pCO_2	pO_2	References
Man	101	+ 2.5	- 4.9	Rahn, et al (14)
Man*	67	+ 2.6	- 3.7	Lesser, et al (13)

* These end-tidal samples were obtained by aspiration from the oral cavity.

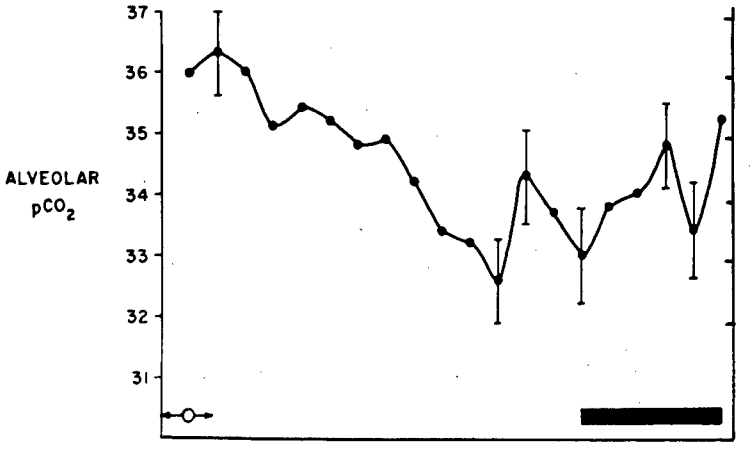


FIGURE 6

Average alveolar CO_2 changes during sixteen menstrual cycles of nine subjects taken from the time of ovulation ←O→ through the end of the next menstrual cycle. This time span has been scaled to an average length of nineteen days. The vertical bar indicates one standard error. From Goodland and Pommerenke (15).

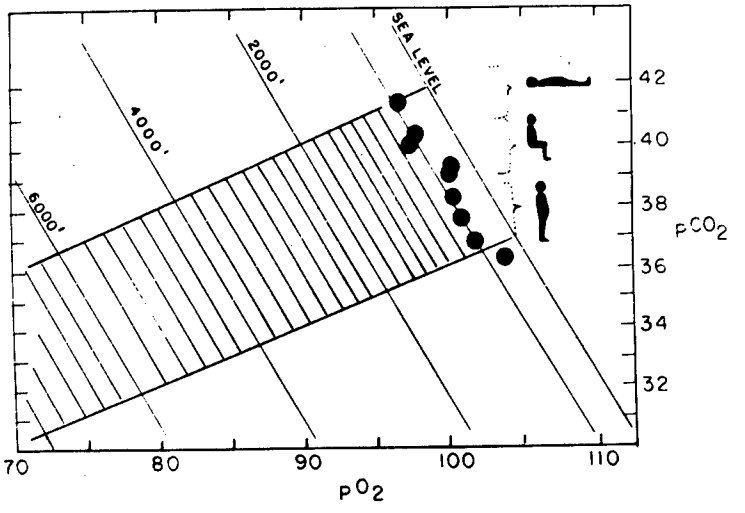


FIGURE 7

The effects of posture upon the alveolar O_2 and CO_2 tensions. Each point represents an average of approximately 200 minute-to-minute readings on the O_2 and CO_2 meters for a large number of male subjects. These points fall around the diagonal representing an RQ of 0.8 at a barometric pressure of 747. Similar RQ lines are indicated for other altitudes. The sloping cross-hatched band indicates in addition to the anticipated changes with posture the gradual fall of pCO_2 in persons residing at altitudes up to 6,000 feet.

menstrual cycle. The highest pCO_2 is reached at ovulation, followed by a 4 mm. drop premenstrually (15) (figure 6).

More rapid fluctuations will be found, for example, after the ingestion of meals with the ventilatory response to the alkaline tide, during sleep, and with changes in the normal activities during the day's work. Frequently less appreciated are the pCO_2 fluctuations seen with changes in posture. By a passive shift from the supine to the standing position or vice versa, the pCO_2 will change approximately 5 mm., accompanied by a somewhat greater change in pO_2. Thus in reporting alveolar values in the literature it would seem worth while to mention the posture in order that valid comparisons can be made. For instance, the change in pCO_2 from the supine to the erect position is of the same magnitude as that achieved by acclimatizing oneself from sea level to an altitude of 6,000 feet. Over the years we have accumulated a large number of analyses on subjects who have been tilted passively from one position to another. These values, in turn, have been compared with subjects quietly resting in the sitting position. Over 1,700 minute-to-minute analyses by automatic alveolar air sampling have yielded the values shown in figure 7 where the pCO_2 has been plotted against the pO_2. These values all fall around the RQ = 0.8 diagonal for a mean barometric pressure of 747 mm. Hg. At a barometric pressure of 760 these alveolar points would all be shifted to the sea-level RQ = 0.8 diagonal. If one assumes that similar shifts in alveolar ventilation occur at reduced barometric pressure then the cross-hatched band indicates not only the differences anticipated by the changes in posture but also the general lowering of the pCO_2 level in people residing at elevations up to 6,000 feet. The mechanism which induces this hyperventilation upon standing is not understood, but it is probably associated with concomitant circulatory adjustments. The magnitude of these changes, however, is large enough to introduce caution in comparing alveolar CO_2 values at rest with those taken under a stress condition which necessitates a change in posture.

REFERENCES

1. Rahn, H. Am. J. Physiol. 158:21 (1949).
2. Riley, R. L., and A. Cournand. J. Appl. Physiol. 1:825 (1949).
3. DuBois, A. B., A. G. Britt, and W. O. Fenn. J. Appl. Physiol. 4:535 (1952).
4. DuBois, A. B. J. Appl. Physiol. 5:1 (1952).
5. Otis, A. B., H. Rahn, and W. O. Fenn. Am. J. Physiol. 152:674 (1948).
6. Riley, R. L., J. L. Lilienthal, Jr., D.D. Proemmel, and R. E. Franke. Am. J. Physiol. 147:191 and 199 (1946).
7. Rahn, H., and A. B. Otis. J. Appl. Physiol. 1:717 (1949).
8. Suskind, M., R. A. Bruce, M. E. McDowell, P. N. Yu, and F. W. Lovejoy Jr. J. Appl. Physiol. 3:282 (1950).
9. Suskind, M. Am. J. Physiol. 177:277 (1954).
10. Saxton, G. A., Jr. Federation Proc. 12:125 (1953).
11. Galdston, M., B. Benjamin, and M. Huerwitz. Federation Proc. 10:47 (1951).
12. Lundgren, N. P. V. Comparison of Rahn-Otis technique with other methods of intermittent and continuous sampling of expired air. (Unpublished paper related to USAF School of Aviation Medicine Project No. 21-1201-0007).
13. Lesser, G., M. Galdston, and M. Pruss. Federation Proc. 8:94 (1949).
14. Rahn, H., J. Mahney, A. B. Otis, and W. O. Fenn. J. Aviation Med. 17:173 (1946).
15. Goodland, R. L., and W. T. Pommerenke. Fertility and Sterility 3:394 (1952).
16. Lambertsen, C. J. Personal communication)
17. DuBois, A. B., R. C. Fowler, A. Soffer, and W. O. Fenn. J. Appl. Physiol. 4:526 (1952).
18. Filley, G. F. (Personal communication)
19. Carter, E. T. (Unpublished data)

CORRECTION OF ERRORS INTRODUCED BY THE END-TIDAL AIR SAMPLING DEVICE INTO THE MEASUREMENT OF VENTILATION AND CALCULATION OF THE DEAD SPACE

R. E. Nye, Jr.[1] and H. Rahn

The continuous end-tidal air sampling device may be incorporated into an open circuit system for measuring ventilation, expired gas tensions and oxygen consumption, permitting simultaneous observation of alveolar gas tensions and calculation of alveolar ventilation and physiological dead space by the Bohr formula. We have analyzed the effect of the device upon the measurement of these factors and derived formulae for making proper corrections. The analysis revealed an obscure but important source of error which we had not suspected, and we present our conclusions here.

The device is depicted in Figure 1. As previously described end-tidal air is aspirated continuously down the end-tidal sampling hose at a known rate "S", usually 100 ml/min., resulting in a small and easily calculable error in the volume and composition of mixed expired air. A more significant error is introduced by the functioning of the balloon, which will now be described.

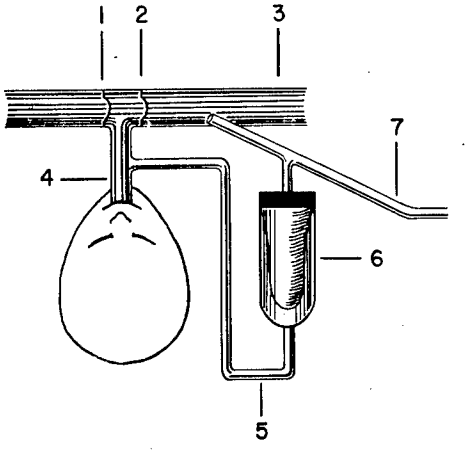


Figure 1

1 - intake valve
2 - output valve
3 - expired air hose
4 - mouthpiece
5 - balloon chamber hose
6 - balloon chamber
7 - end-tidal sampling hose

End-Tidal Air Sampling Device

---

[1] From the Department of Medicine.

Effect of the device upon volume measurement:

During expiration the lungs contract by a volume V_T. Of this, a volume V_B enters the balloon chamber, forcing the contents of the balloon (filled from previous inspiration and also of volume V_B) into the expired air hose. The remainder of V_T enters the expired air hose through the valve. At the next inspiration the balloon expands, removing a volume V_B from the expired air hose. The net volume remaining in the expired air hose is therefore $V_T - V_B$. This is repeated during each respiratory cycle. If respiratory frequency is f/minute, and V_{E_m} is the measured minute ventilation, then

$$V_T f = \dot{V}_E = \dot{V}_{E_m} + S + V_B f \qquad \text{-----} \qquad (1)$$

This correction will usually amount to 0.5 L/minute or more.

Effect of the device upon composition of expired air:

Of the volume V_B which enters the balloon chamber during expiration a part is dead space air, V_{BD}, and the remainder is alveolar air, V_{BA}, (see Appendix for a method of measuring these volumes). Let V_A be the volume of alveolar air expelled through the output valve. Let V_D be the personal physiological dead space plus the volume of the mouthpiece including the region between the valves but not the balloon chamber (which is obliterated at the beginning of expiration).

During a single expiration, V_{BD} dead space air enters the balloon chamber and $(V_D) - V_{BD}$ passes the output valve. Next V_{BA} of alveolar air enters the balloon chamber, and V_A passes the output valve. In the course of a minute $\dot{V}_{E_m}$ of O_2 concentration F_{Eo2_m} consists of $(V_D - V_{BD})$ f of O_2 concentration F_{Io_2} and of $\dot{V}_A - S$ of O_2 concentration F_{Ao_2} (measured from the continuously sampled aliquot).

Calculation of alveolar ventilation and personal dead space:

From the foregoing paragraph two equations may be written:

$$\dot{V}_{E_m} = (\dot{V}_A - S) + (V_D - V_{BD})\, f \qquad \text{-----} \qquad (2)$$

and $$\dot{V}_{E_m} \cdot F_{Eo2_m} = (\dot{V}_A - S)\, F_{Ao_2} + (V_D - V_{BD})\, f \cdot F_{Io_2} \qquad \text{-----} \qquad (3)$$

Solving equations (2) and (3) simultaneously.

$$\dot{V}_A = \dot{V}_{E_m} \left\{ \frac{F_{Io_2} - F_{Eo_{2m}}}{F_{Io_2} - F_{Ao_2}} \right\} + S \qquad \text{-----} \qquad (4)$$

or $$V_D f = \dot{V}_D = \dot{V}_{E_m} \left\{ \frac{F_{Eo_{2_m}} - F_{Ao_2}}{F_{Io_2} - F_{Ao_2}} \right\} + V_{BD} f \qquad \text{-----} \qquad (5)$$

Calculation of oxygen consumption:

The gas in the balloon chamber cannot mediate gas exchange after the first few breaths since it is always inspired again. The only correction necessary for $\dot{V}o_2$ is that for the end-tidal air aliquot "S". When $F_{Ico_2} = 0$, then

$$\dot{V}o_2 = \dot{V}E_m \frac{F_{Io_2}(1-F_{Eco_2}) - F_{Eo_{2m}}}{1 - F_{Io_2}} + S \frac{F_{Io_2}(1-F_{Aco_2}) - F_{Ao_2}}{1 - F_{Io_2}} \quad \text{-----} \quad (6)$$

The correction usually amounts to 6 or 7 ml/min. when S is 100 ml/min. (Approximately $(F_{Io_2} - F_{Ao_2}) \times 100$).

Effect of the sampling device upon tidal volume:

Attempts to measure the effect of the device on the tidal volume in this laboratory have failed because the effect is smaller than the normal spontaneous variation. However, one may predict the effect as follows:

When the dead space of an ordinary mouthpiece is added to the physiological dead space of a normal subject, the tidal volume increases by a little less than the added dead space. The alveolar ventilation decreases very slightly, providing a small increase in P_{Aco_2} which stimulates and maintains the increase in tidal volume. This change may be expressed thus (with no mouthpiece):

$$V_T = V_A + V_{DP} \quad \text{-----} \quad (7)$$

where V_{DP} is personal physiological dead space; and (with a mouthpiece of volume V_{DM})

$$V_T' = V_A' + V_{DP} + V_{DM} \quad \text{-----} \quad (8)$$

This is the relationship which holds when the sampling device is applied with the balloon chamber hose clamped off. When the clamp is removed, then

$$V_T'' = V_A'' + V_{BA} + V_{DP} + V_{DM} \quad \text{-----} \quad (9)$$

Assuming that V_A, V_A' and V_A'' are virtually equal, then

$$V_T'' - V_T' = V_{BA} \quad \text{-----} \quad (10)$$

But the effect of the balloon on the net measurement of the tidal volume is:

$$V_{T_m}'' = V_T'' - V_B \quad \text{-----} \quad (11)$$

Combining equations (10) and (11),

$$V'_T - V''_{T_m} = V_B - V_{BA} = V_{BD} \quad \text{-----} \quad (12)$$

Therefore, when the clamp is removed from the balloon chamber hose, the average tidal volume increases by V_{BA} (equation 10) while the average measured tidal volume decreases by V_{BD} (equation 12).

DISCUSSION

The fraction of alveolar air, V_{BA}, which enters the balloon chamber at each breath has not been considered as part of the alveolar ventilation, for the obvious reason that it does not mediate gas exchange, since it is inspired again during the following inspiration. At the end of expiration it forms part of the functional residual air. However, it differs from the functional residual air of a subject breathing through an ordinary mouthpiece in the following sense: with an ordinary mouthpiece, every cc of alveolar air delivered into the large respiratory passages and mouthpiece displaces an equal volume of gas ahead of it through the output valve. The displacement of V_{BA} into the balloon chamber, on the other hand, requires contraction of the lungs by a like volume, but without any net gas passing into the expired air hose as a result, because the ensuing inspiration fills the balloon again from below the output valve. In effect, the dead space expands by this amount during expiration. It can be compared to a hypothetical tracheal diverticulum in the neck which fills during expiration and collapses during inspiration, requiring useless work on the part of the chest bellows. It is this useless work which accounts for the required increase in mechanical tidal volume when the balloon chamber is introduced into a conventional mouthpiece (v. sup., equation (10)).

The displacement of dead space air, V_{BD}, into the balloon chamber does not require extra work on the part of the lungs. This air must be displaced from the respiratory passages in any case, and whether it passes the output valve, as in an ordinary mouthpiece, or is shunted to the next inspired tidal volume, as in the end-tidal sampling device, is of no moment for gas exchange. However, when the dead space is calculated by the Bohr formula, this volume will not be accounted for and must be added to the result before the mouthpiece volume is subtracted, as indicated in equation (5).

SUMMARY AND CONCLUSIONS

The end-tidal air sampling device modifies ventilation and its measurement by two means: first, the continuous removal of end-tidal air at a small, constant known rate; second, by the alternating collapse and filling of the balloon, which removes an aliquot of every expired breath, thus appreciably diminishing the measured ventilatory volume and slightly altering its composition.

If one is interested only in the functionally effective portion of ventilation, that is to say the effective minute volume, the oxygen consumption, carbon dioxide excretion, and alveolar ventilation, then he need only collect and analyze mixed expired air and introduce corrections for the constant sampling of end-tidal air.

On the other hand, if one wishes to calculate the physiological dead space, he must take the second source of error into account, since a portion of the air from the dead space (personal plus mouthpiece) escapes measurement at each breath. The resulting value may be about 10% too low unless the correction is applied.

Assessment of the actual mechanical tidal excursion of the lung requires that both sources of error be recognized and corrected for, the second source being the more important.

Formulae for making these corrections have been devised and presented.

The effect of the balloon, as distinct from the mouthpiece, upon the tidal volume required for maintenance of a given level of gas exchange, has been calculated from theoretical grounds. Introduction of the functioning balloon into the mouthpiece increases the required mechanical tidal volume, but decreases its measured value. The arithmetical sum of the two effects equals the volume excursion of the balloon for each breath.

APPENDIX

Measurement of V_B, V_{BD} and V_{BA}

V_B may be measured quite simply by filling the balloon chamber with water and measuring the amount displaced when the balloon expands to the extent observed when a subject breathes into the device.

V_{BA} may be measured as follows: A subject breathes quietly into the device for several minutes and a sample of end-tidal air is collected over mercury. Immediately afterwards a clamp is placed on the balloon chamber hose near the mouthpiece at the end of expiration. The trapped gas is then transferred to a mercury-filled sampling tube after a washout. Both samples are analyzed for CO_2 in the Scholander 0.5 ml gas analyzer. If F_{Aco_2} is end-tidal CO_2 concentration and F_{Bco_2} is CO_2 concentration of balloon chamber gas, then

$$V_{BA} = V_B \frac{F_{Bco_2}}{F_{Aco_2}}$$

(During steady respiration the ratio of dead space gas to alveolar air in the balloon chamber gas approximates that in the gas introduced at each breath.) In our instrument the value of V_B was 28 ml and the value of V_{BA} (mean of 10 determinations $\pm$ S.D.) was V_B (0.42 ± 0.09) or 12 cc.

THE COMPOSITION OF THE ALVEOLAR AIR DURING BREATH HOLDING WITH AND WITHOUT PRIOR INHALATION OF OXYGEN AND CARBON DIOXIDE

by

Wallace O. Fenn and Pierre Dejours[1]

In this paper we wish to report the results of a series of experiments which help to describe and explain the changes in the composition of the alveolar gases which occur during breath holding. The general principles which govern these changes have already been described in a series of papers from this laboratory (1,2,3).

During breath holding it is assumed that during the first 20 seconds, i.e., before appreciable recirculation occurs, the composition of the venous blood remains constant. So long as the alveolar oxygen tension is sufficient to saturate the arterial blood, therefore, the oxygen uptake will vary only with the variations in cardiac output. The oxygen concentration in the alveoli will then depend upon the volume of oxygen remaining in the lung and the instantaneous volume of the lung. Since the glottis is closed no new gas enters from the dead space (except for some mixing between alveolar and dead space gas). The influx of carbon dioxide is assumed to depend on the blood flow and the venous-arterial CO_2 content difference. Since the content difference over a narrow range is proportional to the Pco_2 difference, the Pco_2 in the lung rises exponentially toward the oxygenated venous Pco_2 level. One additional factor of significance appears to be the CO_2 combining capacity of the mass of lungs with their contained blood. This serves to store some CO_2 when the Pco_2 is rising and gives up its stores when the Pco_2 falls, thus diminishing the Pco_2 fluctuations which normally occur during the respiratory cycle or any other respiratory maneuvers. The data obtained in a series of 10 experiments on 5 subjects provides a method of measuring this CO_2 combining capacity and indicates that it is a factor of measurable importance in normal respiration.

METHOD

The subject sits quietly at rest throughout the experiment. In his hand he holds a 3-way respiratory stop cock, one arm of which is connected to a mouthpiece. With the cock in one position he can inhale a desired gas mixture in measured amount from a 5 liter spirometer and with the cock in the other position

---

1 On leave of absence from Faculty of Medicine, University of Paris.

he exhales into a long tube open at the far end. The gases thus expired can be sampled through a small tube near the stop cock. At the end of a normal expiration the subject quickly turns the stop cock to the spirometer and inhales a measured volume of 2 or 3 liters of air or CO_2-O_2 mixture. He holds this in the lungs for a measured period of time, then at a signal from the operator he turns the stop cock to the sampling tube and exhales maximally. At the end of this expiration the stop cock is again turned to the spirometer thus trapping the expired air in the sampling tube. Normal alveolar air samples are taken in the same way as the breath holding samples, except that no time intervenes between the end of a normal expiration and the forcible exhalation of alveolar air. The expired air in the sampling tube is drawn through the CO_2 and O_2 analyzers and the concentrations of these gases recorded. For analysis we used the Pauling oxygen tensimeter and the Cambridge Instrument Co. CO_2 thermal conductivity analyzer. Both instruments were repeatedly calibrated, the former against air and the latter against a known CO_2 mixture. The CO_2 analyzer is not completely satisfactory because of its slow response. It was, however, accurate enough for the purpose and the variations encountered in duplicate observations were more physiological than analytical.

ANALYSIS OF DATA

In analyzing our data the Pco_2 of each sample was plotted as ordinate against the corresponding Po_2 as abscissa. This is the same as plotting Pco_2 against time so long as the cardiac output remains constant. If, however, the cardiac output should vary for any reason during the short period of breath holding, this change would affect both oxygen uptake and carbon dioxide output equally and would therefore have no effect on the slope of the Pco_2 vs. Po_2 curve. It would, however, affect the slope of a Pco_2 vs. time curve. As already explained, the slope of this Pco_2 vs. Po_2 curve should always be proportional to the difference between the Pco_2 of the alveoli and the oxygenated venous blood. This is true provided the rates of Pco_2 and Po_2 change are corrected for the simultaneous rate of change of lung volume — for a decrease in lung volume which occurs in breath holding increases the rate of change of the Pco_2 when that is increasing and decreases the rate of change of the Po_2 which is decreasing.

The slopes between any two points on the Pco_2-Po_2 curve are corrected by calculating the values of Pco_2 and Po_2 which the second of any two points would have had if the volume of the lung had remained constant during the intervening period, i.e., if the Pn_2 had remained constant. The corrected slope was then obtained by subtracting ordinates and abscissae of the two points and obtaining the ratio of the Pco_2 change to the Po_2 change. The corrected slope so obtained was plotted against the mean Pco_2 (uncorrected for Pn_2) which obtained during that interval. If the theory is correct, all the points so plotted should lie on a straight line. This should be true whether the alveolar Pco_2 is unusually low as after the inhalation of 2 liters of air or when it is unusually high as after the inhalation of a high CO_2-O_2 mixture. Further, on such a straight line the slope should be zero or

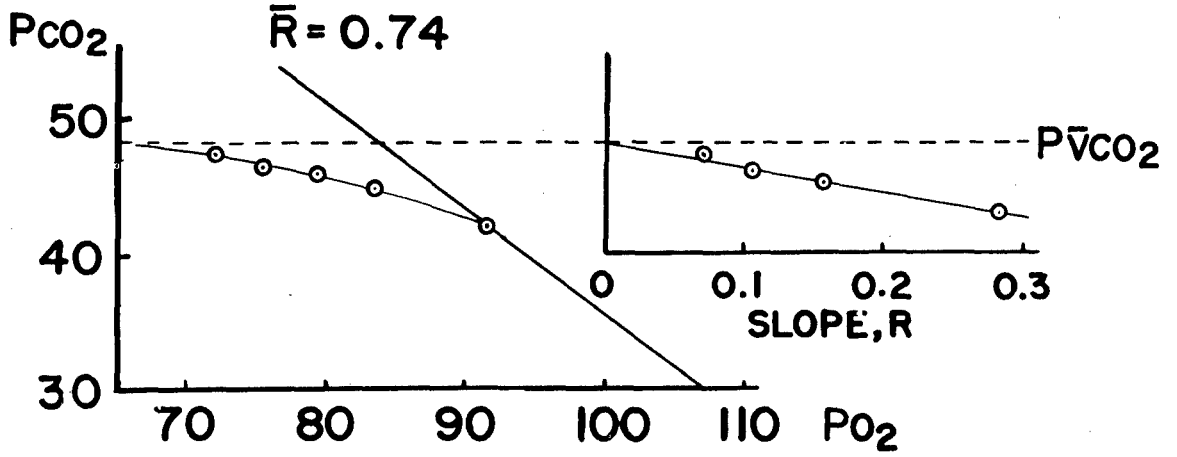


Figure 1

Breath holding curve on the left plotted on a CO_2-O_2 diagram. On the right the slopes of this curve are plotted against the corresponding Pco_2 values to give a straight line. A slope = 0 indicates the oxygenated venous CO_2 tension represented by the broken line.

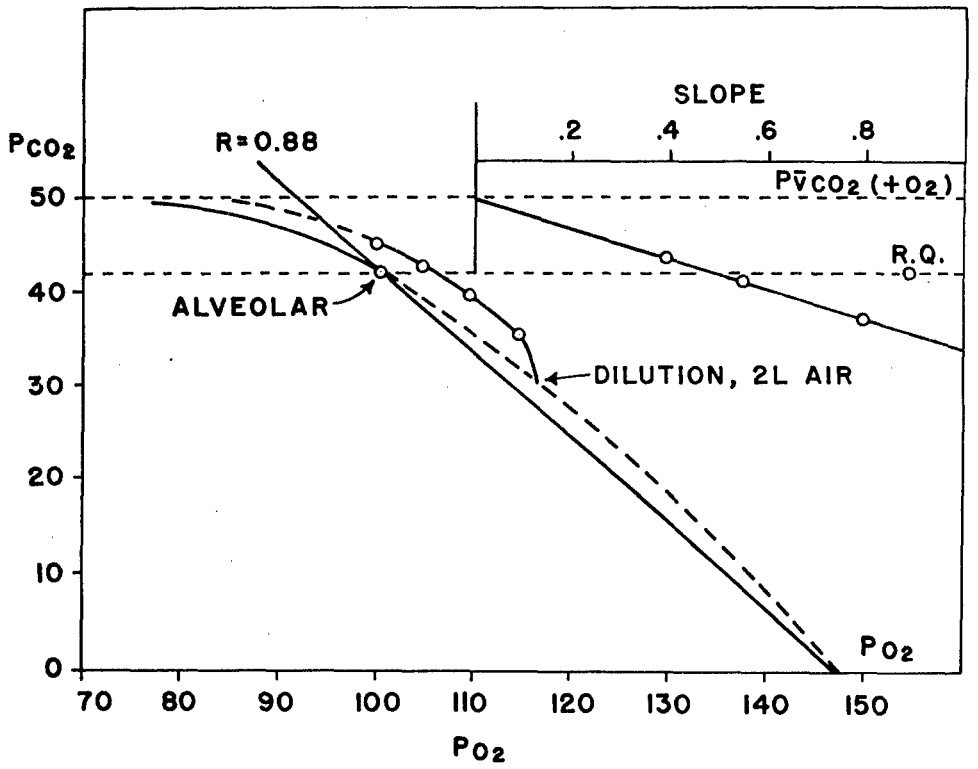


Figure 2

Breath holding concentrations after dilution of the lung volume with 2 L of air (see text).

should change from positive to negative at the alveolar Pco_2 value representing the oxygenated venous Pco_2, this being the asymptote which is being approached sometimes from below and sometimes from above.

RESULTS

A sample normal breath holding curve is shown on the left in Figure 1. The initial point on the R diagonal was an end expiratory alveolar sample and is for this reason rather high and the exchange ratio, R, rather low. Four points were obtained after holding the breath for 5, 10, 15 and 20 seconds, respectively. The mean slope of the curve between each pair of points has been calculated (with the correction described) and is plotted on the left using the same ordinates but another scale of abscissae. These points lie on a straight line which intercepts the line of zero slope at a Pco_2 value of 48.5 mm which represents then the asymptote or the oxygenated venous Pco_2.

Figure 2 shows a similar plot for breath holding after the inhalation of 2 liters of air beginning after a normal expiration when the exchange ratio was 0.88. In this case the calculated dilution point might be expected to lie on a straight line connecting the alveolar point with the inspired air point. If, however, allowance is made for the CO_2 combining power of the lungs, then the dilution point should lie on the curved dotted line, the equation for which will be given later. The observed points lie still higher than the broken line, each point being obtained after a different period of breath holding varying from 0 to 20 seconds. The slopes of the curve between each pair of points was obtained (after correction for nitrogen fraction), and the values plotted as before against the same Pco_2 ordinates but with new abscissae. Again these points appear to lie on a straight line which intersects the line of zero slope at the venous oxygenated Pco_2 value indicated by the horizontal dotted line. A normal breath holding curve is indicated at the left of this figure beginning at the alveolar point but the experimental points are not included. It is difficult to complete two breath holding curves on the same subject at one sitting without change in the alveolar point and perhaps the venous Pco_2.

A similar pattern is found for breath holding after inhalation of a high CO_2 mixture as shown in Figure 3. Here the theoretical dilution point might be expected to lie somewhere on a line connecting the alveolar and the inspired mixture point but because of the extra CO_2 absorbed by the lungs the theoretical dilution lies not as a straight line but on the broken curved line as indicated. The subsequently observed breath holding points lie on the solid line, the dotted curve being the same points as they would have appeared if the nitrogen fraction had remained at the theoretical dilution value. Each of these corrected points lies on a straight line connecting the observed point with the origin of the chart where Po_2 and Pco_2 are both zero. The slope of the corrected curve represents the true exchange ratio and the points so calculated have been plotted on the insert figure to the right at the appropriate Pco_2 value for that interval. Two slopes for the

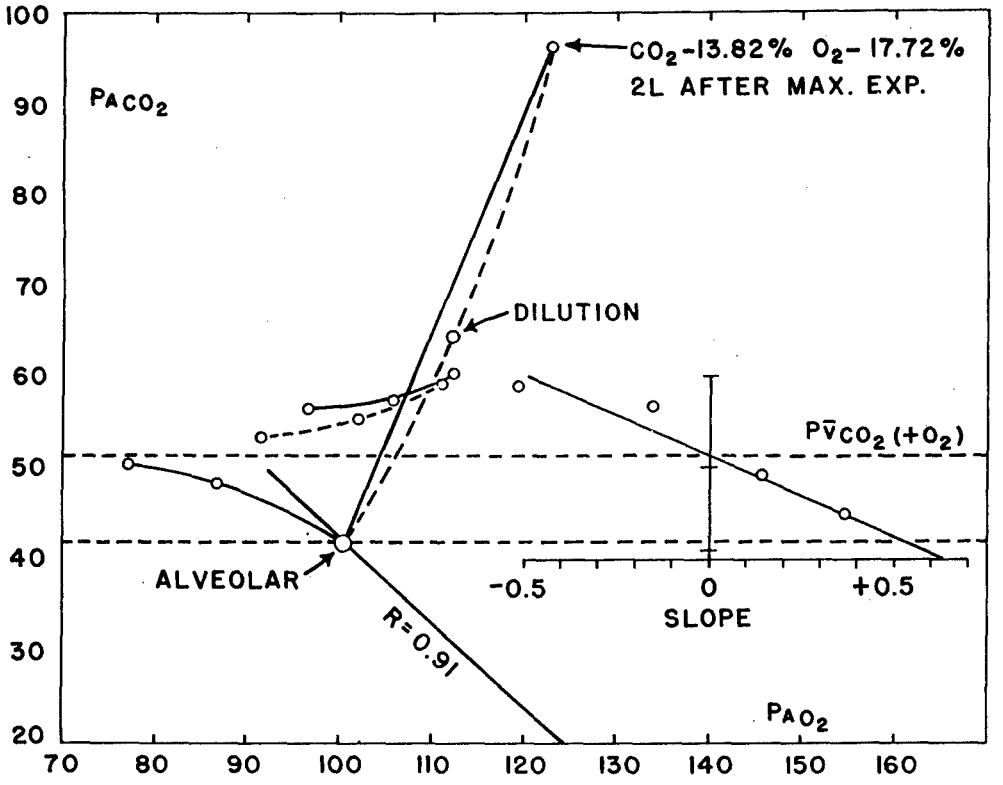


Figure 3

Breath holding concentrations after inspiring 2 L of a gas mixture containing 13.8% CO_2 (see text).

normal breath holding curve of the same subject have been included for comparison. It is clear that all four points can be considered as lying on the same straight line cutting the line at zero slope at Pco_2 = 51 which is the oxygenated venous tension.

A plot of all the data for one of our subjects by all three types of experiments is given in Figure 4. Since the venous CO_2 tension was not the same on different days, it was necessary to plot not actual Pco_2 values but venous-alveolar pressure differences as ordinates against the slopes of the breath holding curve as abscissae. The normal, dilution and CO_2 inhalation regions are indicated on the chart. As indicated by the symbols there were three different normal breath holding experiments, two dilution experiments and one for CO_2 inhalation. It is remarkable how accurately the points from the first two types of experiments fall along the same straight line. For unknown reasons the points for all our CO_2 inhalation

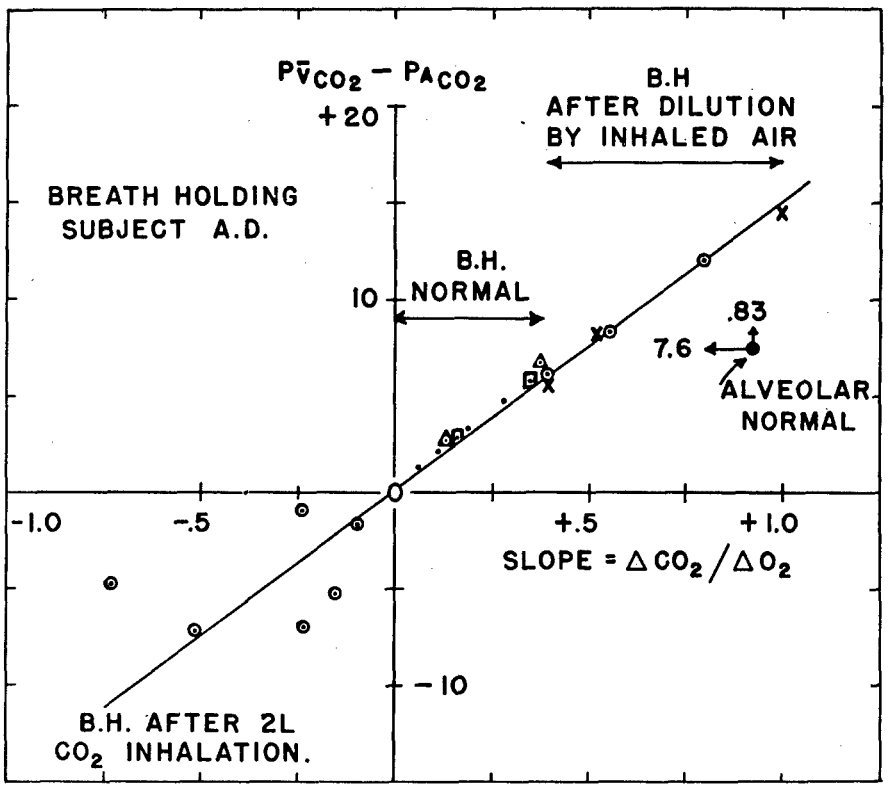


Figure 4

Relationship between the alveolar-venous Pco_2 difference and the instantaneous exchange ratio during normal breath holding, during breath holding after a 2 liter dilution with air and after a 2 liter dilution with a high CO_2-air mixture.

experiments are less predictable but possibly they scatter uniformly around the expected positions. The irregularity suggests, however, that CO_2 may be exerting some effect upon the ventilation perfusion ratios in the different alveoli. This point requires further investigation. The irregularity, however, is probably not due to incomplete mixing because in several air-inhalation experiments we compared the 10 sec. breath holding gas tensions with those obtained after 10 sec. of rebreathing to a bag. Since no significant differences were found, it is apparent that inadequate mixing is not a factor of critical importance in these experiments.

DISCUSSION

1. The dilution curve:

The location of the theoretical dilution point after inhalation can be calculated from the composition and volume of gas inhaled and of that originally present if perfect mixing be assumed. Actually if there is a significant CO_2 combining capacity in the lungs themselves, the dilution point will lie not on the R.Q. diagonal, but on the broken curved line which parallels it and rejoins it at the inspired air point. The reason for this is that CO_2 escapes from the walls of the lungs as dilution proceeds and prevents the Pco_2 from falling as low as it otherwise would. The oxygen in other words is diluted more than the CO_2. When the volume inhaled becomes very large indeed, then the small amount of CO_2 which enters the lungs from the walls becomes negligible and the broken line deviates less from the solid line. This explains why the two lines coincide again at the inspired air point where the volume inhaled is infinite.

Let V_A and V_I equal, respectively, the volumes of alveolar and inspired gases, measured at BTPS. V_A represents all the gas in the lungs and dead space at the end of a normal expiration. V_I represents the inhaled volume minus the dead space. These then are the volumes actually mixed. The composition of the resulting mixture is calculated as follows, assuming complete mixing and no gas exchange with the blood. Subscripts I, A and M refer, respectively, to inspired, alveolar, and mixed gases. V'_A is the equivalent lung volume for CO_2 and is therefore slightly larger than V_A. Thus

$$P_{Ao_2} V_A + P_{Io_2} V_I = P_{Mo_2} (V_A + V_I) \tag{1}$$

$$P_{Aco_2} V'_A = P_{Mco_2} (V'_A + V_I) \text{ since } P_{Ico_2} = 0 \tag{2}$$

Combining these equations and eliminating V_I gives

$$\frac{P_{Mo_2} - P_{Ao_2}}{P_{Io_2} - P_{Mo_2}} \times \frac{V_A}{V'_A} = \frac{P_{Aco_2} - P_{Mco_2}}{P_{Mco_2}} \tag{3}$$

This is the equation for the broken line of Figures 2 and 3 when $\frac{V_A}{V'_A} = 0.83$ as found by DuBois (2). When this ratio = 1, the dilution curve is, of course, a straight line connecting the points on the diagram which represent the composition of V_A and V_I.

It is not easy to prove in the human lung that dilution follows equation 3 rather

than a straight line. Some confirmation, however, is provided by some unpublished data of A. B. DuBois obtained in this laboratory which he has kindly permitted us to quote.

His experiment consisted in inhaling quickly 2 liters of air, beginning at the end of a normal expiration and then exhaling maximally as quickly as possible. The exhaled gases were analyzed to give the composition of the mixture resulting from the maneuver. The average results compiled from his data on 9 subjects are given in Table 2 and show that the Po_2 of the mixture was within 1 mm of the predicted value (calculated from equation 1), while the Pco_2 was 28.9 compared to the value of 24 mm calculated from equation 2. Using equation 3 the value of V_A' is calculated as 5.48 giving a V_A/V_A' ratio of 0.62. If 2 mm is added to the P_{Ao_2} and 1.6 mm is subtracted from the P_{Aco_2} to allow for 2 sec. of gas exchange during the maneuver, the equivalent lung volume is calculated as 5.3 L and the V_A/V_A' ratio as 0.64. While for some reason this value is undoubtedly too low, it does indicate rather clearly that CO_2 behaves differently in the lung than O_2 because of its greater solubility in the slightly alkaline solutions.

From our own records of 14 experiments on 5 subjects there are available data similar to those in Table 2. In these experiments 2 or 3 liters of air were inhaled beginning either after a forced expiration (to the residual air) or after a normal expiration. Comparisons were made between the observed and the calculated values of the dilution points. Theoretical CO_2 values were calculated on the assumption that the lung behaves toward CO_2 exactly as it does toward O_2, i.e., that $V_A/V_A' = 1$. Values were calculated for the ratio of "Observed minus calculated CO_2" to "Calculated minus observed O_2." In one of our subjects, age 60 yrs., there was obviously poor mixing in the lungs and the ratio had a value of 1.0 or less. In 2 subjects the ratio was 1.5 to 2.0 which is about the expected initial slope of the breath holding curve after sudden dilution of the CO_2 to about half the normal value. The other 2 subjects behaved very much like the subjects studied by DuBois with a ratio of 4-5, i.e., the calculated oxygen values agreed closely with the observed values but the Pco_2 was much too high. If, however, 2 or 3 mm Pco_2 is subtracted from the "Observed minus calculated CO_2 difference", then the ratio is about 2. We conclude that 3 of our subjects showed various degrees of incomplete mixing and that some of the high CO_2 discrepancies are due to escape of CO_2 from the walls of the lungs.

2. The initial slope of the breath holding curve

In Figure 2 it is evident that the initial slope of the breath holding curve is less than that of the R.Q. diagonal. Looking at the insert plot of slope vs. Pco_2, it is evident that the straight line would have to be extrapolated to the right to considerably lower Pco_2 values to reach a slope of 0.74. This discrepancy is obviously due to the fact that the alveolar sample was taken from an end expiratory sample and it

does not represent ideal alveolar air. If there were no CO_2 binding capacity of the lungs, then the initial slope of the breath holding curve should be equal to the mean R.Q. at the ideal alveolar air point. It seems possible therefore to use our data to obtain a value for the ratio of V_A to V_A'.

Let $\underline{d}_{O_2}$ = the instantaneous arterio-venous oxygen content difference in liters of gas per liter of blood (assumed equal to the mean value);

$\underline{d}_{CO_2}$ = the same for carbon dioxide; and

$d_{\overline{CO_2}}$ = the mean normal value of the same before breath holding;

R = the exchange ratio at any time during breath holding, $\overline{R}$ being the mean normal value before breath holding;

P_{Aco_2} and P_{Ao_2} = alveolar tensions of CO_2 and O_2 during breath holding;

$P_{\overline{V}co_2}$ = the mean (oxygenated) venous CO_2 tension;

$P_{\overline{A}co_2}$ = the mean alveolar CO_2 tension before breath holding;

S = the reciprocal slope of the P_{Aco_2} vs. R curve (Fig. 1, right) or

$$S = \frac{R}{P_{Vco_2} - P_{Aco_2}} \tag{4}$$

Then at any time during breath holding, if the lung volume be held constant

$$\frac{dP_{Ao_2}}{dt} = \dot{Q}\,\frac{\underline{d}_{O_2}}{V_A} \quad \text{(B-47)} \tag{5}$$

$$\frac{dP_{Aco_2}}{dt} = \dot{Q}\,\frac{\underline{d}_{CO_2}}{V_A'} \quad \text{(B-47)} \tag{6}$$

Dividing equation (6) by equation (5) gives

$$R = \frac{dP_{Aco_2}}{dP_{Ao_2}} = \frac{\underline{d}_{CO_2}}{\underline{d}_{O_2}} \frac{V_A}{V'_A} \qquad (7)$$

Since in the steady state $\bar{R} = \underline{d}_{\overline{CO_2}} / \underline{d}_{O_2}$

$\frac{R}{\underline{d}_{CO_2}} = \frac{\bar{R}}{\underline{d}_{\overline{CO_2}}} \frac{V_A}{V'_A}$ or, since d_{CO_2} and $d_{\overline{CO_2}}$ are proportional, respectively,

to the corresponding CO_2 tension differences

$$\frac{R}{P_{\bar{V}co_2} - P_{Aco_2}} = \frac{\bar{R}}{P_{\bar{V}co_2} - P_{\bar{A}co_2}} \times \frac{V_A}{V'_A} = S \qquad (8)$$

$$\text{and } \frac{V_A}{V'_A} = \frac{S}{\bar{R}} \left(P_{\bar{V}co_2} - P_{\bar{A}co_2}\right) \qquad (9)$$

In Table 1 are given mean values of S, $\bar{R}$ and $(P_{\bar{V}co_2} - P_{\bar{A}co_2})$ for 4 subjects in 10 different experiments. The last column gives the values of $\frac{V_A}{V'_A}$ calculated from equation (9).

As already mentioned this calculation gives too low a value for $\frac{V_A}{V'_A}$ because we used end expiratory alveolar air samples.

