The Vascular Site of Action of Hypoxia in the Neonatal Pig Lung

LEIF D. NELIN, DAVID A. RICKABY, JOHN H. LINEHAN, AND CHRISTOPHER A. DAWSON

Departments of Pediatrics [L.D.N.] and Physiology [D.A.R., C.A.D.], Medical College of Wisconsin, Milwaukee, Wisconsin 53226; Research Service [L.D.N., D.A.R., J.H.L., C.A.D.], Zablocki Veteran's Administration Medical Center, Milwaukee, Wisconsin 53295; and Biomedical Engineering Department [J.H.L.], Marquette University, Milwaukee, Wisconsin 53233

ABSTRACT. To determine the vascular site(s) of action of hypoxia in the neonatal pig, isolated lungs were perfused at a constant flow rate and left atrial pressure; arterial, venous, and double occlusions were performed. The distribution of the total pulmonary vascular resistance and the total dynamic vascular compliance were calculated using a model of the pulmonary circulation consisting of upstream, central, and downstream compliances and resistances upstream and downstream of central compliance. In addition, the static vascular compliance was measured by venous followed by arterial occlusion, and the total vascular volume was measured by dye-dilution. In this preparation during control conditions alveolar $PO_2 = 12 \pm 2$ kPa, total pulmonary vascular resistance was nearly evenly divided between resistance upstream and downstream of double occlusion pressure and total dynamic vascular compliance was concentrated mainly in the central compliance (7% upstream compliance, 82% central compliance, and 11% downstream compliance). Hypoxia (alveolar $PO_2 = 4 \pm 1$ kPa) increased both resistance upstream of double occlusion pressure ($p < 0.005$) and resistance downstream of double occlusion pressure ($p < 0.02$) and decreased central compliance ($p < 0.005$). Hypoxia also decreased total pulmonary blood volume ($p < 0.02$). These results suggest that in the pulmonary vasculature of the neonatal pig, hypoxia results mainly in 1) arterial constriction as evidenced by a large increase in upstream resistance and a decrease in total pulmonary blood volume and 2) a smaller but significant venous constriction. This venous constriction may have implications in the pathogenesis and therapy of pulmonary vascular diseases associated with hypoxia such as postasphyxial lung disease and bronchopulmonary dysplasia. (*Pediatr Res* 35: 25–29, 1994)

Abbreviations

P_a , pulmonary arterial pressure
 P_v , left atrial pressure
 P_d , double occlusion pressure
 R_L , total pulmonary vascular resistance
 R_u , resistance upstream of P_d
 R_d , resistance downstream of P_d
 C_{st} , total pulmonary vascular static compliance
 C_{dyn} , total pulmonary vascular dynamic compliance
 C_u , upstream compliance
 C_c , central compliance
 C_d , downstream compliance
 Q_L , total pulmonary blood volume

VOAO, venous followed by arterial occlusion

VO, venous occlusion

DO, double occlusion

AO, arterial occlusion

$\bar{S}$, pressure relaxation

$\bar{t}_R$, mean relaxation time

The neonate is at a high risk for pulmonary vascular diseases that manifest increased pulmonary vascular resistance such as persistent pulmonary hypertension of the newborn, bronchopulmonary dysplasia, and certain forms of congenital heart disease (1). The neonatal pig has been used extensively as a model for pulmonary vascular development and disease (2–14) because the postnatal morphometric pulmonary development closely parallels the human but on a more compact time scale (14). Typically, pulmonary arterial pressure and flow have been measured during conditions that mimic certain aspects of pulmonary vascular disease (3–14), such as alveolar hypoxia. The pressure and flow data alone provide an incomplete picture of the pulmonary vascular response. For example, the arterial and/or venous site of action may be important in determining the impact on cardiopulmonary function. In the adult, it has been shown that hypoxia causes arterial constriction (15–21), which implies a risk for right ventricular failure, but not necessarily for pulmonary edema because capillary pressure would not be affected. On the other hand, in the neonatal pig (2) and lamb (22) there is some evidence that the pulmonary veins may be involved in the hypoxic response. This would have implications for lung fluid balance, and thus, in the pathogenesis and treatment of vascular diseases in which hypoxia is a major component, such as postasphyxial lung disease of the neonate.

Certain aspects of pulmonary vascular function are more easily studied in isolated lungs than in the intact animal. Therefore, the present study was carried out to determine the influence of hypoxia on this preparation in terms of site of action and impact on viscoelasticity of the vascular bed.

