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J Clin Invest. 1961;[40\(9\)](#):1785-1796. <https://doi.org/10.1172/JCI104402>.

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CARDIORESPIRATORY EFFECTS OF EXPERIMENTAL LUNG EMBOLISM *

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(Submitted for publication October 10, 1960; accepted May 18, 1961)

Respiratory embarrassment and pulmonary hypertension are important consequences of pulmonary embolism. Respiration is affected at several levels. Changes in rate and depth have been summarized by Whitteridge (1) as "rapid shallow breathing" unaffected by the inhalation of 100 per cent oxygen (2, 3). Sectioning or cooling of the vagi prevented this phenomenon which was therefore regarded as neurogenic, caused by the excitation of (unspecified) lung receptors.

Embolism is usually followed by an increased resistance to lung inflation in the artificially respired animal (4, 5) or a rise in the intrapleural pressure swing in those breathing spontaneously (6). This was thought to be due to bronchoconstriction.

A fall in arterial oxygen saturation has also been reported to accompany pulmonary embolism; several mechanisms were suggested to explain this change. An acceleration of blood flow through the non-occluded areas of the lung (= decreased contact time) was proposed by Binger, Brow and Branch (2). A fall in the pulmonary diffusing capacity for oxygen was assumed by Williams (7) to be due to a reduction in the area of the alveolocapillary membrane. Venous admixture was not abolished, however, by breathing 100 per cent oxygen (8, 9), and it also occurred after the intravenous injection of oxygen itself (10). This prompted the conclusion that arterial hypoxia was caused by the opening of pulmonary arteriovenous anastomoses (9).

These changes do not seem to account for the often distressing dyspnea seen in clinical pul-

monary embolism. It occurred to us that changes in lung mechanics—the most common causes of dyspnea—have not yet been investigated in this condition, and we therefore decided to include lung mechanics in our study of experimental lung embolism.

The dose-response relationship in embolic pulmonary hypertension, as demonstrated by several investigators, suggests that the rise in pressure is related to the number of occluded vessels. This implies that pulmonary hypertension would occur only in widespread embolization, since a 50 per cent occlusion of the pulmonary circulation is followed by mild changes only (Table I). Two-thirds of the pulmonary vascular bed had to be excluded in order to create a more marked pulmonary hypertension (14, 15).

These data are difficult to reconcile with some other observations. Repeated intravenous injections of blood clots into rabbits resulted in a marked right ventricular hypertrophy, suggesting pulmonary hypertension. Yet postmortem angiography of the lung vessels failed to reveal obstruction (16). This finding and numerous others not mentioned here appeared to indicate that reactive vasoconstriction contributes to this type of pulmonary hypertension. Embolic constriction of the systemic arteries was shown to be neurogenic. It was expected that neuroplegic procedures might also modify the pulmonary vascular response to embolism, but in the majority of technically acceptable experiments, spinal cord section, vagotomy, and chemical and surgical sympathectomy were found ineffective (7, 17–19). Only Price, Hata and Smith (20) obtained a reduced response.

It was decided to study two aspects of these changes. By using two different doses of embolic material (one 10 times larger than the other), an attempt was made to assess the quantitative nature of the response. By using different drugs,

* This study was supported in part by grants from the National Health and Medical Research Council of Australia, The Postgraduate Foundation and the Consolidated Medical Research Fund of the University of Sydney, and The Joint Coal Board.

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TABLE I
Changes of pulmonary circulation with pulmonary vascular occlusion *

Subjects	Pulm. art. mean press.		Cardiac output		Ventil.		Pulm. art. resist.		Ref.
	C	O	C	O	C	O	C	O	
	<i>mm Hg</i>		<i>L/min</i>		<i>L/min</i>		<i>dynes-sec-cm⁻⁵</i>		
5 men	16	23	7.9	8.2			162	224	(11)
15 men	13	15	9.3	8.4	8.6	8.3	112	143	(12)
9 dogs	15	18	3.1	3.1	3.2	4.3	387	464	(12)
6 men	21	30	5.8	5.5			290	435	(13)

* C = control; O = occlusion.

the possibility of a non-neurogenic pulmonary vasoconstriction was explored.

METHODS

Material. Forty-six sheep weighing 21 to 48 kg were used in these experiments. The supine animals were anesthetized with thiopentone and intubated. The femoral artery and vein were dissected free and a thermometer was inserted into the rectum.

Circulation measurements. A cardiac catheter was passed via the femoral vein into the pulmonary artery and a cannula was introduced into the femoral artery. Oxygen saturation of the arterial (S_{aO_2}) and mixed venous ($S_{\bar{v}O_2}$) blood and hemoglobin content were measured spectrophotometrically (21). In experiments in which 100 per cent oxygen was breathed instead of air, oxygen content and capacity were measured manometrically (22). Expired air was collected for 1.5 to 2.5 minutes in Douglas bags; their content was measured and analyzed by the Haldane method. In later experiments oxygen uptake, tidal volume (V_T) and rate of breathing (f) were measured from the record obtained with a Pulmotest twin-spirometer.¹ The animal breathed air from a closed-circuit system, oxygen being fed from the second bell at the rate at which it was removed from the first system. The same arrangement was used for experiments performed with 100 per cent oxygen, both systems being washed out and filled with oxygen.

Blood samples were taken in the mid-period of ventilation measurements. The Fick principle was used to calculate pulmonary arterial blood flow ($\dot{Q}$), the shunt-formula ($C_{CO_2} - C_{aO_2}/C_{CO_2} - C_{\bar{v}O_2}$) to calculate venous admixture (Q_s) in per cent of $\dot{Q}$. Oxygen content of the pulmonary capillary blood (C_{CO_2}) was estimated by subtracting 0.60 vol per cent from the oxygen capacity of the arterial blood (23). In other experiments (24) this method gave good agreement with the more laborious procedure of calculating alveolar oxygen tension, measuring blood pH and obtaining the saturation of pulmonary capillary blood from the oxygen dissociation curve for sheep's blood.

Pulmonary ($P_{p.a.}$) and femoral ($P_{f.a.}$) arterial pressures were measured by Sanborn transducers (no. 267)

and recorded on a 6-channel direct-writing Sanborn oscillograph and expressed in millimeters of mercury. Total pulmonary (R_{pulm}) and total systemic (R_{sys}) resistances were calculated by the usual formulas and expressed in dynes-sec-cm⁻⁵.

