Alveolar Hypoxia Increases Small Pulmonary Wedge Pressure in Awake Young Lambs

THOMAS A. HAZINSKI AND KATHLEEN A. KENNEDY

Department of Pediatrics, Vanderbilt University, School of Medicine, Nashville, Tennessee 37232

ABSTRACT. Alveolar hypoxia increases pulmonary artery pressure in lambs and sheep but increases lung lymph flow only in lambs; the reasons for this are unknown. To test the hypothesis that hypoxia-induced pulmonary venous constriction could in part explain the fluid filtration response in young lambs, eight young lambs (13 ± 3 days old) and four older lambs (60 ± 4 days old) were prepared for chronic studies of pulmonary hemodynamics, gas exchange, and fluid filtration. In all animals, a 5 Fr catheter was intermittently wedged into a distal pulmonary artery to indirectly estimate pulmonary venous pressure. The pressure measured in this manner was termed the "small wedge pressure." Animals were awake, spontaneously breathing, and unsedated, and were exposed to both acute and chronic isocarbic hypoxia ($\text{FIO}_2 0.12$). We found that hypoxia significantly increased both small pulmonary wedge pressure and lung lymph flow in young lambs but that neither of these effects occurred in the older lambs. In young lambs, the hypoxia-induced increase in small wedge pressure could be lowered by sodium nitroprusside administration, and small wedge pressure could be increased by angiotensin II infusion. We conclude that alveolar hypoxia increases pulmonary venous tone and the critical pressure of pulmonary veins in young lambs, and that these effects disappear with maturation. These data suggest that alterations in pulmonary venous tone can have important effects on lung fluid balance in the newborn. (*Pediatr Res* 22: 679-682, 1987)

Abbreviations

TPVR, total pulmonary vascular resistance
DSPVR, distal segment pulmonary vascular resistance
PVR, pulmonary vascular resistance

Hypoxia increases pulmonary vascular resistance, yet the sites and mediators of this effect are still uncertain (1, 2). However, the sites of hypoxia-induced vasoconstriction should strongly influence lung fluid balance, since transvascular pressure gradients may also be affected (3). This is illustrated by the contrasting effects of hypoxia on the pulmonary circulation of lambs and sheep. In awake lambs, alveolar hypoxia increases cardiac output, pulmonary artery pressure, and lung lymph flow; left atrial pressure does not change and the protein concentration of lymph

relative to plasma falls (4); the fluid filtration response also occurs in anesthetized mechanically ventilated lambs whose cardiac output does not increase during hypoxia (5, 6). In sheep, however, an equivalent degree of hypoxia causes similar increases in pulmonary artery pressure and cardiac output, but lymph flow and its protein concentration do not change (7, 8). These data suggest that hypoxia increases microvascular pressure in hypoxic lambs but not in hypoxic sheep, but the reasons are unknown. In lambs, possible mechanisms could be either nonuniform arterial vasoconstriction, pulmonary venous constriction, or a combination of both. Recently, Hansen *et al.* (9) showed that in anesthetized young lambs, hypoxia increased lymph flow and changed the distribution of lung perfusion and that these changes occurred in normoxic lambs given angiotensin II. They proposed that nonuniform arterial vasoconstriction accounted for the increase in lung lymph flow. However, it is equally possible that any redistribution of blood flow was the result of uniform venous constriction with a subsequent uniform increase in microvascular filtration pressure (10, 11). The purpose of this study was to examine this latter possibility; *i.e.* that constriction of pulmonary veins was, at least in part, responsible for the lymph flow response to hypoxia in lambs. To test this hypothesis, young and older lambs were prepared for chronic studies of pulmonary hemodynamics, gas exchange, and lung fluid filtration; pulmonary venous pressure was measured indirectly. We interpret our results to indicate that pulmonary venous pressure increased in hypoxic young lambs, that this venous pressure drove lymph flow, and that these changes did not occur in the older animals.

