THE EFFECTS OF HEMORRHAGE ON PULMONARY CIRCULATION AND RESPIRATORY GAS EXCHANGE *†

By PAUL H. GERST, CHRISTEN RATTENBORG‡ AND DUNCAN A. HOLADAY

(From the Departments of Surgery and Anesthesiology, College of Physicians and Surgeons, Columbia University, and the Surgical and Anesthesiology Services, The Presbyterian Hospital, New York, N. Y.)

(Submitted for publication August 18, 1958; accepted November 25, 1958)

A close relationship between pulmonary ventilation and blood flow exists in the normal functioning of the lungs. Thus, primary alterations in one of these processes are difficult to distinguish from secondary changes in the other. In order to study these two functions in the intact animal, we have separated them by utilizing a technique which allows us to induce alterations in pulmonary blood flow while keeping ventilation constant in rate and tidal volume. This report describes changes observed in the pulmonary circulation and respiratory gas exchange of dogs in whom blood flow was decreased by hemorrhage and then restored by blood replacement.

Studies on experimental animals and human subjects have indicated that all pulmonary vessels are not open at the same time (1), and that the pulmonary circulation is able to accommodate a marked increase in blood flow with little rise in the pulmonary arterial blood pressure (2–7). An increase in blood flow, then, must be accompanied by a decrease in vascular resistance, presumably due to expansion of the pulmonary bed. However, the mechanisms by which such accommodation occurs have not been fully elucidated, and questions remain as to the relative importance of physical forces, the effectiveness of vasomotor control and the significance of local pressor and chemo-reflexes. Moreover, only fragmentary data are available regarding the effects of primary *reduction* in the pulmonary blood flow, as in hemorrhagic shock (8–10), or after diversion of blood around the lungs, as in open heart surgery.

The results of the present study contribute information on the response of the pulmonary vessels to a reduction in blood flow. Our findings suggest that as flow is diminished portions of the pulmonary vascular bed close completely, and that with restoration of flow there is some delay before these vessels reopen.

METHODS

Eight dogs, ranging in weight from 12 to 19 Kg. (mean, 15 Kg.), were used in these experiments. The animals were anesthetized with sodium pentobarbital (35 mg. per Kg.) and infused with succinylcholine (0.4 μg. per ml.) at a rate sufficient to arrest respiratory muscular activity; no supplemental anesthesia was administered.

a). Respiratory measurements. The animals were intubated with a cuffed endotracheal tube and ventilated with room air by a specially designed respirator, which intermittently delivered a known tidal volume at a constant flow rate ("square wave") and of uniform duration (11). Expiration was passive with the airway open to the atmosphere. The expired gas was passed through a dry gas flow meter in which it was thoroughly mixed; at selected intervals samples were collected and analyzed for oxygen and carbon dioxide concentrations (12). In addition, a small stream of gas from the endotracheal tube was constantly drawn through an infrared carbon dioxide gas analyzer[1] so that a continuous record of the end-tidal carbon dioxide partial pressure could be obtained (13, 14).

At the outset of each experiment the respiratory frequency and tidal volume were adjusted so as to maintain the end-tidal gas carbon dioxide partial pressure within the normal range; once set, the ventilation was kept constant throughout the course of each study.

The endotracheal pressure was continuously measured, so that a pressure-volume curve for each inflation could be obtained. Since the tidal volume remained constant, the slope of this curve (Figure 1) directly reflects the total lung-thorax compliance as the change in intrapulmonic volume (tidal volume) per unit change in transthoracic (endotracheal) pressure (15–17).

* Preliminary results reported before the Federation of American Societies for Experimental Biology, April 15, 1958.

† Aided by Grant No. H 2506 from the National Heart Institute of the United States Public Health Service, and a Medical Research Grant from the National Tuberculosis Association through its Medical Section, The American Trudeau Society.

‡ Present address: Bispebjerg Hospital, Copenhagen, Denmark.

[1] Liston-Becker, Model 16.

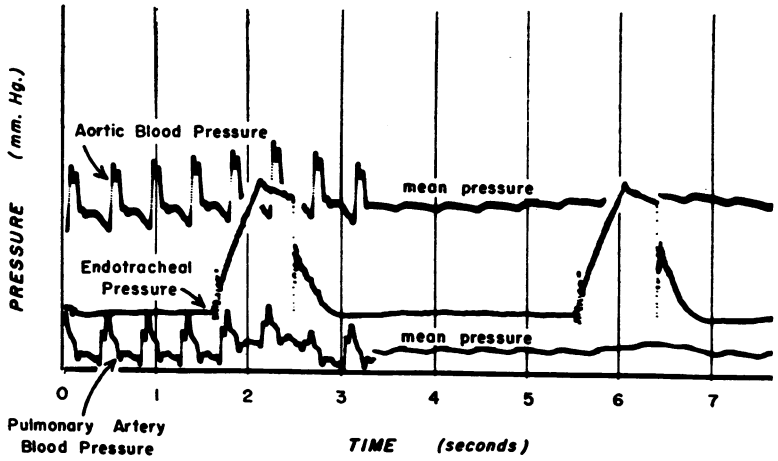

FIG. 1. SEGMENT OF CONTINUOUS RECORD OF INSTANTANEOUS AND ELECTRICALLY INTEGRATED MEAN SYSTEMIC AND PULMONARY ARTERIAL BLOOD PRESSURES AND ENDOTRACHEAL AIR PRESSURE

b). *Blood pressure measurements.* A cardiac catheter was passed via the external jugular vein and positioned, under fluoroscopic guidance, so that its tip rested in the main pulmonary artery. Another catheter was placed in one femoral artery. Using P23D Statham strain gages, we obtained simultaneous tracings of the pulmonary and femoral arterial blood pressures on a cathode ray oscilloscope; these were photographically recorded (Figure 1).

c). *Blood samples.* At appropriate intervals during each experiment, blood samples totaling 15 ml. [approximately 1 per cent of the estimated blood volume (18)] were obtained simultaneously from the femoral and pulmonary arteries and analyzed as follows:

1). Oxygen saturation was determined spectrophotometrically using the Beckman D.U. spectrophotometer and the Nahas cuvette, according to the method of Holling, MacDonald, O'Halloran and Venner (19).

2). Oxygen and carbon dioxide contents were determined by the micromanometric method of Natelson as modified by Holaday and Verosky (20).

3). pH was determined by passing blood directly from the catheters in the femoral and pulmonary arteries through a glass electrode pH meter, as described by Holaday (21).

4). Hematocrit was measured using the microcentrifuge technique (22).

5). Lactic acid concentration of arterial blood was determined by the method of Barker and Summerson (23).

d). *Calculations.* From the simultaneously obtained blood and gas samples we calculated the following:

1). Carbon dioxide tension of arterial and mixed venous blood from the Singer-Hastings nomogram (24) using the values obtained for the blood carbon dioxide content, pH and hematocrit.

2). Pulmonary blood flow by the direct Fick principle using the values for the blood and gas oxygen contents.

3). Respiratory (physiological) dead space by the Bohr formula using the carbon dioxide values and substituting the arterial for the alveolar carbon dioxide tensions (25). Thus:

$$\text{respiratory dead space} = \frac{(Pa_{CO_2} - P_{ECO_2})\, V_T}{Pa_{CO_2}}$$

where Pa_{CO_2} and P_{ECO_2} are the carbon dioxide tensions (mm. Hg) in the arterial blood and mixed expired gas, respectively, and V_T is the tidal volume. When used in this manner, the total respiratory (physiological) dead space is equivalent to that portion of the tidal volume which does not undergo gas exchange with pulmonary capillary blood (26).

