

THE EFFECT OF CARBON DIOXIDE ON THE PULMONARY CIRCULATION *

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At present there is experimental and clinical evidence to support the view that alteration in alveolar oxygen tension has a direct effect on pulmonary circulation. Animal experimentation (1-4) and hemodynamic studies in human subjects (5-8) indicate that pulmonary vascular resistance increases and blood flow is thereby reduced in hypoxic areas of the lung. This is apparently a mechanism by which the body decreases perfusion of poorly ventilated lung and thus maintains efficient respiration.

The effect of changes in alveolar carbon dioxide tension on pulmonary hemodynamics is less well understood. Von Euler and Liljestrand (1) showed in cats that pulmonary hypertension ensued when the concentration of carbon dioxide in the inspired air was increased to 6.5 per cent. Variable responses of the pulmonary vascular dynamics have been reported by Nisell (9, 10), who studied the effect of carbon dioxide on the isolated cat lung. Stroud and Rahn (11) reported that pulmonary vascular resistance did not change when animals were ventilated with mixtures containing 5 per cent carbon dioxide. Weil, Salisbury and State (12), in an open chest dog preparation, observed that carbon dioxide can cause pulmonary vasomotion. Borst, Whittenberger, Berglund and McGregor (13), using dogs, found a redistribution of blood away from the lung ventilated with 5 per cent carbon dioxide and air mixture and concluded that local vasoconstriction occurred. In 20 patients with congenital heart disease, Shephard (14) found that 5 per cent carbon dioxide given during catheterization produced moderate but consistent degrees of pulmonary hypertension.

This was attributed to an increase of the total pulmonary vascular resistance as well as to a moderate increase in cardiac output and possibly also to an elevation of the pressure gradient across the lungs. On the other hand, Peters (15) observed that an increase in alveolar carbon dioxide tension in the dog lung, isolated by bronchspirometric technique, was followed by an increase in oxygen consumption and presumably by a decrease in vascular resistance and an increase in blood flow through that lung.

This study was designed to investigate the effects of carbon dioxide on the pulmonary vascular bed and its mechanism of action. Preliminary experiments, carried out in this laboratory on intact anesthetized dogs, suggested that inhalation of air containing a high concentration of carbon dioxide may alter the dynamics of the lesser circulation. Several factors were identified or suspected to be "indirectly" responsible for these changes, *i.e.*, stimulation of the respiratory center with variations of transpulmonary resistance, modification of airway resistance, and alteration of systemic circulatory hemodynamics. To evaluate the possibility of a "direct" effect of carbon dioxide on the pulmonary vascular bed, all these factors should be eliminated or controlled. This report describes the effect of carbon dioxide on the circulation of the isolated lung lobe.

METHODS

In 15 healthy medium size dogs the left lower lobe was exposed, ventilated, and perfused under controlled conditions as shown in Figure 1. A Bird respirator was connected by a large plastic tube to the left lower lobe main bronchus in order that this lobe could be ventilated independently of the remaining lung. Intermittent positive pressure not exceeding 25 mm Hg was used, and ventilation was kept constant throughout the experiment. A similar respirator connected with an endotracheal cannula ventilated the remaining parts of the lungs with normal minute volume for the animal. The pulmonary