MATERIALS AND METHODS

Eight young lambs (age 6 ± 4 days) and four older lambs (age 49 ± 2 days) were surgically prepared using previously described methods (5, 6). After local anesthesia was administered, catheters were inserted into the inferior vena cava and descending aorta through hindlimb vessels. After general anesthesia was induced with 50% nitrous oxide and 1-2% halothane, a left thoracotomy was performed, and catheters were inserted into the pulmonary artery and left atrium, and a thermister wire (3 FR, American Edwards Labs, Irvine, CA) was placed in the pulmonary artery for subsequent measurement of cardiac output. After a 3-day recovery period a right thoracotomy was performed and a catheter was placed in the efferent duct of the caudal mediastinal lymph node in four young and three older lambs; the node was transected and systemic lymphatics were identified and divided. A catheter was placed in the pleural space for measurement of pleural pressure. Finally, in all animals the right jugular vein was punctured percutaneously and a rubber-sealed vascular sheath (Cordis Corp, Miami, FL) was inserted, through which a balloon-tipped, double lumen pulmonary wedge catheter (5 FR, outer diameter 1.67 mm) was positioned in the distal pulmonary artery. This catheter could be intermittently advanced and wedged (with the balloon uninflated) to measure pulmonary wedge pressure in pulmonary veins of a size equal to the wedged

Received March 17, 1987; accepted July 30, 1987.

Correspondence: Thomas A. Hazinski, M.D., Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN 37232.

Supported in part by a grant from the American Lung Association (48-541) and by Newborn Lung SCOR HL14214. K.K. was supported by a training grant from the American Lung Association and by NIH Training Grant HL07246. T.A.H. is the recipient of a Career Investigator Award from the American Lung Association.

catheter (12, 13). This pressure was termed "small wedge pressure" (13). Animals recovered from surgery for at least 72 h before studies began. The young lambs were 13 ± 3 days old and the four older lambs were 60 ± 4 days old when they were studied.

Mean vascular and pleural pressures were measured at end-expiration using saline-filled catheters and standard pressure transducers; these pressures were recorded continuously on a Hewlett-Packard 8-channel recorder. Vascular pressures were referenced to mean pleural pressure; pleural pressure was referenced to a location on the chest identified at surgery to be at the level of the left atrium. Before pleural pressure measurement, the catheter was flushed with 0.1 ml bubble-free saline. The outflow height of the lymph catheter was initially placed at the level of the olecranon, and all lymph catheters were the same diameter and length. The outflow height of the lymph catheter was adjusted if inferior vena cava pressure changed, as recently suggested (14). Lymphatic resistance and catheter resistance were not calculated.

Lymph and plasma protein concentrations were estimated by a calibrated refractometer and confirmed by an automated biuret method (15). Arterial blood gas tensions and pH were analyzed using standard electrodes and the values were corrected for body temperature. Cardiac output (measured as pulmonary blood flow) was obtained using the thermodilution technique (Cardiac Index Computer SP1435, Gould-Statham, Oxnard, CA); three injections of cold saline were performed over a 30-s period and the mean was calculated.

Calculations of TPVR were computed using the formula: $TPVR = (\text{pulmonary artery pressure} - \text{left atrial pressure}) / \text{pulmonary blood flow}$. DSPVR was computed using the formula $DSPVR = (\text{small pulmonary wedge pressure} - \text{left atrial pressure}) / \text{pulmonary blood flow}$.

Statistics. For comparison of means between normoxic and hypoxic lambs, the paired *t* test was used. To compare young lambs with older lambs, the unpaired *t* test was used. When a mean was compared more than once, Bonferroni's correction was used (16). All data in tables and text are presented as the mean $\pm$ 1 SD.

STUDY PROTOCOLS

Acute isobaric hypoxia. While the animals breathed air, baseline measurements of pleural pressure and the vascular pressure in the inferior vena cava, left atrium, aorta, pulmonary artery, and pulmonary wedge position were recorded for at least 1 h. In two young lambs and two older lambs, the position of the wedged catheter was identified fluoroscopically. In these animals, the wedge catheter tip was less than 2 cm above or below the left atrial catheter tip, indicating, along with other physiologic evidence that the catheter was measuring hydrostatic pressure under zone 3 conditions (see "Discussion"). The same pressure was recorded each time regardless of catheter tip position.

Determinations of cardiac output were performed every 15 min for 1 h. Then the breathing mixture was changed to 12% oxygen in nitrogen; this gas was delivered into a large clear plastic bag which was placed over the animal's head. To keep arterial pH constant during hypoxia, flow into the bag and the leak around the animal's neck were adjusted to maintain the arterial PO_2 near 40 torr and the arterial PCO_2 similar to that measured when the animals breathed air. Each animal breathed this gas for 10 min, and all variables were recorded again. We chose to expose lambs to 10 min of hypoxia, although previous studies (5, 7) showed that the hemodynamic response to acute hypoxia was near steady-state after 6 min. Then the lamb resumed room air breathing and all variables were measured until they returned to baseline levels.

