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The Longitudinal Distribution of Pulmonary Vascular Resistance during Unilateral Hypoxia

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Pulmonary capillary hydrostatic pressure and the longitudinal distribution of pulmonary vascular resistance (arterial and venous components) can be determined by analysis of pressure decay curves following pulmonary artery occlusion. To validate this technique in intact animals, pulmonary artery occlusion pressure decay curves were obtained from both lungs in six anesthetized sheep during control conditions (100% O_2) and during unilateral hypoxic ventilation (100% O_2 *versus* 100% N_2). Analysis of pulmonary artery occlusion pressure curves indicated the following: 1) in the hypoxic lung, unilateral hypoxia increased the precapillary portion of pulmonary vascular resistance from 72% of the total resistance to 89% of the total resistance in that lung; 2) in the nonhypoxic lung, unilateral hypoxia did not significantly affect the distribution of pulmonary vascular resistance; and 3) unilateral hypoxia produced no significant change in pulmonary capillary pressure in the hypoxic lung compared with control; however, pulmonary capillary pressure was significantly greater in the nonhypoxic lung. These results are consistent with other evidence that hypoxic pulmonary vasoconstriction acts locally and primarily affects resistance at the arteriolar level. Pulmonary artery occlusion pressure decay curve analysis appears to be a valid technique for the measurement of pulmonary capillary pressure and the longitudinal distribution of pulmonary vascular resistance in intact anesthetized animals. These measurements pertain only to the vasculature distal to the site of pulmonary artery occlusion with the catheter, and, thus, caution must be used when applying this technique in a setting of nonhomogenous lung injury. (Key words: Lung, blood flow: capillary pressure; hypoxic pulmonary vasoconstriction. Lung, vascular resistance: longitudinal distribution. Monitoring, pulmonary artery occlusion pressure.)

PULMONARY CAPILLARY hydrostatic pressure is the major force responsible for the formation of pulmonary edema. Pulmonary artery occlusion pressure has been used to estimate both left atrial pressure and pulmonary capillary hydrostatic pressure.[1–3] Pulmonary capillary pressure is equivalent to left atrial pressure only in the absence of pulmonary venous resistance; however, under normal conditions, venous resistance accounts for approximately 40% of pulmonary vascular resistance.[4] The relative division of pulmonary vascular resistance into pulmonary arterial resistance and pulmonary venous resistance components may vary with pharmacologic interventions and pathophysiologic abnormalities.[5]

Pulmonary capillary pressure cannot be measured directly in intact animals. Gravimetric and micropuncture techniques have been used to measure capillary pressure in the perfused lung;[6,7] however, these methods cannot be used in intact animals. In studies using the isolated perfused lung, the pulmonary circulation has been mathematically modelled with an electrical circuit analog and the pressure curves following arterial occlusion have been analyzed to derive pulmonary capillary pressure and the longitudinal distribution of pulmonary vascular resistance.[8–11] Investigators have extended the technique of pulmonary artery occlusion pressure curve analysis to intact animals and human subjects; however, this technique has had little validation in such settings.[9]

There are major differences between the isolated perfused lung and the lung of the intact animal. Potential problems which must be considered include the effects of pulsatile flow *versus* constant flow, the effects of instantaneous occlusion *via* external vascular clamping *versus* intravascular balloon inflation, and the effects of the isolated lung preparation *versus* the intact closed chested animal. Thus, it is important to validate the occlusion technique for measurement of pulmonary capillary pressure in intact animals.

To validate pulmonary artery occlusion pressure curve analysis as a method of determining the longitudinal distribution of pulmonary vascular resistance, experimental conditions with altered distributions must be studied. Hypoxia alters the distribution of pulmonary vascular resistance by reversibly causing pulmonary arterial vasoconstriction.[12] We therefore studied unilateral hypoxia anticipating that pulmonary artery occlusion pressure curve analysis would demonstrate a selective increase in the precapillary (arterial) resistance during hypoxia in the hypoxic lung and no increase in the contralateral nonhypoxic lung.