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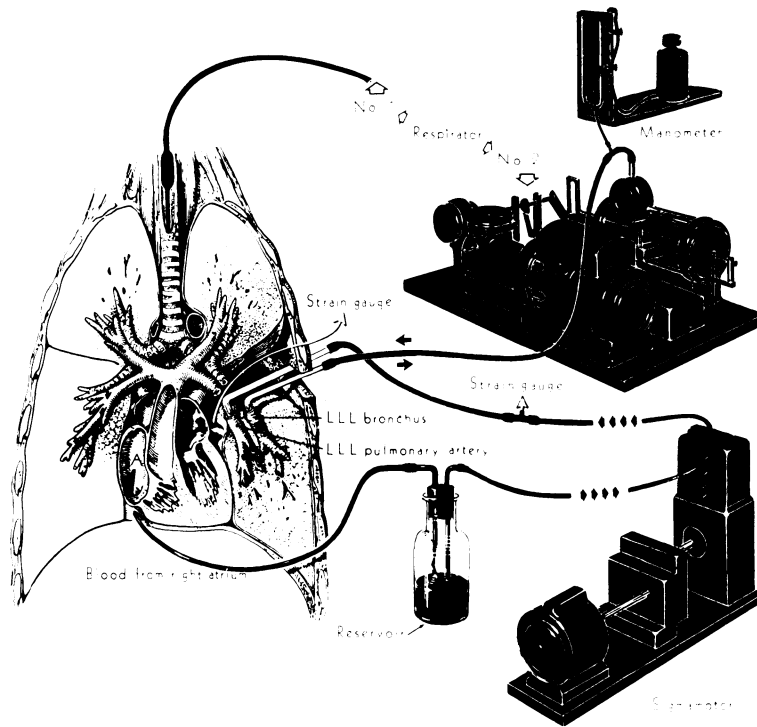


FIG. 1. SCHEME OF EXPERIMENTAL PREPARATION. LLL = left lower lobe.

artery to the left lower lobe was perfused with a Sigma-motor pump under constant flow, using venous blood obtained from the right atrium and collected into a reservoir. The remainder of the lung was perfused in normal fashion by the right ventricle.

Pressures were recorded continuously from the pulmonary artery and pulmonary vein of the isolated lobe. Pulmonary vascular resistance was calculated from the pressure gradient and the controlled flow rate and expressed as millimeters of mercury per cubic milliliter per minute. Positive pressure in the left lower lobe main bronchus was continuously monitored by a mercury manometer connected to the plastic cannula. Blood samples were obtained from the left lower lobe pulmonary artery and vein during phases of the experiment for gas and pH determinations. Blood oxygen content and saturation were measured by the photometric method of Hickam and Frayser (16). Blood carbon dioxide was determined by the method of Peters and Van Slyke (17). The pH of whole blood was measured with a Cambridge Model R pH meter with enclosed glass electrode; measurements were corrected to 37° C, using Rosenthal's factor (18). Plasma carbon dioxide content was calculated from the blood carbon dioxide content, pH, and hemoglobin, using the line chart of Van Slyke and Sendroy (19). Carbon dioxide tension was calculated from this value, using the Henderson-Hasselbalch equation. All determinations were done in duplicate. Venous $p\text{CO}_2$ was taken to represent alveolar $p\text{CO}_2$.

This technique allowed the elimination or control of all factors that may indirectly interfere with perfusion of

blood through the lungs, such as cardiac output, left auricular pressure, airway resistance, and transthoracic pressure. It also permitted the oxygen and carbon dioxide tension to be varied as desired in the alveoli and pulmonary veins of the explored lobe by ventilating this lobe with various gas mixtures. Oxygen and carbon dioxide tension were also varied in the blood perfusing the isolated lobe by adjusting the rate of ventilation and/or changing the respiratory gas administered to the remaining parts of lung.

RESULTS

The results of the study are summarized in Table I. In nine animals, the administration of 5 per cent and 10 per cent carbon dioxide in 20 per cent oxygen and nitrogen mixture to the explored lobe resulted in an increase in the alveolar and pulmonary venous carbon dioxide tension within one minute. No change was observed in the endobronchial or pulmonary venous pressures. The mean pulmonary artery pressure of the isolated lobe increased, however, from a mean for the group of 21 to 27 mm Hg. Since the blood flow was constant, the calculated pulmonary vascular resistance increased significantly in each case (Figure 2). The mean for the group changed from 0.20 to 0.29 mm Hg per ml per minute.

With the resumption of air breathing, alveolar and venous carbon dioxide tension, pulmonary artery pressure, and pulmonary vascular resistance returned toward control values.