To correct this to a true alveolar value we take $P_{Io_2} = 146$ at B = 747 and assume $P_{Aco_2} = 39$ mm Hg. Then with an average R = 0.803, $P_{Ao_2} = 99.6$ from the alveolar air equation. According to Rahn, et al (1946), the ideal alveolar value should be 2.5 mm Pco_2 lower and 4.8 mm Po_2 higher. Using, therefore $P_{Aco_2} = 36.5$ and $P_{Ao_2} = 104.4$, the $\bar{R}$ calculates to 0.85.[1] From equation 5 we then obtain $V_A/V'_A = \frac{.0763\ (7.32 + 2.5)}{.85} = .88$. The value obtained by DuBois (2) was 0.83 (S.E. .08) when

1 Rahn found the R.Q. by the Haldane method.0 31 R.Q. units too low compared to the expired air R.Q. (6).

Table 1

SUMMARY DATA FROM NORMAL BREATH HOLDING CURVES OF 4 SUBJECTS

Subject	Slope, S	$\bar{R}$	$P_{\bar{V}co_2} - P_{\bar{A}co_2}$	$\frac{V_A}{V'_A}$
S	.0783	.839	7.5	.70
		.935	8.7	.73
		.74	8.0	.85
A	.0875	.84	7.0	.73
		.78	6.0	.67
		.91	10.0	.96
C	.0670	.70	5.3	.52
		.77	7.0	.63
		.73	7.5	.71
D	.0725	.79	6.2	.57
Average	.0763	.803	7.32	.71
Corrected	.0763	.866	9.82	.88

Table 2

SUMMARY OF DILUTION OF ALVEOLAR GAS BY INHALATION OF AIR: DATA OF DuBOIS

	Alveolar	Inspired	Calc.	Obs.
CO_2 mm	37.7	0	24	28.9
O_2 mm	101.3	146	117	116
Volume, L BTPS	3.4	1.95*		

* 2 L corrected to BTPS and minus 200 cc dead space.

the curve of each subject was taken individually and 0.89 when the mean breath holding curve was used.

Admittedly this is a very precarious correction to rely upon. It is difficult, however, to make any reasonable correction of our average values which will make $V_A/V'_A = 1.0$. It can be done, for example, by subtracting 5 mm from our values for P_{Aco_2} and adding 6 mm to P_{Ao_2} and taking our $P_{Aco_2} = 40$ and $P_{Ao_2} = 98$. A 5 mm Pco_2 correction seems, however, impossibly large in this condition.

In this paper we present a method of analyzing breath holding curves which is different and perhaps somewhat simpler than that used by DuBois, although it is based upon the same general principles. Our data also confirm the general conclusion that the CO_2 combining capacity of the lung and its contained blood makes the lung effectively slightly "larger" for CO_2 than for O_2, the corrected ratio of V_A/V'_A being 0.88. In a lung weighing 1 kgm with a volume of 3 liters, this indicates a storage of CO_2 of 0.45 cc per kgm of lung per mm tension. If only half the lung is close enough to the alveoli to store CO_2 then the calculated storage capacity per kg is twice as great.

Since the slope of the breath holding curve becomes progressively less with time, and since breath holding really begins at the end of inspiration, there must be some point where the slope is equal to the mean exchange ratio, $\overline{R}$. If the CO_2 storage capacity of the lungs were negligible, this point of equality would be at a Pco_2 equal to the mean of the respiratory cycle. Our data would confirm those of DuBois in indicating that even at this mean alveolar air point the slope of the breath holding curve is less (0.88) than the mean exchange ratio.

It is obvious that this breath holding experiment could be used for the determination of cardiac output because it provides a value for the oxygenated or virtual venous CO_2 tension. In our hands, however, the accuracy and convenience is not sufficient to recommend the method for practical use. With a continuous CO_2 and O_2 recorder, however, the situation might be different. The method should work equally well if instead of holding the breath the subject were to rebreathe into a small bag with continuous records of the gas concentrations of the in-going and outgoing mixture. A single record of such a rebreathing experiment together with a measurement of the CO_2 output rate would permit a calculation of cardiac output.

SUMMARY

1. The breath was held after a normal expiration, or after a large inhalation of air or of a CO_2-O_2 mixture. The composition of the alveolar gases was followed by analyzing the air exhaled after varying periods of time not exceeding a

recirculation time of 20 seconds. The oxygen tension was always sufficient to saturate the hemoglobin and the carbon dioxide tension changes were analyzed in reference to the changes in oxygen tension rather than time in order to avoid errors due to transient changes in cardiac output.

2. The exchange ratio ($\Delta Pco_2 / \Delta Po_2$) was found to be proportional to the venous-alveolar Pco_2 difference.

3. The CO_2 combining capacity of the lung is calculated to be 0.45 cc per kgm of lung per mm increase in Pco_2.

4. It is shown that when the alveolar air is diluted by inhalation the alveolar point proceeds along a curved line on a Pco_2-Po_2 diagram depending upon the CO_2 combining capacity of the lung.

5. The functional residual capacity of the lung is found to be about 0.88 times as great as the equivalent lung volume for CO_2 at the end of a normal expiration.

REFERENCES

1. DuBois, A. B., A. G. Britt and W. O. Fenn J. Appl. Physiol. 4: 535, 1952.
2. DuBois, A. B. J. Appl. Physiol. 5: 1, 1952.
3. DuBois, A. B., W. O. Fenn and A. G. Britt J. Appl. Physiol. 5: 13, 1952.
4. Field, H., Jr., A. B. Bock, F. F. Gildea and F. L. Lathrop J. Clin. Invest. 1: 65, 1924.
5. Rahn, H., J. Mohney, A. B. Otis and W. O. Fenn J. Aviation Med. 17: 173, 1946.
6. Rahn, H. Am. J. Physiol. 158: 21, 1949.

THE EFFECTS OF POSTURE UPON THE GAS EXCHANGE AND ALVEOLAR GAS COMPOSITION

by

H. Rahn and R. Ament

Probably no mammal subjects its circulatory system more frequently to greater changes in gravitational vectors than man. His daily activity is carried on in the standing, sitting or supine position and their effects upon the circulatory adjustments are well recognized. The circulatory changes in turn provide an answer to many of the peculiar and subtle changes which one observes in the ventilation as well as the gas exchange, the gas exchange ratio and the alveolar gas composition. It is with these pulmonary changes that this study concerns itself and for a review of the older literature the reader is referred to Hellebrandt and Franseen (1) and Owe-Larsson (2). One can summarize the essential changes that follow the tilting from the supine to the erect posture in the following manner: the cardiac output is reduced, while the metabolic rate is increased; the ventilation, on the other hand, increases relatively more than the metabolic rate with the results of a lowered alveolar or arterial P_{CO_2} and an increase in the arterial pH. It is this paradox of a more alkaline arterial blood and lowered arterial P_{CO_2} associated with a true hyperventilation during the standing posture that has given rise to much speculation. In addition we have observed changes in the respiratory exchange ratio and rather large transient changes in the oxygen uptake and ventilation, all of which appeared to us rather baffling in the beginning. Some of the newer concepts developed during the recent years provide for a partial answer, we believe, to the observation made during the change of posture.

METHODS

Our approach consisted in recording continuously, as far as possible, the changes in ventilation, frequency of breathing, O_2 uptake, CO_2 output, alveolar CO_2 and O_2 as well as the heart rate when healthy subjects were tilted from the supine into the standing position, or vice versa. During 'standing' the subject stood on his feet while his back was supported by the tilt table at an angle of 20° from the vertical.

Technically, the experiments fell into two groups. In one the ventilation, alveolar O_2 and CO_2 and heart rate were studied. In the other the chief emphasis was placed upon obtaining O_2 uptake and CO_2 output values at frequent intervals. For the former the methods previously employed were used involving the end-tidal gas sampler and continuous analysis of the alveolar O_2 and CO_2 (3). For the

determination of the metabolic rate at 1-minute or longer intervals a rather cumbersome apparatus had to be constructed which consisted of two 100-liter spirometers and two 15-liter spirometers. Thus in a typical run the expired gas could be collected in a large spirometer for 8 minutes at the end of 10-minute supine period. Upon tilting, the expired air was shunted for 1 minute each into each of the small spirometers and for the remaining 8 minutes again into the large spirometer. A series of large metal stopcocks allowed for the uninterrupted shunting of expired gas from one spirometer into the next. This also required the exact knowledge of the connecting hose volume as well as spirometer dead space in order to make proper corrections for the collected expired air in each individual spirometer. These dead spaces were determined by the air dilution technique using N_2 as the diluting gas. One other artifact had to be taken into consideration, namely, the change in the functional residual capacity upon tilting. This change was determined for each subject and amounts to approximately 700 ml. Going into the standing position this volume is inspired but not returned in the expired air. However, its O_2 and CO_2 are changed to the alveolar level. Upon tilting from the standing to the supine position approximately 700 ml of alveolar gas is suddenly displaced into the spirometers in addition to the normal expired gas.

In all experiments the subjects were placed in the supine position for at least 20 minutes before any recordings were started. In the first group of experiments observations were made every minute on the minute.

RESULTS

Figure 1 shows the values for 6 subjects recorded each minute and averaged. The heart rate increases immediately upon tilting to standing and continues to rise. The ventilation follows a similar trend, while the alveolar Po_2 shows a rather large initial increase and the alveolar CO_2 falls correspondingly. The most pronounced change, however, is observed when the subject is tilted back to the supine position. Not only is there considerable subjective relief from the stress of passive standing but the subject is usually quite aware of a short period of hyperventilation. This hyperventilation is quite apparent in Figures 1 and 2. When the subject is subjected to a similar routine of sitting, active standing, sitting, a similar but much less pronounced brief hyperventilation is seen. Of particular interest is the fact that during this hyperventilation the alveolar CO_2 rises and the O_2 falls, suggesting that the O_2 uptake and CO_2 output must have suddenly increased. The other interesting feature is that the gas exchange ratio, R, during the period of standing is only elevated during the first 2 or 3 minutes. Thereafter it is the same or usually slightly lower than during the supine period. This is contrary to expectations because a hyperventilation which produces a lowering of the alveolar CO_2 from 4 - 5 mm is expected to release CO_2 stores from the blood and tissues and thus raise the exchange ratio above the control period for many minutes.

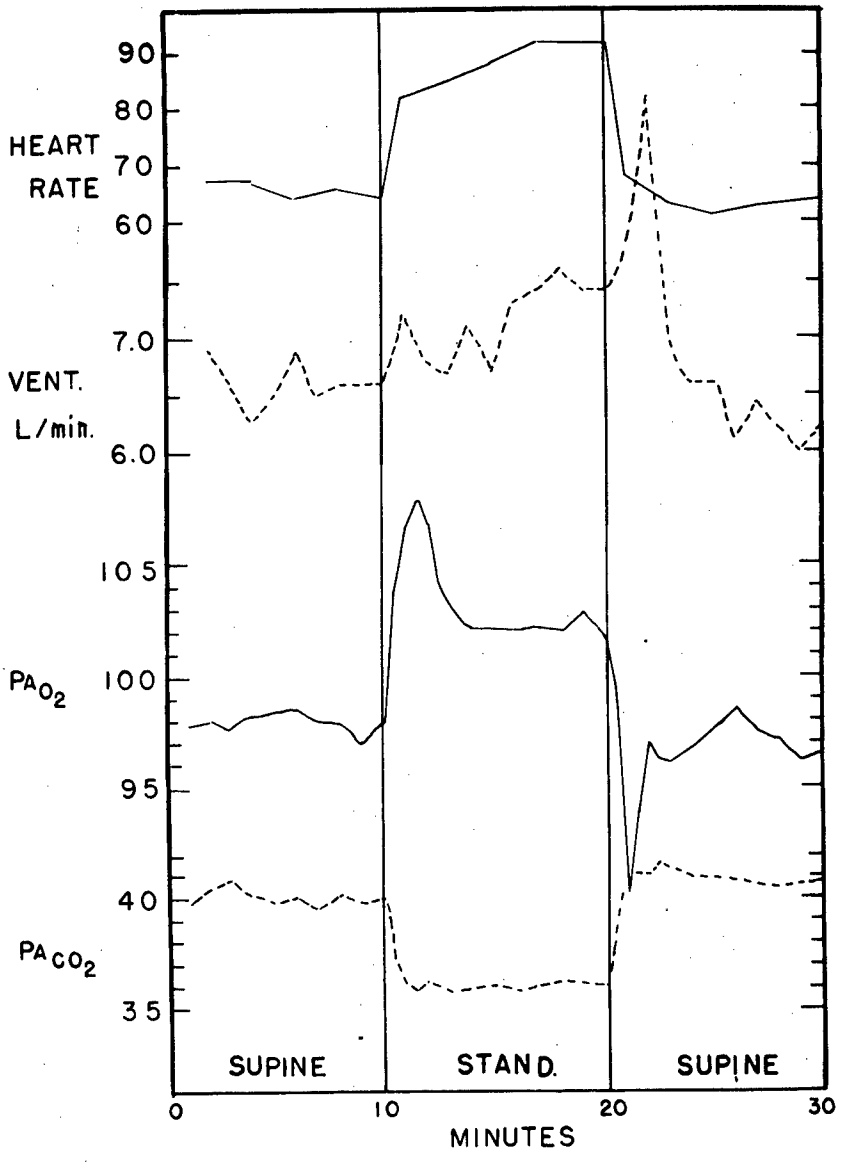


Figure 1

The effects of tilting on the heart rate, total ventilation, alveolar O_2 and CO_2. Average of 6 subjects.

In order that some of these phenomena could be studied in greater detail, the same experimental routine was repeated in five subjects in order to determine the

O_2 uptake and CO_2 output. Due to the limited number of spirometers available, this experiment had to be done in two stages. In the first experiment the changes from the supine to the standing position were determined and in the second experiment the changes from the standing to the supine position as shown by the averages in Table 1. The two sets of data are combined in Figure 2.

TABLE 1

The O_2 and CO_2 Exchange upon Change of Posture. All Values are at S.T.P.D. Average of 5 subjects.

Posture	Minutes	$\dot{V}O_2$ ml/min	$\dot{V}CO_2$ ml/min	R	$\dot{V}_E$ lit/min
Expt. 1					
Supine	2 - 10	286	227	.80	5.23
Standing	0 - 1	293	256	.86	6.28
	1 - 2	254	198	.78	5.19
	2 - 10	319	233	.73	6.16
Expt. 2					
Standing	2 - 10	325	239	.74	6.06
Supine	0 - 1	540	351	.65	7.91
	1 - 2	363	274	.76	6.17
	2 - 10	280	214	.76	5.09

Finally, a summary of the end-tidal alveolar gas concentrations found in our subjects in various postures is given in Table 2. These experiments cover a span of about 5 years and many of them represent control periods of experiments reported elsewhere. They indicate a trend of increasingly lower alveolar CO_2 values as the posture goes from the supine to the standing position. The alveolar Po_2 values vary inversely with the CO_2 values but are subject to the additional effects of changes in barometric pressure which at Rochester, New York, may vary from 735-755 mm, with an average close to 747. Thus one may occasionally obtain Po_2 values which may be 2 mm higher or smaller than that found on the average for a given CO_2 and R. The values in Table 2 are averages of 10 consecutive minute readings for each of the subjects. Altogether 14 male subjects

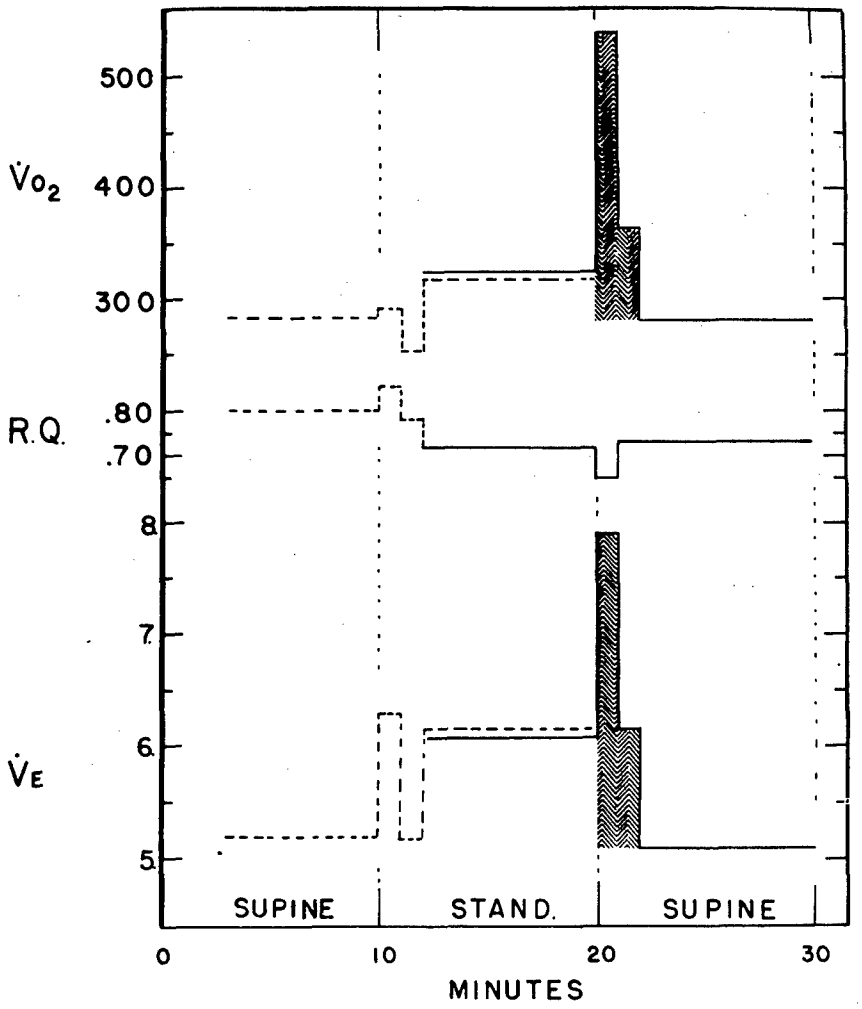


Figure 2

The O_2 uptake, calculated R.Q. and total ventilation during tilting. Average of 5 subjects. For details consult Table 1.

TABLE 2

Posture and the End-Tidal Alveolar Gas Tensions Compiled from Various Experiments over many years. The average Barometric Pressure is 747 mm Hg. For each subject 10 consecutive minute readings were averaged.

Posture	P_{CO_2}	P_{O_2}	No. Subjects
Supine	41.4	96.6	7
Supine	40.4	97.2	5
Supine	40.1	98.8	6
Supine	39.7	100.0	5
Supine	39.3	100.2	5
Reclining Seat	39.3	100.6	10
Reclining Seat	39.1	100.0	10
Straight Seat	38.4	99.2	7
Sitting on Bike	37.6	102.1	6
Standing	36.8	100.4	7
Standing	35.7	103.0	5

contributed to these values. Altogether Table 2 represents more than 700 minute-to-minute readings. The R values averaged from .79 to .84.

DISCUSSION

That the alveolar P_{CO_2} is lower in the standing position than in the sitting or supine position is a well-established fact and similar values to ours have been reported by many others (4,5,6,7,8). The O_2 uptake is also increased and since the alveolar CO_2 falls the alveolar ventilation must increase relatively more than the metabolic rate. With such conditions one must ask what prevents the exchange ratio from rising and what factor is responsible for the maintained hyperventilation in spite of the increased alkalinity of the arterial blood.

If the cardiac output of the supine position were maintained upon standing then one can compute from the tables of Farhi and Rahn (9) that lowering of the alveolar CO_2 by 5 mm should release approximately 300 ml of CO_2 from the stores of the tissues and blood. However, Table 1 indicates that the exchange ratio rises only during the first minute of standing but thereafter actually falls.

The experiment in Figure 1 also allows one to compute the R from the alveolar values and, although not shown, indicates that after the first 2 minutes of standing the R value is .78, while in the supine position the R was .80. Upon returning from the supine position to the standing position, the subject goes into a relative hypoventilation and therefore should now build up his CO_2 stores by approximately 300 ml. This is normally achieved by retention of metabolic CO_2 and therefore a temporary fall in exchange ratio. But again all our experiments show only a reduced R during the first minute or two after regaining the supine position and these values are not low enough to explain a theoretical CO_2 store shift of about 300 ml. Similar tilting experiments reported elsewhere (10) support these findings, and thus agree well with the observations of Hitchcock and Ferguson (6).

It is believed that the rather stable exchange ratio values during the hyperventilation in the standing position can be explained by the reduction in cardiac output. As long ago as 1927 Turner (4) showed that as the alveolar Pco_2 fell from 40 in the reclining position to 35 in the standing posture, the cardiac output was reduced from 6.3 lit/min to 4.8. McMichael and Johnston (11) made similar observations and also showed that when the subject was returned from the standing to the supine position, the cardiac output was markedly increased for the first 30 seconds. With the use of catheterization, Stead et al (12) showed that upon standing the $(A-V)_{O_2}$ difference increased from 3.7 - 5.4 and the cardiac index was reduced 23% upon standing, while the O_2 uptake increased 7%. If we now calculate the amount of CO_2 needed to raise the venous blood and tissue Pco_2 to the level required by a 25% reduction of the cardiac output (9), we find that 280 ml are required which approximately balances the calculated excess produced by the hyperventilation had the cardiac output remained normal. Thus we have upon tilting a rather peculiar state of balance where the reduction in cardiac output balances the hyperventilation in such a way as to leave the CO_2 tensions of the venous blood and tissue approximately the same. This concept obviously applies only to the overall average tissue tensions, while individual organs may be variously affected by the tilting as shown by Hitchcock and Ferguson (6). In fact, it seems that the reduction in cardiac output and its concomitant CO_2 retention slightly outweighs the hyperventilation with its concomitant CO_2 store release since in many experiments the exchange ratio actually falls, indicating a slight CO_2 retention still noticeable after 10 minutes of standing.

Similar calculations can be applied to the O_2 stores. The hyperventilation will theoretically increase the O_2 stores but insignificantly, while the reduction in cardiac output of 25% will reduce the O_2 stores by about 80-100 ml. This amount can be utilized by the tissues directly and will therefore reduce the uptake by this amount as measured in the lung. This may account for the lowered O_2 uptake during the first 2 minutes of standing. During the second minute this uptake was lower than during the supine control period in 4 of the 5 subjects, while in the other subject it was lower during the first minute. It would also explain in part the extra O_2 uptake required at the resumption of the supine posture when this O_2 store has to be refilled. The slightly raised R during the first minute of standing

is probably due to the increased ventilation produced by the increase in the functional residual capacity. This is equivalent to a true alveolar ventilation but does not appear in Table 1 or Figure 1 or 2 since it is not expired until the supine position is again resumed.

In brief, we believe that upon standing, the changes in ventilation and cardiac output influence the O_2 and CO_2 stores of the body in such a way as to explain the reduced O_2 uptake during the first 2 minutes of standing and the rather stable respiratory quotient. The theoretically computed gas store changes (9) support the observed changes surprisingly well.

One must now focus upon the rather drastic changes which occur during the first 2 minutes after resumption of the supine position after a 10-minute period of standing. Not only is the ventilation increased but the O_2 uptake and CO_2 output as well. If the O_2 uptake during the last 8 minutes of the supine period is taken as an index of the normal requirements (280 ml - Table 1), then the extra O_2 uptake is about 400 ml — as indicated by the shaded region in Figure 2. As discussed before, about 80 - 100 ml are due to restoring the O_2 stores as the cardiac output is again increased. This still leaves about 300 ml which cannot be accounted for by blood stagnation alone and can therefore be only explained as a true O_2 debt occurring at the site of muscles and elsewhere. This debt is then quickly repaid and accounts for the major increase in O_2 uptake.

It is interesting to note that the ventilation adjusts itself to this extra metabolic demand but is not quite able to compensate completely — hence a temporary drop in R during the first minute.

Hitchcock and Ferguson (6) were probably the first to call attention to rather dramatic increase in O_2 uptake during the first few minutes. They attributed this also to a true O_2 debt, but their figures also indicated that during the standing posture the O_2 uptake was actually lower in many cases than during their control period of the supine position. Although our figures in Table 1 supply only the average value, in each instance of our 10 experiments, the O_2 uptake was enhanced upon standing. This is in agreement with most other workers (8,11,12).

The increased ventilation associated with a relatively more alkaline arterial blood during standing has provoked considerable discussion in the older literature. One common explanation suggests that the hyperventilation is a carotid sinus reflex triggered off by the reduced arterial pressure. A reduced cerebral circulation has also been associated with this hyperventilation. It is of interest to note that more recently a 21% decrease has actually been measured by Sheinberg and Stead (13) in normal subjects during motionless standing. The $(A\text{-}V)_{O_2}$ difference increased from 6.0 to 7.4, while cerebral O_2 uptake remained constant.

It is furthermore of interest to consider the findings of Lambertsen et al (14) who have shown that the P_{CO_2} of the venous blood draining the brain is much better

correlated with the ventilation than the Pco_2 of the arterial blood. One may thus visualize that in the erect posture the cerebral blood flow is initially reduced by the 22 mm Hg fall in the carotid artery pressure (13). This increases the venous Pco_2 and stimulates the respiratory center (14). The resulting alkalinity and reduced Pco_2 of the arterial blood tends to produce a cerebral vasoconstriction preventing any complete compensation of the blood flow which might have otherwise been accomplished by reflex mechanisms. Thus a new steady state could be maintained between the arterial and respiratory center CO_2 tensions. It is obvious that this is a vicious cycle for should the cerebral flow be further diminished by a falling blood pressure, the respiratory center CO_2 will increase still further, producing greater ventilation and a larger fall in arterial CO_2, which in turn reduces the cerebral flow even more. Whether or not this is the course of events it is interesting to note that in other experiments, not reported here, the imminent collapse of a subject after periods of standing could always be predicted several minutes before by a sudden drop in the alveolar CO_2.

SUMMARY

1. The effects of tilting man from the supine to the standing position and back to the supine position have been reinvestigated by continuous measurements of the ventilation, alveolar O_2 and CO_2, O_2 uptake and CO_2 output, as well as the heart rate. By these continuous measurements certain phenomena were observed which had previously been only incompletely recorded.
2. A new explanation is provided for the fact that the respiratory quotient is not appreciably altered, in fact somewhat reduced during standing in spite of the fact that a real hyperventilation occurs. This is based upon theoretical calculations of the behavior of body CO_2 and O_2 stores when the ventilation is increased at the same time as the cardiac output is reduced, as happens during standing. Some of the minor transient changes in O_2 uptake can also be explained on this basis.
3. The concept of Lambertsen has been applied to explain the continued hyperventilation during the standing position.
4. A table is provided which shows how the alveolar CO_2 and O_2 vary in man at rest in various postures.

REFERENCES

1. Hellebrandt, F. A. and E. B. Franseen Physiol. Rev. 23: 220, 1943.
2. Owe-Larsson, A. O. Acta Physiol. Scand. 6: 324, 1943.
3. Rahn, H. and A. B. Otis J. Appl. Physiol. 1: 717, 1949.
4. Turner, A. H. Am. J. Physiol. 80: 601, 1927.
5. Main, R. J. Am. J. Physiol. 118: 435, 1937.

6. Hitchcock, F. A. and J. K. W. Ferguson Am. J. Physiol. 124: 457, 1938.

7. Mackay, I. F. S. J. Physiol. 102: 228, 1943.

8. Franseen, E. and F. A. Hellebrandt Am. J. Physiol. 138: 364, 1943.

9. Farhi, L. E. and H. Rahn J. Appl. Physiol. (In press)

10. Otis, A. B., H. Rahn and M. Suskind This Report.

11. McMichael, J. and E. A. Johnston Quart. J. Expt. Physiol. 27: 55, 1937.

12. Stead, E. A., Jr., J. V. Warren, A. J. Merrill and E. S. Brannon J. Clin. Invest. 24: 326, 1945.

13. Scheinberg, P. and E. A. Stead, Jr. J. Clin. Invest. 28: 1163, 1949.

14. Lambertsen, C. J., R. H. Cough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke and C. F. Schmidt J. Appl. Physiol. 5: 803, 1953.

A THEORETICAL ANALYSIS OF THE ALVEOLAR-ARTERIAL O_2 DIFFERENCE WITH SPECIAL REFERENCE TO THE DISTRIBUTION EFFECT

by

L. E. Farhi[1] and H. Rahn

With the introduction by Riley, et al (1) of a practical technique for the direct determination of the arterial gas tensions, the evaluation of the alveolar-arterial O_2 differences has become an important tool in the study of the pulmonary gas exchange. Three major causes can be made responsible for the existence of such an A-a difference, namely, (1) the diffusion factor, (2) the direct contribution of venous blood from the pulmonary artery, bronchial veins, etc., and (3) what has been referred to as the distribution factor. The contribution of diffusion limitations effecting an end-capillary O_2 difference at various alveolar O_2 tensions has been estimated by various workers (2,3,4). The effects of mixing a certain volume of venous blood of assumed composition to the mixed arterial blood can also be calculated readily. On the other hand, the effects of mixing the blood from various alveoli having different O_2 tension (produced by different ventilation/perfusion ratios) will result by itself in an A-a difference independently of the diffusion or venous admixture. This effect, henceforth referred to as distribution, is rather difficult to evaluate without certain assumptions (5). This study is a renewed attempt to estimate this particular factor and its relation to the other two, so that one may visualize the contribution of each upon the total resulting O_2 difference between the alveolar and arterial blood when the lung is exposed to different O_2 concentrations.

In this theoretical study it had to be assumed that an equilibrium was obtained between pulmonary capillary blood and alveolar gas in each alveolus, after which each alveolus contributed to the mixed arterial blood and the mixed alveolar gas according to its individual perfusion and ventilation rate, respectively. Since one may assume identical composition for all the mixed venous blood perfusing each alveolus and identical composition for the inspired gas ventilating each alveolus, the composition of the blood and gas leaving an alveolus will be solely a function of the alveolar ventilation/perfusion ratio, $\dot{V}_A/\dot{Q}$, existing in this alveolus. How the gas tensions will vary with the $\dot{V}_A/\dot{Q}$ ratio have been described previously (5,6), and the greater this ratio the higher the Po_2 and the lower the Pco_2.

When each alveolus has the same $\dot{V}_A/\dot{Q}$ ratio and therefore the same Po_2 and Pco_2, then one would expect no tension difference between the mixed alveolar and end capillary O_2. If on the other hand the $\dot{V}_A/\dot{Q}$ ratio is not the same in all alveoli,

[1] On leave of absence from Hadassah-Hebrew University, Jerusalem, Israel.

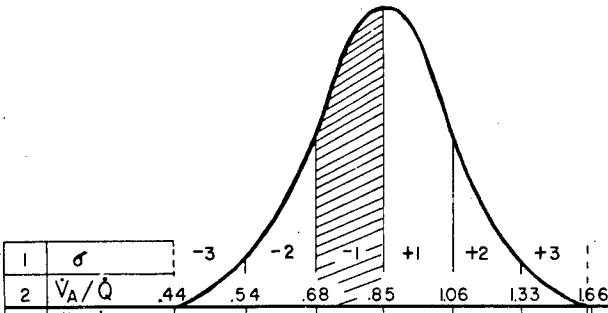
the Po_2 and Pco_2 must vary and then an O_2 difference is to be expected between the mixed alveolar gas and mixed end capillary blood even though equilibrium is assumed to have been obtained in each alveolus. This is due to two causes which can be illustrated with a left and right lung, one having a high $\dot{V}_A/\dot{Q}$ ratio with a Po_2 of 120, the other a low $\dot{V}_A/\dot{Q}$ ratio with a Po_2 of 80. If we take equal volumes of gas from each and mix it, we obtain a mixed alveolar Po_2 of 100. The blood leaving the first lung has an O_2 content of 19.7 vols. %, the other 19.1 vols. % and mixing equal volumes of blood we obtain an O_2 content of 19.4 which corresponds to a Po_2 of 94, thus giving rise to an O_2 difference of 6 mm, due to the non-linearity of the O_2 dissociation curve. However, in reality this difference becomes even greater since we are not dealing with equal volumes of blood and gas from each lung. The lung with the large $\dot{V}_A/\dot{Q}$ ratio contributes more gas volume of Po_2 120 than the other lung with a Po_2 80 and thus the mixed alveolar gas will have a mean tension > 100. On the other hand the lung with small $\dot{V}_A/\dot{Q}$ ratio will contribute more blood with a low Po_2 of 80 than the other lung with Po_2 120 and yield a mixed end-capillary composition with a $Po_2 < 94$.

Thus assuming in man a certain type of distribution of $\dot{V}_A/\dot{Q}$ among his alveoli and taking into account these two factors, one can by tedious statistical calculations obtain the resulting O_2 differences (1) for different standards of deviation of $\dot{V}_A/\dot{Q}$ and (2) for different inspired O_2 tensions.

Calculation of $\dot{V}_A/\dot{Q}$ distribution upon the mixed alveolar-mixed end-capillary O_2 differences

When air is breathed, we have assumed P_{Io_2} of 150 and a mixed venous Po_2 of 40 and Pco_2 of 46 which allows one to construct a $\dot{V}_A/\dot{Q}$ line on O_2-CO_2 diagram (5,6). Such a line is similar to the one shown in Figure 3 which is designated as $F_{Io_2} = .20$. The simultaneous O_2 and CO_2 tensions on such a line represent the result of all possible $\dot{V}_A/\dot{Q}$ ratios ranging from 0 at the mixed venous point, $P_{\bar{v}}$, to ∞ at the inspired point, P_I;

We have chosen a $\dot{V}_A/\dot{Q}$ ratio of .85 to represent the mean ratio of all the alveoli in the lung. If each alveolus actually had this ratio, then the mixed alveolar and mixed end capillary blood would have the same Po_2 of 101 and Pco_2 of 40.5. On the other hand, if one assumes a distribution of $\dot{V}_A/\dot{Q}$ around this mean the simplest assumption is a logarithmic distribution of this ratio as had been suggested previously (5). Such a distribution may be caused by independent variations of $\dot{V}_A$ or $\dot{Q}$ or by simultaneous variations in both. In the physiological range a logarithmic distribution of this ratio results from a simple arithmetic distribution of both $\dot{V}_A$ and $\dot{Q}$. Although there is no evidence that the parameters are distributed in this fashion, it nevertheless constitutes probably the simplest working assumption. Figure 1 represents an example for the calculation of the mixed alveolar-mixed end-capillary O_2 difference when a mean $\dot{V}_A/\dot{Q}$ ratio of .85 is assumed with a variance around the mean where one standard deviation is equal to log 1.25. The resulting O_2 difference is 3.4 mm Hg. When the standard



1	σ	-3	-2	-1	+1	+2	+3	
2	$\dot{V}_A/\dot{Q}$	.44	.54	.68	.85	1.06	1.33	1.66
3	$\dot{V}_A/\dot{Q}$	.49	.61	.77	.96	1.20	1.50	TOTAL
4	% N	2.14	16.30	31.43	31.43	16.30	2.14	99.74
5	$\dot{V}_A$	65	76	87	98	109	120	555
6	$\dot{Q}$	134	124	113	102	91	80	644
7	P_{O_2}	75	87	97	105	112	117	
8	C_{O_2}	19.02	19.52	19.84	20.02	20.20	20.27	
9	4 x 6	287	2021	3552	3206	1483	171	10720
10	9 x 8	5460	39410	70400	64180	29930	3460	212850

Figure 1

The assumed distribution of relative number of alveoli plotted against the $\dot{V}_A/\dot{Q}$ ratio on a logarithmic scale. The mean $\dot{V}_A/\dot{Q}$ is .85 with a standard deviation of log 1.25. For example, +1 st. dev. is log .85 + log 1.25 or log 1.06, while -1 st. dev. is log .85/1.25 or log .68. The shaded region represents 31.4% of all alveoli having approximately a mean $\dot{V}_A/\dot{Q}$ ratio of .77.

Col. 1 the number of standard deviations from the mean.

2 the $\dot{V}_A/\dot{Q}$ value found at ±1, 2, 3 S.D. from the mean, when the mean is .85, and the S.D. is log 1.25.

3 the approximate mean $\dot{V}_A/\dot{Q}$ within each standard deviation range.

4 percent of all alveoli found in each range for a Gaussian distribution.

5 & 6 numbers of the same dimensions representing $\dot{V}_A$ and $\dot{Q}$ and whose ratio (5)/(6) is equal to column 3. Each column shows distribution along an arithmetic scale. The $\dot{V}_A/\dot{Q}$ ratio of 1 is represented by $V_A = 100$, $Q = 100$.

7 the O_2 tension of the gas and end-capillary blood leaving the alveoli of column 3.

8 the O_2 content (vol. %) of the end-capillary blood leaving the alveoli of column 3.

9 the relative amount of blood contributed by the alveoli represented in column 3. It is obtained by multiplying column 4 by column 6.

10 the amount of oxygen carried in the blood coming from the alveoli in column 3. Column 9 x column 8.

Calculations: The total oxygen carried by the blood is the sum of all the figures in column 10, while the total amount of blood perfusing the lung is obtained by the sum in column 9. The mixed end-capillary blood O_2 content is, therefore, obtained by dividing the sum in column 10 by the sum in column 9. A value of 19.85 vol. % is obtained, representing an oxygen tension of 98.

Similarly, the mean $P_{A_{O_2}}$ is $\frac{\Sigma\left((4) \times (5) \times (7)\right)}{\Sigma\left((4) \times (5)\right)}$, yielding a value of 101.4.

Thus a difference of 3.4 mm is obtained between the mixed alveolar and mixed end-capillary O_2 tension.

deviation of the distribution is increased from log 1.25 to 1.5, 2.0 and 3.0, the O_2 difference will increase from 3.4 to 10, 21 and 40, respectively.

The effects of changing the inspired O_2 tension

By applying the same method the resulting O_2 differences were calculated when the inspired O_2 tension was varied so that the P_{AO_2} ranged from 50 to 660. The following conditions were assumed: R, the exchange ratio = .8, the (A-V) O_2 difference 5. vols. %, the standard deviation of the distribution of $\dot{V}_A/\dot{Q}$ = log 1.25, the mean P_{ACO_2} was 40 when alveolar P_{AO_2} was >100 and at lower P_{AO_2} the P_{ACO_2} decreased according to the acute low O_2 exposure figures given by Rahn and Otis (7).

In Figure 2 the solid black area indicates how the mixed capillary-mixed alveolar O_2 difference varied with the changing alveolar O_2 tension. For this distribution of log 1.25 the largest O_2 difference is obtained with P_{AO_2} from 70 to 90.

The overall alveolar-arterial O_2 difference

Having established how a particular assumed distribution of $\dot{V}_A/\dot{Q}$ contributes to gas-blood O_2 difference, it is of interest to compare this distribution factor with (1) the diffusion factor and (2) the venous blood admixture. The theoretical considerations of Dirken and Heemstra (2), Riley and Cournand (3) and Bartels and Rodewald (4) all indicate that the end-capillary O_2 difference which results from diffusion limitation when low O_2 is breathed practically disappears under ordinary conditions when the P_{AO_2} is around 100. The particular diffusion contribution for various P_{AO_2} plotted in Figure 2 has been taken from the tables of Riley and Cournand (8).

On the other hand, when 100% O_2 is breathed, the distribution and diffusion factors are negligible and the A-a O_2 difference must be all due to direct venous blood contribution from direct shunts, bronchial vessels, etc. Bartels and Rodewald (4) have summarized the available literature which with one exception agrees well, indicating an A-a O_2 difference of 30-40 mm in normal man breathing high O_2 concentrations. A difference of 31 mm corresponds to a venous admixture of 2% of the cardiac output if the arterio-venous O_2 difference is 5.0 vols. %. This value of 2% has been used in Figure 2 for calculation of the venous admixture curve in normal man.

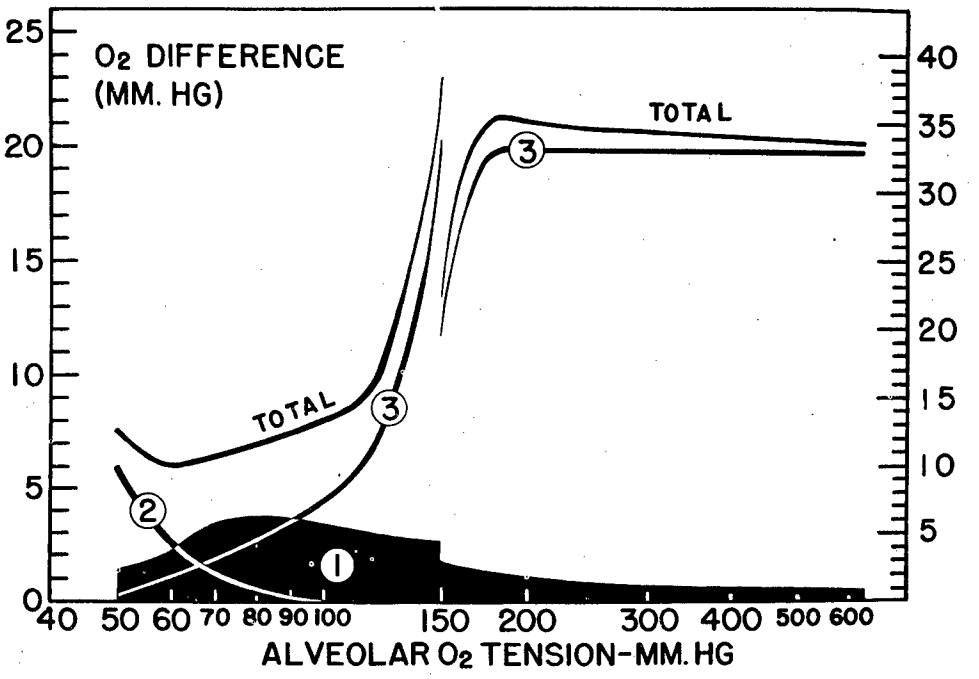


Figure 2

The O_2 difference between mixed alveolar gas and that found in the arterial blood at various alveolar O_2 tensions from 50 to 660 mm Hg. No. 1, the solid black region represents the distribution effect as discussed. No. 2 represents diffusion limitation which becomes negligible at P_{AO_2} of 100. No. 3 represents the effects of direct venous blood admixture from sources other than pulmonary capillaries. The sum of these 3 factors represents the total difference. Note that the ordinate scale changes at 150 mm.

Thus, without the distribution factor one would be left with a total A-a difference of about 4 mm due to venous admixture alone when the P_{AO_2} is 100. Since most of the recent values for normal man indicate a total A-a O_2 difference of about twice this value a distribution factor is needed to explain the observed values, provided the direct venous admixture contribution is constant at various

O_2 tensions. It is for this reason that in our theoretical treatment of the $\dot{V}_A/\dot{Q}$ distribution a standard deviation of log 1.25 was chosen, since this variance yields a 3.4 mm O_2 difference which when added to the O_2 difference resulting from a venous admixture equal to 2% of the cardiac output yields a total A-a O_2 difference of about 8 mm, a value which has been commonly reported for normal man breathing air at sea level.

Strictly speaking, it is not possible to add the mm O_2 differences for the various components in Figure 2 to obtain a total difference. However, the resulting error is slight and smaller than the errors arising from the various assumptions which have to be made for each of the components. Furthermore, it should be emphasized that the analysis in Figure 2 is based on many assumptions made by us as well as other authors and that it serves primarily to show one systematic approach in the evaluation of a distribution of $\dot{V}_A/\dot{Q}$ ratios and its contribution to the total A-a O_2 difference.

Distribution effect when P_{IO_2} and $P_{\bar{v}}$ remain constant but F_{IO_2} is varied

It is of interest to point out that when P_{IO_2} and $P_{\bar{v}}$ are kept constant, the $\dot{V}_A/\dot{Q}$ line which is constructed is a function of the inspired O_2 fraction. One may change the total barometric pressure inversely with the F_{IO_2} in such proportions that P_{IO_2} remains 150 mm. For example, at an altitude of 33,000 ft. where the total barometric pressure is 197 mm Hg, breathing 100% O_2 (F_{IO_2} = 1.0) yields a P_{IO_2} of 150. At the other extreme, a pressure of 20 atmospheres, 15000 mm Hg, breathing an O_2 fraction of 0.01 also yields a P_{IO_2} of 150. The construction of a $\dot{V}_A/\dot{Q}$ line is obtained by connecting the various points where the blood R line and gas R line for any particular value of R meet. All the blood R lines radiating from $P_{\bar{v}}$ in Figure 3 remain constant no matter what P_{IO_2} is. On the other hand, as Fenn, et al (9) pointed out, the slope of the gas R lines for a given P_{IO_2} is a function of the F_{IO_2}. The smaller F_{IO_2} the greater is the slope for a given R. At F_{IO_2} = 1.0 all R lines converge to a slope of 1.0. Thus, for example, the blood R = .8 line will be intercepted at different O_2 and CO_2 tensions by the gas R = .8 line depending upon the F_{IO_2}. The complete $\dot{V}_A/\dot{Q}$ lines must therefore vary with the F_{IO_2} and several of these lines are shown in Figure 3. There is only one alveolar-arterial gas tension they have in common, namely, when R = 1.

