(2)

ANNUAL REPORT

June 1, 1963 - May 31, 1964

John J. Byrne, M.D.
John J. Cahill, M.D.
Edward A. Gaensler, M.D.
Denise Jouasset-Strieder, M.D.

Third (Boston University) Surgical Research Laboratory
Boston City Hospital, Boston, Massachusetts

PULMONARY VENTILATION AND DIFFUSION IN SHOCK

DA-49-193-M.D.-2206

ABSTRACT

1. Institution: Third (Boston University) Surgical Research Laboratory, Boston City Hospital, Boston 18, Massachusetts

2. Title: Pulmonary Ventilation and Diffusion in Shock

3. Investigators: John J. Cyrre, M.D.
John M. Cahill, M.D.
Edward A. Gaensler, M.D.
Denise Jousset-Strieder, M.D.

4. Number of pages: 30 pages
Date: June 1, 1964

5. Contract number: DA-49-193-M.D.-2206

6. Supported by: U.S. Army Medical Research and Development Command
Department of the Army
Washington 25, D.C.

Previous studies in dogs have demonstrated that acute hemorrhage results in a rise in lung compliance and a fall in resistance to airflow if the lungs are intermittently inflated.

Recent studies indicate that injection of endotoxin in dogs, results in a sudden fall in compliance and a rise in resistance to airflow immediately following injection. These changes are transitory and less constant in animals which are heparinized.

Further studies of pulmonary diffusion in dogs confirm the fall in the diffusion capacity for carbon monoxide (DLCO) and in lung capillary blood volume Vc during both acute and irreversible shock. The fall in DLCO was always proportional to the volume of red blood cells in the lung capillaries (Vrbc). The fall in Vc was not related to the duration of the anesthesia nor to the retransfusion of blood.

Control studies have been carried out as a preliminary to the evaluation of patients in shock.

Note: Copies of this report are filed with the Armed Services Technical Information Agency, Arlington Hall Station, Arlington 12, Virginia, and may be obtained from that agency by qualified investigators working under Government contract.

KEY WORDS:
SHOCK - PULMONARY VENTILATION - PULMONARY DIFFUSION - COMPLIANCE
AIRWAY RESISTANCE - ENDOTOXIC SHOCK - PULMONARY CAPILLARY BLOOD VOLUME

A. COMPLIANCE AND AIRWAY RESISTANCE

1. Studies in dogs.

Previous study of the ventilatory mechanics in hypovolemic shock in dogs revealed a rise in compliance and a fall in resistance to airflow if the lungs were intermittently inflated.[1-2] This was noted whether the hemorrhage was massive and acute, or of a graduated type.[2] If the lungs were not inflated following the inception of shock, a fall in compliance occurred which was less than that seen in dogs merely anesthetized and kept in the supine position without shock, and without inflation of the lungs.[2] We are reporting similar studies in dogs during shock induced by the injection of gram negative endotoxin.

Methods

Nine dogs were lightly anesthetized with Sodium Pentobarbital and a cuffed endotracheal tube inserted. A catheter was placed in the femoral artery to monitor blood pressure, and a vein cannula inserted for injection of drugs. Lung mechanics were measured by previously described techniques utilizing the body plethysmograph, esophageal balloon and a Silverman pneumotachometer.[2] Following careful inflation of the lungs, control studies were carried out and the animal then given a large dose of E. coli (gram negative)* endotoxin intravenously. The amount given was at least two times the calculated LD 70-80 dose.[3] Blood pressure and ventilatory mechanics were then monitored over a one-half to one hour period with intermittent inflation of the lungs. Four dogs received heparin prior to administration of the endotoxin and five did not.

* Obtained from Difco Laboratories. Lipopolysaccharide E. coli O11:B4

Results

The results of the studies in nine dogs are seen in Table I. The first three dogs (Dogs 1-2-3) received heparin to prevent clotting in the tubing. It will be noted that little change is to be seen in the ventilatory mechanics. We then became aware of studies indicating that heparin protected against endotoxin shock.[4] While it appeared to afford no protection against shock in our cases and all the animals died within twenty-four hours, we decided to carry out the study without heparin administration. In three of the next four dogs (Dogs 4-5-7) a sudden fall in compliance and a rise in airflow resistance was noted. Improvement in mechanics began shortly after this change. The one animal of the four without change (Dog 6) was already in shock during the control run. In the next animal (Dog 8) despite full heparinization compliance fell, and resistance to airflow rose following the administration of the endotoxin.

At present four dogs received heparin and one of these showed changes in mechanics.(Dog 8). The others had little or no change. Five dogs received no heparin and four of these showed the fall in compliance and rise in resistance to airflow. All dogs died following endotoxin administration. A fall in blood pressure occurred in all dogs but in one nonheparinized dog, (Dog 9) changes in lung mechanics preceded the fall in blood pressure.

Discussion

These studies indicate that intravenous injection of endotoxin may result in changes in ventilatory mechanics, characterized by a sudden fall in compliance and a rise in resistance to airflow. These changes appear to be independent of changes in blood pressure to some extent, in that a fall in blood pressure was seen even in the dogs apparently

protected by heparin (Dogs 1-2-3) and occurred prior to the fall in blood pressure (Dog 9). Whether or not shock itself protects against these changes (Dog 6) is questionable.

The dosage of endotoxin given these dogs was very large which may account for lack of protection by heparin in one animal (Dog 8).

In order to study more subtle changes and protective effects, a smaller dose of endotoxin will have to be used.

Evidence has been presented by Hardaway[4] to show that heparin protects dogs against death from endotoxic shock.