Blood flows, resistances and ventilated volumes were expressed on the basis of 1 m² body surface area (BSA). The latter was calculated by the formula: $8.3 \sqrt[3]{w}$ where w = body weight in grams (25). Details of the circulation measurements were described elsewhere (26).

Intrapleural pressure (P_{p1}) was measured via a specially prepared 17 gage needle introduced into the third or fourth interspace, 7 to 10 cm from the anterior surface of the chest. A pneumothorax of 60 to 80 ml was induced. The needle was connected by 70 cm polyethylene tubing to a Sanborn transducer no. 267 B. P_{p1} was recorded relative to atmosphere in centimeters of water.

Air flow rate and tidal volume were obtained with a Godart pneumotachometer and integrator.¹ The pneumotachometer is similar to that described by Silverman and Whittenberger (27) and the one used in these experiments covered the range of flow from 0 to 100 L per minute. The integrator consists of a high stability D.C. amplifier with an extremely effective time constant and a low drift rate so that the error of V_T measurements from this source was not likely to exceed 1 per cent. The P_{p1} , airflow and volume changes were electrically amplified and recorded simultaneously on the oscillograph.

Method of analysis. Lung compliance (C_L), expressed in milliliters per centimeter water per kilogram, was obtained by dividing the V_T by the simultaneously recorded P_{p1} between points of zero flow; 6 to 10 breaths were measured from a recording made at 25 to 50 mm per second and the mean value taken. Mean frictional (= nonelastic) resistance was calculated at points of equal volume (28). Differences in pressure and rate of airflow were read from the recording. Due allowance was made for the resistance of the instrument. Five breaths were analyzed for each period.

Calibration. Pressure, volume and flow were all linear within 2 per cent. The coefficient of variation for a single measurement of C_L averaged 5.6 per cent and duplicate measurements invariably agreed within 10 per cent. Details of the lung mechanics measurements are described elsewhere (24).

¹ Godart-Mijnhart, Utrecht, Holland.

Volume-pressure relationship over an extended range. On three occasions in three animals the volume-pressure relationship of the lung over an extended range was studied by a method similar to that described by Cook and co-workers (29). The measurements were performed after the injection of 0.20 ml per kg barium sulfate while the animals were paralyzed with succinylcholine. Increments of 150 ml were introduced in 1 second with 5 seconds between each step. The transpulmonary pressure was measured with a Sanborn differential pressure transducer 267 B. Inflation was continued until the transpulmonary pressure was approximately 30 mm Hg

greater than in the resting position. The gas was then removed in a stepwise fashion at the same time intervals as for the inflation. An approximate correction for change in gas volume from ATP to BTPS and for gas exchange was made by taking the volume increments as 160 ml BTPS for both inflation and deflation. *Statistical methods* were used as recommended by Snedecor (30). *Embollic material* consisted of a 33 vol/vol emulsion of barium sulfate injected into the pulmonary artery.

Groups. The animals were divided into two main groups. Group I (Table II), consisting of 19 animals, was given 0.20 ml per kg barium sulfate. Group II

TABLE II
Cardiorespiratory effects of the administration of 0.20 ml per kg barium sulfate emulsion in sheep *

Group I	†	Intact	Vagot.	Atrop.	Bretyl.	Lysergic acid
No. of animals		6	3	4	2	4
Cardiac output (L/min/m ² BSA)	0 5 30	3.12 3.12 2.87	3.50 4.13	3.29 3.42	2.75 2.91	3.19 3.06
Femoral art. mean pressure (mm Hg)	0 5 30	123 135 109	107 111	118 123	115 120	125 128
Syst. art. resistance (dynes-sec-cm ⁻⁵ /m ² BSA)	0 5 30	3,289 4,014 3,169	2,439 2,408	2,999 2,950	3,449 3,477	3,179 3,392
Pul. art. mean pressure (mm Hg)	0 5 30	13 32 24	15 30	17 32	14 25	16 29
Pulm. art. resistance (dynes-sec-cm ⁻⁵ /m ² BSA)	0 5 30	344 896 670	357 693	435 776	432 717	396 753
Art. oxygen saturation (%)	0 5	91.6 81.7	90.9 79.4	77.1 68.8	81.1 73.5	78.0 76.4
Venous admixture (% cardiac output)	0 5 30	13 33 45	16 39	37 47	30 39	37 38
Ventilation (L/min/m ² BSA)	0 5 30	6.4 11.7 8.9	10.5 12.1	16.5 19.6	8.2 12.2	9.2 15.3
Breathing rate (min)	0 5 30	30 48 50	31 33	60 83	41 56	43 57
Tidal volume (ml/m ² BSA)	0 5	219 253	338 370	271 248	198 216	226 272
Lung compliance (ml/cm H ₂ O/kg)	0 5 30 I	3.49 0.75[21] 1.06[33] 1.51[43]	2.58 0.79[31] 1.10[43]	3.33 0.83[25] 1.19[36]	2.52 0.34[13]	2.90 0.99[34] 1.51[52]
Mean airway resistance (cm H ₂ O/L/sec)	0 5	2.21 5.81	1.82 4.60	1.20 2.94		

* Italicized figures = significant difference ($p < 0.05$). Numbers in brackets attached to compliance measurements = values in per cent of control.

† 0 = control period; 5 and 30 = 5 and 30 minutes after the injection of embolic material; I = after inflation of the lung.

(Table III), 28 animals, was given 0.02 ml per kg of the same substance, 0.1 of the previous dose.

After a control period (0) six animals of group I and 5 of group II were injected with barium sulfate. Pressures were continuously measured; other parameters were measured 5 minutes later. In some animals of group I, measurements were again repeated at 30 minutes. After the last measurement the lungs were inflated to a pressure of 30 mm Hg and CL was again determined (I, Tables II and III). The remaining animals were subjected to various procedures prior to the control period.

Bilateral cervical vagotomy was carried out in 7 sheep; 0.2 to 0.4 mg per kg atropine sulfate was administered intravenously to 4 vagotomized and 4 intact animals. Ten mg per kg bretylium tosylate (Darenthin) was administered intravenously to 2 animals 30 minutes prior to the control period. N,N,N',N',-3-pentamethyl-N,N',-diethyl-3-aza-pentane-1-5-diammonium-dibromide (Pendiomid) was injected intravenously into 1 animal in a dose of 2 mg per kg; 100 to 150 mg promethazine hydrochloride

(Phenergan, May and Baker) was intravenously administered to 5 animals 30 minutes prior to the control period; 0.5 mg per kg lysergic acid butanolamide (Deseril) was injected intravenously into 4 sheep 30 minutes prior to the control period.