If one assumes a standard deviation of log 1.25 for the distribution of $\dot{V}_A/\dot{Q}$, distributed around a mean $\dot{V}_A/\dot{Q}$ which is found at a P_{CO_2} of 40, then we can calculate the effect of this distribution on the resulting O_2 differences between arterial blood and alveolar air by the same method as outlined above. These differences are shown plotted against the particular F_{IO_2} in the inset of Figure 3. The lower the F_{IO_2} the larger is the O_2 difference in spite of the fact that the inspired and mixed venous gas tensions are the same.

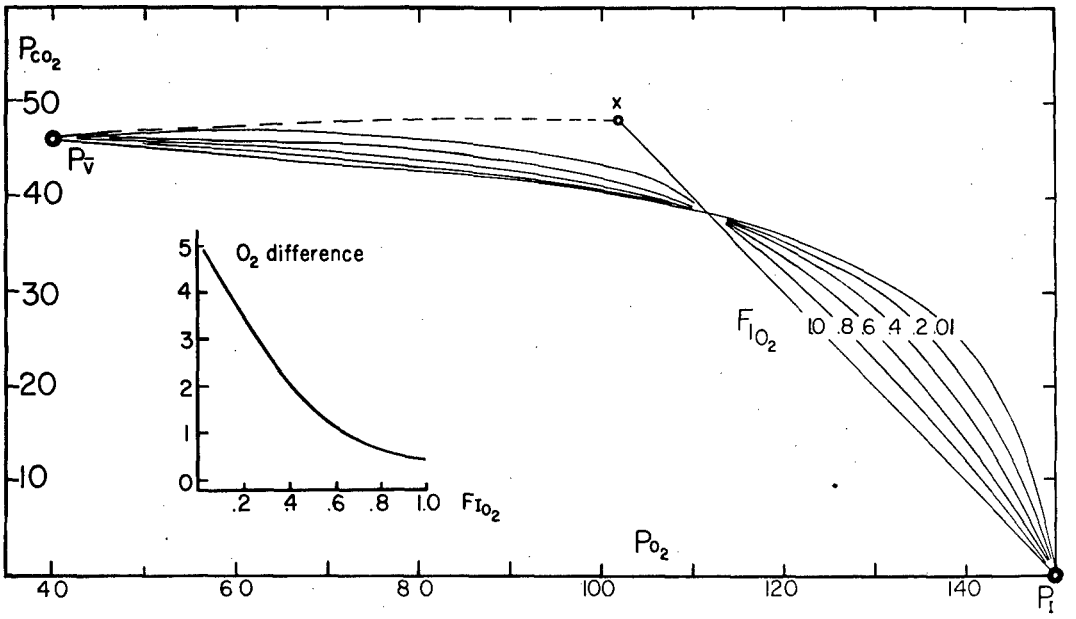


Figure 3

The $\dot{V}_A/\dot{Q}$ lines representing all the theoretically possible O_2 and CO_2 tensions in the alveolar gas and capillary blood when P_I and $P_{\bar{v}}$ are constant, but F_{IO_2} is altered from 0.01 to 1.0 (see text). Point X represents the alveolar gas composition of a perfused, but non-ventilated alveolus when $F_{IO_2} = 1.0$. Insert: The O_2 difference between mixed alveolar gas and mixed capillary blood under the above conditions of varying F_{IO_2} when the distribution of $\dot{V}_A/\dot{Q}$ among all the alveoli was assumed to be constant.

The $\dot{V}_A/\dot{Q}$ line when $F_{IO_2} = 1$

Attention must be called to the $\dot{V}_A/\dot{Q}$ line when 100% O_2 is breathed. Irrespective of the ventilation or the R all alveolar points must lie on the slope of -1 and, therefore, whatever the $\dot{V}_A/\dot{Q}$ ratio all alveoli must likewise conform to this line since $P_{AO_2} + P_{ACO_2} = P_{IO_2}$. Of particular interest is the point marked X (Figure 3) which is the gas concentration when $\dot{V}_A/\dot{Q} = 0$, i.e., of the non-ventilated, but perfused alveolus. Its concentration has a considerably higher O_2 and CO_2 tension than that of the incoming venous blood at point $P_{\bar{v}}$, while under normal conditions of air breathing ($F_{IO_2} = .209$) the O_2 and CO_2 composition of such an alveolus will be practically the same as $P_{\bar{v}}$. When F_{IO_2} is 1.0, the venous blood in such an alveolus will become oxygenated and its $P_{\bar{v}CO_2}$ will rise because it is unable to hold as much CO_2 in the arterialized state. The consequence of this is a continued O_2 uptake by diffusion but no exchange of CO_2. Such an unventilated

alveolus will have an R of 0 and its O_2 uptake will be proportional to the perfusion. The Po_2 of the end-capillary blood will be nearly the same for non-, poorly- or well-ventilated alveoli and thus an F_{IO_2} of 1.0 thus becomes essential for estimating the contribution of venous admixture from sources other than pulmonary capillaries. As soon as small fractions of N_2 are present in the inspired mixture, the composition of the non-ventilated, but perfused alveolus will rapidly move toward the $P_{\bar{v}}$ point along the dotted line (blood R = 0) and its blood will now contribute venous blood to the arterialized blood in the same manner as a direct shunt.

SUMMARY

The alveolar-arterial O_2 difference can be attributed to three independent phenomena: (1) diffusion impairment; (2) admixture of venous blood from sources other than pulmonary capillaries; and (3) the existence of unequal ventilation/perfusion ratios among the alveoli. By assuming a distribution of ventilation/perfusion ratio in healthy lungs the contribution of this phenomenon toward establishing an A-a O_2 difference can be evaluated under conditions of various inspired O_2 tensions.

REFERENCES

1. Riley, R. L., D. D. Proemmel and R. E. Franke J. Biol. Chem. 161: 621, 1945.
2. Dirken, M. N. J. and H. Heemstra Arch. neerl. physiol. 28: 501, 1947.
3. Riley, R. L. and A. Cournand J. Appl. Physiol. 4: 77, 1951.
4. Bartels, H. and G. Rodewald Pflugers Archiv. f. d. ges. Physiol. 258: 11, 1953.
5. Rahn, H. Am. J. Physiol. 158: 21, 1949.
6. Riley, R. L. and A. Cournand J. Appl. Physiol. 1: 825, 1949.
7. Rahn, H. and A. B. Otis Am. J. Physiol. 150: 202, 1947.
8. Riley, R. L., A. Cournand and K. W. Donald J. Appl. Physiol. 4: 102, 1951.
9. Fenn, W. O., H. Rahn and A. B. Otis Am. J. Physiol. 146: 637, 1946.

Alveolar-Arterial O_2 and CO_2 Differences in the Dog Breathing Air and Low O_2 Mixtures

MITZI SUSKIND

THE DIFFERENCE between the oxygen pressure of the mixed arterial blood and that found in the alveolar air depends on the absolute alveolar oxygen pressure as well as on the particular slope of the oxyhemoglobin dissociation curve in this region. Dirken and Heemstra (1) pointed out that the rate at which equilibrium is attained between the alveolar air and the arterial blood is faster at the higher levels of oxygenation than at the lower levels where a greater volume of oxygen has to pass the alveolar membrane for the same change in pressure. For this reason these authors believed that complete equilibrium is relatively easily attained across the pulmonary capillary when the subject breathes pure oxygen or probably even room air, and suggested, therefore, that any gradient found under such conditions is due to a venous admixture, arising from some undetermined source. Berggren found an 11-mm alveolar-arterial oxygen pressure gradient in subjects breathing pure oxygen. Assuming a normal arterial-venous oxygen content difference, he concluded that 0.6% of the circulating arterial blood was of venous origin (2). On the other hand, when gas mixtures with a low oxygen content are inspired, the arterial oxygen pressures lie on the steep part of the oxygen dissociation curve and a venous admixture of similar magnitude has a negligible effect in terms of mm Hg on the A-a oxygen gradient. Therefore, a gradient found under such conditions can be attributed primarily to incomplete equilibration between alveolar O_2 and the O_2 of pulmonary capillary blood (3).

Many investigators have found the gradient to become smaller when a low oxygen mixture was inspired. Bock *et al.* (4) reported an oxygen difference of 20 mm in his subjects breathing room air, and a 3–4 mm difference with an alveolar pO_2 of less than 60 mm. Dill and Hall (5) found that the normal resting gradient decreased to 3.6 mm at 10,000 ft. of altitude. During moderately hard work at sea level the oxygen gradient was 15–30 mm, but during slightly less intensive work at altitude this gradient decreased to 11–17 mm. Matthes attributed a similar decrease of the O_2 gradient in his subjects to an increased capillarization in the pulmonary bed (6, 7). More recently Pappenheimer *et al.* (8) and Williams (9) have also reported a reduction of the O_2 difference when dogs were subject to low oxygen pressures.

On the other hand, Gemmill's work suggested an alveolar-arterial oxygen gradient increase at altitude, both while the subject was resting and during work (10, 11). Lilienthal *et al.* (12) found the oxygen gradient of 9 mm to be the same at sea level and at a simulated altitude of 7,000–14,000 ft. With moderate exercise the gradient increased to 16.5 mm both at sea level and at high altitude. Analysis of these data led the authors to conclude that since diffusion factors could not contribute to the oxygen gradient while breathing air at sea level, this difference was caused by venous admixture. As the venous admixture could not contribute substantially to the gradient when the subjects were breathing low oxygen mixtures, the difference here was caused by a diffusion factor, or an increased 'pulmonary membrane component.'

METHODS

The experiments were conducted on dogs weighing approximately 20 kg, either awake or anesthetized by an intravenous injection of pentobarbital. The pressure levels of oxygen and carbon dioxide of the alveolar air were compared with those of the circulating arterial blood. A continuous analysis of alveolar air was made

possible by using an automatic sampling device by means of which the last 10–15 cc of each tidal were separated from the earlier part of the expired air (13). This last portion was then pumped through a Pauling oxygen tensimeter and a Cambridge carbon dioxide analyzer. Arterial blood, having been drawn anaerobically into a heparinized syringe from the femoral artery, was analyzed for its oxygen and carbon dioxide tensions by the Riley modification of the Roughton-Scholander technique for 1-cc blood samples (14). Here a 14-mm² bubble of alveolar air was equilibrated at 37°C with 1 cc of blood. Following equilibration the blood was discarded, and the bubble analyzed for oxygen and carbon dioxide content by differential absorption. The majority of the blood samples were analyzed in duplicate.

This method of analyzing blood yields values which vary from laboratory to laboratory. It was therefore necessary to equilibrate blood samples with known gas mixtures in order to obtain a measure of the reliability of the method as well as to obtain correction factors. The gas mixtures had been analyzed previously by Haldane apparatus. The blood-gas equilibrations included 46 such comparisons for oxygen and 41 for carbon dioxide. The gas mixture had oxygen pressures ranging from 30.4–143.8 mm. The carbon dioxide pressures had a range of 31.4–69.8 mm. It was found that on the average the equilibrated blood had 1.1 mm less carbon dioxide and 1.0 mm more oxygen than had the gas mixture. These differences were essentially the same in all ranges tested. Table 1 summarizes the data from these equilibrations.

TABLE 1. DIFFERENCES BETWEEN THE EQUILIBRATING GAS TENSIONS, mm Hg AND THE EQUILIBRATED BLOOD AS ANALYZED BY THE RILEY METHOD

	Range	Gas-Blood Difference	S. D.	*N*
pO_2	30–144	−1.0	±4.08	46
pCO_2	31–70	+1.1	±3.04	41

The automatic sampling and analysis of alveolar air is particularly well suited for comparative studies of alveolar air and arterial blood tensions. With the continuous analysis it is possible to await a relatively stable alveolar pO_2 and pCO_2 before drawing the arterial blood and the continuous sampling in no way disturbs the respiratory pattern during the experiment. The changing levels of concentration of the respiratory gases during a single respiration have recently been studied by DuBois (15). This analysis would suggest that the automatic sampler selects that portion of the expired air which is a good representation of the mean alveolar air concentration. As is shown below this method yields CO_2 values which are in good agreement with the simultaneously collected arterial pCO_2 and has given equally satisfactory results when applied to man at rest (16).

Two series of experiments were included in this study. The first was conducted in 1948 when 78 samples were taken on three dogs. These animals were trained to lie in a supine position, wearing individually fitted masks to which the alveolar air sampler could be attached. After procaine was injected around the femoral artery and stable alveolar gas concentrations were recorded on the analyzers, blood was drawn from the artery. Nine such samples were drawn on awake dogs. Similar observations were made during sodium pentobarbital anesthesia while the animals were breathing air and while inspiring gas mixtures of various low oxygen tensions.

The second experimental series were conducted in 1950 when 33 samples were taken on four dogs. Here the anesthetized dogs were placed in a supine position with endotracheal tubes. In this series the inspiration of low oxygen mixtures was alternated with inspiration of room air, blood samples being drawn under both conditions.

RESULTS

The individual analyses of the tensions of oxygen of the alveolar air and the arterial blood from both the 1948 and 1950 experiments are shown graphically in figure 1. It can be seen that the alveolar-arterial O_2 differences on awake dogs and anesthetized dogs breathing air are essentially the same. Furthermore, a low alveolar oxygen could be produced either by the inspiration of a low oxygen mixture or by the respiratory depression of deep anesthesia. However, A-a gradients that exist under these two conditions are quite different (table 2). In the 1948 experiments the average gradient present during the inspiration of low oxygen mixtures was 5.9 mm, while the average gradient in the deeply anesthetized dogs possessing an alveolar pO_2 comparable to that

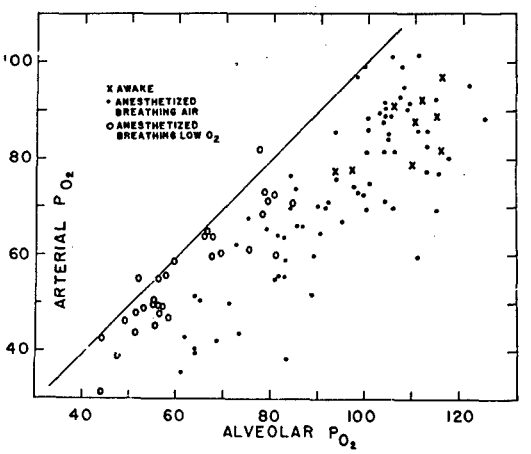


FIG. 1. Alveolar pO_2 plotted against arterial pO_2 of awake dogs (×) and anesthetized dogs (●) breathing room air and dogs breathing low oxygen mixtures (○). Points falling on the line represent no alveolar-arterial pressure difference.

TABLE 2. AVERAGES OF THE ALVEOLAR AND ARTERIAL O_2 AND CO_2 TENSIONS IN THE DOG UNDER VARIOUS CONDITIONS

Series	Exptl. Condition	Inspired Gas	No. of Expers.	O_2 Tensions, mm Hg				CO_2 Tensions, mm Hg			
				Alveolar	Arterial	Diff.	S.D. Mean	Alveolar	Arterial	Diff.	S.D. Mean
	1948										
1	Awake	Air	9	108.4	85.4	23.0	±2.2	29.3	30.4	1.1	±1.8
2	Lightly anesthetized	Air	50	99.3	74.8	24.5	±1.3	39.3	38.0	1.3	±0.6
3	Deeply anesthetized	Air	6	67.3	42.1	25.2	±1.1	46.9	46.5	0.4	±2.1
4	Lightly anesthetized	12–14% O_2	13	56.8	50.9	5.9	±1.3	38.1	35.6	2.5	±1.6
	1950										
5	Lightly anesthetized	Air	16	88.5	76.4	12.1	±2.0	43.4	44.2	0.8	±0.9
6	Lightly anesthetized	13–15% O_2	17	66.2	60.9	5.3	±1.4	33.7	33.5	0.2	±1.1

produced by the inspiration of a low oxygen mixture was 25.2 mm of Hg. These mean gradients were found to be significantly different at the 1% level of probability.

In the 1950 experiment the average alveolar-arterial oxygen gradient was 12.1 mm when air-breathing, anesthetized animals had an average alveolar pO_2 of 88 mm. This decreased to an average of 5.3 mm when the animals breathed 13–15% oxygen in nitrogen with an average alveolar pO_2 of 66 mm. The difference between these two gradients is significant at the 5% level of probability.

DISCUSSION

These data suggest that in the dog the importance of the membrane component between the alveolar gas and the pulmonary capillary blood in effecting an A-a oxygen gradient must be relatively small. Such a barrier is expected to increase the gradient when the alveolar O_2 tension decreases. In the 30 experiments on dogs breathing 12–15% O_2 this O_2 difference averaged 5 mm while the 19 experiments by Williams (9) gave an average difference of 3 mm when dogs breathed 8–10% O_2.

With higher alveolar O_2 pressures theoretical considerations would lead one to anticipate even smaller barrier provided by the alveolar membrane (1). *Column 1*, *2*, and *5* of table 1, however, indicate considerably larger O_2 difference from 12–24 mm, with dogs breathing room air. This difference is interpreted as arising from two main sources. They are: *a*) direct shunting of venous blood into the arterialized blood, and *b*) pulmonary capillary blood from various regions of the lung having different ventilation/perfusion ratios (17, 18). When breathing air it is not possible to distinguish between these two causes. When the alveolar pO_2 is lowered to the steep linear part of the O_2 dissociation curve these two sources become negligible in their contribution to a gradient. With higher than normal oxygen tensions, the alveolar O_2 is likewise on a linear portion of the oxygen content curve and the unequal ventilation/perfusion effect also becomes negligible but the direct contribution of venous blood remains as the only major source of an O_2 gradient.

The relatively large O_2 difference breathing air is probably largely the result of the pooling of pulmonary capillary blood from various regions of the lung having different ventilation/perfusion ratios. If direct venous blood shunting alone were responsible approximately 15–20% of the cardiac output would have to be shunted to explain these differences (assuming as A-V O_2 difference of 5 vol. %). William's studies on dogs breathing 100% O_2 likewise suggest that direct venous admixture is not sufficient to account for such a gradient.

Of particular interest is the large difference in O_2 gradient observed in dogs which were deeply anesthetized breathing room air and those which were lightly anesthetized breathing 12–14% O_2 (*column 3* and *4*, respectively). In both cases the alveolar pO_2 were similar, 67 and 57, respectively. Yet the former had a 4 times greater O_2 gradient. In spite of the low alveolar O_2 when air was breathed the unequal ventilation/perfusion factor has still the possibility of expressing itself in a large O_2 gradient because the O_2 pressure in various alveoli could theoretically range from 146 mm to the venous pO_2 covering the steep as well as flat

portion of the O_2 dissociation curve. On the other hand in the dogs breathing the low O_2 mixture the theoretically possible O_2 tensions cover a range between 70 mm and the venous tension. This steep and relatively linear portion of the dissociation curve would make the contribution of the unequal ventilation/perfusion factor comparatively small. It might also be pointed out that the relatively lower ventilation (23%) of the deeply anesthetized dogs breathing air might have furthered larger than usual ventilation/perfusion differences in various regions of the lung although the data of Williams (9) suggest otherwise.

SUMMARY

The alveolar-arterial pressure difference for O_2 and CO_2 were recorded in the dog breathing air and 12–15% O_2. The alveolar gases were recorded continuously from an end-tidal sampler while arterial blood samples were drawn for analyses. A comparison of the CO_2 values showed no statistical difference. The oxygen differences varied from 24 mm in the awake or lightly anesthet zed dog breathing air to 5–6 mm when the inspired O_2 tension was lowered. The O_2 differences breathing air are attributed largely to unequal ventilation/perfusion ratios existing in the lung.

REFERENCES

1. DIRKEN, M. N. J. AND H. HEEMSTRA. *Arch. neerl. physiol.* 28: 501, 1947.
2. BERGGREN, S. M. *Acta physiol. scand.* 4, Suppl. 11, 1942.
3. RILEY, R. L., J. L. LILIENTHAL, JR., D. D. PROEMMEL AND R. E. FRANKE. *Am. J. Physiol.* 147: 191, 1946.
4. BOCK, A. V., D. B. DILL, H. T. EDWARDS, L. J. HENDERSON AND J. H. TALBOTT. *J. Physiol.* 68: 277, 1929.
5. DILL, D. B. AND F. G. HALL. *J. Aero. Sc.* 9: 220, 1942.
6. MATTHES, K. *Arch. exper. Path. u. Pharmakol.* 181: 640, 1936.
7. MATTHES, K., M. BOHME AND K. TIETZE. *Arch. Exper. Path. u. Pharmakol.* 181: 666, 1936.
8. PAPPENHEIMER, J. R., A. P. FISHMAN AND L. M. BORRERO. *J. Appl. Physiol.* 4: 855, 1952.
9. WILLIAMS, M. H., JR. *Am. J. Physiol.* 173: 77, 1953.
10. GEMMILL, C. L. *J. Aviation Med.* 18: 483, 1947.
11. GEMMILL, C. L. *Federation Proc.* 4: 23, 1945.
12. LILIENTHAL, J. L., JR., R. L. RILEY, D. D. PROEMMEL AND R. E. FRANKE. *Am. J. Physiol.* 147: 199, 1946.
13. RAHN, H. AND A. B. OTIS. *J. Appl. Physiol.* 1: 717, 1949.
14. RILEY, R. L., D. D. PROEMMEL AND R. E. FRANKE. *J. Biol. Chem.* 161: 621, 1945.
15. DUBOIS, A. B., A. G. BRITT AND W. O. FENN. *J. Appl. Physiol.* 4: 535, 1952.
16. SUSKIND, M., R. A. BRUCE, M. E. MCDOWELL, P. N. G. YU AND F. W. LOVEJOY, JR. *J. Appl. Physiol.* 3: 282, 1950.
17. RAHN, H. *Am. J. Physiol.* 158: 21, 1949.
18. RILEY, R. L. AND A. COURNAND. *J. Appl. Physiol.* 1: 825, 1949.

Relationship Between Cardiac Output and Ventilation and Gas Transport, With Particular Reference to Anesthesia

MITZI SUSKIND AND H. RAHN

THE OVERALL effectiveness of the gas transport system could probably be best evaluated by the determination of O_2, CO_2 and H^+ concentration at the site of the tissues. Since this direct approach at the tissue level is technically difficult, one might achieve the next best evaluation from the mean gas and H^+ concentration of the capillary or venous blood. When one examines the total pressure head available for driving the O_2 into the tissues and the CO_2 out of the tissues, one finds that over $\frac{2}{3}$ of it is utilized in transporting the gas from the environment to the capillaries or vice versa, and the remainder serves for diffusion between the capillaries and tissues. Thus, the mean capillary O_2 pressure head available for diffusion into the tissues may be 60 mm, while 90 mm (150 − 60) are used to bring the inspired O_2 to the capillary. At the venous end of the capillary the O_2 tensions are even lower and reflect the tensions available to the cells with the lowest pressure head. In this study the gas tension of the mixed venous blood is employed as an 'index' of tissue tensions, bearing in mind that *a*) the venous tensions vary from organ to organ, and *b*) that this is at best only an approximation of the tissue tension. Nevertheless, this assumption allows one a quantitative approach in evaluating the contribution of each of the two transport systems, the cardiac output and the alveolar ventilation, to the gas tensions available at the tissue site. Furthermore, it allows one to see how these two transport systems interlock and which one must be altered in order to change the tissue gas tension in a particular direction.

This approach, therefore, becomes important when one tries to predict the effects of sudden changes in cardiac output and/or ventilation in such cases as resuscitation, anesthesia, and where it is important to evaluate these two transport systems separately in their effect upon the gas pressures available at the tissue level. It has particular application to the design and function of extracorporal heart-lung machines because it allows one to predict the consequences of changing the ventilation and blood flow at will.

The first part of this study deals with the theoretical aspects developed by one of us (*H. R.*) and employs the technique used previously in evaluating the O_2 transport system during exposures to high altitude (1). The second part deals with the observations made by *M. S.* and illustrates the actual gas tension changes observed when the gas transport systems are altered by administration of sodium pentobarbital to dogs.

RELATIONSHIP BETWEEN CARDIAC OUTPUT, ALVEOLAR VENTILATION AND MIXED VENOUS BLOOD GAS TENSION

In order to evaluate either the ventilation or the blood flow independently or the combined effect of both upon the gas tensions of the mixed venous blood, certain assumptions are helpful. These are *a*) that the metabolic rate and the respiratory exchange ratio remain constant, and *b*) that there is no alveolar-arterial pressure difference for O_2 and CO_2. It is also convenient to describe the effects of these two pumps in terms of the same dimensions; namely, the partial pressures of O_2 and CO_2. Since the pressure drop in the blood or the lungs is proportional to the total amount of gas carried divided by the flow, each pump rate can be evaluated and compared in terms of the partial pressure drop of O_2 or CO_2.

Effect of Ventilation Rate. When breathing air at one atmosphere, the inspired gas tensions can be described as the maximum pressure head and sink, respectively, for O_2 and CO_2. The inspired air is represented as an O_2 pressure of 149 and a CO_2 pressure of 0 at the right hand side of figure 1. As this air is inhaled it can exchange at various exchange ratios. If it exchanges at a ratio of 0.8, then it must be somewhere on the slope of the solid line arising from the inspired air point. The exact slope of this line is calculated from the alveolar air equation (2). The exact point the alveolar gas will occupy on this line is a function of the alveolar ventilation (2) and depends upon the ratio of the metabolic rate to the alveolar ventilation.

Thus, $P_{A_{CO_2}} - P_{I_{CO_2}} = (\dot{V}_{O_2} \times R \times .86)/\dot{V}_A$ where $P_{A_{CO_2}}$ is the alveolar CO_2 tension, the inspired CO_2 tension, $P_{I_{CO_2}}$, is zero, $\dot{V}_{O_2}$ is the oxygen uptake/min. (STPD), R is the exchange ratio, 0.86 a constant and $\dot{V}_A$ is the alveolar ventilation in l/min. (BTPS).

We may now arbitrarily express the alveolar ventilation as normal or 100%, which will give a $P_{A_{CO_2}}$ of 35 mm when the exchange ratio is .8. This point is so marked on the solid line. From this equation we can also determine the simultaneous values of CO_2 and O_2 for any other ventilation rate. If the ventilation is doubled, we move down exactly half the distance in CO_2 to the $P_{A_{CO_2}}$ of 17 and a relatively high O_2 tension. A 50% reduction of alveolar ventilation will double the $P_{A_{CO_2}}$ and reduce the O_2 to 68 mm.

Effect of Cardiac Output Rate. If there is no A-a gradient, then the alveolar values also represent arterial blood tensions. The translation of pO_2 and pCO_2 of the arterial blood into blood gas contents, hemoglobin saturation or pH can be most easily visualized from figure 2 which represents the O_2 and CO_2 content of the whole blood of man for any given pCO_2 and pO_2 tension. These data were obtained from the nomogram of Dill, Edwards and Consolazio (3). This figure, therefore, serves as a background for figure 1 and allows one to go from the lung gas phase to the blood phase on the same diagram in terms of gas partial pressures. Isopleths for plasma pH can also be added to this diagram and run approximately horizontal, bending slightly upwards at the lower O_2 tensions.

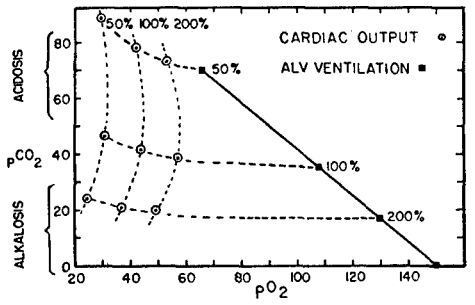


FIG. 1. Effects of changes in ventilation and cardiac output on O_2 and CO_2 tension in alveoli, arteries, and mixed venous blood.

Since the straight-solid line of figure 1 represents all the possible arterial points which could exist at an R.Q. of .8 and at various alveolar ventilation rates from 50% of normal to infinity, it is now possible with the help of figure 2 to establish the venous partial pressure for O_2 and CO_2 for any cardiac output corresponding to any particular arterial point. For example, the arterial O_2 and CO_2 pressure for a normal ventilation of 100% is indicated in figure 1 by the square dot. In figure 2 the corresponding blood gas content can be obtained. If we now choose arbitrarily an $(A\text{-}V)_{O_2}$ difference of 5 vol. % as indicating a normal cardiac output with an R.Q. = .8, we can locate the mixed venous point on figure 2 having a blood gas O_2 content of 5 vol. % less than the artery and a CO_2 content 4 vol. % greater than the artery. This will yield a mixed venous pO_2 and pCO_2 of 42 and 41 mm, respectively. In figure 1 this particular point is intersected by two dotted lines. The vertical curved line represents all points located exactly 5 vol. % O_2 distant from all the possible arterial points and has therefore been given the arbitrary designation of 100%, or normal cardiac output. Similar vertical dotted lines indicate all the various gas tensions of the venous blood to be found when the cardiac output is doubled (200%) or halved (50%).

The horizontal dotted lines represent the blood R.Q. lines. In other words, they indicate where mixed venous blood must be if it exchanges at an R.Q. of .8 with a particular arterial point, the distance from the arterial point being determined by the cardiac output.

Interpretation: This scheme allows one to

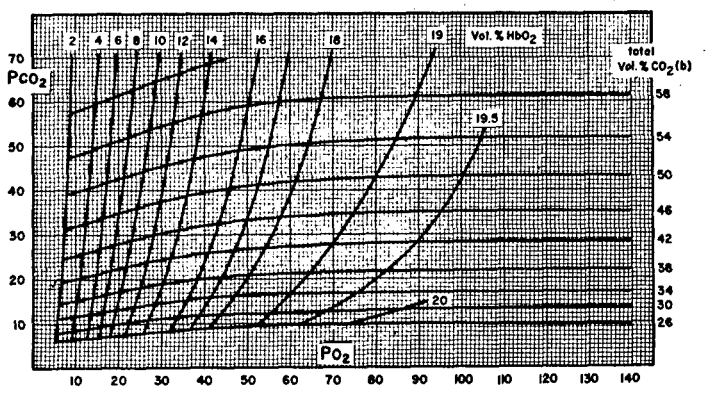


FIG. 2. Combined O_2 and CO_2 dissociation curve of human whole blood, obtained from nomogram of Dill *et al.* (3).

compare an infinite number of combinations of cardiac output and alveolar ventilation and their final effects upon the mixed venous blood, which in turn might serve as index of the gas pressures of tissues. It should also be pointed out that in this simplified scheme the whole body is considered as a single capillary bed, whereas each organ has its own venous gas tensions and blood flow. Furthermore, the distribution of the blood between these different organs may be altered so as to permit one organ, such as the brain, to prosper at the expense of other less essential tissues. All predictions based on this type of analysis are necessarily subject to modification by such special circumstances.

Several interesting conclusions present themselves in figure 1. In spite of the large differences in arterial O_2 tensions (ranging from 130 mm with 200% ventilation to 65 mm with 50% ventilation) the mixed venous O_2 tensions are within a few mm for a given cardiac output. The arterial blood O_2 saturation is 90% when the ventilation is reduced to 50%, yet the venous O_2 tension for a given cardiac output is nearly the same as in the case for nearly fully-saturated arterial blood with an O_2 tension of more than 100. Another interesting fact emerges; namely, that for a given cardiac output the highest venous pO_2 is obtained when the arterial pCO_2 is in the normal range of 35–40 mm. Even hyperventilation with a marked increase in arterial O_2 tension is associated with a definite decrease in venous O_2 tension. This fact can be expressed in another way, namely, that in order to maintain a particular venous O_2 tension the work by the heart is smallest when the arterial pCO_2 is in the normal range.

This analysis can be generalized with the statement that *a*) the venous pO_2 is largely controlled by the cardiac output and is relatively independent of the ventilation, and *b*) the venous pCO_2 and pH is relatively independent of the cardiac output but is largely decided by the alveolar ventilation. A practical appraisal, breathing air or higher O_2 mixtures, would lead to the conclusion that even with a cardiac output $\frac{1}{2}$ of normal, the tissues are supplied with a proper O_2 tension ($>$ 25 mm) regardless of the ventilation (50–200%) but that the CO_2 or pH of the tissues may be severely affected by inadequate ventilation rate regardless of the cardiac output.

Effect of Sodium Pentobarbital Upon Gas Transport in the Dog. Acute changes in ventilation and possibly in cardiac output can be produced in dogs by administration of pentobarbital in order to follow the resultant changes in gas transport. In this case the situation is much more complex than outlined above since *a*) the oxygen uptake is not necessarily constant, *b*) a rather large alveolar-arterial O_2 gradient is found in the dog (4, 5) and *c*) the gas exchange ratio is profoundly altered with a sudden respiratory depression (6, 7).

METHOD

One series of experiments was conducted with three dogs (20–25 kg) which were trained to lie in the supine position, wearing individually fitted masks. An alveolar air sampler (6) was attached to the mask for the automatic collection of 'end tidal' air which was continuously analyzed on the Pauling oxygen tensimeter and the Cambridge thermo-conductivity carbon dioxide analyzer. When a stable alveolar air concentration was indicated, procaine was injected into the region of the femoral artery and arterial blood withdrawn for the determination of the partial pressures of O_2 and

TABLE 1. CHANGES IN GAS TENSIONS, EXCHANGE RATIO AND CARDIAC OUTPUT AFTER INTRAVENOUS ADMINISTRATION OF PENTOBARBITAL SODIUM IN THE DOG

Time Intervals, min	Conscious Control	0–30	31–60	61–90	91–120	121–150	151–180	181–360
pO_2								
Alv.	108 (9)	79 (11)	85 (12)	101 (8)	103 (8)	105 (7)	108 (4)	103 (16)
Art.	85 (9)	60 (11)	71 (12)	84 (8)	89 (8)	92 (7)	87 (4)	82 (16)
Δ	23	19	14	17	14	13	21	21
pCO_2								
Alv.	29 (9)	40 (10)	44 (12)	39 (9)	37 (8)	40 (7)	33 (4)	36 (15)
Art.	30 (9)	44 (10)	45 (12)	38 (9)	38 (8)	39 (7)	32 (4)	38 (15)
Δ	1	4	1	−1	1	−1	−1	2
Cardiac output, l/min/kg		0.13 (3)	0.13 (4)	0.18 (2)	0.12 (1)	0.13 (4)	0.10 (2)	0.12 (8)
pN_2 Alv.	563	581	571	560	560	555	559	561
Alv. Exch. Ratio	0.73	0.54	0.67	0.83	0.82	0.96	0.83	0.79

Figures in parentheses indicate number of experiments.

CO_2 by the Riley method (8). Correction factors for the gas determination had been previously established by equilibrating blood with gases of known concentration (4). After such control samples on awake dogs were obtained, sodium pentobarbital was given intravenously. The animals were depressed to the level of cessation of eye reflex. This plane of anesthesia was deeper than is usually obtained with the standard dose of 25 mg/kg body weight. Throughout the ensuing period of anesthesia arterial blood samples were drawn and analyzed for comparison with the simultaneously determined alveolar gas tensions. The arterial O_2 saturation was either determined from the oxygen content and oxygen capacity by the Van Slyke technique or estimated from the O_2 and CO_2 tensions and blood saturation curves previously established for the dog (9).

The second series included 12 experiments on 7 untrained dogs of similar weight which had been anesthetized intravenously with pentobarbital. A cardiac catheter was inserted in the pulmonary artery for the collection of mixed venous blood. A tracheal tube was inserted and the alveolar sampler attached. The expired air was collected in a well-rinsed spirometer. Simultaneously with this collection venous blood was drawn through the catheter and blood was taken from the femoral artery. The alveolar air was analyzed immediately preceding or succeeding these collections. The first samples were collected ½ hour after the administration of the anesthetic and at various intervals thereafter. The bloods were analyzed for partial pressures and contents of oxygen and carbon dioxide. The collected gas yielded the oxygen consumption and output of carbon dioxide. The cardiac output was determined from the Fick equation.

RESULTS

The average alveolar pressure of oxygen of the nine determinations of awake supine dogs was 108.4 mm Hg. The arterial oxygen pressure was 85.4 mm Hg with a resulting alveolar-arterial oxygen gradient of 23.0 mm. The alveolar P_{CO_2} was 29.3 mm, while the arterial P_{CO_2} was 30.4 mm, giving an initial difference of +1.15 mm. The oxygen and carbon dioxide pressures of the alveolar air indicate a respiratory quotient of 0.73. Beginning with the anesthesia, the data from the first and second series of experiments were pooled and are averaged in table 1 for half-hour intervals except for the last column, which represents a 3-hour interval.

After the intravenous injection of pentobarbital, many changes took place. The first gross change was a depression of the respiration, both the total minute volume and the rate of respiration being diminished by approximately 45% from the recovery value. This large respiratory change was followed by a decrease in the alveolar P_{O_2} to a minimum of 76 mm in the first 30 minutes following the intravenous injection of anesthetic, and an 18 mm rise in alveolar N_2. At the same time the P_{CO_2} increased to 42.3 mm. Within the next 30

minutes the respiration was stimulated enough so that the P_{O_2} rose to 90 mm, but the P_{CO_2} still continued to rise to a maximum of 44.4 mm. The arterial blood gases changed parallel to the alveolar levels. The arterial P_{O_2} reached a low of 58.1 mm and the P_{CO_2} reached a high of 46.5 mm. The alveolar-arterial oxygen and carbon dioxide gradients did not change in any predictable manner during anesthesia. They showed no relationship to either the the ventilation or the cardiac output. The average oxygen gradient of the total experiment was 16.2 mm and the average carbon dioxide gradient was +1.4 mm. The latter cannot be considered significant.

The cardiac output could not be obtained in the awake dogs. During anesthesia no consistent changes were observed over a period of 6 hours. The partial pressure of the venous blood was estimated from the dissociation curve of dogs' blood (9). In figure 4 these averaged data have been plotted on the $P_{O_2} - P_{CO_2}$ diagram in order to represent the whole gas transport system from the inspired air to the mixed venous blood. The tissues would theoretically lie to the left of the mixed venous points.

DISCUSSION

Alveolar Gas Exchange. In figure 3 the changes in alveolar O_2 and CO_2 are plotted against each other and are connected by a solid line indicating the time course. The double ring marks the control value of the awake animals. The mean composition for consecutive half-hour intervals after induction are indicated by numbers 1, 2, 3, etc. Point 7 represents the composition between the 3rd and 6th hours. This alveolar air loop is typical for the unsteady state whenever the alveolar ventilation is acutely reduced by various means and reflects the great discrepancy between the CO_2 and O_2 stores of the blood and tissues (10). When the alveolar CO_2 is increased, the blood and tissue CO_2 increases (provided the cardiac output remains the same). Since it takes a relatively long time to fill the large CO_2 reservoirs, the CO_2 tension rises slowly and uses metabolic CO_2 to fill them. This in turn reduces the CO_2 output. The oxygen stores are relatively small and are quickly exhausted so that the pO_2 drops rapidly. If the two gas stores of the body were equal in volume as well as in their rates of adjustments, then one would expect the alveolar air point to move upwards along the original gas exchange ratio line or R line. The straight lines in figure 3 represent the R = .6, .8, and 1.0. Or, returning to figure 1, the alveolar air point would move from the 100% ventilation point slowly up to the 50% ventilation point, a reduction in alveolar ventilation similar in magnitude to that experienced in these dogs. If the CO_2 and O_2 gas stores were negligible, then such a change would have been immediate. Thus, the relatively large CO_2 stores act as a buffer preventing a rapid rise in CO_2 or fall in pH when the ventilation is suddenly reduced.

Another consequence of this large discrepancy between O_2 and CO_2 stores is the marked alteration in the gas exchange ratio, R. This produces a marked fall in R initially with a gradual recovery and even values above the normal R upon recovery from the ventilatory depressant action. The recovery of the R with time occurs actually faster than one would anticipate. This is due to the fact that the alveolar ventilation does not remain constant but gradually recovers after the first initial depression following the injection of pentobarbital. This can also be appreciated from the fact that the alveolar CO_2 begins to fall after the first hour.

The relative ventilation changes can be best evaluated by making the assumption that the ventilation is normal, or 1.0, when the alveolar

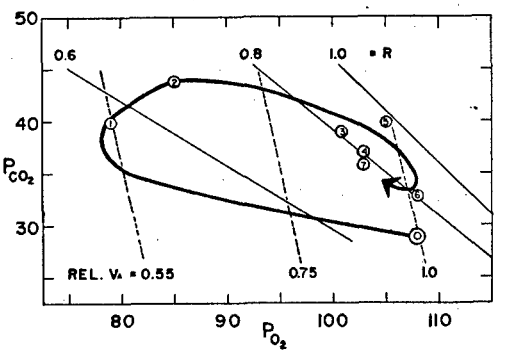


FIG. 3. Changes in alveolar gas concentrations of the dog after administration of pentobarbital. *Double circle* indicates the awake value. *Nos. 1–6* indicate changes during the next 3 hr. at ½-hr. intervals. *No. 7* indicates concentration between 3 and 6 hr. R = exchange ratio isopleths. V_A = % alveolar ventilation (see text).

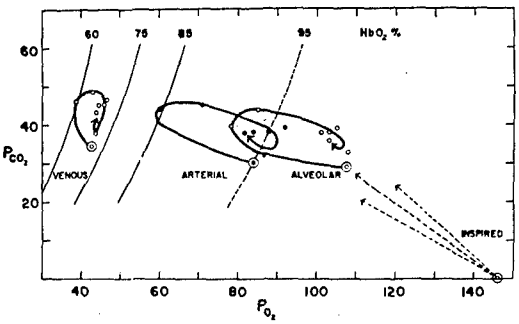


FIG. 4. Summary diagram indicating changing O_2 and CO_2 partitions between inspired gas concentration (*lower right corner*) and mixed venous blood. *Double circles* for the mixed venous, arterial and alveolar values represent control values of the awake dog. Each of the next 6 points indicates changes at ½-hour intervals following injection of pentobarbital. A few isopleths for the HbO_2 % saturation are indicated (for details see text).

gases have the concentration of the control value (7). Thus Va = 1.0 = (K × 0.73)/29 according to the alveolar air equation (see **Effect of Ventilation Rate**), and K in our example becomes equal to 39.8. Figure 3 shows the iso-ventilation line of 1.0 going through our control point. Any point on this line represents the gas concentrations which by definition are the result of a normal alveolar ventilation of 1.0. Using the same K factor we can determine the relative alveolar ventilation for any other point and the lines for relative alveolar ventilation (REL. VA) of .75 and .55 are indicated in figure 3.

The advantage of this definition of alveolar ventilation is that we need not know the metabolic rate nor the changes in frequency of breathing and, finally, that actual ventilation measurements are unnecessary. Thus at the end of 30 minutes the alveolar gas concentration indicates a ventilation which is .55 of that necessary to achieve the normal control gas concentration. These relative ventilation indices show that after the initial ventilatory depression (30 min.) the respiratory center slowly recovers and is eventually able to maintain fairly normal alveolar gas concentrations. An additional injection of pentobarbital at such a time will repeat the whole sequence of events. Similar changes after injection of Pentothal sodium in man and dogs have been previously reported (7).

Thus the alveolar gas composition indicates a continuously changing state which reflects the interplay between the O_2 and CO_2 gas stores of the body and a continuously changing relative alveolar ventilation.

Alveolar-Arterial Gas Gradient. A comparison of the simultaneous values of pO_2 and pCO_2 in the arterial blood and alveolar air indicated no significant CO_2 difference. The O_2 difference, however, is large and has recently been explained elsewhere (4, 5). This O_2 difference remains approximately the same throughout the whole period of anesthesia. The arterial values are plotted together with the alveolar values in figure 4 and simply indicate the magnitude of the O_2 pressure lost across the alveolar membranes due largely to unequal ventilation/perfusion relationships in the various regions of the lung (4). A few isopleths for oxyhemoglobin saturation are indicated in figure 4. They are derived from a diagram similar to figure 2 but determined for the dog (9). It is of interest to point out that the arterial O_2 saturation drops to values of about 85% during the first 30 minutes and later on slowly recovers to initial, awake concentrations. This drop can therefore be largely attributed to the effects of hypoventilation and the large alveolar-arterial O_2 difference. A similar change in ventilation in man with a small A-a O_2 difference would have produced an inconsequential change in arterial O_2 saturation.