Thomas et al.[5] have studied the ventilatory mechanics following the administration of endotoxin in dogs. They demonstrated a protective effect of heparin and anti-serotonin drugs against changes in lung mechanics. A marked fall in platelets was noted after endotoxin in all cases (even when heparin was given) but changes in mechanics were less severe. They have implicated serotonin as the mediator of the lung changes, and although conclusive proof is lacking evidence for a humoral response appears good. It appears that the ventilatory changes are at least partly unrelated to the occurrence of shock and death in these animals. Certainly large doses of serotonin, causing far more marked changes in lung mechanics, are not lethal to dogs.[6] Furthermore, the changes in mechanics appear to revert rapidly in the direction of the controls, although shock persists.

What relationship all this may have to the patient suffering from the endotoxemia is, of course, questionable. The model used for these studies is artificial, and probably unlike true endotoxemia particularly at its inception.

Studies using a more suitable model are planned as well as the study of patients.

II. Studies on patients.

Control studies have been carried out on a series of patients and volunteers to evaluate new equipment and a slightly altered technique of study.

Method

Since the body plethysmograph is unsuitable for the study of patients, tidal volume was integrated from airflow using a standard Silverman pneumotachometer. Transpulmonary pressure was measured from a latex balloon placed in the esophagus as in previous studies. The majority of controls were studied while the patient was sitting. Several volunteers and patients were also studied in the supine and left lateral positions, since it is doubtful whether shock patients can tolerate sitting up. Approximately twenty patients were studied. Of these about thirteen qualify as reasonably normal controls. Two patients with known lung disease were studied and one patient who had suffered a pulmonary embolus.

Results

The ventilatory mechanics of the patients studied are listed in Table II. The first thirteen studies are normal controls. The last three in patients with lung disease. The mean compliance for the controls was .18 liters / cm. H_2O $\pm$ .043 and mean resistance to airflow was 2.5 cm. H_2O / liters / sec. $\pm$ .3 during normal breathing. This compares reasonably well with other studies[7-8] of patients in the sitting position.

When patients were placed in the supine position there was a marked decrease in compliance. Five studies were done with the patients

lying on their left side. This resulted in a moderate decrease over the sitting position (- .05 liters / cm. H_2O).

Discussion

These results indicate that the method is satisfactory for the study of patients in shock. We feel that the left-side position will probably be the most frequently used since the shock patient may be unable to tolerate the sitting position. In any case studies in the same patient (during and after shock) will always be carried out in the same position.

The most vexing question in these studies is over the ability of the esophageal balloon to accurately measure true transpulmonary pressure. There is good evidence to indicate that it does under ideal conditions;[7] however, the position of the ballon and of the patient are well known variables.[9] We have utilized a type of balloon and a technique described to us by Dr. Milic-Emili, and recently reported by him.[10-11] This technique has aided in proper positioning of the balloon. However, the stability of pressures noted during position change in his static studies has not been completely reproducesble during our dynamic studies, especially in the supine position. Our controls are within the normal range (sitting and left side) and suitable for clinical studies of shock.

TABLE I

		CONTROL				Post injection 2 hr.				Post injection 10 min.				Post injection 1-1 hr.			
DOG	WT	BP	TV	C	R	BP	TV	C	R	BP	TV	C	R	BP	TV	C	R
I*		115/80	323	.13	2.7	66/50	270			66/50	255	.11	2.1				
II*	10	160/110	120	.07	5.3	33/22	104	.07	4.1	68/65	105	.08	3.7	82/72	115	.09	3.2
III*	18	144/90	368	.13	3.5	126/90	275	.12	3.5	122/85	245	.10	4.0	72/41	245	.11	3.4
IV	10	120/77	126	.05	3.0	44/14	40	.02	9.0	61/41	67	.03	3.3	88/55	90	.04	3.3
V	13	140/110	200	.07	2.2	60/40	150	.05	3.0	50/36	150	.08	2.7				
VI	10	91/54	177	.09	3.0	70/38	150	.09	2.3	56/27	144	.15	2.7	50/27	145	.10	2.7
VII	14	145/124	110	.07	1.8	Very low	115	.04	2.1	77/55	100	.05	2.2	82/55	105	.08	2.7
VIII*	10	140/110	130	.15	3.0	55/40	145	.05	3.6	82/60	130	.07	2.7	82/60	120	.07	3.2
IX	10	135/100	90	.05	3.1	135/108	85	.03	5.1	120/84	75	.04	3.8	108/84	115	.05	4.0

WT = Weight in Kg.
BP = Blood Pressure mm. Hg.
TV = Tidal Volume in ml.
C = Lung Compliance L/cm. H_2O
R = Airflow Resistance cm. H_2O
* = Heparinized dogs

TABLE II

VENTILATORY MECHANICS IN PATIENTS

Pt.	Age	Smoker Pk/day	Lung Disease	Pt. Sitting TV	C	R	Pt. on Left Side TV	C	R
F.R.	29	0	0	1.0	.18	2.6	0.5	.17	2.6
P.R.*	29	0	0	1.5	.23	1.8			
H.C.	34	0	0	0.7	.26	2.7	1.0	.17	2.6
R.B.	21	1.0	0	0.8	.13	1.9			
P.P.	25	0	0	1.0	.20	1.5	2.0	.13	2.2
P.P.*	25	0	0	1.0	.17	1.9	1.3	.13	2.4
B.J.	26	1.0	0	0.5	.15	3.5			
J.M.	46	3.0	bron-chitis	0.6	.15	4.5			
R.S.	43	0.5	0	1.5	.12	2.9			
J.P.	20	0.1	0	1.7	.19	2.7	1.3	.19	3.7
J.S.	41	1.0	0	1.0	.21	3.3			
D.S.	25	0	0	0.8	.20	3.0	1.0	.15	4.0
T.E.	24	0	0	0.10	.20	2.0	1.0	.14	2.9
L.J.	25	-	pulm.emb.	0.5	.06	2.9			
G.K	45	-	tbc.	0.5	.08	6.5			
W.D.	68	-	chr.lung disease	0.7	.06	6.3			

C = Lung Compliance L/cm. H_2O
R = Resistance to Airflow cm. H_2O /L/sec.
TV = Tidal Volume in Liters

* Repeat study 2 weeks later

References A.