MATERIALS AND METHODS

The lungs from eight neonatal pigs [2.8 ± 0.7 (SD) kg, 8.9 ± 5.3 d old] were used in an isolated perfused preparation as previously described (23). Each pig was anesthetized with a mixture of ketamine hydrochloride (30 mg/kg) and acepromazine maleate, (1.5 mg/kg) given intramuscularly. A carotid artery catheter was inserted and an arterial sample was obtained for blood gas analysis and hematocrit with the following result: PO_2 12.0 ± 2.0 kPa (90 ± 15 mm Hg), PCO_2 5.6 ± 0.5 kPa (42 ± 4 mm Hg), pH 7.22 ± 0.07 , and hematocrit 0.22 ± 0.05 ($22 \pm 5\%$). Then 1250 units/kg of heparin and 15 to 20 mL/kg of 10%

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Correspondence: Leif D. Nelin, M.D., Research Service 151, Zablocki VA Medical Center, 5000 W. National Avenue, Milwaukee, WI 53295.

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dextran were given intra-arterially and the piglet was exsanguinated. The autologous blood (resultant hematocrit 0.13 ± 0.03 or $13 \pm 3\%$) was used to prime the perfusion system. The perfusion system consisted of a reservoir, a Masterflex roller pump with a 7016 head, a heat exchanger, and an injector. The trachea was clamped and a median sternotomy was performed. Rigid cannulas were placed in the main pulmonary artery and the left atrium. The lungs and heart were removed en bloc and suspended in a heated humidified perfusion chamber. The blood was recirculated through the lungs at a flow rate of $95 \pm 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. The venous effluent drained into a reservoir, the height of which could be adjusted to set the venous pressure at the desired level. The P_a , P_v , and airway pressures were continuously recorded. Vascular pressures were referenced to the height of the left atrium. Ventilation was begun with a gas mixture containing $\sim 6\% \text{ CO}_2$, $15\% \text{ O}_2$ in N_2 using a Harvard piston-type respirator with a tidal volume of $91 \pm 19 \text{ mL}$ and a frequency of 22 breaths/min.

When the arterial pressure was stable, the respirator was turned off at end expiration. The following vascular occlusion maneuvers were carried out in zone III conditions as described previously (15, 24, 25), VOA and then a second VOA, DO, and AO. The first VOA was carried out as a conditioning maneuver (26). The second VOA and the DO, and AO pressure curves, digitized at 40 Hz, were analyzed as described below. The time interval between the venous and arterial occlusion for the VOA maneuver was approximately 3 s ($3.3 \pm 0.6 \text{ s}$ during the control condition and $3.1 \pm 0.4 \text{ s}$ during hypoxia).

In seven of the lungs, indicator dilution measurements of Q_L were also made before and after the occlusion maneuvers. A bolus of indocyanine green ($50 \mu\text{g}$ in 0.4 mL of water) was introduced into the arterial inflow via the injector. A portion of the venous effluent was continuously passed through a Gilson densitometer. The output from the densitometer was digitized at 40 Hz for later analysis.

After the measurements described above were completed, the ventilating gas mixture was changed to $4\% \text{ O}_2$, and $6\% \text{ CO}_2$ in N_2 and the respirator was turned on. When arterial pressure had stabilized, the respirator was turned off at end expiration and the vascular occlusions and dye dilution measurements were repeated as described above.

Calculations. The pressure *versus* time curves obtained from a typical VOA experiment are shown in Figure 1A. After the relatively sudden jump in P_v after occlusion from the preocclusion value, $P_v(0)$, the venous pressure curve, $P_v(t)$, increases in an almost linear fashion. For a short time after VO, the arterial pressure is nearly constant at its preocclusion value, $P_a(0)$. Subsequently, the arterial pressure curve, $P_a(t)$, is also observed to increase with time nearly in parallel with $P_v(t)$. These slow increases in vascular pressure after VO are caused by the linear increase in lung vascular volume, Q_L , resulting from the constant inflow, Q . The rate at which vascular pressure increases after VO is inversely proportional to the vascular compliance (24). That is

$$C_{\text{dyn}} = \frac{dQ_L}{dP} = \frac{dQ_L/dt}{dP/dt} = \frac{\dot{Q}}{\dot{P}} \quad (1)$$

where C_{dyn} is the dynamic vascular compliance obtained from the venous occlusion data and $\dot{P}$ is the slope of the pressure *versus* time curve over the interval from 0.2 to 1.0 s after VO. For the data such as in Figure 1A, the slopes of $P_a(t)$ and $P_v(t)$ during this time interval are not exactly equal. Therefore, we use the mean slope defined as

$$\dot{P}_m = \frac{\dot{P}_a + \dot{P}_v}{2} \quad (2)$$

in equation 1.

