Anesthesiology
75:475–480, 1991

A Thromboxane Analog Increases Pulmonary Capillary Pressure but Not Permeability in the Perfused Rabbit Lung

George E. Wakerlin, Jr., M.D.,* Gail V. Benson, B.S.,† Ronald G. Pearl, M.D., Ph.D.‡

Thromboxane has been implicated as a mediator of pulmonary hypertension and pulmonary edema in acute respiratory failure. Pulmonary edema may result from increased pulmonary capillary hydrostatic pressure or from increased pulmonary vascular permeability. We therefore studied the effects of a stable thromboxane analog, U46619, on these two parameters in the perfused rabbit lung. Pulmonary capillary pressure was measured by the double vascular occlusion method, and pulmonary vascular permeability was estimated by measurement of the pulmonary fluid filtration coefficient (Kf). U46619 infusion produced pulmonary hypertension and lung weight gain; increased both the arterial (precapillary) and venous (postcapillary) components of pulmonary vascular resistance; and increased pulmonary capillary pressure from 4.7 ± 0.5 to 9.0 ± 0.7 mmHg ($P < 0.01$). The isogravimetric pressure (equivalent to the capillary pressure corresponding to no lung weight gain) was 4.0 ± 0.4 mmHg before U46619 and 4.6 ± 0.4 mmHg during U46619. Therefore, U46619 significantly increased capillary pressure above isogravimetric pressure and resulted in the development of pulmonary edema. U46619 did not affect vascular permeability as measured by Kf. We conclude that pulmonary venoconstriction resulting in increased pulmonary capillary hydrostatic pressure is the major mechanism by which thromboxane produces pulmonary edema in isolated lungs. (Key words: Lung, circulation: pulmonary capillary pressure; pulmonary edema; pulmonary hypertension; pulmonary vascular resistance; venoconstriction. Metabolism, arachidonic acid: thromboxane; U46619.)

PULMONARY EDEMA may result from increased pulmonary capillary pressure or increased vascular permeability or both. Depending upon the longitudinal distribution of pulmonary vascular resistance (precapillary *vs.* postcapillary components), increases in pulmonary artery pressure (PAP) may increase pulmonary capillary pressure (PCP) to a variable extent. The development of pulmonary hypertension parallels the clinical severity of acute respiratory failure (adult respiratory distress syndrome) and is a major prognostic factor in this disorder.[1] Thromboxane A_2 is a mediator of pulmonary hypertension and pulmonary edema formation occurring in association with sepsis,[2] endotoxemia,[3] complement activation,[4] neutrophil activation,[5] microembolism,[6] protamine administration,[7] and monocrotaline-induced pulmonary hypertension.[8] In these settings, thromboxane may produce pulmonary venoconstriction and thereby increase PCP and promote pulmonary edema formation. It is not definitely known whether thromboxane also increases pulmonary vascular permeability. The isolated perfused rabbit lung preparation allows estimation both of PCP (as measured by the double vascular occlusion pressure) and of pulmonary vascular permeability (as measured by the pulmonary fluid filtration coefficient [Kf]). Therefore, the current study was designed to determine the effect of U46619, a stable thromboxane A_2 analog,[9,10] on PCP and fluid filtration coefficient in the isolated perfused rabbit lung.

Materials and Methods

Isolated Perfused Lung Preparation

The protocol was approved by the Stanford Panel on Laboratory Animal Care. A standard isolated perfused rabbit lung preparation[11] was modified as described below.