Prolonged isobaric hypoxia. In four young lambs and three older lambs, measurements of lung fluid filtration and hemodynamics were made for a 1.5- to 3-h baseline period, and during

1.5-4 h of isobaric hypoxia. These studies of prolonged hypoxia were done on the day after the acute studies.

RESULTS

Acute hypoxia. In every young lamb, acute isobaric hypoxia significantly increased pulmonary artery and wedge pressures and increased the pressure difference between the pulmonary wedge position and the left atrium (Table 1). A typical experiment depicting two episodes of hypoxia is shown in Figure 1. Total PVR increased from 5.4 ± 1.2 to 8.1 ± 2.3 torr/liter/min ($p < 0.01$), and distal segment PVR increased from 0.54 ± 0.21 to 2.05 ± 0.44 torr/liter/min ($p < 0.01$).

In every older lamb, acute isobaric hypoxia increased only pulmonary artery pressure and cardiac output, and only total PVR significantly increased from 3.9 ± 0.4 to 5.4 ± 0.7 torr/liter/min ($p < 0.02$). Distal segment PVR fell slightly but the difference was not significant.

Ventilation and gas exchange data are shown in Table 2. In hypoxic young lambs, only arterial PO_2 and respiratory frequency changed significantly ($p < 0.03$). In hypoxic older lambs, only arterial PO_2 was significantly different.

Table 1. Pulmonary vascular pressures and cardiac output in study animals in air and after 10 min of isobaric hypoxia (mean $\pm$ 1 SD)

	Vascular pressure (torr)			
	Pulmonary artery	Small pulmonary wedge	Left atrium	Cardiac output (liter/min)
Young lambs (<i>n</i> = 8)				
Air	18 ± 4	3 ± 2	2 ± 2	2.83 ± 0.40
12% O ₂	$32 \pm 3^*$	$8 \pm 2^*$	1 ± 2	$3.40 \pm 0.71^*$
Older lambs (<i>n</i> = 4)				
Air	15 ± 3	4 ± 2	2 ± 3	3.26 ± 0.43
12% O ₂	$25 \pm 4^*$	4 ± 2	2 ± 3	$4.23 \pm 0.50^*$

* Significant difference, $p < 0.05$.

Fig. 1. Pulmonary vascular pressure and arterial gas tensions recorded during two consecutive episodes of alveolar hypoxia in a 12-day-old lamb. The gradient between pulmonary wedge (PW) pressure and left atrial (LA) pressure shown as the shaded area.

Table 2. Gas exchange and respiratory variables in study animals before and during acute hypoxia (mean $\pm$ 1 SD)

	pH	PCO ₂ (torr)	PO ₂ (torr)	Respiratory frequency (breaths/min)	Pleural pressure (torr)
Young lambs (n = 8)					
Air	7.42 $\pm$ 0.07	42 $\pm$ 3	89 $\pm$ 6	60 $\pm$ 11	-2 $\pm$ 1
12% O ₂	7.44 $\pm$ 0.10	40 $\pm$ 4	39 $\pm$ 3*	78 $\pm$ 21*	-3 $\pm$ 1
Older lambs (n = 4)					
Air	7.40 $\pm$ 0.04	40 $\pm$ 2	91 $\pm$ 5	55 $\pm$ 16	-3 $\pm$ 1
12% O ₂	7.42 $\pm$ 0.08	41 $\pm$ 3	40 $\pm$ 4*	61 $\pm$ 17	-4 $\pm$ 2

* $p < 0.04$.Table 3. Fluid filtration variables in study animals (mean $\pm$ 1 SD)

