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Research Article

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Ventilation-Perfusion Abnormalities in Experimental Pulmonary Embolism *

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The changes in pulmonary function that occur as a result of experimental pulmonary vascular occlusion have been intensively investigated. The techniques employed for producing pulmonary vascular occlusion have included balloon occlusion (1–3) and the injection of particulate matter (4) into the pulmonary artery. The results of such studies are not directly comparable to clinical pulmonary thromboembolism, where vascular occlusion is produced by autogenous thrombi. It might be anticipated, a priori, that substantial differences would occur because of the different physicochemical nature of the embolic material and the different pattern of embolization. In the present studies the effects of autogenous thromboemboli on ventilation-perfusion relationships, pulmonary gas exchange, pulmonary mechanics, and the ultrastructure of the lung are described.

Two questions related to pulmonary thromboembolism are of particular interest. First is the problem of redistribution of ventilation after embolization. Several investigators have described a shift of pulmonary ventilation away from nonperfused lung segments after balloon occlusion of a pulmonary artery (1, 5, 6). We have developed a technique to evaluate whether redistribution of ventilation occurs after autogenous pulmonary thromboembolism. Second is the evaluation of the mechanisms resulting in arterial hypoxemia after autogenous pulmonary thromboembolism.

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Methods

Sixty-five healthy, mongrel dogs ranging in weight from 9 to 26 kg were studied. The animals were anesthetized with either pentobarbital, thiopental sodium, or chloralose by intravenous administration and intubated with an endotracheal tube. Thirty-four dogs were studied during spontaneous ventilation (spontaneous ventilation dogs, SVD), and in 31 dogs spontaneous ventilation was abolished by either *d*-tubocurarine or succinylcholine administered intravenously, and ventilation was then maintained with an Etsten bellows pump set to deliver a constant tidal volume at a constant frequency (controlled ventilation dogs, CVD). The total amount of barbiturate administered was such as previously observed to maintain adequate anesthesia in nonparalyzed animals. Autogenous thrombi were produced and released into the pulmonary circulation as previously described (7).

The following measurements were made before and within 30 minutes after embolization in the SVD and CVD while they were breathing room air. Minute ventilation ($\dot{V}_E$) was measured by standard techniques. Femoral arterial blood was analyzed for oxygen content and capacity, and CO_2 content by the technique of Van Slyke and Neill (8). Arterial pH was measured with a glass electrode at 37° C. Plasma CO_2 content was derived with the correction factors of Van Slyke and Sendroy from the whole blood CO_2 content, the arterial hematocrit, and arterial pH (9). Arterial P_{CO_2} (P_{aCO_2}) was calculated from the Henderson-Hasselbalch expression of the mass law or measured directly with a P_{CO_2} electrode. Arterial P_{O_2} (P_{aO_2}) was measured with a modified Clark electrode in the CVD only. End-tidal CO_2 tension (P_{ACO_2}) was monitored continuously with an infrared CO_2 analyzer. The peak values of end-tidal P_{CO_2} in each respiratory cycle were used to approximate "alveolar" P_{CO_2}. Previous studies in this laboratory have shown that in the normal anesthetized dog studied within an hour of anesthesia the mean difference between P_{ACO_2} and P_{aCO_2} averages 1.5 ± SD 1.9 mm Hg (3). Expired CO_2 (F_{ECO_2}) and oxygen (F_{EO_2}) concentrations were measured by analyses of expired gas by the micro-Scholander method (10). P_{aO_2} was measured after 30 minutes of 99.6% oxygen inhalation in the SVD and after 20 minutes in the CVD. In the latter, the postembolic measurement was made during the third hour after embolization, and in the former, during the first 2 hours.

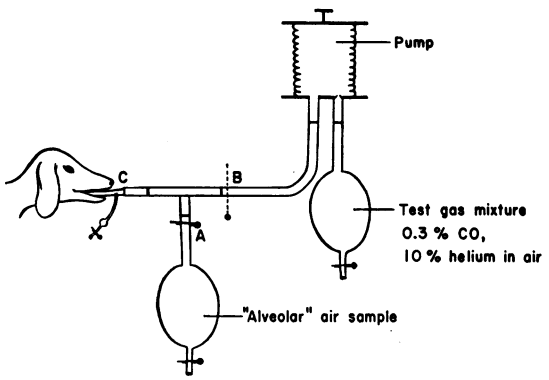

FIG. 1. DIAGRAM OF SYSTEM USED FOR MEASUREMENT OF SINGLE BREATH CARBON MONOXIDE DIFFUSING CAPACITY IN CONSTANT VENTILATION DOGS.

