Final Report

"Definition of Oxygen Tolerance in Man"
(Predictive Studies V)

- - - - -

Contract N00014-81-C-0826

Naval Medical Research and Development Command

and

Office of Naval Research

31 December 1987

C.J. Lambertsen, M.D.
Principal Investigator

Institute For Environmental Medicine
University of Pennsylvania Medical Center
Philadelphia, PA 19104-6068

CONTENTS

This Abstract Report is comprised of Four Component Summary reports from a comprehensive investigation of effects and time courses of oxygen poisoning in human organ systems, during a collaborative research program of uninterrupted breathing of 100 percent oxygen at 3.0, 2.5, 2.0 and 1.5 ATA. Completion of the extensive data correlations will extend beyond the date of Contract "Final Report". The present component reports include

* - - - - - - *

Index of Publications (1940-1984)

Acknowledgement

By interagency agreement, this collaborative Program was supported in part by NMRDC Contract N00014-81-C-0826, NASA contract NAS9-17238, and the State of Pennsylvania through the Benjamin Franklin Partnership.

Individual Summary Reports are reproduced from Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology.

DEFINITION OF OXYGEN TOLERANCE IN MAN

(PREDICTIVE STUDIES V)

INSTITUTE FOR ENVIRONMENTAL MEDICINE
UNIVERSITY OF PENNSYLVANIA

SUMMARY

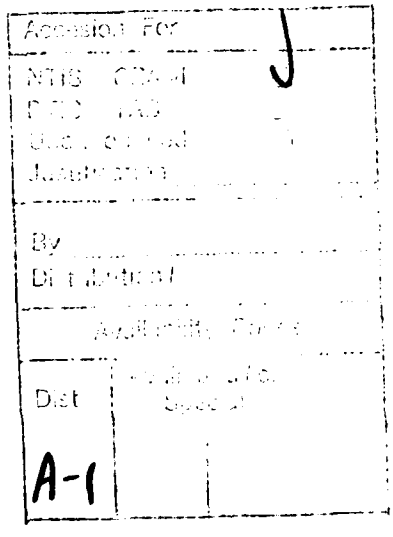
This Program is critical to all present efforts to improve usefulness of oxygenation in medicine and to advance in diving and aerospace activity. Oxygen combines useful effects critical to prevention and relief of hypoxia, with serious toxic effects which limit oxygen use in diving, decompression and therapy of decompression accidents. It also recognized that opportunity now exists, through research, to improve the tolerance to oxygen at normal and higher ambient pressures, with potentially large application to manned undersea and aerospace operations, to therapy and to prevention of residual effects of oxygen poisoning.

The scope of the Program is based upon more than thirty years of leadership in oxygen tolerance investigation by the staff of the Institute For Environmental Medicine. Such studies have led to the requirement to search beyond the pulmonary toxicity and central nervous system convulsions long recognized as prominent consequences of oxygen poisoning.

Goals of the extensive Predictive Studies V research program are to define inherent oxygen tolerance in normal man under conditions that are relevant to therapeutic and aerospace operations. Specific aims of this program have included investigation of the rates of development of oxygen poisoning of critical organ functions at O_2 pressures of 1.0, 1.5, 2.0, 2.5, and 3.0 ATA (the high levels of oxygen pressures encountered in medicine including hyperoxic therapy, in undersea activity and in therapy of diving and altitude decompression sickness).

Concurrent measurements of oxygen effects are made on a broad range of vital organ systems and functions. For measurement of changes in sensory and brain function, monitoring of electroencephalographic activity and intermittent evoked cortical electrical response are accompanied by repeated measurements of perceptual, cognitive, and psychomotor function. Visual functions are monitored by repeated measurements of visual acuity, visual fields, color vision, dark adaptation, and 2-flash discrimination thresholds, with electroretinography in selected conditions. Auditory function is measured by pure tone air conduction audiometric determinations of hearing thresholds. Vestibular reactivity is intermittently tested by thermal stimulation. Changes in blood electrolyte, hormonal and cellular composition are measured upon venous blood, blood gases and pH upon arterial blood. Observations of neurologic oxygen tolerance are correlated with rate of development of pulmonary toxicity, through measurements of the vital capacity and maximal flow rates during inspiration and expiration and other selected indices of pulmonary function.

The range of inspired oxygen pressure of 1.0, 1.5, 2.0, 2.5, and 3.0 ATA was selected for continuous exposure because pulmonary oxygen intoxication occurs at 1.0, 1.5, and 2.0 ATA in the absence of obvious neurologic effects of oxygen toxicity, while definite neurologic symptoms precede the development of prominent pulmonary effects at 3.0 ATA, and because the actual rates of occurrence and recovery of mental or sensory decrement were unknown at any of these pressures. In addition, the measurements provide necessary guidelines for the design of the following Predictive Study VI aimed at (a) optimizing the effectiveness of programmed intermittency of hyperoxic exposure as the most rational method for increasing tolerance to oxygen over a wide range of useful oxygen pressures, and (b) combined use of synthetic blood substitutes and hyperoxygenation to improve oxygen delivery without limitations of oxygen toxicity.



9th International Symposium on Underwater and Hyperbaric Physiology
Undersea and Hyperbaric Medical Society, Bethesda, MD. 1987

DEFINITION OF TOLERANCE TO CONTINUOUS HYPEROXIA IN MAN: AN ABSTRACT REPORT OF PREDICTIVE STUDIES V

C. J. Lambertsen, J. M. Clark, R. Gelfand, J. B. Pisarello, W. H. Cobbs, J. E. Bevilacqua, D. M. Schwartz, D. J. Montabana, C. S. Leach, P. C. Johnson, and D. E. Fletcher

This abstract report has a dual purpose. One purpose is to provide the overall goals, design, and procedures of Predictive Studies V. The subordinate purpose is to describe specific elements of neural effects produced by prolonged hyperoxia. Summary observations on other functions are considered in related papers in this proceedings and elsewhere (1-5).

Predictive Studies V is a multiyear, collaborative investigation of oxygen poisoning in normal men, during uninterrupted exposures to oxygen over the range of hyperbaric oxygen exposure most useful in diving, treatment of gas lesion diseases, and general hyperbaric medicine.

The investigation followed approximately 20 yr of prior investigations of oxygen effects in animals and human subjects, during which necessary concepts of design selection of critical target functions, methods, and safety procedures accumulated to a degree that justified the extensive searches into unknown, essentially unexplored aspects of human oxygen toxicity.

The investigation was designed to determine rates of development and recovery for oxygen-induced effects on multiple selected organ, tissue, or cell functions. It was expected that the nature of specific toxic effects, rates of development, and rates of recovery would differ at different pressures of hyperoxic exposure. Therefore the systematic overall studies were carried out to include exposure to several different pressures of inspired O_2. The pressures selected for 100% breathing selected were 3.0, 2.5, 2.0, and 1.5 ATA. At each pressure a duration of exposure greater than previously systematically investigated was selected. The design thus provided the basis for definition of oxygen "dose-response" in terms of pressure, duration, and effect. It provided

for the analytic derivation of oxygen tolerance tables for multiple critical organ functions over the probable range of usefulness for continuous oxygen exposure.

In this fundamental design, the resting condition and continuous oxygen exposure were chosen to allow determinations of *maximum tolerance* of tissue or organ functions at each level of inspired oxygen pressure. The results would thereby provide the necessary (and presently unavailable) baselines for important medical uses of oxygen in general hyperbaric oxygen therapy, and in hyperoxic treatment of gas lesion diseases in undersea and aerospace activity. The results would also provide the essential baselines for subsequent investigations in man of adverse or advantageous modifying factors relating to rate of development of oxygen poisoning or its effects (e.g., interrupted oxygen exposures, work, drug administration, carbon dioxide inhalation or retention, narcosis, respiratory gas density).

In the investigation emphasis was given not only to pulmonary oxygen poisoning, but to functions for which information concerning rates of development and recovery have been essentially unexplored in man at toxic oxygen pressures greater than 1 atm (e.g., neurologic, respiratory, cardiovascular, endocrine, renal).

Background

This program had its origins in the awareness that, in most uses of oxygen for therapy, the essential life element oxygen combines desirable effects critical to relief of hypoxia in some tissues, with potentially lethal toxic effects of hyperoxia in other tissues. In the absence of adequate information concerning human oxygen tolerance, fear of oxygen poisoning has for many years limited the therapeutic and operational use of hyperoxia to its full potential. This information concerning actual tolerance is needed to replace the arbitrary and nonoptimal patterns of diver and patient oxygen exposure employed over the past several decades. The required detailed definition of toxic effect and recovery encompasses organ systems and functions beyond the occurrence of pulmonary "irritation" and the occurrence of a convulsion.

At the onset of the Predictive Studies V program, the status of detailed information concerning development and recovery in human organ oxygen poisoning is grossly indicated by Fig. 1. Such studies of human pulmonary oxygen poisoning had not been accomplished at oxygen pressures greater than 2.0 atm or even between 1.0 and 2.0 atm.

Except for symptomatic, brain circulatory, and EEG observations (6-10) no systematic investigation of human CNS oxygen tolerance had been accomplished at pressures greater than 1 ATA. While *physiologic* effects of oxygen have been investigated to pressures as high as 4.0 ATA (10-14), systematic determinations of onset and recovery of *toxic* effects of oxygen on cardiovascular and other critical organ functions had not been made at pressures greater than 2.0 ATA.

Tolerance to Continuous Hyperoxia

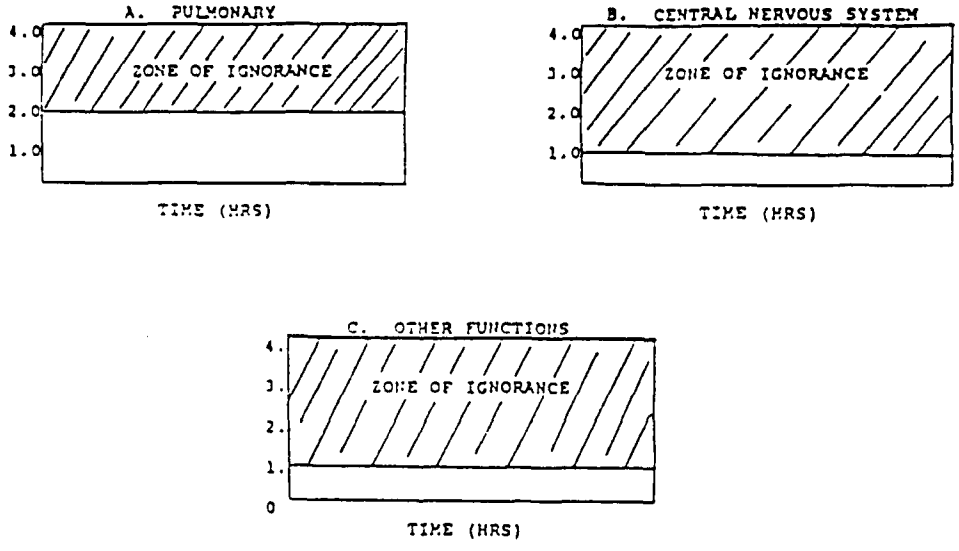


Fig. 1. Status of information concerning human tolerance to continuous hyperoxia.

Against the background of prior investigations, it was recognized that no organ or system (e.g., the brain, the eye, the heart, or even the lung) has a single function, single oxygen dose, or single oxygen tolerance in any hyperoxic exposure (6) (Fig. 2). It was therefore a goal of the program to measure not only effects on multiple organ systems, but discrete effects within the system being investigated.

Moreover, it was considered philosophically that development of cytochemical oxygen poisoning began from the moment of exposure to hyperoxia, and progressed at a rate related to the absolute pressure of oxygen at the discrete sites of the molecular process involved. Functional expressions of these myriad loci of oxygen poisoning in any tissue or organ system could be expected to develop at different rates, and in much of the mass of body tissue the progressive poisoning will not become physiologically obvious and must be sought by selective chemical searching.

Because any observed effects of oxygen poisoning must be recognized as consequences of a pathologic process, it was considered that measurements of *rates of recovery* had even greater significance than the operationally important measures of *rates of development* of adverse effects.

For these several reasons cited, the overall Predictive Study of Human Oxygen Tolerance combined measurements of rates of development and recovery of measurable physiologic changes, with measurement of corresponding chemical changes reflected in blood.

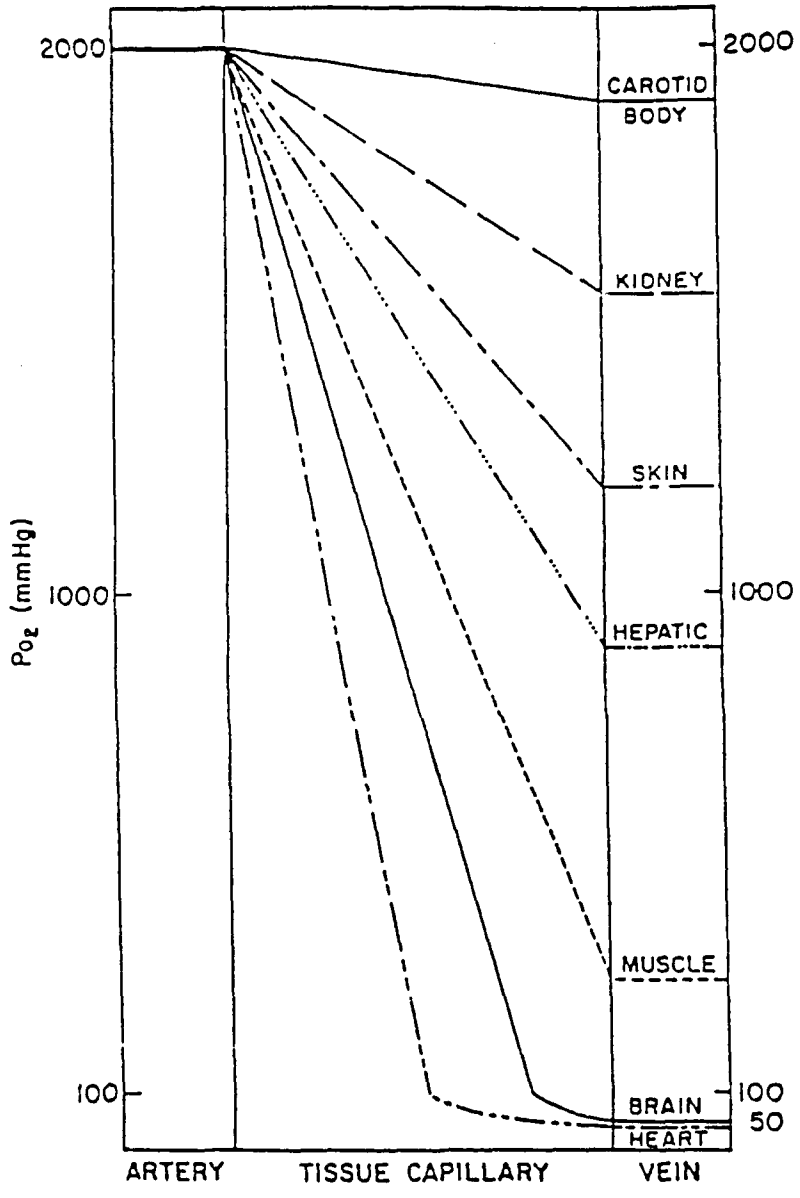


Fig. 2. Fall in PO_2 across the capillary bed in various tissues during oxygen breathing at 3.5 ATA. From Lambertsen (6).

Goal of Program Design

In our previous investigations aimed at defining human pulmonary tolerance to hyperoxia, a system of *pulmonary oxygen tolerance curves* was derived (6, 15, 16) (Fig. 3). For these, based on decrements in vital capacity, measurements obtained in studies by several investigators at oxygen pressures of 2.0, 1.0, 0.8, 0.7, and 0.5 ATA were combines (15, 16). This subsequently allowed predictive estimation of *cumulative pulmonary toxic dose* (CPTD) for oxygen, in terms of a *unit pulmonary toxic dose* (UPTD) defined as that producing the toxic effect of 100% O_2 for 1 min at 1 ATA (17, 18).

An applied goal of Predictive Studies V has been to obtain the measurements necessary to improve on these previously derived pulmonary oxygen tolerance curves, and to generate the information required for equivalent oxygen tolerance tables for other critical organ or tissue functions, including brain, sensory, neural, muscle, cardiac, blood, and endocrine.

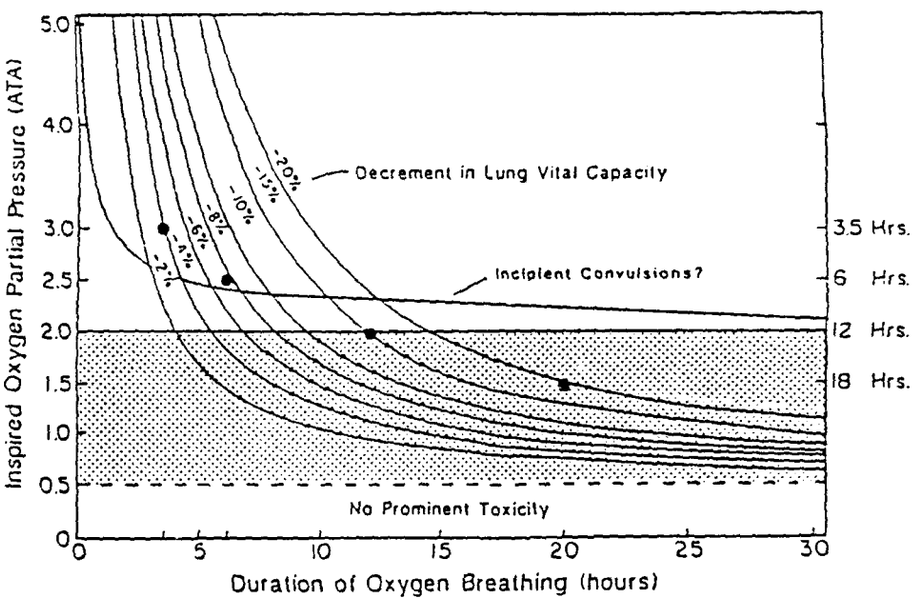


Fig. 3. Progression of pulmonary oxygen toxicity during continuous exposure to hyperoxia. Shaded area represents levels of inspired PO_2 at which investigations had been carried out before Predictive Studies V. Black dots indicate pressure/durations for oxygen exposures in present program. Modified from Lambertsen (6).

PROCEDURES AND METHODS

Oxygen exposure pressure and duration limits planned, and approved by the formal university procedures for research involving human beings, are as outlined in Table 1.

Young men were selected as subjects from volunteers, following the successful completion of detailed clinical medical examinations including special examinations of the systems under study (e.g., auditory/vestibular, neurologic, ophthalmologic, cardiac, pulmonary, hematologic). Numbers of subjects to be used at each pressure were determined by needs and practicality of statistical evaluation, as a particular toxic effect was encountered.

Table 1
Planned Pressures and Durations of Hyperoxic Exposures

Ambient Pressure, ATA	P_{O_2}, ATA	Duration, h
1.0	0.21	24
1.5	1.5	18
2.0	2.0	12
2.5	2.5	6
3.0	3.0	3.5

To accomplish the fundamental and applied goals cited required repeated measurements of multiple functions (Table 2) before, during, and after exposures of the normal subjects to each of the several different increased oxygen pressures (Fig. 4). It is clearly not possible or necessary to measure each of these functions continuously over the entire period of an oxygen exposure. Modules of measurement performance were therefore used, as in previous Predictive Studies (19, 20) (Fig. 5). These were repeated before, at planned times during, and after the oxygen exposures. At the highest oxygen pressure (3.0 ATA), measurements were repeated at short intervals. At the lower degrees of hyperoxia, intervals between measurement modules could be longer (Fig. 4).