4). Percentage of venous admixture from the blood oxygen contents (ml. O_2 per 100 ml. blood), using the ratio of the concentration differences of arterial to end-pulmonary capillary blood:mixed venous to end-pulmonary capillary blood, as: $(Cc'_{O_2} - Ca_{O_2})/(Cc'_{O_2} - C\bar{v}_{O_2})$ (27); "Ca_{O_2}" and "$C\bar{v}_{O_2}$" refer to the oxygen concentrations in the arterial and mixed venous bloods, respectively, and "Cc'_{O_2}" refers to the "ideal" end-pulmonary capillary blood which is assumed to be fully saturated.

5). Buffer base of arterial and mixed venous blood from the Singer-Hastings nomogram, using the values obtained for carbon dioxide content, oxygen saturation, pH and hematocrit (24).

e). *Estimates of errors in the methods.* All analyses were performed in duplicate. The reproducibility (one standard deviation) of the analytical methods was as follows:

1). Blood analyses: oxygen saturation, ±1 per cent; oxygen content, ±0.2 volume per cent; carbon dioxide content, ±0.1 mM per L.; pH, ±0.007; hematocrit, ±1.0 per cent; lactic acid, ±10 μg. per ml.; buffer base, ±0.5 mEq. per L.

2). Gas analyses: oxygen and carbon dioxide concentrations, ±0.04 per cent; carbon dioxide partial pressure, ±0.5 mm. Hg.

f). *Estimates of variance.* The above data are contained in Tables I through VI. Wherever possible the standard deviation $\left(\text{S.D.} = \sqrt{\frac{\Sigma\,(\bar{x} - x)^2}{n - 1}}\right)$ and the standard error

TABLE I

Relative changes in mean systemic and pulmonary arterial blood pressures and lung-thorax compliance during hemorrhage

Estimated blood volume reduction (%)	Control	7	12	17	22	27	32	37	42	48
Number of dogs	8	8	8	8	8	6	5	3	2	1
Mean femoral arterial blood pressure (% of control)	100*	89	78	68	52	45	39	42	33	30
(Range)		(70–98)	(60–93)	(42–90)	(30–80)	(25–72)	(75–65)	(30–60)	(20–47)	
± 1 standard deviation		9.6	13.4	15.6	17.9	17.2	15.4			
Standard error of mean		3.4	4.8	5.5	6.3	7.0	6.8			
Mean pulmonary arterial blood pressure (% of control)	100*	93	85	78	73	67	65	68	65	65
(Range)		(90–100)	(72–100)	(70–93)	(65–90)	(60–83)	(55–82)	(55–80)	(55–75)	
± 1 standard deviation		7.8	10.8	9.4	9.2	10.6	11.4			
Standard error of mean		2.8	3.8	3.3	3.2	4.3	5.1			
Lung-thorax compliance (% of control)	100*	99	98.0	97.5	96.0	94.5	90.0	89.5	88.5	85.0
(Range)		(97–100)	(95–100)	(92–100)	(88–100)	(92–97)	(88–95)	(87–92)	(87–90)	
± 1 standard deviation		1.26	2.43	2.48	4.80	1.70	3.32			
Standard error of mean		0.44	0.86	0.91	1.70	0.69	1.48			

* The actual mean values during the control period were: 135 mm. Hg for the femoral arterial blood pressure, 13.0 mm. Hg for the pulmonary arterial blood pressure, and 30.5 ml. per mm. Hg for the lung-thorax compliance.

of the mean $\left(\text{S.E.}_m = \frac{\text{S.D.}}{\sqrt{n}}\right)$ are given ("$\bar{x}$" represents the mean, "x" the individual variation and "n" the number of determinations). In those cases where only the mean values and the range are given, we intend to show merely the direction of change, the degree of which was proportional to the percentage of the blood volume removed which varied from animal to animal.

g). Procedure. After a 30 minute equilibration period two sets of control blood and gas samples were obtained one hour apart. We then began to bleed the animals from the other femoral artery in successive steps, each approximating 5 per cent of the assumed blood volume [estimated as 10 per cent of the body weight (18)], until the systemic blood pressure fell to between 25 and 50 per cent of the control level. After each aliquot of blood was removed, three minutes were allowed for re-equilibration. A sustained hypotension was obtained after approximately one-third of the estimated blood volume had been removed.

Over the next hour we collected three more sets of blood and gas samples, after which all the blood was replaced in similar step-wise increments.[2] Another two sets of data were obtained during the hour following reinfusion. We then sacrificed the animals by injecting concentrated potassium chloride into the left ventricle. As soon as the heart beat ceased, the chest was rapidly opened and the hilum of one lung clamped to prevent leakage of air and blood. The lungs were removed, fixed in formalin and microscopic sections prepared.

[2] Three of the eight animals died before complete data could be obtained for the postreinfusion period.

RESULTS

A. *Systemic and pulmonary arterial blood pressure values*

Figure 2 and Tables I and II portray the relative changes in the mean systemic and pulmonary arterial blood pressures and total lung-thorax compliance in terms of the percentage of their control values. The data plotted are the averaged values of the mean pressures obtained three minutes following completion of each successive step in the process of bleeding and reinfusion.

During blood volume depletion the systemic and pulmonary arterial blood pressures both decreased until the pulmonary pressure reached approximately two-thirds of its control value (from 13 to 8.5 mm. Hg). Despite additional blood

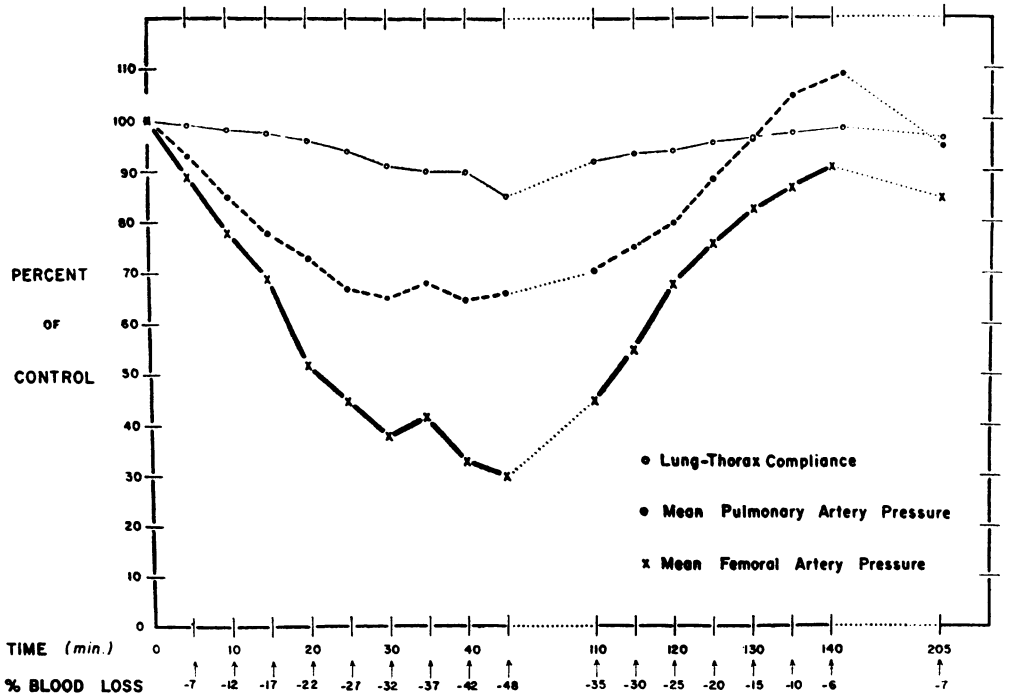

FIG. 2. RELATIVE CHANGES IN AVERAGE MEAN SYSTEMIC AND PULMONARY ARTERIAL BLOOD PRESSURES AND TOTAL LUNG-THORAX COMPLIANCE DURING HEMORRHAGE AND DURING BLOOD REPLACEMENT

Values for the control period are: main pulmonary artery blood pressure, 13 mm. Hg; femoral artery blood pressure, 135 mm. Hg; lung-thorax compliance, 30.5 ml. per mm. Hg.

loss, the pulmonary pressure then stabilized at this level, falling only slightly, whereas the systemic pressure continued its marked decline. When the blood was replaced, the systemic pressure returned to only 90 per cent of its prehemorrhagic level, whereas the pulmonary pressure *exceeded* its control value by 10 per cent.