In the SVD the effect of intermittent positive pressure breathing (IPPB), nebulized isoproterenol, and parenteral aminophylline on the a-A P_{CO_2} difference before and after embolization was observed. In addition, in the SVD functional residual capacity (FRC) was measured by a closed circuit helium technique and nitrogen washout by the technique of Darling, Cournand, and Richards before and after embolization (11). Total lung resistance (R_L) and lung compliance (C_L) were measured in the SVD before and after embolization by the techniques described by Mead and Whittenberger (12), and Marshall and DuBois (13). Thirteen of the SVD were allowed to survive for 4 days after embolization so that the time course of the observed changes could be studied.

In the CVD diffusing capacity for carbon monoxide (D_{LCO}) [1] was measured before and after embolization by a modification of the single breath technique of Ogilvie, Forster, Blakemore, and Morton (14) as follows: A bellows pump was set to deliver a fixed volume ranging from 700 to 800 ml (Figure 1). The anesthesia bag used to collect alveolar air was evacuated. The system was then flushed with a mixture of 0.3% CO and 10% helium in air from a second anesthesia bag. The apneic dog was attached to the system at point C in the Figure. The fixed volume of test gas mixture was rapidly pumped as a single inspiration into the dog's lungs and held there for 10 seconds. Then with an assistant compressing the dog's thorax, 200 ml of end-expired (alveolar) air was collected in the anesthesia bag by transferring the clamp at position A to position B. The dog was then ventilated with room air for 1 minute and the measurement of diffusing capacity repeated. Helium concentrations of the inspired gas and alveolar air were measured with a catharometer, and the carbon monoxide concentration of the respective gases was measured with an infrared carbon monoxide analyzer, after passing the gas through a drying agent. The FRC used to calculate D_{LCO} had been measured by the nitrogen washout technique before embolization and was not remeasured after embolization, since as will be shown, it was not found to be significantly changed after embolization of the type produced in these experiments.

Five minutes before sacrifice of each animal with intravenous barbiturate, heparin was administered intravenously to prevent post-mortem clotting. After sacrifice the lungs were examined for evidence of infarction and atelectasis. An estimate of the degree of pulmonary arterial occlusion was made in all animals. In the SVD an arbitrary scale of degree of embolism ranging from 1 to 4+ was used (15). In the CVD the degree of embolization was expressed as a percentage of the number of pulmonary arteries containing thromboemboli. In nine of the CVD an india ink infusion technique (see below) was used to quantitate more accurately the amount of embolized and nonperfused lung. In all of the CVD, sections of embolized and nonembolized lung selected at random were studied by light and electron microscopy. India ink injection was used to quantitate the degree of embolized and nonperfused lung in nine CVD as follows: The right ventricle was catheterized immediately before sacrificing the animal. Twenty ml of 50% india ink was rapidly infused through the catheter, followed by 20 ml of saturated potassium chloride, which produced immediate cardiac arrest. The lungs were rapidly removed and fixed in Bouin's solution. Forty-eight hours later the lungs were dissected and carbon stained and noncarbon stained lung segments separated. There was usually a clear delineation between the areas of carbon stained and noncarbon stained lung tissue. The weight and volume (as determined by water displacement) of carbon stained and noncarbon stained lung segments were measured, and the relation of carbon staining to gross embolic occlusion of pulmonary arteries was noted.

Calculations. Standard formulae were used to calculate alveolar oxygen tension ($P_{A_{O_2}}$), respiratory exchange ratio (RER), FRC, R_L, C_L, D_{LCO}, and the arterial-alveolar CO_2 tension difference (a-A P_{CO_2} difference).

The following equation (see Appendix) was used to calculate alveolar dead space ($V_{D_{alv}}$) as a percentage of the tidal volume entering the alveoli with each breath:

$$\frac{V_{D_{alv}}}{(V_T - V_{D_{anat}})} = \frac{P_{a_{CO_2}} - P_{A_{CO_2}}}{P_{a_{CO_2}} - P_{A_{CO_2}} + P_{E_{CO_2}}} \times 100,$$

where V_T = tidal volume in milliliters, $V_{D_{anat}}$ = anatomic dead space in milliliters, $P_{a_{CO_2}}$ = arterial CO_2 tension in millimeters Hg, $P_{A_{CO_2}}$ = alveolar CO_2 tension in millimeters Hg, and $P_{E_{CO_2}}$ = CO_2 tension in expired air in millimeters Hg.

The per cent decrease in effective alveolar ventilation ($V_{A_{eff}}$) in the CVD after embolization was calculated by the following formula: Since V_E before = V_E after, and assuming a value of 100% to $V_{A_{eff}}$ before embolization,

[1] Measurements of the D_{LCO} by the steady-state technique proved unsatisfactory presumably because of small errors in the determination of $P_{a_{CO_2}}$. This parameter significantly affects the calculation of physiologic dead space, and with the proportionately large dead spaces encountered in these experiments, there were significant errors in calculation of $P_{A_{CO}}$ and hence, D_{LCO}.