The study was begun with investigations at 3.0 ATA to assure detection of any neurologic or other effects not encountered or searched for in prior studies at 2.0 or 1.0 ATA. This emphasis provided guidance in final design and safety for the exposures at lower pressures. On the same basis the study at the intermediate pressure of 2.5 ATA was then performed last, to assure awareness and preparation for investigations of potential interactions of neural, pulmonary, cardiovascular, and other effects.

Details of subject instrumentation, measurement, and analysis will be provided in the full documentation of major study components. The methods employed will be cited below in describing specific observations.

SUMMARY OF OBSERVATIONS

Throughout the study the most striking observations related to effects on visual function, on the lung, and probable interactions of preconvulsive neural

Table 2
Measurements During Continuous Oxygen Exposure in Man

Electroencephalography
clinical interpretation
spectral analysis
response to photic stimulation
Visual function
visual evoked cortical response
electroretinography (dark and light adapted)
fields (rodenstock perimeter)
pupillary reaction
acuity
accommodation
color vision
Auditory-vestibular function
audiometry (air conduction)
brainstem auditory evoked response
high frequency audiography
eye tracking, nystagmography
caloric stimulation
Muscle power (skeletal, respiratory)
Performance (perceptual, cognitive, and psychomoter)
Pulmonary function
flow-volume loops
spirometry
density dependent flow rates
closing volumes
peak inspiratory and expiratory pressures
airway resistance and conductance
frequency dependence of compliance
carbon monoxide diffusing capacity
arterial blood gases and acidity (PCO_2, PO_2, pH)
Cellular and chemical composition of bronchoalveolar lavage fluid
Respiration-respiratory gas exchange
Temperature

Table 2 Cont.

Cardiovascular function
- electrocardiography
- cardiac output, rate, stroke volume
- mean thoracic impedance
- blood pressure, systemic vascular resistance
- orthostatic reflex responses

Liver blood flow and function

Renal function

Endocrine activity, via plasma hormone levels
- insulin
- cortisol
- aldosterone
- vasopressin
- growth hormone
- beta-endorphin
- adrenocorticotropic hormone
- thyroid stimulating hormone

Hematologic effects

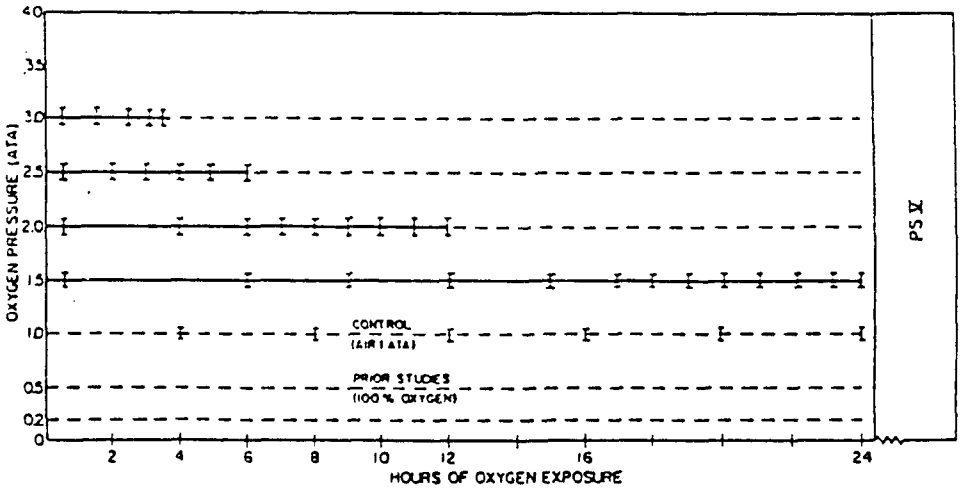


Fig. 4. Plan for continuous oxygen exposures in man.

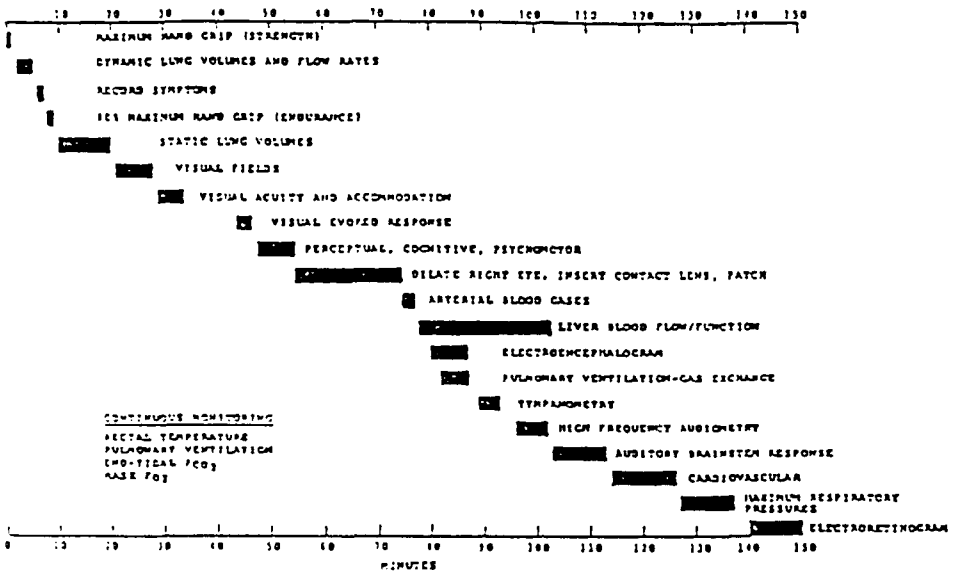


Fig. 5. Predictive Studies V measurement module for 2.0 ATA and 1.5 ATA studies.

activity with effects on cardiovascular and respiratory-pulmonary functions.

Table 3 indicates in simple form the presence or absence of an oxygen-related effect for major components of the overall study. Relations of these effects are summarized below. Details of specific observations and circumstances will be provided elsewhere.

Mental and Psychomotor Function

Consciousness was maintained throughout each oxygen exposure, even up to the moment of occurrence of a convulsion at 3.0 ATA in 1 subject. The selected measures of mental and psychomotor function (short-term memory, visual reaction time, finger dexterity, and general reasoning, all administered by the IFEM Performance Measurement System) have been remarkably stable at each of the oxygen pressures investigated. While no significant decrements occurred, comparisons of mental and psychomotor performance during oxygen exposure at 3.0 ATA and air at 1.0 ATA indicate that small "learning trends" in air exposure may have been masked during this highest oxygen exposure.

Convulsion and Associated Measurements

Only 1 convulsion has occurred during the entire sequence of the Predictive Study V exposures. This followed 3.0 h of oxygen breathing at 3.0 ATA.

Table 3
Summary of Specific Toxic Effects Observed

Function	O_2 ATA 1.5	2.0	2.5	3.0
Brain cortical				
Convulsion	o	o	o	•
Perception, cognition, psychomotor	o	o	o	o
Pre-convulsive cortical electrical activity (EEG)	o	o	o	o
Somatosensory evoked potential				o
Thermal	o	?	?	•
Respiratory	•	?	?	•
Neuromuscular power				
Hand grip	o	o	o	o
Inspiratory	o	o	o	o
Expiratory	o	o	o	o
Cardiovascular	?	•	•	•
Pulmonary	•	•	•	•
Hearing/vestibular				
Hearing thresholds	o	o	o	o
Auditory brainstem potentials	o	o	o	o
Vestibular response	o	o	o	o
Visual				
Central vision acuity	o	o	o	o
Peripheral vision	o	•	•	•
Retinal electrical response (ERG)	•	•	•	•
Pattern evoked cortical potential	o	o	o	o
Color vision	o	o	o	o
Accommodation	o	•	•	•
Pupil size, reactivity	o	o	•	•
Hepatic	•	•	•	•
Renal	•	•	•	•
Endocrine	•	•	•	•
Blood	•	•	•	•

Key: o = Measured, no change; • = Change observed; * = Measured, not reported here; ? = Change observed. May be physiologic or mixed effect.

Normal mental and psychomotor performance measurements were obtained 30 min before the convulsion. An observation of large significance was a normal subject-investigator cooperative performance of audiometric measurement at 3.0 ATA of oxygen, during the 4-min period before the occurrence of convulsion. This confirms the equivalent observation in open-sea diving that capability for intelligent performance is retained up to the moment of abrupt electrical disorganization that initiates the convulsion (21).

Respiratory and thermal changes associated with the single convulsion, during oxygen exposure at 3.0 ATA, are shown in Figs. 6 and 7. Respiratory components and end-tidal gases were monitored because each is related to the neural or neurochemical control of respiration, which were therefore considered in the program design as potential targets of neurologic oxygen poisoning, rather than having primary relation to direct pulmonary oxygen poisoning. The findings represent the first such tracking of preconvulsive respiratory events, and complement equivalent preconvulsive measurements of brain circulation and metabolism (10).

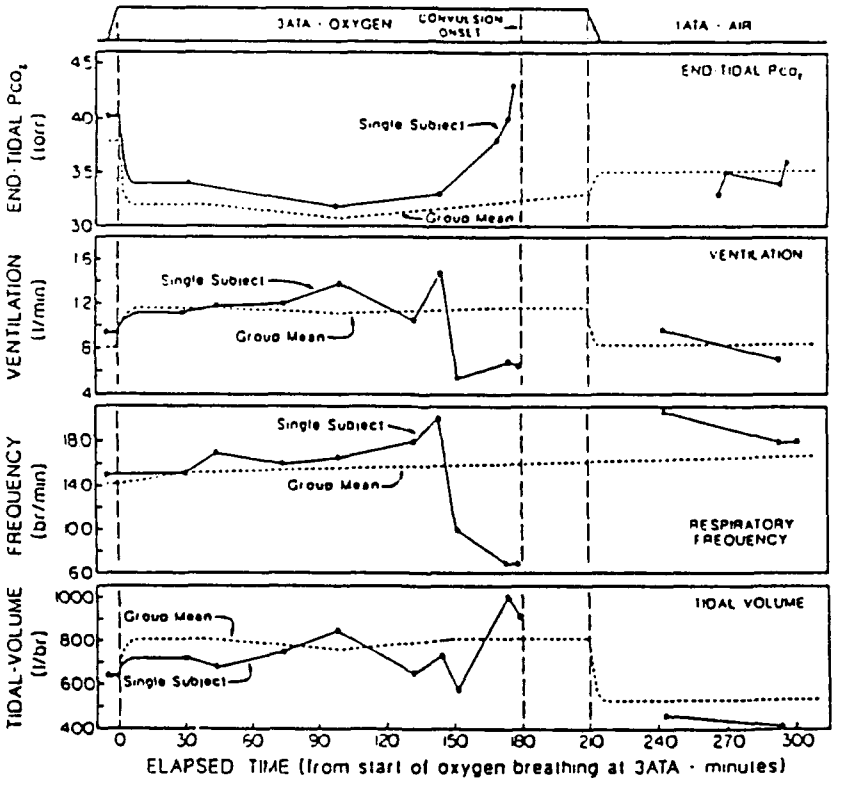


Fig. 6. Effects on ventilation of O_2 breathing at 3 ATA for 3.5 h. Comparison of 1 subject who convulsed with group of 12 subjects.

A progressive decrease in respiratory frequency occurred before the convulsion. An associated rise in end-tidal Pco_2, in spite of increased tidal volume, indicated a decrease in alveolar ventilation. The special significance of the rise in alveolar Pco_2 is the inevitable effect of hypercapnia on brain blood vessels, with a cerebral vasodilatation, increased blood (oxygen) flow, and consequent exposure of brain tissue to further increase in oxygen partial pressure. A vicious cycle of accelerated progression of brain oxygen poisoning should result (6, 10, 11).

The fall in deep body temperature before convulsion resembles that observed in toxic oxygen exposures of small animals (22). The rise following the oxygen convulsion reflects the vigorous physical tonic and clonic "exercise" of the generalized convulsion (21).

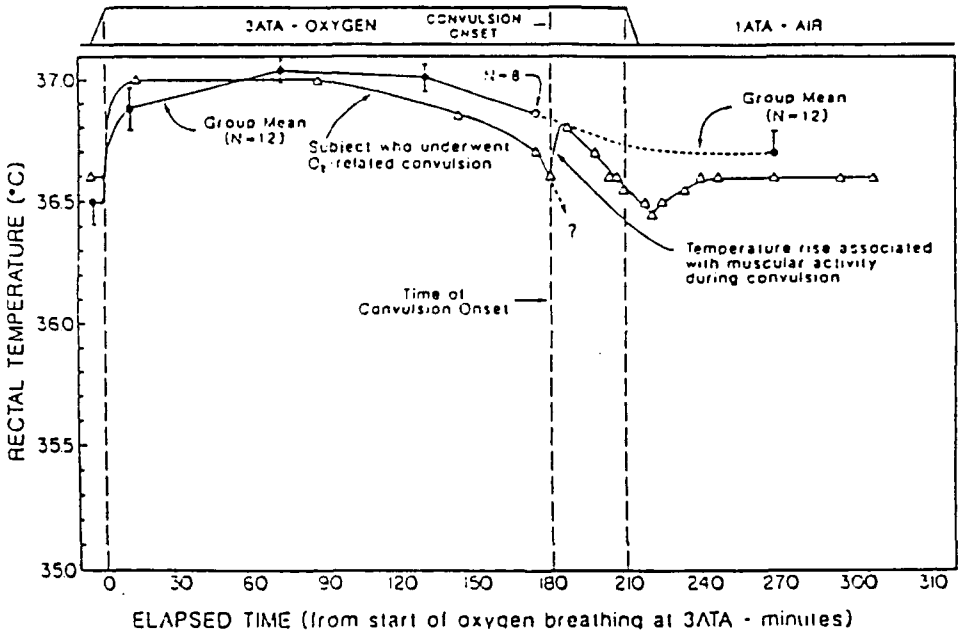


Fig. 7. Effects on body temperature of O_2 breathing at 3 ATA for 3.5 h. Comparison of 1 subject who convulsed with group of 12 subjects.

Recovery of consciousness was characteristic of previous experience in oxygen convulsions (21), with a time course equivalent to that in recovery from an episode of grand mal epilepsy. Monitoring of EEG, ECG, impedance cardiograph, and temperature were continuous during and following the convulsion. Other postoxygen exposure measurements were begun 1 h after the onset of the convulsion.

Brain Cortical Electrical Activity (ECG-EEG)

Change in brain cortical electrical activity (measured from 12 scalp electrodes placed according to International 10-20 System) was not evident in continuous clinical recordings during oxygen exposure at rest, even at 3.0 ATA for 3.5 h. Definite EEG changes were found at 3.0 ATA in only 2 subjects. One, cited above, had classical EEG manifestations of the seizure at 3.0 h of exposure, and postictal phases of a typical oxygen convulsion. No preconvulsive EEG changes were observed. The other subject had an approximately 10-s interval of flat EEG in association with a 20-s period of hypotensive loss of consciousness due to an episode of extreme bradycardia immediately after a 2.5 h exposure. Return to consciousness was accompanied by a mild clonic seizure and a 30-s interval of disorganized EEG activity, followed by resumption of normal EEG activity.

No clinically evident EEG changes were observed in any subjects during 5 to 6-h exposures at 2.5 ATA, 8 to 12-h exposures at 2.0 ATA, and 16 to 19-h exposures at 1.5 ATA. Detailed energy spectral analyses of the taped EEG records obtained at 3.0, 2.5, 2.0, and 1.5 ATA are not complete at this stage.

Somatosensory Evoked Cortical Response

No evident changes in somatosensory cortical evoked response (stimulus to median nerve at wrist) were observed in any subject at 3.0 ATA oxygen exposure. The measurement was not utilized at the lower exposure pressures.

Temperature Regulation

Deep body temperature (rectal) was continuously monitored, along with repeated measurements of carbon dioxide production, in search for toxic neural or metabolic disruptions of temperature regulation. Following an onset lag after start of hyperoxia, progressive hypothermia was found at 3.0 ATA in the single subject who experienced an oxygen convulsion (Fig. 7), in most subjects at 2.5 and 2.0 ATA, but in none of the subjects at 1.5 ATA.

Respiration and Respiratory Reactivity

Details of ventilatory changes in prolonged oxygen exposures are described in this symposium (3). This investigation of respiratory control was emphasized for its vital importance as a neurologic control system, the normal functions and reactivity of which could be quantitatively examined for evidence of toxic disruptions.

Previously described physiologic increases in ventilation, with associated decreases in end-tidal P_{CO_2} (6), were observed in all hyperbaric exposure conditions of this study. No clear indication of diminished effectiveness of respiratory control function occurred except in the subject who experienced a convulsion at the 3.0 ATA oxygen pressure. An important finding related to safety in hyperoxic exposures was that respiratory reactivity, either to carbon dioxide or to hypoxic stimuli, was not diminished in spite of observation of reduced carotid chemoreceptor response in cats following extreme oxygen

poisoning at 1 ATA (23).

Cardiovascular-Neurologic Interactions

Recognizing the dual central neurologic control of cardiac activity (vagal, sympathetic) and the importance of baroreceptor reflex regulation of blood pressure, cardiac electric activity (ECG) was monitored continuously, with periodic measurement of orthostatic reflex function. Effects on cardiovascular function were observed at all oxygen pressures investigated (4). These ranged from the previously documented bradycardia (8, 12), to a single episode of exaggerated bradycardia resulting in loss of consciousness and a gross diminution of the normal tachycardial response to standing. Details of each of these observations are provided in a companion report in this proceedings (4). Their special significance is the indication of oxygen-induced neurologic (presumably vagal) influence on cardiac rate function, with the additional possibility of oxygen effect on intrinsic cardiac electrical functions.

Pulmonary Functions

The extensive previous studies of pulmonary oxygen poisoning at 0.5 to 2.0 ATA (12, 24) were successfully expanded to include oxygen exposures at 1.5, 2.0, 2.5, and 3.0 ATA. Descriptions of measurements provided in this proceedings (2) reveal differences in rates of onset and rates of recovery at the several different levels of hyperoxic exposure, and contribute the first empirical data establishing pulmonary oxygen tolerance guidelines at oxygen pressures greater than 2.0 atm. Special significance in this component of the Predictive Study is given to the observations during oxygen exposure at 2.5 ATA of an abrupt and large decrease in vital capacity, superimposed on the progressive decrement characteristic of that induced by lower oxygen pressures. This abrupt respiratory handicap, as for the above-mentioned exaggerated bradycardia, requires consideration and investigation of a possible neurologic influence on lung structures directly poisoned by oxygen.

Neuromuscular Power

Potential neural or neuromuscular effects of prolonged hyperoxia were investigated in relation to respiratory and pulmonary functions, and to function of purposeful muscular activity. The observations indicate no serious handicap to motor, respiratory, or pulmonary functions.

Skeletal muscle force and endurance were measured by handgrip dynamometer, with maximum force and duration of maintenance of 80% of maximum forces recorded electrically. Maximum force showed less than 10% increment or decrement from preexposure control levels. Endurance changes were within 20% of controls. For both force and maintenance of force, improvement occurred in exposure to oxygen at 3.0, 1.5 ATA, and 0.2 ATA, whereas small decrement was associated with exposure to 2.0 and 2.5 ATA O_2.