Twenty male New Zealand White rabbits weighing 2.0 to 3.4 kg were anesthetized with intramuscular ketamine 65 mg/kg and intravenous (iv) pentobarbital 15–25 mg/kg. A tracheostomy was performed, and the lungs were mechanically ventilated with oxygen at a rate of 18 breaths per min, a peak airway pressure of 10–13 mmHg, and 2.5 cmH_2O positive end-expiratory pressure. After sternotomy, 1,000 units/kg iv heparin was administered, and the pulmonary artery and left atrium were cannulated *via* right and left ventriculostomies, respectively. Lungs then were ventilated with 5% carbon dioxide in air using the same parameters as before. The pulmonary circulation initially was perfused with 200–300 ml Krebs-Henseleit solution containing 3% bovine serum albumin at 37° C and *p*H 7.4 until the effluent was clear. The heart and lungs then were excised from the chest and suspended in a warmed humidified chamber by the tracheostomy tube from a counterbalanced force-displacement transducer (Grass FT03) for continuous measurement of lung weight. Lungs were hyperinflated to reverse any atelectasis and then were ventilated as before with 5% carbon dioxide in air and 2.5 cmH_2O positive end-expiratory pressure. Lungs then were perfused in a recirculating manner with Krebs-Henseleit solution containing 2% bovine serum albumin *via* a Masterflex pump (Cole-Parmer) at a flow of 150 ml/min. The perfusate reservoir temperature was maintained at 37° C with a heated water bath. The total

* Fellow in Anesthesia.
† Research Assistant in Anesthesia.
‡ Assistant Professor of Anesthesia.

Received from the Department of Anesthesia, Stanford University Medical Center, Stanford, California. Accepted for publication May 6, 1991. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1990.

Address reprint requests to Dr. Pearl: Department of Anesthesia, H3580, Stanford University Medical Center, Stanford, California 94305.

circuit volume was 500 ml. PAP and left atrial pressure (LAP) were continuously measured *via* side holes in the cannulas and were recorded with an eight-channel Hewlett Packard recorder. Vascular pressures were referenced to the level of the left atrium (approximately the apex of the lung). The venous reservoir height was adjusted to maintain LAP at 2 mmHg. The left atrium was wrapped loosely with string and glued to maintain constant left atrial volume.

Measurement of Pulmonary Capillary Pressure

PCP was estimated by the double vascular occlusion method.[12-14] This method is based on the finding that the major source of vascular compliance in the lung is the pulmonary capillary bed. Thus, when arterial inflow and venous outflow are occluded simultaneously, all vascular pressures equalize with PCP. For measurement of PCP, ventilation was discontinued and the arterial and venous cannulas were occluded simultaneously. PCP was measured as the average of the arterial (PAP) and venous (LAP) pressures 3 s after double occlusion. After measurement of PCP, pulmonary vascular resistance ($R_P = [PAP - LAP]/\dot{Q}$) was divided into arterial (R_A) and venous (R_V) components so that $R_A = (PAP - PCP)/\dot{Q}$, $R_V = (PCP - LAP)/\dot{Q}$, and $R_P = R_A + R_V$, where $\dot{Q}$ = flow.

Measurement of Isogravimetric Pressure and Pulmonary Capillary Filtration Coefficient

Isogravimetric pressure (P_{isog}) is the PCP at which the Starling forces are balanced so that the lung neither gains nor loses weight.[15] P_{isog} was determined by discontinuing flow and opening a shunt between the arterial and venous tubing so that PAP and LAP were equal. The venous reservoir height (LAP) then was altered in 1-mmHg increments, and the effect on lung weight was examined. P_{isog} was defined as the highest LAP at which the lung did not gain weight over a 3-min period. Kf was then measured by a modification of the method of Drake *et al.*[15] After determination of P_{isog}, LAP (and PAP) were increased to 7 mmHg over P_{isog}, and the weight gain from min 3 to min 10 was recorded and analyzed. This method of measurement of Kf is based on the fact that when PCP equals P_{isog}, the Starling forces are balanced so that $Jv = Kf([P_{isog} - P_{is}] - \sigma[II_{pc} - II_{is}]) = 0$, where Jv is the net fluid flux, Kf is the fluid filtration coefficient, P_{isog} is the pulmonary capillary hydrostatic pressure, P_{is} is the interstitial hydrostatic pressure, σ is the osmotic reflection coefficient, II_{pc} is the intravascular oncotic pressure, and II_{is} is the interstitial oncotic pressure. When the venous reservoir height is raised so that PCP is abruptly increased from P_{isog} to P_{isog} + 7 mmHg, the other Starling forces are initially unchanged so that edema formation occurs at a rate Jv = Kf × 7 mmHg. However, lung weight gain after the increase in PCP is due both to intravascular volume expansion and to pulmonary edema formation. The intravascular volume expansion is rapid and essentially complete within several minutes. Therefore, Jv was calculated by extrapolating the slow component of weight gain (3–10 min) back to time zero. The resulting value of Jv was then used to calculate Kf, which is expressed in $ml \cdot min^{-1} \cdot mmHg^{-1} \cdot 100\ g\ lung^{-1}$.