1. Cahill, J.M. and Byrne, J.J.: Ventilatory Mechanics in Hypovolemic Shock. J. Appl. Physiol. In press.

2. Byrne, J.J., Cahill, J.M. and Gaensler, E.A.: Pulmonary Ventilation and Diffusion in Shock. Annual Report to Army - Contract No. DA-49-193-M.D.-2206, June 1, 1962 - May 31, 1963.

3. Zweifach, B.W.: Aspects of Comparative Physiology of Laboratory Animals Relative to the Problem of Experimental Shock. Federation Proceedings. Vol. 20, No. 2, Part III, 18-27, July, 1961.

4. Hardaway, R.M., Husni, I.A., Geever, E.F., Noyes, H.E. and Burns, J.W.: Endotoxin Shock - a Manifestation of Intravascular Coagulation. Ann. Surg. 154: 79, 1961.

5. Thomas, D., Tanabe, G., Kahn, M. and Stein, M.: The Role of Platelets in Endotoxin Induced Broncho-Constriction in Dogs. Clin. Res. Vol. XII. No. 2, 294, April, 1964.

6. Cahill, J.M. and Byrne, J.J. Unpublished data.

7. Mead, J. and Whittenberger, J.L.: Physical Properties of Human Lungs Measured During Spontaneous Respiration. J. Appl. Physiol. 5: 779, 1953.

8. Marshall, R. and DuBoise, A.B.: The Measurement of the Viscous Resistance of the Lung Tissues in Normal Man. Clin. Science 15: 1-11, 1956.

9. Mead, J. and Gaensler, E.A.: Esophageal and Pleural Pressures in Man - Upright and Supine. J. Appl. Physiol. 14: 81-83, 1959.

10. Milic-Emili, J., Mead, J., Turner, J.M. and Glauser, E.M.: Improved Technique for Estimating Pleural Pressure from Esophageal Balloons. J. Appl. Physiol. 19:207-211, 1964.

11. Milic-Emili, J., Mead, J. and Turner, J.M.: Topography of Esophageal Pressure as a Function of Posture in Man. J. Appl. Physiol. 19: 212-216, 1964.

B. PULMONARY DIFFUSION STUDY

1. Studies in dogs.

Diffusion capacity for carbon monoxide (DLCO) was studied in dogs using the single-breath technique. A modification of the single-breath method was used to determine the membrane diffusing capacity (Dm) and the volume of blood in the lung capillary (Vc). The present studies represent a continuation of those on pulmonary diffusion in hypovolemic and irreversible shock, as well as additional studies made in an effort to rule out factors other than shock as a cause for the changes seen.

Method

The technique for studying DLCO in dogs, as well as the method of obtaining the Dm and Vc has been discussed previously in detail.[1] The following further studies were carried out without technical modification.

a. The study of pulmonary diffusion in acute and irreversible shock was completed (three dogs successfully studied).

b. The effect of retransfusion after a short period of shock was investigated (four dogs). After control studies, hypovolemic shock to a blood pressure of 30 mm. Hg. was induced for fifteen to thirty minutes. The dogs were then reinfused and diffustion studies repeated.

c. The effect of prolonged anesthesia without shock was ascertained (three dogs). These dogs were anesthetized and gas analysis carried out immediately, and at two-hour intervals for four hours. Shock was not induced. The animals' lungs were intermittently inflated to prevent atelectasis.

d. Our technique was slightly modified to evaluate the effect of the lung inflation preceding the administration of the test gas on the values of Vc. Such an effect was considered of possible significance because the three lung inflations performed immediately before each

determination of diffusion capacity were similar to a Valsalva maneuver. The latter, has been shown[2] to be followed by an increase in Vc. In two dogs the tests were carried out one minute after lung inflation when no significant degree of pulmonary atelectasis should be expected, but when the hemodynamic effect of the inflations had subsided.

e. Pulmonary artery and left ventricular catheterization were used during the diffusion studies in six dogs. In only two of these dogs was it possible to complete the experiments. The results of diffusion studies in these dogs are included in groups a. and b. respectively. Complications occurred in the other four dogs during catheterization and the animals went into shock prior to the control studies.

The hemodynamic data obtained in the one animal successfully studied during irreversible shock suggested that changes in pulmonary surface tension might be present during shock similar to those which have been shown to occur during cardiopulmonary bypass.[3] An attempt was made to evaluate this hypothesis without opening the chest, as would be required for direct measurement of alveolar-lining surface tension by the method of Clements.[4]

The lung static hysteresis was studied utilizing the technique used by Mead[5] in intact dogs placed in a body plethysmograph. The dogs were intubated and changes in lung volume calculated from the pressure changes within the plethysmograph. A small pneumothorax was instituted and a mushroom catheter placed in the pleural space. A balloon was inserted in the esophagus as well and transpulmonary pressure was measured by both techniques. Both volume and trans-

pulmonary pressures were recorded simultaneously on a Sanborn, four-channel recorder and later plotted on a volume pressure diagram. The lung was inflated by steps of approximately 100 ml., with about 1.5 second intervals between each increasing inflation. A total of 500 ml. to 800 ml. volume change was carried out, followed by a step-wise deflation of the lung. Apnoea for the study was produced by hyperventilation of the animal just prior to each test.