In four animals, carbon dioxide was subsequently administered to the remaining parts of the

lungs (Table I). This produced a marked elevation of the carbon dioxide tension in the systemic blood ($p\text{CO}_2$ up to 82 mm Hg) and therefore in the blood perfusing the artery and vein of the left lower lobe, as well as in the alveoli of the same lobe. However, no significant change of the cal-

TABLE I
Effect of carbon dioxide on pulmonary circulation

Exp. no.	Remaining lung	Left lower lobe								
	Gas (respirator no. 1)	Gas (respirator no. 2)	Blood flow	Mean PA* pressure	Mean PV* pressure	Calculated vascular resistance	PA pH	PV pH	PA pCO ₂	PV pCO ₂
			ml/min	mm Hg	mm Hg	mm Hg/ml/min				
1	air	air	60	12	4	0.13				12.21
	air	10% CO ₂	60	20	4	0.26				27.07
	air	air	60	12	4	0.13				
2	air	air	100	15	3	0.12				10.10
	air	10% CO ₂	100	19	3	0.16				23.13
	air	air	100	15	3	0.12				
3	air	air	45	14	3	0.24	7.51		37.91	10.88
	air	10% CO ₂	45	20	3	0.37	7.51		40.68	27.28
	air	air	45	15	3	0.26	7.49		37.66	
4	air	air	60	15	5	0.16	7.19	7.32	31.03	10.84
	air	10% CO ₂	60	20	5	0.25	7.13	7.03	30.81	28.07
	air	air	60	15	5	0.16	7.06	7.18	37.28	14.09
5	air	air	100	15	5	0.10	7.32	7.13	21.02	17.02
	air	5% CO ₂	100	21	5	0.16	7.34	7.14	27.01	26.78
	air	air	100	16	5	0.11				
6a	air	air	120	45	6	0.32	7.30	7.41	45.03	27.09
	air	10% CO ₂	120	52	7	0.37	7.26	7.17	48.72	52.12
	air	air	120	44	7	0.30	7.17	7.35	56.31	27.00
6b	air	air	120	45	7	0.31				
	10% CO ₂	air	120	45	7	0.31	7.07	7.18	69.44	41.42
	air	air	120	45	7	0.31				
7a	air	air	100	39	4	0.35	7.32	7.40	42.13	26.18
	air	10% CO ₂	100	48	4	0.44	7.25	7.13	46.51	60.67
	air	air	100	39	4	0.35	7.24	7.34	46.56	28.13
7b	air	air	100	40	4	0.36				
	10% CO ₂	air	100	40	4	0.36	7.09	7.07	67.01	58.93
	air	air	100	40	4	0.36				
8a	air	air	60	20	7	0.21		7.39	32.14	21.09
	air	10% CO ₂	60	24	5	0.31	7.50	7.35	32.12	30.50
	air	air	60	19	6	0.21		7.38		20.01
8b	air	air	60	18	4	0.23				
	10% CO ₂	air	60	17	3	0.23	7.07	7.18	73.04	59.16
	air	air	60	18	4	0.23				
9a	air	air	60	17	4	0.21	7.28	7.33	36.83	25.73
	air	10% CO ₂	60	23	3	0.33	7.34	7.25	29.15	28.81
	air	air	60	21	3	0.30				
9b	air	air	60	21	5	0.26				
	10% CO ₂	air	60	18	5	0.21	6.92	6.95	82.00	68.50
	air	air	60	18	8	0.16				

* PA = pulmonary artery; PV = pulmonary vein.

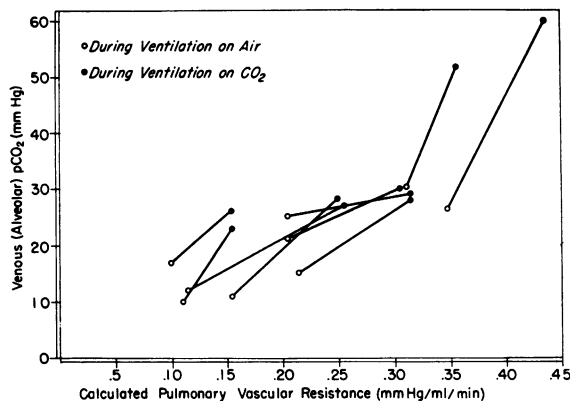


FIG. 2. SIMULTANEOUS CHANGES IN PULMONARY VENOUS (ALVEOLAR) $p\text{CO}_2$ AND CALCULATED PULMONARY VASCULAR RESISTANCE DURING VENTILATION OF LEFT LOWER LOBE WITH CARBON DIOXIDE MIXTURE.

culated pulmonary vascular resistance was observed in the isolated lobe (Figure 3). Moreover, perfusion with hypocapnic blood ($p\text{CO}_2$ of 16 mm Hg) produced no significant change in pulmonary arterial pressure or vascular resistance in three experiments.