B. *Blood flow*

During the control period the blood flow averaged 2.6 L. per minute. Following blood removal, the flow fell to between 21 to 35 per cent of the control value. After the blood was reinfused the blood flow returned to 68 per cent of the control level (Table III, Figure 3).

C. *Respiratory dead space*

The total respiratory (physiological) dead space, as derived by the above methods, is the sum of the "anatomical" or airway dead space, and the so-called "alveolar" dead space (28–34). The "anatomical" portion of the dead space is a virtual volume equivalent to the volume of the respiratory passages leading to the alveoli. The "alveolar" dead space represents the volume of air ventilating alveoli which are either not perfused, or inadequately perfused, and depends upon the overall ventilation-perfusion relationship in the alveoli throughout the lung (26).

Under normal conditions, the ventilated alveoli are well perfused so that the "alveolar" dead space is negligible and the total respiratory (physiological) dead space is equivalent to the "anatomical" dead space alone (31, 32). When, however, blood flow is diminished in relation to ventilation, a significant "alveolar" dead space may develop in addition to the "anatomical" dead space (26, 34).

During the control period the total dead space comprised 33 per cent of the tidal volume (dead space, 74 ml.; tidal volume, 220 ml.) (Table III, Figure 3). There was no significant arterial to end-tidal carbon dioxide tension difference (Table

IV, Figure 4), so that we can assume that no significant "alveolar" dead space existed, all the dead space being "anatomical." Following removal of one-third of the estimated blood volume, the total respiratory (physiological) dead space increased to 55 per cent of the same tidal volume (120 ml.), and an arterial to end-tidal carbon dioxide tension gradient appeared which averaged 8 mm. Hg. This indicates the development of a significant "alveolar" dead space. When the blood volume was restored (minus the 6 per cent expended for samples) the dead space volume returned toward the control volume (90 ml.) and the carbon dioxide tension difference decreased to 2.5 mm. Hg. The increase in the mixed venous blood carbon dioxide tension presumably reflects only the decreased cardiac output; it returned to its control level after blood restoration (Tables III and IV, Figures 3 and 4.)

The percentage of venous admixture was reduced, following hemorrhage, from a control value of 18 to 11 per cent. After blood volume was restored, this was further decreased to 5 per cent, and then rose to 7 per cent one hour after blood volume restoration (Table III).

During the control period the average oxygen saturation of the arterial blood was 95 per cent and of the mixed venous blood, 72 per cent. Following hemorrhage, the mixed venous blood oxygen saturation decreased to only 30 per cent, and the arterial blood achieved 90 per cent saturation (Table V, Figure 4). This fall in the arterial oxygen saturation is commensurate with the degree of admixture of markedly unsaturated venous blood and the decreased effective alveolar ventilation. There is thus no evidence of a barrier to gas diffusion; with blood replacement both values rapidly returned to their control levels.

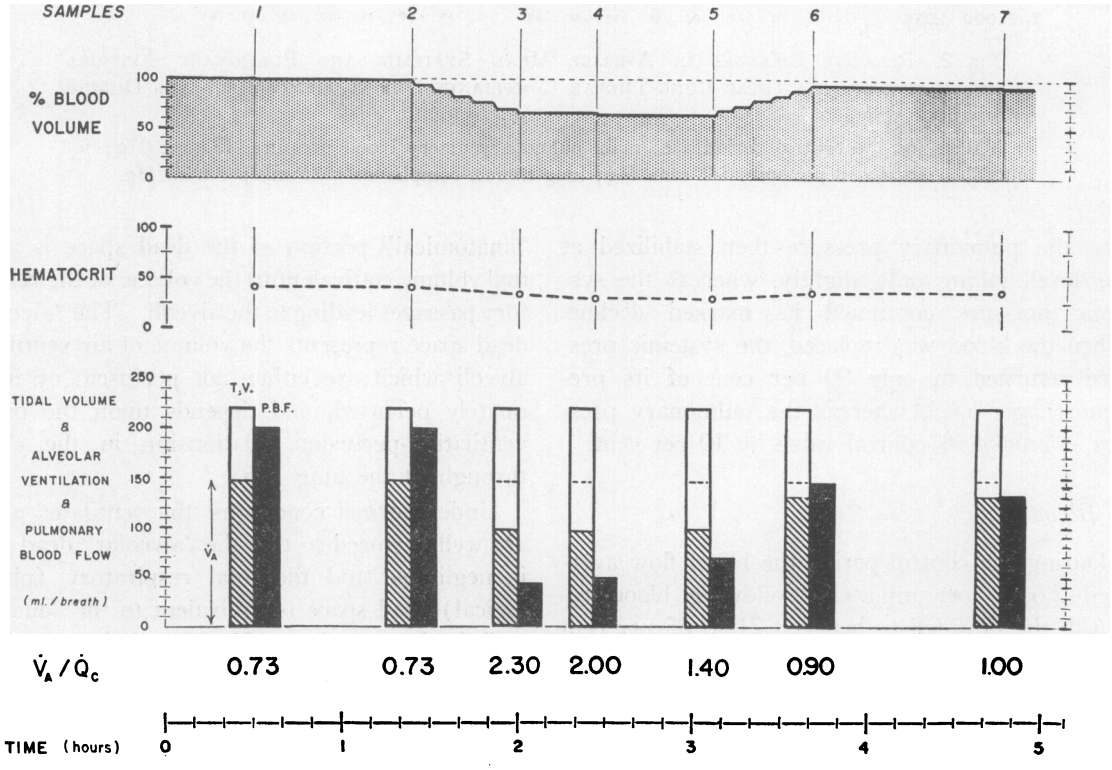

FIG. 3. CHANGES IN PULMONARY BLOOD FLOW PER INFLATION, Q_c (BLACK COLUMNS), AND TIDAL VOLUME, TV, DURING CONTROL PERIOD (1, 2), FOLLOWING HEMORRHAGE (3, 4, 5) AND AFTER BLOOD RESTORATION (6, 7)

The tidal volume is divided into alveolar ventilation, V_A (hatched area), and total respiratory dead space (white area). The dead space is further divided by the broken line into "anatomical" dead space above, and "alveolar" dead space below.

TABLE II

Relative changes in mean systemic and pulmonary arterial blood pressures and lung-thorax compliance during reinfusion

Estimated blood volume reduction (%)	35	30	25	20	15	10	6	7*
Number of dogs	3	5	5	5	5	5	5	5
Mean femoral arterial blood pressure (% of control)	41	55	68	76	83	87	91	85
(Range)	(25–65)	(30–75)	(35–85)	(45–95)	(55–100)	(60–100)	(65–100)	(55–100)
± 1 standard deviation	19.0	17.0	19.8	19.7	18.9	15.8	14.7	19.7
Standard error of mean	11.0	7.0	8.8	8.8	8.5	7.1	6.6	8.8
Mean pulmonary arterial blood pressure (% of control)	71	74	80	88	96	105	110	95
(Range)	(60–90)	(60–90)	(65–100)	(70–110)	(80–120)	(85–125)	(90–130)	(65–120)
± 1 standard deviation	16.1	13.2	14.5	14.5	14.1	15.4	16.9	22.2
Standard error of mean	9.3	5.9	6.5	6.5	6.3	6.9	7.6	9.9
Lung-thorax compliance (% of control)	92.0	94.0	95.0	95.5	96.5	98.0	99.0	98.0
(Range)	(88–95)	(90–98)	(90–100)	(91–100)	(93–100)	(93–100)	(95–100)	(93–100)
± 1 standard deviation	2.85	3.46	4.80	4.58	3.00	2.92	2.23	3.10
Standard error of mean	1.65	1.55	2.15	2.10	1.34	1.31	1.00	1.52

* One hour after all the blood was returned.