Results

a. Table I indicates the results obtained in six dogs during the control state, hemorrhagic shock and irreversible shock.

During hypovolemic shock DLCO fell to 60 per cent of control and Vc to 53 per cent. The blood Hgb. was essentially unchanged. During irreversible shock DLCO was only 81 per cent of the control value and Vc remained as low as 58 per cent. This confirms our previous report that Vc fails to return to normal in the irreversible shock preparation. Changes in Dm did not follow a symmetrical pattern.

The proportionality between DLCO and the volume of red blood cells in the lung capillaries (Vrbc) which we observed in our preliminary anemia experiments[6] appears to hold true in hemorrhagic and irreversible shock as well.

b. Four dogs were studied with retransfusion within thirty minutes after the inception of hypovolemic shock. No studies were carried out during acute hypovolemia in these dogs, and it was assumed that the changes during this period were similar to those seen in the

complete shock studies (a). Following early retransfusion no significant change was noted in DLCO, Vc, Vrbc or Dm, and all the dogs survived. The results of these studies are noted in Table II.

c. The results of the study with prolonged anesthesia without shock are indicated in Table III.

The slight increase in Vc and decrease in Dm, although not significant, suggest that prolonged anesthesia might well result in some degree of pulmonary congestion. However, the changes noted in pulmonary diffusion are in all respects opposed to those observed in irreversible shock.

d. In two dogs the timing of the lung inflation preceding the injection of the test gas was observed to have had little effect upon the results. The capillary blood volumes observed when a one-minute interval was allowed to intervene between the lung inflation and the diffusion test were 91 and 95 per cent respectively of the values obtained by our usual technique.

e. Catheterisation of the pulmonary artery and left ventricle was carried out on a number of dogs in an effort to evaluate the effect of the lung inflation on the vascular dynamics and to correlate changes in pulmonary diffusion during shock with hemodynamic data.

Studies were initiated in six animals. However, in four hypotension developed during the preparation of the animal and the control studies at normal blood pressure were impossible. Only one dog had combined pulmonary diffusion and hemodynamic studies during acute and irreversible shock (Table I, Dog No. XXII). The other dog was in the early retransfusion group. In this animal the catheter slipped out of the pulmonary artery during shock

and could not be replaced accurately during hypotension (Table II, Dog No. XIX). No valid conclusions could be drawn from these single studies and this aspect of the project has been temporarily set aside.

Since the equipment for such a study was already available to us, a rapid survey of lung hysteresis during acute and irreversible shock was carried out in four dogs.

Evaluation of the results, however, quickly convinced us that the pressure volume relationship changed markedly with the number and degree of preliminary lung inflations used to prevent atelectasis and to make the animal apnoeic during the study. The study of lung surface tension during shock appears to require other methods[4] and was discontinued.

Discussion

Studies of DLCO, Vc and Dm. have now been completed in anemia[1,6] and during acute and irreversible shock. The results do not appear to be influenced by the length of anesthesia or the timing of the preliminary inflation of the lungs. The retransfusion of blood does not appear to be responsible for the changes in irreversible shock. In both the shock state and anemia the changes in DLCO appear to be directly related to the volume of red cells present in the lung capillaries.

During the anemia studies Vc remained at or about control levels, while in both acute and irreversible shock it was markedly reduced. Hematocrit was markedly altered in anemia but changed little in either acute or irreversible shock.

A fall in Vc was predicted by Burrows[7] on a basis of his diffusion studies, although his technique did not permit direct measurements.

The effect of ganglionic blockade has been reported by Lewis et al.[8] who demonstrated a fall in Vc associated with marked lowering of the systemic blood pressure in human volunteers.

From a review of the literature no valid conclusions can be drawn as to the mechanism responsible for the fall in Vc in hypotension either induced by drugs or hemorrhage. Active pulmonary vasomotor changes could be at work, or changes in the pulmonary bed could be passive, secondary to the fall in systemic blood pressure. Gerst et al.[9] studied certain aspects of the pulmonary change in hypovolemia and noted an enlarged gradient between alveolar and arterial CO_2. He interpreted this as due to a lack of perfusion of some alveoli, which were still ventilated with resulting development of an alveolar dead space. This merely implies a fall in Vc but does not explain why it falls. Furthermore, his animals were ventilated at a set volume which may have artificially produced or increased the ventilation perfusion imbalance in the lung.

During acute shock a fall in Vc was more or less to be expected since it can readily be theorized that the vascular bed would conform to the smaller volume of blood available in the body.

In irreversible shock, the failure of Vc to improve in relation to the return of T.B.V. and blood pressure to close to normal levels is more difficult to explain. A return of pulmonary artery pressure to normal in irreversible shock has been demonstrated by others using

a similar model.[10] A careful analysis of changes in pulmonary vascular resistance during shock may help clarify this problem but the difficulty of valid interpretation of vascular activity in the pulmonary bed is well known.[11]

Studies in humans

In the experimental animal certain changes in pulmonary diffusion have been found to occur during acute and irreversible shock. Information on the alterations in pulmonary circulation accompanying these changes is difficult to obtain. Of more immediate consideration is whether similar changes accompany shock in humans. In preparation for the evaluation of clinical shock in patients the following studies have been carried out. First, to evaluate the accuracy of estimating lung volume from the He dilution during a single breath test and second, to evaluate the relationship of Vc to total blood volume (T.B.V.) in a group of normal volunteers.