Maximum Respiratory Pressures

Maximum inspiratory pressures at residual volume of functional residual capacity were not consistently decreased during and after oxygen breathing at 1.5, 2.0, 2.5, or 3.0 ATA. Maximum expiratory pressures at both total lung capacity and functional residual capacity were decreased most consistently by a mean value of about 17% near the end of the prolonged exposures at 1.5 ATA O_2. However, similar decrements also occurred during prolonged periods of air breathing at 1.0 ATA.

Auditory-Vestibular Function

Auditory-vestibular function was determined under controlled conditions (Hearing Laboratory) before oxygen exposure, and repeated about 10 h after termination of oxygen exposure. These measurements were supplemented by performance of extended high frequency audiometry during oxygen exposures (Fig. 5), along with monitoring of brainstem auditory evoked responses. No significant difference in any of the measured hearing functions was found in comparison with control exposures to 0.2 ATA O_2. The 1 subject who convulsed after 3.0 h of oxygen exposure at 3.0 ATA performed normally on a full-range, high-frequency audiometric test that was in progress at the onset of the convulsion.

Electronystagmographic responses to caloric stimulation were subnormal in many subjects after oxygen exposures at 2.5, 2.0, and 1.5 ATA. Since this measurement requires maintenance of an alert mental state and can be influenced by subject fatigue, the finding may not be specifically due to hyperoxia. Similar changes were found in some control subjects after 20-h air exposures at 1.0 ATA.

Effects on Visual Functions

The initial observation of oxygen-induced decrease in peripheral visual fields was made by Behnke et al. (12) in a subject exposed continuously to oxygen at 3.0 ATA for 3.5 h. This essentially unexplored neural effect of hyperoxia required measurements of multiple components of visual function at each of the oxygen pressures of this Predictive Study. The effects observed thus far in continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA are summarized in Table 4 and Fig. 8.

SIGNIFICANCE

In this integrated investigation of oxygen tolerance in normal men permitted detailed examination and quantitation of oxygen effects in a manner not possible without the cooperative and intelligent intercommunication between subject and investigator. The information obtained therefore is not only more detailed and extensive than could be obtained through the preliminary research in various lower animals; it is of direct and permanent relevance to the expanding importance of hyperoxygenation in diving,

Table 4
Effects of Continuous Oxygen Exposure on Visual Function in Man

Pressure	Acuity	Accommodation	Color	Pupils	VER	ERG	Fields
3.0 ATA	17 of 18 showed no change	11 of 18 had lengthened nearpoint	no change	6 of 18 had small increase in diameter	no change	3 of 10 had decrement in B-waveamplitude (16-30%)	mean decrement 50% in 18 at 3.5 h (range 8-91%) onset at 2.5-3.0 h
2.5 ATA	no change	1 of 8 had lengthened nearpoint	no change	1 of 8 had oscillating pupils	no change	1 of 8 had 39% amplitude loss during exposure (recovery by 0.7 h post). 1 other had 0.14% amplitude loss at end of exposure followed by postexposure loss of 62% (recovery by 12.3 h)	2 of 8 had decrement (35%) during exposure (recovery by 0.6 and 1 h)
2.0 ATA	no change	1 of 7 had lengthened nearpoint	no change	no change	no change	4 had a mean amplitude decrement of 50%. Recovery within 12-16 h postexposure	definite decrement in 1 subject (35%) Recovery delayed
1.5 ATA	no change	no change	no change	no change	no change	1 of 9 subjects showed amplitude decrement of 31%	no change

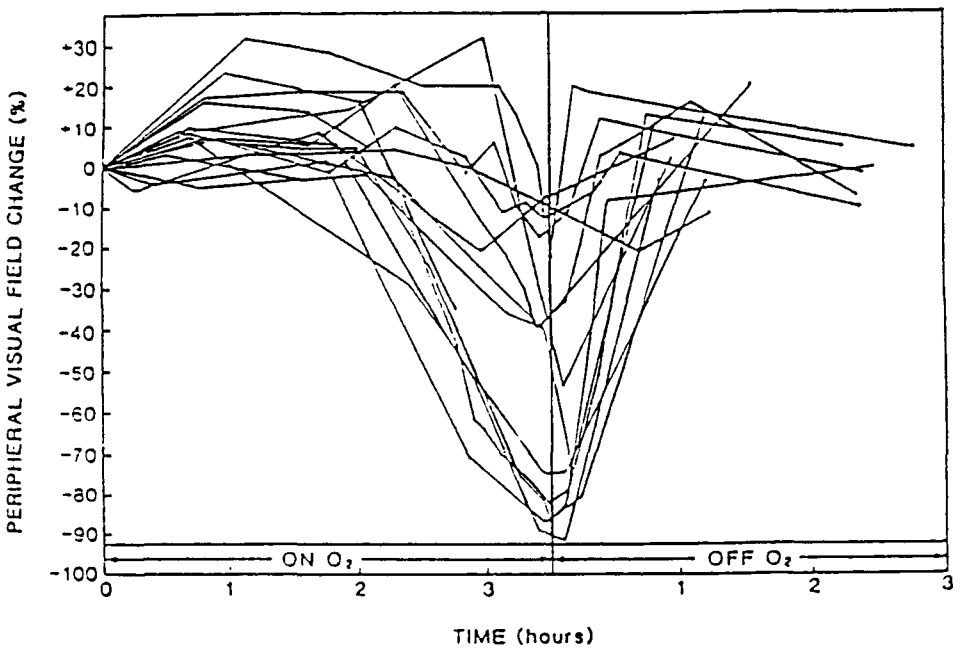


Fig. 8. Peripheral visual field changes in man during and after oxygen exposure at 3.0 ATA.

aerospace, hyperbaric, and general medicine.

Details of quantitative measurements made on multiple organ systems establish function, tissue, and chemical targets which can be most rationally and profitably investigated at each different level of oxygen pressure/duration exposure. The overall program is further intended to provide the essential baselines for both basic and applied research related to extension of oxygen tolerance by overcoming the limits posed by oxygen poisoning. This topic will remain at the forefront of research endeavor related to life, medicine, undersea activity, and ultimate aerospace operations.

The present study in resting subjects is a prerequisite to investigation of oxygen effects in active physical states, in exposures to external environmental stresses, or in attempts to modify oxygen effect by pharmacologic means. It is for the present considered that basic chemical processes of oxygen poisoning, which generated the functional changes observed in resting subjects, will also occur in situations of large practical importance in nonresting states such as underwater swimming or performance of other physical work. However, it is considered that the oxygen dose (Po_2) experienced in some tissues will be modified by carbon dioxide (11), whereas the oxygen dose in other tissue sites (e.g., lung) will not. It is also considered that functional influences of certain of these chemical changes will be modified by factors such as exercise, and other influences will not. The availability of baseline information in the resting

state provides the opportunity to investigate these considerations, and makes it possible to investigate the influences of factors modifying oxygen tolerance, including intermittent exposure and drugs.

References

1. Lambertsen CJ, Clark J, Gelfand R, et al. Predictive Studies V—Tolerance of human organs and functions to continuous hyperoxia. Undersea Biomed Res 1984; 11(Suppl 1):34.
2. Clark JM, Gelfand R, Flores ND, Lambertsen CJ, Pisarello J. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA in Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
3. Gelfand R, Clark JM, Lambertsen CJ, Pisarello J. Effects on respiratory homeostasis of prolonged continuous hyperoxia in man at 1.5 to 3.0 ATA in Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the 9th international symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
4. Pisarello JB, Clark JM, Gelfand R, Lambertsen CJ. Human circulatory responses to prolonged hyperbaric hyperoxia in Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the 9th international symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
5. Clark JM, Gelfand R, Flores ND, Pisarello JB, Lambertsen CJ. Pulmonary mechanics and gas exchange in man during and after oxygen exposure at 1.5 ATA for 16 to 19 h. Am Rev Respir Dis 1986; 133:A31.
6. Lambertsen CJ. Effects of hyperoxia on organs and their tissues. In: Robin ED, ed. Extrapulmonary manifestations of respiratory disease. New York: Marcel Dekker, 1978:239-303.
7. Yarbrough OD, Welham W, Brinton ES, Behnke AR. Symptoms of oxygen poisoning and limits of tolerance at rest and at work. U.S. Naval Experimental Diving Unit, Project X-337 (Sub. No. 62, Rep 1). Washington, DC, 1947.
8. Donald KW. Oxygen poisoning in man. Br Med J 1947; 1:667-672, 712-717.
9. Cohn R, Gersh I. Changes in brain potentials during convulsions induced by oxygen under pressure. J Neurophysiol 1945; 8:155-160.
10. Lambertsen CJ, Kough RH, Cooper DY, Emmel GL, Loeschcke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 1953; 5:471-486.
11. Lambertsen CJ, Ewing JH, Kough RH, Gould R, Stroud MW III. Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. J Appl Physiol 1955; 8:255-263.
12. Behnke AR, Forbes HS, Motley EP. Circulatory and visual effects of oxygen at 3 atmospheres pressure. Am J Physiol 1936; 114:436-442.

13. Whalen RE, Saltzman HA, Holloway DH Jr, McIntosh HD, Dieker HO, Brown IW Jr. Cardiovascular and blood gas responses to hyperbaric oxygenation. Am J Cardiol 1965; 15:638-646.
14. Egger GWN Jr, Paley HW, Leonard JJ, Warren JV. Hemodynamic responses to oxygen breathing in man. J Appl Physiol 1962; 17:75-79.
15. Clark JM, Lambertsen CJ. *Pulmonary oxygen tolerance and the rate of development of* pulmonary oxygen toxicity in man at 2 atmospheres inspired P_{O2}. In: Lambertsen CJ, ed. Underwater physiology. Proceedings of the third symposium on underwater physiology. Baltimore; Williams & Wilkins, 1967:439-451.
16. Clark JM, Lambertsen CJ. Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 ATA. J Appl Physiol 1971; 30:739-752.
17. Peterson RE. Tracking of cumulative oxygen toxicity dose in diving, decompression and therapy. In: Lambertsen CJ, ed. Decompression sickness and its therapy. Allentown, PA: Air Products & Chemicals, 1979:125-141.
18. Bardin H, Lambertsen CJ. A quantitative method for calculating pulmonary oxygen toxicity. Use of the "Unit Pulmonary Toxicity Dose" (UPTD). Institute for Environmental Medicine Report. Philadelphia: University of Pennsylvania, 1970.
19. Lambertsen CJ, Gelfand R, Peterson RE, et al. Human tolerance to He, Ne and N_2 at respiratory gas densities equivalent to He-O_2 breathing at depths to 1200, 2000, 3000, 4000 and 5000 feet of sea water. Aviat Space Environ Med 1977; 48:843-855.
20. Lambertsen CJ, Gelfand R, Clark JM, eds. Predictive Studies IV. Work capability and physiological effects in He-O_2 excursions to pressures of 400-800-1200 and 1600 feet of sea water. Institute for Environmental Medicine Report 78-1. Philadelphia: University of Pennsylvania, 1978.
21. Lambertsen CJ. Effects of oxygen at high partial pressure. In: Fenn WO, Rahn H, eds. Handbook of physiology. Sec. 3, Respiration, vol. 2. Washington, DC: American Physiological Society, 1965:1027-1046.
22. Puglia CD, Glauser EM, Glauser SC. Core temperature response of rats during exposure to oxygen at high pressure. J Appl Physiol 1974; 36:149-153.
23. Lahiri S, Mokashi A, Mulligan E, Andronikou S. Loss of carotid chemoreflex function in oxygen toxicity. Fed Proc 1985; 44:1000.
24. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. Pharmacol Rev 1971; 23:37-132.

Acknowledgment

Supported in part by NMRDC contract N00014-81-C-0826, NASA contract NAS9-17238, and the State of Pennsylvania through the Benjamin Franklin Partnership.

9th International Symposium on Underwater and Hyperbaric Physiology
Undersea and Hyperbaric Medical Society, Bethesda, MD, 1987

PULMONARY TOLERANCE IN MAN TO CONTINUOUS OXYGEN EXPOSURE AT 3.0, 2.5, 2.0, AND 1.5 ATA IN PREDICTIVE STUDIES V

J. M. Clark, R. Gelfand, N. D. Flores, C. J. Lambertsen, and J. B. Pisarello

This summary report is part of a comprehensive study of specific organ oxygen tolerance (Predictive Studies V). Oxygen effects on pulmonary function were measured in normal, resting men who breathed oxygen continuously at 3.0, 2.5, 2.0, and 1.5 ATA to predefined limits of CNS, cardiac, or pulmonary tolerance (1-3). Pulmonary-related measurements obtained before and after exposure included arterial blood gases while breathing air at rest and during exercise; carbon monoxide diffusing capacity; spirometry; flow-volume loops on air and helium-oxygen; nitrogen closing volumes; airway resistance; and lung compliance. Arterial blood gases on oxygen and maximum respiratory pressures were measured early and late in the oxygen exposure period, whereas flow-volume maneuvers and spirometry were repeated at regular intervals during oxygen exposures. Comparisons of data obtained over the range of oxygen pressures will be emphasized in this presentation. Parameters selected for comparison include lung volumes and flow rates, lung compliance, and CO diffusing capacity.

In preparation for this series of experiments, it was anticipated that oxygen tolerance would be limited by neurologic effects of oxygen toxicity at 3.0 ATA and by pulmonary effects at 2.0 and 1.5 ATA, with oxygen exposure at 2.5 ATA in a transitional zone between neurologic and pulmonary limitations (1, 4, 5). Based on all the information that was available at the outset of this study, maximum exposure durations were established for each oxygen pressure and, as part of a comprehensive system to ensure safety of the subjects, criteria were established for exposure termination before the predetermined limits. The selected limits of continuous exposure duration were 3.5 h at 3.0 ATA, 6 h at 2.5 ATA, 12 h at 2.0 ATA, and 20 h at 1.5 ATA.

Our previously derived pulmonary oxygen tolerance curves (4, 5) were used to predict degrees of pulmonary effect for the maximal durations of exposure at each pressure (Fig. 1). The curves indicated that continuous oxygen exposures of 12 h at 2.0 ATA and 20 h at 1.5 ATA would both produce average vital capacity (VC) decrements of 15 to 20% and would therefore be limited by pulmonary effects of oxygen toxicity. On the other hand, it did not seem likely that pulmonary intoxication would be limiting at 3.0 and 2.5 ATA, where predicted VC decrements for maximal exposure durations were about 4 and 8%, respectively.

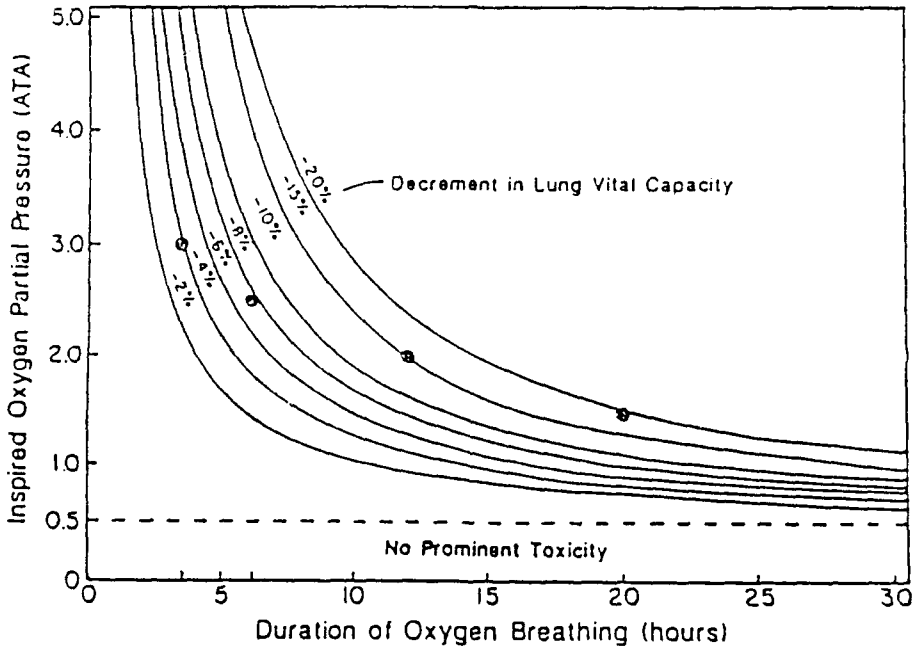


Fig. 1. Predicted pulmonary oxygen tolerance in man. Points indicate predicted changes in VC for maximum exposure durations at 3.0, 2.5, 2.0, and 1.5 ATA.

Progression of Subjective Pulmonary Symptoms During Oxygen Exposure at 3.0, 2.5, 2.0, and 1.5 ATA

At regular intervals during oxygen exposure, each subject was given a list of symptoms that are known to be caused by pulmonary or neurologic oxygen toxicity (4). The symptoms were rated as absent (0), mild (1+), moderate (2+), or severe (3+), and average ratings for the entire subject group were calculated. An overall "pulmonary symptom" rating was derived by combining average ratings for chest pain, cough, chest tightness, and shortness of breath. Pulmonary symptom ratings were then plotted against duration of exposure for each oxygen pressure (Fig. 2). Pulmonary symptoms were moderate (2+) on the

average by the end of oxygen exposure at 1.5 and 2.0 ATA, and mild (1+) before exposure termination at 2.5 and 3.0 ATA. Rates of symptom development increased progressively, as expected, with increase in oxygen pressure. However, the increment in the rate of symptom progression for the transition from 1.5 to 2.0 ATA was much greater than that observed for comparable transitions to 2.5 and 3.0 ATA. It is possible that longer oxygen exposures at 2.5 and 3.0 ATA, beyond the tolerance limits found at these pressures, would be associated with a wider separation of pulmonary symptom curves than that observed for mild symptoms.

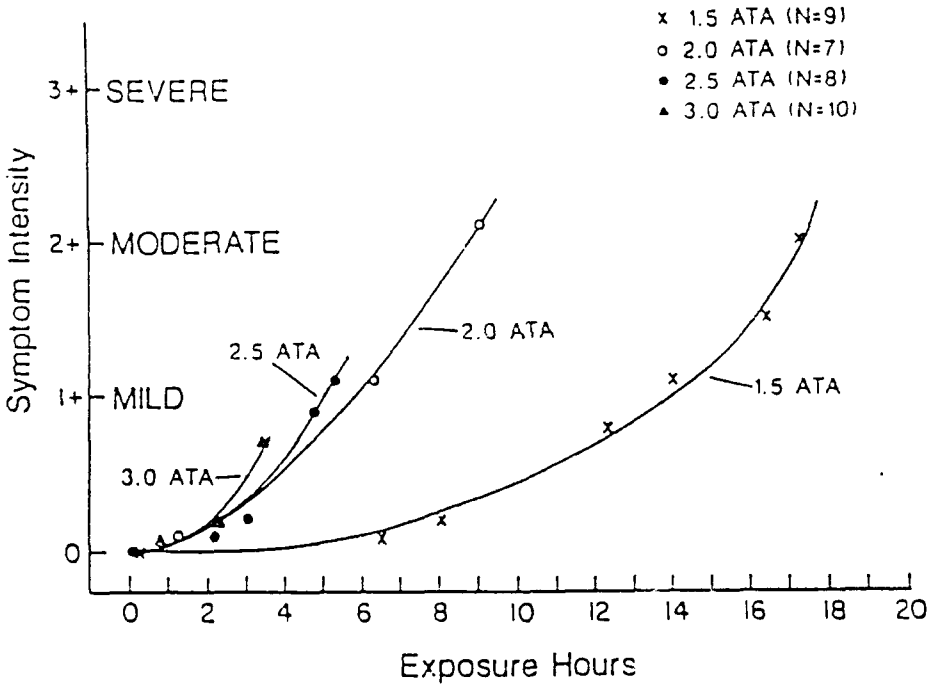


Fig. 2. Pulmonary symptoms during oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA. The overall pulmonary symptom curve for each oxygen pressure combines average ratings for chest pain, cough, chest tightness, and shortness of breath.