The arterial and mixed venous blood pH values declined after hemorrhage, as did the values for the buffer base concentration (Table V, Figure 5). These changes were accompanied by a simultaneous rise in lactic acid concentration, suggesting that products of anaerobic metabolism were the source of the metabolic acidosis which developed.

The total lung-thorax compliance declined to 90 per cent of its control level with blood removal and then returned to the control value following blood replacement (Tables I and II, Figure 2). This decrease could mean either that the lungs became "stiffer" as pulmonary blood flow was reduced, possibly owing to increased bronchomotor tone or changes in pulmonary blood volume, or that there was a decrease in the functioning lung tissue owing to collapse of alveoli (35–38). Histological sections of the sealed lungs from dogs that died during hypotension showed areas of collapse, particularly in the hilar regions (Figure 6), which would tend to support the latter explanation.

DISCUSSION

The findings obtained in this study are significant in two respects. First, with reduction in blood flow the systemic arterial blood pressure decreased continuously, whereas the blood pressure in the main pulmonary artery leveled off after an initial decline. Second, there was a marked increase in the total respiratory (physiological) dead space attributable to the development of a significant "alveolar" dead space. Following the restoration of blood volume, the systemic blood pressure did not return completely to its pre-hemorrhagic level, whereas the pulmonary pressure actually *exceeded* its control value. The total dead space decreased towards the control volume, but remained somewhat greater than before hemorrhage, and the lung-thorax compliance returned to its starting level.

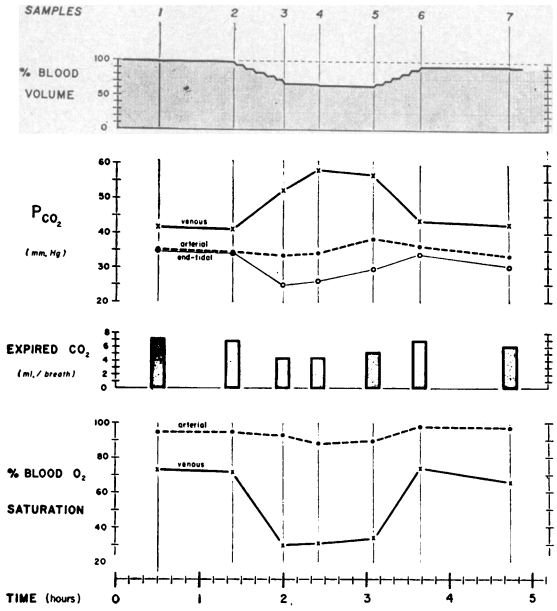

FIG. 4. VARIATIONS IN ARTERIAL AND MIXED VENOUS BLOOD AND END-TIDAL GAS CARBON DIOXIDE TENSIONS, VOLUME OF CARBON DIOXIDE EXPIRED PER VENTILATION, AND ARTERIAL AND MIXED VENOUS BLOOD OXYGEN SATURATIONS DURING THE CONTROL PERIOD (1, 2), FOLLOWING HEMORRHAGE (3, 4, 5) AND AFTER BLOOD RESTORATION (6, 7)

Note the arterial to end-tidal carbon dioxide tension gradient which developed after hemorrhage.

In the face of an equivalent reduction in blood flow, maintenance of the central pulmonary arterial blood pressure, despite a continuous decline of the systemic arterial blood pressure, suggests either an elevation of left auricular pressure or an increase in the pulmonary vascular resistance. To evaluate the first possibility we measured left auricular pressure by direct needle puncture in two additional dogs and found a progressive *decrease* during hemorrhage (Table VI). Thus, it must be assumed that as blood flow decreases the pulmonary vascular resistance rises more rapidly than the systemic resistance. This could occur as a result of: *a*) uniform and progressive vasoconstriction throughout the lungs, or *b*) complete closure of an ever-increasing number of pulmonary vascular channels, or both processes occurring simultaneously. An "alveolar" dead space could develop with either alternative. A distinction between these two mechanisms can be made from our data by examining the blood and gas carbon dioxide tensions, and the blood oxygen saturations.

Normally, there is adequate perfusion of the ventilated alveoli so that an equilibrium for a readily diffusible gas, such as carbon dioxide, will exist between alveolar gas when sampled as end-tidal gas, and end-pulmonary capillary blood when sampled as arterial blood (25, 27, 39–41). We found this to be true for our control determinations. Figure 7 is a schematic portrayal of the lung showing the relationship between pulmonary circulation and ventilation, according to the values obtained from the blood and gas analyses during the *control* period.

Following blood volume depletion, if the blood flow to the ventilated alveoli were reduced *uniformly* throughout the lung, as by partial vasoconstriction, a carbon dioxide equilibrium between end-tidal gas and arterial blood would still exist because of the great diffusibility of this gas (42–44). Our findings, however, show that the end-tidal gas carbon dioxide tension fell below that of the arterial blood (Table IV, Figure 4), so that a marked arterial to end-tidal carbon

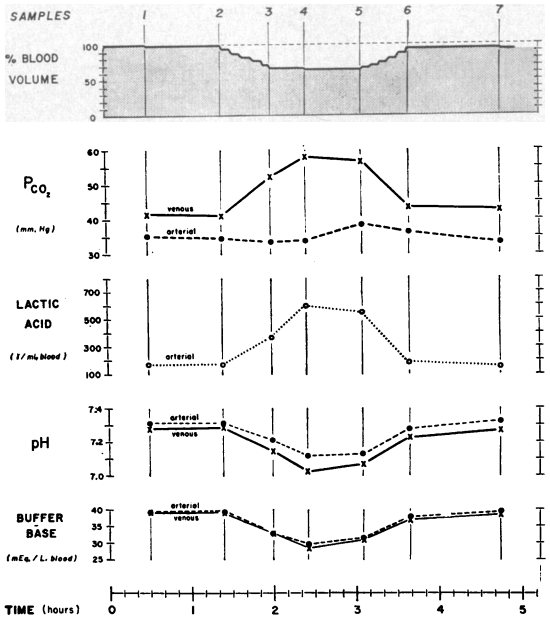

FIG. 5. CHANGES IN ARTERIAL AND MIXED VENOUS BLOOD CARBON DIOXIDE TENSIONS, pH VALUES, AND LACTIC ACID AND BUFFER BASE CONCENTRATIONS DURING CONTROL PERIOD (1, 2), FOLLOWING HEMORRHAGE (3, 4, 5) AND AFTER BLOOD RESTORATION (6, 7)