Methods

a. The results of ventilatory studies of nineteen patients with alveolar capillary block were reviewed. These patients were suffering from Beryllium disease of the lungs, sarcoidosis, interstital pneumonitis, etc. The alveolar volume (V_A) of these patients was calculated by two techniques: First, by adding the residual volume as determined by the closed He technique[12] to the volume inspired for breathholding during a single breath test. Second, by calculating V_A directly from the He dilution ratio obtained during the single breath test assuming 250 cc. to be anatomic dead space during breathholding.

b. Five presumably normal volunteers have thus far been studied in the following manner. Total blood volume has been obtained by the tagged radioactive albumin technique with samples measured in a Picker Hemolitre and results corrected for hematocrit. Pulmonary function studies were then carried out consisting of timed vital capacity, residual volume measured by the closed He technique and pulmonary diffusion by the single breath method for carbon monoxide. For the diffusion studies two test gas mixtures were used each containing 0.3 per cent CO, 10 per cent He, either 21 or 90 per cent O_2 and the balance nitrogen.

In addition the diffusion studies were carried out at two levels of inspiration. 1.) Total lung capacity and 2.) Functional residual capacity plus tidal volume. DLCO, Vc and Dm were calculated by the methods previously described.[1]

Results

a. In Figure I are charted the results in nineteen patients with lung disease resulting in alveolar capillary block. It will be noted that in only one instance was a poor correlation noted between the two methods of calculating V_A. This was a case of severe emphysema included intentionally where it is well known that the He ratio may grossly underestimate V_A.

b. In all five volunteers thus far studied DLCO was observed to increase with the lung volume. This fact has been previously noted.[13-14] We find that this increase is entirely due to an increase in Vc with no significant change in Dm. At total lung volume Vc was almost double that found in the tidal volume range where it approximated 1 per cent of T.B.V.

Discussion

a. The good correlation between the two methods for calculating V_A means that the He dilution method during a single breath test alone will be required for the study of patients in shock. This will greatly simplify the procedures necessary in very ill patients. Patients with emphysema will not be studied.

b. The results of the diffusion studies on normal volunteers will give us an estimate of the relationship of Vc to T.B.V. in our hands. We will then have a comparison for the study of patient in shock.

The change in DLCO and Vc with change in lung volume suggests that great technical precautions will have to be taken in carrying out ward studies, and results carefully evaluated on a basis of the lung volumes found.

TABLE I

SHOCK EXPERIMENTS

	CONTROL					HYPOTENSION					IRREVERSIBLE SHOCK				
Dog	Hb	DLCO	Vc	Vrbc	Dm	Hb	DLCO	Vc	Vrbc	Dm	Hb	DLCO	Vc	Vrbc	Dm
IX	14.2	26.4	124	59	40	11.5	11.0	53	21	18	15.4	14.2	46	24	25
X	13.9	27.2	85	40	53	12.3	16.7	35	15	80	14.2	23.7	54	35	132
XI	15.7	14.5	28	15	52	17.0	9.5	18	10	29	17.4	11.8	20	11	51
XVII	13.1	26.7	58	26	104	13.4	14.9	41	18	35	15.9	21.4	43	23	65
XXI	12.8	12.0	36	16	26	12.5	8.7	32	13	16	14.3	14.7	30	14	54
XVII	14.0	8.7	27	13	28	17.8	8.2	14	8	28	19.2	7.9	15	10	20
Mean	13.9	19.3	60	28	49	14.1	11.5*	32*	14*	34	15.9	15.6	35*	20	58
S.D.	1.0	8.4	38	18		2.6	3.5	14	5		1.8	5.6	15	10	

Hb = gms. %
DLCO = ml./minute/mm. Hg.
Vc = ml.
Vrbc = ml.
Dm = ml./minute/mm. Hg.

* Significantly different from its control value. $P < .05$

TABLE II

EARLY RETRANSFUSION AFTER HEMORRHAGIC SHOCK - 30 MINUTES

Dog No	CONTROL					RETRANSFUSION				
	Hb	DLCO	Vc	Vrbc	Dm	Hb	DLCO	Vc	Vrbc	Dm
XV	15.9	19.8	50	27	45	14.5	17.8	50	25	37
XVI	17.4	17.0	31	18	63	19.3	17.4	27	18	112
XVIII	15.3	22.5	64	33	44	18.4	22.6	53	33	44
XIX	13.9	20.2	51	24	44	13.0	17.5	46	20	41
Mean	15.6	20.0	49	26	49	16.3	19.0	44	24	59
Mean change as per cent of control						104	94	90	92	120

Hb = gms. %
DLCO = ml./minute/mm. Hg.
Vc = ml.
Vrbc = ml.
Dm = ml./minute/mm. Hg.