	Pulmonary artery (torr)	Small pulmonary wedge (torr)	Left atrium (torr)	Cardiac output (liter/min)	Lymph flow (ml/h)	I/P ratio*
Young lambs (n = 4)						
Air	17 $\pm$ 2	4 $\pm$ 1	3 $\pm$ 1	2.88 $\pm$ 0.03	3.5 $\pm$ 0.4	0.65 $\pm$ 0.2
12% O ₂	31 $\pm$ 3†	11 $\pm$ 2†	3 $\pm$ 1	3.52 $\pm$ 0.11†	6.9 $\pm$ 0.5†	0.52 $\pm$ 0.2†
Older lambs (n = 3)						
Air	15 $\pm$ 2	5 $\pm$ 1	4 $\pm$ 1	3.05 $\pm$ 0.41	4.1 $\pm$ 0.4	0.63 $\pm$ 0.2
12% O ₂	24 $\pm$ 3†	5 $\pm$ 2	4 $\pm$ 1	3.67 $\pm$ 0.34†	4.2 $\pm$ 0.8	0.61 $\pm$ 0.3

* Lymph to plasma protein concentration ratio.

† Indicates $p < 0.05$ compared to baseline period in air.

Fig. 2. Effect of sodium nitroprusside infusion on vascular pressures during hypoxia in a 14-day-old lamb. This nonspecific vasodilator reduced the vascular pressure in the pulmonary artery (PA), pulmonary wedge position (PW), and left atrium (LA) with no change in aortic pressure (AO). This response was consistent in three young lambs.

Fluid filtration during prolonged hypoxia. Fluid filtration variables in four young lambs and three older lambs are shown in Table 3. Because the vascular pressure in the inferior vena cava increased by less than 1 torr during hypoxia, only small adjustments in lymph catheter height were necessary. In young lambs, as expected (4–6), prolonged hypoxia increased lymph flow and decreased the protein concentration of lymph relative to plasma. In the hypoxic older lambs, as expected (7, 8), neither lymph flow nor lymph protein concentration changed. In all study animals, the plasma protein concentration remained unchanged so that the fall in this ratio always reflected the fall in lymph protein concentration.

Additional studies. To determine whether the increase in small pulmonary wedge pressure and in distal segment PVR could be accounted for by contraction of vascular smooth muscle, sodium nitroprusside (ESI Pharmaceuticals, Cherry Hill, NJ), a nonspecific vasodilator, was administered by continuous infusion to three hypoxic young lambs. The drug was given by continuous infusion at a dose of 1 mg/kg/min. An example of the response to nitroprusside infusion is shown in Figure 2. Nitroprusside decreased both pulmonary artery and pulmonary wedge pressure with little change in either left atrial pressure or in cardiac output. This response was consistent in all three lambs.

Finally, in three normoxic young lambs (two of whom had lymph cannulas), we administered the pulmonary vasoconstrictor angiotensin II (Angiotensin, Ciba, Summit, NJ), 11–15 μ g/kg/min, for 90 min after a 2-h baseline period. Angiotensin II infusion was adjusted to maintain pulmonary artery pressure at twice the baseline level; when this occurred, small pulmonary wedge pressure increased from 3 ± 1 to 10 ± 2 torr. Left atrial pressure and arterial blood gases did not change and cardiac output fell by $4 \pm 2\%$. In two young animals with lymph catheters, lymph flow increased 48 and 60% after 45 min of infusion, and the average lymph-to-plasma protein concentration ratio fell from 0.62 to 0.50. This demonstrates that angiotensin II infused at a rate sufficient to double pulmonary artery pressure without increasing pulmonary blood flow can also increase pulmonary wedge pressure and lymph flow.

DISCUSSION

We found that, in young lambs, alveolar hypoxia increased small pulmonary wedge pressure, shifted the arterial-to-venous distribution of vascular resistance toward the left atrium, and increased lung lymph flow. None of these changes occurred in hypoxic older lambs.

Several lines of evidence suggest that this hypoxia-induced increase in small pulmonary wedge pressure represents pulmonary venous constriction in the young lambs. First, a catheter wedged into a small pulmonary artery (under zone 3 conditions) has been shown to accurately measure the pressure in pulmonary

veins of similar size (13). In our lambs, the catheter was wedged satisfactorily as indicated by 1) the similarity of its phasic pressure waveform to the left atrial pressure waveform at all times; 2) the fact that when all animals breathed air the small pulmonary wedge pressure was always 1–2 torr higher than left atrial pressure; and 3) the inability to obtain mixed venous blood from the wedged catheter, indicating that the catheter was not in series with an adjacent small pulmonary artery. We did not directly cannulate pulmonary veins in this study, since an additional thoracotomy would have been required.