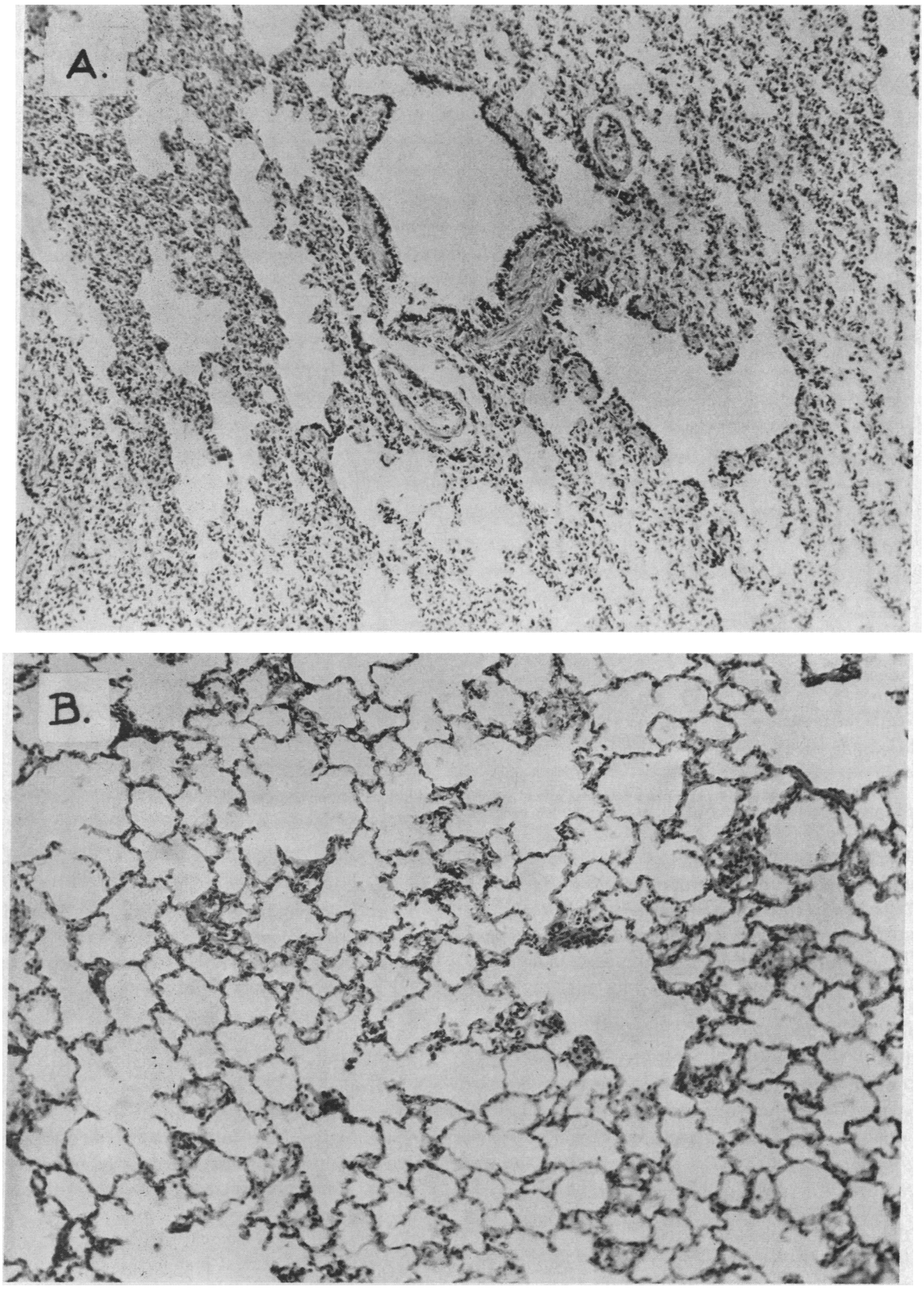

FIG. 6. MICROSCOPIC APPEARANCE OF LUNG SECTIONS FROM A DOG THAT DIED DURING HYPOTENSION

A. Hilar portion showing collapse of alveoli. B. Peripheral portion showing air filled alveoli and relatively avascular parenchyma.

TABLE III

Respiratory and circulatory observations during hemorrhage and reinfusion

	Control		Hemorrhage			Restoration	
Sample	1	2	3	4	5	6	7
Number of dogs	8	8	8	8	8	5	5
Tidal volume (ml.)	220	220	220	220	220	224	224
(Range)	(200–270)	(200–270)	(200–270)	(200–270)	(200–270)	(200–270)	(200–270)
Ventilations per minute	13	13	13	13	13	12	12
(Range)	(11–15.5)	(11–15.5)	(11–15.5)	(11–15.5)	(11–15.5)	(11–13)	(11–13)
Total (physiological) respiratory dead space (ml.)*	74	75	122	120	124	90	88
(Range)	(61–87)	(66–88)	(98–144)	(98–145)	(98–150)	(76–107)	(78–100)
% of control	100	100	164	162	167	120	118
Effective alveolar ventilation (ml. per inflation)*	146	145	98	100	96	134	136
(Range)	(115–206)	(115–204)	(60–168)	(55–167)	(54–163)	(80–163)	(78–177)
% of control	100	100	67	69	66	94	93
Pulmonary blood flow (L./min.)*	2.6	2.6	0.55	0.65	0.92	1.75	1.60
(Range)	(1.1–8.1)	(1.1–5.7)	(0.19–1.1)	(0.25–1.6)	(0.31–2.8)	(1.1–2.4)	(0.63–2.2)
ml. per inflation	200	200	42	50	71	146	134
% of control	100	100	21	25	35	68	62
Estimated blood volume (% of control)*	100	100	67 (52–79)	66 (51–78)	65 (50–77)	94	93
Venous admixture* (% of cardiac output)	16	18	9	11	12	5	7
Ventilation/perfusion ratio*	0.73	0.73	2.30	2.00	1.40	0.90	1.00
Respiratory exchange ratio*	0.90	0.94	1.10	1.10	1.15	0.97	0.90

* The mean value for the entire group is given to indicate the direction of change. The degree of change was proportional to the amount of blood removed, which varied from animal to animal.

dioxide tension difference was present. This indicates that the development of a significant "alveolar" dead space is responsible for the increase in the total (physiological) dead space. Thus, under conditions of reduced pulmonary blood flow we must view the lung as though portions of the pulmonary bed close completely, leading to *nonuniform* perfusion as indicated in Figure 8. Those ventilated alveoli which are no longer perfused cease to take part in gas exchange, and thus contain only that carbon dioxide washed into them from the dead space during inflation (34). On expiration, the gas coming from these alveoli dilutes the carbon dioxide coming from the perfused alveoli, lowering the end-tidal carbon dioxide tension and leading to the development of a carbon dioxide tension gradient between the end-tidal air and the arterial blood. Such a concept is compatible with our findings.

A probable mechanism by which such nonuniform closure of blood vessels could occur involves the relationship between the forces which keep blood vessels open and those which tend to close them. The primary force which distends the vessels is the intravascular blood pressure. This is opposed by the tension within the vessel walls, the surrounding tissue pressure and, in the case of the lung during intermittent positive pressure ventilation, the intrapulmonic air pressure which tends to compress the delicate pulmonary capillaries suspended in an air matrix with little solid support.

As the blood flow decreases there occurs, initially, a fall in the central pulmonary arterial blood pressure. When the blood pressure drops to a

TABLE IV

Arterial and mixed venous blood and end-tidal gas carbon dioxide tensions, and end-tidal to arterial carbon dioxide tension gradients

	Control		Hemorrhage			Restoration	
Sample	1	2	3	4	5	6	7
Number of dogs	8	8	8	8	8	5	5
%Estimated blood volume removed	1	2	33	34	35	6	7
(Range)			(21–48)	(22–49)	(23–50)		
Mixed venous blood P_{CO_2} (mm. Hg)*	41.5	41.0	52.3	57.5	56.5	45.3	42.5
(Range)	(35–56)	(30–57)	(34–78)	(34–91)	(39–87)	(39–56)	(30–57)
Arterial blood P_{CO_2} (mm. Hg)*	35.5	35.5	33.6	34.0	36.0	36.5	33.5
(Range)	(27.9–43.0)	(26.7–42.0)	(23.9–48.3)	(19.5–47.5)	(18.4–44.8)	(27.6–44.1)	(22.3–42.0)
End-tidal gas P_{CO_2} (mm. Hg)*	35.2	34.9	25.3	26.0	28.2	34.0	31.0
(Range)	(29.0–39.0)	(29.5–40.5)	(18.0–32.5)	(15.5–38.0)	(14.0–36.0)	(30.0–39.0)	(21.0–38.0)
Average end-tidal to arterial P_{CO_2} gradient (mm. Hg)*	0.3	0.6	8.3	8.0	7.8	2.5	2.5
(Range)	(−2.3–4.0)	(−2.8–2.9)	(4.2–18.7)	(2.6–21.0)	(1.6–26.7)	(−2.4–6.1)	(−0.4–5.0)

* The mean value for the entire group is given to indicate the direction of change. The degree of change was proportional to the amount of blood removed which varied from animal to animal.