In 3 animals control measurements of lung mechanics were followed by continuous breathing of 100 per cent oxygen. After an equilibration period of 10 minutes, circulation measurements were taken, barium sulfate administered and at 5 minutes, circulation measurements were repeated while the animals were still breathing oxygen. Oxygen breathing was then discontinued and measurement of lung mechanics repeated.

A continuous infusion of adrenalin (0.4 μ g per kg per minute) was administered to 4 animals; a continuous infusion of isoproterenol hydrochloride (Isuprel; 0.03 μ g per kg per minute) to 6 others. Control measurements and embolization were performed during the infusion.²

² Darenthin was supplied by Burroughs Wellcome & Co. (Aust.) Ltd.; Pendiomid by Ciba Co., Pty. Ltd.;

TABLE III
Cardiorespiratory effects of the administration of 0.02 ml per kg 33% barium sulfate emulsion in sheep *

Group II		Intact	Vagot. + atrop.	Pendiomid†	Oxygen 100%	Promethazine	Adren.	Isoproterenol
No. of animals		5	4	1	3	5	4	6
Cardiac output (L/min/m ²)	0	3.93	2.91	5.31	3.27	3.64	5.16	5.00
	5	4.09	3.73	4.93	3.80	4.37	5.84	5.09
Femoral art. mean pressure (mm Hg)	0	120	107	115	131	102	133	76
	5	117	111	127	136	107	145	71
Syst. art. resist. (dynes-sec-cm ⁻⁵ /m ²)	0	2,468	2,970	1,732	3,218	2,497	2,172	1,216
	5	2,489	2,433	2,062	2,912	2,057	2,001	1,148
Pulm. art. mean pressure (mm Hg)	0	15	16	16	15	19	17	9
	5	20	23	30	25	22	20	10
Pulm. art. resist. (dynes-sec-cm ⁻⁵ /m ²)	0	302	440	241	381	446	271	153
	5	384	506	487	514	414	280	169
Art. oxygen sat. (%)	0	90.4	84.2	86.9	105.9	81.3	88.8	93.8
	5	86.8	81.0	69.7	105.5	72.0	88.0	94.0
Venous admixture (% cardiac output)	0	16	26	27	18	33	29	8
	5	22	30	50	19	45	32	8
Ventilation (L/min/m ²)	0	8.7	10.8	16.9	8.0	14.5	10.6	11.0
	5	12.3	11.8	23.8	10.2	19.0	13.5	11.0
Breathing rate (min)	0	35	26	58	31	48	33	35
	5	44	26	71	41	53	39	34
Tidal volume (ml/m ²)	0	253	415	288	250	304	317	302
	5	284	447	334	243	359	338	293
Lung compliance (ml/cm H ₂ O/kg)	0	3.13	3.24	4.10	4.41	3.01	4.14	4.02
	5	1.46[47]	1.78[55]	0.67[16]	1.96[44]	1.91[63]	2.94[71]	4.22[105]
	I	3.16[101]	2.66[82]	3.69[90]	3.24[73]		4.38[106]	
Mean airway res. (cm H ₂ O/L/sec)	0	2.15						
	5	3.06						

* See footnote to Table II.

† Ciba; see formula in Methods.

At the end of the experiments the lungs were in some cases removed and macroscopically assessed for edema.

RESULTS

Results are summarized in Tables II and III.

A. Intact animals

1. *Effects on circulation.* $\dot{Q}$ remained practically unchanged in both groups. The slight increase in $\bar{P}_{f.a.}$ and R_{syst} at 5 minutes in group I was significantly different ($0.02 < p < 0.05$) from the slight decrease in group II. The injection of the embolic material was followed by a rapid rise in $P_{p.a.}$. The peak value was reached within 30 to 60 seconds (Figure 1). At this stage the difference between the average peak values obtained after the injection of 0.20 ml per kg (= 52 mm Hg) and 0.02 ml per kg (= 44 mm Hg) was not statistically significant ($p = 0.30$). From then on $P_{p.a.}$ gradually declined and at 5 minutes the difference between the two groups was statistically significant ($p < 0.01$).

2. *Effect on arterial oxygen saturation and ventilation.* Sa_{O_2} decreased significantly in group I only. There was a significant rise in $\dot{V}_E$ in both

Deseril by Sandoz (Aust.) Pty. Ltd.; and Isuprel by Winthrop Labs. Their courtesy is gratefully acknowledged.

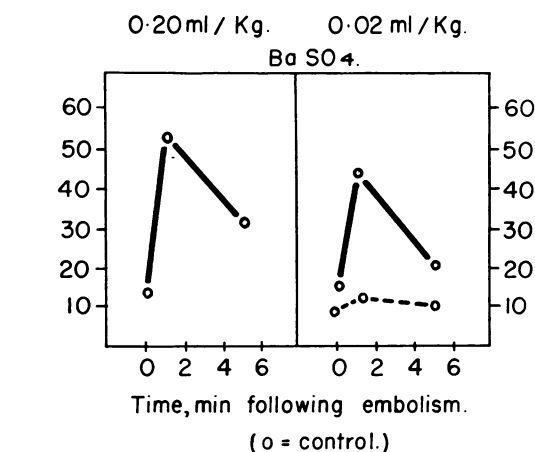


FIG. 1. AVERAGE VALUES OF THE MEAN PULMONARY ARTERIAL PRESSURE BEFORE (o), 1 MINUTE AND 5 MINUTES AFTER THE INJECTION OF 0.20 AND 0.02 ML/KG BARIUM SULFATE IN UNTREATED (SOLID LINES) AND ISOPROTERENOL-TREATED (DOTTED LINE) ANIMALS. Pressures in mm Hg.

groups; the values were higher in group I. The increase in f was significant in group I only. V_T increased in both groups, significantly in group II only.