TABLE I

*Mean values for pulmonary ventilation and gas exchange before and after embolization**

Dogs		$\dot{V}_E$	Decrease in $\dot{V}_{A_{eff}}$	Pa_{CO_2}	a-A P_{CO_2} difference	Sa_{O_2}	Pa_{O_2}	Pa_{O_2} after 100% oxygen	P_{AO_2}	D_{LCO}
		L/min	%	*mm Hg*	*mm Hg*	%	*mm Hg*	*mm Hg*	*mm Hg*	*ml/min/mm Hg*
SVD										
3 to 4+	B	7.1 (21)		43 (19)	5 (19)	90 (19)		533 (14)		
(21)	A	12.3		39	19	84		333		
		.01 >p >.001		.05 >p >.025	p	.01 >p >.001		.05 >p >.025		
1 to 2+	B	5.5		41	2	92		566		
(13)	A	13.0 (10)		35 (13)	12 (13)	92 (13)		446 (7)		
		.02 >p >.01		.025 >p >.01	p	.6 >p >.5		.1 >p >.05		
CVD										
Group 1	B	2.4 (18)	(18)	33 (18)	3 (17)	94 (18)	95 (11)	466 (13)	105 (18)	12.8 (11)
(19)†	A	2.3	19	42	11	88	78	460	94	11.5
		.2 >p >.1		p <.001	p <.001	.025 >p >.01	p <.001	p >.9	p <.001	.05 >p >.025
Group 2	B	2.4 (6)	(6)	33 (6)	1 (4)	92 (4)	78 (1)	433 (3)	109 (4)	13.1 (3)
(6)		2.5	4	34	0	92	81	466	108	12.5
		.7 >p >.6		.7 >p >.6	.4 >p >.3	.6 >p >.5		.2 >p >.1	.6 >p >.5	.5 >p >.4

* Abbreviations: SVD, spontaneous ventilation dogs; CVD, controlled ventilation dogs; B, before embolization; A, after embolization; $\dot{V}_E$, total ventilation; $\dot{V}_{A_{eff}}$, effective alveolar ventilation; Pa_{CO_2}, arterial carbon dioxide tension; a-A P_{CO_2} difference, arterial-alveolar carbon dioxide tension difference; Sa_{O_2}, arterial oxygen saturation; Pa_{O_2}, arterial oxygen tension; P_{AO_2}, alveolar oxygen tension; D_{LCO}, diffusing capacity (single breath) for carbon monoxide. Figures in parentheses indicate number of animals studied. p values represent the statistical significance of the difference between the mean values.

† One animal died immediately after release of thromboemboli.

then the per cent decrease in $\dot{V}_{A_{eff}} =$

$$\left(1 - \frac{Pa_{CO_2}\text{ before} \cdot P_{E_{CO_2}}\text{ after}}{Pa_{CO_2}\text{ after} \cdot P_{E_{CO_2}}\text{ before}}\right) \times 100,$$

where Pa_{CO_2} before = arterial CO_2 tension in millimeters Hg before embolization, Pa_{CO_2} after = arterial CO_2 tension in millimeters Hg after embolization, $P_{E_{CO_2}}$ before = CO_2 tension in expired air in millimeters Hg before embolization, and $P_{E_{CO_2}}$ after = CO_2 tension in expired air in millimeters Hg after embolization.

A fall of 10% or more was accepted as significant, since changes of 9% or less could result from errors in the measurement of Pa_{CO_2}.

Unperfused lung = per cent of noncarbon stained lung = [weight (grams) or volume (milliliters) noncarbon stained lung]/[total weight (grams) or volume (milliliters) of lungs]. The values for weight and volume were averaged together.

The per cent of apparent air shift = (per cent unperfused lung − per cent decrease in $\dot{V}_{A_{eff}}$)/per cent unperfused lung.

Results

The SVD consisted of two groups: 21 dogs with 3 to 4 + emboli and 13 dogs with 1 to 2 + emboli. The CVD consisted of three groups: group 1 included 19 dogs in which there was a significant fall in $\dot{V}_{A_{eff}}$ after embolization, i.e., 10% or more, or a decrease in Pa_{O_2} disproportionately great for the decrease produced by the fall in $\dot{V}_{A_{eff}}$, or both. There were 6 dogs in group 2 in which the fall in $\dot{V}_{A_{eff}}$ was less than 10% and without a disproportionate fall in Pa_{O_2}. In the 6 dogs in group 3 no pulmonary emboli were found at autopsy.