Materials and Methods

ANIMAL PREPARATION

Seven male sheep (16–28 kg) were studied with the approval of the Stanford University Panel on Laboratory Animal Care. Anesthesia was induced with thiopental, 20 mg/kg iv and maintained by an infusion of 5–20

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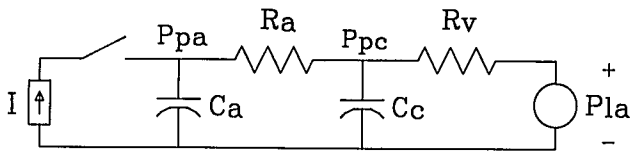

FIG. 1. Circuit model of the pulmonary circulation. Arterial and venous resistance are represented by R_a and R_v. Blood flow into the segment is denoted I. Pulmonary artery pressure (P_{pa}) and pulmonary capillary pressure (P_{pc}) are represented as circuit nodes. Arterial capacitance is denoted C_a, capillary capacitance is denoted C_c, and P_{la} represents the left atrial pressure. Inflation of an occlusive balloon is represented by the opening of the switch that results in the decay of P_{pa} toward P_{la}.

$mg \cdot kg^{-1} \cdot h^{-1}$. Following oral tracheal intubation, femoral venous and arterial catheters were inserted. Using fluoroscopy, two pulmonary artery catheters (American Edwards®, 93A-131H-7F) were advanced *via* external jugular veins into the left and the right main pulmonary arteries. These fluid-filled catheters were connected to 53-600F Trantec disposable pressure transducers (American Edwards, Santa Ana, CA). A 39-Fr left double lumen endobronchial tube (Mallinckrodt, Bronchocath®) was inserted through a tracheostomy until the distal tip entered the left main stem bronchus. Bilateral 1-cm window thoracotomies and frequent fluoroscopy allowed observation of the lungs throughout the experiment to insure proper tube positioning. One of the seven sheep was eliminated from the study because airway anatomy precluded separate ventilation of each lung. Asynchronous mechanical ventilation was instituted at a tidal volume of 12 ml/kg, a rate of 6 breaths per minute, and 2.5 cm H_2O positive end-expiratory pressure. Ventilator rates were adjusted in parallel to maintain arterial CO_2 tension at 35–45 mmHg.

Experimental Protocol

Unilateral hypoxia was produced by ventilating one lung with 100% N_2 while the other lung was ventilated with 100% O_2. The study design allowed each lung to receive hypoxic gas ventilation. Control periods preceeding and following each period of unilateral hypoxia were achieved by ventilation of both lungs with 100% O_2. The sequence of experimental conditions was as follows:

1. Control: $FI_{O_2} = 1.0$ bilaterally.
2. Unilateral hypoxia was achieved by ventilating one lung with 100% N_2 while the contralateral lung was ventilated with 100% O_2. Measurements were obtained after 10–15 min.
3. Control: Forty-five minutes was allowed for recovery with $FI_{O_2} = 1.0$ bilaterally. Control measurements were then obtained.
4. Unilateral hypoxia was achieved by delivering 100% N_2 to the lung which had received O_2 during step 2. Measurements were obtained after 10–15 min.
5. Control: Forty-five minutes was allowed for recovery with $FI_{O_2} = 1.0$ bilaterally. Final control measurements were then obtained.

Animals were randomized with regard to the choice of the left or the right lung for the initial hypoxic challenge.

Data Acquisition

Thermodilution cardiac output was measured in triplicate by injection of 10 ml of room temperature normal saline at end-expiration during each experimental condition. Arterial p_{O_2}, arterial p_{CO_2}, and mixed venous p_{O_2} were measured during each condition. Pulmonary artery occlusion pressure curves were obtained from each lung during each experimental condition. Each curve was obtained during 15 s of apnea, and between three and six curves were obtained with each experimental condition. For each pulmonary artery occlusion pressure curve, pressure was measured using an 892018 Trantec Supercable® and a Hewlett-Packard® 8826A interconnection tray. Data were filtered with a 100 Hz, 24 dB/octave low-pass filter (Krohn-Hite, model 3750, Cambridge, MA) and sampled at 200 Hz with a 12-bit A/D converter (Data Translations, DT-2801, Marlboro, MA) in an IBM PC/AT computer. Mean pulmonary artery pressure was computed as the mean of the three complete beats preceding the decay. Each decay curve was digitally filtered at 55 Hz with the five-point least squares quadratic.[13]