TABLE V

Changes in blood values during hemorrhage and reinfusion

	Control		Hemorrhage			Restoration	
Sample	1	2	3	4	5	6	7
Number of dogs	8	8	8	8	8	5	5
Percentage blood oxygen saturation*							
Arterial	94.7	94.8	93.0	90.0	90.0	98.0	97.0
(Range)	(90.2–97.9)	(89.0–99.1)	(75.8–100)	(70.0–100)	(72.7–100)	(96.1–99.7)	(95.9–98.6)
Venous	72.9	71.7	30.2	32.0	31.2	74.1	66.0
(Range)	(48.1–84.2)	(50–87.2)	(7.2–61.5)	(10.0–66.3)	(11.0–76.7)	(69.2–81.1)	(61.0–71.9)
Hematocrit*							
Arterial	40.3	40.7	34.0	31.0	30.5	35.8	36.9
(Range)	(34.4–48.2)	(34.6–47.8)	(26.9–42.7)	(20.4–41.3)	(24.0–37.0)	(24.3–41.8)	(30.0–42.0)
Venous	41.0	41.5	33.3	31.2	30.8	35.1	37.2
(Range)	(34.2–51.8)	(34.6–49.0)	(27.6–41.5)	(24.5–37.0)	(24.5–37.0)	(30.0–38.6)	(29.1–45.0)
Blood pH*							
Arterial	7.315	7.318	7.212	7.140	7.135	7.285	7.322
(Range)	(7.233–7.388)	(7.218–7.411)	(6.921–7.388)	(6.699–7.388)	(6.700–7.361)	(7.230–7.331)	(7.272–7.402)
Venous	7.281	7.286	7.146	7.053	7.068	7.228	7.270
(Range)	(7.152–7.361)	(7.184–7.390)	(6.827–7.361)	(6.582–7.363)	(6.630–7.314)	(7.168–7.311)	(7.168–7.358)
Blood buffer base (mEq./L.)*							
Arterial	39.6	39.6	33.1	29.6	31.5	37.9	39.3
(Range)	(36.3–44.8)	(36.2–42.8)	(21.8–39.6)	(15.6–40.0)	(15.5–40.2)	(34.2–42.0)	(37.0–42.2)
Venous	39.3	39.4	33.3	28.4	31.0	37.0	38.5
(Range)	(36.0–44.3)	(36.9–42.8)	(20.7–40.6)	(14.2–40.7)	(14.6–40.1)	(33.1–42.3)	(36.4–42.1)
Lactic acid concentration (μg./ml.)*							
Arterial	190	172	380	677	557	182	155
(Range)	(76–338)	(75–257)	(125–965)	(117–1,347)	(165–1,570)	(140–240)	(99–199)

* The mean value for the entire group is given to indicate direction of change. The degree of change was proportional to the amount of blood removed which varied from animal to animal.

TABLE VI

Average mean systemic and pulmonary arterial blood pressures and left atrial pressure in two dogs during hemorrhage and reinfusion

	Control	During hemorrhage								During reinfusion									
Estimated blood volume reduction (%)	0	5	10	15	20	25	30	35	40	40*	35	30	25	20	15	10	5	0	0†
Femoral arterial blood pressure (mm. Hg)	140	135	130	120	115	105	90	70	40	50	75	100	115	120	125	130	135	138	135
Pulmonary arterial blood pressure (mm. Hg)	11.5	10.8	9.5	9.0	8.5	8.0	7.5	7.0	6.5	7.5	9.8	13.0	12.5	13.1	15.3	15.7	17.2	18.0	16.5
Left atrial pressure (mm. Hg)	4.0	3.0	2.5	1.5	1.0	0.5	0	0	0	0	0.5	1.5	2.5	3.5	4.5	5.0	5.5	6.0	5.5

* Measured after a 10 minute interval.
† Ten minutes after all the blood was returned.

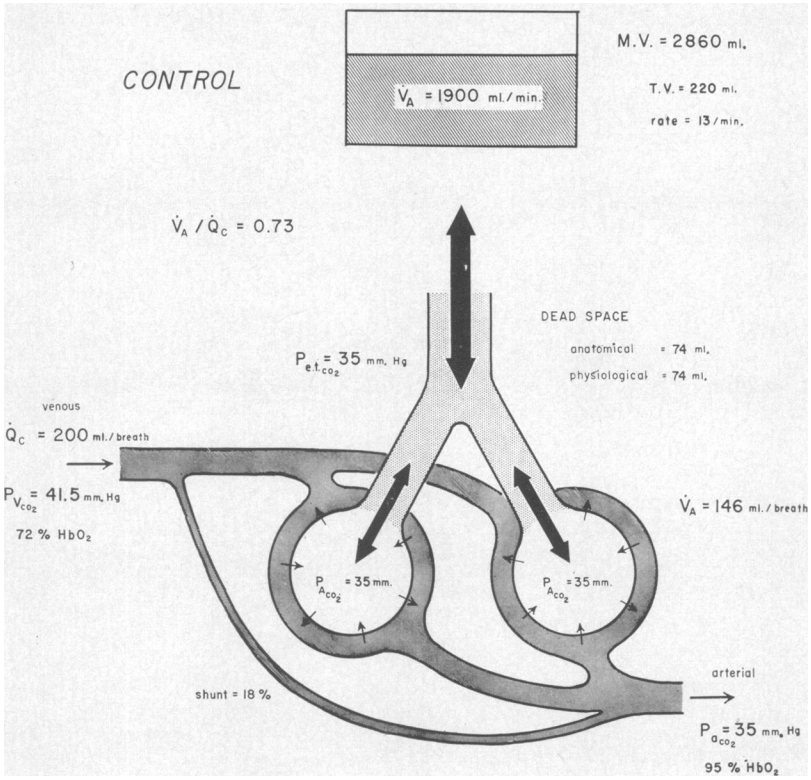

FIG. 7. SCHEMATIC PORTRAYAL OF THE RELATIONSHIP BETWEEN PULMONARY CIRCULATION AND VENTILATION ACCORDING TO THE VALUES OBTAINED DURING THE *CONTROL* PERIOD

The alveoli are represented by the circular areas into which are directed shaded tubes designating conducting airway or "anatomical" dead space. The darkly shaded channels surrounding the alveoli represent pulmonary blood flow. The large arrows entering the alveoli indicate the distribution of the inspired air, and the small arrows represent diffusion of respiratory gases across the alveolar capillary walls. The rectangular block above designates the minute volume, which is divided into total respiratory dead space (white area) and effective alveolar ventilation (hatched area) (26).

$\dot{Q}_c$ = pulmonary blood flow (per inflation), $_A$ = alveolar ventilation, TV = tidal volume, and P_v, P_a, P_A and $P_{e.t.}$ represent the carbon dioxide tensions in mixed venous and arterial bloods, and alveolar and end-tidal gases, respectively. The figures shown are the mean values.