Ventilation and blood gases. The effect of embolization on these parameters is summarized in Tables I and II, which contain mean values for each group. In the SVD after the release of emboli, there was an increase in $\dot{V}_E$. This was produced for the most part by increases in the frequency of respiration. $\dot{V}_{A_{eff}}$ increased in all the SVD. In the CVD obviously no essential change of $\dot{V}_E$ occurred after embolization, and in the absence of compensatory hyperventilation, there was a mean decrease in calculated $\dot{V}_{A_{eff}}$ of 19% in the

TABLE II

*Mean values for a-A P_{CO_2} difference after embolization in SVD**

		Before embolization	After embolization			
			Day 1	Day 2	Day 3	Day 4
		mm Hg†	*mm Hg*†	*mm Hg*	*mm Hg*	*mm Hg*
Ventilation with room air		4 (13)	14 (13)	9 (13)	7 (13)	6 (13)
Ventilation with IPPB, isoproterenol, or aminophylline	B	2 (7)	16 (5)	12 (1)		7 (1)
	A	6	18	14		11

* Abbreviations: IPPB, intermittent positive pressure breathing; B and A before and after IPPB, isoproterenol, or aminophylline. Figures in parentheses indicate number of animals studied.

† Measurement made within 30 minutes of release of thrombi.

group 1 dogs and 4% in the group 2 dogs. In SVD and the group 1 CVD there was an increase in alveolar dead space and in the a-A P_{CO_2} difference. In the group 2 CVD the change in alveolar dead space and a-A P_{CO_2} difference fell within the range of experimental error. It is well known that there are changes in $\dot{V}_A/\dot{Q}_C$ (capillary blood flow) ratios in the lung of anesthetized dogs not subject to any other experimental procedure. The effect of this factor on calculated $\dot{V}_{A_{eff}}$ was eliminated by using each dog as his own control. Also in the 6 dogs (group 3) in which no pulmonary emboli were found there was no significant change in calculated $\dot{V}_{A_{eff}}$ after the experimental procedure. Thus, the changes found in the group 1 dogs clearly occurred as a result of pulmonary vascular occlusion. As shown in Table II, in the SVD the a-A P_{CO_2} difference decreased with each successive day after embolization, and by the fourth postembolic day was usually near control levels. Bronchodilators and IPPB caused the a-A P_{CO_2} difference to increase both before and after the release of emboli. In the SVD with the 3 to 4 + emboli and the group 1 CVD, the arterial blood oxygen saturation (Sa_{O_2}) and the Pa_{O_2} fell substantially. In the former group the decrease in Sa_{O_2} apparent during inhalation of ambient air persisted for 3 to 36 hours and could not be restored to normal with room air administered by IPPB. In the 1 to 2 + SVD and the group 2 CVD the Sa_{O_2} did not change significantly.

In 6 of 11 group 1 CVD the fall in Pa_{O_2} could not be explained entirely on the basis of the fall in $\dot{V}_{A_{eff}}$. In 4 dogs the fall in Pa_{O_2} could be explained on this basis, and in 1 dog there was no postembolic change in Sa_{O_2} or Pa_{O_2}.

In the 3 to 4 + SVD the Pa_{O_2} after 99.6% oxygen inhalation was significantly reduced after embolization as compared with changes in Pa_{O_2} before embolism, whereas in the CVD there was no significant change.

In the CVD the RER was greater than 1.0 before embolization in most of the dogs, indicating the presence of an unsteady state. This was presumably related to the decreased metabolic rate and CO_2 production after induction of anesthesia and muscle paralysis with maintenance of ventilation at a preanesthesia level. By the time the postembolic studies had been carried out, the majority of the dogs showed an RER of less than 1.

Nitrogen washout curves before and after embolization showed no significant change.

Diffusing capacity. There was a mean fall of borderline significance of 1.3 ml per minute per mm Hg of the $D_{L_{CO}}$ in 11 of the group 1 CVD (Table I). There were wide variations in the preembolization values with a range from 3.8 to 21.2 ml per minute per mm Hg. Of the 6 group 1 CVD with a disproportionate fall in Pa_{O_2}, the $D_{L_{CO}}$ was measured in 4; in 3 there was a fall ranging from 0.8 to 2.9 ml per minute per mm Hg, whereas in 1 there was a 1.2 ml per minute per mm Hg rise. $D_{L_{CO}}$ did not change significantly in 3 of the group 2 CVD.

Pulmonary mechanics. Immediately after embolization in the SVD there were large increases in R_L and large decreases in C_L (Table III). Although changes in lung mechanics occurred in the presence of a single embolus, these abnormalities tended to be greater in the 3 to 4 + SVD. Four to 30 minutes after embolization, R_L and C_L returned to normal. At the time of the major changes in R_L, the a-A P_{CO_2} difference was large, and although it gradually fell, was still abnormal when the mechanical abnormality was no longer detectable (Figure 2).

The FRC when measured by helium dilution in the SVD did not change significantly within 30 minutes after embolization.