3. *Effect on mean frictional resistance.* A statistically significant rise, which averaged 250 per cent, occurred in group I only. The administra-

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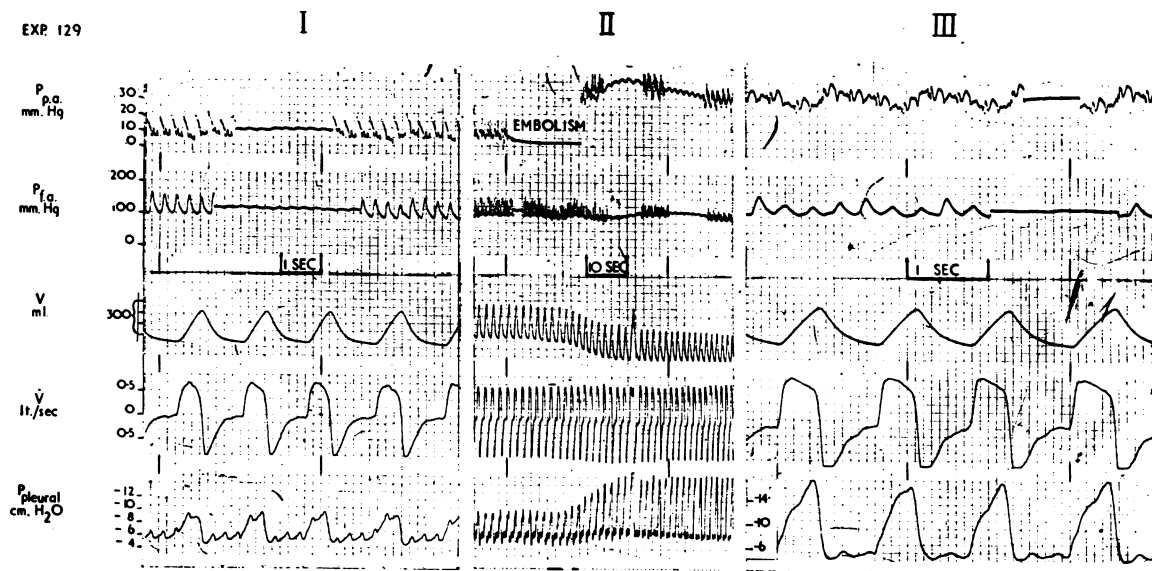


FIG. 2. INSTANTANEOUS EFFECTS OF EXPERIMENTAL PULMONARY EMBOLISM. I. Control measurement. II. Embolism. Note the instantaneous increase in the negativity of intrapleural pressure. III. Three minutes after embolization. $P_{p.a.}$ = pulmonary arterial pressure. $P_{f.a.}$ = femoral arterial pressure. V = integrated volume. $\dot{V}$ = air flow (pneumotachograph).

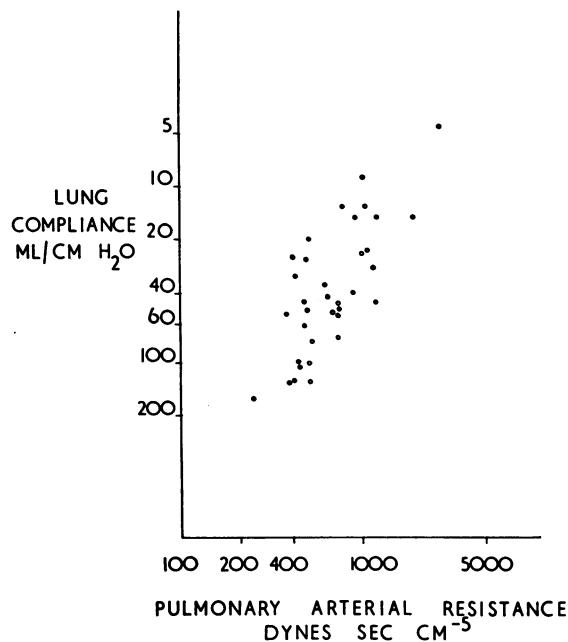


FIG. 3. RELATIONSHIP OF LUNG COMPLIANCE AND PULMONARY ARTERIAL RESISTANCE IN LUNG EMBOLISM. Black dots represent sheep subjected to barium sulfate embolization. Open circles indicate measurements taken in spontaneous pulmonary embolism due to blood clots.

tion of the smaller dose resulted in a lesser rise not statistically significant.

4. *Effect on lung compliance.* Embolism was followed by a gross fall in CL , as illustrated by Figure 2 and Tables II and III. The fall was more severe after the large dose and increased only slightly throughout the first 30 minutes. Inflation to 30 mm Hg produced a variable improvement in group I but restored CL in group II.

A definite correlation was obtained between R_{pulm} and CL (Figure 3). A decrease in CL was associated with an increase in R_{pulm} .

A further correlation was established between CL and mean frictional resistance (Figure 4). A sizable rise in the latter occurred only with a gross fall in CL .

Effective capillary blood flow ($Q_E = 100 - Q_S$) was plotted against values of CL between the range of 10 to 60 ml per cm H_2O (Figure 5). The regression coefficient (+0.47) would have occurred by chance less frequently than 1 in 100 times ($p < 0.01$).

5. *Effect on lung volume.* During the first 20 seconds after the injection of the embolic material,

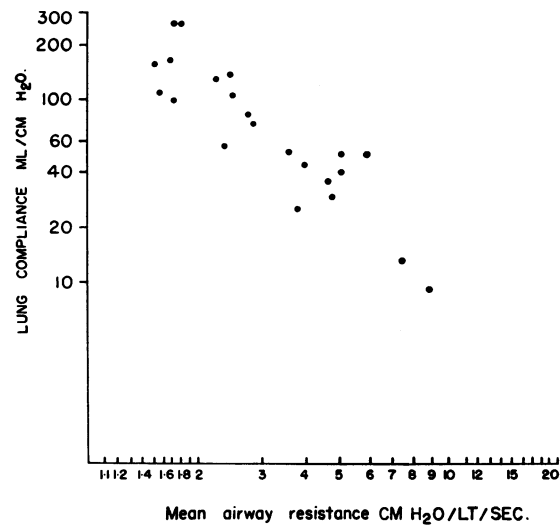


FIG. 4. RELATIONSHIP OF LUNG COMPLIANCE AND MEAN FRICTIONAL ("AIRWAY") RESISTANCE IN EXPERIMENTAL PULMONARY EMBOLISM.

air was expelled from the lungs, as illustrated by the volume trace on Figure 2. This was also confirmed by spirometer records not shown here. Parallel to this change there was an increase in end-expiratory transpulmonary pressure—i.e., the P_{pi} became more negative, as shown by the rise