The dynamic vascular compliance obtained from the VO data is, in general, smaller than vascular compliance calculated from

Fig. 1. A, Typical VOA in an isolated perfused neonatal pig lung during control (solid lines) and hypoxic (dashed lines) conditions. The instant of VO is designated by the arrow at time 0; the instant of AO is designated by the arrow at about 3.0 s. The ΔQ_L that occurred between VO and AO is equal to the time between VO and AO (Δt) multiplied by the flow rate (Q). $P_a(0)$ and $P_v(0)$ represent the arterial and venous pressures before occlusion and P_f is the final equilibrium pressure after VOA. B, Typical DO in an isolated perfused neonatal pig lung during control (solid line) and hypoxic (dashed line) conditions. The instant of occlusion is designated time 0 and P_d indicates the DO pressure. In this case $\Delta t = 0$ and therefore $\Delta Q_L = 0$. C, Typical AO in an isolated perfused neonatal pig lung during control (solid line) and hypoxic (dashed line) conditions. The instant of occlusion is designated time 0, and τ_c and τ_h represent the time when $P_a(t)$ reaches P_d for control and hypoxic conditions, respectively. The term area used in equation 7 is defined as the integral from 0 to τ of $(dP_a(t) - P_d)$ and is shown graphically in the inset for the hypoxic $P_a(t)$ curve.

static (equilibrium) conditions (24). A measure of the C_{st} can also be obtained from the occlusion experiments. During the VO portion of the VOA maneuver, the lobar vascular volume increases linearly with time. If after a given time, the arterial outflow is also occluded, AO, a known volume increment of blood, ΔQ_L , is trapped within the lungs, *i.e.* $\Delta Q_L = Q\Delta t$, where Δt is the time interval between VO and AO (Fig. 1A). Under the isovolumic conditions following AO, both P_a and P_v decreased to a common asymptotic equilibrium pressure (P_f). When the pulmonary artery and vein are simultaneously occluded, both $\Delta t = 0$ and $\Delta Q_L = 0$ and the resulting final equilibrium pressure is denoted the double occlusion pressure, P_d (Fig. 1B) and represents the microvascular pressure (15, 24). The average value of C_{st} over the pressure range studied during the VOA maneuver can then be calculated as

$$C_{st} = \frac{\Delta Q_L}{P_f - P_d} \quad (3)$$

The VOA data provided additional information related to the viscoelasticity of the pulmonary vascular bed. The pressure curves after AO exhibit stress relaxation, *i.e.* P_f is less than either P_a or P_v were at the time of AO (Fig. 1A). The magnitude of S , in millimeters of mercury per milliliter change in blood volume, that the vessels undergo after AO is

$$S = \frac{1}{C_{\text{dyn}}} - \frac{1}{C_{st}} \quad (4)$$

The mean relaxation time in seconds characterizing the time course of the relaxation pressure after AO can be estimated by fitting the pressure curve after AO to

$$P_a(t) - P_f = A_1 e^{-\beta_1 t} + A_2 e^{-\beta_2 t} \quad (5)$$

by nonlinear regression (24). The $\bar{t}_R$ is then defined as

$$\bar{t}_R = \frac{\frac{A_1}{\beta_1} + \frac{A_2}{\beta_2}}{A_1 + A_2} \quad (6)$$

The occlusion data were also used to characterize the compartmental distribution of the dynamic vascular compliance and vascular resistance as defined previously (27). In the compartmental model used to interpret the data, the large arteries and veins are represented by C_u and C_d , respectively. The small vessels are represented by R_u and R_d , respectively, which are located upstream and downstream from C_c representing the compliance of the microvasculature including the capillaries. Changes in R_u and R_d are considered to represent mainly changes in the vascular resistance of the small arteries and veins, respectively (27). The data obtained from the VO, DO, and AO maneuvers (examples are shown for control and hypoxia in Fig. 1) were used to estimate R_u , R_d , C_u , C_d , and C_c using the following equations (25).