India ink studies. In the group 1 CVD the anatomical estimate of the degree of pulmonary ar-

TABLE III

*Mean values for lung mechanics before and after embolization in SVD**

	Before embolization	After embolization	
R_L, *cm/L/sec* (19)	3.2	6.0	$p < .001$
C_L, *L/cm* (19)	0.09	0.06	$p < .001$
a-A P_{CO_2} difference, *mm Hg* (19)		17	$p < .001$
FRC, *ml*			
3 to 4 + (9)	1,170	1,320	$p > 0.5$
1 to 2 + (3)	1,060	1,190	$p > 0.5$

* Abbreviations: R_L, total lung resistance; C_L, lung compliance; a-A P_{CO_2} difference, arterial-alveolar carbon dioxide tension difference; FRC, functional residual capacity. Figures in parentheses indicate number of animals studied. p values represent the statistical difference between the mean values.

terial occlusion judged by the number of thromboemboli in the pulmonary arterial tree averaged 64%. In approximately a third of this group the entire pulmonary arterial tree contained thromboemboli, i.e., 100% occlusion. In the group 2 CVD the anatomical estimate of pulmonary arterial occlusion averaged 40%. India ink infusion in 3 group 3 CVD in which no emboli were found in the pulmonary arteries showed that all lung tissue became darkly carbon stained. Noncarbon stained lung, which was clearly discernible, was invariably associated with an embolus in the regional pulmonary artery. However, when carbon stained lung was found, it was not uncommonly associated with an embolus in the regional pulmonary artery. Thus, not all emboli effectively prevented perfusion of the involved lung segments by dye, and presumably emboli may be present without a total cessation of blood flow. It should be emphasized that these dogs were sacrificed by inducing asystole within seconds after the infusion of the india ink. Assuming that noncarbon stained lung represents totally nonperfused lung, then the amount of nonperfusion ranged from 11 to 48% in 5 of the group 1 CVD so studied (Figure 3). On the basis of this assumption, the apparent degree of air shift ranged from 0 to 69% in these 5 animals (Figure 3).

Necropsy studies. In none of the 65 dogs was gross or microscopic evidence of pulmonary infarction or pulmonary edema found. Scattered areas of atelectasis were observed in most dogs, but were unrelated to the degree or location of emboli. The only anatomical difference between the 3 to 4 + SVD and group 1 CVD and in the 1 to 2 + SVD and group 2 CVD was the volume of thromboemboli in the pulmonary arteries. In the SVD that were allowed to survive 96 hours, large amounts of thromboemboli were still present. In the 6 group 3 CVD no thromboemboli were found. Each of these dogs had severe metabolic acidosis possibly related to the barbiturate anesthesia and the experimental procedure.

Electron microscopy showed no essential difference in the appearance of alveolar walls, blood vessels, or subcellular structures in the affected versus nonaffected areas of the lung. The appearance was identical to that found in control dogs without pulmonary emboli.

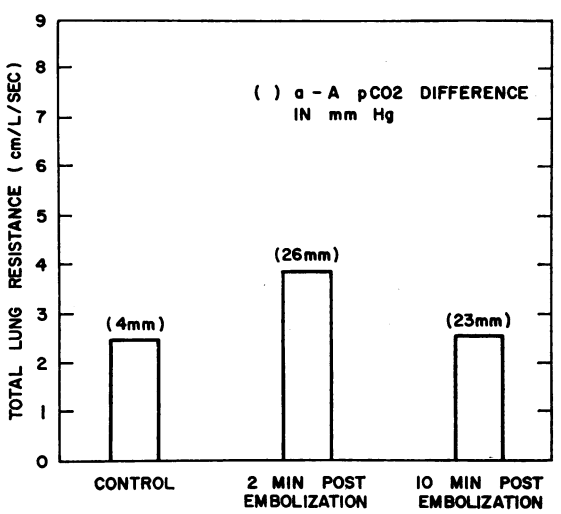

FIG. 2. TOTAL LUNG RESISTANCE AND ARTERIAL-ALVEOLAR CARBON DIOXIDE TENSION (a-A P_{CO_2}) DIFFERENCE BEFORE AND AFTER EMBOLIZATION IN A SPONTANEOUS VENTILATION DOG.

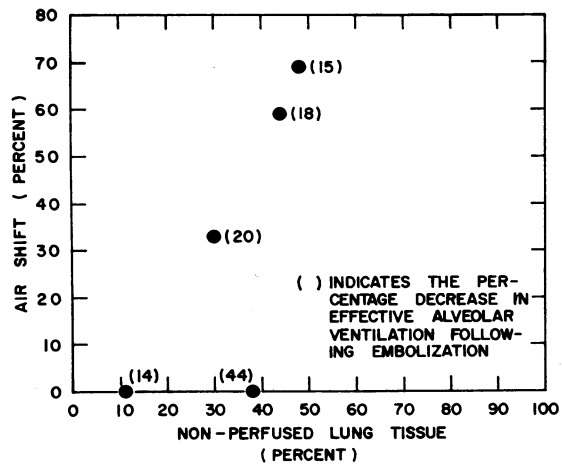

FIG. 3. RELATIONSHIP BETWEEN NONPERFUSED LUNG TISSUE, DECREASE IN EFFECTIVE ALVEOLAR VENTILATION, AND AIR SHIFT IN 5 GROUP 1 CONSTANT VENTILATION DOGS AFTER EMBOLIZATION.