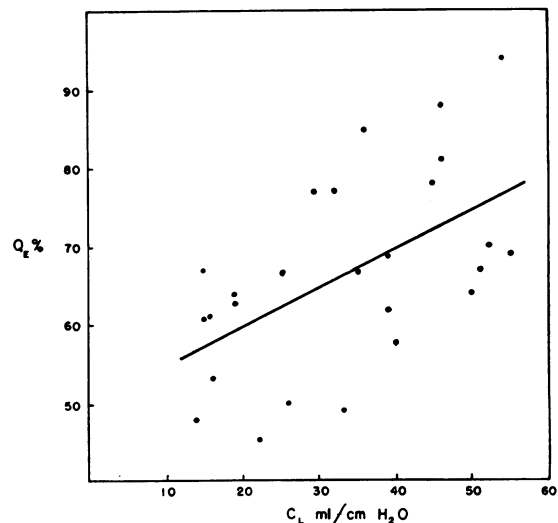


FIG. 5. RELATIONSHIP OF EFFECTIVE PULMONARY CAPILLARY BLOOD FLOW (Q_E) IN PER CENT OF TOTAL PULMONARY ARTERIAL BLOOD FLOW AND LUNG COMPLIANCE (CL) IN EXPERIMENTAL PULMONARY EMBOLISM 5 MINUTES AFTER INJECTION OF THE EMBOLIC MATERIAL. Only animals with a compliance value of less than 60 ml/cm H_2O were included.

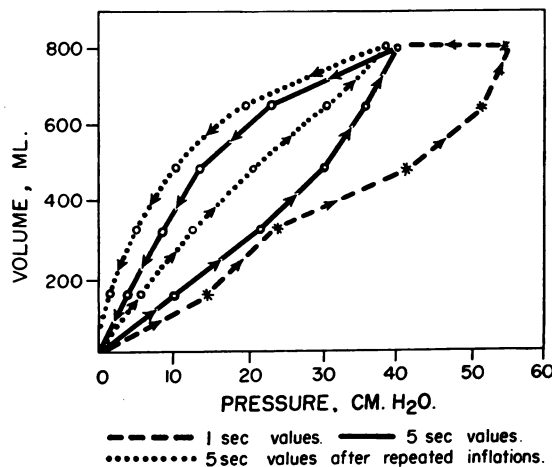


FIG. 6. VOLUME-PRESSURE CURVE OVER AN EXTENDED RANGE IN AN EMBOLIZED LUNG (0.20 ML/KG BARIUM SULFATE). For explanation see text.

in the expiratory level of the P_{pl} trace (bottom line) on Figure 2. The amount of air expelled was 150 to 200 ml. The end-expiratory transpulmonary pressure gradually returned toward the control level.

6. *Volume-pressure relationship over an extended range.* The result of a typical experiment is shown in Figure 6. The solid-line loop in the middle represents the volume-pressure curve measured at 5 seconds corresponding to the interval between successive volume steps. The curve for the pressure at 1 second lies to the right. There was a small fall in pressure between 1 and 5 seconds for each volume step in the tidal range. At higher levels of inflation the fall in pressure between 1 and 5 seconds increased to 10 to 15 cm H_2O . The total lung volume at 50 cm H_2O inflating pressure was still markedly reduced. After inflation the slope of the 5-second volume-pressure curve increased somewhat, but the total lung volume remained unchanged. Compliance, taking a pressure value between 1 and 5 seconds, equaled 13.4 ml per cm H_2O . The compliance measured during spontaneous breathing was 15.2 ml per cm H_2O .

7. *Postmortem findings.* Extensive lung edema was found in only one animal in group I.

B. Animals subjected to neuroplegic procedures

In vagotomized animals, f was lower than in the intact ones and failed to rise after embolism. V_T

was higher and the rise in $\dot{V}_E$ was less than in the controls. Mean airway resistance was lower in the atropine-treated group. The postembolic rise, expressed as per cent of control value, was not different from that of the untreated group. With these exceptions the embolic response in these groups was essentially similar to that seen in the intact animals.

C. Other procedures

Lysergic acid butanolamide. The only difference in the response was a lesser rise in Q_s .

Oxygen breathing. The response was unchanged.

Promethazine. This group had the highest initial $P_{p.a.}$ and $R_{pulm.}$ Embolism produced the same initial rise in $P_{p.a.}$ as in the controls; at 5 minutes, however, $\bar{P}_{p.a.}$ was only slightly elevated. Because of a simultaneous increase in Q , no rise in $R_{pulm.}$ occurred. The rise in $\dot{Q}$ was not statistically significant ($0.05 < p < 0.10$). The difference between the change in $\dot{Q}$ in this group and in the corresponding control group was not statistically significant ($p = 0.30$).

Adrenalin. The adrenalin infusion resulted in a gross rise in $\dot{Q}$ and in some increase in $\bar{P}_{f.a.}$. Both increased further after embolism. The postembolic rise in $\bar{P}_{p.a.}$ was considerably less than in the corresponding control group and $R_{pulm.}$ remained unchanged. The fall in CL was less than in the preceding groups.

Isoproterenol. Infusion with this substance caused a gross rise in $\dot{Q}$, a fall in systemic and pulmonary arterial pressure and resistance, and a rise in Sa_{O_2} . Embolism was followed by a marginal rise in $\bar{P}_{p.a.}$ and virtually no change in $R_{pulm.}$ The initial peak rise in $\bar{P}_{p.a.}$ was also largely abolished (Figure 1). Changes in Q_s , $\dot{V}_E$ and CL were completely prevented.

DISCUSSION

1. *Ventilation.* These experiments have thrown some doubt on the view that hypoxemia contributes to the ventilatory response to embolism as suggested by previous workers (12); the response was not significantly affected by 100 per cent oxygen breathing. Contrary to the widely held belief, V_T increased in both intact groups and decreased only after the repeated injection of large doses of

embolic material. Vagotomy or the administration of atropine, or both, reduced but did not abolish the response, while bretylium, lysergic acid butanolamide, promethazine, or adrenalin was without effect. Hyperventilation was completely abolished by isoproterenol infusion.

2. *Lung mechanics.* The most surprising change was the gross fall in CL, the extent of which appeared to be related to the amount of embolic material injected. CL is the sum of compliances of all distensible units within the lungs. When part of the lung was removed CL showed a proportional fall (31). A reduction of the number of distensible units due to surface tension forces created by the alveolar transudate in lung edema was shown to be responsible for the fall in CL (29, 32). A gradual collapse of the terminal airways was suggested to account for a part of the spontaneous fall in CL in anesthetized dogs (33). This mechanism, the sudden exclusion of a significant portion of the distensible units, appears to be the only possible cause for a gross and rapid fall in CL; changes in lung blood volume would account only for minor changes (34, 35).