Data Analysis

Pulmonary artery occlusion curves contain two distinct exponential decays.[8,14] Analysis of the circuit model shown in figure 1 results in a biexponential decay of pulmonary artery pressure, P_{pa}, which is consistent with experimentally observed decay curves.[10] The magnitude and time constants of these decay components can be related to the circuit model:

$$P_{pa}(t) = ge^{-\beta t} + he^{-\gamma t} + P_{la} \quad (1)$$

$$P_{pc} = g + h + P_{la} \quad (2)$$

$$\frac{R_a}{R_t} = \frac{g\beta + h\gamma}{(g + h)\left(\beta + \gamma - \frac{(g + h)\beta\gamma}{g\beta + h\gamma}\right)} \quad (3)$$

P_{pa} is expressed as the sum of two exponential decays and a constant that is the terminal value. In this model, the

terminal value is the occlusion pressure (P_{pao}) that is produced by the left atrial pressure (P_{la}) (equation 1). Pulmonary capillary pressure (P_{pc}) can be expressed in terms of the parameters of this biexponential decay (equation 2). In the absence of a measurement of flow into the segment of lung being studied, the absolute value of arterial or venous resistance cannot be obtained; however, the ratio of the arterial resistance to the total resistance, R_a/R_t, can be derived (equation 3). This ratio allows separation of pulmonary vascular resistance into precapillary (arterial) and postcapillary (venous) components.

Typically, γ is approximately 1.0 s^{-1} corresponding to a half-time of 0.7 s. Thus, 5 s of data starting with the decay from mean pulmonary artery pressure were analyzed. Data from at least three curves obtained during the same experimental condition were simultaneously analyzed by superimposing the curves on the same time axis. A least squares fit to the biexponential decay (equation 1) was obtained with the computer program MKMODEL.[15] Thus, the parameters g, β, h, γ, and P_{la} were experimentally determined by curve fitting. P_{pc} and R_a/R_t were calculated according to equations 2 and 3. The pressure gradient across the arterial resistance was calculated as the difference between mean pulmonary artery pressure and capillary pressure or $P_{pa} - P_{pc}$. Similarly, the pressure gradient across the venous resistance was calculated as the difference between capillary pressure and the terminal occlusion pressure or $P_{pc} - P_{pao}$. Pulmonary vascular resistance (PVR) was calculated according to the formula $PVR = (P_{pa} - P_{pao})/CO$.

STATISTICS

Data were analyzed by repeated measures analysis of variance followed by the Scheffe F-test. $P < 0.05$ was considered significant.

Results

The three control conditions did not differ significantly with respect to cardiac output (CO), pulmonary artery pressure (P_{pa}), pulmonary artery occlusion pressure (P_{pao}), pulmonary vascular resistance (PVR), pulmonary capillary pressure (P_{pc}), or the ratio of the arterial resistance to the total resistance (R_a/R_t). Values from the three control conditions were combined. As compared with control, unilateral hypoxia increased mean pulmonary artery pressure by 3–4 mmHg, did not significantly increase pulmonary vascular resistance, and did not affect pulmonary artery occlusion pressure (table 1). Arterial pa_{CO_2} was maintained in the normal range throughout the study. Unilateral hypoxia produced a significant decrease of arterial pa_{O_2} and of mixed venous pv_{O_2} (table 1).