Cardiac Output. Unfortunately the cardiac output during the awake control period could not be obtained. The values obtained during the period of anesthesia suggest that no large differences with time occur. The $(A\text{-}V)_{O_2}$ differences of the 24 determinations also indicate no consistent trend. The average was 4.8 vol. % ± S.D. 1.55. For the summary diagram (fig. 4) it was therefore assumed that the $(A\text{-}V)_{O_2}$ difference remained constant with an R equal to that of the alveolar values, and this allowed one to plot the venous pO_2 and pCO_2 by subtracting the appropriate value from the arterial points with the help of the combined blood dissociation curve of the dog. It should be pointed out that in figure 4 the mixed venous point for the awake, unanesthetized dog (*double circle*) was assumed on the basis of an $(A\text{-}V)_{O_2}$ difference of 4.8 vol. %.

Thus in spite of the large differences in

alveolar and arterial O_2 tensions during the anesthesia cycle (some 30 mm Hg) the venous O_2 tensions did not vary more than 10 mm on the average.

SUMMARY

A theoretical approach is outlined for study of the interrelationship of ventilation rate and cardiac output on the O_2 and CO_2 tension of the mixed venous blood. These considerations indicate that the O_2 tensions are largely determined by the cardiac output rate and are nearly independent of the alveolar ventilation. The CO_2 tensions and pH are primarily determined by the alveolar ventilation rate and nearly independent of the blood flow.

The O_2 and CO_2 tensions were obtained directly or indirectly for the alveolar air, arterial blood and mixed venous blood in dogs after administration of sodium pentobarbital and the recovery period of up to 6 hours. While the ventilation is greatly altered in the beginning, the cardiac output remains essentially stable. The effects of the ventilatory depression and subsequent recovery upon the alveolar and arterial gas tensions, arterial saturation and exchange ratio are discussed.

REFERENCES

1. Fenn, W. O., H. Rahn and L. E. Chadwick. Air Force Tech. Report No. 6528, 314, 1951.
2. Fenn, W. O., H. Rahn and A. B. Otis. *Am. J. Physiol.* 146: 637, 1946.
3. Dill D. G., H. T. Edwards and W. V. Consolazio. *J. Biol. Chem.* 118: 635, 1937.
4. Suskind, M. *Am. J. Physiol.* 177: 227, 1954.
5. Williams, M. H., Jr. *Am. J. Physiol.* 173: 77, 1953.
6. Rahn, H. and A. B. Otis. *J. Appl. Physiol.* 1: 717, 1949.
7. Ament, R., M. Suskind and H. Rahn. *Proc. Soc. Exper. Biol. & Med.* 70: 401, 1949.
8. Riley, R. L., D. D. Proemmel and R. E. Franke. *J. Biol. Chem.* 161: 621, 1945.
9. Rahn, H. and H. T. Bahnson. *J. Appl. Physiol.* 6: 105, 1953.
10. Farhi, L. E. and H. Rahn. *Federation Proc.* 13: 42, 1954.

THE ACCUMULATION OF CARBON DIOXIDE IN APNEIC DOGS DURING INTERMITTENT OXYGEN INSUFFLATION[1]

WALLACE O. FENN, PH.D., ARTHUR B. OTIS, PH.D., AND MITZI SUSKIND, PH.D.

This work originated from the suggestion by one of us that emergency artificial respiration might be supplied by a modification of the phenomenon described by Whitehead and Draper (1944) as "diffusion respiration". This term was applied to the gas exchange which occurs when apneic animals are exposed to an atmosphere of pure oxygen. Once the lungs are filled with oxygen the arterial blood remains saturated with oxygen because any oxygen which is absorbed from the lungs is replaced by a mass movement (not a diffusion) of oxygen through the trachea. Survival then is limited by the accumulation of CO_2 which cannot escape against the incoming stream of oxygen unless the animal breathes. With ample oxygen 30 minutes is considered a safe period of apnea and anesthetized dogs have been kept alive for 45 minutes with an average alveolar pCO_2 at the end of this period of 271 mm. Hg (Roth *et al.*, 1947). Without anesthesia, on the other hand, dogs are reported to tolerate CO_2 at this pressure for 2 hours (Leake and Waters, 1929). With gradually increasing concentrations, survival is longer than with an acute exposure. High CO_2 therefore is not fatal for some time although it has a severe narcotic effect.

To be useful for emergencies it should be possible to leave patients exposed to the air between periods of oxygen inhalation. One operator could then presumably take care of 5 or 6 patients by ventilating each one in turn with a few breaths of oxygen through a mask applied by hand over the nose and mouth. This would wash out a certain amount of CO_2 and N_2 and would renew the oxygen tension in the alveoli. Between inhalations air would be drawn into the lungs and the oxygen tension would gradually fall by a combination of dilution with nitrogen and utilization by the body. The duration of the period which could be permitted between inhalations would depend upon the size of the lung and the rate of oxygen consumption. The purpose of this work was to investigate the practical aspects of this method in general and in particular to study the accumulation of CO_2 which occurs during the process.

METHOD

Dogs were anesthetized with 26 mg. pentobarbital sodium per kg. body weight intravenously. A tracheal tube was inserted and was connected to expiratory and inspiratory valves. Expired gas was collected for the measurement of the initial

[1] This work was undertaken as a result of discussion held at the Army Chemical Center, Edgewood, Md., on the subject of methods of artificial respiration for military use under the chairmanship of Dr. D. Bruce Dill.

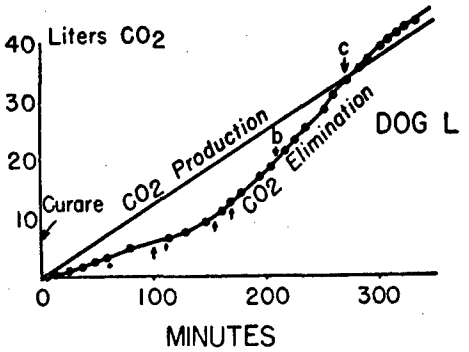


FIG. 1. The cumulative CO_2 produced in Dog L as a function of time after the injection of curare. The lower curve represents the CO_2 actually eliminated by the intermittent ventilations. Small arrows below the curve indicate times of injection of tensilon as an antidote for the curare. Prostigmine was injected at *b* and at *c* regular spontaneous breathing was resumed.

rates of oxygen consumption and CO_2 output and the normal ventilation rate. A sample of alveolar air was obtained by compression of the chest. The dead space was calculated. The tracheal tube was then connected to a 4-way cock by which connections could be made at will with the following: 1) the ambient air, 2) a recording spirometer containing air, 3) a pure oxygen tank through a reduction valve set at 20-cm. water pressure for inflation of the lungs, and 4) a recording spirometer for the collection of expired air.

After attachment to the 4-way valve, apnea was produced by the intravenous injection of curare[2] or Intocostrin (Squibb). When breathing stopped, the lungs were ventilated 15 times by turning the cock alternately to the pressurized oxygen, which inflated the lungs, and then to the expired air spirometer allowing passive expiration to occur. The cock was then turned to the air spirometer and a record was taken of the inflow of air which occurs in proportion to the excess of oxygen taken in over the CO_2 given out. At the end of the period of apnea, varying from 6 to 10 minutes, an alveolar air sample was taken after which the lungs were again ventilated with oxygen at (usually) 15 breaths per minute for 1 minute. The amount of CO_2 thus removed from the body could be determined from analyses of the expired air and the volume. When ventilating with pure oxygen, the rate of oxygen consumption cannot be followed. From the volume of the inflation produced by 20 cm. pressure, the extensibility or compliance of the chest can be determined. In some experiments an ear oximeter was clamped over the dog's tongue. This permitted approximate measurements of the saturation of the arterial blood with a time lag of about 2 minutes. Expired CO_2 was analyzed by the Cambridge Instrument Co. thermal conductivity apparatus, while alveolar air determinations were carried out by means of the Scholander micro gas analyzer.

RESULTS

One of the most prolonged experiments is illustrated in figure 1 on dog "Laddie"weighing 29 kg. Nembutal was injected intravenously at 10:20 A.M. With

[2] 1.2 mg. of α-tubocurarine chloride (Squibb) per kg. of body weight.

the dog breathing pure O_2 curare was injected intravenously at 11:49. Immediately thereafter spontaneous breathing ceased. The first 1-minute period of artificial ventilation with oxygen began 10 minutes later and continued at intervals of about 10 minutes for over 6 hours. Before injecting the curare, the rate of CO_2 output was found to be 124.6 cc. per minute (STPD) as indicated by the straight line in figure 1. The cumulative amount of CO_2 actually eliminated is given by the curve and experimental points indicated in figure 1. Tensilon (Hoffmann-LaRoche) was injected after 1 hour and at intervals thereafter as an antidote for curare and recovery was further aided after about 2 hours by an injection of prostigmine. The maximum storage of CO_2 occurred at about 150 minutes and thereafter the dog took an occasional breath between "refills"; at 270 minutes, regular spontaneous breathing was established. By this time the total CO_2 output had become equal to the amount anticipated (cross over point of curve) and eventually somewhat more CO_2 was eliminated than was predicted from the initial measured rate of CO_2 output.

Alveolar samples were taken during the first 169 minutes of this experiment and indicated a steady rise in pCO_2 during that period. The values were 77 mm. at 9 minutes; 111 mm. at 12 minutes; 146 mm. at 48 minutes; 156 mm. at 59 minutes; and 225 mm. at 169 minutes. Presumably the values fell slowly to normal after this point as the CO_2 storage diminished.

1. CO_2 Storage

The volume of CO_2 stored is the difference between the CO_2 formation and the CO_2 actually eliminated. The amount formed is estimated from the normal rate of CO_2 output prior to the administration of curare. The amounts of CO_2 stored per kg. of body weight have been determined for 17 of our experiments on 9 dogs. The average values have been used to construct figure 2. The slope of the straight diagonal line represents the average observed rate of CO_2 production or 3.5 cc

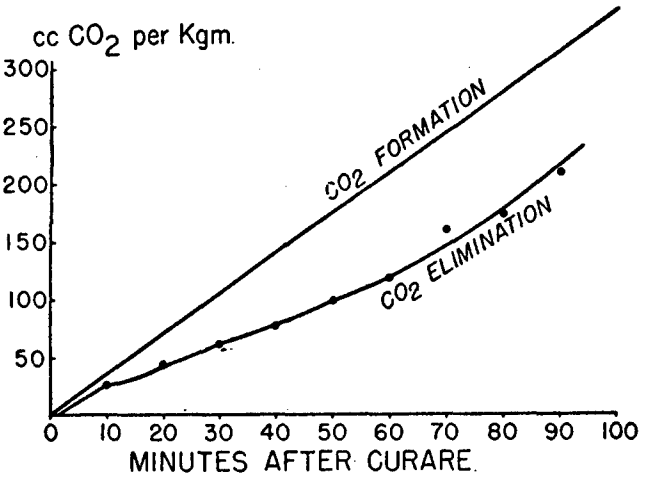
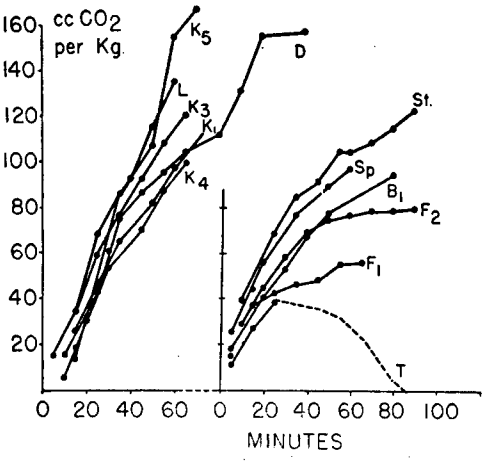


FIG. 2. The expected CO_2 formation as measured before curare (*upper curve*) and the CO_2 actually eliminated by the periodic ventilations (*lower curve*). Average values from 12 experiments.



FIGS. 3 and 4. Volumes of CO_2 retained per kg. body weight in individual experiment Each letter represents a different dog and each curve represents a different experiment. *Abscissae* represent time in minutes after the administration of curare.

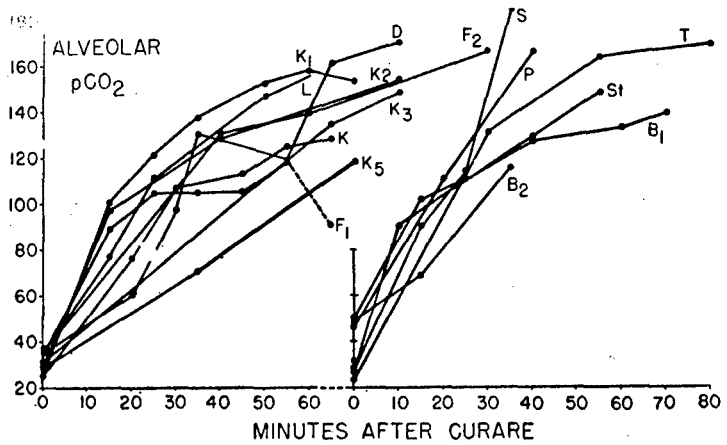
per kg. per minute. Subtracting from this the amounts stored gives the lower curve representing the amounts of CO_2 actually eliminated at different times.

In connection with figure 2, it should be pointed out that the number of figures averaged together is less for the later points because not all of the dogs survived for 90 minutes or the experiment was discontinued for other reasons. It is not believed, however, that this fact invalidates the averages obtained. It is reasonable to suppose that all the dogs would have behaved more or less similarly if the experiments could have been continued for equal periods and since the storage is calculated per kg. of body weight the difference between dogs of different size is allowed for.

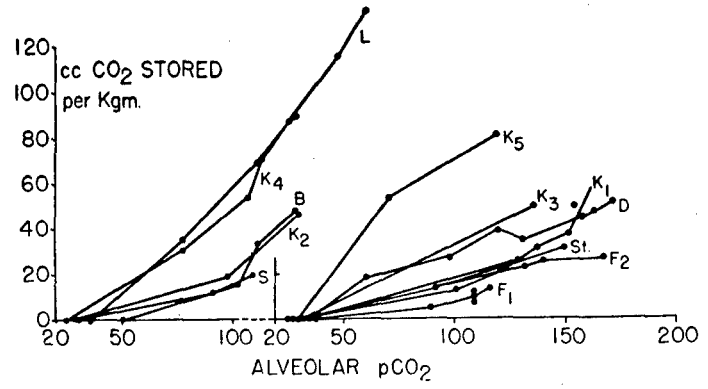
The volumes of CO_2 stored in individual experiments are plotted in figures 3 and 4 as a function of time. It is evident that the steady state is reached in only a few of the experiments after 90 minutes. In one case (fig. 4) the CO_2 storage passed through a maximum at 30 minutes and then declined as spontaneous breathing began to reappear.

The partial pressure of CO_2 in the alveoli at the end of each successive period of apnea shows a progressive increment during the course of the experiment, thus indicating that the CO_2 stored in the body is increasing. Figures 5 and 6 show the progress of this increase as a function of time in 14 different experiments. In general the rate of increase is somewhat more rapid at first and then gradually decreases. The curve would become horizontal at a time when the pCO_2 had built up to a level which would suffice to deliver into the lung during any single ventilation period as much CO_2 as could be formed in the tissues during the preceding interval of apnea. When the CO_2 eliminated becomes equal to the CO_2 formed, the pCO_2 remains constant.

Normal alveolar samples prior to the giving of curare were obtained in 15 experiments in 10 dogs. These showed average values of 34.1 for pCO_2 and 104.7 for pO_2. The average inspired pO_2 was 146 mm. From these values the exchange



FIGS. 5 and 6. Curves from individual experiments showing the increase in the alveolar CO_2 tension at various times after the administration of curare. The individual experiments are labelled as in figures 3 and 4.



FIGS. 7 and 8. Curves from individual experiments showing the volumes of CO_2 retained in the body as a function of the corresponding alveolar CO_2 tension. The experiments are numbered to correspond with figures 3 to 6.

ratio can be calculated as 0.80. This value for unknown reasons is slightly higher than the exchange ratio (0.7) from directly measured rates of O_2 intake and CO_2 output (see below).

It has been shown that the pCO_2 and the CO_2 storage increase during the experiment along curves which are approximately similar. If they were exactly the same in shape, then it could be said that the CO_2 storage increased in direct proportion to the increase in pCO_2. Plotting the former against the latter, as in figures 7 and 8 it can be seen that in general the CO_2 storage increases more rapidly as the pCO_2 increases. This is the reverse of an ordinary CO_2 dissociation curve. It must be concluded therefore that the CO_2 stored is not in true equilibrium with the partial pressure of CO_2 in the lungs. In other words the whole body is not saturated with CO_2 at the pCO_2 value existing in the lungs. When a steady state is reached, these curves will simply stop rising. When that occurs it

may be concluded that all parts of the body including the fat depots which are poorly supplied with blood will have received their complete quota of CO_2 at the existing alveolar partial pressure.

The effective CO_2 storage capacity of the body in the unsteady state existing in these experiments may be calculated from the ratio of the average maximum amount of CO_2 stored per kg. body weight (107 ml.) to the corresponding average increment in pCO_2 above the normal alveolar value (161 mm.). The value of this ratio is 0.67 cc. per kg. per mm. In corresponding units the slope of a CO_2 dissociation curve of normal human blood in the physiological range is about 4.5. The slope of the CO_2 dissociation curve of isolated dog lung was found to be 2.3 cc. per kg. per mm. (Dubois, Fenn and Britt, 1952). In whole mice Freeman and Fenn (1953) obtained a high value of 11.6 when time was allowed for exchange with bones. In cats for periods of 2.5 hours Shaw (1928) obtained values of 1.6 cc. per kg. per mm. From these comparisons it is evident that the value obtained in the present series of experiments (0.67) is exceedingly low and actually not even so great as the corresponding figure for the solubility of CO_2 in pure water (0.75). This confirms the conclusion that under the conditions of these experiments the body of the dog as a whole does not come into equilibrium with the alveolar pCO_2.

2. Compliance of the Chest

In refilling the lungs with oxygen at the end of each period of apnea the lungs are first connected to a source of oxygen at a pressure of 20 cm. of water and are then allowed to deflate into a collecting spirometer at atmospheric pressure. The volume of gas collected in the spirometer was measured at BTPS and divided by the number of breaths to obtain the chest compliance. This represents the volume change for an increase of pressure of 20 cm. of water. In all cases the compliance gradually increased as the experiment progressed. Average values plotted in figure 9 show an increase from 300 to over 650 ml. This presumably represents the gradual recovery from the effects of the curare without which some reflexes may be supposed to occur which facilitate the expansion of the chest in response to pressure. A chest with completely curarized muscles is relatively unyielding and stiff. It is realized that results of this type indicating apparent stiff-

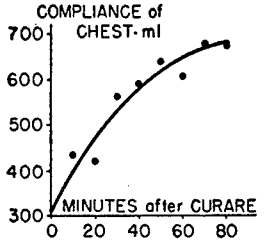


FIG. 9. Average values showing the increase in compliance of the chest as the paralyzing effect of the curare gradually wears off during the experiment. The compliance is measured in ml. increase in lung volume for an increase in pulmonary pressure of 20 mm. Hg.

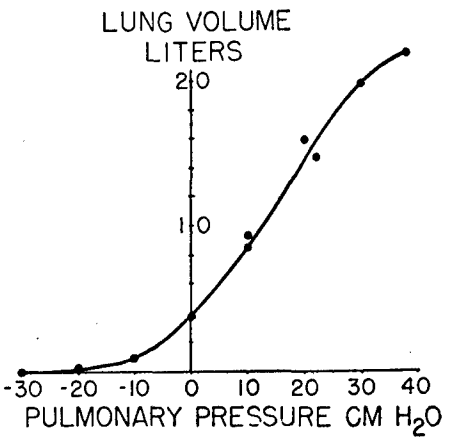


FIG. 10. The relaxation pressure curve of one dog obtained by inflating or deflating the lungs with different pressures. Experiment on a 22-kg. dog. Volume at −30 cm. H_2O is arbitrarily taken as zero. Volumes are expressed in liters at body temperature and saturated.

ness of the chest might be obtained with a high airway resistance if time were not allowed during the procedure for full completion of the inflation and deflation. While further check of this point might be desirable it is our recollection that response to every pressure change was substantially finished before the next movement was initiated. Moreover the extra stiffness of the chest in the early parts of the experiment was very obvious and in some cases more than 20 cm. of water pressure was required at that time in order to obtained adequate ventilation.

In our dogs the average lung volume at the end of expiration was 425 cc. or 18.9 cc. per kg. body weight. Thus an increase of 20 cm. of water pressure more than doubled the volume of the lung since the compliance was usually greater than 425 ml. as shown in figure 9.

In one dog this procedure was varied by applying a series of different pressures to the lung, both positive and negative. The results permit the construction of a "relaxation pressure curve" as illustrated in figure 10. This has a shape similar to those obtained in human subjects except that the relaxation volume at atmospheric pressure is nearer the point of complete expiration. In this dog very little additional collapse of the chest could be obtained by the application of negative pressures.

3. Air Intake During Apnea

The intake of air during the period of apnea was recorded on a small light spirometer containing 50 cc. per cm. The volume of air taken in is a measure of the difference between the CO_2 given out and the oxygen uptake. It was found that this difference is not quite linear during the period of apnea, the fall of the spirometer bell with time being slightly S-shaped. The slow initial rate of fall is due to the high rate of CO_2 output immediately after the oxygen refill when the alveolar pCO_2 is low. The slow terminal rate is due to a decrease in the oxygen intake due to the falling alveolar pO_2.

4. Calculation of Lung Volume

From the volume of air passively inhaled during a period of apnea (V_I) and the nitrogen content of the alveolar air at the end of the apnea (F_{AN_2}) it is possible to calculate the volume of the lung (V_L) (minus dead space, V_D). It is assumed that at the beginning of the apnea both V_L and V_D contain only O_2 and CO_2 and that V_D contains only air at the end of apnea with a nitrogen fraction of 0.791. All volumes are corrected to BTPS.

Then $.791\ V_I = .791\ V_D + F_{AN_2}\ V_L$

and
$$V_L = (V_I - V_D)\frac{.791}{F_{AN_2}} \qquad (1)$$

The average value for V_L obtained in this way in 8 dogs was 396 cc. (BTPS), the average weight of the dogs being 21.6 kg. The body weights were fairly uniform (18.6 to 24.7 kg.) but the lung volumes varied from 251 to 537 cc. On the average then, the volume of the lung was 18.3 cc. per kg. The dead space amounted to 142 cc. but this included the tubing and stop cock.

5. Oxygen Consumption During Apnea

The average rate of oxygen consumption during the control period in 14 experiments on 8 dogs was 112 cc. (STPD) per minute and the average rate of CO_2 output was 78 cc. per minute. This gives a rather low exchange ratio of 0.7 suggesting that the tracheal tube and stop cock may have raised the alveolar pCO_2 slightly. The average weight of these dogs was 22.6 kg.

The above values were obtained on the anesthetized dogs before giving curare. It is of interest to calculate the rate of O_2 consumption during the periods of apnea using the lung volumes calculated as described above and the oxygen fraction found in the alveolar air at the end of each apneic period. To obtain maximum values and to simplify the calculation it is assumed that at the beginning of each apneic period V_D and V_L contain only oxygen and water vapor and that at the end of apnea V_D contains air and V_L contains F_A fractions of O_2 and N_2. Then the O_2 consumed in t minutes ($\dot{V}_{O_2}\ t$) is equal to the O_2 lost from $V_L + V_D$ plus the O_2 taken in from the spirometer with the inhaled volume of air V_I. For this calculation all volumes are expressed STPD.

Then
$$\dot{V}_{O_2}t = V_L\ (1 - F_{AO_2}) + V_D\ (1 - 0.209) + .209\ V_I \qquad (2)$$

This calculation was carried out for every apneic period. Taking representative periods from each of 11 experiments on 7 dogs it is found that the actual O_2 consumed during the apneic period is only 54 per cent of the amount expected from the initially measured rate. This presumably means that the rate of oxygen intake is correspondingly greater than normal during the brief periods of oxygen insufflation when the measurements of the volumes consumed were impossible with our apparatus. Thus if the apnea lasted 9 minutes at 54 per cent of normal rate, the intake during the 1 minute of ventilation must have been 5.14 times the normal rate. This could occur only if: 1) the venous blood during this minute

were almost completely desaturated and 2) the cardiac output were somewhat greater than normal due to the respiratory movements and pressure alternations. During the periods of apnea then, it must be supposed that 0.46 of 112 cc. per minute or 52 cc. per minute or in 9 minutes 468 cc. in all must have been taken from O_2 stores. This is probably not far from the volume that might reasonably be considered available. Thus a 22.5-kg. dog contains 8 per cent blood or 1.8 liters and at 1 atm. alveolar pO_2, each liter contains 210 cc. as HbO_2 and 24 cc. as free O_2, or 234 cc. in all. If one-third of the blood is arterial at 234 cc/L and two-thirds is venous at 184 cc., then the total blood $O_2 = .6 \times 234 + 1.2 \times 184 = 360$ cc. If all the muscle myoglobin is saturated with oxygen, it would contain about 12 cc. O_2 per kg., or 108 cc. in all, in 40 per cent of the average body weight. Thus the total O_2 in the body is 360 + 108, or 468 cc., which just equals the calculated deficit. While these calculations are very rough approximations, the agreement is good enough to suggest that the oxygen intake comes close to meeting the needs of the body. If this were not the case, there would be a progressive development of an oxygen debt and the allowable periods of apnea would show a progressive decrease during the experiment, which did not occur.

6. CO_2 Elimination During O_2 Insufflation

Since the average lung volume in our dogs was 425 cc. and the average dead space (including apparatus) was 139 cc. (total 564 cc.), and the average tidal inflation volume increased from 300 to 670 cc. during the experiment (fig. 9), it is evident that each inflation will remove approximately half of the CO_2 in the lungs. If no more CO_2 diffused in during the 15 tidal inflations which occurred in the minute of ventilation, all of the CO_2 in the lungs would be removed, most of it in the first 4 or 5 breaths. Actually the amount in the lungs at the beginning of the oxygen refill is only a small fraction (perhaps one-fifth) of the amount eliminated in 1 minute of ventilation and indeed there is surprisingly little decrease in the amount of CO_2 eliminated per breath as the ventilation proceeds. This can be determined by collecting the first 3 breaths in one bag, the second 3 breaths in another bag, etc., and analyzing each bag separately. In this way the figures in table 1 were collected on one of our dogs in two separate experiments.

TABLE 1. *CO_2 per breath in percentage of total*

Period No.	CO_2 PER BREATH			
	Breaths No.			
	1–3	4–6	7–9	10–21
	%	%	%	%
1	6.5	5.9	4.8	4.3
2	7.6	6.3	5.8	5.8
3	7.3	7.0	6.0	5.6
4	7.7	7.7	6.8	4.8
5	8.5	7.1	5.6	5.2
Average	7.5	6.8	5.8	5.1

The figures show the volume eliminated per breath in percentage of the total CO_2 eliminated in the whole ventilation period of 15 to 20 breaths. On the average this turned out to be 7.5 per cent in each of the first three breaths and 5.1 per cent in each of the terminal breaths. Evidently the CO_2 diffuses out of the blood into the lung so rapidly that the pCO_2 does not fall much during the ventilation. If this were not the case, it would not be worthwhile to continue the ventilation for as long as 1 minute. Actually, the more the ventilation the better the chance that the CO_2 will be kept from increasing in the body. Under some conditions also a slightly longer ventilation or slightly shorter apnea might just suffice to meet the oxygen requirement of the body.

The rapid diffusion of CO_2 into the lungs was verified in one experiment by ventilating the lungs after the death of the dog. Previous to death the standard ventilation technique eliminated 582 cc., but after death the same ventilation produced only 160 cc.

7. Alveolar Air Changes

No determinations have been made of the changing composition of the alveolar air during the period of apnea but it is possible to make some hypothetical calculations which are of assistance in visualizing the process. It is known that the total amount of oxygen consumed during the period of apnea is only about 54 per cent of the normal amount for the same period. Nevertheless it seems that the rate of intake must be nearly normal at the beginning of the apnea when the pO_2 is high. If it is assumed that at the beginning of apnea there is only pure oxygen in the dead space and lung and that O_2 is consumed at the normal rate, then the rate of CO_2 output at any time can be calculated from the rate of intake of air from the spirometer (since this equals O_2 consumed minus CO_2 output). In this way the diagram of figure 11 was obtained showing the O_2, CO_2 and N_2 fractions in the alveolar air as a function of time. Until the dead space has become filled with air from the spirometer there will be no nitrogen in the alveoli, but only increasing amounts of CO_2 as the amount of oxygen diminishes. Then air reaches the alveoli and the nitrogen begins to dilute the oxygen already present, thus

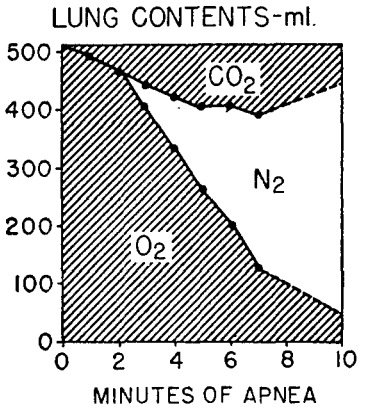


FIG. 11. Semidiagrammatic representation of the changing composition of the alveolar air during a period of apnea. The lung is full of pure oxygen at the beginning of the period of apnea and fills up with air as the oxygen is consumed and the CO_2 given off.

causing an accelerated fall in the pO_2 without much change in the rate of CO_2 accumulation. So long as the arterial blood remains saturated the rate of oxygen consumption should remain nearly normal, but thereafter the alveolar pO_2 will fall rapidly and when the arterial blood returns as venous blood, it might well find the alveolar pO_2 no higher than the venous pO_2. From this point on it becomes difficult to predict the time course of events. It is even possible that as the O_2 becomes deficient the rate of CO_2 formation may decrease to such an extent that the blood might even carry CO_2 away from the lungs for deposition in some poorly perfused and still unsaturated storage depots. This possibility is indicated by the dotted lines. At the end of the apnea period the oxygen percentage in the alveoli is 10 per cent or less and the oxygen remaining is sufficient for only 1 or 2 minutes. In some experiments an oximeter on the tongue of the dog read about 80 per cent saturation at the end of apnea but this reading was not checked by actual analysis of arterial blood and evidently lags considerably behind the actual fact. Once the saturation begins to fall it proceeds very rapidly and the conditions become very critical for further survival. This is certainly one of the great disadvantages of this procedure as a method of emergency artificial respiration.

DISCUSSION

These experiments have demonstrated that in curarized dogs not breathing spontaneously it is possible to maintain life by filling the lungs with pure oxygen once every 5 to 10 minutes. Between these periods of intermittent oxygen insufflation the lungs gradually fill with air as the oxygen contained in them is consumed. Carbon dioxide accumulates during these periods of apnea but is partly eliminated during the 1-minute periods of ventilation with oxygen. Accumulation will continue until a steady state is reached, when the CO_2 eliminated is equal to the CO_2 formed. Meanwhile there is probably no cumulative oxygen debt although the oxygen taken in during each period of apnea is only about 54 per cent of the demand. The remainder is either taken from oxygen stores in the body or represents a temporary oxygen debt which is paid off during the periods of oxygen ventilation. While no effort has been made to determine the maximum possible survival of dogs under this regime, it can be said that 11 dogs have been maintained for periods of 60 minutes and with less regular use for another 2 hours of gradual recovery.

Since no determinations of this sort have been possible in man it is important to consider the factors which determine the necessary frequency of oxygen refills. This results in the probable conclusion that man could survive by this method even longer than a dog.

The immediately critical factor is not the accumulating CO_2 but the fall in pO_2 in the alveoli during each successive period of apnea. When the hemoglobin oxygen saturation begins to fall, it diminishes very rapidly so that the end point is very critical. The most important factor in determining the duration of the apnea period is the ratio (r) of the rate of oxygen consumption (in cc. per min.) to the lung volume in cc. The greater the lung volume and the smaller the rate of O_2 consumption, the longer the O_2 supply in the lung will last.

Starting as in equation 1 with the assumption that the fraction of O_2 in the dead space (V_D) and the lung (V_L) at the beginning of apnea is F_{iO_2} and the fraction at the end is F_{AO_2} in V_L and 0.21 (air) in V_D, we have $\dot{V}_{O_2}t = V_L (F_{iO_2} - F_{AO_2} + V_D (F_{AO_2} - 0.21) + .21\ V_I$ where V_I is the volume of air inspired. For the sake of calculation assume $F_{iO_2} = 0.95$ and $V_D = .05\ V_L$. Further $V_I = \dot{V}_{O_2}t\ (1 - Q)$, where Q is the exchange ratio. The value of Q will vary somewhat during the experiment but has relatively little effect on the calculation so that a figure of 0.5 may be taken as a fair approximation. Using these values one can calculate the time, t, required for the oxygen fraction to fall to 0.1.

$$\dot{V}_{O_2}t = V_L\ (.95 - 0.1) + .05\ V_L\ (.95 - 0.21) + .21 \times .5\ \dot{V}_{O_2}t$$

Simplifying and putting $r = \dfrac{\dot{V}_{O_2}}{V_L}$

$$.9rt = .85 + 0.37 = .89$$

and

$$t = \frac{1}{r} \text{ (approximately)}$$

In our experiments the average value of r was 112 cc. per min/425 cc. = 0.263. In our dogs $V_D = .33\ V_L$. Using this value in place of the value of 0.05 for man, $t = \dfrac{1.2}{r} = \dfrac{1.2}{.263} = 4.5$ min. Actually the periods of apnea lasted twice as long as this because the rate of O_2 consumption during apnea was only half the normal.

In man there is reason to believe that r is about half as great as in dogs so that the period of apnea should be tolerated twice as long. Thus for 50 healthy males, Hurtado and Boller (1933) give a value of 2.34 ± 0.49 (st. dev.) liters for the midcapacity (expiratory reserve and residual air). The O_2 consumption of this same group of subjects can be estimated from the data of Boothby *et al.* (table in Sunderman and Boerner) since the average age was 23 years, the height 176 cm. and the weight 72.5 kg. This gives 265 cc. per min. Hence $r = 265/2340 = 0.113$. From this value the time, t, to reduce the alveolar O_2 to 10 per cent can be calculated as 1/.113 or 8.9 minutes.

Still another estimate of the value of r in man comes from the data of Hurtado and Boller who give 19.5 ± 3.3 as the ratio between the vital capacity and the O_2 consumption and state that the midcapacity is 37.9 per cent of the vital capcity. Hence $r = 100/19.5 \times 37.9 = 0.135$.

This difference between dogs and man is supported also by a study of lung weights of different animals derived from data of Skelton as quoted by Gregersen in Bard's 8th edition of *Macleod's Physiology*, p. 904 (1938). According to these data it can be calculated that the lung weight divided by the two-thirds power of the body weight (or surface area) is 28 gm. in men and 13.9 gm. in the dog. Since surface area can be taken as proportional to the rate of oxygen consumption, this indicates that the value of r should be twice as great in the dog as in man in confirmation of our previous estimate.[3]

[3] We cannot regard this as a very reliable estimate because it is based on lung weights of one 65-kg. man and one small 4-kg. dog. The lung weights in per cent of body weight were 0.69 and 0.88, respectively.

These figures suggest therefore that man might prove to be a particularly favorable organism for the use of this method of artificial respiration because of his relatively large lung volume and/or small rate of oxygen intake. Although we have had no actual experience in applying this intermittent oxygen type of resuscitation to man we feel that it might be a practical method in certain emergencies such as a large scale nerve gas attack in a densely populated area where large numbers of victims may become apneic and mechanical resuscitators cannot possibly be obtained in sufficient numbers. It is not applicable in forward areas on the battlefield but only in cities or rear military areas where oxygen tanks can be available. The necessary equipment is, however, simpler than other artificial respiration devices except the hand bellows which requires one operator for every victim. In this intermittent oxygen method one operator could serve perhaps five or six victims, ventilating each one in turn and then returning to the first one in about 5 minutes or possibly more.

The necessary equipment is an oxygen tank, a reduction valve, and a mask. The mask should be supplied with a hand-operated valve so that the oxygen can be turned on by finger pressure when the mask is securely applied over the nose and mouth. The operator observes the chest and stops the flow when the chest is inflated. The mask is then lifted from the face until expiration is complete, when the process is repeated. After five or six such inflations it can be calculated that further ventilation will not prolong the periodic survival time more than a half minute although it would lower the pCO_2 and might thereby increase the ultimate tolerance of the patient for this type of resuscitation.

The procedure is not recommended as ideal treatment for an apneic victim, but there is reason to believe that it would be adequate for an emergency. As soon as circumstances permit, each patient should be given an individual operator with a hand bellows or should be removed to some hospital where a mechanical resuscitator could be made available. The intermittent oxygen insufflation method has the advantage over the hand bellows method that a patient can be transported on a stretcher for a 5-minute period without the necessity of an operator walking alongside the stretcher and endeavoring to work the bellows. The proposed method suffers, however, from the disadvantage that it would not protect the patient from residual toxic gas in the atmosphere which would enter the lungs in small amounts between refills. Nevertheless, it might be reasonably successful since most of the victims with sublethal doses would presumably be found in marginal areas where the gas concentration would be small and would probably be promptly dissipated or blown away.

The method has admittedly little merit except by comparison with other possible procedures. The nearest competitor would seem to be a single alternating valve delivering intermittent pulses of air pressure from some sort of an electric pump which would require some source of emergency power other than the usual city lines. One such pump might deliver into a manifold to which a number of patients could be attached through suitable masks. This seems to us a much more elaborate apparatus and one which would require a skilled operator who knew how to fit the masks quickly and keep them all tight. It is doubtful whether one

operator could handle any more victims by this method than by the intermittent oxygen method which we have suggested. Moreover, if the mask of any one patient became detached, it would tend to short circuit all the other patients on the same manifold. Constant attention would therefore be required. The intermittent oxygen insufflation method has the disadvantage that it requires pure oxygen, but the requirement is only two or three liters per patient per minute. It is also a risky method at best because of the abruptness with which the oxygen supply in the lung becomes inadequate as apnea proceeds. In a 3-liter lung volume and at a normal rate of oxygen consumption the oxygen percentage could drop from 15 to 5 per cent in 1 minute. In a dire emergency, however, such risks must be taken and there seems to be reason to believe that this simple procedure might be as useful in saving lives as any other method which has been suggested.

SUMMARY

Anesthetized dogs have been used to test the possibility of using intermittent oxygen insufflation as an emergency means of artificial respiration for large numbers of victims. Between oxygen refills the patient is left exposed to the air so that the oxygen tension in the lungs is gradually diluted. Dogs were curarized to produce apnea and were then ventilated with pure oxygen for 1 minute every 6 to 10 minutes. Measurements were made of the composition of the alveolar gases at the end of each period of apnea and of volume of ventilation and its CO_2 content at each period of oxygen insufflation. Dogs were maintained in this way for periods of 1.5 to 2 hours and the following specific effects were noted:

1. The oxygen used during a single period of apnea was 54 per cent of the requirement, the remainder being taken from oxygen stores in the body or represented by a transient oxygen debt.

2. At the beginning of the experiments the CO_2 eliminated during each ventilation period was only half of that formed in the previous period of apnea, but as the pCO_2 increased, the amount eliminated in successive periods of ventilation gradually became equal to the amount formed. The amount of CO_2 thus stored in the body was never as great as would be expected from complete saturation of the body at the pCO_2 observed in the alveoli.

3. The compliance of the chest and lungs was measured at each ventilation period. It was found much reduced immediately after curare but gradually increased during the experiment as the effect of the curare wore off.

REFERENCES

1. Draper, W. B., and Whitehead, R. W. Anesthesiology, **5**: 262, 1944; also **8**: 294 and 524, 1947.
2. Roth, L. W., Whitehead, R. W., and Draper, W. B. Anesthesiology, **8**: 294, 1947.
3. Leake, C. D., and Waters, R. M. Anesth. & Analg., **8**: 17, 1929.
4. Capraro, V., and Pasargiklian, M. Experientia, **3**: 2, p. 77, 1947.
5. Freeman, F. H., and Fenn, W. O. Am. J. Physiol., **174**: 422, 1953.
6. DuBois, A. B., Fenn, W. O., and Britt, A. G. J. Applied Physiol., **5**: 13, 1952.
7. Shaw, L. A. Am. J. Physiol., **85**: 158, 1928.
8. Hurtado, A., and Boller, C. J. Clin. Investigation, **12**: 793, 1933.
9. Sunderman, F. W., and Boerner, F. *Normal Values in Clinical Medicine*, Table 301, p. 383. Saunders, Philadelphia, 1949.

A BAROMETRIC METHOD FOR MEASURING VENTILATION IN NEWBORN INFANTS

by

J. E. Drorbaugh and W. O. Fenn

Plethysmographic techniques have been used by several workers (1,2,3,4,5,6, 7,8) to measure ventilation in newborn infants. The maximal error has been reported to be ±10%. It is probable that the great majority of measurements have an accuracy of less than ±5%. However, the methods used depend upon attaching a collar either around the infant's face (1) or around his neck (2,3,4,5,6,7,8). It was felt that this limited the usefulness of the techniques employed by previous workers. Therefore, we have attempted to develop a system for measuring tidal and minute volumes which could be operated while the infant was allowed to remain unrestrained in a closed chamber similar to an incubator.

The theoretical basis for the method may be presented by considering the conditions influencing air temperature and vapor pressure within a closed chamber, the temperature and vapor pressure of air contained within the lungs of an animal within the chamber, and the effect on the pressure within the chamber of transferring a tidal volume of air from the chamber to the lungs of the animal on inspiration. If an animal is placed in a closed chamber at room temperature, the flow of heat from the animal will warm the interior of the chamber and initiate a flow of heat from the chamber to the room. When these rates of heat exchange are equal, equilibrium will be established. The air temperature within the chamber, represented by the symbol T_c, will be less than the body temperature of the animal, represented by T_a, and greater than room temperature. Any water within the chamber will result in a vapor content which will approach saturation pressure. The final vapor pressure reached will depend, in part, on T_c and in part on the relative humidity within the chamber. If we let P_c be the final vapor pressure, P_s be the saturation vapor pressure for temperature T_c, and RH be relative humidity in percent then:

$$P_c = \frac{RH}{100} \times P_s \qquad \text{--------} \qquad (1)$$

The above considerations would determine the temperature and vapor pressure of inspired air for an animal in a closed chamber. The rate at which values of T_c and P_c are reached depends on size of the chamber, heat conductivity of its wall, temperature differential between animal and room air, circulation of air within the chamber, and availability of water for saturation of air within the chamber.

Air within the animal's lungs is present at body temperature T_a, and saturated with water vapor which may be represented by P_a. As the animal breathes, air is inspired at temperature T_c and vapor pressure P_c. At the end of inspiration a volume of air which we have assumed to be approximately equal to the volume of the inspired air is now present at temperature T_a and pressure P_a. That volume of air which is now at P_a and T_a will thus be present at a higher pressure because of added heat and water vapor than prior to inspiration. This increased pressure will be transmitted to all parts of the chamber and the resulting increase in pressure within the chamber may be represented by P. P will be directly proportional to the volume of air warmed and wetted within the animal and inversely proportional to the size of the chamber in which the animal rests. Therefore, P is a measure of the tidal volume which may be designated V. On expiration the reverse process will occur and pressure in the chamber will be reduced by P.

If the animal has a respiratory quotient, or exchange ratio, which is constant, the total number of dry gas molecules within the chamber will change at a constant rate, and the total number of molecules present before and after inspiration of a tidal volume V_T may be expressed as follows:

$$\frac{V_O(P_B-P_c)}{T_c} + \frac{V_I(P_B-P_a)}{T_a} = \frac{(V_O-V_T)\,(P_B+P-P_c)}{T_c} + \frac{(V_I+V_T)\,(P_B+P-P_a)}{T_a} \quad \text{---- (2)}$$

In the above, equation V_O equals the volume of the chamber outside the animal, V_I equals the volume of air inside the animal to which the tidal volume is added, and P_B equals barometric pressure.