Pulmonary edema has occurred under certain conditions (36) and after a variable latent period (37) in lung embolism. Postmortem inspection of the lung revealed edema in only one of our animals. Further evidence against the presence of edema is the effect of inflation. In the presence of fluid in the airways, large inflations tend to promote its distribution, resulting in no improvement or a further drop in CL (24). Inflation of the lung had a variable effect in group I (intact) and restored CL in group II (intact). A normal CL, a few minutes after embolization, is incompatible with lung edema.

The increase in mean frictional resistance was remarkably well correlated with the fall in CL. This may represent flow through a smaller number of patent airways which in effect reduces the mean diameter of the sum of airways through which flow occurs. However, it is likely that part of the increase was due to bronchoconstriction.

Otis and colleagues (38) have demonstrated that the distribution of ventilation is influenced by breathing frequency if the time constants (products of compliance and resistance) of the separate areas in the lung are different. The problem, therefore, is how much of the fall in CL is due to

the inclusion of a dynamic element, in the measurement after bronchoconstriction, that was not present before.

The dynamic element in vagotomized animals is largely abolished by the inspiratory pause; the fall in CL was, however, unchanged. The increased elastic resistance could also be demonstrated under semistatic conditions, as shown by the volume-pressure curve. This inflation through an extended range also indicates that the increase is not restricted to the tidal range. The agreement between CL values taken under semistatic conditions and during spontaneous breathing indicates that the fall in CL after embolism has not been overestimated.

A gross fall in pressure in the interval between inflations occurred only at higher levels of inflation. This indicates three possible causes: 1) surface hysteresis, 2) tissue relaxation, 3) opening of distensible units.

The behavior of the embolic lung differs from that of the edematous lung in which one observes an earlier increase in slope, and the volume at 30 cm H₂O pressure is not much different from the normal lung (29). This suggests that the increased resistance to inflation is not due to surface forces and is consistent with a hypothesis that the alteration in lung mechanics is due to airway closure.

The airway musculature in man and animals extends over both the proximal (supported) and distal (unsupported) parts of the bronchial tree, with muscular rings surrounding the orifices of the atria (39), also referred to as "alveolar sphincters" (40). Muscular contraction of the proximal part of the airways, if unaccompanied by hypersecretion or mucosal swelling, or both, can only cause a narrowing of the lumen; the presence of cartilagenous rings prevents complete occlusion. Muscular contraction in the distal unsupported segments would result in airway closure with exclusion of the more peripheral alveoli from expansion. This suggested action might be facilitated by the thickness of these muscular bands; they are relatively five times thicker than the muscle rings of the cartilagenous bronchi (39).

It is suggested that pulmonary embolism is followed by a contraction of the smooth muscles of the airways. In the proximal segments this contraction causes some narrowing in the lumen, as

indicated by the moderate rise in mean frictional resistance. In the distal segments the same contraction would cause widespread closure of the terminal airways with a fall in ventilated lung volume and CL . This appears to be the "unknown mechanism" (41) that produces a shift of ventilation toward the unaffected parts of the lungs, as demonstrated by fluoroscopy (42) and bronchospirometry (43) and by means of a balloon-catheter (44, 45).

The fall in CL after embolization was accompanied by a decrease in lung volume amounting to 150 to 200 ml. If muscular contraction squeezed out air one would expect the end-expiratory P_{pl} to become more negative. Since compliance of the chest wall in the sheep is on the average 150 ml per cm H_2O (24), the expected rise in end-expiratory transpulmonary pressure could not exceed 1 to 2 cm H_2O . This was the change actually observed in the first half-minute following the embolus. Its subsequent return to normal can be accounted for by a gradual further expansion of the ventilated areas of the lung. In other cases the return to normal was apparent rather than real owing to active expiration, the P_{pl} at the end of expiration at the moment of zero flow remaining more negative than before embolism.

Robin (8) and Julian (44), and their associates, observed an increased alveolar dead space based on a widened alveolar-arterial P_{CO_2} difference in pulmonary embolism. In view of the gross mechanical nonhomogeneity of the lung after embolism, alveolar sampling is invalid. This may account for the gross variation in their results.

Because of the tendency of the anesthetized animal to breathe at a fixed V_T —i.e., constant transpulmonary pressure swing— CL is likely to remain reduced until a large inflation is performed. The apparent duration of the stimulus responsible for the fall in CL can therefore only be assessed by the period of time that must elapse after embolization before CL can be restored by inflation. This period varied with the amount of embolic material injected. With larger doses, 30 minutes was not sufficient; with small doses, CL was successfully restored a few minutes after embolization.

The inability of vagotomy and atropine to prevent the embolism-induced rise in mean frictional resistance is at variance with the findings of Binet and Burstein (5) and Boyer and Curry (6) and

confirms the observations reported by Singh (4). The parasympathetic nervous system is apparently not involved in this change.

The fall in CL remained unaffected by neuroplegic procedures and by the administration of antihistaminic and antiserotonin drugs. It seems safe to conclude that the suggested constriction of the airway musculature is unrelated to neurogenic stimuli and to the release of histamine or serotonin. The fall following the small dose of embolic material was reduced by adrenalin and completely abolished by isoproterenol. This proved the functional nature of airway closure and appears to suggest that some yet unidentified substance, causing a constriction of the airway musculature, might be released as a response to embolism.

The severe fall in CL as demonstrated in these experiments is bound to increase the strain of the respiratory muscles already burdened by hyperventilation. We suggest that the resulting increase in the work of breathing could well be responsible for the severe dyspnea seen in some cases of clinical pulmonary embolism. Since the administration of isoproterenol abolished both hyperventilation and the rise in elastic resistance, it is likely to be beneficial in patients.

3. *Arterial hypoxemia.* Closure of the terminal airways, if relatively more extensive than obstruction of the vessels, may result in the perfusion of nonventilated alveoli with consequent venous admixture. This explanation is consistent with the inability of 100 per cent oxygen to abolish venous admixture (8, 9), and appears to be supported by the partial correlation between Q_E and CL (Figure 5).