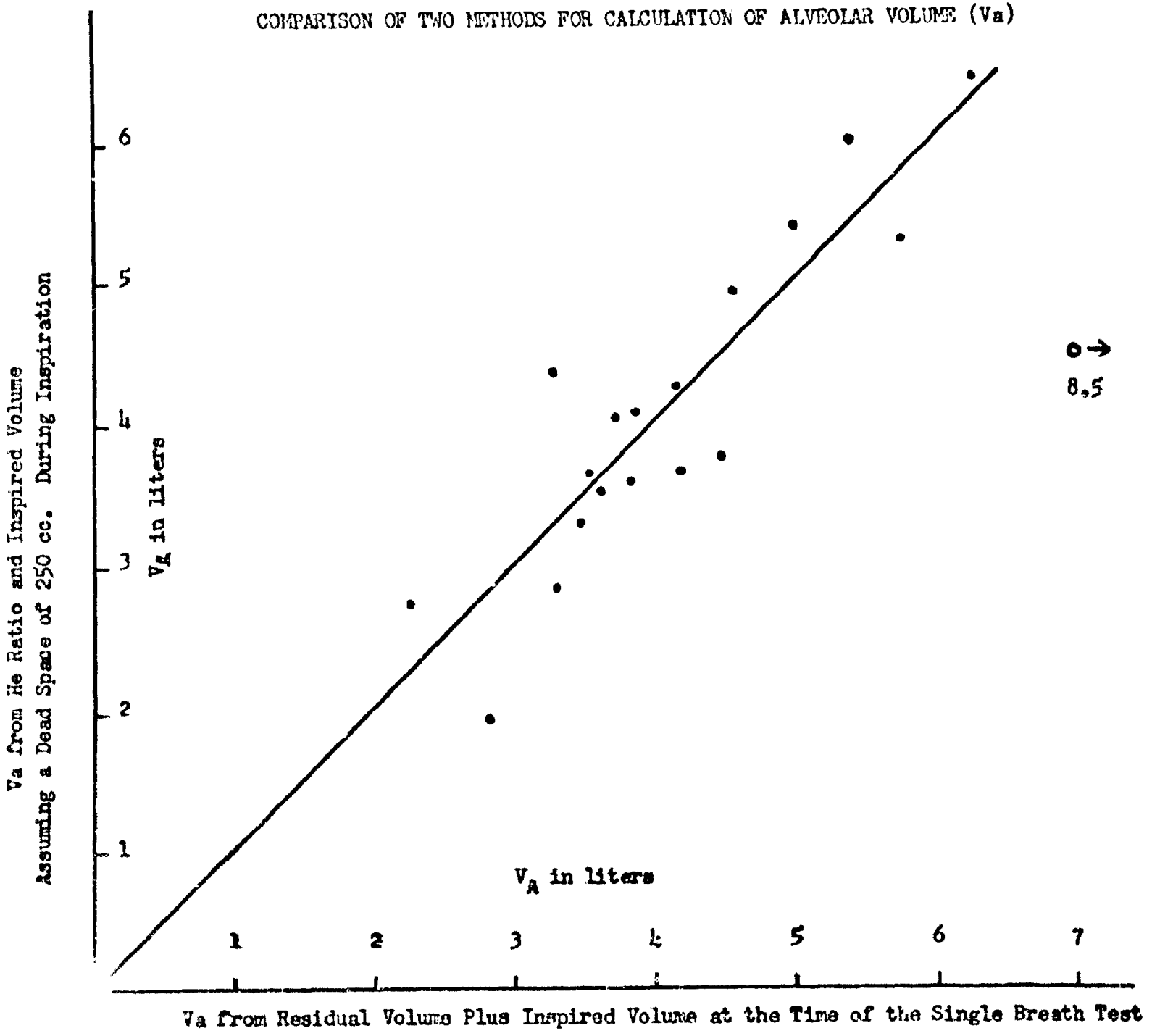
TABLE III

EFFECT OF PROLONGED ANESTHESIA ON PULMONARY DIFFUSION CAPACITY

Dog No.	CONTROL					2 Hours					4 Hours				
	Hb	DLCO	Vc	Vrbc	Dm	Hb	DLCO	Vc	Vrbc	Dm	Hb	DLCO	Vc	Vrbc	Dm
XII	15.8	33.3	68	36	100	16.2	25.2	105	57	37	15.3	21.0	60	31	41
XIII	16.0	32.2	70	38	39	15.3	20.3	48	25	50	15.3	20.5	70	36	36
XIV	17.4	29.8	61	36	75	18.8	33.3	57	34	155	18.9	36.6	106	67	51
Mean	16.4	28.4	66	37	71	16.8	26.3	69	39	81.8	16.5	26.0	79	45	43

The reduction in Dm from control to after four hours is significant at the .05 confidence level.

Hb = gms. %
DLCO = ml./minute/mm. Hg.
Vc = ml.
Vrbc = ml.
Dm = ml./minute/mm. Hg.


COMPARISON OF TWO METHODS FOR CALCULATION OF ALVEOLAR VOLUME (Va)
Va from He Ratio and Inspired Volume
Assuming a Dead Space of 250 cc. During Inspiration
V_E in liters
V_A in liters
Va from Residual Volume Plus Inspired Volume at the Time of the Single Breath Test
1
2
3
4
5
6
7
o →
8,5

References B.

1. Byrne, J.J., Cahill, J.M. and Gaensler, E.A.: Pulmonary Ventilation in Shock. Annual Report to Army. Contract No. DA-49-193-MD-2206, June 1, 1962 - May 31, 1963.

2. Daly, J.J., Roe, J.W.: The Effects of Valsalva Manoeuvre on the Pulmonary Diffusing Capacity for Carbon Monoxide in Man. Clin. Science 23: 405-409, 1962.

3. Hopps, S.A., Roe, B.B., Wright, R.R. and Gardner, R.E.: Amelioration of the Pulmonary Post Perfusion Syndrome with Hemodilution and Low Molecular Weight Dextran. Surgery 54: 232-241, 1963.