Discussion

The changes in pulmonary function that take place after pulmonary thromboembolism are complex and involve interrelated alterations in ventilation-perfusion relations, pulmonary mechanics, and pulmonary gas exchange.

Redistribution of ventilation. Effective occlusion of a pulmonary artery by an embolus should result in a segment of lung that is ventilated, but not perfused. Such areas are referred to as alveolar or parallel dead space. Severinghaus and

Stupfel (16) and Julian, Travis, Robin, and Crump (3) have demonstrated an increase in alveolar dead space after pulmonary arterial occlusion due to air embolism and balloon occlusion of the pulmonary artery, respectively, in the dog. In the absence of any change in the proportion of the ventilation delivered to the embolized, nonperfused lung segments, the relative increase in alveolar dead space theoretically could be used to quantitate the amount of embolized, nonperfused lung tissue. This has been the basis for the clinical use of the a-A P_{CO_2} difference to determine the presence of pulmonary emboli and to quantitate the amount of involved lung (3, 16). Recent work by Severinghaus and others (1) indicates that the assumption of a change in perfusion alone after pulmonary arterial occlusion may be incorrect. In the dog, they demonstrated that after balloon occlusion of the pulmonary artery to one lung, there was a relative decrease in ventilation to this lung. It was postulated that hypocapnea subsequent to the loss of perfusion resulted in bronchiolar constriction, and in some areas complete airway closure with atelectasis, and that these mechanical changes were responsible for the shift in ventilation away from the nonperfused lung. Recent data have suggested that the bronchoconstriction subsequent to experimental pulmonary thromboembolism produced by autogenous thromboemboli is related to the release of humoral agents from the platelets coating the thromboembolus (17). Moore, Humphreys, and Cochran, in dogs, also found that ventilation to a nonperfused lung decreased (5). On the other hand, Julian and associates (3) and Lategola and Rahn (18) in the dog, and Folkow and Pappenheimer (19) in the cat, found no significant shift in ventilation after loss of perfusion to one lung. Marshall and his associates (20) were unable to demonstrate any shift in ventilation after release of an aged autogenous thromboembolus to one lung in dogs. They did not, however, exclude the possibility that a shift had occurred only within the involved lung, and not from one lung to the other.

In the absence of compensatory hyperventilation after thromboembolism a shift in ventilation from nonperfused to perfused lung segments would decrease the predicted change in $\dot{V}_{A_{eff}}$. The india ink technique has permitted a study of the relationship between the degree of nonperfusion and the decrease in $\dot{V}_{A_{eff}}$ in the CVD after embolization. An air shift was considered to have occurred when the per cent decrease in $\dot{V}_{A_{eff}}$ was less than the relative amount of nonperfused lung. In 3 of the 5 group 1 CVD subjected to dye infusion, the decrease in $\dot{V}_{A_{eff}}$ was substantially less than the relative amount of nonperfused lung, indicating that an air shift had taken place. In the remaining 2 dogs, no air shift could be demonstrated (Figure 3). There are alternative explanations for the results of these 5 experiments. *1*) If there was an increase in excretion of CO_2 by the bronchial circulation after thromboembolism, the calculated decrease in $\dot{V}_{A_{eff}}$ would have been underestimated. This possibility seems unlikely since it has been shown that, acutely, after pulmonary arterial obstruction there is insignificant carbon dioxide excretion by the bronchial circulation (21). *2*) If some of the noncarbon stained lung segments were actually perfused, with the carbon not grossly apparent, the degree of nonperfusion would have been overestimated.

Figure 3 shows the relation between the relative amount of nonperfused lung and the degree of apparent air shift. Although the number of observations is too few to permit statistical evaluation, it would appear that as more lung is embolized and nonperfused, the degree of air shift increases in a more or less linear fashion. Even though varying degrees of air shift may occur in autogenous pulmonary thromboembolism, its magnitude is insufficient to prevent significant increases in the a-A P_{CO_2} difference. Thus, the a-A P_{CO_2} difference may be used to detect the presence of massive thromboemboli.