The results for an individual experiment are plotted in Figure 4 and relate change in pulmonary arterial and venous carbon dioxide tension, mean

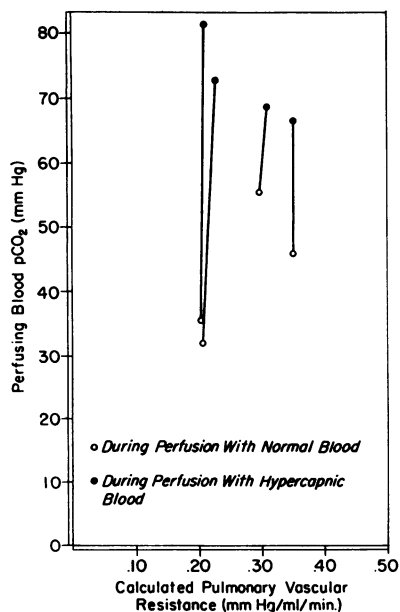


FIG. 3. CHANGES IN LEFT LOWER LOBE PULMONARY ARTERY $p\text{CO}_2$ WERE NOT ASSOCIATED WITH SIGNIFICANT VARIATIONS OF LOCAL CALCULATED PULMONARY VASCULAR RESISTANCE.

arterial and venous pressures, and calculated pulmonary vascular resistance in the isolated lobe. With narrowing of the arteriovenous gradient for carbon dioxide, pulmonary arterial pressure and calculated pulmonary vascular resistance increased. Although the carbon dioxide tension of the perfusing blood was markedly elevated in the second phase of the experiment, a normal arteriovenous gradient for carbon dioxide was maintained, and no change in pulmonary hemodynamics was observed.

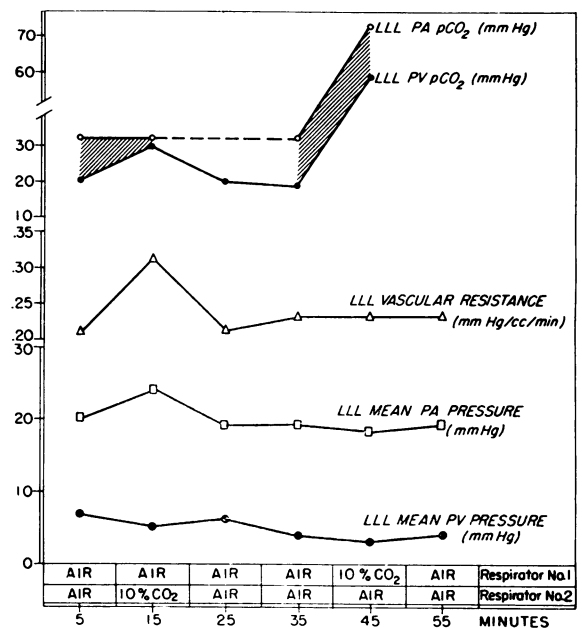


FIG. 4. EXAMPLE OF AN INDIVIDUAL EXPERIMENT (SEE TEXT). LLL = left lower lobe; PA = pulmonary artery; PV = pulmonary vein.

In Figure 5 the changes in pulmonary arteriovenous carbon dioxide tension gradient are plotted against calculated pulmonary vascular resistance for seven experiments. As the arteriovenous difference for carbon dioxide narrowed, calculated pulmonary vascular resistance increased.

In three animals, ventilation of the left lower lobe with low oxygen mixtures (13 to 16 per cent) resulted in a mean change in pulmonary venous oxygen saturation from 94.0 to 79.0 per cent. Mean increases were observed in pulmonary arterial pressure and calculated pulmonary vascular resistance from 19 to 24 mm Hg and from 0.33 to 0.37 mm Hg per ml per minute, respectively. Perfusion of the lobe with hypoxic blood (oxygen

saturation of 20 per cent) produced no change in the calculated pulmonary vascular resistance.