V_O and V_I are not known. However, their sum may be obtained by changing V_O by a known amount which may be designated V_k, and observing the change in pressure which may be designated P_k:

$$\frac{(V_O+V_k)\,(P_B-P_c)}{T_c} + \frac{V_I(P_B-P_a)}{T_a} = \frac{V_O(P_B+P_k-P_c)}{T_c} + \frac{V_I(P_B+P_k-P_a)}{T_a} \quad \text{----- (3)}$$

Equations (2) and (3) may be combined eliminating V_O and V_I. Solving for the tidal volume then gives:

$$V_T = \frac{P}{P_k} \times V_k \times \frac{T_a\,(P_B-P_c)}{T_a\,(P_B-P_c+P) - T_c\,(P_B-P_a+P)} \quad \text{--------- (4)}$$

The tidal and minute volumes obtained by the barometric method are calculated by equation (4). When making the calculation P is omitted from terms where it is added to P_B since P is very small compared to P_B. The ratio of P/P_k is obtained from the experimental record in units of millimeters of galvanometer deflection rather than in absolute pressure units. Volumes are expressed in cubic centimeters,

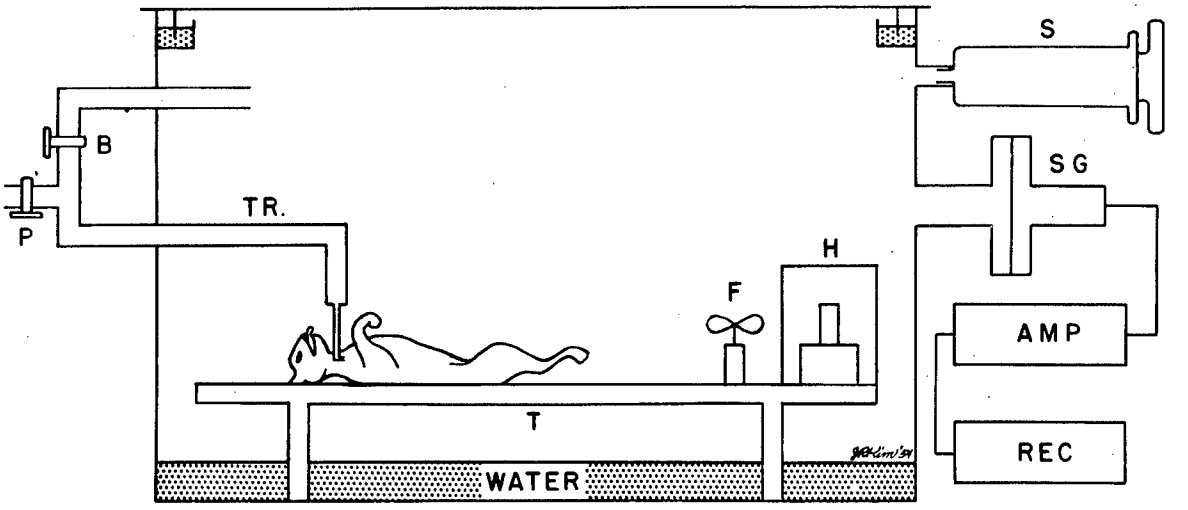
temperature as absolute temperature in degrees centigrade, and barometric pressure in millimeters of mercury.

In this paper, animal experiments are reported which compare minute volumes and tidal volumes by standard methods with the same quantities measured by the barometric method described above. In addition simultaneous records of pressure changes within the chamber and respiratory air flow are shown. Tidal and minute volume records of five premature infants are presented as a preliminary evaluation of the method's applicability to the study of ventilation in newborn infants.

METHODS

A modified Castle sterilizer was used as a chamber for animal experiments (see Figure 1). The chamber was equipped with a tray to support animals and equipment beneath which water was placed so that the final air volume of the sterilizer was approximately 44.0 liters. A fan was placed on the tray to stir the air. A pipe was put through the side of the chamber, with the inside end connected to a tracheotomy tube in the experimental animal and the outside end attached to a T-tube. One arm of the T-tube was led into the chamber again and the other to the outside air. The arms of the T-tube were equal in volume so that the animal would have the same dead-space whether breathing from the air or from the chamber. In this way without opening the box the animal could be made to breathe from either the chamber or the outside air. When breathing from the chamber, a record of ventilation could be made by the barometric method and when breathing from the outside, measurements could be made by plethysmographic or spirometric methods. Humidity inside the chamber was measured by an electric hygrometer manufactured by American Instrument Co., and accurate to $\pm 1\%$ relative humidity. Temperature of the experimental animal was measured by rectal thermometer. This and the chamber temperature were read to the nearest degree centigrade. Pressure inside the chamber was measured by means of a Statham differential strain gage made for ranges of ± 0.05 PSI (approximately ± 30.0 mm H_2O). The gage was connected to a Hathaway strain gage amplifier and oscillograph. The oscillograph galvanometer gave a direct current sensitivity of 980 mm/ma/M. This pressure recording system was used for both the plethysmographic and barometric methods. When used in the barometric method, pressures in the range of 0.1 to 1.0 mm of water were measured and a linear response was obtained when the volume of the system was changed by known amounts ranging from 1.0 to 10.0 cc. A glass syringe was attached to the side of the chamber for this purpose.

The barometric method was compared with three standard methods: (1) Spirometric measurements were made by attaching the tracheotomy tube to water valves so that expired air could be collected in a rubber balloon (to minimize resistance) and transferred to a small Tissot spirometer. The number of expirations so collected and the frequency of breathing was recorded in order to calculate tidal and minute volumes. (2) Plethysmograph measurements were obtained by allowing the animal to breathe through the pipe in the chamber wall



CALIBRATING CHAMBER

Figure 1

An anesthetized cat with tracheotomy tube in place resting on a tray within the calibrating chamber. P and B are removable clips. If P is in place and B removed, the animal is breathing from the chamber. If B is in place but P removed, the animal is breathing from outside the chamber. The drawing is schematic and not meant to show the relative size of the parts involved. Tr. - tracheotomy tube; T - tray; W - water; F - fan; H - humidity sensing element; SG - strain gage; Amp. - Hathaway amplifier; Rec. - Hathaway oscillograph recorder; S - calibrating syringe.

while the pressure changes within the chamber were recorded. (3) A pneumotachometer made by Dr. Benjamin Ross was used to record respiratory airflow while the barometric method was in operation.

The chamber used for studies on premature infants was a Bloxsom airlock of approximately 65 liters volume, equipped with carbon dioxide absorber and hygrometer. The humidity measurement was necessary since the chamber was not saturated with water vapor. After an infant had been maintained in the airlock for 30 minutes, oxygen and carbon dioxide concentrations were measured by means of a Scholander gas analyzer and found to vary less than 1.0% from their initial concentrations.

Animals used in the calibrating experiments were cats weighing from 1.7 to 4.8 kgm and anesthetized with approximately 25 mgm/kgm of sodium pentobarbital injected intraperitoneally prior to tracheotomy. Initially the animal was

allowed to breathe from the chamber until temperature and vapor pressure equilibrium was established. This required from 10 to 15 minutes. A record of pressure changes within the chamber was made and calibrated after which the animal was switched immediately to the standard method used for comparison. The pneumotachometer, however, could be operated simultaneously with the barometric method.

The procedure followed with infants was exactly the same as that for cats except that only barometric records of ventilation were made. The values obtained were compared with those from plethysmographic methods reported in the literature. The infants varied in age from 4 to 39 days and in weight from 1.8 to 2.3 kgm. The records were made from 30 minutes to 3 hours after the last feeding. No rigid criteria were required for activity on the part of the baby except that he be quiet enough to allow a record within the pressure range of the recording instrument.

RESULTS

Tidal and minute volumes obtained in animal experiments by standard methods are compared to the same measurements obtained by the barometric method in Table 1. The differences in percent of the standard method value vary from -5.3 to +13.2% with an average difference of ± 8%. Comparing, however, average values found by the two methods, the difference is only 1%. Figure 2 shows simultaneous barometric and pneumotachometric records and demonstrates that changes in flow at the onset of inspiration and at the end of expiration are recorded by the barometric method within 0.1 second.

The results of the measurements on premature infants are presented in Table 2. A sample record is reproduced without reduction in size of the observed deflections in Figure 3.

DISCUSSION

The barometric method for recording ventilation was first used by Dr. John Chapin (9) in the Department of Physiology of this University. Calibration by means of a set of syringes which warmed and wetted a known volume of air without changing the volume of the chamber produced calculated and observed results agreeing within 8%. Our series of animal experiments comparing tidal and minute volume measurements by standard methods with those obtained barometrically indicate about the same degree of accuracy. Chapin found the method sufficiently sensitive to record tidal volumes of unanesthetized hamsters in the range of 1.0 to 3.0 cc. at frequencies of 20 to 120 per minute. It was therefore utilized in investigating the effects of autonomic drugs on ventilation of small animals (10). Since simultaneous pneumotachometric and barometric records show close correspondence between chamber pressures and changes in respiratory air flow,

TABLE I

Average tidal and minute volumes measured by a standard method and the barometric method under the same conditions. The standard method used in experiments 1, 2, and 3 was spirometric, in 4 and 5 plethysmographic, and in 6 and 7 pneumotachometric. All volumes are at BTPS. f = frequency of breathing per minute. V_T = tidal volume in cc. $\dot{V}$ = minute volume in cc.

Expt.	f	Standard Method V_T	Barometric Method V_T	Standard Method $\dot{V}$	Barometric Method $\dot{V}$	Percent Error
1	18	19	18	342	324	-5.3
2	8	32	35	256	280	+9.4
3	11	28	31	318	341	+10.7
4	12	37	35	445	420	-5.4
5	7	36	38	252	266	+6.7
6	10	38	33	380	330	-13.2
7	18	31	20	558	522	-6.5

TABLE II

Ventilation data obtained from five premature infants. Volumes are at BTPS. $\dot{V}$ = average minute volume in cc. f = average frequency of breathing per minute. V_T = average tidal volume in cc.

Baby	$\dot{V}$	Range	f	Range	V_T	Range
N	280	240-360	21	18-23	13	4-32
B	400	360-440	45	44-46	9	4-23
A	590	450-720	37	31-43	16	6-71
G	400	300-500	57	51-69	7	3-45
K	410	320-470	75	57-85	5	2-8

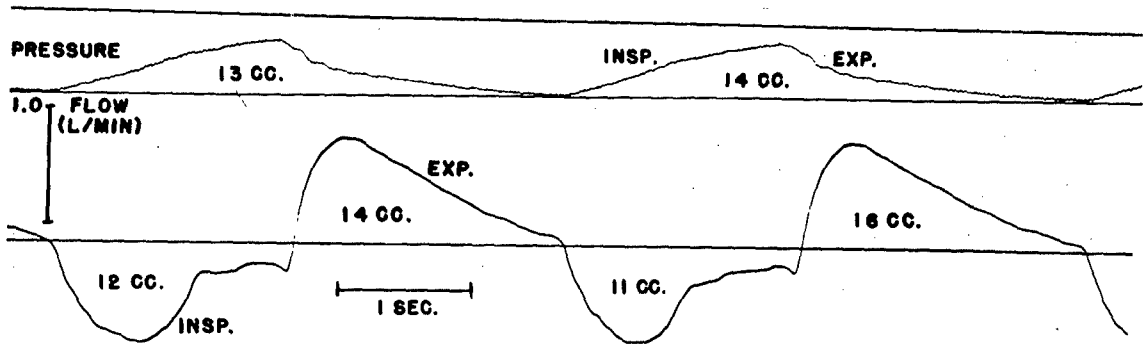


Figure 2

Simultaneous record of air flow in the airway of the cat and pressure changes within the calibrating chamber. Note that the onset of inspiration and end of expiration is at the same instant in each record. The values of 13 cc and 14 cc for the tidals in the pressure record were obtained by averaging the inspiration and expiration volumes obtained by planimetry from the airflow record.

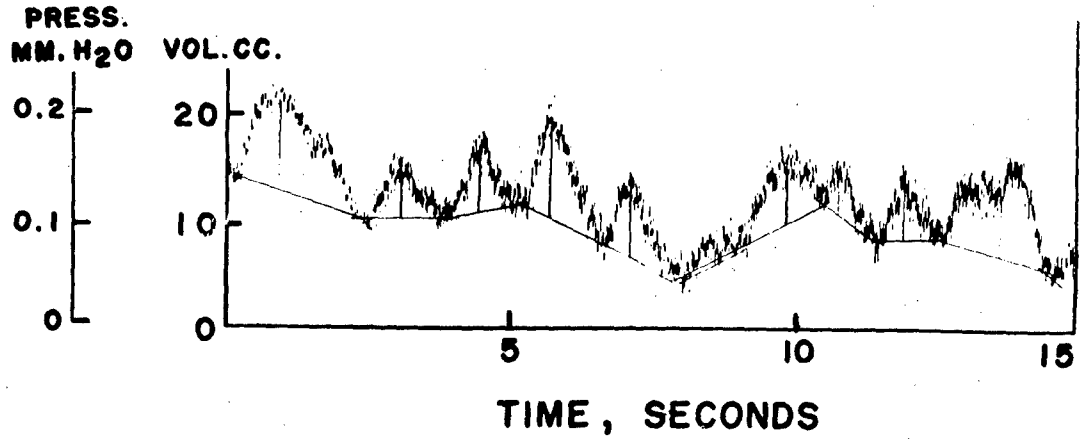


Figure 3

Pressure changes produced by infant G within a closed chamber. The pressure scale was calculated by assuming an approximate volume of 66 liters for the chamber. The volume scale represents the volume of air which must be inspired or expired by the infant in order to produce the observed pressure changes. High frequency oscillations are artifacts.

expired air must come into temperature and vapor pressure equilibrium with chamber air very rapidly. Another indication of the rapid transfer of heat and water from expired air is the fact that the baseline remains approximately steady except for slow rhythmic fluctuations in both directions. Therefore relatively high frequencies of breathing need not interfere with application of the method.

The results for minute volume and frequency of breathing of premature infants listed in Table 2 are in the same range as those recorded by Cross (1) and by Boutourline-Young and Smith (2) using plethysmographic methods. Cross gives values of 396.3 $\pm$ 96.2 cc for minute volume and 34.39 $\pm$ 8.63 for frequency per minute. Smith gives 430 cc and 32.8 breaths per minute for average values of the same functions. We have not averaged our values since only five experiments are presented and no attempt was made to exclude babies not in a "basal" state of ventilation.

At the present stage of development three factors limit the usefulness of the barometric technique. (1) When the baby is active, the baseline is so unsteady that it is not possible to measure individual tidals accurately. During activity such baseline changes might be explained by muscular activity of the baby resulting in compression of air within the lungs or gastrointestinal tract thus producing a change in pressure within the chamber. This was suggested by Chapin who noted the same phenomenon during his study of hamsters. Such changes could also result from large changes in the infant's functional residual capacity. (2) It is necessary to wait at least 10 minutes before records can be made since time is required for vapor pressure and temperature equilibrium in a relatively large chamber. (3) The chamber must be opened every 20 to 30 minutes in order to prevent oxygen concentration in the inspired air from falling more than 1%. These disadvantages must be weighed against the advantage of being able to study ventilation of a seriously ill newborn infant without the necessity of interfering with his medical care. Further experiments will be necessary before the usefulness of the method can be definitely established.

CONCLUSIONS

1. A barometric method for measurement of ventilation of newborn infants is described.
2. Experiments with cats are reported to show the degree of accuracy obtainable at present. The variation from standard methods was found to average -6%.
3. Minute volume, frequency, and tidal volume of premature infants measured by the barometric method are within the range of such measurements made by plethysmographic methods.
4. The barometric principle deserves further study since it offers the possibility of securing ventilation data with a minimum of disturbance to the infant.

REFERENCES

1. Cross, K. W. J. Physiol., 109: 459, 1949.
2. Boutourline-Young, H. J. and C. A. Smith Am. J. Dis. Child., 80: 753, 1950.
3. Howard, P. J. and A. R. Bauer Am. J. Dis. Child., 77: 592, 1949.
4. Wilson, J. L., S. B. Long and P. Howard Am. J. Dis. Child., 63: 1080, 1942.
5. Murphy, P. P. and E. S. Thorpe J. Clin. Invest., 10: 545, 1931.
6. Deming, J. and A. H. Washburn Am. J. Dis. Child., 49: 108, 1935.
7. Deming, J. and J. P. Hanner Am. J. Dis. Child., 51: 823, 1936.
8. Shaw, L. A. K. and F. R. Hopkins Am. J. Dis. Child., 42: 335, 1931.
9. Chapin, J. Am. J. Physiol., 1954 (in press).
10. Tawab, S. A. A. Thesis for M.S. Degree, University of Rochester, Rochester, New York, 1950.

Ventilatory Response of the Unrestrained and Unanesthetized Hamster to CO_2

JOHN L. CHAPIN

IT WAS OBSERVED in this laboratory that in a closed chamber containing a man the pressure increases on inspiration due to the wetting and warming of the air. It was suggested to the author that this principle might serve as a method for the measurement of respiration in small animals where it is difficult to make use of masks and where immobilization by anesthetics or by physical restraint is undesirable. With the help of Dr. Otis this suggestion was tested and the method proved well adapted to the determination of the CO_2 sensitivity of the respiratory center of the hamster under wide variations of the inspired CO_2 percentage.

METHODS

In these experiments an airtight brass chamber with a volume of about 1400 cc was used. The pressure changes were transmitted through a plastic tube to an 0.2. psi strain gauge pressure transducer (Statham) coupled with a carrier wave amplifier and oscillograph (Hathaway). This chamber was submerged in a constant temperature water bath provided with a stirrer. A small inside fan kept the chamber air in motion. A few cubic centimeters of water in the bottom of the chamber kept it saturated at the water bath temperature. Two screens separated the experimental animal from the fan and from the water. A 1-cc. tuberculin syringe was connected to the outlet of the chamber so that known amounts of air could be injected into the chamber for calibration purposes.

The use of this method in determinining ventilation is based on the following assumptions: that the chamber pressure increases are due to the heating and moistening of the experimental animal's tidal air when the animal inspires; that both the pressure and the temperature effects are equilibrated to pre-existing conditions after expiration and before another inspiration. If the latter conditions were not met one might expect that the pressure in the chamber would continually rise as the animal breathed. This was not found to be the case. In order to simulate a breathing animal in the chamber and to discover whether changing the temperature and water vapor alone could produce changes of the same order of magnitude as a breathing animal, a calibrator was constructed. This consisted of a pair of syringes mounted parallel to each other and perpendicular to the top of the chamber. Each syringe communicated with the inside of the chamber by way of a small hole. The syringes were mounted upon a frame such that when the plunger of one syringe was pushed in, the other automatically was pulled out to the same extent keeping the combined volume of chamber and syringes constant. Into one syringe was placed wet gauze and the outside of this syringe was wrapped with nichrome wire which led to a power source so it could be used as a heater. A thermocouple was also incorporated into this syringe and this was connected with a galvanometer which registered the syringe temperature. When the plunger of this syringe was pulled out and the other automatically went in to keep the volume constant, a pressure change was noted in the chamber due to the heating and wetting of the air in the syringe connected with the chamber. The temperature of the syringe could be controlled so that the twin syringe setup actually simulated a breathing animal. It was found that the pressure changes produced using this calibrator were of the same order of magnitude as those predicted from gas law calculations. It was also found that equilibration to pre-existing conditions after simulated expiration took less than one-tenth of a second which is sufficient to allow for the fastest respiratory frequencies found in the experimental animals used in these experiments.

Hamsters were chosen as experimental animals. The primary reason for the choice of this animal was that most of the procedures were carried out in the daytime when hamsters are rather dormant. If the experimental animal moved about while pressure changes were being recorded, the recording was very erratic and, in addition to the respiratory pressure changes, there were many others probably due to compression and decompression of gas in the body cavities. Because of these extraneous pressures it was found necessary to wait until the animal had become quiet before recording respiration. Twelve different male hamsters were used. Their weights varied from 90–130 gm. Each animal was exposed successively to several different gas concentrations.

Environmental temperature can effect the volume of respiration. If the environment is too warm, an experimental animal may pant, if it is too cold, the animal

may shiver. Between is the zone of thermal neutrality of Benedict and Lee (1) where the respiration is minimal. This zone was determined for the animal used in these experiments as 27–28°C. The resting ventilation was found to be twice as large when the temperature was 22 or 32°. All experiments were carried out with water bath temperature in this zone of thermal neutrality.

The chamber containing the animal was ventilated with air or other gas mixtures at a rate of about 5 l/min. for from 20–30 minutes which was considered to be long enough for an animal the size of a hamster to achieve a steady state. Each gas mixture had been prepared in a small gas cylinder under pressure and its contents analyzed by a Haldane Gas Analyzer. At the end of this period of ventilation with air or a test gas the inlet was closed, the outlet was connected with the strain gauge, a recording of the pressure changes was taken, and the run was calibrated with the 1-cc tuberculin syringe. The whole procedure took less than a minute so there was little chance for the gas concentrations in the chamber to change. Each run on a test mixture was preceded by a run in which the animal breathed air for a period of 20–30 minutes. A series of mixtures which varied from 3–35% CO_2 was used. The oxygen in each mixture was kept at 20%. The balance was nitrogen.

RESULTS

Tidal volumes were calculated in the following manner: When an animal's body temperature was found to be 37°C, the chamber temperature 27°, the total barometric pressure in the chamber 760 mm Hg and the gas in the chamber saturated at 27°, the pH_2O of the chamber gas was 27 mm Hg leaving 733 mm for dry gas. When the animal inspired, the inspired gas would be heated to 37°C and saturated at this temperature. The pH_2O of the inspired gas would be increased from 27 mm to 47 mm Hg or a 20-mm increase in total pressure due to the addition of water vapor molecules. In addition this volume would be heated from 27° to 37° or from 300° to 310° absolute. The total volume of the inspired gas would be increased by a factor of $780/760 \times 310/300$ or by 6%. This would produce a deflection of the galvanometer.

If this same deflection could be produced by injecting .06 cc of air into the chamber with the connected tuberculin syringe, the calculated tidal volume would be 1 cc. Actually the degree of deflection produced by injecting air in this manner was found to be proportional to the volume injected. Therefore, it was not necessary to inject an amount which would exactly match the galvanometer deflection produced by breathing of the experimental animal.

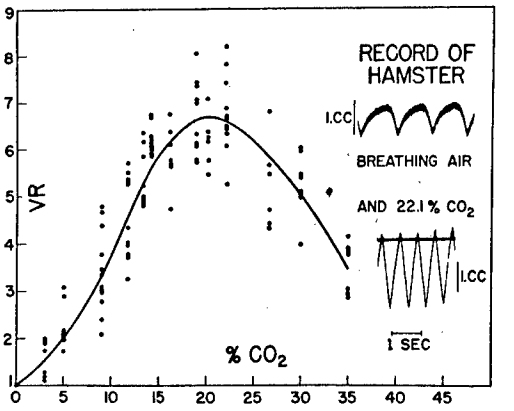


FIG. 1. Ventilatory response of hamster to CO_2. Left portion shows measured ventilation ratios of hamsters at each of several CO_2 concentrations. A smooth curve is drawn through the points. Right portion shows samples of records obtained.

Figure 1 shows photographic recordings of air and CO_2 breathing. It also shows the individual determinations of ventilatory response plotted as ventilation ratios (the ratios of ventilation breathing CO_2 mixtures to the ventilation of the same animal breathing air) against percentages of CO_2 breathed.

A smooth line connects what appears to be the average of plots at each concentration. The peak ventilation appears to have occurred when the animals breathed 20% CO_2. It should be borne in mind that these CO_2 percentages represent inspired, not alveolar CO_2.

The resting respiratory rate showed an inverse ratio with body weight. At 130 gm the mean resting rate was 30, at 100 gm it was 32 and at 90 gm the mean rate was 33.

The tidal volume was directly related to body weight. At 130 gm the mean tidal was 1.4 cc, at 100 gm it was 1.03 cc, and the 90-gm group averaged .91 cc tidals.

The mean minute volumes for the 130, 100, and 90-gm groups were, respectively, 42 cc, 33 cc, and 30 cc. CO_2 breathing increased the rate more than the tidal. The means for the 100-gm group breathing 22% CO_2 were: rate 113, tidal 1.96 cc, minute volume 222 cc.

DISCUSSION

The peak ventilation was found here when the animals breathed about 20% CO_2 in 20%

O_2 and 60% N_2. This figure compares with 9% CO_2 which Nielsen (2) states evokes maximum ventilation in man. Other published figures are generally from anesthetized animals or were measured in unsteady states.

Another comparison may be made with experiments of Guyton (3) who measured the ventilation of small animals and found resting ventilations which were generally higher than those reported here. The immobilization and possible struggling of his experimental animals may have contributed to their higher ventilations. His environmental temperatures may also have been outside the zone of thermal neutrality. An assumption used in calculating the data reported here may constitute another source of difference. This study assumes that the entire tidal volume reached and was saturated at body temperature. If dead space air or other portions of the tidal failed to do this, the ventilation volumes reported here would tend to be lower than they really were.

SUMMARY

A method is presented for measuring ventilation of small animals without the use of anesthesia or any physical restraint. Hamsters were exposed to a spectrum of CO_2 concentrations (0–35%) in 20% O_2 and N_2. The ventilatory responses were recorded. Peak ventilation appeared to occur when the inspired gas mixture contained about 20% CO_2.

REFERENCES

1. BENEDICT, F. D. AND R. C. LEE. Carn. Inst. Pub. #497, 1938.
2. NIELSEN, M. *Skand. Arch. Physiol.* 74: 299, 1936.
3. GUYTON, A. C. *Am. J. Physiol.* 150: 70, 1947.

THE GAS EXCHANGE IN DIFFERENT TYPES OF BODY GAS POCKETS WITH PARTICULAR REFERENCE TO THE LUNG:THEORY

by

Hermann Rahn and Hugh D. Van Liew

The gas pockets that may occur in the body can be classified into three different types: 1) open and ventilated pockets such as the normal lung alveoli; 2) open but unventilated pockets such as non-ventilating alveoli, the sinuses, and the middle ear chamber; and 3) completely sealed pockets such as atelectatic alveoli, intestinal gas, pneumothorax, and pneumoperitoneum. Figure 1 is a schematic representation of these types of gas pockets as they might occur in the lung where 1 is a normal ventilated and perfused alveolus, 2 is a non-ventilated but perfused alveolus, and 3 is an atelectatic alveolus caused by the blocking of a bronchiole. In each type of pocket, the gas can be expected to diffuse into the nearby tissue and blood. As will be explained later, type 1 exchanges CO_2 and O_2 but has no net exchange of N_2, type 2 exchanges N_2 and O_2 but not CO_2, while in type 3 all three gases are absorbed.

Some generalizations can be listed which will apply to all three types of pockets. These are modifications of the five generalizations pertaining to closed pockets made by Dale and Rahn in a paper on artificially-induced atelectasis (1).

1.) The total pressure of a gas pocket remains essentially atmospheric but the sum of all the gases in the blood-tissue environment is less than atmospheric. In the case of an open pocket, gas will enter to maintain pressure equilibrium with the outside. Measurements of the total pressure inside closed pockets indicate that they always remain within a few mm of the outside air. On the other hand, the total pressure of the gases dissolved in the tissues and blood surrounding the pocket must be less than atmospheric. This is largely due to the nature of the hemoglobin saturation curve which allows a far greater pressure drop for a given quantity of oxygen removed than is gained from a similar quantity of CO_2 added.

2.) It follows that there will be a partial pressure difference between pocket and tissue-blood environment for at least one of the gases in the pocket.

3.) Because of the pressure gradient the gas will exchange with the environment.

4.) The composition of a gas pocket will eventually become constant provided the gas tensions remain unchanged in the blood-tissue environment. This occurs

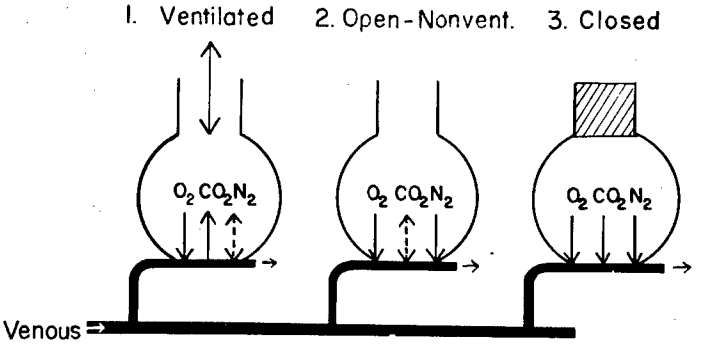


Figure 1

Schematic representation of the 3 types of gas pockets in their steady state perfused by venous blood. Type 1 is the ventilated alveolus with normal O_2 and CO_2 exchange but no net exchange of N_2. Type 2 is the open but non-ventilated pocket where only N_2 and O_2 are absorbed with no net CO_2 exchange. Type 3 is the closed pocket in which all 3 gases are resorbed until the pocket eventually collapses.

because the diffusion of a gas tends to decrease the concentration of that gas in the pocket. Therefore the pressure heads of the gases come to a minimum which is dependent only on the gas content of the tissue and blood and independent of the original concentrations in the pocket.

5.) During this state of constant composition the pressure head for each gas does not change so the uptake of the gas must be constant if the diffusing area stays the same.

a.) In the open-unventilated pocket the amount of a particular gas absorbed in the constant composition state must be equal to the amount coming in through the opening and therefore its rate of uptake will be proportional to the concentration of the incoming volume. This assumes that the instreaming gas prevents the outward diffusion of gas from the pocket.

b.) In the closed pocket, the total volume will decrease as gas is absorbed

and the rate of disappearance of a particular gas will be proportional to its fractional concentration.

The Alveoli as Gas Pockets

The rate of absorption of a gas by its tissue-blood environment will depend upon (1) the pressures of the gas in the pocket and the environment, (2) the metabolism of the surrounding tissue (including bacteria in the case of intestinal gas), (3) the magnitude of the blood perfusion, and (4) the barrier to diffusion of the gas. In the case of lung tissue it can be assumed that the gas metabolism of the tissue and the barrier to diffusion are negligible so that the perfusion and the tensions of the gas in the pocket and the blood are the only important variables.

The N_2 Exchange of Ventilated and Perfused Alveoli

The gas composition of ventilated alveoli can be predicted provided we know the relative perfusion rate when a given mixed venous and inspired gas concentration is assumed. The theoretical approach to this problem has been given elsewhere (2). Alveoli may have different ventilation/ perfusion ratios which determine the exact gas composition. Thus, theoretically, we may have alveoli which have a ratio of ∞ (ventilated but non-perfused alveoli), and at the other extreme a ratio 0 (perfused but non-ventilated alveoli), while most alveoli have normally a ratio of about 1.0 (the alveolar volume flow equal to the perfusion volume). All these possible combinations can be described on the O_2-CO_2 diagram by the $\dot{V}_A/\dot{Q}$ line.

It is of interest here to describe the N_2 and CO_2 concentration for all the possible $\dot{V}_A/\dot{Q}$ ratios and to point out the possibility of a continuous N_2 exchange existing in certain alveoli. Figure 2A represents all the possible N_2-CO_2 combinations which could theoretically exist when the $\dot{V}_A/\dot{Q}$ ratio ranges from 0 (at point A) to infinity (at point I). In this example the mixed venous P_{O_2} and P_{CO_2} are 40 and 46 and the inspired P_{n_2} is 563 = (.791·713). The gas exchange ratio, R, lines are also indicated, as well as the approximate $\dot{V}_A/\dot{Q}$ ratio for points B, C, and D.

Point C represents an average alveolar composition where R = .8, P_{CO_2} = 40. This composition is the result of a $\dot{V}_A/\dot{Q}$ ratio of approximately 1.0. Since the average alveolar P_{n_2} is 571 (about 8 mm higher than P_{In_2}) it can be assumed that the arterial blood as well as the returning mixed venous blood will have the same tension since N_2 is not exchanged in the tissues.

This is the ideal state where all alveoli have the same $\dot{V}_A/\dot{Q}$ ratio and therefore identical gas composition and exchange ratio. It seems, on the other hand, most likely that normally, and particularly in various pathological conditions, $\dot{V}_A/\dot{Q}$ is not the same but varies around a mean with some alveoli having higher ratios (such as point D) and others having lower ratios (point B). The mean ratio is still at C and the blood P_{n_2} is 571. But the mixed venous blood P_{n_2} is 28 mm lower than that of alveolus B and 18 mm higher than that of alveolus D. Thus N_2 is removed by the blood in B but excreted in alveolus D, while alveoli in the

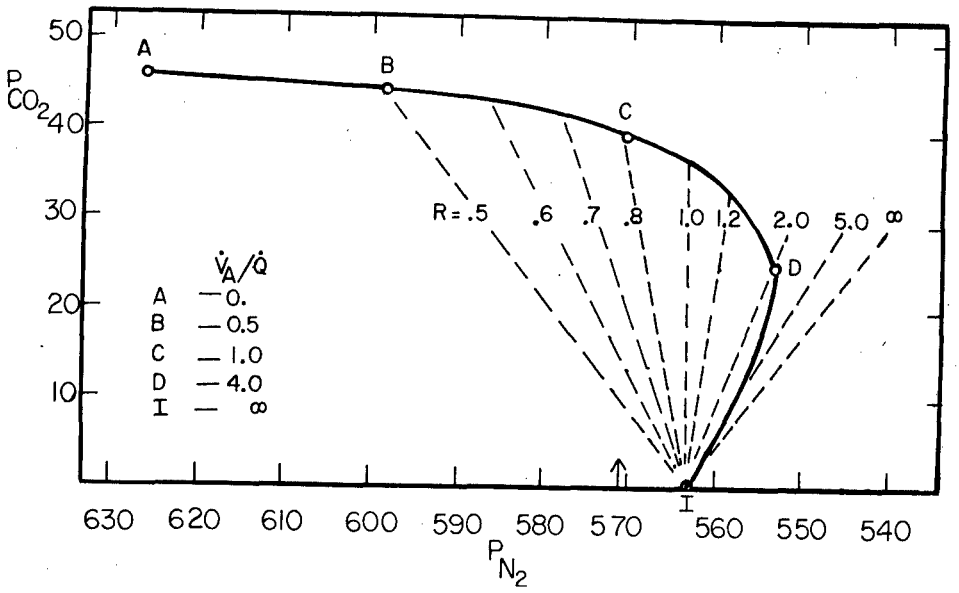


Figure 2A

The ventilation/perfusion line plotted as a CO_2-N_2 diagram representing all combinations which could possibly exist for a given mixed venous blood (A) and inspired gas tension (I). Each particular point is a function of a given $\dot{V}_A/\dot{Q}$ ratio and the approximate values for this ratio are given for points A, B, C, D and I. In addition the exchange ratio, R, isopleths are drawn. Point C would represent the average normal alveolar gas composition with a Pn_2 of 571 (see arrow). The arterial and mixed venous blood would also have this N_2 tension. On the other hand, alveolus B would have a Pn_2 of 599 and would lose N_2 to the mixed venous blood while alveolus D has a Pn_2 of 553 and would gain N_2. The net N_2 exchange for the whole lung is zero.

neighborhood of C do not exchange at all. This generalized picture is shown in Figure 2B. The net exchange of N_2 is zero since the amount of N_2 lost in B is recovered in D and if this is true, then the mixed arterial Pn_2 is the same as that of the mixed venous blood.

If one assumes, therefore, that all alveoli do not have the same $\dot{V}_A/\dot{Q}$ ratio, then one is left with a concept that a continuous N_2 absorption takes place in alveoli with a lower than average $\dot{V}_A/\dot{Q}$ which is balanced by an equal N_2 excretion in the alveoli with a higher than normal $\dot{V}_A/\dot{Q}$. The net N_2 exchange in the lung is zero and the mixed venous Pn_2 is the same as that of the mixed arterial.

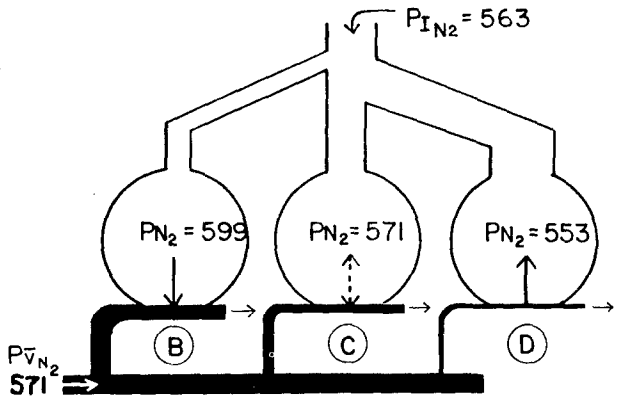


Figure 2B

Illustrating the excretion and absorption of nitrogen by alveoli with different ventilation-perfusion ratios. B, C, and D correspond to alveoli having low, average, and high $\dot{V}_A/\dot{Q}$ ratios, respectively, and correspond to points B, C, and D on Figure 2A. The N_2 tension in C is in equilibrium with the incoming blood but in B it is higher and in D is lower so that nitrogen must be absorbed by alveolus B and excreted by alveolus D.

The Non-ventilated Gas Pocket

When the $\dot{V}_A/\dot{Q}$ ratio of an alveolus becomes 0, then we have type 2 (Figure 1), the perfused but non-ventilated alveolus. This is essentially the same situation as that existing in the sinuses and the cavity of the middle ear. One can appreciate from Figure 2A that as one approaches this ratio of 0, the alveolar N_2 attains its greatest possible concentration. In this particular example it is 626 mm, which is 55 mm greater than that of the mixed venous blood supplying it. Ventilation no longer occurs but the N_2 absorption by the blood still continues and consequently additional inspired gas is drawn in which raises the O_2 pressure. A small amount of O_2 is continuously absorbed and, therefore, the Po_2 must be slightly higher than that of the venous blood. We have in the steady state of such a cavity a continuous instreaming of inspired gas which opposes the outward diffusion of CO_2. If the inflow of O_2 and N_2 prevents the outward diffusion of CO_2, then there is no net exchange of CO_2 and the CO_2 must be the only gas in perfect equilibrium with the mixed venous blood. This situation is depicted by the double arrow in Figure 1.

Prediction of the Gas Composition of the Open Non-ventilated Gas Pocket

Under the usual conditions of air breathing, the CO_2 tension is assumed to be equal to that of the incoming blood (see above), the O_2 tension is a fraction of a mm greater than that of the blood, while the remaining pressure head is occupied by the N_2. On the other hand, when the inspired O_2 fraction is increased and approaches 1.0 (100% O_2) the difference between the venous Po_2 and alveolar Po_2 becomes very large and the total volume uptake must equal that of ventilated alveoli having a similar perfusion rate.

If one assumes (a) constant tension of the mixed venous blood gases, and (b) that the perfusing blood comes into equilibrium with the alveolar gas (no end capillary difference), one can compute the alveolar gas composition for any given inspired gas mixture by application of equations described below.

Let $\dot{V}$ = volume of gas uptake ml(S.T.P.D.) / min

P = partial pressures - mm Hg

F = fraction of gases

$\dot{Q}$ = perfusion rate of pocket - liter blood/min

α, β, γ = respectively, the solubility coefficient (including chemical affinity) for O_2, CO_2 and N_2 expressed as ml/liter of blood/mm pressure difference

Subscripts I = inspired

B = barometric

A = alveolar

$\bar{v}$ = venous

T = total

O_2, CO_2, N_2 = molecular species

Then in the steady state of an open, non-ventilated pocket

$$\dot{V}_{I_T} = \dot{V}_{Io_2} + \dot{V}_{In_2} = \dot{V}_{I_T} F_{Io_2} + \dot{V}_{I_T} F_{In_2} = \dot{Q}\left[\alpha (P_{Ao_2} - P_{\bar{v}o_2}) + \gamma (P_{An_2} - P_{\bar{v}n_2})\right] \text{ -- (1)}$$

or in words, the volume flow into the pocket must equal the amount absorbed by the blood. The problem can be restated in terms of Fick's principle:

$$\dot{Q} = \frac{\dot{V}_T F_{I_{O_2}}}{\alpha (P_{A_{O_2}} - P_{\bar{v}_{O_2}})} = \frac{\dot{V}_T F_{I_{N_2}}}{\gamma (P_{A_{N_2}} - P_{\bar{v}_{N_2}})} \quad \text{-----} \quad (2)$$

and finally $\dot{V}_T$ can be cancelled and one can express the ratio of the pressure difference for O_2 and N_2:

$$\frac{P_{A_{N_2}} - P_{\bar{v}_{N_2}}}{P_{A_{O_2}} - P_{\bar{v}_{O_2}}} = \frac{\alpha F_{I_{N_2}}}{\gamma F_{I_{O_2}}} \quad \text{-----} \quad (3)$$

In this equation everything is known or assumed except $P_{A_{N_2}}$ and $P_{A_{O_2}}$.

Since the pressure in the pocket must be atmospheric:

$$P_{A_{O_2}} + P_{A_{N_2}} = P_B - 47 - P_{\bar{v}_{CO_2}} \quad \text{-----} \quad (4)$$

and

$$(P_{A_{O_2}} - P_{\bar{v}_{O_2}}) + (P_{A_{N_2}} - P_{\bar{v}_{N_2}}) = P_B - 47 - P_{\bar{v}_{CO_2}} - P_{\bar{v}_{O_2}} - P_{\bar{v}_{N_2}} \quad \text{----} \quad (5)$$

Thus the right and left sides of equation 5 represent the difference between the total pressure and the sum of the partial pressures of the venous blood. Equation 3 gives the ratio (between the O_2 and N_2 pressure) by which this difference is divided between these two gases, and equation 5 expresses the sum of these 2 pressure differences between the alveolus and venous blood. From these simultaneous relationships, $P_{A_{O_2}}$ and $P_{A_{N_2}}$ in an open unventilated pocket may be calculated for any inspired gas mixture.

Computations have been made for conditions breathing various fractions of O_2 up to 100% and the necessary data are given in Table 1. It was assumed that in the normal remaining lung the R = .8, the alveolar P_{CO_2} was 40 mm, P_B = 760, and the arterial-venous O_2 difference 5 vol. %. These calculations assume that the open but non-ventilated pocket is relatively small so that its gas exchange does not influence the overall gas transport. It should also be pointed out that as the pressure difference ($P_{A_{O_2}} - P_{\bar{v}_{O_2}}$) increases, the α for O_2 (which represents the amount chemically bound and physically dissolved) changes. Figure 3 is a graphical expression of equation 5 and represents the partial pressures in the blood as well as the non-ventilated alveoli in the steady state when breathing different fractions of O_2 up to 100%. One can see that with the lower fractions of O_2 the alveolar O_2 is for practical purposes the same as that of the venous blood. At higher fractions one obtains an interesting concentration effect of N_2 in

TABLE 1

Prediction of the steady state composition of an open-unventilated and a closed alveolus.

		Open unventilated alveoli						Closed alveoli					
1	F_{IO_2}	.209	.40	.60	.80	.90	1.00	.209	.40	.60	.80	.90	1.00
2	$P_{\bar{A}CO_2}$	40	40	40	40	40	40						
3	$P_{\bar{A}O_2}$	101	237	384	528	602	673						
4	$P_{\bar{A}N_2}$	572	436	289	145	71	0						
5	$P_{\bar{V}CO_2}$	46	46	47	47	47	48						
6	$P_{\bar{V}O_2}$	41	46	48	51	53	55						
7	$P_{\bar{V}N_2}$	572	436	289	145	71	0						
8	ΔP	54	185	329	470	542	610						
9		464	155	54.5	8.5	0.7	0	.0016	.0055	.0098	.0141	.0163	.0184
10	ΔP_{CO_2}	0	0	0	0	0	0	0.1	0.1	0.1	0.1	0.2	0.2
11	ΔP_{O_2}	0.1	1.3	6.0	50	314	610	0.1	0.1	0.2	0.5	0.6	1.0
12	ΔP_{N_2}	54	184	323	420	228	0	54	185	329	469	541	609
13	P_{ACO_2}	46	46	47	47	47	48	46.1	46.1	47.1	47.1	47.2	48.2
14	P_{AO_2}	41.1	47	54	101	367	665	41.1	46.1	48.2	51.5	53.6	56
15	P_{AN_2}	626	620	612	565	299	0	626	621	618	614	612	609
16	α_{O_2}	2.3	1.9	1.5	.62	.12	0.08	2.1	1.8	1.8	1.3	1.2	1.1

Lines 1 through 8 are the same for both cases.
Assumed values are the inspired oxygen percentage, line 1; the mean alveolar air composition for the total lung, lines 2, 3, and 4; and the mixed venous blood composition for an R = .8 and $(A-V)_{O_2}$ = 5 vol.%, lines 5, 6, and 7. The changing solubility for O_2 is given in each case, 16. β, the solubility for CO_2 is 4.8 and γ, the solubility for N_2 is .0184. Line 8 is the difference between the sum of partial gas pressures in the venous blood and the total pressure in the pocket. Line 9 gives the ratio of equation (3) for the open unventilated alveolus and the ratio constant of equation (8) for the closed pocket. Lines 10, 11, and 12 are the calculated pressure difference between alveolus and blood, and lines 13, 14, and 15 are the predicted pressures in the alveolus.