Rates of Development of Pulmonary Intoxication During Oxygen Exposure at 3.0, 2.5, 2.0, and 1.5 ATA

In parallel with periodic assessment of symptoms, rates of development of pulmonary intoxication during oxygen exposure at 2.5, 2.0, and 1.5 ATA were monitored by repeated performance of flow-volume maneuvers and spirometry. Pulmonary function was evaluated objectively only before and after the 3.5 h exposures at 3.0 ATA. Of the many lung volumes and flow rates that were measured, VC was selected for comparison across different pressures, because

it decreased consistently and significantly at each of the oxygen pressures that were studied (Fig. 3). Data shown for the 1.5 and 2.5 ATA exposures represent average measurements in 9 and 8 subjects, respectively. The 2.0 ATA curve describes average data obtained previously in 11 subjects (6) and more recently in 7 additional subjects. All 3 curves were derived by fitting regression lines to the data for each pressure on probability-linear coordinates and then translating the lines to linear—linear coordinates. The single point for 3.0 ATA is an average of measurements obtained in 13 subjects about 2 to 4 h postexposure.

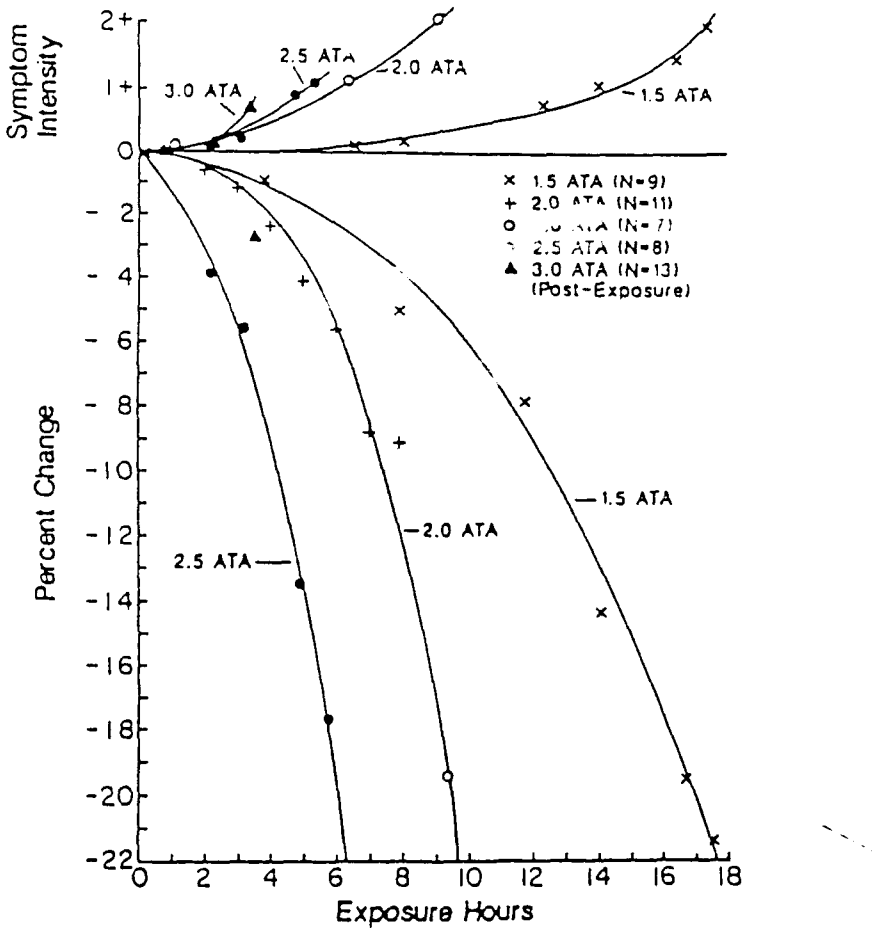


Fig. 3. Pulmonary symptoms and VC changes in man during oxygen exposure at 3.0, 2.5, and 2.0, and 1.5 ATA. Vital capacity measurements during the oxygen exposures at 1.5 and 2.5 ATA were obtained in the present series of experiments. The 2.0 ATA data represent 2 groups of subjects. The last exposure point (0) is the average value for 7 subjects in the present series of experiments. All other points at 2.0 ATA are average data from an earlier group of 11 subjects (6).

The curves for 1.5, 2.0, and 2.5 ATA all show a progressive fall in VC with continued duration of exposure, and the rates of fall are greater at higher oxygen pressures. Location of the 3.0 ATA point between the 2.0 and 2.5 ATA curves is not inconsistent, because these measurements were obtained after 2 to 4 h of recovery from the previous exposure. At the outset of this study, the rapid rate of vital capacity recovery after exposure to oxygen pressures above 2.0 ATA was not expected. Rates of recovery from similar vital capacity decrements at different oxygen pressures are compared below.

Figure 3 also compares rates of decrease in VC at 2.5, 2.0, and 1.5 ATA with progression of pulmonary symptoms at the same pressures. The data show that prominent decrements in VC were concurrent with mild symptoms and are therefore consistent with the conclusion that pulmonary symptoms did not contribute significantly to the observed changes in lung volumes and flow rates. This confirms the overall impression of investigators who remained inside the chamber that the subjects were highly motivated and delivered maximal effort even when symptoms were prominent.

Abrupt Exacerbation of Pulmonary Effects at 2.5 ATA

The 8 subjects who breathed oxygen at 2.5 ATA for an average duration of 5.7 h had a VC decrement of nearly 18%. This observed change was more than twice the prediction of about 8% from our previously derived pulmonary oxygen tolerance curves (Fig. 1). However, if the data for 2 subjects who had very large changes in lung volumes and flow rates are excluded from the group, the average decrease in vital capacity at the end of oxygen exposure for the remaining 6 subjects is 9.3%, which agrees well with the predicted change of 8%.

Percent changes in VC and maximal mid-expiratory flow rate (FEF_{25-75}) during oxygen exposure at 2.5 ATA and during the early recovery period at 1.0 ATA for 1 of the 2 subjects with large changes are shown on Fig. 4. Both parameters decreased during the early exposure period, reversed partially, and then decreased prominently near the end of a 5.1 h exposure. Percent changes in VC and FEF_{25-75} at the end of oxygen exposure were 44 and 67%, respectively. During the first 1.5 h of recovery at 1.0 ATA, VC remained at about the same level, but FEF_{25-75} fell further to a decrement of 87 to 88%. Vital capacity recovered to a level 22% below the preexposure control value at 2 h of recovery and was decreased by only 5% at 5 h postexposure. Mid-expiratory flow rate increased only slightly at 2 h and then rose sharply to within 2% of the control value by 5 h of recovery. During the period of maximal pulmonary function impairment at 1 to 2 h of recovery, the subject had no chest pain and only mild cough and dyspnea. He was not wheezing and felt that he could inspire fully, but rapid expiration was very difficult for him.

The observed rapid rates of development and reversal of oxygen effects in this subject are more commonly associated with neurologic rather than pulmonary effects of oxygen toxicity and are consistent with an interaction of

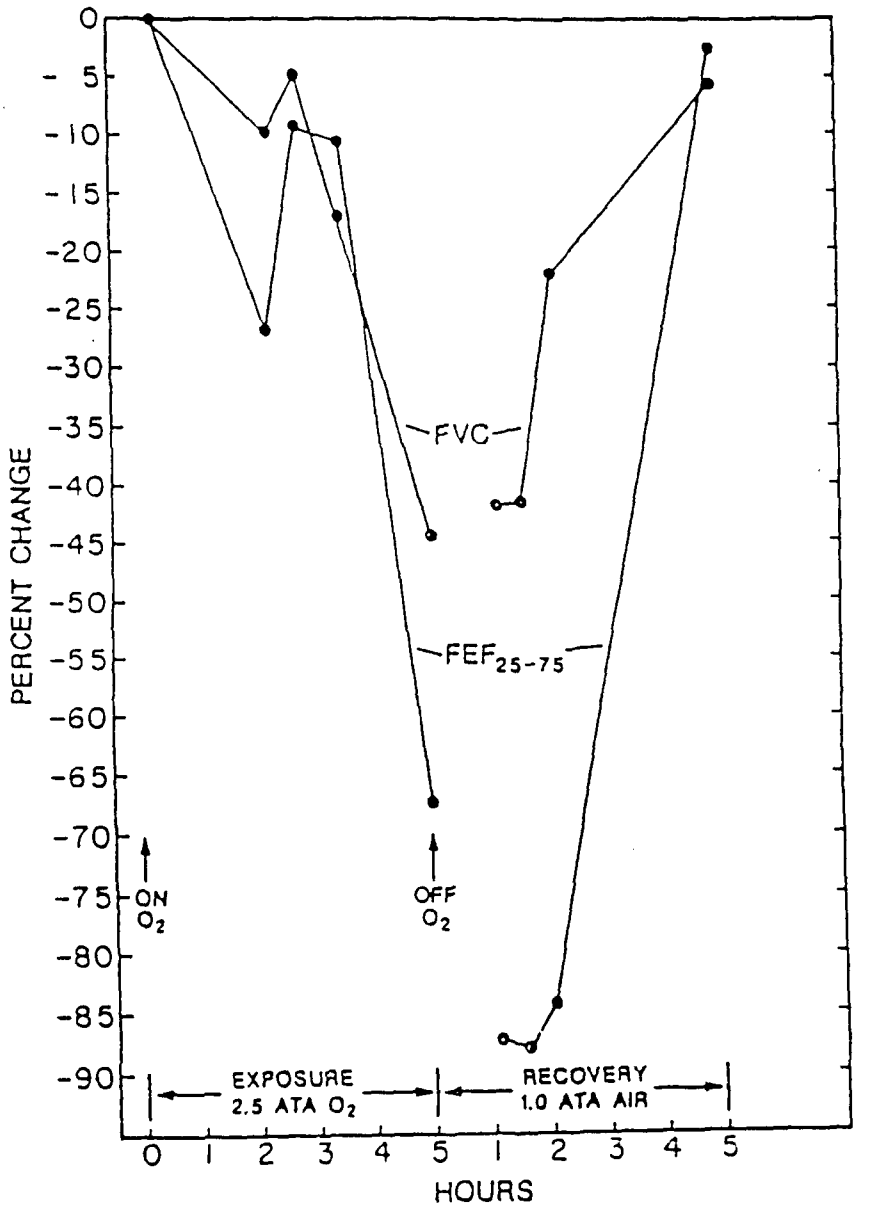


Fig. 4. Changes in VC and maximal FEF_{25-75} in 1 man during and after oxygen exposure at 2.5 ATA. Values obtained during a 5.1 h exposure and the first 5 h of recovery are shown. Control measurements at 2.5 ATA were obtained during early oxygen exposure. Preexposure control measurements at 1.0 ATA were used for the postexposure data.

toxic effects on the CNS and lungs (4, 7). Such an interaction could explain the observation that 2 of 8 subjects at 2.5 ATA developed pulmonary effects of oxygen toxicity much more rapidly than predicted from pulmonary tolerance curves derived from measurements at oxygen pressures of 2.0 ATA or less.

Patterns of Oxygen Effects on Lung Volumes and Flow Rates at Different Oxygen Pressures

Comparison of relative changes in selected lung volumes and flow rates after oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA revealed that the changes observed after exposure at 3.0 and 2.5 ATA had a different pattern than those found after exposure at 2.0 and 1.5 ATA (Fig. 5). The measurements selected for comparison are the forced vital capacity (FVC), 1-s forced expired volume ($FEV_{1.0}$), FEF_{25-75}, and peak expiratory flow rate (PEFR). Although the changes observed after exposure at 3.0 ATA are generally the smallest in magnitude, their interrelationships are most consistent with an increase in small, peripheral airway resistance as a cause of the associated restriction in expiratory flow rates (8, 9). Large airway resistance, as measured in a body plethysmograph (10), was not significantly altered after any of the oxygen exposures.

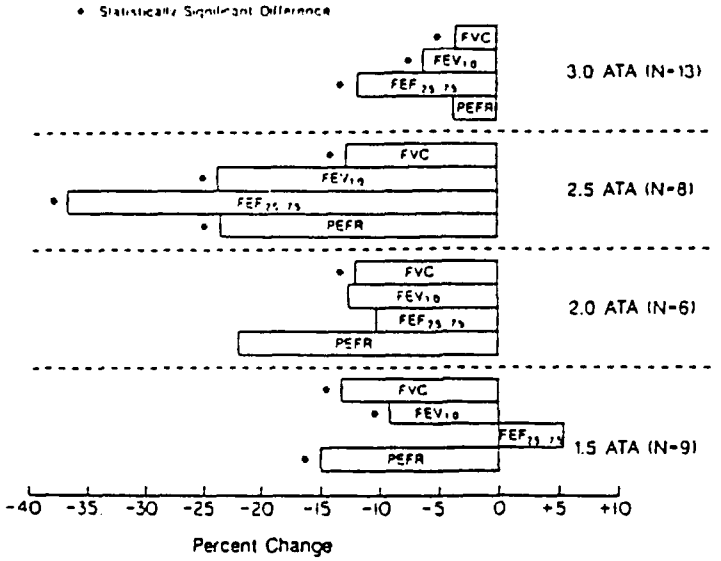


Fig. 5. Patterns of effects on lung volumes and flow rates after oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA. Average changes in selected lung volumes and flow rates measured at comparable postexposure intervals after oxygen exposures at 3.0, 2.5, 2.0, and 1.5 ATA are shown. Changes in the same parameters measured near the end of oxygen exposure at 2.5, 2.0, and 1.5 ATA were larger, but the smaller postexposure values were used for comparison with the data for 3.0 ATA, where pulmonary function was not evaluated during exposure to allow more time for measurements of neurologic functions.

After exposure at 3.0 ATA, PEFR known to be highly effort dependent (11), was not significantly changed, whereas FVC had a statistically significant but quantitatively small reduction. The largest change was in the FEF_{25-75}, which is effort independent (11). In addition, the $FEV_{1.0}$ was reduced more than FVC. A similar pattern of effects was found after oxygen exposure at 2.5 ATA except that all changes were larger and PEFR was also significantly reduced.

It is of interest that FEF_{25-75} were not significantly reduced either during or after oxygen exposure at 2.0 and 1.5 ATA, despite the fact that these exposures caused the most prominent pulmonary symptoms and VC decrements. The observed patterns of effects are consistent with the interpretation that small airway function is impaired more selectively by oxygen exposure at 3.0 and 2.5 ATA than at 2.0 and 1.5 ATA.

Recovery of VC After Oxygen Exposure at 2.5, 2.0, and 1.5 ATA

Vital capacity was measured repeatedly at 1.0 ATA after oxygen exposure at 2.5, 2.0, and 1.5 ATA to determine rates of recovery (Fig. 6). The most rapid recovery occurred after exposure at 2.5 ATA, where an average VC decrement of 4.4% at 2.2 h postexposure was not statistically significant. Recovery of VC after exposure at 1.5 ATA was also relatively rapid. The average value was still significantly reduced by 7.4% at 13 h postexposure, but was slightly above the preexposure control at 24 h. Despite the similarity of pulmonary symptoms and VC changes at the termination of oxygen exposures at 2.0 and 1.5 ATA (Fig. 3), recovery was slower after the 2.0 ATA exposure. An average decrement of 6.6% at 24 h postexposure was statistically significant, but a 3.6% reduction at 48 h was not.

Performance of bronchoalveolar lavage at about 9 h after both the 2.0 and 1.5 ATA exposures provided additional evidence of different recovery states. This procedure is known to cause transient reductions in lung volumes and flow rates (12). The 2.0 ATA subjects had a reversal of recovery, as indicated by pre- and postlavage VC values of -12.9 and -20.3%, respectively, whereas the 1.5 ATA subjects continued to recover with pre- and postlavage changes of -12.7 and -7.4%, respectively.

Effects on Lung Compliance

Dynamic and static lung compliance were measured in a body plethysmograph with an intraesophageal balloon (13) before and after oxygen exposure at 2.5, 2.0, and 1.5 ATA. Dynamic lung compliance at breathing rates of 15, 30, and 60 was not reduced after oxygen exposure at any pressure.

Static lung compliance was not altered after oxygen exposure at 2.5 ATA, but it was significantly reduced after the 2.0 and 1.5 ATA exposures (Fig. 7). Again, exposure at 2.0 ATA for an average time of 9.7 h produced greater changes than exposure at 1.5 ATA for 17.6 h. Both overall lung compliance and specific lung compliance (compliance per liter of lung volume) were significantly reduced by 30.8 and 36.8%, respectively, after exposure at 2.0 ATA.

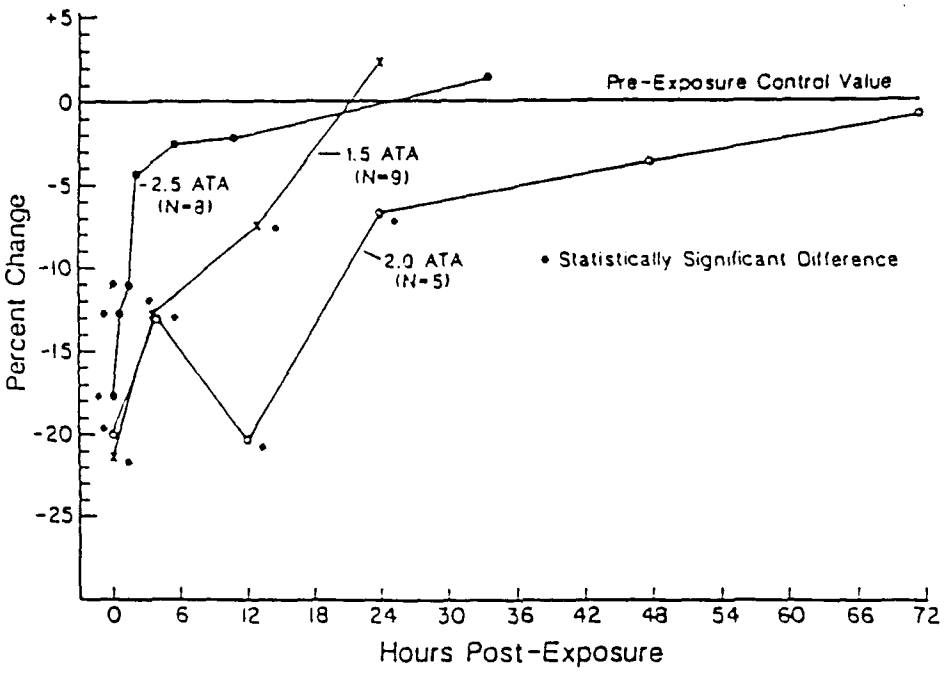


Fig. 6. Recovery of VC after oxygen exposure at 2.5, 2.0, and 1.5 ATA. Average percent changes in VC relative to preexposure control values are shown, and statistically significant differences are indicated. Recovery from pulmonary oxygen poisoning was followed more closely in these subjects than in any previous group.

Following the 1.5 ATA exposure, only the 25.7% reduction in specific lung compliance was statistically significant.