DISCUSSION

In the isolated lung lobe used for these studies, all the factors capable of producing circulatory changes, such as blood flow, airway resistance, and left heart hemodynamics, were controlled. Therefore, variations in the calculated pulmonary vascular resistance were taken as expression of pulmonary vasomotor activity. Moreover, in the technique of isolating the lobe, most of its nervous supply was resected and the hemodynamic alterations observed were interpreted as reflecting a local rather than a central response to change in alveolar gas tensions. The data presented indicate that the partial pressure of carbon dioxide, as well as of oxygen, at the level of the alveolus has a role in regulating the alveolar perfusion.

Simultaneous changes of either carbon dioxide or oxygen tension in the pulmonary artery and in the pulmonary vein of the isolated lobe had no effect on local hemodynamics. On the other hand, an increase in alveolar and venous $p\text{CO}_2$, whereby the gradient for $p\text{CO}_2$ between the blood reaching the alveolus and the blood leaving the alveolus is lowered, produces a local elevation of the calculated pulmonary vascular resistance. This is exemplified by the schematic drawing shown in Figure 6. The sections on the right in each of the three drawings indicate the explored pulmonary segment, namely the left lower lobe. Drawing 1 represents the baseline situation when the pulmonary arteriovenous gradient in the explored lobe for one of the respiratory gases, in this case carbon dioxide, is 11 mm Hg. After administration of carbon dioxide to the left lower lobe, the gradient decreases to 1 mm Hg, and local vascular constriction ensues (Drawing 2). After administration of carbon dioxide to the remaining lobes of the lungs, the $p\text{CO}_2$ in the perfusing blood increases markedly, but the gradient remains wide and no vasomotor response is detected (Drawing 3).

Apparently a decrease in gradient of carbon dioxide or oxygen tension across the alveolus is capable of regulating local resistance and pressure levels. The site of action of this vasomotor response has not been definitely identified. Pulmonary arteriolar constriction has been suggested

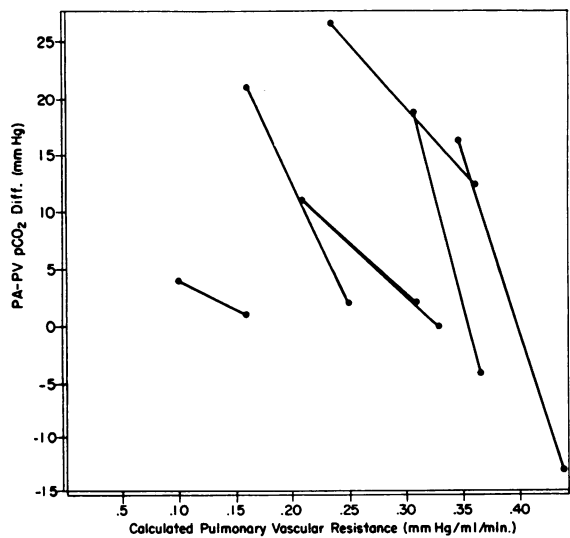


FIG. 5. SIMULTANEOUS CHANGES IN PULMONARY ARTERIOVENOUS $p\text{CO}_2$ GRADIENT AND CALCULATED PULMONARY VASCULAR RESISTANCE IN THE ISOLATED LEFT LOWER LOBE. PA = pulmonary artery; PV = pulmonary vein.

by von Euler and Liljestrand (1), Siebens, Smith and Storey (7), Rahn and Bahnsen (20), Hürliemann and Wiggers (21), and Stroud and Conn (22). It has also been proposed that the vasomotor activity of the alveolar capillaries could be responsible for the hemodynamic changes that follow alterations in alveolar oxygen tension (4). Finally, there is suggestive evidence that the pulmonary veins may play an important role in this vasomotor reaction (10, 23). With the use