4. Clements, J.A.: Surface Tension in the Lungs. Scientific American 207: 120-130, 1962.

5. Cook, C.D., Mead, J., Schreiner, G.L., Frank, N.R. and Craig, J.M.: Pulmonary Mechanics During Induced Pulmonary Edema in Anesthetized Dogs. J. Appl. Physiol. 14: 177-186, 1959.

6. Jouasset-Strieder, D., Cahill, J.M., Byrne, J.J. and Gaensler, E.A.: Pulmonary Diffusing Capacity and Capillary Blood Volume in Normal and Anemic Dogs. J. Appl. Physiol. In press.

7. Burrows, B. and Niden, A.H.: Effects of Anemia and Hemorrhagic Shock on Pulmonary Diffusing Capacity in the Dog Lung. J. Appl. Physiol. 18: 123, 1963.

8. Lewis, B.M., McElroy, W.T., Heyford-Welsing, E.J. and Samberg, L.C.: The Effects of Body Position, Ganglionic Blockade and Norepinephrine on the Pulmonary Capillary Bed. Jour. Clin. Invest. 39: 1345-1352, 1960.

9. Gerst, P.H., Rattenborg, C., and Holaday, D.A.: The Effects of Hemorrhage on Pulmonary Circulation and Respiratory Gas Exchange. Jour. Clin. Invest. 38: 524, 1959.

10. Guyton, A.C. and Crowell, J.W.: Dynamics of the Heart in Shock. Federation Proceedings. Vol. 20, No. 2, Part III, 51-60, 1961.

11. Fishman, A.P.: Dynamics of the Pulmonary Circulation. Handbook of Physiology. Section 2, Circulation, Vol. II, Chapter 48, American Physiological Society, Wash. D.C., 1963.

12. Comroe, J.H., Forster, R.E., Dubois, A.B., Briscoe, W.A. and Carlsen, E.: The Lung. 15-17, 2nd Edition, Year Book Publishers Inc., Chicago, 1962.

13. Krogh, M.: The Diffusion of Gas Through the Lungs of Man. J. Physiol. (Lond.). 49: 271, 1914.

14. Cadigan, J.B., Marks, A., Ellicott, M.R., Jones, R.H., and Gaensler, E.A.: An Analysis of Factors Affecting the Measurement of Pulmonary Diffusing Capacity by the Single Breath Method. Jour. Clin. Invest. 40: 1495-1514, 1961.

C. HEMODYNAMIC AND EXPERIMENTAL THERAPEUTIC STUDIES

1. Mesenteric Sympathectomy and Hemorrhagic Shock

Sixty mongrel dogs were premedicated with 1.5 mg./Kg. of morphine sulphate following which the femoral artery and vein were cannulated, and heparin (2.5 mg./Kg.) injected into the femoral vein and heparin (30 mg.) into a reservoir to be used for the bleeding out preperation. Arterial pressure was continuously monitored with a mercury manometer. Fine's method of graded hemorrhage was employed to induce and maintain shock. Animals were bled from the femoral artery into a reservoir 40 cm. above the level of the right atrium, and a mean pressure of approximately 30 mm. Hg. was maintained. All the blood in the reservoir was reinfused when 40 per cent of the maximum bleeding volume was taken up spontaneously; or six hours after the onset of shock, if the 40 per cent uptake was not completed by this time. Dogs alive 24 hours after the onset of the experiment were considered to be permanent survivors.

The experiment was done in two stages. In the first, 30 dogs were divided into three groups of 10 animals:

Group I. - Control I. The animals were shocked as described.

Group II. The animals were given Dibenzyline (.5 mg./Kg.) one hour prior to the onset of hemorrhage.

Group III. The animals were subjected to abdominal postganglionic sympathectomy under nembutal anesthesia. Seven to 12 days after operation, the animals were subjected to hemorrhagic shock in a manner identical to the other two groups.

In the second stage, 30 dogs were used and divided into three groups of ten animals.

Group IV. - Control II. The animals were shocked as in Group I.

Group V. The animals were subjected to mesenteric sympathectomy similarly as before except that the interval between sympathectomy and exposure to hemorrhagic shock was extended to six weeks.

Group VI. The animals were subjected to hemorrhagic shock as in the control group. Thirty minutes after the onset of shock, however, the celiac and superior mesenteric ganglion with their respective arteries were exposed and infiltrated with 10 cc. of 1 per cent novocain. The results were analyzed in terms of survival, bowel changes, maximum bleeding time and total uptake time.

Pretreament with Dibenzyline resulted in a 60 per cent survival rate as compared to a 100 per cent mortality rate in the control group. The amount of blood shed into the reservoir (MBV) was reduced as was the rate of bleeding (MBT) and rate of uptake (UT). The smaller bleeding volume and the reduced rate of bleeding suggests that the sympathetic vasoconstrictor response to hemorrhage was modified in the early stages of shock, and prolongation of the uptake time reflects some preservation of vascular tone in the advanced stages of hypotension. Animals who were shocked 7 to 10 days after sympathectomy demonstrated a slightly higher (20 per cent) but statistically insignificant survival rate than the control group. The reduction in MBV was observed, but the bleeding time was not significantly changed. As in the Dibenzyline group, the uptake time was prolonged.

Extension of the interval between denervation and hemorrhage to six weeks did not alter survival rates. The only hemodynamic change consisted of an increased uptake time.

Chemical blockage of the mesenteric sympathetics after the onset of shock resulted in a 100 per cent mortality. In addition, an overall

deterioration of the hemodynamic parameters were observed, presumable as a result of the added trauma of a laparotomy during the hypertensive stage.