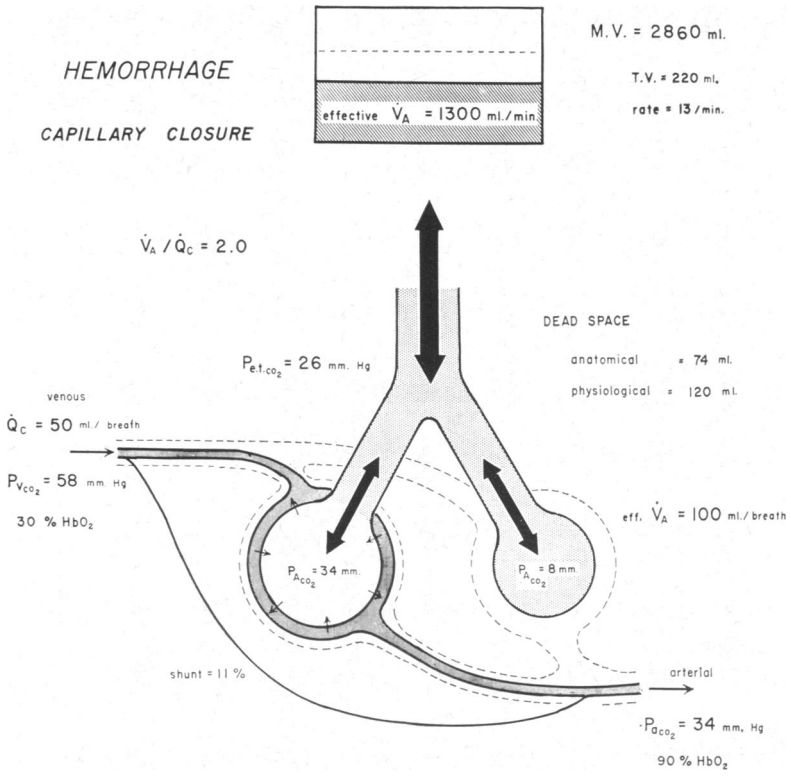

FIG. 8. SCHEMATIC PORTRAYAL OF THE RELATIONSHIP BETWEEN PULMONARY CIRCULATION AND VENTILATION, BASED UPON DATA OBTAINED DURING THE MID-POINT OF THE *HYPOTENSIVE* PERIOD (POINT 4)

The lung is portrayed as if some portions of the pulmonary vascular bed were closed completely, all the "alveolar" dead space being limited to the nonperfused alveoli. In the block representing the minute volume the dead space ventilation, indicated by the white area, is divided by the broken line into "anatomical" dead space above, and "alveolar" dead space below.

critical level below the opposing pressures, some of the pulmonary capillaries may then close completely (45–52). This would evoke a reduction in the size of the vascular bed leading to a rise in vascular resistance; the central pulmonary arterial blood pressure could then be maintained despite a progressive reduction in blood flow. Since these pressure relationships may not be uniform throughout the lung, this process may take place in scattered portions of the lung and lead to closure of vessels despite a blood pressure in the main pulmonary artery considered adequate for perfusion. When the blood flow again increases, the resistance offered by the closed vessels to passive reopening would initially require a driving force in excess of that necessary to maintain flow in patent channels. This force must be provided by increased work on the part of the right ventricle resulting in a rise in the pulmonary arterial blood pressure (Figure 2) (53), or the cardiac output could not be maintained at its control level (54).

We feel that the evidence presented here supports the concept that decrease in pulmonary blood flow can lead to complete closure of pulmonary vessels (55, 56), at least during intermittent positive pressure ventilation. Such a mechanism may be responsible for some of the phenomena ascribed to pulmonary vasomotor activity (57), and may, in part, account for the variations in pulmonary diffusing capacity noted under different circumstances (42, 44, 58–60). It may also help to explain some of the respiratory difficulties occasionally seen during hemorrhagic shock in patients receiving artificial ventilation, or

following complete circulatory bypassing of the lungs, as in open heart surgery (61).

SUMMARY

1. Blood flow in eight anesthetized dogs was decreased by removal of one-third of the estimated blood volume and then restored by blood replacement.

2. The pulmonary and systemic arterial blood pressures, total lung-thorax compliance and end-tidal carbon dioxide gas tension were continuously measured. Pulmonary and systemic arterial blood samples were analyzed for oxygen and carbon dioxide contents, pH, hematocrit values and lactic acid concentrations. Samples of mixed expired air, obtained simultaneously with the blood samples, were analyzed for carbon dioxide and oxygen concentrations. From these data we calculated pulmonary blood flow, respiratory dead space, venous admixture, carbon dioxide tensions and buffer base.

3. The significant findings were as follows:

a. With reduction in blood flow the systemic arterial blood pressure declined continuously, whereas the pulmonary arterial blood pressure stabilized after an initial decline, thereafter dropping only slightly.

b. The respiratory dead space increased following hemorrhage, with the appearance of a marked carbon dioxide tension gradient between the arterial blood and the end-tidal gas, indicating development of a significant "alveolar" dead space.

c. Upon restoration of blood volume the pulmonary blood pressure initially rose above its control level. The respiratory dead space decreased toward its control volume and the carbon dioxide tension gradient was reduced.

4. We conclude that, with intermittent positive pressure ventilation, reduction of pulmonary blood flow may lead to complete closure of portions of the pulmonary bed and that, following restoration of blood flow, there is some delay before these vessels again reopen.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the helpful criticism of Drs. Aaron Himmelstein and Alfred P. Fishman throughout the course of this work. We thank Miss Marieagnes Verosky, Mrs. Jean MacLachlan and Mrs. Iris Schwartz for performing the laboratory analyses, and Mr. Wallace Luke for very able technical assistance.

REFERENCES

1. Wearn, J. T., Ernstene, A. C., Bromer, A. W., Barr, J. S., German, W. J., and Zschiesche, L. J. The normal behavior of the pulmonary blood vessels with observations on the intermittence of the flow of blood in the arterioles and capillaries. Amer. J. Physiol. 1934, **109**, 236.
2. Williams, M. H., Jr. Relationships between pulmonary artery pressure and blood flow in the dog lung. Amer. J. Physiol. 1954, **179**, 243.
3. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A. Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Amer. J. Physiol. 1948, **152**, 372.
4. Cournand, A., Riley, R. L., Himmelstein, A., and Austrian, R. Pulmonary circulation and alveolar ventilation-perfusion relationships after pneumonectomy. J. thorac. Surg. 1950, **19**, 80.
5. Cournand, A. Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary diseases. Circulation 1950, **2**, 641.
6. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K. Studies of the pulmonary circulation in man at rest. Normal variations and the interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure, and high pulmonary "capillary" pressures. J. clin. Invest. 1950, **29**, 602.
7. Brofman, B. L., Charms, B. L., Kohn, P. M., Elder, J., Newman, R., and Rizika, M. Unilateral Pulmonary artery occlusion in man. J. thorac. Surg. 1957, **34**, 206.
8. Eaton, R. M. Pulmonary edema; experimental observations on dogs following acute peripheral blood loss. J. thorac. Surg. 1947, **16**, 668.
9. Rounthwaite, H. L., Scott, H. J., and Gurd, F. N. Changes in the pulmonary circulation during hemorrhagic shock and resuscitation *in* Surgical Forum, 1952. Philadelphia, W. B. Saunders & Co., 1953, p. 454.
10. Merriman, J. E. The pulmonary circulation in hemorrhagic shock *in* Shock and Circulatory Homeostasis, Transactions of the Fourth Conference, H. D. Green, Ed. New York, Josiah Macy, Jr. Foundation, 1954.
11. Rattenborg, C. Basic mechanics of artificial ventilation *in* Management of Life-Threatening Poliomyelitis, H. C. A. Lassen, Ed. London, E. and S. Livingstone, Ltd., 1956, p. 23.

12. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J. biol. Chem. 1947, **167**, 235.
13. DuBois, A. B., Fowler, R. C., Soffer, A., and Fenn, W. O. Alveolar CO_2 measured by expiration into the rapid infrared gas analyzer. J. appl. Physiol. 1952, **4**, 526.
14. DuBois, A. B., Britt, A. G., and Fenn, W. O. Alveolar CO_2 during the respiratory cycle. J. appl. Physiol. 1952, **4**, 535.
15. Rahn, H., Otis, A. B., Chadwick, L. E., and Fenn, W. O. The pressure-volume diagram of the thorax and lung. Amer. J. Physiol. 1946, **146**, 161.
16. Otis, A. B., Fenn, W. O., and Rahn, H. Mechanics of breathing in man. J. appl. Physiol. 1950, **2**, 592.
17. Mead, J., and Whittenberger, J. L. Physical properties of human lungs measured during spontaneous respiration. J. appl. Physiol. 1953, **5**, 779.
18. Gregersen, M. I., and Root, W. S. Experimental traumatic shock produced by muscle contusion with a note on the effects of bullet wounds. A study of the clinical signs of shock in the dog and of the role of blood volume reduction in the development of the shock syndrome. Amer. J. Physiol. 1947, **148**, 98.
19. Holling, H. E., MacDonald, I., O'Halloran, J. A., and Venner, A. Reliability of a spectrophotometric method of estimating blood oxygen. J. appl. Physiol. 1955, **8**, 249.
20. Holaday, D. A., and Verosky, M. Improved micromanometric methods for the analysis of respiratory gases in plasma and whole blood. J. Lab. clin. Med. 1956, **47**, 634.
21. Holaday, D. A. An improved method for multiple rapid determinations of arterial blood pH. J. Lab. clin. Med. 1954, **44**, 149.
22. Guest, G. M., and Siler, V. E. A centrifuge method for the determination of the volume of cells in blood. J. Lab. clin. Med. 1934, **19**, 757.
23. Barker, S. B., and Summerson, W. H. The colorimetric determination of lactic acid in biological material. J. biol. Chem. 1941, **138**, 535.
24. Singer, R. B., and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine 1948, **27**, 223.
25. Riley, R. L., and Cournand, A. Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: Theory. J. appl. Physiol. 1951, **4**, 77.
26. Comroe, J. H., Jr., Forster, R. E., DuBois, A. B., Briscoe, W. A., and Carlsen, E. The Lung. Chicago, The Year Book Publishers, Inc., 1955.
27. Riley, R. L., and Cournand, A. "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. appl. Physiol. 1949, **1**, 825.
28. Fowler, W. S. Lung function studies. II. The respiratory dead space. Amer. J. Physiol. 1948, **154**, 405.
29. Pappenheimer, J. R., Fishman, A. P., and Borrero, L. M. New experimental methods for determination of effective alveolar gas composition and respiratory dead space, in the anesthetized dog and in man. J. appl. Physiol. 1952, **4**, 855.
30. Hatch, T., Cook, K. M., and Palm, P. E. Respiratory dead space. J. appl. Physiol. 1953, **5**, 341.
31. Fishman, A. P. Studies in man of the volume of the respiratory dead space and the composition of the alveolar gas. J. clin. Invest. 1954, **33**, 469.
32. Folkow, B., and Pappenheimer, J. R. Components of the respiratory dead space and their variation with pressure breathing and with bronchoactive drugs. J. appl. Physiol. 1955, **8**, 102.
33. Gray, J. S., Grodins, F. S., and Carter, E. T. Alveolar and total ventilation and the dead space problem. J. appl. Physiol. 1956, **9**, 307.
34. Severinghaus, J. W., and Stupfel, M. Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. J. appl. Physiol. 1957, **10**, 335.
35. Moore, R. L., Humphreys, G. H., and Cochran, H. W. The effect of sudden occlusion of either primary branch of the pulmonary artery on cardiac output and pulmonary expansion. J. thorac. Surg. 1934, **3**, 573.
36. Rodbard, S. Bronchomotor tone. A neglected factor in the regulation of the pulmonary circulation. Amer. J. Medicine. 1953, **15**, 356.
37. Daly, M. DeB., Lambertsen, C. J., and Schweitzer, A. The effects upon the bronchial musculature of altering the oxygen and carbon dioxide tensions of the blood perfusing the brain. J. Physiol. 1953, **119**, 292.
38. Nisell, O. I., and DuBois, A. B. Relationship between compliance and FRC of the lungs in cats, and measurement of resistance to breathing. Amer. J. Physiol. 1954, **178**, 206.
39. Bock, A. V., Dill, D. B., Edwards, H. T., Henderson, L. J., and Talbott, J. H. On the partial pressures of oxygen and carbon dioxide in arterial blood and alveolar air. J. Physiol. 1929, **68**, 277.
40. Riley, R. L., Lilienthal, J. L., Jr., Proemmel, D. D., and Franke, R. E. On the determination of the physiologically effective pressures of oxygen and carbon dioxide in alveolar air. Amer. J. Physiol. 1946, **147**, 191.
41. Rahn, H. A concept of mean alveolar air and the ventilation-bloodflow relationships during pulmonary gas exchange. Amer. J. Physiol. 1949, **158**, 21.
42. Krogh, M. Diffusion of gases through the lungs of man. J. Physiol. 1915, **49**, 271.
43. Krogh, A. The rate of diffusion of gases through animal tissues, with some remarks on the coefficient of invasion. J. Physiol. 1919, **52**, 391.
44. Forster, R. E. Exchange of gases between alveolar air and pulmonary capillary blood: Pulmonary diffusing capacity. Physiol. Rev. 1957, **37**, 391.

45. Fenn, W. O., Otis, A. B., Rahn, H., Chadwick, L. E., and Hegnauer, A. H. Displacement of blood from the lungs by pressure breathing. Amer. J. Physiol. 1947, **151**, 258.
46. Edwards, W. S. The effects of lung inflation and epinephrine on pulmonary vascular resistance. Amer. J. Physiol. 1951, **167**, 756.
47. Burton, A. C. On the physical equilibrium of small blood vessels. Amer. J. Physiol. 1951, **164**, 319.
48. Nichol, J., Girling, F., Jerrard, W., Claxton, E. B., and Burton, A. C. Fundamental instability of the small blood vessels and critical closing pressures in vascular beds. Amer. J. Physiol. 1951, **164**, 330.
49. Burton, A. C. Laws of physics and flow in blood vessels *in* Visceral Circulation, Ciba Foundation Symposium, G. E. W. Wolstenholme, Ed. Boston, Little, Brown & Co., 1953, p. 70.
50. Bjurstedt, H., and Hesser, C. M. Effects of lung inflation on the pulmonary circulation of anesthetized dogs. Acta physiol. scand. 1953, **29**, 180.
51. Barer, G. R., and Nüsser, E. Pulmonary blood flow in the cat. The effect of positive pressure respiration. J. Physiol. 1957, **138**, 103.
52. Howell, J. B. L., Permutt, S., and Proctor, D. F. Effects of lung inflation upon the pulmonary vascular bed of excised dog lungs. Fed. Proc. 1958, **17**, 74.
53. Sancetta, S. M., and Rakita, L. Response of pulmonary artery pressure and total pulmonary resistance of untrained, convalescent man to prolonged mild steady state exercise. J. clin. Invest. 1957, **36**, 1138.
54. Fishman, A. P., and Richards, D. W. The management of cor pulmonale in chronic pulmonary disease, with particular reference to the associated disturbances in the pulmonary circulation. Amer. Heart J. 1956, **52**, 149.
55. Lilienthal, J. L., Jr., and Riley, R. L. Diseases of the respiratory system. Circulation through the lung and diffusion of gases. Ann. Rev. Med. 1954, **5**, 237.
56. Borst, H. G., McGregor, M., Whittenberger, J. L., and Berglund, E. Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. Circulat. Res. 1956, **4**, 393.
57. Daly, I. de B. Intrinsic mechanisms of the lung. Quart. J. exp. Physiol. 1958, **43**, 2.
58. Riley, R. L., Shepard, R. H., Cohn, J. E., Carroll, D. G., and Armstrong, B. W. Maximal diffusing capacity of the lungs. J. appl. Physiol. 1954, **6**, 573.
59. Filley, G. F., MacIntosh, D. J., and Wright, G. W. Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. J. clin. Invest. 1954, **33**, 530.
60. Lewis, B. M., Lin, T., Noe, F. E., and Komisaruk, R. The measurement of pulmonary capillary blood volume and pulmonary membrane diffusing capacity in normal subjects; the effects of exercise and position. J. clin. Invest. 1958, **37**, 1061.
61. Dodrill, F. D. The effects of total body perfusion upon the lungs *in* Extracorporeal Circulation, J. G. Allen, Ed. Springfield, Ill., Charles C. Thomas Co., 1958, p. 327.