Effects on Pulmonary Diffusing Capacity for Carbon Monoxide

Average values of pulmonary diffusing capacity for carbon monoxide, measured by the single breath method (14), were significantly reduced after oxygen exposure at 2.5, 2.0, and 1.5 ATA, but not after the 3.0 ATA exposure (Fig. 8). The 3.0 ATA data indicate that oxygen effects on pulmonary gas exchange occur later than effects on lung volumes and flow rates during the progression of pulmonary intoxication at that pressure (15). Average carbon monoxide diffusing capacity after oxygen exposure at 1.5 ATA was significantly reduced only at 13 h postexposure, but after exposure at 2.0 and 2.5 ATA, average decrements, though small, were statistically significant for at least 8 to 9 d. The magnitude of change after exposure at 2.0 ATA exceeded that after exposure at either 1.5 or 2.5 ATA.

Because average values measured at 8 to 18 d postexposure had not fully returned to preexposure control levels, extended follow-up measurements were obtained from 2 wk to 5 mo. after oxygen exposure. Average values for the

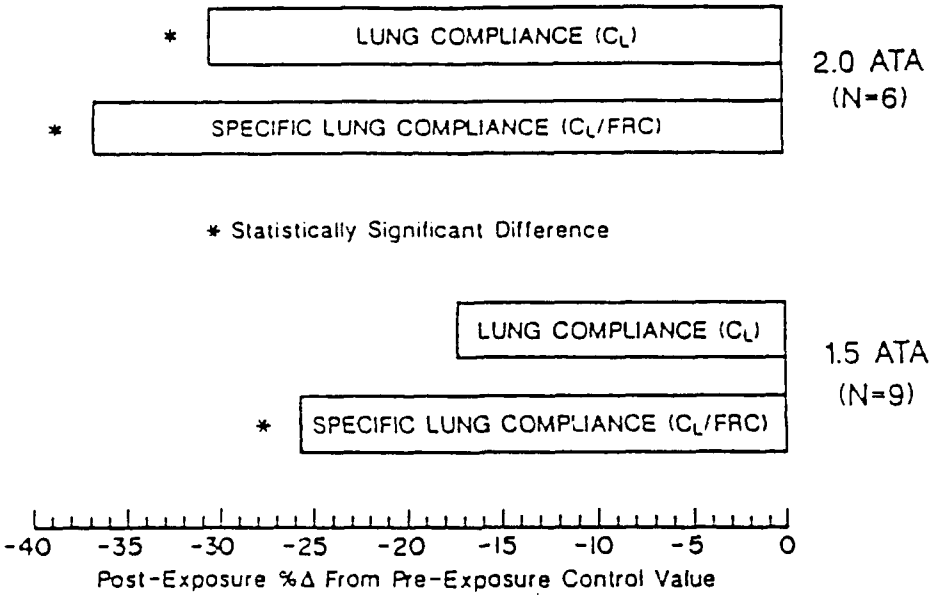


Fig. 7. Effects of oxygen exposure at 2.0 and 1.5 ATA on lung compliance. Static lung compliance was calculated from a plot of lung volume against intrathoracic pressure during slow, controlled inspiration. Measurements were obtained about 4 h postexposure in both series of experiments. Follow-up measurements at 3 to 5 wk postexposure were normal in all subjects.

subject groups exposed at 1.5 and 2.5 ATA had fully returned to the preexposure control level, whereas the diffusing capacity for the 2.0 ATA group was reduced by only 0.6 $ml \cdot min^{-1} \cdot mmHg^{-1}$ or less than 2% of the control value. Four of the 7 subjects in this group were not available for long-term follow-up, and it was necessary to use values obtained earlier in the postexposure period. Pulmonary diffusing capacity for carbon monoxide may prove to be a sensitive index of complete recovery from pulmonary oxygen poisoning.

SUMMARY AND CONCLUSIONS

Rates of pulmonary symptom intensification and decrease in VC are progressively increased with elevation of inspired oxygen pressure. Although VC decrements occur concurrently with symptoms, the lung volume changes become prominent when symptoms are still mild. In contrast to the progressive fall in VC with increasing pulmonary intoxication at each oxygen pressure that was studied, patterns of associated changes in other lung volumes and flow rates are not the same at each oxygen pressure. The observed patterns of effects are consistent with the interpretation that small airway function is impaired more selectively by oxygen exposure at 3.0 and 2.5 ATA than by exposure at 2.0 and 1.5 ATA.

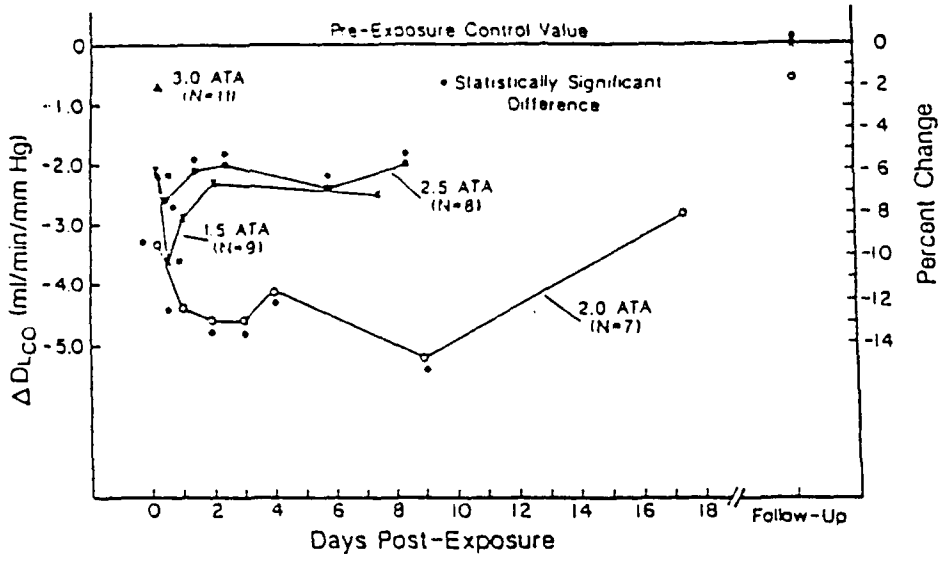


Fig. 8. Lung carbon monoxide diffusing capacity in man after oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA. Average changes in carbon monoxide diffusing capacity relative to preexposure control values are shown, and statistically significant differences are indicated. Subsequent measurements of diffusing capacity in all subjects who were available for follow-up equaled or exceeded the preexposure control value.

Magnitude of decrement in vital capacity does not always reflect overall degree of pulmonary intoxication or subsequent rate of recovery. Despite similar VC changes after oxygen exposure at 2.0 ATA for nearly 10 h and exposure at 1.5 ATA for almost 18 h, the 2.0 ATA exposure caused greater impairment of pulmonary function and required a longer recovery period. Conversely, the rapid occurrence of large decrements in VC during oxygen exposure at 2.5 ATA was followed by an equally rapid rate of recovery after exposure termination. Rapid onset and reversal of oxygen effects on the lung at high pressures are consistent with interaction of neurologic and pulmonary effects of oxygen toxicity.

No single measure of pulmonary function is ideally satisfactory for monitoring rate of pulmonary intoxication during oxygen exposure or for tracking rate of recovery after exposure termination. In the absence of a single measure that accurately monitors progression and reversal of pulmonary oxygen poisoning, one possible approach involves the development of a composite index of pulmonary intoxication that incorporates multiple measures of pulmonary function. A second approach that can be used in lieu of or along with the first involves selective applications of one or more toxicity indices to specific conditions of exposure or recovery. An important objective in the continuing analysis of pulmonary data obtained during and after continuous

oxygen exposures at 1.5 to 3.0 ATA consists of testing the accuracy and precision of such methods for defining pulmonary oxygen tolerance in man.

References

1. Lambertsen CJ, Clark JM, Gelfand R, et al. Definition of tolerance to continuous hyperoxia in man. An abstract report of predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ, eds. Undersea and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
2. Gelfand R, Clark JM, Lambertsen CJ, Pisarello JB. Effects on respiratory homeostasis of prolonged continuous hyperoxia at 1.5 to 3.0 ATA in man in predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ,eds. Undersea and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
3. Pisarello JB, Clark JM, Lambertsen CJ, Gelfand R. Human circulatory responses to prolonged hyperbaric hyperoxia in predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ, eds. Undersea and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
4. Clark JM. Oxygen toxicity. In: Bennett PB, Elliott DH, eds. The physiology and medicine of diving and compressed air work, 3rd ed. London: Ballière-Tindall, 1983:200-238.
5. Lambertsen CJ. Effects of hyperoxia on organs and their tissues. In: Robin ED, ed. Extrapulmonary manifestations of respiratory disease, vol. 8. In: Lenfant C, ed. Lung biology in health and disease. New York: Marcel Dekker, 1978:239-303.
6. Clark JM, Lambertsen CJ. Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 atm abs. J Appl Physiol 1971; 30:739-752.
7. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. Pharmacol Rev 1971; 23:37-133.
8. Mcfadden ER, Keker R, Holmes B, deGratt WJ. Small airway disease: an assessment of the tests of peripheral airway function. Am J Med 1974; 57:171-181.
9. Mcfadden ER, Linden DA. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. Am J Med 1972; 52:725-737.
10. Dubois AB, Botelho SY, Comroe JH. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. J Clin Invest 1956: 35:327-335.
11. Metzger LF, Altose MD, Fishman AP. Evaluation of pulmonary performance. In: Fishman AP, ed. Pulmonary diseases and disorders. New York: McGraw Hill, 1980:1751-1777.
12. Tilles DS, Goldenheim PD, Hales CA. Bronchoalveolar lavage causes deterioration in lung function. Am Rev Resp Dis 1984; 129:A67.
13. Mead J, Whittenberger JL. Physical properties of human lungs measured during spontaneous respiration. J Appl Physiol 1953; 5:779-796.

14. Ogilvie CM, Forster RE, Blakemore WS, Morton TW. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J Clin Invest 1957; 36:1-17.

15. Clark JM, Lambertsen CJ, Pisarello JB, Jackson RM, Gelfand R. Cardiopulmonary effects of continuous O_2 exposure at 3.0 ATA for 3.5 hours in man. Undersea Biomed Res 1984; (1)Suppl:29.

Acknowledgment

Supported in part by NMRDC contract N00014-81-C-0826, NASA contract NAS9-17238, and the State of Pennsylvania through the Benjamin Franklin Partnership.

9th International Symposium on Underwater and Hyperbaric Physiology
Undersea and Hyperbaric Medical Society, Bethesda, MD, 1987

EFFECTS ON RESPIRATORY HOMEOSTASIS OF PROLONGED, CONTINUOUS HYPEROXIA AT 1.5 TO 3.0 ATA IN MAN IN PREDICTIVE STUDIES V

R. Gelfand, J. M. Clark, C. J. Lambertsen, and J. B. Pisarello

Acute hyperoxia at 1.0 to 3.0 ATA produces well-known effects on respiratory homeostasis and on the respiratory response to CO_2 (1) which are rapid in onset following administration of oxygen. These effects are mediated by a direct action of hyperoxia on peripheral respiratory chemoreceptors, and by an indirect action of hyperoxia on CNS acid-base balance. During spontaneous breathing of 100% oxygen, even at 1 ATA, electrical activity of the carotid body is diminished (2). Central venous P_{CO_2} rises due to reduction in the CO_2 buffering capacity of hemoglobin (1). The result of these two opposing actions on respiratory drive (decrement due to reduced peripheral input to the CNS; increment due to elevated P_{CO_2} in the CNS) is a net increase in ventilation and reciprocal decrease in arterial CO_2 tension (1). Furthermore, suppressed electrical activity of the peripheral chemoreceptors in hyperoxia contributes to a reduction in slope of the ventilatory response to CO_2 (respiratory CO_2 reactivity) (3). These "physiologic" effects of hyperoxia are considered modifications of otherwise intact physiologic processes, not the result of its "toxic" effects (1).

The several phases of Predictive Studies V (4) have involved prolonged exposures of men to continuous hyperoxia at 3.0, 2.5, 2.0, and 1.5 ATA for definition of CNS oxygen tolerance and for investigation of effects of prolonged hyperoxia on CNS and other organ functions (4-6). Its design provided an opportunity to search for toxic effects of supranormal oxygen pressures that might develop in respiratory functions only during extended exposures. Before these investigations there was virtually no information concerning such effects of prolonged toxic exposures to hyperoxia on respiratory functions in man. There is little current information even in animals (7, 8).

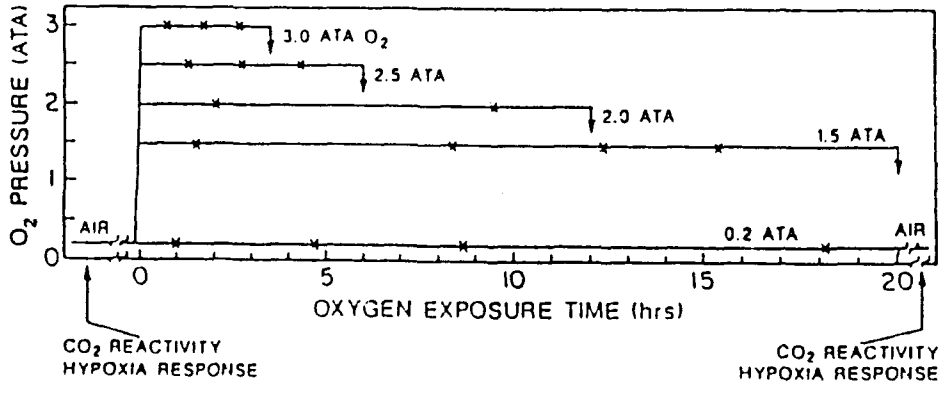
Ventilation and related parameters were measured in this program for several purposes. They were to: a) monitor the subject's respiratory status for safety, b) investigate potential changes in these parameters as possible indicators of hyperoxic effects on the integrated neural and neurochemical mechanisms of respiratory control, c) investigate changes in these parameters as potential indicators of hyperoxic effects on neuromechanical functions of the airways, lungs, and respiratory muscles, and d) investigate changes in ventilatory responses to hypercapnia and to hypoxia as potential indicators of hyperoxic effects on chemoreception of CO_2 and O_2.

Since changes in body temperature can alter ventilation (9), and hyperoxia has been associated with decrease in body temperature of rats (10), rectal temperature was monitored in all phases of Predictive Studies V, both as a potential indicator of CNS O_2 toxicity and for its potential effects as a modifier of O_2-related ventilatory change.

PROCEDURES AND METHODS

Oxygen Pressure-Time Exposures

The Predictive Studies V Program includes continuous hyperoxic exposures at pressures of 1.5, 2.0, 2.5, and 3.0 ATA, with normoxic controls at 1.0 ATA (Fig. 1). This summary report does not include information obtained at 2.0 ATA because that series is at present incomplete. Respiratory reactivity to CO_2 and hypoxic ventilatory response were measured at 1.0 ATA both before and after the exposures to hyperoxia at 1.5 and 2.5 ATA.



Respiratory-metabolic measurements during quiet period of EEG recording:

Ventilation	End-tidal PCO_2
Tidal volume	Rate of CO_2 elimination
Frequency	

Fig. 1. Pressure-time "profiles" for Predictive Studies V investigations at 3.0, 2.5, 2.0, 1.5, and 0.2 ATA oxygen pressure. Symbols (X) indicate approximate times at which ventilatory measurements were made during quiet periods of EEG recording.

Procedures for Measurement of Ventilatory Parameters During Hyperoxic Exposures

Inspired respiratory flow, end-tidal P_{CO_2}, body temperature, and inspired oxygen concentration were monitored continuously. Expired gas was accumulated in a bag over a 3-min collection period for measurement of volume and analysis of gas composition. These collection periods were scheduled during predetermined "quiet" intervals when the subject was at rest for recording the EEG. These intervals were a component part of integrated "measurement modules," during which sequences of measurements were made related to a variety of physiologic systems in these investigations of specific organ oxygen tolerance (4). The pressure-time profiles indicating times at which resting ventilatory parameters were measured at each exposure pressure are shown in Fig. 1.

Apparatus for Measurement of Resting Ventilatory Parameters During Hyperoxic Exposures

Inspiratory flow for each breath was measured by pneumotachograph, recorded onto a magnetic tape recorder, and displayed on an oscilloscope for visual monitoring of flow pattern. Expired gas was collected into a meteorological balloon which was emptied promptly through the chamber hull to a dry gasometer for measurement of collected volume. A portion of this gas was bypassed through electronic gas analyzers to determine mixed expired CO_2 and O_2 concentrations. A sample of expired gas from each expiration was diverted from the space just distal to the expiratory check valve of the subject's lightweight oronasal mask (approx. 100 cc dead space) through the chamber hull to a rapid response CO_2 analyzer for measurement of end-tidal P_{CO_2}. The end-tidal values were recorded for all breaths as the peaks of the end-expiratory "washout" curves. Mean values of end-tidal P_{CO_2} for each expired-gas collection period were obtained from the largest peak values, corresponding to the largest tidal volumes in the period. This procedure minimized the effect of mask dead space and provided close agreement between end-tidal and arterial P_{CO_2} values. A sample of gas was taken from a fitting on the mask to a rapid response oxygen analyzer outside the chamber for measurement of inspired O_2 level. Any leak which might dilute the oxygen within the mask could thereby be detected rapidly. Chamber ambient and subject rectal temperatures were monitored with thermistor sensors.

Procedures and Apparatus for Pre- and Postexposure Measurement of Ventilatory Responses to Hypercapnia and to Hypoxia at 1.0 ATA

Preexposure ventilatory responses to progressive hypercapnia and to progressive hypoxia of supine subjects were determined in duplicate, in a laboratory room at 1.0 ATA by rebreathing methods (11, 12), an hour or more following a light breakfast. They preceded the 1.5 ATA exposures by about 6 h and were 10 h before exposure at 2.5 ATA. Postexposure measurements were obtained 2 or 3 h after exposure at 1.5 or 2.5 ATA, respectively. Little or no

sleep was possible in the intervening period, and sustenance was primarily a 5% dextrose solution by continuous intravenous infusion, supplemented by light carbohydrate snacks.

RESULTS

Focus in this summary report is on comparison of mean values at the different hyperoxic pressures investigated. Results are presented in Fig. 2 for ventilation, end-tidal Pco_2, and rate of CO_2 elimination; in Fig. 3 for ventilatory responses to CO_2; in Fig. 4 for ventilatory responses to hypoxia; and in Fig. 5 for body temperature changes.