4. *Pulmonary hypertension.* The sudden steep rise in $\bar{P}_{p.a.}$ after the injection of embolic material (Figure 1) does not appear to be dependent on the amount injected. The extraordinary rise in $\dot{Q}$ that would be necessary of itself to cause such a rise is unlikely to have occurred. It is more probable that the rise represents a time lag between the embolism-induced obstruction and the opening of reserve capillaries. In this case one would expect the rise to be reduced or largely absent after repeated doses of emboli, but this is not the case; an equal initial rise was regularly observed with repeated injections. It is therefore suggested

that this sudden steep rise represents pulmonary vasoconstriction.

The argument most frequently used against the occurrence of embolic pulmonary vasoconstriction is mainly based on the absence of pulmonary hypertension following lobar emboli (18). This implies that local embolism does not cause generalized vasoconstriction in the lungs. The situation is analogous in the systemic circuit where localized emboli also fail to cause a generalized vasoconstriction. Lobar emboli are, however, of little assistance in excluding the occurrence of a local response, i.e., constriction of vessels actually containing the embolic particles. This mechanism is consistent with the dose-response relationship and would also explain how a relatively small dose of particles, as in our group II, can cause pulmonary hypertension.

The lack of effect of neuroplegic procedures to prevent postembolic pulmonary hypertension has been confirmed in these experiments. Even 100 per cent oxygen, an otherwise potent pulmonary vasodilator, proved ineffective. The lack of protection by lysergic acid butanolamide suggests that serotonin release is probably not involved in this mechanism.

The administration of promethazine failed to affect the immediate pressure response but reduced the 5-minute values considerably. Changes in lung mechanics were not influenced. This finding, therefore, does not provide evidence for the release of histamine, which is known to produce bronchoconstriction but no pulmonary hypertension (46).

The effect of adrenalin and even more the effect of isoproterenol provide conclusive evidence that pulmonary hypertension after the small dose of barium sulfate is predominantly functional. Isoproterenol has been demonstrated to be a potent pulmonary vasodilator in animals (47). In patients suffering from various types of heart disease isoproterenol in considerably smaller doses reduced R_{pulm} by increasing $\dot{Q}$; $P_{p.a.}$ remained unchanged (48). It is not clear whether this difference is due to the lower dose or to the different mechanism of pulmonary hypertension in those patients.

From these observations isoproterenol emerges as a substance which, if administered in high doses and continuously, effectively prevents all major

consequences caused by the intravenous administration of 0.02 ml per kg barium sulfate. No other substance is known to offer a similar protection. It remains to be decided how effectively this drug can block the effects of larger doses of embolic material and what its action is if administered after embolism.

SUMMARY

Experimental pulmonary embolism was produced in sheep, by means of graded amounts of a barium sulfate emulsion. Ventilation, lung mechanics and circulation were measured. The effect of various neuroplegic procedures, oxygen breathing, the administration of antihistaminic and antiserotonin drugs, and continuous adrenalin and isoproterenol infusions was assessed.

In addition to the already known consequences of pulmonary embolism (hyperventilation, arterial hypoxemia, pulmonary hypertension and bronchoconstriction), a gross fall in lung compliance was shown to occur, unrelated to lung edema.

All but one of the procedures used in these experiments were ineffective in altering the onset or severity of the above changes, but the effect of the smaller dose of embolic material was completely prevented by the administration of isoproterenol.

It is concluded that postembolic pulmonary hypertension and compliance-fall after a small dose of embolic material are predominantly functional and probably caused by the release of an unknown substance as a response to embolism. The physiological and clinical implications of these findings are discussed.

ACKNOWLEDGMENTS

We are indebted to Mr. P. Donnelly, Miss Maureen Woodward and Mr. T. Miller, members of our technical staff. Many parts of this work depended on their collaboration. It was a privilege to enjoy Prof. C. R. B. Blackburn's constant interest and support.

REFERENCES

1. Whitteridge, D. Multiple embolism of the lung and rapid shallow breathing. *Physiol. Rev.* 1950, **30**, 475.
2. Binger, C. A. L., Brow, G. R., and Branch, A. Experimental studies on rapid breathing. II. Tachypnea, dependent upon anoxemia resulting from mul-