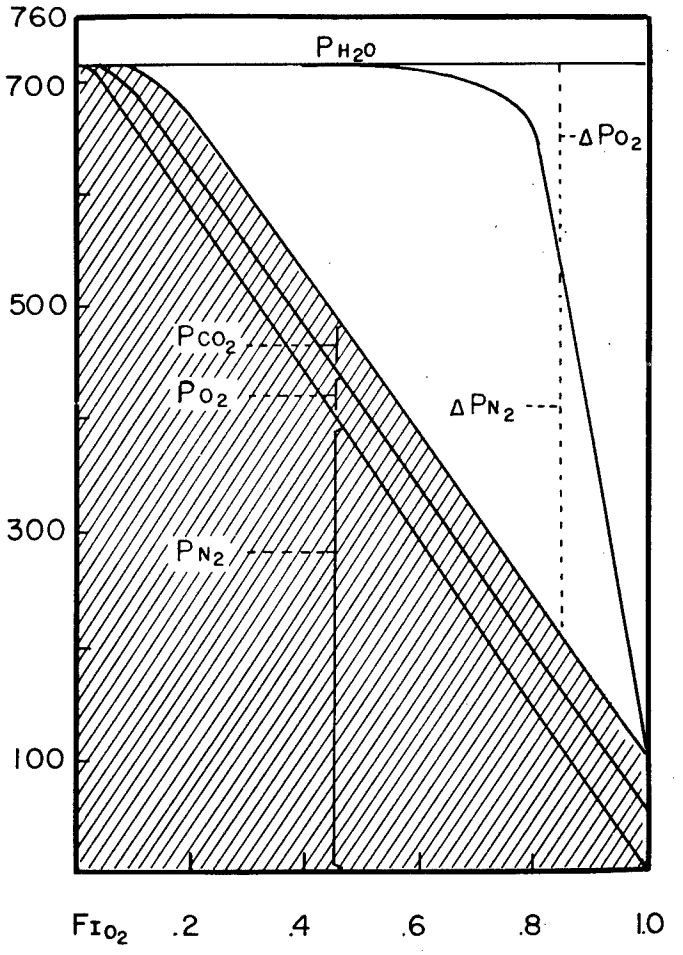


Figure 3

Graphic representation of the effect of different inspired O_2 percentages on the tensions of gases in an open-unventilated alveolus in the steady state. The shaded portion represents venous blood tensions. At the right of the figure with pure O_2 breathing, the venous blood contains only O_2 and CO_2 at tensions a little higher than when breathing air, so that the sum of their partial pressures in the blood is only 103 mm Hg, while the remaining pressure head (713-103) or 610 is occupied by the O_2 in the alveolus. On the other hand, when air is breathed, $F_{I_{O_2}} = .21$, the sum of partial pressures in venous blood is 659 and the remaining pressure head of 54 mm is occupied largely by N_2 and only 0.1 mm by O_2.

The gas pocket will always have a total pressure equal to atmospheric so the total dry gas pressure is 713, as is shown by the horizontal line at the top of the diagram. The pocket will have the venous tension of all three gases plus an increment of O_2 and N_2 pressure, shown as ΔP_{O_2} and ΔP_{N_2} in the unshaded area. This ΔP value is the pressure driving gas into the blood. It is seen that the gradient for O_2 remains small until about $F_{I_{O_2}}$ of .7 when it increases rapidly with increased $F_{I_{O_2}}$. The N_2 tension in this unventilated alveolus is greater than the blood tension showing that N_2 is actually concentrated by the process of exchange with the blood.

the alveolus. For example, with an inspired N_2 fraction between 10 and 20% the alveolar N_2 is concentrated to about 4 fold. Furthermore, assuming a constant Q, one can compute the relative total volume uptake using equation 2. With 100% O_2 breathing the total volume uptake is 40 times larger than breathing air.

Prediction of Gas Composition of the Closed Gas Pocket

In this case we are able to say that the fractional composition of gas leaving the alveolus is the same as the pressure head of gas in the closed alveolus (see generalization 5b of the introduction). Thus we may write an equation analogous to equation (2) and add the term for CO_2 which in this case must also be absorbed.

$$\frac{\dot{Q}}{\dot{V}_T} = \frac{F_{Ao_2}}{(P_{Ao_2}-P_{\bar{v}o_2})\,\alpha} = \frac{F_{Aco_2}}{(P_{Aco_2}-P_{\bar{v}co_2})\,\beta} = \frac{F_{An_2}}{(P_{An_2}-P_{\bar{v}n_2})\,\gamma}$$

and since $F = \frac{P}{P_B-47}$

$$\frac{P_{Ao_2}}{\alpha\,(P_{Ao_2}-P_{\bar{v}o_2})} = \frac{P_{Aco_2}}{\beta\,(P_{Aco_2}-P_{\bar{v}co_2})} = \frac{P_{An_2}}{\gamma\,(P_{An_2}-P_{\bar{v}n_2})} \quad \text{-----} \quad (6)$$

We also know that

$$P_{Ao_2} + P_{An_2} + P_{Aco_2} = P_B-47 \quad \text{-----} \quad (7)$$

With equations (6) and (7) one is able to predict the P_A values if the mixed venous blood values are assumed. This can be done by a method of successive approximations and is outlined below. In order to facilitate the handling of terms, equations (6) and (7) may be rewritten as follows:

$$\frac{A}{\alpha\,(A-a)} = \frac{B}{\beta\,(B-b)} = \frac{C}{\gamma\,(C-c)} \quad \text{or} \quad \frac{(A-a)\alpha}{A} = \frac{(B-b)\beta}{B} = \frac{(C-c)\gamma}{C} = K \quad \text{-----} \quad (8)$$

and $A + B + C = P_B-47$ ----- (9)

The values of a, b, c, β, and γ are assumed as in the case of the open-unventilated pocket. The value of α is the slope of the oxygen dissociation curve at the oxygen tensions being considered and therefore will depend on the value of A.

The first step is to arbitrarily choose first approximation values for A_1, B_1, and C_1 such that they satisfy equation (9). These are applied in equation (10), which is a part of equation (8), to give a value for K_1:

$$K = \frac{(C-c)\,\gamma}{C} \qquad \text{-----} \qquad (10)$$

The second approximations for A_2, B_2, and C_2 can be obtained using K_1 by the following equations which are derived from equations (8) and (9):

$$A = \frac{a\,\alpha}{\alpha - K}, \quad B = \frac{b\,\beta}{\beta - K}, \quad C = P_B - 47 - A - B \qquad \text{-----} \qquad (11)$$

The C_2 value can then be used to obtain a value for K_2 by equation (10). The new value of K can then be used for a third approximation of A, B, and C by equations (11). The process can be repeated until the desired accuracy is attained. In practice it was found that only three approximations were needed. Since the value of α depends on A, each approximation requires a new value for α from an O_2 dissociation curve.

To demonstrate the method, the composition of a closed alveolus when $F_{Io_2} = .6$ will be calculated. From lines (6), (5), and (7), respectively of Table 1 are obtained $a = 48$, $b = 47$, and $c = 289$. The first approximation is arbitrarily chosen $A_1 = 50$, $B_1 = 50$, and $C_1 = 613$ so that $A_1 + B_1 + C_1 = 713$. The value of α is found to be 1.7 in the region of $Po_2 = 48$ to 50 on an O_2 dissociation curve. β is given to be 4.8 and $\gamma = .0184$.

The C_1 value is used to compute K_1 by equation (10).

$$K_1 = \frac{(C_1-c)\gamma}{C_1} = \frac{(613-289).0184}{613} = .00974$$

K_1 is used to calculate A_2 and B_2 and C_2 by equations (11):

$$A_2 = \frac{a\,\alpha}{\alpha - K_1} = \frac{48 \cdot 1.7}{1.7 - .0097} = 48.3$$

$$B_2 = \frac{b\,\beta}{\beta - K_1} = \frac{47 \cdot 4.8}{4.8 - .0097} = 47.1$$

$$C_2 = 713 - A_2 - B_2 = 713 - 48.3 - 47.1 = 617.6$$

The process is repeated, this time using the new α_2 for the region of $Po_2 = 48$ to 48.3, which is 1.8.

$$K_2 = \frac{(617.6 - 289).0184}{617.6} = .0098$$

$$A_3 = \frac{48 \cdot 1.8}{1.8 - .0098} = 48.2$$

$$B_3 = \frac{47 \cdot 4.8}{4.8 - .0098} = 47.1$$

$$C_3 = 713 - 48.2 - 47.1 = 617.7$$

$$K_3 = .0098$$

K_3 is the same as K_2 so that the problem is solved. The value of α_3 is still 1.8 at $Po_2 = 48.2$. A_3, B_3, and C_3 are as accurate as the data warrants so they are the values used in the table, lines (14), (13), and (15), respectively.

Lines (10) to (15) show the results of such calculations assuming different values of F_{IO_2}. It is interesting to note that the values for the O_2 difference between the blood and alveolus remain small no matter what the inspired O_2 fraction. In this regard the closed pocket differs markedly from the open non-ventilated pocket where the O_2 difference with 100% O_2 becomes 610 mm. The CO_2 difference also remains insignificantly small. If these results are plotted as in Figure 3, the only difference is that nearly all of the total pressure difference (clear area) would be occupied by the N_2 and only a small part (too small to draw) would be occupied by the CO_2 and O_2 difference.

For a constant $\dot{Q}$, the total volume uptake with 100% O_2 breathing is 12 times larger than breathing air, contrasted to 40 times larger seen in the case of the open unventilated alveoli.

SUMMARY

1. Gas pockets that occur in the body are classified as open and ventilated, open but unventilated, and closed. All three types of pocket exchange with their tissue-blood environment, and tend to reach a state of constant composition. However, it is shown that in this steady state the open-unventilated pockets absorb O_2 and N_2 but not CO_2 whereas the closed pockets absorb all three gases.

2. On the assumption that the $\dot{V}_A/\dot{Q}$ ratio is not the same for all alveoli in the lung, it is shown that some alveoli are constantly excreting nitrogen while others are absorbing it, although there is no net exchange of nitrogen by the total lung.

3. The compositions of open-unventilated and closed alveoli are predicted and are shown to be independent of the blood perfusion. In open-unventilated alveoli the nitrogen tension is always higher than in the inspired air and can be concentrated as much as 4 times when the inspired N_2 fraction is 10-20%. The Po_2 in the pocket becomes increasingly larger as the inspired O_2 fraction increases until with 100% O_2 breathing, it occupies all of the volume except for the CO_2. On the other hand in a completely closed pocket the alveolar O_2 as well as CO_2 tension never exceed the venous blood value by more than 1 mm and all the remainder is occupied by the N_2.

REFERENCES

1. Dale, W. A. and H. Rahn Am. J. Physiol., 170: 606, 1952.
2. Rahn, H. Am. J. Physiol., 158: 21, 1949.

VOLUME CHANGES AND THE STEADY STATE BEHAVIOR OF GAS POCKETS WITHIN BODY CAVITIES

by

H. Rahn and R. E. Canfield

Compressible gas pockets completely sealed off by the tissues of the body must eventually be resorbed completely, because the total pressure of these gas depots remains close to atmospheric pressure while the sum of the partial pressures of the blood and tissues surrounding the gas is always less than ambient atmosphere (1,2,3). When breathing air at sea level, this pressure difference is approximately 50 mm Hg and constitutes the driving force for the continued resorption. Thus, gas pockets within the body cavity can only arise accidentally (spontaneous pneumothorax, atelectasis, or by artificial injection, including air swallowing). The only exceptions are gas pockets which are infected or normally contain gas producing microorganisms such as the bowel and the gas producing glands in the swim bladder of teleost fish.

While innumerable analyses of the gas composition of various gas pockets have been made in the past, very little information has been obtained concerning the precise volume changes. Older methods employed gas dilution methods for determination of volume changes in man (4,5) while more direct methods for atelectasis (2) and pneumoperitoneum (6) volume changes have recently been employed in animals. All of these methods are at best unsatisfactory for routine work. However, the accidental discovery (by Dr. F. Carpenter and H. Rahn) that a discreet air pocket could be maintained under the skin of a rat has proved an excellent tool. This pocket can be completely aspirated into a syringe for volume determination and immediately reinjected. Thus, rather precise volume measurements can be made at frequent intervals in large numbers of animals. It is the purpose of this paper not only to describe the composition in such pockets, but also the exact volume changes when various inert gases are introduced. In addition some composition data for other closed body cavities taken from the literature has been included and discussed.

METHODS

Preparation of Pocket

The changes of volume with time were measured in gas pockets introduced under the subcutaneous tissues on the dorsal surface of a rat (Figure 1). These

Figure 1

Rat with inflated subcutaneous pocket

pockets are easily formed by injecting about 20 cc of gas through a 20-gauge needle into the subcutaneous tissue in the interscapular fossa. Thus a closed cavity is formed whose volume can be measured at any given time without disturbing the composition by withdrawing the contents through a needle into a calibrated syringe and then reinjecting the gas. If the rats are shaved, one can easily ascertain when all the gas has been withdrawn into the syringe.

With the introduction of a foreign body under the skin the vascularization is modified and during the first few days the gas composition differs from that found later on. Twenty cc of air was injected five days prior to our experiments in order to avoid this initial reaction and to establish a constant perfusion. Such pockets lose about 2 cc/day, but they can be maintained for months when adequate refills are given. It was also observed that 30,000 units of procaine penicillin/rat/week prevented local infections due to repeated punctures.

During all our work no indications were ever obtained which suggested that gas leaked out through the puncture hole in the skin. In other words, these skin pockets behave like self-sealing tanks. This is most likely due to the fact that when the skin is held by the fingers, the various skin fascia are no longer in their usual alignment as the needle pierces them. When the needle and fingers are withdrawn, the realignment of the fascia seals the hole.

In the experiments reported here 240 gm female rats were prepared as described. When a particular gas was to be tested, all existing gas was withdrawn and replaced with 20 cc of test gas. Twenty animals were used for each test (except in the N_2O test when only 10 rats were used), and volumes were recorded every day or more frequently depending upon the nature of the test gas. At the termination of the experiments the remaining gas was collected in a 10 cc syringe and analyzed for O_2 and CO_2 on the .5 cc Scholander gas analyzer. The remaining gas volume was calculated by difference.

Two experimental runs are described: (I) A comparison of gas composition and volume uptake when Air, N_2, A, He, SF_6 and N_2O are introduced into the pockets of air breathing animals. (II) A comparison of gas composition and volume uptake from a N_2 pocket when the animal inspires 100% O_2.

In order to expose animals to 100% O_2 the rats were kept in two circular tiers of a horizontally rotating cage covered with a plastic tent. An atmosphere of 100% oxygen was maintained inside the tent (exhaust checked with a Pauling oxygen analyzer), and the rats were withdrawn periodically for about 30 seconds through a zipper for pocket volume measurement. With this design one may duplicate as much as possible the normal living conditions, i.e., food, water, temperature (27° C), etc. In order to decrease the length of time necessary for pocket gas equilibrium and thus decrease the total time in an atmosphere of O_2, the gas pockets were filled with a 9% O_2, 9% CO_2 in N_2 mixture after a 1-1/2 hour denitrogenation period in the O_2 environment. One hour later (2-1/2 hours after being placed in O_2) the first volume measurement was made. Three additional volume measurements were made at 2-hour intervals.

RESULTS AND DISCUSSION

The O_2 and CO_2 concentrations in gas pockets initially filled with Air, N_2, He, and SF_6 are given in Table I, while the changes in their gas volumes are presented in Figure 2. The rate of uptake from a N_2 pocket while breathing 100% O_2 is presented in Figure 3, and a comparison of composition and volume uptake in Air and O_2 breathing is given in Table II. Unfortunately, the ventilation of our oxygen tent was not sufficient to remove all the expired CO_2, and the inspired gas contained about 1.5% CO_2 thus accounting for the unusually high pocket P_{CO_2} in the O_2 breathing animals.

Effects of various inert gases upon the gas resorption rate

As the subcutaneous pocket of the rat is quite compressible the total pressure within it is practically atmospheric. On the other hand, the pressures of the venous blood and tissues surrounding the pocket can be fairly well estimated as will be discussed later on. This has been done in Table III where the estimated partial pressures in the arterial blood, subcutaneous venous blood and gas pockets are given when the animal breathes air. The arterial pressures are estimated

TABLE III

Gas Pressure Changes in Pocket Absorption

Air Breathing				O_2 Breathing			
Gas	Arterial	Venous	Pocket	Gas	Arterial	Venous	Pocket
P_{H_2O}	47	47	47	P_{H_2O}	47	47	47
P_{O_2}	100	43	43	P_{O_2}	651	58	58
P_{CO_2}	36	42	42	P_{CO_2}	49	54	54
P_{N_2}	563	563	615	P_{N_2}	0	0	588
TOTAL	747	695	747	TOTAL	747	159	747
$\Delta P_{N_2} = 52$				$\Delta P_{N_2} = 588$			

of a mm less than that of the pocket (3). The venous N_2 is assumed to be the same as the alveolar or arterial N_2 tension since this gas does not exchange and since the N_2 contribution of the pocket to the venous blood is very small and is, furthermore, eliminated in the lungs. We are thus left with a net partial pressure difference of 52 mm Hg between the venous blood and the gas pocket and practically over 99% of this pressure difference is occupied by N_2. The reason for this unequal distribution of the pressure head is due to the relatively low diffusibility of the N_2 compared to CO_2 and O_2 and has been discussed elsewhere in detail (3). Thus N_2 becomes the gas which controls the rate at which the total pocket volume is resorbed.

When such a pocket is measured daily, the volume changes can be recorded as shown in Figure 2. Various gases were introduced initially into the pocket. When pure N_2 is introduced, the volume actually increases slightly at first due to the O_2 and CO_2 which rapidly enter (7). By the end of 6 hours, no matter what gas is introduced, the O_2 and CO_2 compositions are stable as is seen in Table I where such analyses are indicated. Thus the difference between an initial N_2 and initial air pocket is only very temporary and thereafter the gas composition as well as the total volume absorption rates are essentially similar (see air and N_2 curve in Figure 2). The initial displacement between these two curves is due to the initial unsteady state difference as discussed in detail by Van Liew (7).

When foreign gases are introduced into such a pocket, these gases will tend to disappear at a rate commensurate with their diffusibility and pressure head, while N_2 from the blood and tissues will diffuse into the pocket. The net result of these two opposing diffusion currents determines where (1) the pocket will increase or decrease, and (2) at what rate. It will be seen from Figure 2 that all gases tested,

with the exception of SF_6, will diffuse out of the pocket faster than the N_2 can enter and therefore produce a net decrease. In general the more soluble the gas, the faster the absorption rate and N_2O is practically gone at the end of an hour. Argon and helium are probably nearly gone at the end of 100 hours and from this time on the remaining gas is essentially the same as that found in an air or N_2 pocket. Hence the slopes of the absorption curves after such a time should be essentially parallel. From these studies and the physical properties of others not tested here one may draw the conclusion that of all the naturally occurring gases in nature N_2 has the lowest diffusibility (including H_2 and cyclopropane also tested but not reported here).

The synthetic, inert gas, SF_6, on the other hand, is of great interest since it appears to be the only gas known so far which has a lower tissue diffusibility than N_2. Its effects upon the pneumoperitoneum gas pocket have been described in detail elsewhere (6). The behavior of this gas in a skin pocket is essentially the same as in the pneumoperitoneum. This high molecular weight molecule with a rather low solubility diffuses out of the gas pocket more slowly than the tissue N_2 which enters, resulting in a near doubling of the original volume. Judging from the previous data (6) the SF_6 in the pocket is nearly gone by the end of 200 hours and from here on one has essentially a normal composition of O_2, CO_2 and N_2.

From a practical standpoint of sustaining an artificial pneumothorax or pneumoperitoneum in man, one can say that N_2 is better than any other natural gas. Attempts over the last 50 years to employ other gases in man have all met with failure. While quantitative procedures for such evaluation have not been very good, we believe that these studies give a quantitative estimate of the various absorption rates for various gases. There is a slight advantage of using N_2 instead of air but this is probably too small to be useful. SF_6, on the other hand, shows definite promise as a "refill" gas for a pneumoperitoneum and preliminary studies carried out by Dr. W. G. Swalbach on 3 patients over a 1-year period indicate that the time between refills is increased from 2 to 3 times.

Volume changes when breathing air and pure oxygen

When air is breathed, the total pressure difference between the gases in the pocket and those in the venous blood is on the order of about 50 mm Hg (see also Table III) and that almost all of this pressure difference is taken up by the N_2. The volume absorption is, therefore, controlled by the N_2 and its pressure difference. When pure O_2 is breathed, this pressure difference across the tissue-blood system for N_2 can be increased about 11-fold, because now the N_2 in the blood and tissues is zero. Table III indicates the calculated arterial gas tension breathing pure O_2 by the method described previously for air breathing. During these experiments the ventilation of the O_2 tent was not sufficient and thus raised the inspired CO_2 tension with the consequence of an increased arterial as well as pocket CO_2. The pocket Po_2 was increased from 43 mm Hg on air to 58 mm Hg on O_2 and may be explained by an increased arterial content if the $(A\text{-}V)_{O_2}$

difference remained constant. If the venous O_2 and CO_2 tensions are again only slightly lower than those of the pocket, we have now a total pressure difference between the pocket and the blood of 588 mm, practically all of which is due to N_2.

Thus if N_2 is the gas which controls the absorption rates and the blood perfusion to the pocket is the same as when breathing air, one would predict that the N_2 volume uptake should be 588/52, or 11 times faster when pure oxygen is breathed. Even if the N_2 of the pocket does not normally come into equilibrium with the perfusing blood, it can be shown from the N_2 loading curves of the blood that this ratio in N_2 uptake must hold. The relative gas uptakes of O_2, CO_2 and N_2 breathing air and O_2 are given in Table II. The total volume resorption during O_2 breathing is plotted in Figure 3. The bars indicate the standard error and indicate the rather low variability when 20 rats are tested under such conditions. It can be seen that the N_2 uptake breathing O_2 was only 6 times greater than that breathing air. These values are taken from the pocket volume changes (compare Figure 2) over the 12-18 cc volume range, because the appearance of the curves suggests that at 10-12 cc the pocket geometry is altered due to the edges folding in on each other, thus decreasing the absorbing surface.

The best explanation which can be offered for the failure to achieve the predicted 11-fold increase in N_2 uptake is the possibility that the perfusion rate of the pocket was reduced by the O_2 breathing. This concept is supported by observations made on subcutaneous gas tensions in rabbits at high oxygen pressures which suggests that a local vasoconstriction reflex is elicited (8). If this is valid, then the increased pocket P_{O_2} in O_2 breathing must be in part, at least, due to a diffusion barrier made significant by the 6-fold increase in oxygen uptake.

Pocket composition in the steady state

In this study we are dealing with a closed gas depot in the subcutaneous tissues. As pointed out previously (2,3) this type of gas depot is fundamentally no different than others occurring as a result of artificially induced pneumothorax, pneumoperitoneum, pneumoencephalogram, atelectasis, etc. In each instance the gas is surrounded by tissues and subjected to a continuous perfusion. Hundreds of gas analyses of gas pockets at these various sites have been published in the literature for some 60 years and more. They all reveal CO_2 tensions not much higher and O_2 tensions considerably lower than those found in the alveolar or arterial blood. Particularly the O_2 tensions are quite variable, ranging from nearly 0 to values which occasionally approach that of the arterial blood.

Much speculation has been exercised concerning the meaning of these gas tensions (5,9,10). Some authors believe that they represent "tissue tensions" and others that they reflect certain blood gas tensions. One fact seems to be generally recognized, namely, that when the O_2% is low, the CO_2% will be high, and vice versa. In Figure 4 we have collected from the literature the gas analyses from 363 cases of closed gas pockets in man (pneumothorax gas, subcutaneous gas and

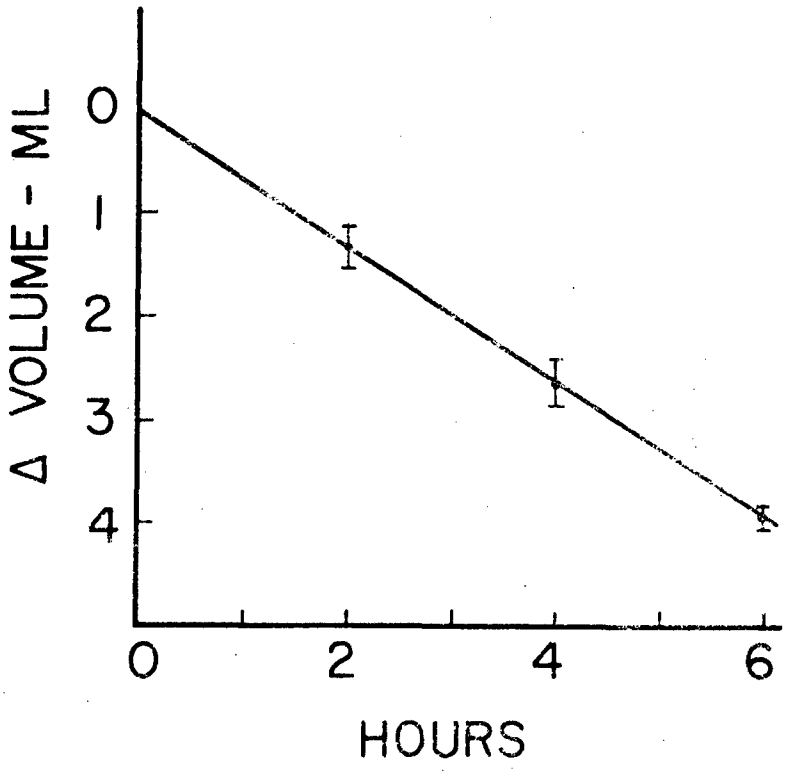


Figure 3

The rate of volume change of a N_2 gas pocket when animals are breathing 100% O_2. Vertical bars represent the standard error..

alveolar gas after bronchial occlusion) and have converted the reported fractional composition of O_2 and CO_2 into partial pressures at B.T.P.S. and plotted the simultaneous values on the Po_2-Pco_2 diagram.

These data behave generally as if each gas tension was in equilibrium with the venous blood perfusing each system. In order to test this concept the particular pocket O_2 and CO_2 tensions were translated into O_2 and CO_2 blood gas contents with the aid of standard blood dissociation curves such as the nomogram of Dill et al (11). In Figure 5 all of the pneumothorax data of Figure 4 (except those marked "wet" pneumothorax - see below) have been converted and plotted as blood O_2 content versus blood CO_2 content. Each point represents an average of 20 points in Figure 4. Furthermore, the slope of such a line, CO_2 content/O_2 content, represents the respiratory quotient, R. This slope was determined by the

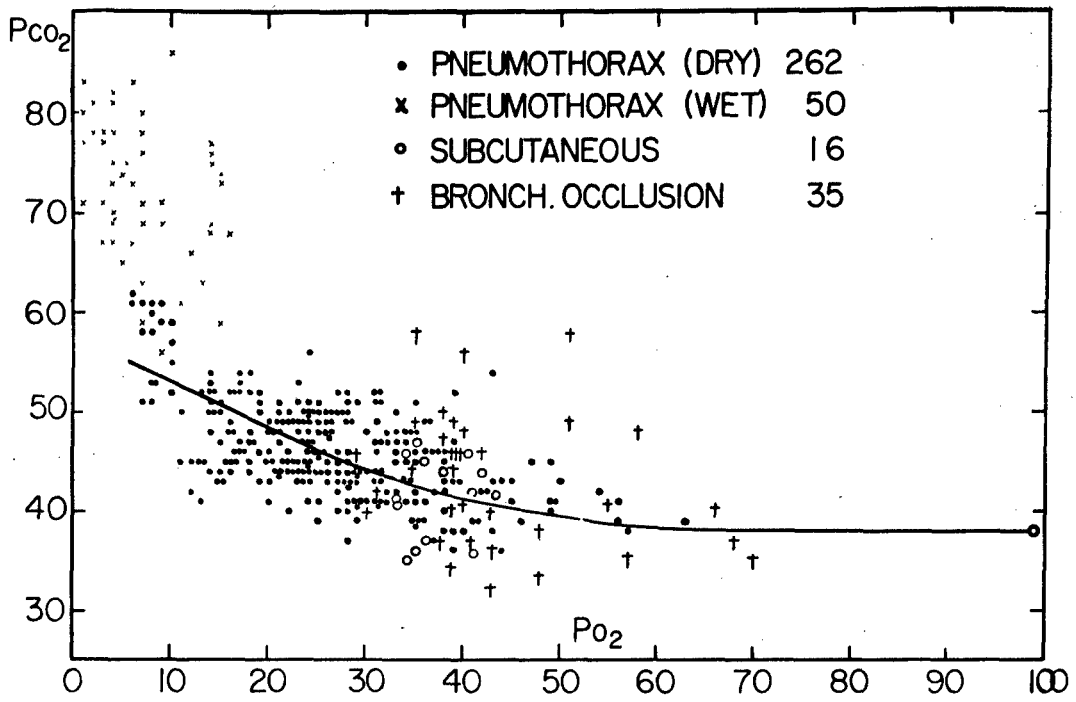


Figure 4

The O_2 and CO_2 tension of various types of closed pockets in man recorded in the literature (see text). The number of analyses for each kind of pocket is indicated.

method of least squares and can be theoretically extrapolated to the arterial point if one assumes an average arterial O_2 content of 20 vols.%. This has been done and the arterial point is indicated by the circle at the right which intercepts the CO_2 content at 48.5 vols.% and corresponds to a Pco_2 of 39 mm. In other words one can say that if the average man has an arterial blood gas content such as indicated by the circle, the venous blood may have various compositions, as indicated by the straight line provided the respiratory quotient of the particular tissue is 0.7. The distance of any point on the line from the arterial point is a function of the perfusion rate. If the oxygen consumption in the pleura is constant, then a highly perfused pleura will have a small arterial-venous difference; and the pneumothorax gas will equilibrate with venous blood gas content near the arterial point, consequently having a relatively high Po_2 and low Pco_2. On the other hand,

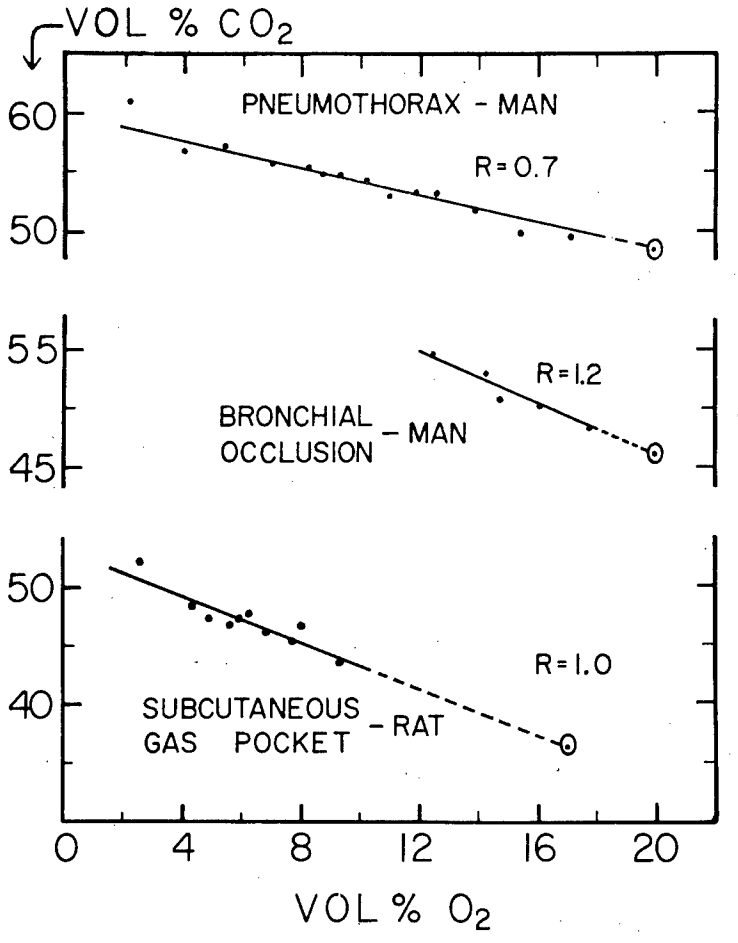


Figure 5

Upper graph: The venous blood gas content (O_2 content, vols.% versus CO_2 content, vols.%) of the blood draining the pleural tissues. The assumption was made that in each dry pneumothorax the O_2 and CO_2 tension is essentially the same as that of the venous blood draining the cavity. The conversion of tensions to blood gas content was done with standard blood gas dissociation curves. Each point is an average of 20 dry pneumothorax points of Figure 2. The straight line is fitted by "least squares" method and is extrapolated to the arterial point (circle) by assuming complete saturation, i.e., 20 vols.% O_2. The slope of the line thus represents the respiratory quotient of the pleural tissues.

Middle graph: The alveolar tensions following bronchial occlusion of Figure 2 treated in a similar fashion. Each point represents an average of 7 values in Figure 4. The assumption was made that the alveolar gases were in equilibrium with the mixed venous blood gas tensions. These values thus represent mixed venous blood gas content. The overall gas exchange ratio in these patients during the time of bronchial occlusion was 1.2.

Lower graph: Partial pressures determined from 58 subcutaneous skin pockets in rats were subjected to similar process employing a blood dissociation curve for rat's blood. Each point represents an average of five values. The arterial point was obtained by extrapolation to the assumed arterial O_2 content of 17 vols.%. The respiratory quotient of the skin tissues yields a value of 1.0.

a poorly perfused pleura will yield a pneumothorax gas composition with low O_2 and relatively high CO_2 and is represented by a venous point at the left hand side of the line. With this assumption one may assign to the abscissae (or the ordinate) of Figure 5 arbitrary perfusion rates of the pleura. The median composition of all these data has a value which falls at 10 vols.% O_2 and 54.5 vols.% CO_2 and thus the $(A-V)_{O_2}$ difference for blood of the pleural tissue in our average man would be 10 vols.%. At 15 vols.% the perfusion would be twice that and at 17.5 vols.% four times that. It has been frequently observed in the literature that a "new" pneumothorax has higher O_2 tension than an old one. This, as others have suggested, indicates initially a higher perfusion or hyperemia as a reaction to the new foreign body and this analysis would allow one to estimate in relative manner the quantitative changes in terms of $(A-V)_{O_2}$ differences.

These perfusion differences will also effect the relative resorption rate of the gas, but a 1:1 relationship between the perfusion and the volume uptake is not necessarily correct. This is due to the fact that N_2 is the gas which controls the rate of absorption and there is good evidence (unpublished data) that in the skin pocket the N_2 of the venous blood does not come into equilibrium with the pocket N_2.

The pneumothorax data discussed are based upon 144 analyses of Ebina (12), 142 analyses of Ornstein et al (10) and 35 analyses of Anthony et al (5). All of these data were pooled and used in the treatment of Figure 5 except those which were classified by these authors as coming from a "wet" pneumothorax. The latter are indicated in Figure 4 by crosses and are recognized by having unusually low O_2 and high CO_2 tension. It would appear that in these infected cases the perfusion is markedly reduced and/or that the typical gas exchange is completely altered.

The large crosses in Figure 4 represent alveolar air values obtained after 15 minutes of occlusion of the lower lobe in man. These remarkable experiments were performed 50 years ago by Loewy and Schrotter (13) in an effort to determine the gas tensions of the mixed venous blood. When these data are treated in the same way as the pneumothorax data and converted to blood gas contents, the grouped data appear as in the middle curve of Figure 5. Each point on this curve represents an average of 7 analyses. The slope of the regression line is 1.2 and may seem rather high for an overall respiratory quotient in these patients. If, on the other hand, one considers the relatively crude techniques at that time as well as the concomitant nervous hyperventilation which must have accompanied these drastic experiments, too much emphasis cannot be placed upon the high respiratory quotient. The extrapolation of this line to an assumed arterial point yields an arterial P_{CO_2} value of 35 mm, while the $(A-V)_{O_2}$ differences for mixed venous blood seem quite reasonable.

Figure 4 carries in addition 16 gas analyses of subcutaneous gas pockets in normal patients (14). These were not scattered well enough to allow the treatment given the other cases but are included in Figure 4 to show that they fall in with the

other values. The curved line of Figure 4 is the blood respiratory quotient line of .7 (similar to the straight lines of Figure 5). The R line for 1.0 lies slightly above it but also has its origin at the same arterial point. Figure 4 suggests that all equilibrated gas pocket compositions, regardless of what kind of gas pocket is considered, should in man with normal arterial values fall somewhere along such an R line as long as the venous blood draining the pocket has an O_2 and CO_2 tension which is nearly equal to that of the pocket.

Finally, the lower graph in Figure 5 treats the gas composition of the N_2 subcutaneous pockets of rats. Fifty-four determinations (from 3 investigators in this Laboratory) were used and each point represents the average of 5 animals. The line of least squares yields a respiratory quotient for the subcutaneous tissues of 1.0. In order to convert originally the gas tensions into blood gas contents the blood dissociation curves of the rat (15) were used. The regression line was extrapolated to the assumed arterial O_2 content of 17 vols. % which allowed one to estimate the alveolar CO_2 tension at 36 mm.

According to this concept we may picture then a gas pocket to behave as if it were being constantly perfused with venous blood and its composition being determined by the ratio of metabolic rate of the tissue to the perfusion. Since O_2, CO_2 and N_2 are constantly leaving the pocket the partial pressures of these gases in the pocket must always be higher than the venous blood gas tension. While for O_2 and CO_2 this difference is probably negligible (3), the N_2 is considerably higher and practically occupies the total pressure difference between the blood and the pocket.

SUMMARY

1. A new technique for studying volume and composition changes in closed body cavities has been described.
2. When various gases such as N_2, Air, He, A and N_2O are injected into a pocket and air is breathed, the pocket volume is sustained longest with N_2. Only SF_6 produces an increase in pocket volume to nearly twice the injected amount before it becomes slowly reduced.
3. The theoretical increase in N_2 absorption from a rat skin pocket when the inspired gas is changed from atmospheric air to 100% O_2 has been predicted to be over 11 fold, while actual measurements showed only a 6-fold increase. The difference between the theoretical and observed increase in N_2 uptake is considered to reflect a lowered pocket tissue perfusion when 100% O_2 is inspired.
4. The variability in O_2 and CO_2 tensions in closed body cavities have been discussed with the viewpoint that these represent perfusion differences and that these values are nearly the same as that of the venous blood draining the pocket tissues.

REFERENCES

1. Henderson, Y. and M. C. Henderson Arch. Int. Med. 49: 88, 1932.
2. Dale, W. A. and H. Rahn Am. J. Physiol. 170: 606, 1952.
3. Rahn, H. and H. D. Van Liew This Report.
4. v. Frisch, A. V. and I. Kugler Beitr. Klin. Tuberk. 83: 633, 1933.
5. Anthony, A. J., W. Schwarz and G. Slotty Beitr. Klin. Tuberk. 88: 474, 1936.
6. Tenney, S. M., F. C. Carpenter and H. Rahn J. Appl. Physiol. 6: 201, 1953.
7. Van Liew, H. D. This Report.
8. Campbell, J. A. J. Physiol. 68: PVII, 1930.
9. Campbell, J. A. Physiol. Rev. 11: 1, 1931.
10. Ornstein, G. G., M. Herman and M. Friedman Quart. Bull. SeaView Hospit. 8: 5, 1946.
11. Dill, D. B., H. T. Edwards and W. V. Consolazio J. Bio. Chem. 118: 635, 1937.
12. Ebina, T. Tohoku J. Exper. Med. 19: 355, 1932.
13. Loewy, A. and H. v. Schrotter Ztschr. f. exper. Path. u. Therap. 1: 197, 1905.
14. Meyer, F. Arch. f. exper. Path. u. Pharm. 177: 693, 1935.
15. Jones, E. S., B. G. Maegraith and H. H. Sculthorpe Ann. Trop. Med. Parasit. 44: 181, 1950.

VOLUME AND GAS COMPOSITION CHANGES OF SUBCUTANEOUS GAS POCKETS IMMEDIATELY FOLLOWING THE INJECTION OF VARIOUS GAS MIXTURES

by

Hugh D. Van Liew

Gas in an enclosed pocket in the body should be expected to exchange by diffusion with gases in the tissue and blood environment. Therefore the gas tensions in the pocket would tend to approach a level near that of the tissue or the venous blood. It has been repeatedly recognized over the last fifty years that the gas composition of a pneumothorax, pneumoperitoneum, subcutaneous gas pocket, etc., sooner or later reaches a constant composition of O_2, CO_2, and N_2 regardless of what gas composition was originally administered.

The composition of such a steady-state gas pocket can be predicted for certain conditions and has been discussed elsewhere (1), but the process of attainment of the steady-state composition is not easily calculated and empirical observations are necessary. Campbell (2) and others have shown how the initial compositions of pockets injected with air or N_2 change with time. However, the volume changes which accompany the initial unsteady state have not been recorded as far as the author is aware. The method recently described by Rahn and Canfield (3) allows one to obtain volumetric changes of subcutaneous pockets in the rat. It is the purpose of this study to describe in detail the volume changes as well as gas composition changes which are observed initially when various mixtures of O_2, N_2 and CO_2 are introduced into the subcutaneous pocket and to follow them as the steady state (state of constant composition) is approached.

MATERIALS AND METHODS

The following gas mixtures were injected: (1) Air, (2) 100% N_2, (3) 100% O_2, (4) 44% O_2 in N_2, (5) 13% CO_2, 19% O_2 in N_2, and (6) 19% CO_2, 1.2% O_2 in N_2.

Twenty young adult female rats were maintained over a period of three months with approximately 30 ml of gas under the skin on the back. Gas exchange measurements were made at least a week following the initial injection to avoid any changes that might occur due to the irritation of formation of the pocket.

The procedure consisted of completely withdrawing the maintenance gas and reinjecting 20 ml of test mixture. After a timed interval, the gas in the pocket was again withdrawn completely and the volume in the syringe noted. The gas was then

either reinjected for another timed interval or was analyzed for O_2 and CO_2 percentages in a Scholander microgas analyzer. The rats were unanesthetized and were restrained only during the few seconds required for injections and withdrawals.

RESULTS

The data are given in Table 1 as the mean of several values, with the number of determinations listed in the n columns. Volumes are listed as wet gas at syringe temperature and atmospheric pressure. Thermocouple measurements showed the temperature inside the syringe after withdrawal to be near 30° C although the temperature inside the pocket was measured as 37° C. Thus it appeared that the syringe more nearly corresponded to the temperature of the operator's hand holding it than to the rat's body temperature. It should be noticed that although the injected volume of 20 ml was dry gas, a correction for H_2O vapor is made in the table which gives the value of 20.9 ml at zero time.

DISCUSSION

The partial pressure of a gas in the pocket depends upon the relative amounts of other gases whereas the tension of gas in the blood-tissue environment is a function of the gas metabolism of the tissue in the case of metabolic gases and the concentration in the lung in the case of inert gases. The fundamental laws of diffusion indicate that a substance will move from a site of higher concentration (partial pressure in the case of gas) to a site of lower concentration, so any time a gas in the pocket has a partial pressure higher than the blood and tissue surrounding it that gas should diffuse out of the pocket. It is well known that all the components diffuse out of closed pockets after the constant composition state is reached and the data presented in Table 1 show how a given gas can move into the pocket or out of the pocket depending on the composition of the pocket at the particular time.