2. Therapy of A New Shock Model

The best therapy for hemorrhagic shock is control of the hemorrhage and adequate blood replacement as soon as possible. The value of numerous ancillary measures used between the onset of shock and blood replacement have been tried with varying degrees of success. Some of the measures under current study are the use of vasoconstrictors, adrenergic blocking agents and anticoagulating materials. In an effort to mimic the clinical situation and produce an experimental model with an LD of approximately 50, the following methods were utilized and results obtained.

Methods

Sixty mongrel dogs were used throughout the experiment. After weighing, each animal was lightly narcotized with morphine, and cannulations to the femoral artery and vein performed. Heparin was administered intravenously and the venous cannula capped with a heparin block. The arterial cannula was connected by a Y-tube to a calibrated Lamson bottle held 40 cm. above the level of the animal's heart. The other connection of the Y-tube was used for a continuous blood pressure monitoring by a Sanborn recorder. Control values were obtained for blood pressure, hematocrit and arterial pH.

The animals were bled into the Lamson bottles for a period of one-half hour. At the conclusion of this period of bleeding, the cannula to the reservoir was clamped and the following determinations made: amount of blood in the reservoir, blood pressure of animal, hematocrit and arterial pH. Through the venous cannula, therapy was begun with

various solutions: (A) 500 cc. of saline (10 dogs); (B) 500 cc. saline plus 2 cc. of l-norepinephrine (10 dogs); (C) 500 cc. saline plus one-half cc. trimethaphan camphorsulfonate (10 dogs); (D) 500 cc. saline plus fibrinolysin 4000 u/Kg. (10 dogs). In two other groups of animals the bleeding period was extended to one hour to increase the LD. After this one hour period the therapy was instituted as follows: (E) 500 cc. saline (10 dogs); (F) 500 cc. saline plus fibrinolysin 4000 u/Kg. (10 dogs).

The animals were monitored for six hours, if possible, with a three-hour check on blood pressure, hematocrit and pH. At the end of the six-hour period the animal was returned to his cage and observed for a 24 hour survival. If death occurred the animal was autopsied, with particular emphasis placed on the condition of the gastrointestinal tract.

The one-half hour bleeding period proved to be a moderate challenge to these animals, offering a control survival of 7 out of 10. The addition of a vasodilator decreased survival. Fibrinolysin increased survival.

The one hour bleeding period was more of a challenge, with a control salvage of only one out of 10 animals. Since l-norepinephrine and trimethaphan camphorsulfonate did not improve survival with one-half hour bleeding, they were not used in this more severe preparation. Fibrinolysin again increased survival.

When the controls and fibrinolysin animals on both the half-hour and one-hour bleeding are grouped together the control salvage was 8 out of 20 as compared to 15 out of 20 for fibrinolysin. These figures have a significance when compared statistically (chi-square 6.4: $P < .01$).

There appeared to be little difference among the groups with regards to average weight, blood loss, or three-hour hematocrits.

The three-hour blood pressure findings are of some significance. In general, if the animals were still alive and the blood pressure was above 100, there was a good chance of survival (26 out of 34 possibilities); whereas if the blood pressure is below 100, there is little chance of survival (2 out of 18 possibilities). These are highly significant figures (chi-square 17: $p < .005$).

Similarly, the three-hour arterial pH was an excellent guide to the quality of tissue perfusion. If the pH was 7.3 or above, there was an excellent chance for survival (22 out of 24 possibilities); whereas if the pH was below 7.3, there was little chance of salvage (6 out of 28 possibilities). Again, these are significant figures (chi-square 22: $p < .005$).[1]

3. Blood Volume and Mixing Time Determinations

Serial blood volume measurements in 26 patients undergoing open heart surgery revealed a significant volume deficit unaccounted for by external loss. This internal loss is attributed to sequestration of blood into vascular pools not in intimate communication with the effective circulatory system. This supposition implies two distinct vascular beds with limited functional communication and diffusing rates of circulation.[2] Injected radioactive substances may not reach the stagnant circuit during the standard time allotted for mixing and a deceptive low blood volume reading may be obtained. Repeated postinjection sampling may detect the sequestered pool and provide a progressive increase in blood volume reading. Pooling of blood also occurs in traumatic shock, and it may reflect an impaired capillary circulation. Detection of slow mixing by

by blood volume determinations may uncover the basic underlying pathogenesis and provide a method of evaluation of the effectiveness of various therapeutic agents.

Base line controls prior to inducing hemorrhagic and toxic shock were obtained. Blood volume determination with I^{131} and CR^{54} were performed in 10 dogs. Postinjection samples were obtained at 10,20,30 and 40 minutes. Splenectomy was then performed on the animals and the same blood volume studies were repeated two weeks later.

No appreciable changes were found with the serial postinjection sampling technique. However, a loss in blood volume was exhibited following the splenectomy by either the Chromate or I^{131} method.

Preliminary results on two experimental animals suggests that after the induction of hemorrhagic shock there is a steady increment of volume readings up to 40 minutes after injection on serial postinjection sampling. These results are similar to those obtained on surgical patients immediately following open heart surgery.

References

1. Byrne, J.J. and Seifert, D.E.: Treatment of Experimental Hemorrhagic Shock. Boston Med. Quart. 15:60-63 (June) 1964.

2. Berger, R.L., Boyd, T.F. and Marcus, P.S.: A Pattern of Blood Volume Responses to Open Heart Surgery. New England J. Med. (In Press).