- tiple emboli in the larger branches of the pulmonary artery. *J. clin. Invest.* 1924-25, 1, 155.
3. Megibow, R. S., Katz, L. N., and Feinstein, M. Kinetics of respiration in experimental pulmonary embolism. *Arch. intern. Med.* 1943, 71, 536.
 4. Singh, I. Certain effects of pulmonary gas embolism. *J. Physiol. (Lond.)* 1936, 87, 11.
 5. Binet, L., and Burstein, M. Nouvelles recherches sur l'embolie pulmonaire expérimentale. *Presse méd.* 1946, 54, 633.
 6. Boyer, N. H., and Curry, J. J. Bronchospasm associated with pulmonary embolism; respiratory failure. *Arch. intern. Med.* 1944, 73, 403.
 7. Williams, M. H., Jr. Mechanical vs. reflex effects of diffuse pulmonary embolism in anesthetized dogs. *Circulat. Res.* 1956, 4, 325.
 8. Robin, E. D., Forkner, C. E., Jr., Bromberg, P. A., Croteau, J. R., and Travis, D. M. Alveolar gas exchange in clinical pulmonary embolism. *New Engl. J. Med.* 1960, 262, 283.
 9. Niden, A. H., and Aviado, D. M., Jr. Effects of pulmonary embolism on the pulmonary circulation with special reference to arteriovenous shunts in lung. *Circulat. Res.* 1956, 4, 67.
 10. Dick, M. The respiratory and circulatory responses to intravenous oxygen and their relation to anoxemia. *Amer. J. Physiol.* 1939, 127, 228.
 11. Brofman, B. L., Charms, B. L., Kohn, P. M., Elder, J., Newman, R., and Rizika, M. Unilateral pulmonary artery occlusion in man; control studies. *J. thorac. Surg.* 1957, 34, 206.
 12. Vuylsteek, K., Van Loon, A., Leusen, I., Van der Straeten, M., Verstraeten, J., Rötgens, M., and Pannier, R. Experimentelle und klinische Untersuchungen bei unilateralem Verschluss der Arteria pulmonalis während des Herzkatheterismus. *Verh. dtsh. Ges. Kreisl.-Forsch.* 1956, 22, 229.
 13. Bücherl, E. S., and Bücherl, R. Die temporäre Pulmonalarterienblockade als klinische Funktionsuntersuchung. *Thoraxchirurgie* 1958, 5, 519.
 14. Carlson, R. F., Charbon, B. C., Charbon, H. G. A., and Adams, W. E. The effect of decreasing the amount of lung tissue on the right ventricular pressures in animals. *J. thorac. Surg.* 1951, 21, 621.
 15. Tauber, K., Keyssler, H., and Parhofer, R. Die Wirkung des Lungenflügelentfernung auf ein nicht voll leistungsfähiges Herz. *Arch. klin. Chir.* 1955, 281, 162.
 16. Harrison, C. V. Experimental pulmonary hypertension. *J. Path. Bact.* 1951, 63, 195.
 17. Haynes, F. W., Kinney, T. D., Hellem, H. K., and Dexter, L. Circulatory changes in experimental pulmonary embolism. *Fed. Proc.* 1947, 6, 125.
 18. Daley, R., Wade, J. D., Maraist, F., and Bing, R. J. Pulmonary hypertension in dogs induced by injection of lycopodium spores into the pulmonary artery, with special reference to the absence of vasomotor reflexes. *Amer. J. Physiol.* 1951, 164, 380.
 19. Courtoy, P., and Salonikides, N. Hypertension pulmonaire aigue expérimentale par embolie pulmonaire; dynamique circulatoire. *Acta cardiol. (Brux.)* 1956, 11, 52.
 20. Price, K. C., Hata, D., and Smith, J. R. Pulmonary vasomotion resulting from miliary embolism of the lungs. *Amer. J. Physiol.* 1955, 182, 183.
 21. Gordy, E., and Drabkin, D. L. Spectrophotometric studies. XVI. Determination of the oxygen saturation of blood by a simplified technique, applicable to standard equipment. *J. biol. Chem.* 1957, 227, 285.
 22. Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, vol. 2, Methods. Baltimore, Williams & Wilkins, 1932.
 23. Fishman, A. P., Turino, G. M., Brandfonbrener, M., and Himmelstein, A. The "effective" collateral blood flow in man. *J. clin. Invest.* 1958, 37, 1071.
 24. Colebatch, H. J. H., and Halmagyi, D. F. J. Lung mechanics and resuscitation after fluid aspiration. *J. appl. Physiol.* 1961, In press.
 25. Altman, P. L., and others, comp. Handbook of Respiration. Philadelphia, Saunders, 1958.
 26. Halmagyi, D. F. J., and Colebatch, H. J. H. Ventilation and circulation in fluid aspiration. *J. appl. Physiol.* 1961, 16, 35.
 27. Silverman, L., and Whittenberger, J. L. Clinical pneumotachograph in Methods in Medical Research, J. H. Comroe, Jr., Ed. Chicago, Year Book Publ., 1950, vol. 2, p. 104.
 28. Frank, N. R., Mead, J., and Ferris, B. G., Jr. The mechanical behavior of the lungs in healthy elderly persons. *J. clin. Invest.* 1957, 36, 1680.
 29. 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.* 1959, 14, 177.
 30. Snedecor, G. W. Statistical Methods Applied to Experiments in Agriculture and Biology, 5th ed. Ames, Iowa State College Press, 1956.
 31. Frank, N. R., Siebens, A. A., and Newman, M. M. The effect of pulmonary resection on the compliance of human lungs. *J. thorac. cardiovasc. Surg.* 1959, 38, 215.
 32. Sharp, J. T., Griffith, G. T., Bunnell, I. L., and Greene, D. G. Ventilatory mechanics in pulmonary edema in man. *J. clin. Invest.* 1958, 37, 111.
 33. Mead, J., and Collier, C. Relation of volume history of lungs to respiratory dynamics in anesthetized dogs. *J. appl. Physiol.* 1959, 14, 669.
 34. Attinger, E. O. Pulmonary mechanics and hemodynamics during changes in ventilation and blood volume. *J. appl. Physiol.* 1960, 15, 429.
 35. Bondurant, S., Mead, J., and Cook, C. D. A re-evaluation of effects of acute central congestion on lung compliance in normal subjects. *J. appl. Physiol.* 1960, 15, 875.
 36. Singer, D., Hesser, C., Pick, R., and Katz, L. N. Diffuse bilateral pulmonary edema associated with

- unilobar military pulmonary embolization in the dog. *Circulat. Res.* 1958, **6**, 4.
37. Dunn, J. S. The effects of multiple embolism of pulmonary arterioles. *Quart. J. Med.* 1919-20, **13**, 129.
38. Otis, A. B., McKerrow, C. B., Bartlett, R. A., Mead, J., McIlroy, M. B., Selverstone, N. J., and Radford, F. P., Jr. Mechanical factors in the distribution of pulmonary ventilation. *J. appl. Physiol.* 1956, **8**, 427.
39. Miller, W. S. *The Lung*, 2nd ed. Springfield, Ill., Thomas, 1950.
40. von Hayek, H. *The Human Lung*. New York, Hafner, 1960.
41. Robin, E. D. Some aspects of the physiologic disturbances with pulmonary embolism. *Med. Clin. N. Amer.* 1960, **44**, 1269.
42. Fleischner, F. G. Pulmonary embolism. *Canad. med. Ass. J.* 1958, **78**, 653.
43. Söderholm, B. Hemodynamics of the lesser circulation in pulmonary tuberculosis; effect of exercise, temporary unilateral pulmonary artery occlusion, and operation. *Scand. J. clin. Lab. Invest.* 1957, **9**, suppl. 26.
44. Julian, D. G., Travis, D. M., Robin, E. D., and Crump, C. H. Effect of pulmonary artery occlusion upon end-tidal carbon dioxide tension. *J. appl. Physiol.* 1960, **15**, 87.
45. Severinghaus, J. W., Swenson, E. W., Finley, T. N., Lategola, M. T., and Williams, J. Unilateral hypoventilation produced in dogs by occluding one pulmonary artery. *J. appl. Physiol.* 1961, **16**, 53.
46. Storstein, O., Calabresi, M., Nims, R. G., and Gray, F. D., Jr. The effect of histamine on the pulmonary circulation in man. *Yale J. Biol. Med.* 1959, **32**, 197.
47. Aviado, D. M., Jr., and Schmidt, C. F. Effects of sympathomimetic drugs on pulmonary circulation: With special reference to a new pulmonary vasodilator. *J. Pharmacol.* 1957, **120**, 512.
48. Dodge, H. T., Lord, J. D., and Sandler, H. Cardiovascular effects of isoproterenol in normal subjects and subjects with congestive heart failure. *Amer. Heart J.* 1960, **60**, 94.