$$\frac{P_a(0) - P_v(0)}{\dot{Q}} = R_u + R_d = R_L \quad (7)$$

$$R_u = \frac{(P_a(0) - P_d)}{\dot{Q}} \quad (8)$$

$$R_d = R_L - R_u \quad (9)$$

$$C_u = \frac{\text{Area}}{(P_a(0) - P_d)R_u} \quad (10)$$

$$C_c = C_{\text{dyn}} - R_L C_u \cdot \frac{1}{R_d} \quad (11)$$

$$C_d = C_{\text{dyn}} - C_u - C_c \quad (12)$$

In addition to the occlusion data, pulmonary blood volume was measured using a bolus injection of indocyanine green as previously described (23). The first moment and the second moment about the mean of the indicator dilution curves, which represent the mean transit time, and the variance of the transit times for the passage of the dye bolus through the lungs, respectively, were calculated (23). The Q_L accessible to the dye was then the mean transit time times the flow rate. The relative dispersion of the dye bolus as it passed through the lungs was calculated as the square root of the variance divided by the transit time.

Comparisons between control and hypoxic conditions were made using the *t* test for paired samples. Differences are considered significant at $p < 0.05$.

RESULTS

The ventilator settings used for these studies resulted in a peak inspiratory pressure (PIP) of 1.2 ± 0.3 kPa (8.8 ± 2.0 mm Hg), an end-expiratory pressure (EEP) of 0.2 ± 0.1 kPa (1.8 ± 1.0 mm Hg) and a lung compliance, defined as $V_T/(\text{PIP} - \text{EEP})$, of 101 ± 25 mL·kPa⁻¹ (13.5 ± 3.3 mL mm Hg⁻¹) and the lung compliance was stable over the course of an experiment. The blood gas tensions during normoxic ventilation were a P_{O_2} of 12.4 ± 1.6 kPa (93 ± 12 mm Hg) and a P_{CO_2} of 5.5 ± 0.7 kPa (41 ± 5 mm Hg) with a pH of 7.43 ± 0.14 . The blood gas tensions during hypoxic ventilation were a P_{O_2} of 4.0 ± 0.8 kPa (30 ± 6 mm Hg) and a P_{CO_2} of 5.6 ± 0.7 kPa (42 ± 5 mm Hg) with a pH of 7.48 ± 0.06 .

The hemodynamic data are summarized in Table 1. The total pulmonary vascular resistance was nearly evenly divided upstream and downstream of the microvascular pressure, P_d , during control conditions. Hypoxia increased both the R_u and R_d but, the increase in R_u was greater ($p < 0.02$) than the increase in R_d (Table 1). Hypoxia also resulted in a significant decrease in C_{dyn} which could be accounted for by the decrease in C_c (Table 1). However, there was no significant change detected in C_{st} with hypoxia (Table 1). This difference between C_{dyn} and C_{st} suggests an increase in the viscous resistance to distension in vessels that responded to hypoxia. This increase in viscous resistance is also revealed by the increase in the magnitude of S and the decrease

Table 1. Hemodynamic data*

	Control	Hypoxia
$P_a(0)$ (mm Hg)	17.7 ± 1.1	$27.7 \pm 2.2\ddagger$
$P_v(0)$ (mm Hg)	4.1 ± 0.3	4.1 ± 0.3
P_d (mm Hg)	9.8 ± 0.9	$12.2 \pm 1.3\ddagger$
P_f (mm Hg)	26.3 ± 1.7	24.9 ± 2.1
R_L (mm Hg · mL ⁻¹ · s)	3.29 ± 0.42	$5.66 \pm 0.70\ddagger$
R_u (mm Hg · mL ⁻¹ · s)	1.98 ± 0.31	$3.70 \pm 0.57\ddagger$
R_d (mm Hg · mL ⁻¹ · s)	1.47 ± 0.29	$2.09 \pm 0.43\ddagger$
C_{dyn} (mL · mm Hg ⁻¹)	0.67 ± 0.07	$0.50 \pm 0.04\ddagger$
C_u (mL · mm Hg ⁻¹)	0.05 ± 0.01	0.06 ± 0.01
C_c (mL · mm Hg ⁻¹)	0.53 ± 0.05	$0.33 \pm 0.02\ddagger$
C_d (mL · mm Hg ⁻¹)	0.07 ± 0.02	$0.13 \pm 0.03\ddagger$
ΔQ_L (mL)	14.3 ± 1.8	13.3 ± 1.4
C_{st} (mL · mm Hg ⁻¹)	0.87 ± 0.10	0.99 ± 0.08
S (mm Hg · mL ⁻¹)	0.38 ± 0.10	$1.00 \pm 0.13\ddagger$
$\bar{t}_R$ (s)	5.67 ± 0.82	$3.43 \pm 0.43\ddagger$
Q_L (mL)	21.2 ± 1.9	$17.1 \pm 1.8\ddagger$
Relative dispersion	0.48 ± 0.04	0.53 ± 0.06

* Values are $\pm$ SE.