TABLE 1. Hemodynamic and Blood Gas Data

	Control	Left Lung Hypoxia	Right Lung Hypoxia
Cardiac output (l/min)	1.8 ± 0.2	2.4 ± 0.3*	1.7 ± 0.3
P_{pa} (mmHg)	14.7 ± 1.2	18.9 ± 1.5*	17.8 ± 2.0
P_{pao} (mmHg)	5.6 ± 1.0	6.0 ± 2.9	6.2 ± 1.4
PVR (mmHg − min/l)	5.6 ± 0.8	6.3 ± 1.5	7.2 ± 0.9
Pa_{O_2} (mmHg)	319 ± 27	47 ± 9*	49 ± 5*
Pv_{O_2} (mmHg)	44 ± 2	32 ± 3*	30 ± 2*
Pa_{CO_2} (mmHg)	37 ± 1	40 ± 4	38 ± 2

Values are mean ± SEM in six sheep.
* $P < 0.05$ compared with control.

The division of resistance into precapillary (arterial) and postcapillary (venous) components is described by the ratio R_a/R_t, which is the fraction of the total resistance that is precapillary. During control conditions, R_a/R_t was similar in the left lung and the right lung with the precapillary resistance accounting for approximately 70% of the total resistance (fig. 2). During left lung hypoxia, R_a/R_t increased in the hypoxic left lung but was unchanged from control in the nonhypoxic right lung. During right lung hypoxia, R_a/R_t increased in the hypoxic right lung but not in the nonhypoxic left lung. Thus, during conditions of either right lung or left lung unilateral hypoxia, R_a/R_t increased in the hypoxic lung compared with the contralateral nonhypoxic lung and compared with control values in the same lung. Unilateral hypoxia did not affect R_a/R_t in the nonhypoxic lung.

During control conditions, pulmonary capillary pressure (P_{pc}) was approximately 8 mmHg in both the left and the right lung (table 2). During left lung hypoxia, capillary pressure in the left lung was not significantly different from the control measurement; however, during

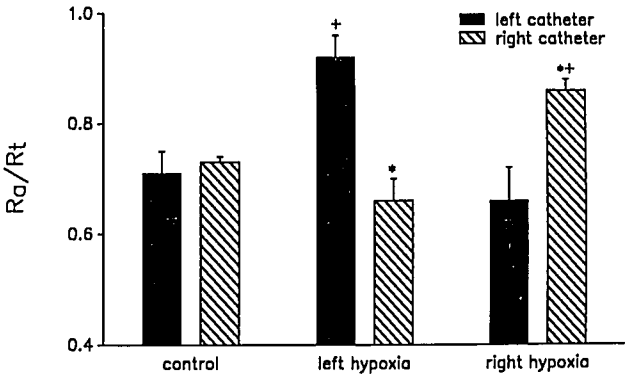

FIG. 2. R_a/R_t is the ratio of the arterial (precapillary) component of resistance to the total resistance. R_a/R_t was measured in the left lung (solid bars) and in the right lung (striped bars). Measurements are shown for control condition, left lung hypoxia, and right lung hypoxia. Values are mean ± SEM in six sheep. *$P < 0.01$ *versus* left catheter. †$P < 0.05$ *versus* control.

TABLE 2. Pressures Determined from Analysis of Pulmonary Artery Occlusion Pressure Decay Curves

	Control		Left Lung Hypoxia		Right Lung Hypoxia	
	Left Catheter	Right Catheter	Left Catheter	Right Catheter	Left Catheter	Right Catheter
Ppc (mmHg)	8.7 ± 1.4	7.8 ± 1.1	7.3 ± 1.1	11.0 ± 1.2†‡	10.6 ± 2.1	7.5 ± 1.4‡
Ppa − Ppc (mmHg)	6.7 ± 0.6	6.7 ± 0.9	11.6 ± 1.9†	7.9 ± 0.8*	7.2 ± 0.6	10.3 ± 1.2*†
Ppc − Ppao (mmHg)	2.9 ± 0.8	2.2 ± 0.4	1.1 ± 0.5	5.3 ± 1.4*	4.2 ± 1.0	1.4 ± 0.2*

Values are mean ± SEM in six sheep.
* $P < 0.01$ *versus* left catheter.
† $P < 0.05$ *versus* control.
‡ $P < 0.05$ *versus* left catheter.