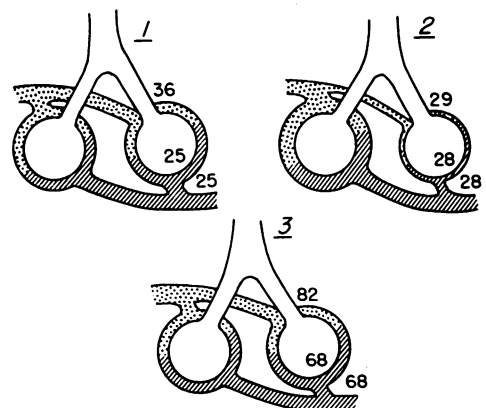


FIG. 6. DIAGRAMMATIC PRESENTATION OF EFFECT OF CARBON DIOXIDE ON PULMONARY VASCULAR RESISTANCE. Values represent carbon dioxide tension in millimeters of Hg; dotted areas, pulmonary arterioles; lined areas, pulmonary venules (see text).

of Knisely's technique (24) for direct visualization of small pulmonary vessels, the problem of identifying the vascular segment responsible for the increase in resistance to blood flow through hypoxic and hypercapnic areas of the lung is being investigated in our laboratory. Preliminary observations on dogs indicate that, when the animals are ventilated with high concentrations of carbon dioxide, a measurable decrease in diameter occurs (mean decreases ranged from 4 to 21 per cent) at the level of the pulmonary arterioles (100 to 200 μ), which return to their previous size when air breathing is resumed (25).

From our experiments the possible role, if any, played by the vascular anastomotic systems within the lungs (bronchial artery-pulmonary artery; pulmonary artery-pulmonary vein; pulmonary vein-bronchopulmonary vein) in producing pulmonary hemodynamic alterations, cannot be ascertained.

No correlation has been found between variations in the pulmonary arterial and venous blood pH, as measured directly, and pulmonary dynamic changes. Therefore, it can be stated that the pH changes, whenever they occur, are not of primary importance in regulating the vascular responsiveness.

Investigations by other workers, and observations made by us as a corollary study to the carbon dioxide experiments, have shown that a decrease in alveolar oxygen tension results in elevation of the pulmonary vascular resistance. It would appear that whenever oxygen uptake across the alveolus is for any reason decreased, a local increase in the resistance to flow of blood ensues. The results of the present study indicate that a similar phenomenon may occur when alveolar function is impaired and there is alveolar carbon dioxide retention with consequent decrease in the local arteriovenous $p\text{CO}_2$ gradient. It is suggested that under these circumstances, arteriolar vasoconstriction takes place in the attempt to divert blood to well ventilated segments of the lungs. Moreover, it is also possible that when rapid carbon dioxide retention occurs in large areas of the lungs, as in acute and diffuse pulmonary diseases, widespread increased resistance to flow may be significant in producing pulmonary hypertension and right-sided failure, along with factors such as hypoxia and increased cardiac output.

SUMMARY

The effect of alveolar and blood carbon dioxide tension changes on the pulmonary vascular dynamics has been studied in 12 dogs, using the left lower lobe isolated and mechanically ventilated and perfused. Corollary observations have also been made for alveolar and blood oxygen tension changes. Increase in alveolar and pulmonary venous carbon dioxide tension, whereby the $p\text{CO}_2$ gradient between pulmonary arterial and pulmonary venous blood was lowered, resulted in a local elevation of pulmonary vascular resistance, probably from pulmonary arteriolar constriction. No significant hemodynamic variation occurred with high or low carbon dioxide tensions in the pulmonary artery, vein, or alveoli of the explored lung segment as long as a large pulmonary arteriovenous gradient for $p\text{CO}_2$ was maintained.

Decrease in alveolar and pulmonary venous oxygen tension, whereby the oxygen tension gradient between pulmonary arterial and venous blood was lowered, resulted also in local elevation of pulmonary vascular resistance. Perfusion of the isolated lobe with hypoxic blood produced no change in local pulmonary vascular resistance.

It is postulated that a local homeostatic mechanism exists, probably similar to the one described for oxygen, which can divert blood from poorly ventilated alveoli that retain carbon dioxide to adequately ventilated segments of the lung.

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