† Different from control, $p < 0.02$.

‡ Different from control, $p < 0.005$.

in $\bar{t}_R$. Hypoxia also resulted in a consistent decrease in Q_L with no significant change in relative dispersion (Table 1).

DISCUSSION

According to the resistor-capacitor model interpretation of the occlusion data, the distribution of vascular resistance in the neonatal pig lung under normoxic zone III conditions was nearly evenly divided upstream and downstream of P_d and C_c . It is generally felt that P_d is close to the average capillary pressure (15, 21, 24, 25, 28, 37). Thus, this observation is consistent with the results of Fike and Kaplowitz (2) who found that vascular resistance was nearly evenly divided upstream and downstream of 10- to 60- μ m diameter subpleural venules in the isolated lungs from 6- to 7-d-old pigs, assuming that the resistance between 10- μ m arteries and veins is small. A nearly equal distribution of vascular resistance upstream and downstream of P_d using vascular occlusions has also been reported in the isolated lungs from 12- to 13-week-old Minipigs and 12-week-old Landrace pigs (29). The distribution of vascular compliance between arterial, microvascular and venous segments under normoxic conditions was about 7, 82, and 11%, respectively. This distribution is consistent with previous studies in isolated adult dog lungs using this and other methods (15, 24, 27, 30, 31).

The results indicate that the increase in total vascular resistance due to hypoxia occurred mainly in the pulmonary arteries in this preparation. This conclusion is based on two observations. First, the vascular occlusion data interpreted according to the compartmental model indicate that much of the increase was in R_u . Second, the decrease in Q_L is consistent with a predominantly arterial site of action (16, 32), because a predominantly venous site of action would be expected to increase rather than decrease Q_L (16, 32). An arterial site of action of hypoxia has been a consistent finding in the adult lungs from many different species (15–21, 24, 25, 32). However, we found that in these neonatal pig lungs there was a significant downstream response as well. This is consistent with the findings of Fike and Kaplowitz (2) in the isolated lungs from 6- to 7-d-old pig lungs. A maturational difference in the hypoxic response has been suggested in some species. For example, in the pig (5) and in the rabbit (33) it has been found that the magnitude of the hypoxic pressure response, expressed as the percent change in pulmonary artery pressure, increases with increasing postnatal age. Also, lung lymph fistula studies in sheep (19, 22) have suggested that hypoxia resulted in an increase in microvascular pressure in the lamb but not in the sheep. However, in the juvenile pig (2–3 mo of age) Mitzner and

Table 2. Pulmonary hemodynamics in intact neonatal pigs*

First author	Reference	Age (d)	Weight (kg)	PBF (mL · min ⁻¹ · kg ⁻¹)	P _a - P _w (mm Hg)	R _L (mm Hg · mL ⁻¹ · s)
Redding	3	5-12	2.6 ± 0.7	200 ± 85	11 ± 4	2.7 ± 1.2
Bradley	4	<10	2.5-4.2	142 ± 57	7 ± 3	0.8 ± 0.1
Our study		9 ± 5	2.8 ± 0.7	95 ± 10	14 ± 3	3.3 ± 0.4
Konduri	5	10	3.4 ± 0.3	241 ± 48	19 ± 9	1.4 ± 0.5
Taylor	6	10-12	2.9 ± 0.6	285 ± 43	15 ± 3	1.1 ± 0.2
Goldberg	7	11 ± 4	3.3 ± 0.8	260 ± 20	10 ± 4	1.0 ± 0.2
Troug	8	10-16	3.2 ± 0.6	215 ± 20	10 ± 3	0.9 ± 0.5
Gibson	9	13 ± 3	3.6 ± 0.5	264 ± 42	11 ± 1	0.7 ± 0.1
Gibson	10	12-18	3.3 ± 0.7	230 ± 67	11 ± 2	0.8 ± 0.1
Troug	11	17 ± 7	4.1 ± 0.8	260 ± 100	10 ± 3	0.5 ± 0.2
Gibson	12	18 ± 4	3.5 ± 1.5	271 ± 85	11 ± 5	0.7 ± 0.1
Rendas	13	14-28	6.7	85 ± 19	10 ± 3	1.1 ± 0.4
Rendas	14	14-28	7.3 ± 3.0	125 ± 24	16 ± 4	1.1 ± 0.4

* Values are either mean ±SD or range, order is approximate with respect to average postnatal age. Abbreviations are: PBF, pulmonary blood flow; P_a - P_w, pulmonary arterial minus wedge (or left atrial) pressure.