Mechanical alterations related to air shift. An attempt was made in the present studies to relate the apparent air shift observed to the mechanical alterations that took place after embolization. There were increases in total pulmonary resistance within 20 seconds after release of the thromboemboli, lasting 4 to 30 minutes. The a-A P_{CO_2} difference, however, persisted for periods up to 4 days and did not increase as R_L returned toward normal, as would have been expected if the increased resistance reflected regional bronchiolar narrowing in the embolized, nonperfused lung segments. Although there was an increase in the a-A P_{CO_2} difference with the administration of bronchodilator drugs, a similar increase was observed

after bronchodilator drugs before embolization. It seems likely that the increase in R_L was due to generalized and not regional airway narrowing, and could not be equated with the apparent air shift. Furthermore, the apparent air shift was calculated on the basis of perfusion measurements made 2 to 3 hours after mechanical alterations had returned toward normal. Although it is reasonable to assume that there were changes in the mechanical properties of the lung after embolization that were responsible for the apparent air shift, they were either masked by the generalized changes that did occur or they were too small to be measured by present techniques.

Arterial hypoxemia. Another aspect of this study was concerned with the mechanisms responsible for arterial hypoxemia, a common finding in experimental as well as clinical pulmonary thromboembolization. Various mechanisms have been proposed to explain this finding: alveolar hypoventilation, a decrease in lung diffusing capacity (22), abnormally rapid passage of blood through a pulmonary capillary bed decreased in volume, ventilation-perfusion abnormalities, localized right-to-left shunts, and atelectasis.

Alveolar hypoventilation was certainly a contributory factor to the fall in Pao_2 in the group 1 CVD. However, in 6 of 11 of these animals, the postembolic drop in Pao_2 was disproportionate to the degree of hypoventilation, indicating that an additional mechanism was responsible. The development of arterial hypoxemia after embolization in the SVD was not associated with alveolar hypoventilation.

Lung diffusing capacities were measured only in the CVD. It is unlikely that the observed decreases in Pao_2 could be accounted for quantitatively by the small changes in D_{LCO}. Furthermore, anatomically the alveolar-capillary membrane in the embolized and nonembolized lung segments showed no ultrastructural abnormality. It has been noted that balloon occlusion of a pulmonary artery will result in a fall in D_{LCO} (23) with no change in Sa_{O_2} (24). The small decreases in D_{LCO} may reflect decreased pulmonary capillary blood volume, while gas exchange across nonembolized segments continues unchanged.

Abnormally rapid passage of blood seems unlikely, as the occurrence of arterial hypoxemia in pulmonary embolism is associated with a marked decrease rather than increase in cardiac output (25–27).

A ventilation-perfusion abnormality such as regional hypoventilation is an unlikely cause of the postembolic arterial hypoxemia, as the nitrogen washout curves after embolization were normal. Furthermore, the abnormal postembolic response to 100% oxygen in many of the SVD indicated that regional hypoventilation could not be the only cause of the arterial hypoxemia, unless there was widespread atelectasis, and this was not observed.

The majority of the SVD developed a right-to-left shunt after massive embolization. Since the experimental model was the same in the SVD and CVD, the right-to-left shunting would have been expected to develop in CVD. Possible explanations as to why it did not are *1*) the anatomic degree of embolization may have been substantially greater in the SVD, and *2*) the shunts were shown to be transient in many of the SVD, lasting only a few hours. Since the measurements were made in the CVD during the third hour after embolization, the shunting may no longer have been present. The anatomic pathway of the right-to-left shunt is unknown. Although perfusion of atelectatic lung may be important, it is probably not the only pathway, as the post-mortem observation of atelectasis was related neither to the location nor the quantity of emboli.

It seems likely that the arterial hypoxemia after pulmonary thromboembolism is related to more than one mechanism.

Lung ultrastructure. The preservation of a normal ultrastructural appearance of the lung in the CVD suggests that pulmonary arterial perfusion is not of prime importance in the nourishment of the pulmonary tissue up to periods of 3 hours. Whether this function is subserved by the bronchial circulation or by the inspired air cannot be determined from the present studies. This finding correlates well with the relative rarity of pulmonary infarction after clinical pulmonary embolism.

General comments. The occurrence of air shift away from nonperfused lung segments is of general interest. There are data that demonstrate a reverse process, namely a shunting of blood away from nonventilated lung segments (28, 29). This suggests an autoregulatory system within the lung that maintains optimal ventilation-perfusion relations.

Another point of interest was the fact that branches of the pulmonary artery may contain thromboemboli but still permit blood flow. This is indicated by several lines of evidence. The apparent maintenance of cardiac output and survival of dogs with 100% involvement of the mainstem pulmonary artery indicate that blood must have flowed around the thromboemboli. Carbon staining of lung segments containing thrombi in some dogs likewise indicates maintenance of blood flow through these segments. Marshall has also shown that reduced but continued perfusion of pulmonary arteries containing large thromboemboli may occur (20). The fact that after 4 days the a-A P_{CO_2} difference returned to control levels despite the anatomic presence of thromboemboli in the pulmonary arteries indicates that perfusion may have been re-established. In the present study, total exclusion of blood flow was most effectively produced by relatively small emboli firmly impacted in regional branches of the pulmonary artery. It is reasonable to conclude that under appropriate circumstances, clinical pulmonary thromboembolism may produce increases in pulmonary flow resistance without completely interrupting regional pulmonary blood flow.