left lung hypoxia, capillary pressure in the right lung (the nonhypoxic lung) was significantly increased compared with control and compared with the pressure in the left lung. During right lung hypoxia, capillary pressure in the left lung (the nonhypoxic lung) was significantly greater than capillary pressure in the right lung. During right lung hypoxia, capillary pressure in the hypoxic right lung was unchanged from control. When the right hypoxia and left hypoxia conditions were pooled, capillary pressure in the hypoxic lung (7.4 ± 0.9 mmHg) was not significantly different compared with control (8.3 ± 0.9 mmHg). During unilateral hypoxia, capillary pressure was significantly greater in the nonhypoxic lung (10.8 ± 1.2 mmHg) compared with control ($P < 0.05$) and also compared with the contralateral hypoxic lung ($P < 0.05$).

The difference between mean pulmonary artery pressure and capillary pressure ($P_{pa} - P_{pc}$) is the pressure drop across the pulmonary arterial (precapillary) circulation. Under control conditions $P_{pa} - P_{pc}$ in the left lung was similar to $P_{pa} - P_{pc}$ in the right lung (fig. 3). Left lung hypoxia increased $P_{pa} - P_{pc}$ in the hypoxic left lung but did not change $P_{pa} - P_{pc}$ in the nonhypoxic right lung. Right lung hypoxia increased $P_{pa} - P_{pc}$ in the hypoxic right lung but did not change $P_{pa} - P_{pc}$ in the nonhypoxic left lung. In summary, unilateral hypoxia increased the pressure drop across the precapillary arterial circulation in the hypoxic lung but not in the nonhypoxic lung.

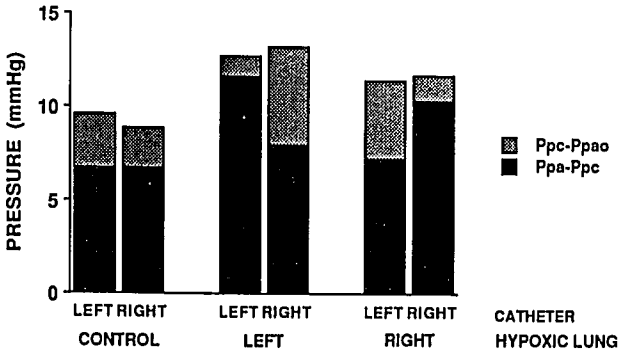

FIG. 3. The difference between mean pulmonary artery pressure and capillary pressure ($P_{pa} - P_{pc}$) is the pressure drop across the pulmonary arterial (precapillary) circulation. Similarly, the difference between capillary pressure and occlusion pressure ($P_{pc} - P_{pao}$) is the pressure drop across the pulmonary venous (postcapillary) circulation. Unilateral hypoxia increased the pressure drop across the precapillary arterial circulation in the hypoxic lung but not in the nonhypoxic lung.

Discussion

The ability to measure pulmonary capillary pressure and the longitudinal distribution of pulmonary vascular resistance may permit advances in the understanding of the pathophysiology of pulmonary hypertension, pulmonary edema, and lung injury. It is not presently possible to measure pulmonary capillary pressure directly in intact animals or patients. Pulmonary capillary pressure can be measured in the isolated perfused lung lobe using the isogravimetric technique.[6] Studies of the isolated perfused lung lobe have shown correlation of vascular occlusion methods for measuring pulmonary capillary pressure with the isogravimetric technique.[16] Thus, there has been interest in applying the vascular occlusion method to the estimation of capillary pressure in intact animals.

Although pulmonary artery occlusion pressure decay curve analysis has been proposed as a method for determining the longitudinal distribution of pulmonary vascular resistance, this method has been only partially validated for use in intact animals.[8,14] Such validation is important because substantial differences exist between the perfused lung model and the intact animal model. Measurement in the intact animal is complicated by the use of an intravascular balloon rather than an external clamp occluder, the presence of pulsatile rather than constant blood flow, and the use of closed chest ventilation. Unfortunately, the inability to measure capillary pressure directly in the intact animal makes validation of the occlusion technique difficult. To further validate the technique in intact animals, it is necessary to demonstrate that the longitudinal distribution of pulmonary vascular resistance as measured by the technique changes in a predictable manner with appropriate experimental conditions.