The conventional measurement of pulmonary wedge pressure by using balloon inflation technique ("large wedge pressure") can be influenced by the vertical height of the wedged catheter tip relative to the heart (17), and this same effect might possibly influence the measurement of small wedge pressure as well. However, we believe that our measurements were made under zone 3 conditions as evidenced by the following: 1) when the catheter was pulled back 1–1.5 cm from the wedged position and the balloon inflated, we always measured a "large wedge pressure" that was within 1 torr of the directly measured left atrial pressure (13, 18); 2) the fluoroscopic results indicated that the wedged catheter was nearly level with the left atrium; 3) the fact that in small supine animals most of the lung is in zone 3 condition (18); and 4) the fact that all reported pressures were measured at end-expiration when alveolar pressure equaled zero, so that left atrial pressure was at least 4 torr higher than alveolar pressure.

Our results in young, awake hypoxia lambs are similar to those of Mitzner and Sylvester (19) who found in isolated perfused pig lungs that hypoxia increased fluid filtration into the lung by an amount that was independent of blood flow. They interpreted these data to indicate that hypoxia increased microvascular filtration pressure by increasing the critical pressure of a vascular segment either in capillaries or in pulmonary veins. The idea of a critical pressure was first presented to account for the failure of Poiseuille's law to adequately predict flow through vessels which had both elastic properties and active tone. This idea was extended by others (11, 20) who suggested that in the pulmonary circulation, alveolar pressure was a critical pressure in that it, not outflow pressure, (*i.e.* left atrial pressure) could determine the actual pressure gradient for flow. Recently, Jasper *et al.* (21) have extended this idea by showing that even under zone 3 conditions (*i.e.* where outflow pressure is greater than alveolar pressure), a spectrum of critical pressures may be present. Our data in hypoxic young lambs are consistent with this line of reasoning, and suggest that in young lambs, alveolar hypoxia increases pulmonary venous tone, which increases the average critical pressure in these vessels, and thus increases microvascular filtration pressure.

A second line of evidence that pulmonary venous constriction is occurring in the young lambs is the small wedge pressure response to nitroprusside and angiotensin II infusions. Pulmonary venous pressure can be passively increased if bronchial blood flow increases (22) or if severe edema compresses pulmonary veins (23). However, these mechanisms are unlikely, since in our study two vasoactive agents immediately altered small wedge pressure. These responses indicate that smooth muscle constriction within the walls of pulmonary veins was responsible for the increase in wedge pressure during hypoxia.

Other investigators using different methods and species have also found that pulmonary venous pressure increases during hypoxia (24–28). Recently, investigators using the micropuncture method have reported that venous pressure increases during hypoxia in isolated young lamb and adult cat lungs (29, 30). Fung and coworkers (31, 32) have shown that pulmonary veins are uniquely anatomically suited to control microvascular pressure, since they are tethered by elastic elements and thus cannot

easily collapse but can actively constrict. The present study suggests that the hypoxia-induced increase in pulmonary venous tone explains why lymph flow increases in hypoxic lambs but not in hypoxic sheep. These data suggest further that alterations in venous tone can have important effects on lung fluid balance in the newborn lung, but that this vasoactivity may change with maturation.