Summary

1. After experimental pulmonary thromboembolism due to autogenous thrombi there is a redistribution of ventilation away from nonperfused to perfused lung segments.

2. This air shift is not of sufficient magnitude to prevent an increase in alveolar dead space and significant arterial-alveolar carbon dioxide tension difference.

3. The air shift cannot be explained on the basis of the measured mechanical changes that follow autogenous thromboembolism.

4. Arterial hypoxemia was observed only in the presence of massive thromboembolism. One important mechanism is right-to-left shunting.

5. A small decrease in diffusing capacity for carbon monoxide was observed after thromboembolism, which did not account for the degree of hypoxemia observed.

6. Not all pulmonary thromboemboli result in complete cessation of blood flow to the involved lung segment.

7. Acute thromboembolism as produced in these studies does not lead to any ultrastructural change in the lung for periods up to 3 hours.

Appendix

V_E = volume of expired air in liters body temperature and pressure, saturated (BTPS).

V_A = total volume of alveolar air (perfused and unperfused calculated from $P_{A_{CO_2}}$) in liters BTPS.

V_D = volume of series dead space calculated from $P_{A_{CO_2}}$.

$F_{E_{CO_2}}$ = fraction of CO_2 in expired air; $P_{E_{CO_2}}$ tension of CO_2 in expired air.

$F_{a_{CO_2}}$ = fraction of CO_2 in perfused alveoli; $P_{a_{CO_2}}$ tension of CO_2 in perfused alveoli.

$F_{A_{CO_2}}$ = fraction of CO_2 in perfused and unperfused alveoli; $P_{A_{CO_2}}$ tension of CO_2 in perfused and unperfused alveoli.

$F_{A_uCO_2}$ = fraction of CO_2 in unperfused alveoli.

fp = fraction of total alveoli perfused by pulmonary arterial blood.

1 − fp = fraction of total alveoli unperfused by pulmonary arterial blood.

Volume of expired CO_2 = volume CO_2 from perfused alveoli + volume of CO_2 from unperfused alveoli:

$$V_E \times F_{E_{CO_2}} = V_A \times F_{a_{CO_2}} \times fp + V_A \times F_{A_uCO_2} \times (1 - fp). \quad [1]$$

Volume of CO_2 leaving unperfused alveoli = volume of CO_2 entering unperfused alveoli from dead space:

$$F_{A_uCO_2} \times V_E\,(1 - fp) = F_{A_{CO_2}} \times V_D\,(1 - fp), \quad [2]$$

or

$$F_{A_uCO_2} = \frac{F_{A_{CO_2}} \times V_D}{V_E} \text{ but, } \frac{V_D}{V_E} = \frac{F_{A_{CO_2}} - F_{E_{CO_2}}}{F_{A_{CO_2}}},$$

so that

$$F_{A_uCO_2} = F_{A_{CO_2}} - F_{E_{CO_2}}. \quad [3]$$

If Equation 3 is substituted in Equation 1, then,

$$\frac{V_E}{V_A} \times F_{E_{CO_2}} = F_{a_{CO_2}} \times fp + F_{A_{CO_2}} - F_{E_{CO_2}} \times fp + F_{E_{CO_2}} \times fp.$$

If one solves for fp and substitutes for $(V_E/V_A) \times F_{E_{CO_2}}$, its equal, $(F_{A_{CO_2}}/F_{E_{CO_2}}) \times F_{E_{CO_2}}$,

$$fp = \frac{F_{E_{CO_2}}}{F_{a_{CO_2}} - F_{A_{CO_2}} + F_{E_{CO_2}}}.$$

$$(1 - fp) = \frac{F_{a_{CO_2}} - F_{A_{CO_2}}}{F_{a_{CO_2}} - F_{A_{CO_2}} + F_{E_{CO_2}}}.$$

Percentage of alveoli unperfused,

$$\frac{V_{D_{alv}}}{(V_T - V_{D_{anat}})} = \frac{F_{a_{CO_2}} - F_{A_{CO_2}}}{F_{a_{CO_2}} - F_{A_{CO_2}} + F_{E_{CO_2}}} \times 100,$$

and as gas tensions equals,

$$\frac{P_{a_{CO_2}} - P_{A_{CO_2}}}{P_{a_{CO_2}} - P_{A_{CO_2}} + P_{E_{CO_2}}} \times 100.$$

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