Figure 1 illustrates the early events after air injection and N_2 injection, with percentages of each gas in the top part of the figure. In the lower portion of the figure the simultaneous volume measurements are graphed. The mean total volume is shown by the points and the heavy lines. It is seen that with air injection the total volume of the pocket makes a quick initial increase which reverses itself after the first half hour. This is due to the rapid initial influx of CO_2 which is balanced a little later by the O_2 leaving. The amount of these gases which entered or left was calculated from the percentages and total volumes and are shown as the Δ volumes with the light lines. The N_2 pocket on the right side of the figure has a longer lasting increase in volume since both O_2 and CO_2 enter the pocket initially.

As discussed by Rahn and Canfield (3) it would appear that in the steady state the gas pocket O_2 and CO_2 are nearly in equilibrium with the tensions of the

TABLE I

Time Hours	Total vol. ml.	n	CO_2	O_2	N_2	n
AIR						
0	20.9*		0.0	20.9	79.1	
1/4	21.4	23	4.6	17.7	77.7	8
1/2	21.2	27	5.9	16.4	77.7	5
1	20.4	27	6.5	14.5	79.0	4
2	19.4	31	7.1	11.8	81.1	4
3	19.0	20	6.9	9.4	83.7	5
4	18.5	8	7.1	7.6	85.3	4
100% N_2						
0	20.9*		0.0	0.0	100.0	
1/4	22.0	10	4.2	0.5	95.3	2
1/2	22.4	10	5.7	0.7	93.6	2
1	22.1	11	6.2	2.4	91.4	2
2	23.0	5	6.7	3.0	90.3	2
3	22.1	6	6.8	3.5	89.7	2
4	22.5	7	6.8	4.5	88.7	2
100% O_2						
0	20.9*		0.0	100.0	0.0	
1/4	20.7	15	4.6	87.8	7.6	4
1/2	20.4	18	6.5	86.3	7.2	4
1	19.8	16	7.8	82.5	9.7	2
2	16.9	14	8.3	77.5	14.2	2
3	13.3	16	7.9	71.1	21.0	3
4	11.9	16	8.3	71.9	19.8	3

Time Hours	Total vol. ml.	n	CO_2	O_2	N_2	n
44.2% O_2 in N_2						
0	20.9*		0.0	44.2	55.8	
1/4	20.8	5	3.9	41.8	54.3	2
1/2	20.9	7	6.6	35.8	57.6	2
1	19.7	7	7.5	33.3	59.2	2
2	18.4	5	7.6	30.5	61.9	2
3	16.9	7	6.6	28.4	65.0	2
4	16.2	5	7.2	16.5	76.3	2
13.0% CO_2, 19.8% O_2 in N_2						
0	20.9*		13.0	19.8	67.2	
1/4	19.5	11	8.6	18.8	72.6	2
1/2	18.9	16	8.1	17.9	74.0	1
1	18.2	14	7.7	16.6	75.7	2
2	17.0	14	8.0	11.9	80.1	2
3	16.5	7	---	---	---	-
4	---	--	---	---	---	-
19.4% CO_2, 1.2% O_2 in N_2						
0	20.9*		19.4	1.2	79.4	
1/4	19.5	8	11.7	2.5	85.8	2
1/2	18.6	2	7.7	3.5	88.8	2
1	18.1	5	---	--	---	-
2	18.2	6	6.8	3.9	89.3	2
3	17.2	8	7.5	2.8	89.7	2
4	---	-	---	--	---	-

n = number of determinations

* The initial injected volume of 20 ml dry gas is corrected to saturated at 30° C syringe temperature to give the injected volume of wet gas equal to 20.9 ml.

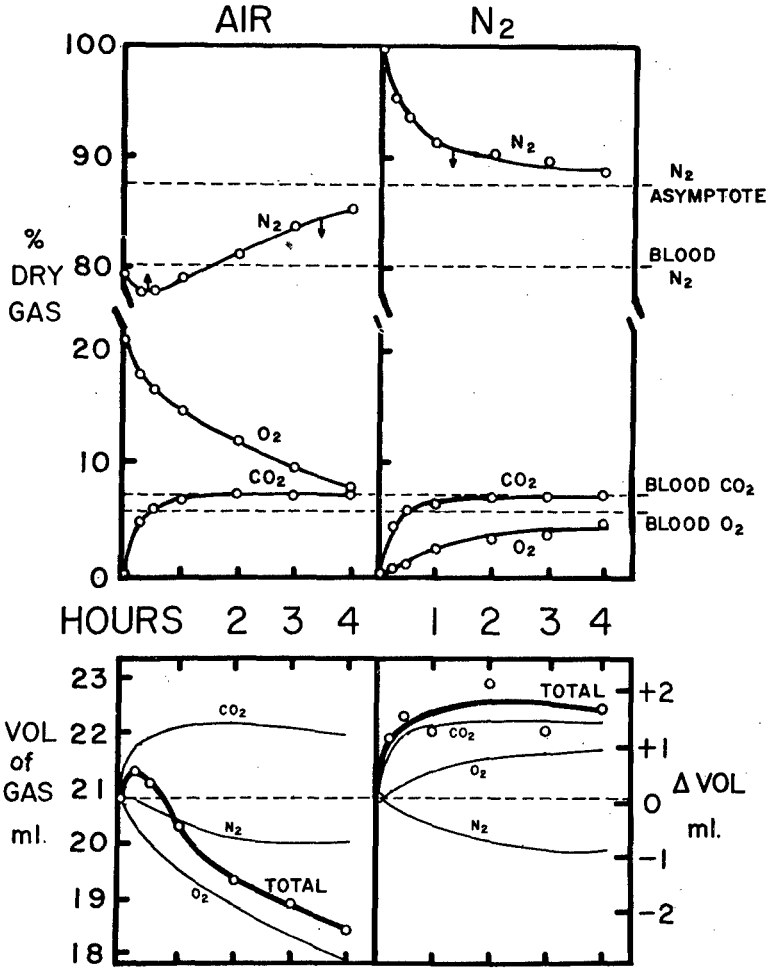


Figure 1

Percentage composition (upper) and volume (lower) of closed gas pockets for four hours after injection with air (left) and N_2 (right). With both injections the O_2 and CO_2 percentages approach an asymptote indistinguishable from an estimate of their venous blood concentration, whereas N_2 approaches an asymptote above its blood level. In the lower part of the diagram the total volume measured as saturated at 30° C is shown by the points and the heavy lines. The change of dry gas volumes of O_2, CO_2, and N_2 are shown by the light lines.

venous blood draining the pocket so that the venous blood gas tensions form essentially the asymptotes which the O_2 and CO_2 approach during the unsteady state. These venous gas tensions have been estimated and are drawn in as dotted lines. The blood N_2 tension can be estimated to be equal to .80 of an atmosphere since this would be the predicted alveolar value at a P_{CO_2} of 40 and an R.Q. of .8. This N_2 pressure is assumed to be the same in all the blood and tissues and has also been indicated by a dotted line. However, the pocket N_2 percentage does not approach this value but levels off at 87.5%. The reason for this has been discussed before (1,4). Briefly, this is due to the fact that N_2 has approximately a 200 times lower solubility in blood than the chemical affinity of O_2 and CO_2. This gives N_2 the role of controlling the rate of volume uptake. Since the CO_2 and O_2 values quickly approach their asymptotes and level off at a pressure of probably no more than 1 mm above the venous blood tension, the N_2 is "left behind" with a pressure head of approximately 8% of an atmosphere.

An interesting example of the concept of interdependence of gases in the pocket can be seen on Figure 1 for the case of air injection. The N_2 percentage takes a sharp drop immediately after injection due to the dilution of the gases in the pocket by the CO_2 which enters quicker than the O_2 is absorbed. Thus during the first 1-1/2 hours N_2 is actually below blood level and must diffuse into the pocket, as indicated by the small arrow. After 1-1/2 hours the CO_2 has nearly reached its asymptote, but O_2 still diffuses out concentrating the N_2 and slowly raising it above blood level. From then on the diffusion of N_2 is from pocket to blood. The actual volume of this early inflow of N_2 is very small and unfortunately the total volume measurements were not accurate enough to show it on the lower curves of Figure 1.

Figure 2 shows on a P_{O_2}-P_{CO_2} diagram the approach of four different test mixtures to the same "target" concentration, which represents the constant composition value of the steady state at which the pocket would remain until completely resorbed. The slopes of the lines from different injection mixtures are apparently dissimilar. It is thought that this may be due to the Bohr-Haldane effect by which O_2 and CO_2 seem to compete with each other for carriage in the blood.

SUMMARY

1. Gas composition and volume of subcutaneous pockets in rats were measured in the first four hours after injection of mixtures of O_2, CO_2, and N_2.
2. The partial pressure of each gas tends toward an asymptote which is independent of the composition of the injection mixture. CO_2 moves most rapidly of the three gases toward its asymptote.

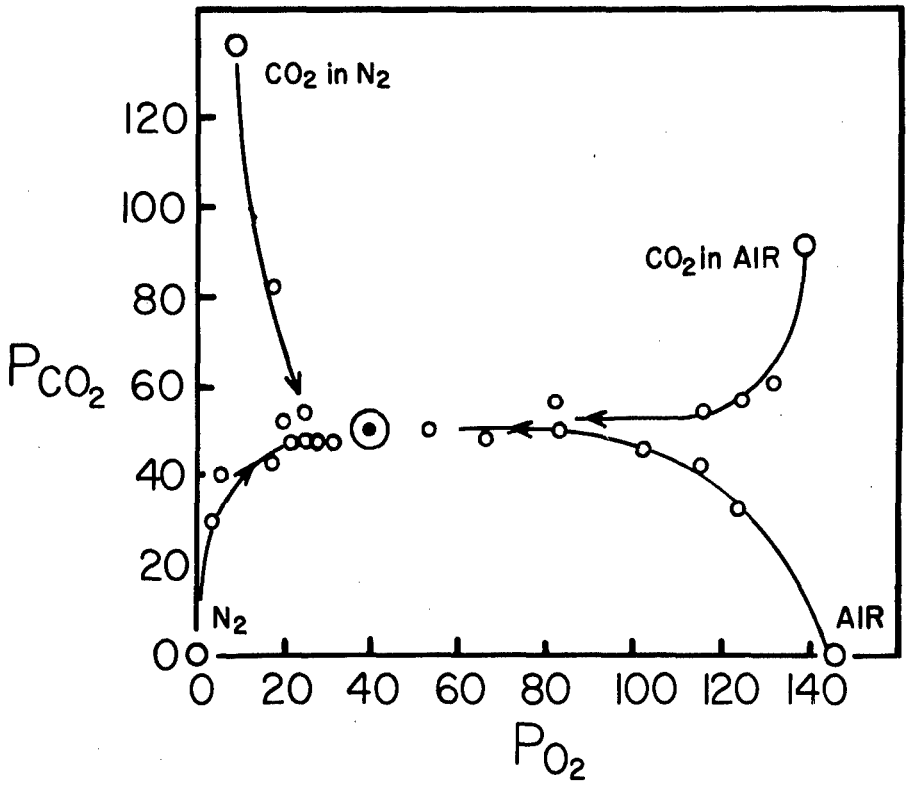


Figure 2

Partial pressure changes in closed subcutaneous gas pockets during the first four hours after injection of four different gas mixtures. The points are calculated from percentage data in Table 1 on the assumption that the total pressure in the pocket is 747 mm Hg, which is the mean barometric pressure at Rochester, N.Y., where the study was done. All four mixtures tend toward the same point as indicated by the arrows.

REFERENCES

1. Rahn, H. and H. Van Liew. This report.
2. Campbell, J. A. J. Physiol. 59: 1, 1924.
3. Rahn, H. and R. Canfield. This report.
4. Dale, W. A. and H. Rahn Am. J. Physiol. 170: 606, 1952.

Rate of Gas Absorption During Atelectasis

W. ANDREW DALE[1] AND HERMANN RAHN

In 1879 LICHTHEIM (1) demonstrated that in a completely obstructed pulmonary lobe the disappearance of air is due to its absorption by the blood. While most studies since that time have concerned themselves with the etiology, prevention and treatment of atelectasis, a few have tried to evaluate the rate of gas absorption under various conditions. Lichtheim (1), for instance, showed that O_2 and CO_2 are absorbed faster than N_2 and Coryllos and Birnbaum (2) in their large and detailed study observed the disappearance of a large number of common and anesthetic gases. However, they point out that at best they were able to determine the approximate *disappearance time* of a gas but not the *rate of absorption.*

The present study attempts to record the rate of gas absorption during the early stages of atelectasis and to formulate the laws which determine this process. As many previous authors have shown (see DISCUSSION), the gases of any sealed off pocket soon attain what may be termed the *state of constant composition,* which is maintained until absorption is complete. After occlusion of a lobe of the lung this state of constant composition is attained in about 6 minutes. This was demonstrated first by Wolffberg (3) in the dog and later by Loewy and v. Schrotter (4) in man. In our experiments, one lung of a dog was connected with a tracheal divider to a small spirometer and allowed to rebreathe until the alveolar gas composition became constant, after which the rate of gas absorption was recorded. It was felt that this phase represented the steady state of the early stages of atelectasis and that the rate of gas absorption would not be altered until the slow collapse of the lung structures mechanically impeded the flow of blood to this part of the lung. Presumably only the rate of collapse, but not the state of constant composition, would be altered by the reduction of blood perfusion as the analyses of Coryllos and Birnbaum (2) suggest.

The laws which determine this gas absorption are common to all sealed-off gas pockets wherever they occur in the body. Gas pockets in the lung are ideally suited for such studies. Not only are they easily accessible, but they also provide relatively enormous surface areas which absorb gases quickly. The absorption of the gas is due to the pressure difference between the gases of the pocket and those of the surrounding tissue or blood. While the total pressure in a pocket remains essentially atmospheric, the sum of the partial pressures of all the gases in the blood or tissues is always less than atmospheric. This peculiar circumstance is largely achieved by the nature of the hemoglobin saturation curve which allows a far greater pressure drop for a given quantity of oxygen removed than is gained from a similar quantity of CO_2 added.

This pressure differential is the driving force of the gas absorption. In a lung

[1] *From the Departments of Surgery*

breathing air it may be about 54 mm. Hg (assuming an A-V oxygen difference of 60 and a V-A carbon dioxide difference of 6 mm.), but can be decreased to a few millimeters by breathing low oxygen mixtures and increased to several hundred millimeters by breathing pure oxygen. By this means the over-all pressure difference between the lung gas and the blood returning to the lung can be altered. The pressure differences for any particular gas depend upon the initial gas mixture in the occluded lung.

Method

Mongrel dogs weighing between 15.2 and 23.6 kg. were anesthetized with intravenous Nembutal (0.026 gm/kg. dosage) mixed with 0.0003 gm. atropine sulfate. Subsequent Nembutal was given as necessary to maintain anesthesia. The animal

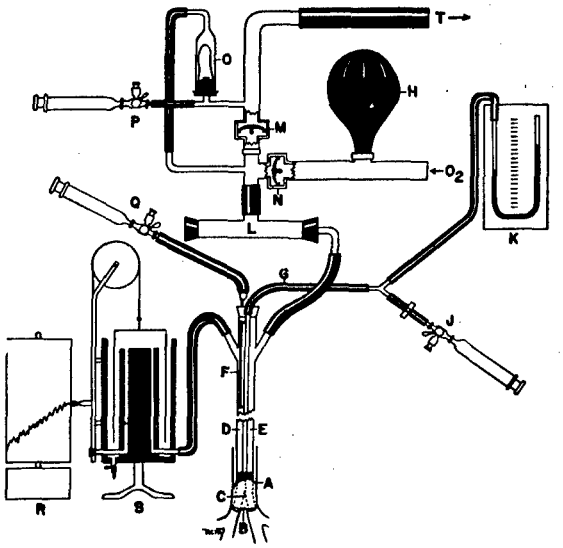


Fig. 1. Apparatus, showing tracheal divider in place with its connections. *A* trachea, *B* carina, *C* balloon fitting tightly against tracheal and carinal walls, *D* and *E* right and left lumens of tracheal divider, *F* polyethylene tube attached to needle inserted through stopper into right lumen for gas sampling, *G* tube connecting balloon to mercury manometer *K* and syringe and stopcock *J* for inflation, *H* rubber bag with T-tube connection to O_2 inlet, *L* T-tube fitted for connection of tracheal divider lumens to its ends or alternately stoppered when only one lumen is connected, *M* check valve allowing outflow, *N* check valve allowing inflow, *O* automatic alveolar gas sampler with *P* syringe for sampling, *R* kymograph, *S* spirometer, *T* outflow tube.

was placed in a supine position. After the tracheal divider was passed through the larynx and seated firmly against the carina, the balloon was inflated to a pressure of 60 to 70 mm. Hg with air, the pressure being continuously indicated on a manometer. Both sides of the tracheal divider were temporarily attached to spirometers in order to test for the complete separation of both lungs. The lumens of the tracheal divider were connected as shown in figure 1.

A bronchoscopic type of bilumen tracheal divider was constructed according to the design and specifications of Dr. George Wright, Saranac, N. Y. It consists essentially of two long metal tubes with angulated ends, soldered together. A rubber balloon about the end may be inflated (via a thin outer tube) so that it effectively seals passage between the two lungs at the carina. Figure 1 illustrates the apparatus. The right lung was used in all experiments for study of gas absorption, and is shown connected to a small spirometer. This spirometer contained no CO_2 absorber and recorded continuously the volume changes of the blocked lung. The initial volume (including the dead space) of the spirometer was 610 ml. at the beginning of the experiment, and was filled with air or oxygen according to the design of the particular experiment. The left lung inspired oxygen or air through a check

valve equipped with an automatic alveolar gas sampler (5). In order to denitrogenate the animals before the test, the apparatus could be rearranged to allow both lungs to breathe O_2.

Gas samples were removed from the right lung at intervals. Their analyses showed a constant composition on the average at 19 and 25 minutes, respectively, in *series A* and *B*, after connecting the lung to the small spirometer. (See fig. 2.) Following this, the average rate of gas absorption was determined from the spirometer records. In *series C*, *D* and *E* no gas samples were analyzed and the absorption rates were determined at 10 minutes after occlusion.

Gas samples were obtained in 10-cc. syringes moistened with 0.5 per cent sulfuric acid and were analyzed on the same day in duplicate by means of the Scho-

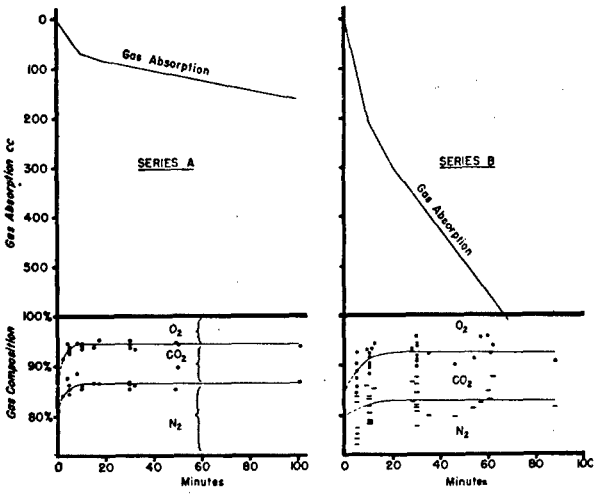


Fig. 2. AVERAGE RESULTS OF *series A and B*. The gas analyses indicate that in about 20 minutes a constant composition is attained, after which the total gas absorption rate is constant. The scatter of the gas analyses points is due to the fact that each dog leveled off at slightly different compositions particularly in *series B*.

lander apparatus (6). In the *series B* experiments the left alveolar gas analyses were done accurately for CO_2 only. When it became apparent in the course of analysis that the N_2 percentage of the oxygen breathing lung was 10 per cent or less, the remaining gas was measured as N_2 without completing the absorption of O_2. Therefore, the O_2 values of the left lung listed in table 1 are actually too small and N_2 values include any O_2 not absorbed during the analysis. These particular alveolar gas determinations were done principally to insure that denitrogenation had occurred and were not used in any calculations.

RESULTS

In each of the following experimental series, the total pressure difference and/or the partial pressure difference of a particular gas existing between the blocked right lung and the mixed venous blood was altered. In order to obtain a large pressure difference the dogs were denitrogenated for at least 1 hour by breathing pure oxygen before the blocking of one lung occurred. To vary the partial pressure difference for a particular gas either air or oxygen was placed in the spirometer.

TABLE 1. ALVEOLAR GAS CONCENTRATIONS AND RATES OF TOTAL GAS ABSORPTION IN SERIES A AND B EXPERIMENTS

ANIMAL NO.	WT.	RATE OF ABSORPTION	ALVEOLAR CONC., %					
			Right lung			Left lung		
			O_2	CO_2	N_2	O_2	CO_2	N_2
	kg.	*cc/min/kg.*						
Series A. Nondenitrogenated								
49-143	17.5	.082	4.76	8.76	86.48	15.77	3.47	80.76
49-149	20.0	.020	5.28	6.18	88.54			
51-11	23.2	.051	6.74	7.31	85.95	12.68	5.23	82.09
51-95	20.9	.046	6.17	8.50	85.33	14.46	5.43	80.11
7-6	19.1	.029	5.97	7.65	86.38	18.95	2.43	78.62
49-193	19.1	.059	4.91	8.88	86.21	14.11	4.85	81.04
Av.	20.0	.046	5.64	7.88	86.48	15.19	4.28	80.52
Av. tension in mm. Hg			40	55	605	106	30	564
Series B. Denitrogenated								
49-177	21.4	.200	7.75	12.38	79.87	90.80*	3.72	5.48*
49-193	19.1	.685	7.20	10.30	82.50	91.50	4.50	4.00
49-149	20.4	.193	5.88	9.90	84.22	92.50	2.14	5.36
51-11	23.6	.054	4.29	9.60	86.11	89.70	2.82	7.48
49-193	18.0	.368	6.93	6.56	86.51	86.33	3.67	10.00
7-6	19.1	.055	6.02	6.63	87.35	91.50	2.07	6.43
49-193	19.1	.331	9.27	10.21	80.52	89.60	5.35	5.05
51-95	20.0	.411	9.02	9.67	81.31	83.0	6.8	10.2
51-11	23.6	.402	10.36	12.02	77.62	85.4	8.1	6.5
51-95	20.0	.434	8.21	9.81	81.98	90.38	4.32	5.30
Av.	20.4	.313	7.49	9.71	82.80	89.07	4.35	6.58
Av. tension in mm. Hg			52	68	580	624	30	46

In the *B* experiments * indicates that the left alveolar oxygen value is minimum while the nitrogen value is maximum, as explained in text. Average gas tensions computed on basis of average barometric pressure 747 mm. and 47 mm. alveolar water tension.

Series A. *Gas absorption in an air-breathing animal.* The right lung was connected to the spirometer containing room air. The left lung breathed room air.

As can be seen in figure 2, the right lung attained a constant composition in approximately 20 minutes. The exact values observed in each dog after this period as well as the average absorption rate, and the alveolar composition of the left, freely breathing lung are recorded in table 1*A*. The average values for all six dogs are given and are also expressed as partial pressures at body temperature, saturated with water vapor.

When the spirometer volume became exhausted the lung collapsed, as could be readily seen by the mediastinal shift to the right under the fluoroscope. Gas samples obtained at this time do not differ from those obtained before collapse and their analyses agree well with those of Coryllos and Birnbaum (2).

TABLE 2. TOTAL GAS ABSORPTION RATES IN SERIES C, D AND E

Absorption rate, cc/min/kg.

ANIMAL NO.	WT.	DENITROGENATED, O_2 IN RT. LUNG INITIALLY, LEFT LUNG BREATHING O_2	NONDENITROGENATED, O_2 IN RT. LUNG INITIALLY, LEFT LUNG BREATHING AIR	DENITROGENATED, O_2 IN RT. LUNG INITIALLY, LEFT LUNG BREATHING AIR
	kg.	*Series C*	*Series D*	*Series E*
49–193	18.4	3.33	3.48	4.61
51–95	19.5	2.59	4.04	3.39
51–24	19.1	2.76	3.43	3.85
49–191	19.5	3.17	3.46	3.68
49–190	18.4	2.52	3.18	3.04
Av.	19.0	2.87	3.52	3.71

Series B. *Gas absorption in a denitrogenated animal, air in right lung initially.* Both lungs breathed 100 per cent O_2 from a demand valve for a minimum of 1 and a maximum of 2 hours. The right lung was then connected to the spirometer containing room air, while the left lung continued to breathe 100 per cent O_2.

Under these conditions the partial pressure of the N_2 in the mixed venous blood is initially very low, resulting in a large net pressure difference between the mixed venous blood and the alveolar gas. However, N_2 is rapidly absorbed from the right occluded lung and thus recharges the blood and tissues in spite of the fact that some of it is lost through the left, oxygen breathing lung.

Data for 10 animals are presented in table 1*B* and show the rates of gaseous absorption to be approximately seven times faster than in *series A*.

Series C. *Gas absorption in a denitrogenated animal, 100 per cent O_2 in right lung initially.* After both lungs breathed 100 per cent O_2 initially for a minimum of 1 and a maximum of 2 hours, the right lung was connected to the spirometer containing 100 per cent O_2 while the left lung continued to breathe 100 per cent O_2.

Series D. *Gas absorption in a nondenitrogenated animal, 100 per cent O_2 in right lung initially.* The right lung was connected to the spirometer containing 100 per cent O_2 while the left lung breathed room air.

Series E. *Gas absorption in a denitrogenated animal, 100 per cent O_2 in right*

lung initially. This is similar to *series C* except that the left lung breathed room air after occlusion of the right lung.

In *series C, D* and *E* no gas analyses were made. The rate of absorption of gases was very rapid and constant until the spirometer became exhausted. The absorption rates for each of five dogs under these three conditions are recorded in table 2.

If we compare the rates of gas absorption in *series A, B, C, D* and *E*, we find a ratio of 1, 7, 63, 76 and 80, respectively. An analysis of the factors contributing to these large differences is outlined below.

Discussion

The empirical observations of many authors (see review of Campbell, refs. 7 and 8) as well as the mathematical analysis of Rist and Strohl (9) allow one to make the following generalizations concerning gas pockets in animal tissues (with the exception of intestinal gas pockets where bacterial decomposition produces gases).

Table 3. Absorption coefficients expressed as cubic centimeters of gas absorbed/liter of blood/1 mm. pressure increment under conditions of series A and B experiments

		Series A	*Series B*
N_2	α	0.0185	0.0185
O_2	β	3.5	2.4
CO_2	γ	4.0	3.5

1) The pressure of a gas pocket remains essentially atmospheric while the sum of the partial pressure of all the gases in the blood-tissue environment is always less than atmospheric.

2) The composition of a gas pocket will eventually become constant provided the gas tensions of the *blood-tissue environment* remain unchanged. This is the state of constant composition.

3) During this state of constant composition the gas volume is absorbed. These 'laws' imply two further generalizations.

4) The partial pressure of each gas in a pocket must be higher than that of the environment.

5) Each particular gas disappears at a rate proportional to its fractional concentration.

Thus, for example, in the *series A* experiments, it has been shown experimentally that the composition becomes constant after a few minutes (fig. 2). At that time for every 86.48 volumes of N_2 absorbed, 5.64 volumes of O_2 and 7.88 volumes of CO_2 disappear (table 1*A*). Since there is continued absorption of each gas, each partial pressure must be higher than the corresponding partial gas pressure in the environment.

Consideration of Gas Pockets in the Lung. While in most gas pockets, the gas tensions of the environment represent a compromise between that of the tissues and that of the blood, in the intrapulmonic gas pocket it may be assumed that the gas tension of the environment is that of the blood alone, since the alveolar membrane offers little resistance to diffusion. The *total pressure gradient* during atelecta-

sis is then the difference between the ambient pressure and the sum of the partial pressures of the gases (including H_2O) of the mixed venous blood. This alveolar-venous pressure difference constitutes the driving mechanism for gas absorption. It can be altered only by changing the gas tensions of the mixed venous blood. The pressure difference for a particular gas, on the other hand, can be altered not only by changing the mixed venous blood gas tension, but also by changing the initial gas tension in the occluded lung.

For any given pressure difference the rate of gas absorption from an occluded lung will depend upon various factors such as the gaseous composition, the absorption coefficient of the gases, surface area and blood flow. We have assumed that diffusion is not a limiting factor and that therefore an equilibrium is reached between all the alveolar gases and the gases in the blood leaving the pulmonary capillaries. This is essentially true for O_2 and CO_2 during normal respiration and Jones's study (10) suggests that one may also assume a N_2 equilibrium. The pressure difference is therefore equivalent to the difference between the gas tensions of the mixed venous blood entering and the arterial blood leaving the lung. The surface area of

TABLE 4. ALVEOLAR-VENOUS PRESSURE DIFFERENCES FOR VARIOUS GASES COMPUTED FROM *equation 1*, ASSUMING A BLOOD FLOW OF 1 LITER/MINUTE THROUGH THE RIGHT LUNG

	O_2	CO_2	N_2	TOTAL	$\frac{\Delta N_2}{\Delta \text{ TOTAL}}$
	mm. Hg	*mm. Hg*	*mm. Hg*	*mm. Hg*	%
Series A	.015	.018	43.	43.033	>99.5
Series B	.199	.177	286.	286.376	>99.5

The ratio of any particular pressure difference to that of any other gas or to the total pressure difference will be constant regardless of the flow (*eq. 4*).

the blocked lung during these experiments may be considered unchanged since all measurements were made before the small spirometer was exhausted and the lung began to collapse.

The *physical solubility* of each gas and *chemical affinity* of blood for each gas are different. O_2 and CO_2 are chiefly chemically bound to blood while N_2 is only physically absorbed. Since the chemical affinity of O_2 and CO_2 under different gas tensions varies, it was assessed for the average of each series from the O_2 and CO_2 dissociation curves of the dog as determined previously in this laboratory (11). The term 'absorption coefficient' in this study has been used to denote the volume of gas in cubic centimeters absorbed by 1 liter of blood of a dog for a pressure increment of 1 mm. Hg at the particular gas tensions under consideration. Thus in the *series A* the O_2 absorption coefficient is 3.5 cc/liter/mm. pressure difference at pO_2 39 mm. and pCO_2 55 mm. The N_2 solubility coefficient (α = .014) becomes .0185 cc/liter/1 mm. pressure difference. The values for the three gases in *series A* and *B* are shown in table 3.

From the foregoing discussion and assumptions, it may be seen that under the conditions of these experiments the rate of gas absorption becomes a function of the pressure difference, absorption coefficient and the blood flow. These relationships can be defined quantitatively by the blood flow equation of Fick.

Let:

$\dot{Q}$ = rate of blood flow through occluded lung,
P_A = partial pressure of alveolar gas in occluded lung,
Pa = partial pressure of gas in blood leaving occluded lung,

Pv = partial pressure of gas in mixed venous blood,
$\dot{V}$ = total volume absorbed per unit time,
F = fractional concentration of gas in occluded lung,
α = absorption coefficient of N_2 expressed as cc/liter blood/mm. pressure difference,
β = absorption coefficient of O_2,
γ = absorption coefficient of CO_2,
O_2, CO_2, N_2 = the particular molecular species.

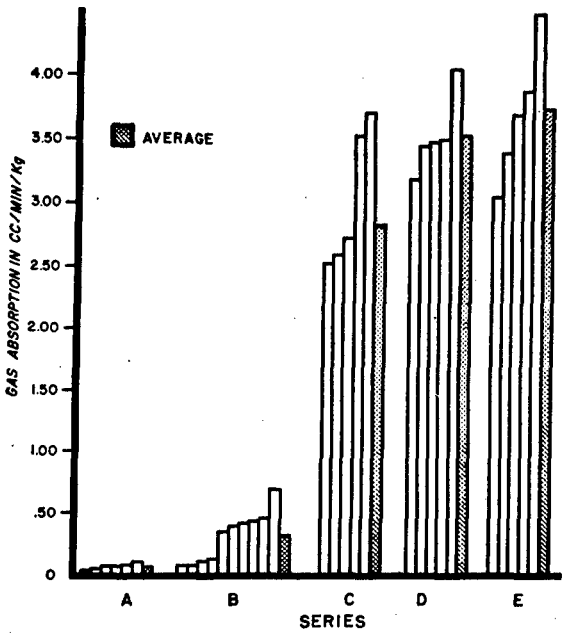


Fig. 3. COMPARISON OF ABSORPTION RATES of gas in the occluded lung in the different series of experiments.

If one assumes that $P_A = Pa$, then according to Fick's equation

$$\dot{Q} = \frac{\dot{V}F_{O_2}}{(P_{A_{O_2}} - Pv_{O_2})\beta} = \frac{\dot{V}F_{CO_2}}{(P_{A_{CO_2}} - Pv_{CO_2})\gamma} \frac{\dot{V}F_{N_2}}{(P_{A_{N_2}} - Pv_{N_2})\alpha} \quad (1)$$

By rearrangement, the rate of lung collapse, expressed as volume absorbed per unit, time may be expressed as follows:

$$\dot{V} = \dot{V}F_{O_2} + \dot{V}F_{CO_2} + \dot{V}F_{N_2} \text{ or} \quad (2)$$

$$\dot{V} = \dot{Q}[(P_{A_{O_2}} - Pv_{O_2})\beta + (P_{A_{CO_2}} - Pv_{CO_2})\gamma + (P_{A_{N_2}} - Pv_{N_2})\alpha] \quad (3)$$

Thus when the gases in the occluded lung have reached constant composition, the rate of collapse, for a given mixed venous blood composition, will be directly proportional to the blood flow through the occluded lung.

If the alveolar gas composition and the volume of total gas absorption are known one may compute from *equation 1* the effective pressure differences between the alveolar gases and those of the mixed venous blood by assuming a particular blood flow through the right (occluded) lung. The results of these calculations,

using the average values for the *A* and *B* series, from table 1, the absorption coefficients from table 3, and assuming a blood flow of 1 liter/minute through the right lung, are shown in table 4.

On the other hand, the relative magnitude of the three pressure differences to each other will be constant regardless of the absolute blood flow, as indicated by rearrangement of *equation 1* which expresses for example the ratio between the N_2 and O_2 gradient.

$$\frac{(P_{A_{N_2}} - P\bar{v}_{N_2})}{(P_{A_{O_2}} - P\bar{v}_{O_2})} = \frac{F_{N_2} \times \beta}{F_{O_2} \times \alpha} \qquad (4)$$

The ratio of the N_2 pressure difference to the total pressure difference is computed in table 4. It becomes clear that the O_2 and CO_2 pressure gradients are negligible in relation to the pressure gradient of N_2 and that for practical considerations the total pressure gradient between the gases of the lung and mixed venous blood is that of the N_2. It should be borne in mind that the absolute values in table 4 are based upon an assumed blood flow, but that the fraction of the total pressure difference occupied by any gas is independent of the absolute flow.

If one assumes the same absolute blood flow of the occluded lung in *series A* and *B* the over-all pressure gradient and absorption rate was approximately seven times larger in *B* than *A*. This is largely due to the change in the N_2 pressure gradient. The denitrogenation preceding the *B* experiments might have induced an even larger gradient were it not for the fact that upon occlusion of the right lung there is an immediate reabsorption of N_2 to elevate the tension of the blood and tissue despite the fact that some is constantly eliminated through the left lung which continues to breathe 100 per cent O_2. It is apparent from table 4 that over 99 per cent of the total pressure difference is represented by the N_2 gradient. This implies that the gas with the smallest absorption coefficient is the one which controls the rate of lung collapse, and makes N_2 the important 'brake' against atelectasis which Coryllos and Birnbaum and others have noted.

The reason for this relatively large N_2 gradient can be described in another way. The law of Constant Composition implies that, for example in *series A*, 15 times as much N_2 is absorbed as O_2. In order to maintain this rate of N_2 absorption with such a small absorption coefficient ($\frac{1}{189}$ as great as that of O_2) it is necessary for the N_2 to maintain a gradient which is $15 \times 189 = 2840$ times larger than that for O_2.

In *series C* the animals were first denitrogenated. The right lung was then blocked off containing oxygen, while the left continued to breathe oxygen. If one neglects the small residual amount of N_2 left in the tissues we deal here with two gases only, namely CO_2 and O_2. No analyses were made of the occluded lung gases but their concentrations can be fairly well predicted. If we assume a CO_2 concentration of 10 per cent, similar to that of *series B*, then the remaining 90 per cent constitutes oxygen. The $P_{A_{O_2}}$ was therefore 0.90 ($P_B - 47$) or 630 mm. Hg. The A-V CO_2 difference must be very small and if the venous P_{O_2} is assumed to be in the neighborhood of 70 mm., then practically the whole pressure difference of 560 mm. (630 − 70) between the blood and alveoli is maintained by oxygen. The equivalent absorption coefficient for oxygen is approximately 0.09 cc/liter/mm. Hg. This coefficient is very much smaller than in *series A* and *B* (table 3), because over most of this large O_2 pressure range the O_2 is not chemically bound, but only physically dissolved.

Because of the low absorption coefficient for oxygen the pressure difference must be large to account for an overall absorption rate which is 63 times faster than in *series A* and 9 times faster than in *series B*. One would expect a very quick attainment of the state of constant composition since only CO_2 and O_2 are involved in this adjustment. Under these conditions the high absorption rate would be maintained, since no N_2 is present to act as a brake.

The results of *series D* and *E* are similar to those of *series C* (table 2, fig. 3), yet their high absorption rates are expected to decline considerably with time as N_2 enters from the mixed venous blood and begins to retard the process. This would occur after the small spirometer was exhausted and therefore could not be observed. During the experimental observation in *series D* and *E* the state of constant composition could not have been realized. This final state should theoretically have the same composition and absorption rate as *series A*, where the alveolar N_2 concentration exceeds the mixed venous level and acts as a brake in retarding gas absorption.

Thus *series D* and *E* differ from the foregoing experiments in that the state of constant composition was not observed. During the period of observation (approximately 10 minutes) before the spirometer became exhausted, relatively little N_2 could have entered the occluded lung and the initial O_2 pressures in the blood and alveoli must have been similar to those in *series C*. This would explain the high initial rates observed.

SUMMARY

Experiments were designed to simulate the early phase of atelectasis in order to study quantitatively the rate of gas absorption from an occluded lung. Under these conditions the rate of gas absorption could be varied more than 60-fold by alteration of the partial pressures of the blood gases as well as by changes in the initial gas composition.

Analyses of the composition of the alveolar gases in the occluded lobe indicate that the state of constant composition is quickly attained. This allows one to set up equations which relate the rate of gas absorption to the blood flow, pressure difference and equivalent absorption coefficient of the various gases concerned. The experimental findings are discussed in light of these factors.

REFERENCES

1. LICHTHEIM, L. *Arch. f. exper. Path. u. Physiol.* 10: 54, 1879.
2. CORYLLOS, P. N. AND G. L. BIRNBAUM. *Am. J. M. Sc.* 183: 317, 326, 347, 1932.
3. WOLFFBERG, S. *Pflügers Arch. f. d. ges. Physiol.* 4: 465, 1871.
4. LOEWY, A. AND H. V. SCHROTTER. *Ztschr. f. exper. Path. u. Pharm.* 10: 54, 1879.
5. RAHN, H. AND A. B. OTIS. *J. Applied Physiol.* 1: 717, 1949.
6. SCHOLANDER, P. F. *J. Biol. Chem.* 167: 235, 1947.
7. CAMPBELL, J. A. *Physiol. Rev.* 11: 1, 1931.
8. HENDERSON, Y. AND M. C. HENDERSON. *Arch. Int. Med.* 49: 88, 1932.
9. RIST, E. AND A. STROHL. *Ann. de med.* 8: 233, 1920.
10. JONES, H. B. *Medical Physics.* Chicago: Yr. Bk. Pub., 1950, 2, 855.
11. RAHN, H., H. T. BAHNSON AND E. MEIER. Unpublished.

Gas Transfers in a Sulfur Hexafluoride Pneumoperitoneum[1]

S. M. TENNEY, F. G. CARPENTER AND H. RAHN

STUDIES DIRECTED towards determining the behavior of isolated volumes of gas in animal or man have considered principally either room air or one of its constituents as the trapped gas in question. Pneumothorax, pneumoperitoneum and the air in a nonventilating lung all disappear in a predictable fashion (1, 2). If the gas so trapped were of significantly lower solubility than nitrogen, then one would anticipate that nitrogen would enter this gas compartment more rapidly than the other gas could diffuse out, and a transient increase in volume and prolonged total volume disappearance time would result. Sulfur hexafluoride, and inert gas of low solubility, provides an interesting example to test this hypothesis.

METHODS

A total of 125 expers. on 7 dogs and 18 cats have been carried out. The animals were loosely restrained and a small area on the ventral abdominal wall was infiltrated with procaine. Through this area a blunt no. 20 gauge needle was passed, and 500 cc of 100% SF_6, and in the control series 100% N_2, were introduced by syringe into the peritoneal space. With similar technique gas was removed by syringe at fixed time intervals. In the cat, at a selected time point, the volume was completely removed, measured, and analyzed for SF_6. For the nitrogen pneumoperitoneum only the total volume of gas present was measured. A rest period of 3–7 days was allowed before an animal was again injected to obtain another experimental point. Early in the series the adequacy of emptying by the syringe method was evaluated by killing the animal after apparently complete evacuation of gas and opening the peritoneal space under water to collect any residual gas. Five observations of this sort revealed that the maximum volume which remained, after apparent complete emptying

† *Department of Medicine*

[1] This work was supported in part by a research grant (H 1204) from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and a Contract between the Office of Naval Research, Department of the Navy and the University of Rochester.

with syringe, was 15 cc. In all subsequent experiments the syringe method alone was employed. In the dog, volume measurements were not performed. Instead, only 300 cc were removed for analysis. After the analysis was completed, a 300 cc volume, of identical composition to that removed, was reinjected in order not to disturb any volume effect on the time course of disappearance.

Analysis of SF_6 was carried out by introducing the aspirated sample into one cell of a Cambridge differential thermal conductivity gas analyzer adapted to SF_6 by a series and shunt resistance in the circuit of a Rubicon galvanometer. The control cell was filled with 5% CO_2, 6% O_2 and 89% N_2, the percentages of CO_2 and O_2 representing the constant composition which these gases reach in a SF_6 pneumoperitoneum. Calibration curves were run by placing known concentrations of SF_6 in 5% CO_2 and 6% O_2 in the test cell. The sensitivity of the galvanometer was adjusted to two levels, one which gave a full scale deflection for 100% SF_6, and the other, full scale for 30% SF_6, thus allowing more accurate measurements in the lower concentrations. A variation of ± 1% CO_2 in the peritoneal gas was shown to cause a ± 0.5% error in the accuracy of the SF_6 measurement.

O_2 and CO_2 were analyzed in the Scholander-Roughton micro gas analyzer (3). Nitrogen was calculated by difference.

Results

Disappearance of Pneumoperitoneum Initially Composed of N_2. Immediately following the introduction of nitrogen into the peritoneal space, CO_2 and O_2 rapidly enter. Within 2 hr. these gases reach a constant composition in the peritoneal gas approximately equal to their concentration in venous blood. From this point on the percentage concentration of O_2, CO_2 and N_2 in the pneumoperitoneum remains at a constant value until all the gas is dissolved. The rapid initial influx of CO_2 and O_2 causes the volume of trapped gas to expand to about 550 cc. From this point on the volume progressively diminishes along an approximately linear course for the first 8 days; after this time the curve appears to slope off alinearly to reach the point of complete disappearance in 23 days, in the cat. These experimental points are plotted in figure 1. The pneumoperitoneum is shrinking at the rate of 30 cc/day, during the first 8 days; allowing 11% volume concentration for CO_2 and O_2 this gives a N_2 uptake of 27 cc/day.

Changes in a Pneumoperitoneum Initially Composed of Pure SF_6. The total volume of an SF_6 pneumoperitoneum rises exponentially during the first 8–9 days, then falls off slowly until some time in the period 20–25 days, and from this point diminishes more rapidly at a rate which roughly parallels the disappearance of a pure N_2 pneumoperitoneum. The initially injected volume of 500 cc is not reattained until 31 days later. These volume changes in the cat are illustrated in figure 1.

In several cats the intraperitoneal pressure was measured with a water manometer at the time of peak volume and was found to differ insignificantly from atmospheric pressure. The maximum pressure measured was 3 cm. H_2O, and this was not considered important in affecting the dynamics studied.