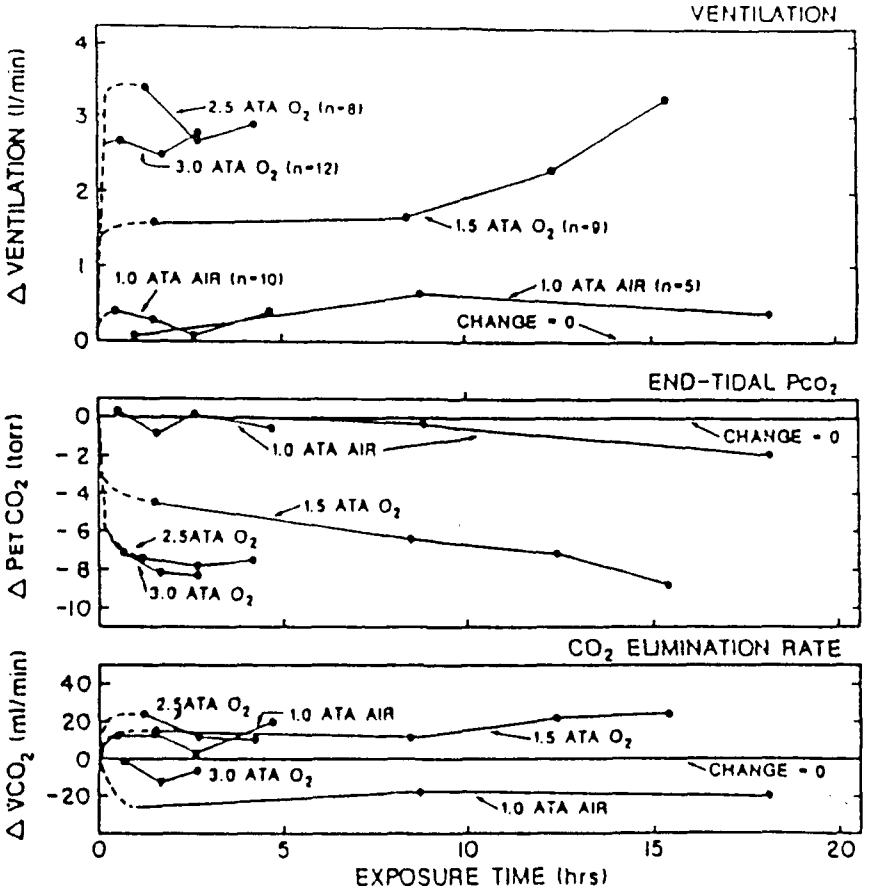


Fig. 2. Effects of oxygen at 0.2, 1.5, 2.5, and 3.0 ATA on ventilation, end-tidal PCO_2, and rate of CO_2 elimination. Changes are from preexposure reference levels in air at 1.0 ATA.

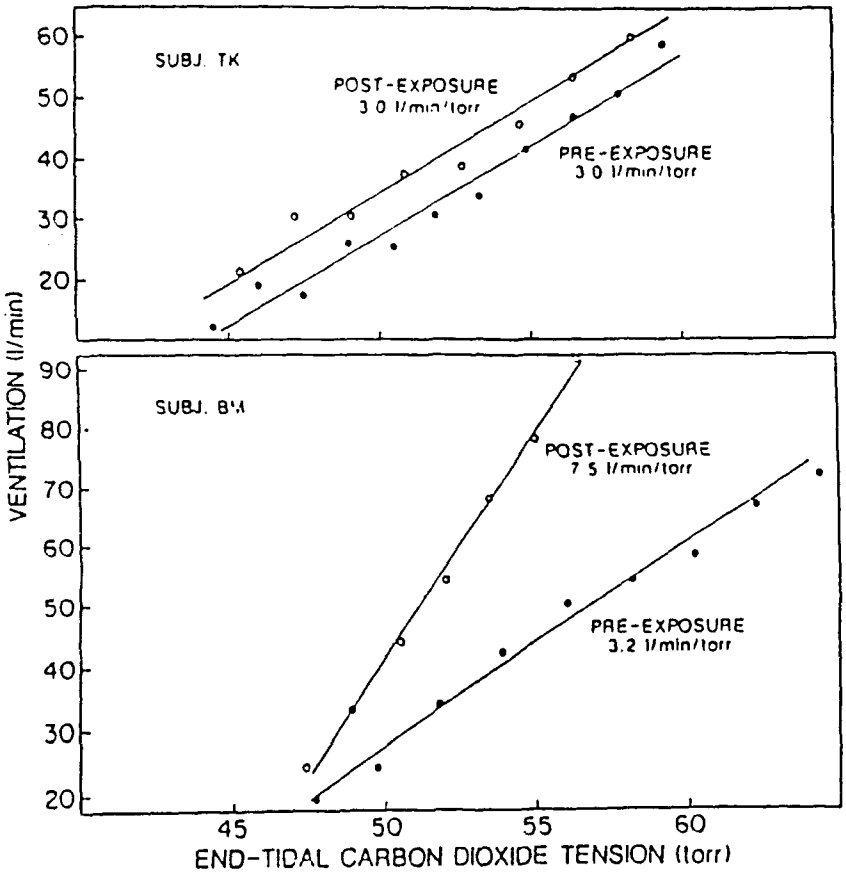


Fig. 3. Effects of hyperoxia on ventilatory response to CO_2 in 2 subjects following exposure at 2.5 ATA O_2. See text for explanation.

Ventilation, End Tidal P_{CO_2}, and CO_2 Elimination Rate

Increments in mean values of ventilation and decrements in mean values of end-tidal P_{CO_2} occurred during hyperoxia at 1.5, 2.5, and 3.0 ATA (Fig. 2). The increased ventilation was greater in magnitude early in exposure at 2.5 and 3.0 ATA than it was early in the 1.5 ATA exposures. Correspondingly, the decrements in end-tidal P_{CO_2} were greater at 2.5 and 3.0 ATA than they were early in exposure at 1.5 ATA.

These changes were of the same magnitude and did not progress with time at the 2.5 and 3.0 ATA pressures. In contrast, although the changes in ventilation and end-tidal P_{CO_2} at 1.5 ATA were smaller in magnitude than were those at 2.5 and 3.0 ATA early in exposure, these changes did become greater over time. By the end of the 1.5 ATA exposures, the increment in ventilation and decrement in P_{CO_2} were as great as those at the higher

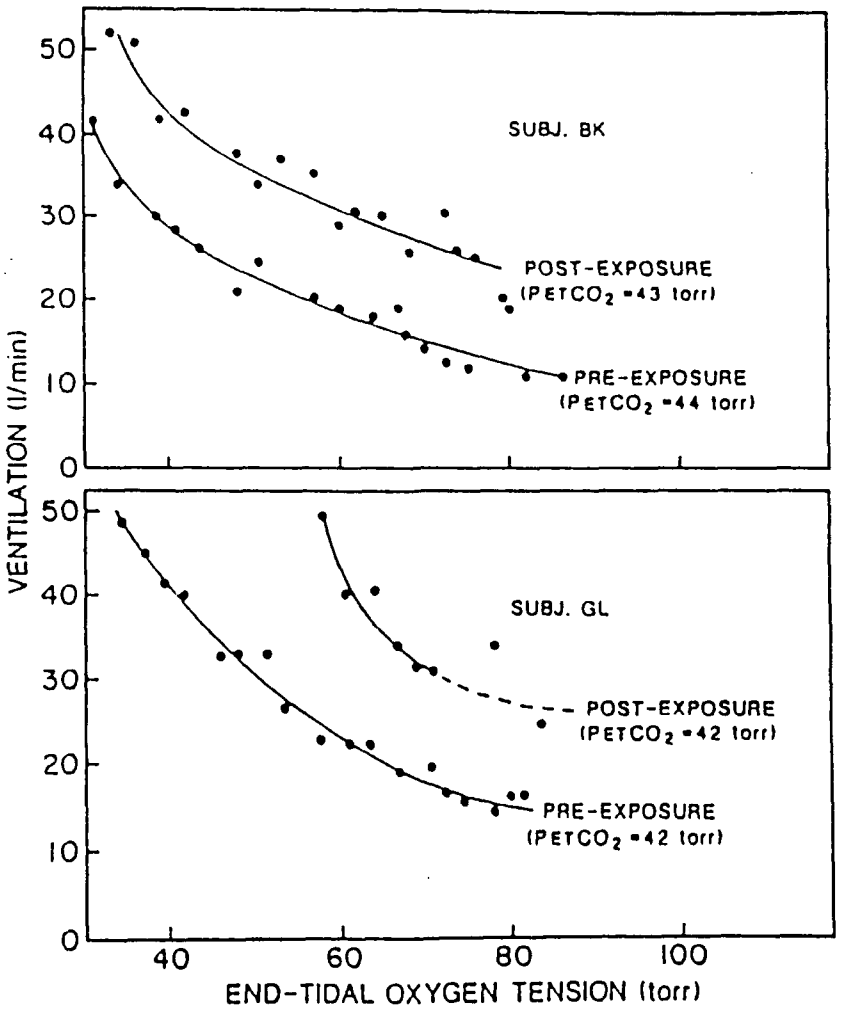


Fig. 4. Effects of hyperoxia on hypoxic ventilatory response in 2 subjects following exposure at 1.5 ATA O_2. See text for explanation.

pressures. There were relatively small increments in mean values of ventilation and correspondingly small changes in mean values of end-tidal P_{CO_2} during normoxic control "exposures."

Changes in rate of CO_2 elimination were small and not progressive at any of the exposure conditions. This parameter was sufficiently stable to not influence the effects of hyperoxia on ventilatory or thermal homeostasis.

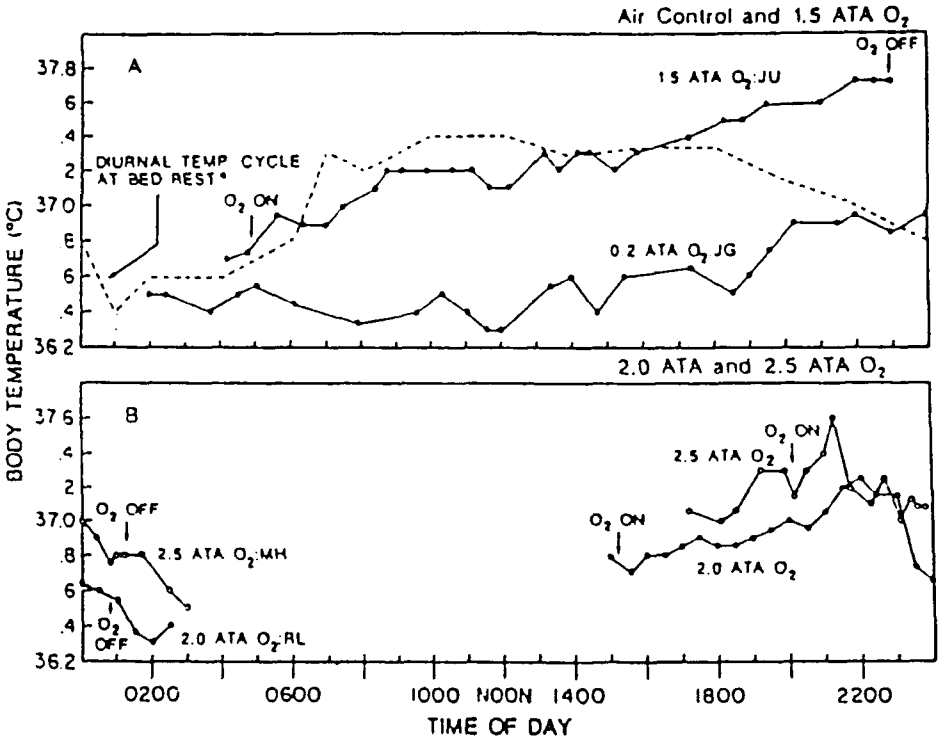


Fig. 5. Body temperatures of individual subjects during exposures. Overall patterns of change are typical for the subjects at each oxygen pressure. See text for explanation.

Respiratory CO_2 Reactivity

Following exposures to oxygen at 0.2, 1.5, and 2.5 ATA, mean values of respiratory CO_2 reactivity were increased above preexposure values for the 1.5 and 2.5 ATA exposure groups. Mean pre- and postexposure reactivities were 3.3 and 4.9 liter·min^{-1}·Torr^{-1} Pco_2, respectively, for the 1.5 ATA exposure group. Corresponding values for the 2.5 ATA group were 3.1 and 4.8 liter·min^{-1}·Torr^{-1} Pco_2. Individual results for 2 of the subjects from this group are shown in Fig. 3 to illustrate the range of responses among subjects. For subject TK (*top*) there was no change in reactivity, whereas for subject BM (*bottom*), postexposure reactivity was more than doubled. Reactivity was increased by 100% or more in 4 of the 1.5 ATA and in 4 of the 2.5 ATA O_2 subjects, whereas in the other subjects changes were small. All the individual postexposure respiratory CO_2 reactivities observed fall into the range of responses of healthy subjects (13). Respiratory CO_2 reactivities measured on subsequent days in the 2.5 ATA O_2 group were back at the preexposure control level.

Ventilatory Responses to Progressive Hypoxia

In no subject was the hypoxic ventilatory response abolished. The postexposure hypoxic ventilatory responses were usually displaced above the preexposure curves after exposure at 1.5 ATA O_2, but not after the 2.5 ATA exposures. There was no increase in degree of curvature in some subjects (Fig. 4, *top*). Other subjects had an increase in degree of curvature (Fig. 4, *bottom*). Quantitative analyses of the hypoxic ventilatory responses, which were obtained before and after the exposures to 0.2, 1.5, and 2.5 ATA O_2, are not currently available. By inspection, the degree of curvature (related to hypoxic respiratory sensitivity) may be increased somewhat in 4 of 9 subjects following exposure to 1.5 ATA O_2, and in 3 of 8 subjects following exposure to 2.5 ATA O_2. Of these 7 subjects with possibly increased hypoxic sensitivity, 6 also had increased respiratory CO_2 reactivity.

Thermal Homeostasis

With a single exception, patterns of change in body temperature were similar for individual subjects of the 1.0 ATA air exposure series and the 1.5 ATA O_2 exposure series. Individual patterns of temperature change are shown in Fig. 5; *A* shows temperature "profiles" for single subjects at 1.0 ATA air and at 1.5 ATA O_2, along with diurnal temperature change of normal individuals on bed rest (14), with nocturnal sleep. The natural diurnal cycle is absent for both the subject at 1.0 ATA air and at 1.5 ATA O_2. The patterns of change at these two pressures are virtually identical. In contrast to the increments in body temperature at 1.0 ATA air and 1.5 ATA O_2, body temperatures decreased following the initiation of hyperoxia at 2.0 and 2.5 ATA (Fig. 5 *B*).

DISCUSSION

Altered respiratory homeostasis during prolonged hyperoxia was evident in the subjects at each of the pressures investigated, in the form of increased ventilation and decreased $P_{ET_{CO_2}}$. The initial changes, which persisted, were presumably physiologic in origin (1). Within the preplanned pressure time limits selected for these exposures, the observed effects were not of sufficient magnitude to impair function. However, continued hyperoxic exposure beyond the limits of these investigations could result in progressive changes of functional significance.

Persistent mild increment in ventilation and decrement in end-tidal P_{CO_2} during hyperoxia at 3.0 and 2.5 ATA were similar in magnitude to those seen in man during shorter exposures to oxygen at 3.5 ATA (15). Although these changes did not progress over the hyperoxic exposures in the majority of subjects at 2.5 and 3.0 ATA (Fig. 3), functionally significant changes in respiratory parameters did develop progressively over the 30 min preceding onset of seizure in the single subject who experienced an O_2-related convulsion at 3 h of exposure at 3.0 ATA (4, 6, 16).

The smaller early exposure increment in ventilation during hyperoxia at 1.5 ATA most likely reflects lesser intensity of the same effects that caused ventilation to increase at 2.5 and 3.0 ATA. The progressive increase in ventilation later in the 1.5 ATA exposure reflects either progressive development of toxic effects of hyperoxia directly on mechanisms concerned with the regulation of respiration, or indirect effects related to progressive increase in severity of pulmonary symptoms (5). It is predictable that the difference in gas density between air at 1.0 ATA (reference level) and oxygen even at 3.0 ATA had only a negligible effect on ventilation (17).

The decrease in end-tidal P_{CO_2} observed at 1.5, 2.5, and 3.0 ATA (Fig. 2, *center*) were entirely a consequence of increased ventilation, since the rates of CO_2 elimination (Fig. 2, *bottom*), and most likely the metabolic rates as well, did not change significantly during hyperoxia as compared to preexposure levels. This current observation for prolonged hyperoxia confirms an earlier observation for a shorter exposure to oxygen at 3.5 ATA (15).

Respiratory reactivity to carbon dioxide is reduced below air-breathing levels when it is measured *during* brief exposures to hyperoxia (3), due to suppression by hyperoxia of peripheral chemoreceptor activity (2) and possibly due to reduction of central respiratory chemoreceptor reactivity as well (18). For several reasons, respiratory CO_2 reactivity could not be measured *during* the oxygen exposures of Predictive Studies V; therefore the effect of hyperoxia on respiratory CO_2 reactivity during prolonged oxygen breathing at 1.5 and 2.5 ATA cannot now be assessed.

Sleep deprivation has been reported to reduce hypercapnic ventilatory response to CO_2; 24 h of sleeplessness reduced reactivity by 24% in 13 healthy men (19). This was not confirmed in the 5 subjects of the 1.0 ATA air × 20 h experiment series of Predictive Studies V. Nevertheless the potential effect of sleep deprivation must be considered in investigations involving prolonged periods of wakefulness.

It is important to note that ventilatory responses to progressive hypoxia were not abolished in any of the subjects of Predictive Studies V. Abolition of carotid body reactivity to hypoxia as well as its associated ventilatory response has been reported for cats exposed to oxygen at 1.0 ATA for 65 h (20). Rather, the enhanced hypoxic responses (Fig. 4) observed for some of the subjects of the 2.5 and 1.5 ATA O_2 exposure series could be related to increased input from peripheral receptors or enhanced central responsiveness to peripheral stimuli.

Altered thermal homeostasis manifested as progressive drop in body core temperature with rate of fall proportional to degree of hyperoxia has been reported for rats (10). A similar effect was expected to be more difficult to detect in man due to immensely greater body mass. Initially, body temperature was recorded only intermittently during the 3.0 ATA O_2 exposures which initiated Predictive Studies V, because it was felt that 3.5-h exposure was too brief to allow any derangement of thermal homeostasis to be expressed. Observed temperature changes were unremarkable until a distinct fall in body

temperature was observed in the single subject who experienced an oxygen-related seizure in the periods preceding and following the convulsion (4, 16). Continuous recordings of body temperature were made in all subsequent exposures. Preliminary analysis indicates that thermal homeostasis may be altered in man by hyperoxia at oxygen pressures greater than 1.5 ATA (Fig. 5). Since rate of CO_2 elimination did not change over the exposure periods (Fig. 2), the observed decreased temperatures seem unrelated to metabolic changes. The observed small decrements are not physiologically important, and are of no significance to use of hypoxia in therapy or in decompression for increased rate of inert gas elimination.

SUMMARY

Altered respiratory homeostasis was evident during exposures at 2.5 and 3.0 ATA O_2 as nonprogressive increment in ventilation and reciprocal decrement in FET_{CO_2}. During exposure at 1.5 ATA O_2 these changes were progressive. Mean values of respiratory reactivity to CO_2 were somewhat increased following prolonged hyperoxia at 1.5 and 2.5 ATA, as compared to preexposure mean values. Hypoxic ventilatory response was unchanged or enhanced after oxygen exposures at 1.5 and 2.5 ATA. Observed respiratory and body temperature changes were not of sufficient magnitude to impair function.

References

1. Lambertsen CJ. Effects of hyperoxia on organs and their tissues. In: Robin ED, ed. Extrapulmonary manifestations of respiratory disease, vol. 8. In: Lenfant C, ed. Lung biology in health and disease. New York: Marcel Dekker, 1978:239-303.
2. Leitner LM, Pages B, Puccinelli R, Dejours P. Etude simultanee de la ventilation et des decharges des chemorecepteures du glomus carotidien chez le chat. II. Au cours d'inhalations breves d'anhydride carbonique. Arch Int Pharmacodyn 1965; 154:427.
3. Lambertsen CJ, Hall P, Wollman H, Goodman MW. Quantitative interactions of increased PO_2 and PCO_2 upon respiration in man. Ann NY Acad Sci 1963; 109:731.
4. Lambertsen CJ, Clark JM, Gelfand R, et al. Definition of tolerance to continuous hyperoxia in man. An abstract report of Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
5. Clark JM, Gelfand R, Flores ND, Lambertsen CL, Pisarello JB. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA in Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.