REFERENCES

1. Fishman AP 1976 Hypoxia on the pulmonary circulation: how and where it acts. *Circ Res* 38:221–231
2. Voelkel NF 1986 Mechanisms of hypoxic pulmonary vasoconstriction. *Am Rev Respir Dis* 133:1186–1195
3. Taylor AE 1981 Capillary fluid filtration: Starling forces and lymph flow. *Circ Res* 49:558–575
4. Bressack MA, Bland RD 1980 Alveolar hypoxia increases effects of alveolar hypoxia on lung fluid and protein transport in unanesthetized sheep. *Cir Res* 40:269–274
5. Hansen TN, Haberkern CM, Hazinski TA, Bland RD 1984 Lung fluid balance in hypoxic lambs. *Pediatr Res* 18:434–440
6. Hansen TN, Hazinski TA, Bland RD 1984 Effects of asphyxia on lung fluid balance in baby lambs. *J Clin Invest* 74:370–376
7. Bland RD, Demling RH, Selinger SL, Staub NC 1977 Lung fluid filtration in unanesthetized newborn lambs. *Circ Res* 46:111–116
8. Coates G, O'Brodovich H, Jefferies AL, Gray GW 1984 Effects of exercise on lung lymph flow in sheep and goats during normoxia and hypoxia. *J Clin Invest* 74:133–141
9. Hansen TN, LeBlanc AL, Gest AL 1985 Hypoxia and angiotensin II infusion redistribute lung blood flow in lambs. *J Appl Physiol* 58:812–818
10. Hultgren HN High altitude pulmonary edema. In: Staub NC (ed) *Lung, Water and Solute Exchange*. Marcel Dekker, Inc., New York, pp 437–469
11. Lopez-Muniz R, Stephens NL, Bromberger-Barnea B, Permutt S, Riley RL 1968 Critical closure of pulmonary vessels analyzed in terms of starling resistor model. *J Appl Physiol* 24:625–635
12. Malik AB, Kidd BSL 1976 Pulmonary arterial wedge and left atrial pressures and the site of hypoxic pulmonary vasoconstriction. *Respiration* 33:123–132
13. Zidulka A, Hakim TS 1985 Wedge pressure in large vs small pulmonary arteries to detect pulmonary venoconstriction. *J Appl Physiol* 59:1329–1332
14. Drake R, Geisler M, Laine G, Gabel J, Hansen T 1985 Effect of outflow pressure on lung lymph flow in unanesthetized sheep. *J Appl Physiol* 58:70–76
15. Gornall AG, Bardawill GJ, David MM 1949 Determination of serum proteins by means of the biuret reaction. *J Biol Chem* 177:751–769
16. Zar JH 1974 *Biostatistical Analysis*. Englewood Cliffs, NJ, Prentice-Hall, Inc
17. Todd TRJ, Baile EM, Hogg JC 1978 Pulmonary arterial wedge pressure in hemorrhagic shock. *Am Rev Respir Dis* 118:613–616
18. West JB, Dollery CT, Naimark A 1964 Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol* 19:713–724
19. Mitzner W, Sylvester JT 1981 Hypoxic vasoconstriction and fluid filtration in pig lungs. *J Appl Physiol* 51:1065–1071
20. Permutt S, Riley RL 1963 Hemodynamics of collapsible vessels with tone: the vascular waterfall. *J Appl Physiol* 18:924–932
21. Jasper AC, Spencer LS, Goldberg HS 1986 Relationship of arterial wedge pressure to closing pressure in the pulmonary circulation. *Am Rev Respir Dis* 143:879–884
22. Warren RL, Powell WJ 1986 Acute alveolar hypoxia increases bronchopulmonary shunt flow in the dog. *J Clin Invest* 77:1515–1524
23. Charan NB, Turk GM, Dhand R 1984 Gross and subgross anatomy of bronchial circulation in sheep. *J Appl Physiol* 57:658–664
24. Furnival CM, Linden RJ, Snow HM 1970 The effect of hypoxia on the pulmonary veins. *J Physiol* 210:43–44
25. Morgan BC, Church SC, Guntheroth WG 1968 Hypoxic constriction of pulmonary artery and vein in intact dogs. *J Appl Physiol* 25:356–361
26. Hyman AL, Kadowitz PJ 1975 Effects of alveolar and perfusion hypoxia and hypercapnia on pulmonary vascular resistance in the anesthetized intubated 2 month old lamb. *Am J Physiol* 228:397–403
27. Kuida H, Tasagari TJ, Hecht HH 1963 Evidence for pulmonary venoconstriction in brisket disease. *Circ Res* 12:182–189
28. Rivera-Estrada C, Saltzman PW, Singer D, Katz LN 1958 Action of hypoxia on the pulmonary vasculature. *Circ Res* 6:10–14
29. Nagasaka Y, Bhattacharya J, Nanjo S, Gropper MA, Staub NC 1984 Micropuncture measurement of lung microvascular pressure profile during hypoxia in cats. *Circ Res* 54:90–95
30. Raj JU, Rorhback J, Chen P 1986 Micropuncture measurement of lung microvascular pressures during hypoxia in newborn lambs. *Clin Res* 34:154A
31. Fung YC, Sobin SS, Tremer H, Yen MRT, Ho HH 1983 Patency and compliance of pulmonary veins when airway pressure exceeds blood pressure. *J Appl Physiol* 54:1538–1539
32. Fung YC 1984 *Biodynamics: Circulation*. Springer-Verlag, New York, pp 213–219