The disappearance of SF_6 as the percentage composition of the pneumoperitoneal gas of dog and cat is shown in figure 2*A*. The percentage of SF_6 falls off rapidly in an exponential course in both animals and disappears completely from the dog in about 20 days while it requires 30 days in the cat. The reason for the species difference can be explained by assuming a greater blood perfusion in the peritoneal space of the dog. The time course of absolute volume of SF_6 remaining can be calculated

from the cat data and reveals an exponential curve (fig. 1) resembling the curve of change in the percentage of SF_6 with time, but without the initial sharp fall off of the latter caused by nitrogen dilution.

The intimate relationship between percentage composition SF_6 and total volume of the pneumoperitoneum is indicated in figure *2B*. Though there is a considerable scatter of points, it is clear that the maximum volume is reached in the 15–20 % range and below 15% the volume is diminishing.

There was no evidence of a toxic effect due to SF_6 in any experimental animal in the series. Postmortem inspection of the peritoneum in several dogs and cats revealed no local changes whatsoever, and a detailed autopsy in one dog who had had repeated SF_6 pneumoperitoneums over a 6-month period disclosed no abnormality in any organ system.

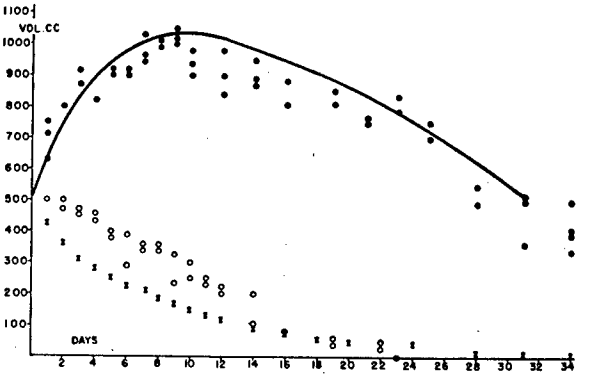


FIG. 1. Volume of peritoneal gas in the cat with time: ● total volume of gas present after injection 500 cc pure SF_6; × absolute volume of SF_6 (mean values) total vol. × % conc. SF_6; ○ total volume of gas present after injection 500 cc pure N_2; —— Predicted total volume curve for SF_6 pneumoperitoneum (see text).

DISCUSSION

Throughout the body, as blood passes from the arterial side of the capillary bed to the venous it loses oxygen and acquires carbon dioxide. However, since the pressure rise due to the influx of CO_2 is less than the pressure drop due to loss of O_2, the sum of the partial pressures of venous blood is less than in arterial blood. This pressure difference is accomplished by the properties of the blood saturation curve for CO_2 and O_2 and the Bohr-Haldane effect when these gases are exchanged simultaneously. In the present experiments, analysis of the peritoneal gas revealed on the average 5.3% oxygen by composition and carbon dioxide 6.3%. The total pressure of the pneumoperitoneal gases ($pN_2 + pO_2 + pCO_2 + pH_2O = 630 + 38 + 45 + 47 = 760$ mm Hg) is equal to one atmosphere. Assuming an arteriovenous pO_2 difference of 60 mm Hg and a venoarterial pCO_2 difference of 6 mm Hg, the total tension of venous blood is 54 mm Hg below atmospheric pressure, ($pN_2 + pO_2 + pCO_2 + pH_2O = 576 + 38 + 45 + 47 = 706$ mm Hg). Whereas this state exists in venous blood in general, the situation in peritoneal venous blood is altered whenever any gas is present in the peritoneal space. In this circumstance the pneumoperitoneal gases exchange with the tissues and capillary and venous blood. For convenience, the blood gas transfers in this instance may be considered in two stages: during the first O_2 is lost and CO_2 is acquired as above (with a resultant total tension drop). In the rest of the discussion this will be referred to as capillary and venous blood. In the second stage the blood approaches a dynamic equilibrium with the peritoneal gases. This phase will henceforth be referred to as occurring in

peritoneal venous blood. In this arbitrary second stage it is doubtful if a true equilibrium between the peritoneal venous blood and peritoneal gas is ever attained. Instead, only some fraction of this equilibrium value is reached, and there is maintained a diffusion gradient between the gas and blood phases. When pure nitrogen is the initial pneumoperitoneal gas, the following sequence of events occurs. After an initial equilibration of CO_2 and O_2 with venous blood, a state of constant composition is reached. The existing net pressure difference of 54 mm Hg, due almost entirely to N_2, tends to drive this gas into the capillary and venous blood to approach equilibrium between the peritoneal venous blood and pneumoperitoneum. As this increment of nitrogen leaves the gas phase the volume shrinks slightly and the pO_2 and pCO_2 are thus raised by a concentration effect. This very slight change creates a pressure difference for CO_2 and O_2 between the pneumoperitoneum and venous blood which favors exodus of these gases until their previous fraction of equilibrium is re-established. This process continues with a net driving pressure of about 54 mm Hg until the total gas volume has been carried away by the venous blood. During the entire process N_2, CO_2 and O_2 are removed proportionally to their fractional concentrations so that the composition of the pneumoperitoneum remains constant.

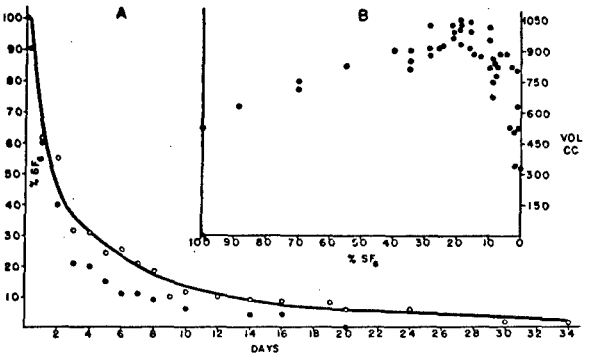


FIG. 2. *A*. Percentage concentration of SF_6 remaining in peritoneal gas, ○ cat, ● dog. *B*. Relationship of total peritoneal gas volume to the percentage concentration SF_6 in SF_6 pneumoperitoneum.

For further analysis certain other assumptions concerning the peritoneal space had to be made. These are: *a*) the mean blood flow to the area remains constant throughout the experiment; *b*) there is no significant change in the capillary area across which diffusion takes place between the limits 300–1000 cc intraperitoneal gas; and *c*) the arterial pSF_6 is effectively zero, i.e. there has been nearly complete clearance of this gas from the mixed venous blood in the lungs while the arterial pN_2 is 80% of B-47. The first assumption seems reasonable; the second, due to the very large exposed area for diffusion with mesentery and loops of bowel is likely true and gains support from the approximately linear shape of the disappearance curve from the nitrogen pneumoperitoneum within the volume limits set. Finally, if there is no terminal diffusion gradient for SF_6 across the alveolar membrane, as suggested for other inert gases (4), it can be calculated that for an alveolar ventilation/perfusion ratio of 1.0 the pSF_6 in the arterial blood would at best never exceed 1 mm Hg (when the SF_6 fraction is 90% in the peritoneum) and thereafter drops proportionately with the SF_6 concentration shown in figure 2. For the mathematical treatment the SF_6 values in the blood have therefore been considered equal to zero. The alveolar N_2 fraction for an animal with a pCO_2 of 39 mm Hg and an R.Q. of .8 is approximately .80. This value was therefore taken to compute the arterial pN_2.

Accepting the above, the factors responsible for the individual gas movements will be their solubilities in blood and the effective pressure difference of each between the gas and liquid (blood) phases, remembering that the effective pressure difference will be less than the true pressure difference if a diffusion gradient is maintained. The absolute amount of gas either removed or delivered will depend on the volume of blood perfusing the area in accordance with the Fick principle. Knowing the blood solubility of nitrogen (0.0147 at 37°, 5) and the magnitude of this driving pressure, one can calculate (see *equation 1*) the minimal (i.e. assuming no diffusion gradient) blood flow which will be required to remove the average 27 cc/24 hr. observed for the first 8 days. This value is 18.7 cc/min.

The SF_6 pneumoperitoneum has a somewhat different course of events. Initially, CO_2 and O_2 enter the gas space and enlarge the total volume as in the previous example. However, now N_2 also enters the space and at a rate more rapid than the SF_6 is able to leave, due entirely to the lower solubility of the latter. The solubility of SF_6 in water is 0.0010 cc @ STP/1 cc H_2O at 25.5°C but in olive oil is 0.21 cc @ STP/cc olive oil at 21.1°C (6). The high fat solubility makes a direct transfer of these data to blood difficult, but the solubility coefficient for 37°C may be calculated from the experimental data (*equation 2*). This calculation is based on the following equation where $\dot{Q}$ represents blood flow/unit of time. ΔV is the change in a particular gas volume for a unit of time, Δp is the partial pressure difference for the gas between capillary and venous blood and the pneumoperitoneum during the time ΔV was displaced, and α is the coefficient of solubility for the gas, at 37°C. The subscripts denote the particular gas in question. K_1 is the fraction of ideal equilibrium between peritoneal gas and venous blood which nitrogen attains; K_2 is this fraction for SF_6. The diffusion gradient for the gas is then $(1 - K)\Delta p$.

$$\dot{Q} = \frac{\Delta VN_2}{\frac{\Delta pN_2}{760} \cdot K_1 \cdot \alpha N_2} = \frac{\Delta V_{SF_6}}{\frac{\Delta pSF_6}{760} \cdot K_2 \cdot \alpha SF_6} \qquad (1)$$

or, rearranging

$$\alpha SF_6 = \frac{\Delta V_{SF_6} \cdot \frac{\Delta pN_2}{760} \cdot \alpha N_2}{\Delta V_{N_2} \cdot \frac{\Delta pSF_6}{760}} \cdot \frac{K_1}{K_2} \qquad (2)$$

Numerical values for the solution of *equation 2* may be obtained from the experimental data in figures 1 and 2. For the time period of the first 8 days in the SF_6 pneumoperitoneum, ΔV_{SF_6} is 330 cc; the integrated mean ΔpSF_6 for this period is 255 mm Hg; ΔVN_2 was measured to be 216 cc and the constant ΔpN_2 is 54 mm Hg. The solubility of nitrogen in whole blood is .0147 at 37°C (5). If K_1/K_2 is 1, then αSF_6 in blood is calculated from *equation 2* to be 0.0044 at 37° or about one-third that for N_2; and it is of interest that this is within the range of values which could be calculated from the solubility of SF_6 in olive oil for the variation in known total blood lipid of the cat (145–607 mg/100 cc, 6). Knowing now the coefficient of solubility of each gas, the initial composition of the pneumoperitoneum, the tension of SF_6 and N_2 in capillary and venous blood and the rate of blood flow it is possible to predict a curve for the total volume at any time.

This calculation is based on the following equation, where V_t = the total volume at time t; V_i is the 'initial' volume of gas, i.e. after the rapid influx of CO_2 and O_2

where $V_i = V_0$ (1 + 0.11), and V_0 is the volume of pure gas introduced. The 0.11 is to correct for the rapid influx of CO_2 and O_2 which occupy approximately 11% of the total volume constantly. ΔV_{N_2} and ΔV_{SF_6} are derived from *equation 1*, using a value of 1 for both K_1 and K_2 and the value for $\dot{Q}$ computed from the nitrogen disappearance curve. For the first time interval a new volume V_t is reached.

$$V_t = V_i + (\Delta V_{N_2} - \Delta V_{SF_6})\ (1 + 0.11)$$

Ideally, the time interval during which ΔV occurs should approach zero, since for every movement of N_2 not only is the pN_2 in the pneumoperitoneum changed, thus creating a new ΔpN_2, but also the pSF_6 is changed since N_2 is diluting the SF_6 present. Similarly, as SF_6 leaves the gas phase the pN_2 is secondarily raised simply by a concentration effect. The calculation is then a step-wise one in which each new value depends on the one immediately preceding. For anytime t_n on the curve then, the preceding equation may be generalized

$$V_{t_n} = V_{t_{n-1}} + (\Delta V_{N_2} - \Delta V_{SF_6})\ (1 + 0.11) \qquad (3)$$

where ΔV is exchanged during time lapse t_{n-1} to t_n. A reasonable approximation to the theoretic curve can be drawn by choosing 6 hr. intervals, and this is indicated by the smooth line in figure 1. The reasonable agreement between the observed and predicted values suggests that the value of K_1/K_2 is approximately 1, but no information concerning an absolute value of either K_1 or K_2 is gained. After the point where the pN_2 in the pneumoperitoneum has reached equilibrium with the venous and capillary blood, it is apparent that ΔV_{N_2} becomes negative in this equation.

Maximum volume is reached on the 10th day when the concentration of SF_6 is about 17%, though at this point, and during the early decline in volume, N_2 is still entering the pneumoperitoneum. The reason for this is that the movement of each gas depends on the product of ΔP and its coefficient of solubility. Thus, the ratio of the flux of nitrogen relative to SF_6 is proportional to the ratio of these two products for nitrogen and SF_6, and it is this ratio that also determines the behavior of the total volume of peritoneal gas.

$$\Delta V_{N_2}/\Delta V_{SF_6} = (-\Delta pN_2 \cdot \alpha N_2 \cdot K_1)/(+\Delta pSF_6 \cdot \alpha SF_6 \cdot K_2) \qquad (4)$$

In this equation (and in fig. 3) the direction of gas movement into the pneumoperitoneum is indicated by a minus sign and the movement out by a plus sign, and K_1/K_2 is made equal to 1.0. After nitrogen reaches an equilibrium with venous and capillary blood, the numerator also becomes positive. These products for SF_6 and N_2 and the ratio of the products are shown in figure 3*A* as a function of time. The insert figure (3*B*) shows the changes in partial pressures alone. The Δp for N_2 rapidly falls to approach zero because the pN_2 in the peritoneum and venous blood approach one another. On the other hand, though the Δp for SF_6 also falls, it does so more slowly because its low solubility retards movement into the blood phase, and the ratio of these two products (fig. 3*A*) determines the relative rates at which N_2 and SF_6 exchange in the pneumoperitoneum (*equation 4*); when the ratio is 1 there is no change in volume, and the maximum volume is reached; this is seen to occur on *day 10*. For a short period beyond this point SF_6 is leaving more rapidly than N_2 is entering, and the ratio is less than 1; during this time (*day 10–14*) the volume is slowly diminishing even though nitrogen is still entering. However, beginning about *day 14* the SF_6 is now 10% by volume concentration and the nitrogen is thus at the same partial pressure (573 mm Hg) in the venous and capillary blood,

and the pneumoperitoneum, and hence will no longer enter the gas space; i.e. $\Delta pN_2 = 0$, and the ratio is also zero. Beyond this point as the SF_6 continues to leave, for each increment drop in pSF_6, the pN_2 rises by the same amount and ΔpN_2 becomes positive.

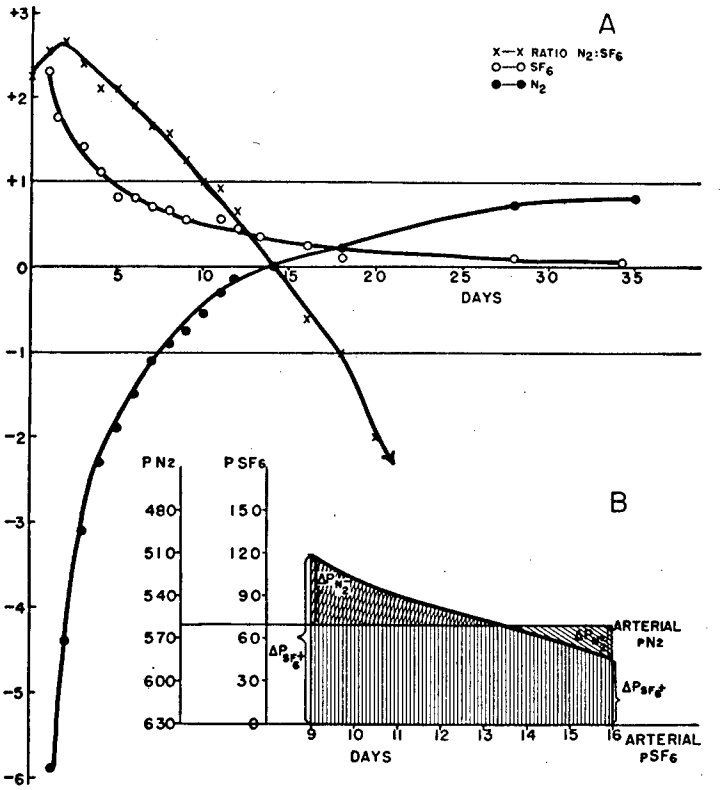


FIG. 3. Dynamic relationships for gas transfer in peritoneal space (for detailed discussion see text). The *ordinate* of fig. 3*A* represents the ratio $(\Delta pN_2 \cdot \alpha N_2)/(\Delta pSF_6 \cdot \alpha SF_6)$, plotted as (X). In addition the relative values for $\Delta pN_2 \cdot \alpha N_2$, plotted as solid dots, and $\Delta pSF_6 \cdot \alpha SF_6$, plotted as open circles, are indicated. The *abscissa* represents time in days. Insert fig. 3*B*—*lower right:* absolute values for partial pressures of SF_6 and N_2 during the period of attainment of maximal volume. Note that the pSF_6 in the peritoneal gas is always above the pSF_6 in arterial blood and therefore ΔpSF_6 remains positive (i. e. the pressure difference throughout favors exodus). On the other hand, the pN_2 in the peritoneal space is lower than in the arterial blood until *day 14* and up to this time nitrogen is entering the peritoneal gas. Between *days 10* and *14* the SF_6 efflux is larger than N_2 influx. On *day 14* $\Delta pN_2 = 0$ and after that the pN_2 is higher in the peritoneal gas than in 'venous and capillary' blood; ΔpN_2 is therefore positive and N_2 also leaves the peritoneal space. Note that the point of maximum volume is reached 4 days before the nitrogen begins to leave.

Since the ΔpN_2 in the pneumoperitoneum is positive and increasing, nitrogen begins to disappear from the gas phase. When the ΔpN_2 is about one-third the ΔpSF_6 both gases will be leaving the pneumoperitoneal space at the same rate and the ratio will again be 1 (shown on graph as -1 to indicate shrinking of total volume). This occurs about *day 16*. The ΔpN_2 will reach a maximum of 54 mm Hg at the time when the SF_6 has effectively disappeared. During this time the ratio approaches

minus infinity as ΔpSF_6 approaches zero. Beyond this point, since the SF_6 has effectively disappeared, only N_2, CO_2 and O_2 remain, and they will be removed in the same fashion as in the nitrogen pneumoperitoneum, except that these concentrations are reached after 30 days.

The prolonged retention of volume in the SF_6 pneumoperitoneum suggests that this substance may be a valuable agent for therapeutic pneumoperitoneum and pneumothorax in man, allowing for at least a doubling of the usual refill intervals.

To recapitulate briefly, the dynamic events in gas transfers which accunt for the observable changes in a SF_6 pneumoperitoneum may be conveniently expressed in terms of three definite phases. *Phase I* occupies the interval 0 through 9 days. During this time nitrogen is entering the pneumoperitoneal space more rapidly than SF_6 is leaving and the total volume continues to increase and reaches a maximum on *day 9*. *Phase II* begins with *day 10* and ends on *day 14*. During this interval the SF_6 is leaving more rapidly than the nitrogen is entering, and the total gas volume is diminishing. Following *day 14* the partial pressure of nitrogen in the pneumoperitoneal space is greater than in venous and capillary blood. From this time on both N_2 and SF_6 are leaving the pneumoperitoneum, the gas volume is progressively diminishing, and this is the final *phase III*.

Summary and Conclusions

A 500 cc initial volume nitrogen pneumoperitoneum diminishes along a nearly linear time course for the first 8 days in the cat at a rate of 30 cc/day total volume decrease. Zero volume is reached in 23 days. If the initial gas is SF_6 (500 cc) the total volume of the pneumoperitoneum doubles by 9 days due to a more rapid influx of N_2 than efflux of SF_6. Beyond the point of maximum volume, the total volume diminishes slowly so that the initial volume is not again reached until *day 30*. After this it diminishes at the same rate as the nitrogen pneumoperitoneum since the SF_6 has effectively disappeared. SF_6 disappears from the peritoneal space exponentially, and at a more rapid rate in the dog than in the cat. The dynamics of the gas transfers causing the changes noted have been discussed.

REFERENCES

1. Rist, E. and A. Strohl. *Ann. de Med.* 8: 253, 1920.
2. Henderson, Y. and M. C. Henderson. *Arch. Int. Med.* 49: 88, 1932.
3. Scholander, P. F. and F. J. W. Roughton. *J. Biol. Chem.* 148: 573, 1943.
4. Jones, H. B. *Med. Physics* 2: 855, 1950.
5. van Slyke, D. D., R. T. Dillon and R. Margaria. *J. Biol. Chem.* 105: 571, 1934.
6. Technical Service Bulletin SF_6-A, General Chemical Division, Allied Chemical and Dye Corporation, 1952.
7. Albritton, E. C. (ed.) *Standard Values in Blood.* AF Tech. Report No. 6039.

Blood and Tissue Gases of Animals Exposed to One and Seven Atmospheres of Oxygen or Air

HENRY T. BAHNSON[1] AND CHARLES M. MATTHEWS

Of the several theories concerning the mechanism of oxygen poisoning, one attributes the toxic effects of O_2 to interference with CO_2 transport (1, 2). Evidence for this comes from experiments which show that animals are more sensitive to CO_2 when exposed to oxygen under high pressure (OHP) (3). Campbell (4) and recently Seelkopf and v. Werz (5) and Taylor (6, 7) found increased amounts of CO_2 and decreased oxygen in gas bubbles in the tissues of guinea pigs and cats at 1 and 3–5 atm. of oxygen. This increased CO_2 and decreased oxygen could be due to inadequate transport of CO_2 from tissues to lungs or to a pulmonary barrier preventing proper arterialization of blood leaving the lungs. The present work is an attempt to determine which if either mechanism is active and deals with blood and tissue gases of animals subjected to 1 and 7 atm. of oxygen.

EXPERIMENTS WITH ONE ATM. OF OXYGEN

Methods

Adult rabbits were exposed to oxygen in a gas-tight chamber which was equipped to allow motion and feeding of the animal, absorption of CO_2, automatic replacement of oxygen consumed by the animal and flushing with oxygen after the chamber was opened. Each animal spent a control period of several days breathing air in the chamber with air injected in the peritoneal cavity before it was subjected to oxygen. In order to estimate tissue gas tension 300–400 ml of air or nitrogen were injected into the peritoneal cavity and samples were intermittently taken by needle aspiration for determination of CO_2 and O_2. At the time abdominal gas was taken, femoral arterial blood was usually obtained by needle puncture. Several animals were allowed to breathe air during this procedure, and in such instances the method of Riley *et al.* (8) was used to measure arterial pO_2 and pCO_2. In some animals oxygen was given by mask during the period of sampling. In order to estimate the higher arterial pO_2 in these animals the analytical method was modified, 16 mm^3 of nitrogen being used as a bubble instead of alveolar air. Since both CO_2 and oxygen entered the nitrogen bubble an increment of pressure was added to the measured pO_2. This increment was determined from the volume of oxygen present in the bubble, the measured 1-ml volume of blood from which oxygen was abstracted and a solubility coefficient of 0.0235 ml O_2/ml of blood/atm.[2] For unexplained reasons this method gave values of pO_2 approximately 10% lower than actual in blood equilibrated with a known pO_2; hence it was used to obtain approximations only. Extraction of CO_2 into the nitrogen bubble caused an insignificant alteration in pO_2 of the blood which was ignored in this study.

Results

Results are shown in figure 1. The elevated pO_2 of the abdominal bubble for the first 36 hours after injection (fig. 1*A*) was noted by Campbell (4) and attributed by him to hyperemia and reaction to the foreign gas. Observations in animals depicted in figure 1 showed a fall in arterial pO_2 and a rise in arterial pCO_2 before such alterations were apparent in the abdominal bubble. Similar changes were seen in the only two other animals in which complete studies were obtained. Signs of increased respiratory effort appeared after 40–60 hours residence in oxygen and became progressively more prominent until death. At autopsy all animals showed pulmonary congestion, edema, hemorrhage and atelectasis. These studies established, as Taylor suggested, the fact that the terminally elevated level of CO_2 in the body is secondary to pulmonary damage caused by exposure to 1 atm. of oxy-

[1] Fellow in the Medical Sciences, National Research Council. Present address: Johns Hopkins Hospital and University, Baltimore, Md.

[2] The formula used is as follows: arterial pO_2 = pO_2 of bubble equilibrated in syringe + (vol. of bubble after equilibration in cc STP × fraction O_2 in bubble × 760 divided by solubility coeff. O_2 × volume of blood.)

gen. It became of interest to assess this factor in poisoning with OHP.

EXPERIMENTS WITH SEVEN ATM. OXYGEN (OHP)

Methods

A compression chamber was modified to allow samples of blood and gas to be drawn from an animal under pressure. The chamber consisted of a 7-inch length of 4-inch pipe threaded on each end to fit iron caps. The cap on one end was welded to the chamber; the other was removable and had a 3-inch hole in the center which was fitted with a Lucite window 1 inch thick and $4\frac{1}{8}$ inches in diameter. The window was seated on rubber washers. An inlet of the chamber was connected to a standard reduction valve and compressed-gas tank. The exhaust was fitted with a needle valve. Steam cocks were fitted into the chamber and into these were soldered short 20-gauge needles to which polyethylene catheters could be attached.

The chamber was large enough to accommodate adult albino rats which were used throughout. They were restrained by leg straps in the supine position on a small trough.

To obtain abdominal gas samples while the animal was under 7 atm. pressure, a polyethylene catheter 0.051 inch o.d. with numerous small holes in the wall at one end was introduced into the abdomen through a 13-gauge needle and directed to lie over the dome of the liver where it was least apt to become entangled with omentum. The other end was attached to a needle fitting in one of the steam cocks. Just before compression, 70 ml of air were injected. The large volume of gas disturbed the animal only briefly, since on compression it shrank to one-seventh of its initial volume. When a sample was drawn, the dead space in the system was flushed with several milliliters, and 3–5 ml were taken for analysis of CO_2 on the Scholander apparatus. Five or six samples could usually be drawn before the supply was exhausted.

In order to evaluate and compare this method with that of Campbell and Taylor who took samples after decompression, in several animals a sample of abdominal gas was taken under pressure; immediately thereafter the animal was rapidly decompressed and another sample taken within 30 seconds of the first.

To obtain arterial samples, the femoral artery was exposed under procaine anesthesia (maximum total dose of 4 mg), and 0.024 inch o.d. polyethylene tubing filled with a 1% heparin solution was inserted and tied in place. An additional 5 mg of heparin was then injected. The small tubing was sealed to 0.051-inch tubing by heat prior to insertion, and the larger size was attached to a needle when the rat was placed in the chamber. One-milliliter samples were easily drawn for control studies at ambient pressure and came with considerable force when the animal was compressed.

When the differences between the gases of arterial and venous blood were desired, the femoral artery was cannulated as above. For venous blood the external jugular vein was exposed just above the clavicle. A measured length of 0.023-inch o.d. polyethylene tubing was threaded through the vein and tied in place. Examination at the conclusion of the experiment showed the tip of the catheter in the superior vena cava in one animal and in the right auricle in all others. Samples from this position may not represent mixed venous blood and vary in gas content depending upon the relative contributions of the superior and inferior venae cavae and the coronary sinus. Consequently only gross changes are significant.

The technique of the analysis for blood gases bore similarity to that described by Bert (9). Four-inch 20-gauge needles were fitted with rubber adapters to fit snugly into the cup of the Van Slyke manometric apparatus. The dead space of both needle and syringe was filled with mercury and heparin-sodium fluoride solution and the barrel was moistened with caprylic alcohol. An additional rubber stopper was provided to seal the tip of the needle and the entire assembly was weighed. When the blood was sampled, several drops were allowed to flush the dead space of the needle valve and a 1-ml sample was obtained. After reweighing, the syringe was stored in ice until analysed. The needle tip was then placed in the Van Slyke apparatus. As much of the blood and effervesced gas as possible was sucked into the chamber under negative pressure

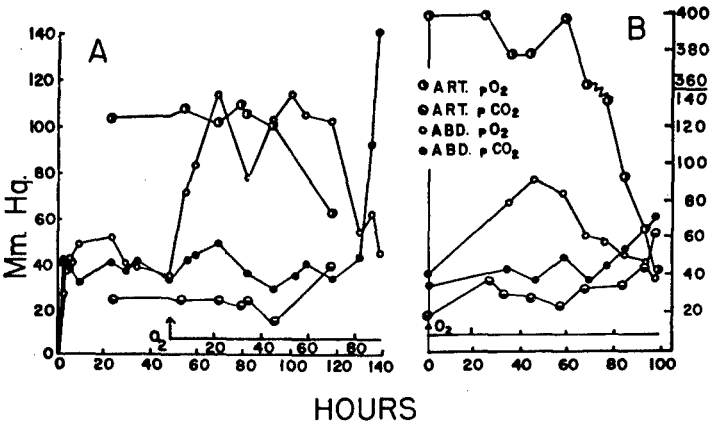


FIG. 1. Arterial and abdominal pO_2 and pCO_2 of rabbit breathing 98–100% oxygen. *A*. Animal breathed air for 10 min. prior to arterial sampling. *B*. Animal breathed oxygen by mask for 10 min. prior to arterial sample.

and the analysis carried out in the usual manner. Correction was not made for the small amount of blood which remained in the syringe, nor for the slight differences in total volume of reagent in the chamber during analysis. Results obtained were expressed in volume of gas/100 gm of blood. Because of the small amount of blood which remained in the syringe, the observed contents were apt to be slightly lower than the actual.

Immediately after drawing the final arterial sample, as much more blood as could be removed was drawn into a 5-ml heparinized syringe. Separate samples of this were then equilibrated with two known partial pressures of CO_2 in oxygen and the whole blood CO_2 content determined on the Van Slyke machine. When these values were plotted on a logarithmic scale as described by Peters (10) with pCO_2 and CO_2 content as abscissa and ordinate, the pCO_2 of the arterial blood could be determined from its CO_2 content. When both arterial and venous blood were drawn, it was often difficult to obtain sufficient blood for a CO_2 dissociation curve. Hence a mean curve was computed from data on five rats using the method of least squares. Individual pCO_2 values were then estimated from this.

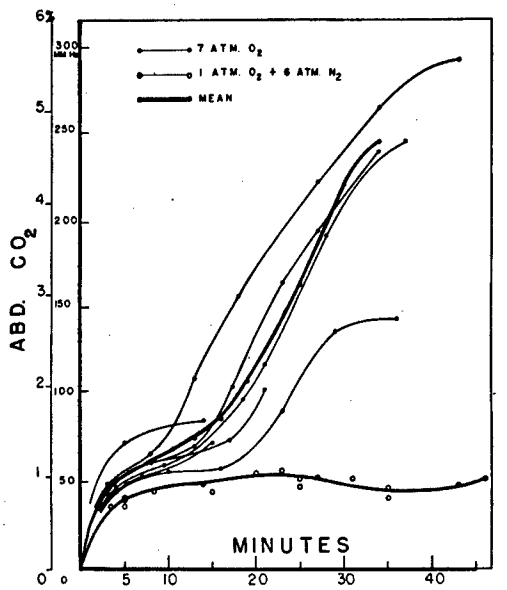


FIG. 2. Percentages and partial pressures of CO_2 in abdominal bubble of rat exposed to 7 atm. of oxygen and to 1 atm. of oxygen with 6 atm. of nitrogen. Air injected into abdomen at zero time.

For each of the above groups of experiments, a control group was run in which the animal was exposed to 7 atm. of 11 or 17% oxygen in nitrogen. This gave a maximum oxygen pressure of 119% of an atmosphere, a pressure generally believed to be nontoxic for periods longer than the duration of these experiments. The chamber was copiously flushed throughout the exposure of all animals in order to remove CO_2. Prior to compression with oxygen the chamber was flushed for 7–10 minutes with oxygen at 1 atm. pressure to eliminate much of the nitrogen in the animal. No flushing was performed before compression in the control experiments.

Results

As noted by previous investigators, there was considerable variation in response of different animals to OHP. The restrained position of the rat made difficult the determination of the interval before the first convulsion but immediately or soon after compression with 7 atm. of oxygen, muscular twitching began, usually first noted about the face. These movements became greater and culminated in convulsions between 5 and 25 minutes after compression. Convulsions occurred several times before the animal lay quietly. Prior to this time and except for periods of apnea after convulsion, respiration was increased in rate and depth. Later respiration slowed, became irregular and ceased between 33 and 60 minutes after beginning exposure. Autopsy performed soon after rapid decompression invariably showed continued vigorous heart action. Gross pulmonary changes included hemorrhagic areas, occasional frothy edema and congestion. Control animals showed no abnormality while under pressure but died soon after, and presumably because of the decompression; numerous bubbles were seen in the blood of autopsied animals.

TABLE 1. PERCENTAGE OF CO_2 IN ABDOMINAL GAS BEFORE AND IMMEDIATELY AFTER RAPID DECOMPRESSION FROM 7 ATM.

	Before	After	Percentage Increase Above Compressed Value
Experiments in oxygen	3.4	6.1	77
	4.6	6.0	30
	5.5	8.5	54
	4.5	5.6	24
Experiments in 17% oxygen in nitrogen	.98	1.3	33
	.98	1.5	53

In figure 2 are plotted the percentages and partial pressures of the abdominal CO_2 in rats under 7 atm. of pressure. Control animals breathed 1, the other 7 atm. of oxygen. The pCO_2 around 50 mm Hg in control animals was slightly higher than that found previously in

rabbits exposed to 1 atm. of oxygen under atmospheric pressure. The shape of the curves obtained from test animals exposed to 7 atm. of oxygen suggested that a plateau was first approached at a pCO_2 of 65 mm Hg. After 12–15 minutes exposure, the CO_2 began to rise rapidly and reached values as high as 290 mm Hg before respiration ceased.

When two samples of abdominal gas were taken before and after rapid decompression but within 30 seconds of each other (4, 6, 7), the sample taken after decompression contained 24–77% more CO_2 than that obtained under pressure (table 1). This might be expected from the rapidity with which the CO_2 of injected gas approaches equilibrium with the tissues. Since the gas bubble is essentially free to expand, the pCO_2 of the tissues will be 7 times that of the abdominal bubble immediately after sudden decompression and CO_2 will rapidly enter the bubble. Transfer of oxygen would be slower as judged by experiments at 1 atm. and because of a lower rate of diffusion; in addition oxygen consumption of the tissues would rapidly lower the tissue oxygen tension.

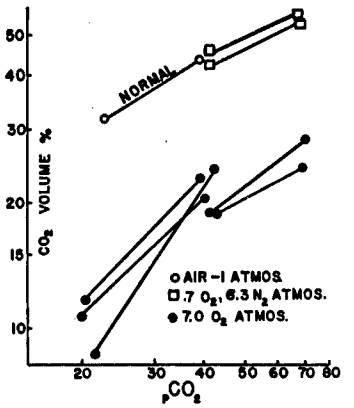


FIG. 3. CO_2 dissociation curves of whole blood of rats exposed to air at 1 atm. (*open circles*), exposed for 30 min. to 0.7 atm. of O_2 and 6.3 atm. of N_2 (*open squares*) and exposed for 26 min. to 7 atm. of O_2 (*closed circles*). Normal control data represent average values of Freeman (11) for untreated rats.

The CO_2 dissociation curves are plotted in figure 3 on logarithmic scale. All test animals showed a significant reduction in CO_2 capacity. It seems unlikely that such a reduction could be caused by excretion of base alone in this short time and the addition of fixed acid is a more logical assumption.

Determinations of arterial and venous CO_2 content with estimations of pCO_2 by use of the chart are listed in table 2. According to Peters (10) this method of extrapolation to determine pCO_2 from CO_2 content and CO_2 dissociation curve is accurate only for values below 100 mm pCO_2. Above that level the observed values fall away from the straight line. Hence the estimated pCO_2 values, which are only approximations, are probably lower than actual. The arterial and venous pCO_2 are in the same range as the abdominal pCO_2 estimated from the mean curve in figure 2. This argues against a large barrier between blood and tissue.

DISCUSSION

These experiments demonstrate the apparently different mode of action of oxygen at 1 atm. and oxygen under high pressure as originally remarked by Smith (12). Under 1 atm. there was no change in the tissue O_2 and CO_2 tensions, as estimated by studies of nitrogen bubble injected into the peritoneal cavity, until signs of a diffusion barrier appeared in the lungs. Death under such circumstances appeared no different from that caused by any extensive pulmonary injury.

On the other hand poisoning with OHP appears to involve a different mechanism. The methods reported here are not sufficiently accurate to demonstrate pulmonary injury if such exists; however, previous workers have practically eliminated pulmonary damage as a primary cause of the effects of OHP. Shilling and Adams (13) showed that convulsions occur in the absence of pulmonary damage. Donald (14) found that in a large series of men exposed to OHP until neurological symptoms appeared there was no evidence of pulmonary damage.

Our studies of the CO_2 dissociation curves of rats poisoned with 7 atm. of oxygen showed significant changes. Behnke *et al.* (15) studied dogs breathing oxygen at 4 atm. for 52–193 minutes and found no change in CO_2 capacity, a slight increase in the difference between arterial and venous pCO_2 and no increase in lactic acid. Bean noted an increase in acidity of the blood with OHP (16) and a transient and reversible increase in blood lactic acid, in

one case to more than 90 mg % (17). Shilling *et al.* (18) noted significant increases in lactic acid of the blood under 3.88 atm. oxygen but did not elaborate upon this. Such a release of fixed acid, possibly the result of inactivation of enzymes, would explain the large reduction in CO_2 capacity in our study and is worthy of further exploration.

Finally, in regard to CO_2 as a causative factor, the frequently cited experiments in favor of accumulation of CO_2 in the tissues are those of Campbell (19) and Bean (16). Seelkopf and v. Werz (5) and Taylor (6, 7) have recently extended the work of Campbell and reported an increased tissue pCO_2 in guinea pigs and cats prior to convulsions under 3–5 atm. of oxygen. These values were obtained after rapid decompression, which method we now have reason to believe gives values which are too high. Behnke *et al.* (15) found an increased venous pCO_2 and acidity in dogs under 4 atm. of oxygen. These slight changes were attributed to failure of reduction of oxyhemoglobin and hence loss of the major vehicle in the normal transport of CO_2 as first suggested by Gesell (20). Lambertson *et al.* (21) studied normal men exposed to 3–4 atm. of oxygen and found an average elevation in internal jugular pCO_2 of only 3 mm Hg. Interference with normal reduction of oxyhemoglobin and a diminished cerebral blood flow accounted for an 8 mm Hg increase in arteriovenous difference of pCO_2 across the brain which was partially offset by hyperventilation and a 5 mm Hg fall in arterial pCO_2. They believed that central accumulation of CO_2 may indirectly reduce exposure of the brain to toxic levels of oxygen by producing hyperventilation and cerebral vasoconstriction. In the early stages of exposure to 7 atm. of oxygen we found an average abdominal pCO_2 of approximately 65 mm Hg. This elevation over the control value may represent increased tissue pCO_2 due to increased acidity of the fully oxygenated venous blood. The later rapid rise in pCO_2 we believe is due to failure of ventilation and cardiac output.

Bean (16) showed an increase in acidity of arterial blood under 3 or more atm. of oxygen and noted changes in respiration and pulse, all of which he thought were due to accumulation of CO_2 in the tissues. He later showed an increase in lactic acid under these conditions. Our data suggest that the acidity may be due to: *a*) accumulation of fixed acids, of which lactic would be the most suspect, and *b*) increased CO_2 probably first caused by failure of reduction of oxyhemoglobin and later by increased arterial CO_2. The cause of the latter may be inadequate ventilation but the mechanism is unclear.

Purposely the studies reported here were carried out after the process of oxygen poisoning was far advanced, and consequently the high arterial CO_2 content, low CO_2 capacity and increased arteriovenous oxygen difference may be secondary manifestations of the disorder, but it is hoped that as such they will give a lead to the earlier, fundamental derangement in this perplexing process.

TABLE 2. ARTERIAL, VENOUS AND ABDOMINAL CO_2 OF RATS UNDER 7 ATM. OF OXYGEN

No. of Rat	Duration of Exposure, min.	Arterial		Venous		Abdominal CO_2 Est. mm Hg
		CO_2 cont. cc/100 gm	Est. pCO_2 mm Hg	CO_2 cont. cc/100 gm	Est. CO_2 mm Hg	
1	19	80.6	151	79.2	149	111
2	19	59.1	110	64.7	121	111
3	16	41.3	76	48.1	89	85
4	20	31.2	57	47.3	87	117
5	20	56.3	105	57.3	107	117
6	20	81.1	152			117

Arterial and venous pCO_2 estimated from mean CO_2 dissociation curve computed by method of least squares from dissociation curves of five animals exposed to OHP for a comparable period of time. (See fig. 3). Abdominal pCO_2 is estimated from the mean curve in figure 2.

SUMMARY AND CONCLUSIONS

Oxygen poisoning has been studied by analyses of gas from an abdominal bubble and arterial blood in rabbits and rats. During exposure to 1 atm. of oxygen there was no significant change in tissue oxygen and CO_2 tension as reflected in the abdominal bubble until there was evidence of pulmonary damage and change in arterial gas contents. The cause of death at 1 atm. of oxygen seems to be asphyxia resulting from pulmonary damage.

Abdominal and arterial and venous blood gases were also studied in rats under 7 atm.

oxygen and under control conditions with 7 atm. total pressure but 1 atm. of oxygen. In the former an abdominal pCO_2 of about 65 mm Hg rapidly appeared in such animals and was maintained for 12–15 minutes. This pCO_2 is 15–20 mm Hg higher than that obtained at ambient pressure and may reflect saturation of venous blood with oxygen and embarrassment of CO_2 transport by hemoglobin. After 12–15 minutes the abdominal pCO_2 rose rapidly and probably represented general failure of the organism.

Evidence is given that exchange of CO_2 between tissues and abdominal bubble is rapid and that samples taken after rapid decompression contain significantly more CO_2 than samples taken under pressure.

A change in CO_2 combining power of the blood has been demonstrated and the suggestion is made that this reflects accumulation of fixed acid.

REFERENCES

1. BEAN, J. W. *Physiol. Rev.* 25: 1, 1945.
2. STADIE, W. C., B. C. RIGGS AND N. HAUGARD. *Am. J. M. Sc.* 207: 84, 1944.
3. HILL, LEONARD. *Quart. J. Exper. Physiol.* 23: 49, 1933.
4. CAMPBELL, J. A. *J. Physiol.* 59: 1, 1924.
5. SEELKOPF, K. AND R. V. WERZ. *Arch. exper. Path. u. Pharmakol.* 205: 351, 1948.
6. TAYLOR, H. J. *J. Physiol.* 108: 264, 1949.
7. TAYLOR, H. J. *J. Physiol.* 109: 272, 1949.
8. RILEY, R. L., D. D. PROEMMEL AND R. E. FRANKE. *J. Biol. Chem.* 161: 621, 1945.
9. BERT, PAUL. *Barometric Pressure.* Hitchock translation. Columbus, Ohio: College Book Co., 1943.
10. PETERS, J. P. *J. Biol. Chem.* 56: 745, 1923.
11. FREEMAN, FLORENCE. Thesis, Univ. of Rochester, 1950.
12. SMITH, J. L. *J. Physiol.* 24: 19, 1899.
13. SHILLING, C. W. AND B. W. ADAMS. *U. S. Nav. M. Bull.* 31: 112, 1933.
14. DONALD, KENNETH. *Brit. M. J.* 1: 667, 712, 1947.
15. BEHNKE, A. R., L. A. SHAW, C. W. SHILLING, R. M. THOMSON AND A. C. MESSER. *Am. J. Physiol.* 107: 13, 1934.
16. BEAN, J. W. *J. Physiol.* 72: 27, 1931.
17. BEAN, J. W. AND J. HALDI. *Am. J. Physiol.* 102: 439, 1932.
18. SHILLING, C. W., R. M. THOMSON, A. R. BEHNKE, L. A. SHAW AND A. C. MESSER. *Am. J. Physiol.* 107: 29, 1934.
19. CAMPBELL, J. A. *J. Phyisol.* 68: proc. VII, 1929.
20. GESELL, R. *Am. J. Physiol.* 66: 5, 1923.
21. LAMBERTSEN, C. J., R. H. KOUGH, D. Y. COOPER, G. L. EMMEL, H. H. LOESCHKE AND C. F. SCHMIDT. *J. Appl. Physiol.* 5: 471, 1953.