Sylvester (34) found that hypoxia increased the rate of weight gain in the isolated lung, suggesting that hypoxia led to an increase in the microvascular pressure due to venous constriction. Thus, the age dependence of the venous response apparent in the sheep may not occur in pigs.

The hypoxic pressor response led to a decrease in the dynamic vascular compliance with no significant change in the static vascular compliance, suggesting that hypoxia resulted in an increase in viscous resistance to distension in those vessels which contribute to the vascular compliance. This observation is similar to that in dog lungs using a similar approach (24). Studies in isolated vessels (26, 35), have suggested that smooth muscle contributes substantially to the viscous behavior of the vessel wall, and that activation of vascular smooth muscle increases the viscous resistance to distension of the vessel wall (26, 35) which is consistent with the increase in S and the decrease in T_R resulting from hypoxia in this study.

The decrease in the dynamic vascular compliance was almost entirely accounted for by the decrease in C_c. This has implications regarding the site of action of hypoxia. Although C_c is thought to consist mainly of the capillary bed, it probably includes reactive small arteries and veins as well (15, 24, 25, 27, 28). The constriction of these small vessels would be expected to decrease their dynamic compliance and may account for the decrease in C_c. Another possibility that has been proposed is that there is active constriction of capillaries (36). The present methods do not differentiate between these possibilities. An increase in heterogeneity in the resistance and compliance of parallel pathways could also contribute to an apparent difference between C_{st} and C_{dyn} (24). An increase in the heterogeneity in the resistance and thus in the flow among parallel pathways would be expected to increase the relative dispersion of the dye bolus as it passed through the lungs. However, the observation that the relative dispersion of the dye bolus was not remarkably altered by hypoxia suggests little contribution to the decrease in the calculated C_c from this source (24).

Isolated perfused lungs have several obvious advantages for experimental studies on pulmonary vascular function and metabolism as reflected by their prevalent use in a wide diversity of mechanistic studies. For hemodynamic studies, the question arises whether the isolated perfused lungs are hemodynamically similar to the lungs of intact animals. One disadvantage of the isolated lung is a limited lifetime for experimentation due to either extravascular fluid accumulation or loss of reactivity. One commonly used strategy to extend the useful time of the preparation is to use relatively low flow rates; previous studies using the neonatal pig isolated lung have used flow rates between 10 and 50 mL · min⁻¹ · kg⁻¹ (2, 37, 38). To put this into perspective the pressure and flow from the present study and those from published studies in intact neonatal pigs in which both P_a and

wedge pressure were measured are compared in Table 2. The available data on intact piglets reveals a fairly wide range of pressures and flows. The pressure and flow in this isolated lung preparation under the control conditions were within the ranges of these variables in the intact animal studies, but on the high and low ends of the ranges, respectively. With respect to vessel reactivity, the magnitude of the hypoxic response was comparable to that reported for intact pigs. The mean increase in pulmonary artery pressure was 56% in our isolated lungs when the breathing gas mixture reduced the PO₂ to 4 ± 0.3 kPa. Rendas *et al.* (13) observed a 44% increase in pulmonary artery pressure in intact neonatal (2-4 wk of age) pigs when the breathing gas mixture reduced the arterial PO₂ to 5.5 ± 1.1 kPa.

In conclusion, we found that in this preparation, the pulmonary vascular resistance was essentially evenly divided upstream and downstream of the central compliance and that most of the vascular compliance was in the microvasculature. Hypoxia resulted mainly in upstream constriction according to the compartmental model used to interpret the data. This conclusion is also consistent with the observed decrease in total vascular volume with hypoxia. However, there was a small but significant downstream constriction. This downstream hypoxic constriction may have implications in lung fluid balance. For example, if human neonates responded in a similar fashion to hypoxia, the increase in microvascular pressure due to downstream constriction may have implications in the pathogenesis and therapy of postasphyxial lung disease and bronchopulmonary dysplasia in the neonate.

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