Hypoxic pulmonary vasoconstriction occurs primarily at the level of the precapillary arterioles and thus predictably alters the longitudinal distribution of pulmonary vascular resistance.[7,17] This response to hypoxia occurs during barbiturate anesthesia and was expected in the experimental preparation used in this study.[18,19] The unilateral hypoxia model allows simultaneous study of two lungs with different alveolar gas compositions, but with the same pulmonary artery perfusion pressure and left atrial pressure. Hypoxia produces an increase in the precapillary resistance that would be expected to be associated with an increase in the pressure drop across the arterial portion of the pulmonary circulation.

In the present study, simultaneously obtained pulmonary artery occlusion pressure curves were different in the hypoxic and nonhypoxic lung during unilateral hypoxia. Analysis of the shape of the pulmonary artery occlusion pressure curves indicates increased pulmonary arterial resistance only in the hypoxic lung. In this study, hypoxia selectively increased $P_{pa} - P_{pc}$ in the hypoxic lung but not in the nonhypoxic lung. These results suggest that analysis of pulmonary artery occlusion pressure decay curves properly predicts the changes in the longitudinal distribution of pulmonary vascular resistance produced by hypoxia.

Capillary pressure is important as the hydrostatic force driving pulmonary edema formation. While unilateral hypoxia did not significantly affect P_{pc} or $P_{pc} - P_{pao}$ in the hypoxic lung, it significantly increased both P_{pc} and $P_{pc} - P_{pao}$ in the nonhypoxic lung when compared with the hypoxic lung. This increase in P_{pc} and $P_{pc} - P_{pao}$ with unchanged R_a/R_t likely reflects redistribution of blood flow away from the hypoxic lung to the nonhypoxic lung. Unilateral hypoxia is known to cause such a redistribution of blood flow.[20] Calculation of shunt cannot be used to estimate the flow through each lung because the capillary oxygen content is unknown. In this model, the lung that is ventilated with 100% N_2 extracts oxygen from the blood and transports it to the alveoli. The extent of this oxygen loss depends on the ventilation perfusion relationship of the lung. Thus, the capillary oxygen content of the two lungs are different and cannot readily be estimated. Differences between the conditions of left lung hypoxia and right lung may be attributed to differences in the sizes of the vascular beds of the two lungs. P_{pc} did not decrease in the hypoxic lung because the rise in mean pulmonary artery pressure offset the effect of an increase in R_a/R_t. If only a small segment of lung were hypoxic, the redistribution of flow would be expected to cause little if any change in pulmonary artery pressure.[20] Thus, hypoxic pulmonary vasoconstriction active in a focal area of lung injury may theoretically lower capillary pressure by altering the local longitudinal distribution of pulmonary vascular resistance. This effect may reduce the likelihood of pulmonary edema formation in the injured area. When a large segment of lung is hypoxic, the alteration in the longitudinal distribution of pulmonary vascular resistance that occurs in the hypoxic area may increase capillary pressure in the nonhypoxic area and thereby increase the risk of edema formation in the nonhypoxic area.

In summary, we have measured the longitudinal distribution of pulmonary vascular resistance using pulmonary artery occlusion pressure curve analysis during unilateral hypoxia. The results of this study demonstrate the expected changes in the distribution in the hypoxic and nonhypoxic lungs, thereby providing evidence for the validity of this technique. Alterations of the pulmonary circulation may occur in a variety of clinical and experimental situations. Estimation of capillary pressure *in vivo* may prove valuable in understanding the mechanisms of pulmonary edema formation, lung injury, and pulmonary hypertension. Using this measurement technique, new insights into one-lung anesthesia, atelectasis, pulmonary hypertension, vasodilator therapy, lung injury, and valvular and congenital heart disease may be gained that will ultimately guide treatment. However, this study shows that estimates of R_a/R_t and P_{pc} derived from analysis of pulmonary artery occlusion pressure curves pertain only to the vasculature distal to the site of pulmonary artery occlusion with the catheter, and thus caution must be used when applying this technique in a setting of nonhomogenous lung injury.

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