6. Pisarello JB, Clark JM, Lambertsen CJ, Gelfand R. Human circulatory response to prolonged hyperbaric hyperoxia in Predictive Studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX.Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
7. Simon AJ, Torbati D. Effects of hyperbaric oxygen on heart, brain, and lung functions in rat. Undersea Biomed Res 1982; 9(3):263-275.
8. Matalon S, Nesarajah MS, Farhi LE. Pulmonary and circulatory changes in conscious sheep exposed to 100% O_2 at 1 ATA. J Appl Physiol 1982; 53(1):110-116.
9. Peterson ES, Vejby-Christensen H. Effect of body temperature on steady state ventilation and metabolism. Acta Physiol Scand 1973; 89:342.
10. Puglia CD, Glauser EM, Glauser SC. Core temperature response of rats during exposure to oxygen at high pressure. J Appl Physiol 1974; 36(2):149-153.
11. Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. Aust Ann Med 1967-68; 16-17:20-32.
12. Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. Am Rev Respir Dis 1974; 109:345.
13. Rebuck AS, Read J. Patterns of ventilatory response to CO_2 during recovery from severe asthma. Clin Sci 1971; 41:13-21.
14. Aschoff J, Wever R. Kern and schale im warmehaushalt des menschen. Naturwissenschaften 1958; 20:447.
15. Lambertsen CJ, Stroud MW III, Gould RA, Kough RH, Ewing JH, Schmidt CF. Oxygen toxicity. Respiratory responses of normal men to inhalation of 6 and 100 percent oxygen under 3.5 atmospheres pressure. J Appl Physiol 1953; 5(9):487-494.
16. Gelfand R, Clark JM, Lambertsen C, Jackson R, Pisarello J. Hyperoxia at 3.0 ATA for 3.5 hours (in Predictive Studies V). Effects on ventilatory parameters. Undersea Biomed Res 1985; 12:(1)Suppl:19-20.
17. Gelfand R, Lambertsen CJ, Strauss R, Clark JM, Puglia CD. Human respiration at rest in rapid compression and at high pressures and gas densities. J Appl Physiol 1983; 54(1):290-303.
18. Gelfand R, Lambertsen CJ. Dynamic respiratory response to abrupt change of inspired CO_2 at normal and high PO_2. J Appl Physiol 1973; 35:903-913.
19. White DP, Douglas NJ, Pickett CK, Zwillich CW, Weil JV. Sleep deprivation and the control of ventilation. Am Rev Respir Dis 1983; 128:984-986.
20. Lahiri S, Mokashi A, Mulligan E, Andronikou S. Loss of carotid chemoreflex function in oxygen toxicity. Fed Proc 1985; 44(4):1000.

Acknowledgment

Supported in part by NMRDC contract N00014-81-C-0826, NASA contract NAS9-17238, and the State of Pennsylvania through the Benjamin Franklin Partnership.

9th International Symposium on Underwater and Hyperbaric Physiology
Undersea and Hyperbaric Medical Society, Bethesda, MD, 1987

HUMAN CIRCULATORY RESPONSES TO PROLONGED HYPERBARIC HYPEROXIA IN PREDICTIVE STUDIES V

J. B. Pisarello, J. M. Clark, C. J. Lambertsen, and R. Gelfand

In its various applications, oxygen breathing in man is limited by toxic effects that become more severe as inspired oxygen pressure and exposure duration are increased. Although all tissues, organs, and systems are potentially susceptible to oxygen effects, only pulmonary and CNS manifestations of oxygen poisoning have been studied extensively during long exposures. With respect to cardiocirculatory phenomena during oxygen breathing in man, most previous studies have focused on acute responses (1, 2), whereas those investigations that contained prolonged exposures have not included detailed evaluation of circulatory parameters (3, 4). Consequently, relatively little is known about physiologic and toxic effects of prolonged hyperbaric oxygen exposure on the cardiocirculatory system in man.

This summary report presents selected results of cardiocirculatory measurements in healthy volunteers who breathed 100% O_2 continuously at 3.0 ATA for up to 3.5 h, at 2.5 ATA for up to 6.0 h, at 2.0 ATA for up to 11.9 h, and at 1.5 ATA for up to 19.0 h. These data were collected as part of a broad program of investigation (Predictive Studies V) designed to measure effects of hyperbaric hyperoxia on human organ systems and functions (5-7).

METHODS

Each experiment included air breathing, sea-level control measurements before measurements during oxygen breathing at increased pressure. During each exposure to hyperoxia, cardiovascular data were obtained repeatedly: early in the oxygen exposure to investigate acute responses and later in the oxygen breathing period to evaluate effects of prolonged exposure (5). All measurements reported here (unless noted otherwise) were performed at rest in the

supine position, after a period of stabilization.

Cardiovascular Measurements

Cardiac electrical activity was continuously monitored during each exposure and stored on magnetic tape for later computer analysis. Electrical impedance cardiography (8) was utilized to follow changes in cardiac output throughout the exposure. Arterial blood pressure was measured intermittently by the cuff method during the 3.0 ATA series and by indwelling catheter in the 2.5 ATA, 2.0 ATA, and 1.5 ATA series. Systemic vascular resistance was calculated from cardiac output and mean blood pressure data, assuming constant right atrial pressure. Values are expressed as percent changes from preexposure values.

Responses to Active Standing

Blood pressure and heart rate responses to active standing (9) were measured before and during the oxygen exposures at 2.5, 2.0, and 1.5 ATA to investigate the effect of hyperbaric O_2 breathing on autonomic modulation of orthostatic reflexes. To perform this measurement, ECG and arterial blood pressure were continuously recorded while the subject actively rose from the supine to the upright position in less than 5 s. Instantaneous heart rates while supine and during the initial 60 to 90 s after active standing were obtained from an ECG-activated cardiotachometer. The pattern of this response has been shown previously to be a reproducible phenomenon in the evaluation of baroreflex autonomic function (9).

Liver Blood Flow

To study possible oxygen effects on regional hepatic circulation, liver blood flow was measured as the rate of indocyanine (ICG) clearance (10) at sea level and during early and late oxygen exposure at 2.0 and 1.5 ATA. For each flow measurement, 0.5 mg/kg of ICG was injected i.v. while the subject was resting in a supine position. Blood sampling was performed at 0, 1, 2, 3, 6, 9, 12, 15, 18, and 21 min from the indwelling arterial catheter. Plasma concentration of ICG was determined spectrophotometrically, using the subjects preinjection arterial sample as a blank to construct a standard calibration curve.

RESULTS

Cardiovascular Oxygen Tolerance Limits at 3.0, 2.5, 2.0, and 1.5 ATA

In the 3.0 ATA series of exposures, all but 2 were continued to the predetermined maximum duration of 3.5 h. One of the 2 exceptions was terminated at 2.5 h because of excessive bradycardia, and the other was stopped at 3.0 h upon the onset of an oxygen convulsion. Two exposures at 2.5 ATA and 1 at 1.5 ATA were stopped at 5.5, 5.8, and 17.7 h, respectively, when the subjects developed asymptomatic, unifocal, ventricular ectopic activity of

increasing frequency. All remaining exposures at 2.5, 2.0, and 1.5 ATA that were terminated before predetermined maximum durations were stopped on the basis of pulmonary symptoms and/or changes in lung volumes and flow rates.

Effects on Resting Heart Rate and Cardiac Rhythm

As observed by others during short hyperbaric oxygen exposures (1, 2), initial responses in the 3.0, 2.5, and 2.0 ATA series were characterized by average reductions in sinus node frequency discharge of approximately 6 to 12 beats/min. An initial average reduction of 3 beats/min was observed in the 1.5 ATA series (Table 1). Sinus arrhythmia, sinus pauses, and occasional periods of nodal control occurred early in the exposures at 3.0, 2.5, and 2.0 ATA (Fig. 1). These phenomena were usually transient and were not associated with symptoms in any subject except the 1 at 3.0 ATA who developed progressive, severe bradycardia. Immediately after termination of oxygen breathing at 2.5 h, this subject had a sinus pause of 13 s in association with a 20-s period of syncope. Sinus rhythm returned promptly at the rate of 60/min and, within 20 s, he became mentally alert. No further ECG abnormalities occurred, and postexposure measurements were completed.

Table 1

Resting Heart Rate During Oxygen Breathing in Man, Beats/Min, Mean ± SE

Pressure	Preexposure	Early Exposure	Late Exposure
3.0 ATA ($n = 12$)	60.1 ± 4	54.2 ± 3	53.0 ± 2
2.5 ATA ($n = 8$)	57.3 ± 2	45.0 ± 2*	47.1 ± 2*
2.0 ATA ($n = 7$)	59.0 ± 4	50.0 ± 4	63.5 ± 2**
1.5 ATA ($n = 7$)	59.1 ± 5	56.2 ± 3	64.2 ± 5

* $P < 0.05$ compared to preexposure. ** $P < 0.05$ compared to early exposure.

In contrast to the sustained decreases in resting heart rate observed at 3.0 and 2.5 ATA, initial decrease in sinus frequency discharge at 2.0 and 1.5 ATA was followed after about 3 h of exposure by progressive acceleration. At 9.8 h of exposure in the 2.0 ATA series, pulse rate was significantly greater than the initial oxygen exposure value (Table 1). Along with increased frequency of sinus discharge at 2.0 and 1.5 ATA, sinus pauses disappeared and periods of nodal control occurred. In some cases, atrial and ventricular premature depolarizations were observed during the later part of the 2.5, 2.0, and 1.5 ATA exposures (Fig. 2). This ectopic activity was infrequent and not associated with symptoms during the 2.0 ATA exposure series. However, in 1 subject at 1.5 ATA, and in 2 others at 2.5 ATA, exposures were terminated because of increasing numbers of unifocal, premature ventricular depolarizations. None of the 3 subjects had associated symptoms, and the continuous monitoring demonstrated complete disappearance of ectopic phenomena within 3 h of exposure termination.

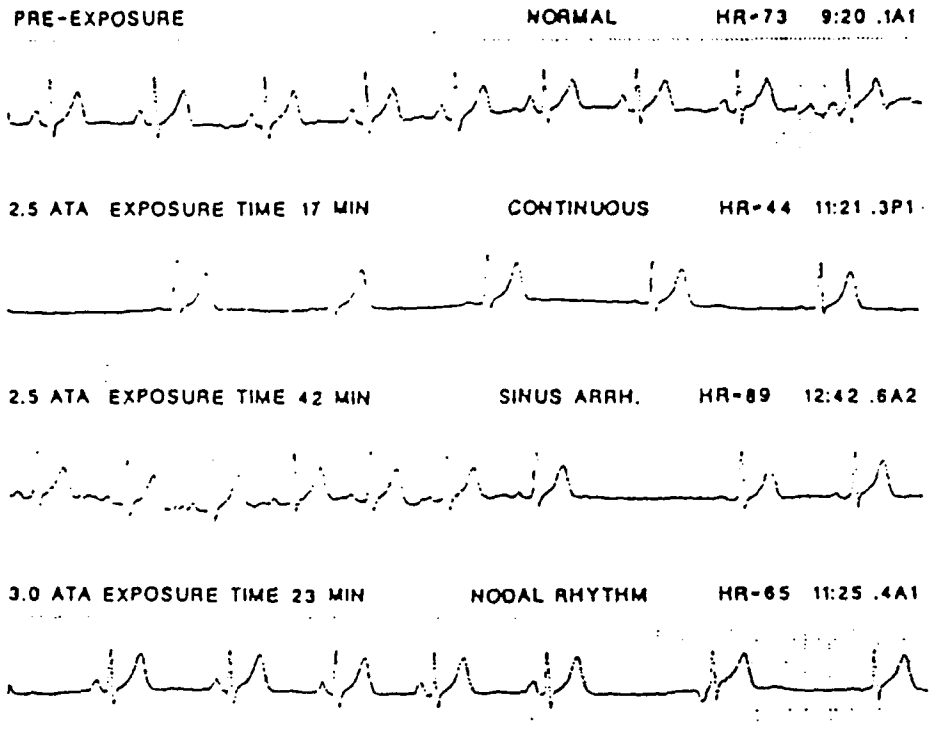


Fig. 1. Electrocardiographic features during the 1st h of oxygen exposure in man at 2.5 and 3.0 ATA. Top to bottom: normal sea-level tracing, sinus bradycardia, sinus arrhythmia, and nodal escape (last two beats).

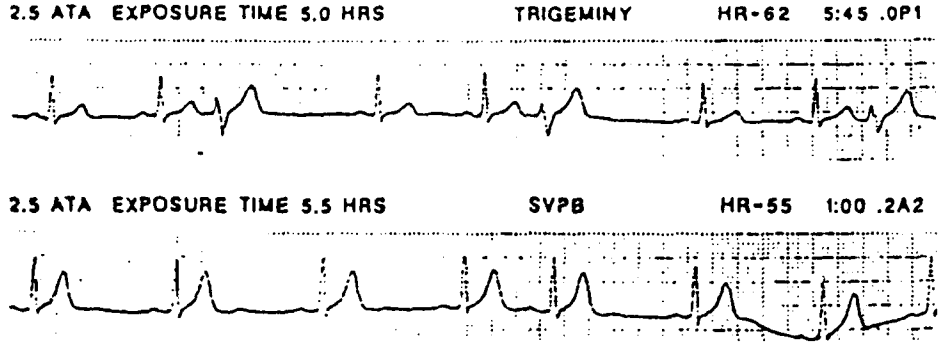


Fig. 2. Electrocardiogram of a subject exposed to oxygen at 2.5 ATA. Ectopic premature beats of ventricular and supraventricular origin are demonstrated in the top and bottom tracings, respectively.

Effects on Cardiac Output and Regional Hepatic Circulation

Resting cardiac output variations during oxygen breathing in general paralleled variations in heart rate (Table 2). Initial decrements were observed at all four pressures, with progressive late increments during the 2.0 and 1.5 ATA exposures, in association with accelerations of pulse rate. These changes were of small magnitude and not statistically significant.

Table 2
Cardiac Output During Oxygen Breathing in Man, % Variation

Pressure	Early Exposure, %	Late Exposure, %
3.0 ATA ($n = 12$)	- 8	- 9
2.5 ATA ($n = 7$)	- 15	- 10
2.0 ATA ($n = 6$)	- 13	- 6
1.5 ATA ($n = 7$)	- 16	- 7

Liver blood flow determinations by the green-dye clearance technique at 1 5 and 2.0 ATA demonstrated no changes in this parameter during early or late oxygen exposure. Results of the 1.5 ATA exposures are shown in Fig. 3.

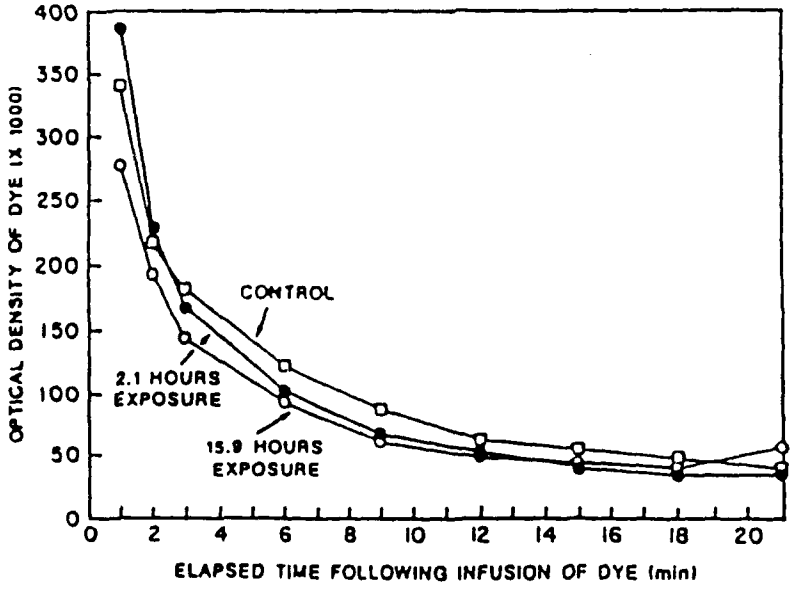


Fig. 3. Indocyanine dye clearance curves reflecting hepatic blood flow at sea level and after 2.1 and 15.0 h of oxygen breathing at 1.5 ATA in man. There are no statistical differences among curves. Average data for 7 subjects are shown.

Effects on Arterial Blood Pressure and Systemic Vascular Resistance

Average changes in resting arterial blood pressure during early oxygen exposure at 3.0, 2.5, and 1.5 ATA indicated decreases of 0.5, 6.2, and 7.7 mmHg, respectively, and an increase of 12.2 mmHg at 2.0 ATA (Table 3). Only the decrement at 2.5 ATA was statistically significant. During late oxygen exposure at 3.0, 2.5, and 2.0 ATA, average values of mean arterial pressure exceeded preexposure control values by 4.4, 1.0, and 3.4 mmHg, respectively (Table 3). The late exposure value at 1.5 ATA was 4.6 mmHg less than control. None of these late exposure changes was statistically significant.

Table 3

Mean Arterial Blood Pressure During Oxygen Breathing in Man, mmHg, Mean ± SE

Pressure	Preexposure	Early Exposure	Late Exposure
3.0 ATA ($n = 12$)	90.0 ± 4	89.5 ± 3	94.4 ± 4
2.5 ATA ($n = 7$)	94.9 ± 4	88.7 ± 3*	95.9 ± 2
2.0 ATA ($n = 6$)	84.4 ± 3	96.6 ± 4	87.8 ± 8
1.5 ATA ($n = 7$)	97.3 ± 4	89.6 ± 3	92.7 ± 4

* $P < 0.05$ compared to preexposure value.

Average calculated values of systemic vascular resistance during early oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA were increased by 8, 9, 31, and 6%, respectively (Table 4). During late oxygen exposure, values of systemic vascular resistance increased further to 16 and 11% above control values at 3.0 and 2.5 ATA, respectively, and decreased at 2.0 ATA to 10% with respect to control values. None of these changes was statistically significant.

Table 4

Systemic Vascular Resistance During Oxygen Breathing in Man, % Variation

Pressure	Early Exposure, %	Late Exposure, %
3.0 ATA ($n = 12$)	+ 8	+ 16
2.5 ATA ($n = 7$)	+ 9	+ 11
2.0 ATA ($n = 6$)	+ 31	+ 10
1.5 ATA ($n = 7$)	+ 6	+ 1

Hemodynamic Responses to Active Standing

Normal acceleration of heart rate in response to an abrupt transition from supine to standing positions occurred during both early and late oxygen exposure in all 9 subjects studied at 1.5 ATA and in 6 of the 7 subjects exposed to oxygen at 2.0 ATA. However, in 1 of the 2.0 ATA subjects, complete blunting of the normal tachycardic response to active standing was observed in follow-up measurements 2 h after termination of an 8-h exposure

(Fig. 4). This event was not associated with symptoms, and arterial blood pressure did not fall.

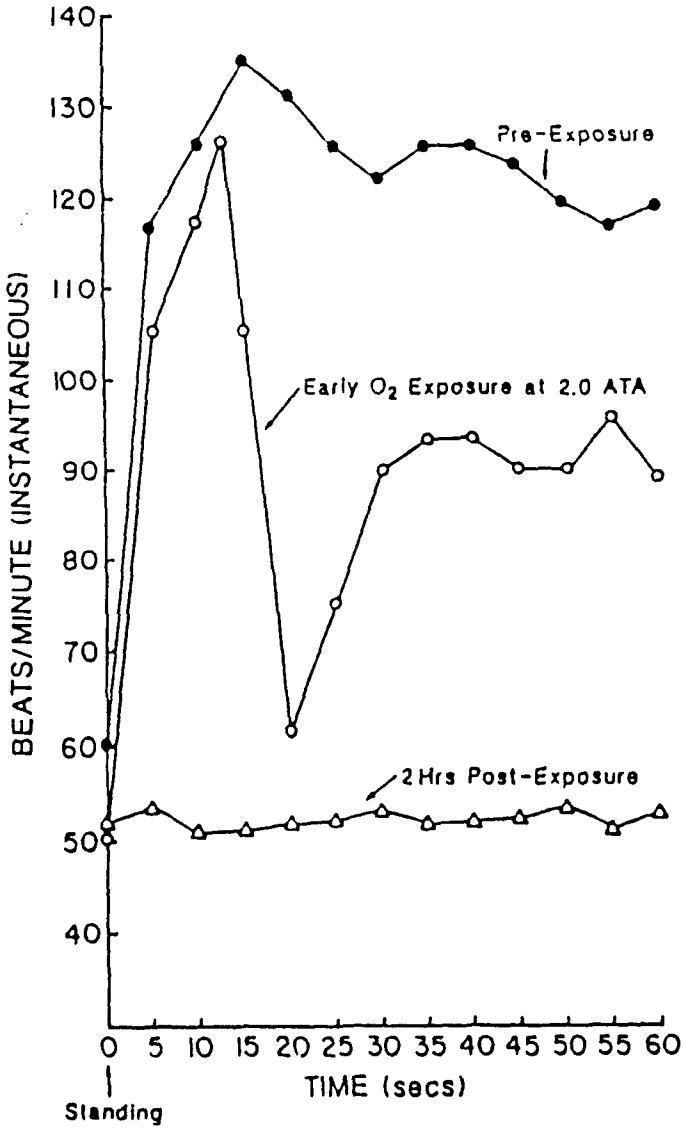


Fig. 4. Immediate heart rate responses to standing in 1 subject before, during, and after 8 h of oxygen breathing at 2.0 ATA. Note the complete blunting of this response in the postexposure curve. Despite failure of pulse rate acceleration, blood pressure in the standing position was maintained and the subject experienced no symptoms.

Similar inhibition of heart rate acceleration upon standing occurred in 4 of the 8 subjects who breathed oxygen for 5 to 6 h at 2.5 ATA (Fig. 5). During late oxygen exposure in these subjects, heart rate increased over the first 15 to 20 s of standing, but then decreased to stabilize at a level only slightly above the supine value. No symptom was associated with this effect, and blood pressure was maintained. In all cases, postexposure measurements at sea level demonstrated complete reversal of this effect, with restoration of normal tachycardic responses to standing.

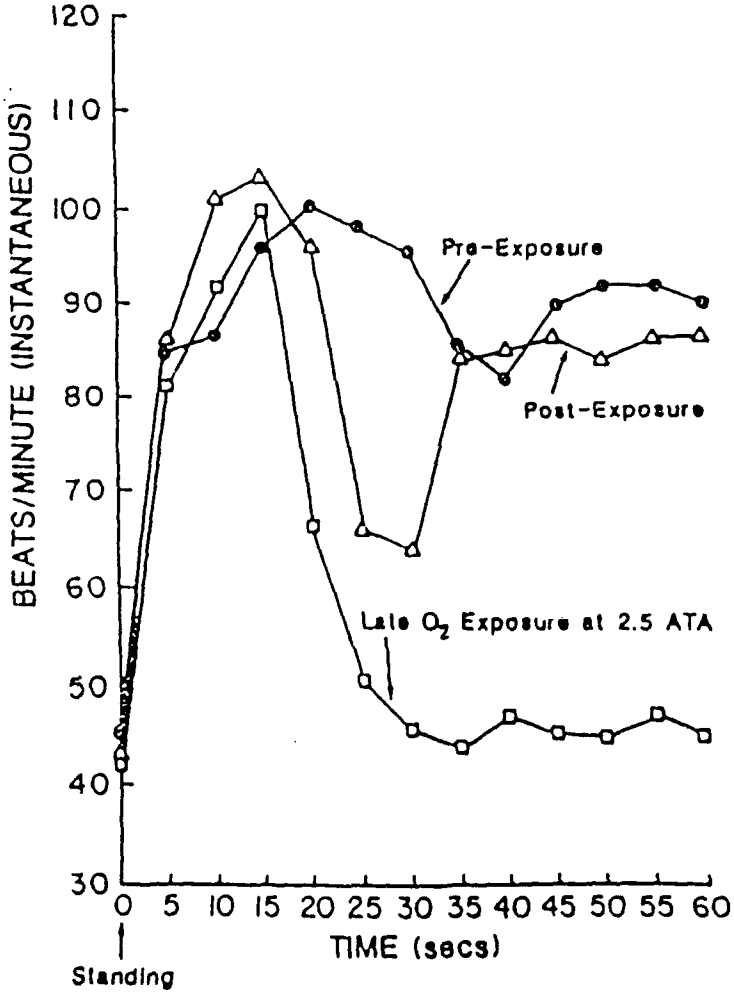


Fig. 5. Immediate heart rate responses to standing in 1 subject before, during, and after 6 h of oxygen breathing at 2.5 ATA. Note the abnormal response during oxygen exposure and its return to normal during the postexposure period.

DISCUSSION

These experiments indicate that resting hemodynamic responses to prolonged hyperbaric oxygen breathing in man usually consist of small deviations from normal sea-level responses. At all four oxygen pressures investigated, rapid onset of bradycardia occurred. This effect, previously shown to be mediated by vagal mechanisms (2), was accompanied by a rate-dependent reduction in cardiac output and a degree of systematic vasoconstriction. All these effects were small in magnitude and appeared to be functionally unimportant.

During late oxygen exposure at 2.5, 2.0, and 1.5 ATA, excitatory influences on cardiac depolarization were manifested by both a progressive acceleration of sinus node frequency discharge and an occasional appearance of ectopic electrical activity of both supraventricular and ventricular origin. These events were not accompanied by symptoms and are not likely to interfere with performance in normal individuals.

While both the early inhibitory and late excitatory cardiac electrical phenomena were generally small in magnitude and were not accompanied by symptoms, it is important to emphasize that four oxygen exposures were terminated on the basis of cardiac depolarization abnormalities. One exposure at 3.0 ATA was stopped when extreme bradycardia occurred, and a total of three exposures at 1.5 and 2.5 ATA were terminated when unifocal ventricular ectopy of increasing frequency developed. These cardiac manifestations may represent direct effects of oxygen on cardiac tissue, or they may be caused indirectly by oxygen effects on neural or neurohormonal influences with secondary modification of cardiac function. Whatever the mechanism, these observations clearly demonstrate that, in selected individuals, cardiac depolarization events can limit the duration of extended, continuous exposures to oxygen at increased pressures.

This initial evaluation of dynamic circulatory events during oxygen breathing indicates the potential occurrence of interference with basic reflex mechanisms during hyperbaric hyperoxia. Furthermore, the observed modification of the normal response to active standing during the 2.0 and 2.5 ATA experiments, with preservation of the vasoconstrictor response, indicates the selective nature of this interference. In those subjects in whom acceleration of heart rate did not occur upon standing, cardiac output was reduced more than the normal physiologic decrement. However, the absence of a fall in blood pressure indicates a compensatory increase in reflex vasoconstriction. It is possible that, in a subject with a marginal state of hydration, even maximal vasoconstriction would be insufficient to assure optimal cerebral perfusion. This may have been the mechanism underlying the orthostatic intolerance observed in some of the subjects exposed to oxygen at 2.0 ATA reported in a previous, related series (11).

References

1. Whalen RE, Saltzman HA, Holloway DH Jr, McIntosh HD, Sieker HO, Brown IW Jr. Cardiovascular and blood gas responses to hyperbaric oxygenation. Am J Cardiol 1965; 15:638-646.
2. Egger GWN Jr, Paley HW, Leonard JJ, Warren JV. Hemodynamic responses to oxygen breathing in man. J Appl Physiol 1962; 17:75-79.
3. Behnke AR, Forbes HS, Motley EP. Circulatory and visual effects of oxygen at 3 atmospheres pressure. Am J Physiol 1935; 114:436-442.
4. Donald KW. Oxygen poisoning in man. I & II. Br Med J 1947; 1:667-672, 712-717.
5. Lambertsen CJ, Clark JM, Gelfand R, et al. Definition of tolerance to continuous hyperoxia in man. An abstract report of predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
6. Clark JM, Gelfand R, Flores ND, Lambertsen CJ, Pisarello JB. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA in predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
7. Gelfand R, Clark JM, Lambertsen CJ, Pisarello JB. Effects on respiratory homeostasis of prolonged continuous hyperoxia at 1.5 to 3.0 ATA in man in predictive studies V. In: Bove AA, Bachrach AJ, Greenbaum LJ Jr, eds. Underwater and hyperbaric physiology IX. Proceedings of the ninth symposium on underwater and hyperbaric physiology. Bethesda, MD: Underwater and Hyperbaric Medical Society, 1987.
8. Denniston JC, Maher JT, Reeves JT, Cruz JC, Cymerman A, Grover RF. Measurement of cardiac output by electrical impedance at rest and during exercise. J Appl Physiol 1976; 40:91-95.
9. Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. J Appl Physiol 1980; 49:809-814.
10. Winkler K, Tygstrup N. Determination of hepatic blood flow in man by cardio-green. Scand J Clin Labs Invest 1960; 12:353-356.
11. Clark JM, Lambertsen CJ. Rate of development of pulmonary oxygen toxicity in man during oxygen breathing at 2.0 ATA. J Appl Physiol 1971; 30:739-752.

Acknowledgment

Supported in part by NMRDC contract N00014-81-C-0826, NASA contract NAS9-17238, and the State of Pennsylvania through the Benjamin Franklin Partnership.

1 July 1990

PUBLICATIONS

1940 - 1984

1990

Gelfand, R., J.M. Clark, and C.J. Lambertsen. Ventilatory response to hypoxia is preserved following prolonged hyperbaric hyperoxia at 1.5, 2.0, and 2.5 ATA in man (Predictive Studies V). Undersea Biomed. Res. 17(Suppl.): 163, 1990.

1989

Clark, J.M. and C.J. Lambertsen. Principles of oxygen tolerance extension defined in the rat by intermittent oxygen exposure at 2.0 and 4.0 ATA. Undersea Biomed. Res. 16(Suppl.): 99, 1989.

Gelfand, R., Clark, J.M. and C.J. Lambertsen. Respiratory control timing characteristics during prolonged hyperoxia at 1.5, 2.0, 2.5 and 3.0 ATA (Predictive Studies V). Undersea Biomed. Res. 16:(Suppl.): 93-94, 1989.

1988

Clark, J.M., C.J. Lambertsen, D.J. Montabana, R. Gelfand and J.H. Cobbs. Comparison of visual function effects in man during continuous oxygen exposures at 3.0 and 2.0 ATA for 3.4 and 9.0 hours (in Predictive Studies V). Undersea Biomed. Res. 15 (Suppl.): 32, 1988.

Gelfand, R., J.M. Clark, C.J. Lambertsen and J.B. Pisarello. Ventilatory responses to hypoxia following prolonged hyperoxia at 2.5 ATA in man in Predictive Studies V. Undersea Biomed. Res. 15 (Suppl): 34, 1988.

Gelfand, R., J.M. Clark, C.J. Lambertsen and J.B. Pisarello. Ventilatory response to CO_2 following prolonged hyperoxia at 1.5 and 2.5 ATA in man. FASEB J. 2: A1508, 1988.

Clark, J.M. Pulmonary limits of oxygen tolerance in man. In: Symposium on Extension of Oxygen Tolerance. Exper. Lung Res. 14: 897-910, 1988.

Lambertsen, C.J. Extension of oxygen tolerance: the philosophy and significance. In: Symposium on Extension of Oxygen Tolerance. Exper. Lung Res. 14:1035-1058, 1988.

Lambertsen, C.J. Relations of decompression to use of oxygen: Harmful effects and their prevention. In: Symposium on Health Examination of Divers - Decompression/Use of Oxygen. Stavanger, Norway, sponsored by Norwegian Petroleum Directorate, February, 1988.

Lambertsen, C.J. Physiologic factors in human organ oxygen tolerance extension. In: On Diving and Hyperbaric Medicine and Diving Medical Advisory Committee Workshop. Aberdeen, Scotland, European Undersea Biomedical Soc., Sept, 1988.

Torbati, D. and K.J. Reilly. Effect of prolonged normobaric hyperoxia on regional cerebral metabolic rate for glucose in conscious rats. Brain Res. 459: 187-191, 1988.

Torbati, D. Hyperbaric Oxygenation. In: Encyclopedia of Medical Devices and Instrumentation. Vol. 3. Webster, J.G., Ed. pp. 1564-1583, 1988.

1987

Clark, J.M., R. Gelfand, N.D. Flores, J.B. Pisarello and C.J. Lambertsen. Pulmonary function alterations and symptoms in man during and after 0_2 exposure at 2.5 ATA for 5-6 hours. Am. Rev. Resp. Dis. 135: A265, 1987.

Gelfand, R., J.M. Clark and C.J. Lambertsen. Effects on body temperature of continuous hyperoxia at 1.5, 2.0 and 3.0 ATA in man (in Predictive Studies V). Undersea Biomed. Res. 14(Suppl.): 28, 1987.

Gelfand, R., J.M. Clark, C.J. Lambertsen and J.B. Pisarello. Ventilatory response to hypoxia following prolonged hyperoxia at 1.5 ATA in man. Fed. Proc. 46: 827, 1987.

Clark, J.M., R. Gelfand, N.D. Flores, C.J. Lambertsen and J.B. Pisarello. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0 and 1 ATA in Predictive Studies V. In: Underwater and Hyperbaric Physiology IX. Bove, A.A., A.J. Bachrach and L.J. Greenbaum, Eds. Bethesda: Undersea and Hyperbaric Medical Soc., pp. 737-749, 1987.

Dise, C.A., J.M. Clark, C.J. Lambertsen and D.B.P. Goodman. Hyperbaric hyperoxia reversibly inhibits erythrocyte phospholipid fatty acid turnover. J. Appl. Physiol. 62: 533-538, 1987.

Gelfand, R., J.M. Clark, C.J. Lambertsen and J.B. Pisarello. Effects on respiratory homeostasis of prolonged continuous hyperoxia in man at 1.5 to 3.0 ATA in Predictive Studies V. In: Underwater and Hyperbaric Physiology IX. Bove, A.A., A.J. Bachrach and L.J. Greenbaum, Eds. Bethesda: Undersea and Hyperbaric Medical Soc., pp. 751-761, 1987.

Lambertsen, C.J., J.M. Clark, R. Gelfand, J.B. Pisarello, W. Cobbs, J.E. Bevilacqua, D.M. Schwartz, D.J. Montabana, C.S. Leach, P.C. Johnson and D.E. Fletcher. Definition of tolerance to continuous hyperoxia in man. An abstract report of Predictive Studies V. In: Underwater and Hyperbaric Physiology IX. Bove, A.A., A.J. Bachrach and L.J. Greenbaum, Eds. Bethesda: Undersea and Hyperbaric Medical Soc., pp. 717-735, 1987.

Pisarello, J.B., J.M. Clark, R. Gelfand and C.J. Lambertsen. Human circulatory responses to prolonged hyperbaric hyperoxia in Predictive Studies V. In: Underwater and Hyperbaric Physiology IX. Bove, A.A., A.J. Bachrach and L.J. Greenbaum, Eds. Bethesda: Undersea and Hyperbaric Medical Soc., 763-772, 1987.

Torbati, D. and C.J. Lambertsen. Effects of hyperbaric oxygenation on regional cerebral glucose utilization rate in the awake rat. In: Proceedings of the Eighth International Congress on Hyperbaric Medicine. Kindwall, E.P., Ed. San Pedro, CA: Best, pp.48-56, 1987.

1986

Clark, J.M., R. Gelfand, N.D. Flores, J.B. Pisarello and C.J. Lambertsen. Pulmonary mechanics and gas exchange in man during and after oxygen exposure at 1.5 ATA for 16 to 19 hours. Am. Rev. Resp. Dis. 133:A31, 1986.

Pisarello, J.B., J.M. Clark, R. Gelfand and C.J. Lambertsen. Human circulatory response during prolonged exposure to oxygen at 2 ATA. Fed. Proc. 45:644, 1986.

Torbati, D. Effect of 8 hours oxygen breathing at 2 atmospheres on brain glucose utilization in the rat. Fed. Proc. 45: 535, 1986.

Torbati, D. and A. Torbati. Blood glucose as a predictive measure for central nervous system oxygen toxicity in conscious rats. Undersea Biomed. Res. 13: 147-154, 1986.

1985

Marsh, R.R., C.J. Lambertsen, D.M. Schwartz, J.M. Clark and R.F. Westmore. Auditory and vestibular function in hyperbaric oxygen. Otolaryngol. Head Neck Surg. 93: 390-393, 1985.

Torbati, D. Regional cerebral metabolic rate for glucose immediately following exposure to 2 atmosphere absolute oxygen in conscious rats. Neurosci. Lett. 55: 109-112, 1985.

Torbati, D. Effect of pentobarbital anesthesia on regional cerebral metabolic rate for glucose during hyperbaric oxygenation in rat. Brain Res. 336: 350-353, 1985.

Torbati, D. Heparin effects during hyperbaric oxygenation in rats. Life Sciences 36: 147-151, 1985.

Torbati, D. and C.J. Lambertsen. The relationship between cortical electrical activity and regional cerebral glucose metabolic rate in rats exposed to 3 atmospheres absolute oxygen. Brain Res. 344: 186-190, 1985.

Torbati, D. Effect of propranolol on the electrical activity of the brain during hyperbaric oxygenation in the rat. Undersea Biomed. Res. 12: 423-429, 1985.

1984

Clark, J.M. and C.J. Lambertsen. Effects of inspired oxygen pressure on the nature and degree of oxygen tolerance modification. In: Underwater Physiology VIII. Bachrach, A.J. and M.M. Matzen, Eds. Bethesda: Undersea Medical Soc., 1984. pp. 31-41.

Jackson, R. The endotoxin-pretreated, oxygen-adapted rat model in 2.0 and 4.0 ATA O_2. In: Underwater Physiology, VIII. Bachrach, A.J. and M.M. Matzen, Eds. Bethesda: Undersea Medical Soc., 1984. pp. 51-59.

Torbati, D. Cellular mechanisms of oxygen toxicity. In: Oxygen: An in-depth study of its pathophysiology. 28th Undersea Medical Society Workshop. Bethesda, MD: Undersea Medical Soc., 1984. pp. 377-409.

Torbati, D. and C.J. Lambertsen. Alterations in rat local brain and spinal cord glucose utilization following 30 to 60-minute exposure to 2 and 3 ATA O_2 and normoxic N_2-O_2 at 3 ATA. In: Underwater Physiology, VIII. Bachrach, A.J. and M.M. Matzen, Eds. Bethesda: Undersea Medical Soc., 1984. pp. 61-68.

Torbati, D., C.J. Lambertsen and J. Greenberg. Regional cerebral glucose utilization rates in rats during asymptomatic period of exposure to 1, 2, and 3, ATA O_2. Neuroscience 11: 947-950, 1984.

Torbati, D., P. Lo and C.J. Lambertsen. Local cerebral glucose utilization rate following intermittent exposures to 2 atmosphere absolute oxygen. Neuroscience Lett. 50: 79-84, 1984.