U46619 Pulmonary Hypertension Protocol

Rabbit lungs (n = 16) were initially perfused as described above at a flow of 150 ml/min and a LAP of 2 mmHg. After 15 min of stable perfusion, PCP, P_{isog}, and Kf were measured. Flow was then resumed at 150 ml/min with LAP of 2 mmHg. Pulmonary hypertension was then produced by the continuous infusion of the stable thromboxane A_2 analog U46619 (9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin $F_2\alpha$; Upjohn). U46619 at a concentration of 500 ng/ml in saline was infused *via* the pulmonary artery cannula at an initial rate of 200 ng/min until PCP was stable at 25–30 mmHg; generally, 15–25 min was required to achieve pulmonary hypertension. The infusion rate then was decreased so that the hourly infusion rate was equal to the total dose of U46619 required initially to produce pulmonary hypertension. After 1 h of stable pulmonary hypertension, PCP, P_{isog}, and Kf were measured.

Control Protocol

Control studies (n = 4) were performed to demonstrate the stability of the perfused rabbit lung preparation. After baseline perfusion, PCP, P_{isog}, and Kf were measured as described above. Flow then was resumed at 150 ml/min and LAP of 2 mmHg. One hour later, PCP, P_{isog}, and Kf measurements were repeated.

Statistics

Data are presented as means ± standard error of the mean. Statistical analysis used two-factor repeated-measures analysis of variance (treatment × time); $P < 0.05$ was considered significant.

Results

All results are summarized in table 1. Control lungs remained stable throughout the study: there was no significant change in PAP, PCP, P_{isog}, or Kf. U46619 administration produced stable pulmonary hypertension, and the lungs developed pulmonary edema as evidenced

TABLE 1. Pulmonary Hemodynamics, Fluid Filtration Coefficient, and Weight Gain

	U46619	Control
PAP baseline (mmHg)	9.2 ± 0.4	9.2 ± 1.0
PAP final	26.1 ± 0.7*†	9.5 ± 1.0
PCP baseline (mmHg)	4.7 ± 0.5	6.2 ± 0.2
PCP final	9.0 ± 0.7*†	5.8 ± 0.2
R_P baseline (mmHg · l^{-1} · min)	48 ± 3	48 ± 7
R_P final	161 ± 4*†	50 ± 71
R_A baseline (mmHg · l^{-1} · min)	30 ± 3†	14 ± 3
R_A final	114 ± 7*†	19 ± 6
R_V baseline (mmHg · l^{-1} · min)	18 ± 3	28 ± 2
R_V final	47 ± 4*†	25 ± 1
Kf baseline (ml · min^{-1} · $mmHg^{-1}$ · 100 g · $lung^{-1}$)	0.21 ± 0.02	0.16 ± 0.03
Kf final	0.23 ± 0.02	0.20 ± 0.03
P_{isog} baseline (mmHg)	4.0 ± 0.4	5.2 ± 1.0
P_{isog} final	4.6 ± 0.4	4.5 ± 0.5
Weight gain baseline (g/min)	0.02 ± 0.01	0.04 ± 0.02
Weight gain final	0.24 ± 0.12*†	0.00 ± 0.00

PAP = pulmonary artery pressre; PCP = pulmonary capillary pressure; R_P = pulmonary vascular resistance; R_A = pulmonary arterial (precapillary) resistance; R_V = pulmonary venous (postcapillary) resistance; Kf = fluid filtration coefficient; P_{isog} = isogravimetric pressure.
* $P < 0.05$ *versus* corresponding baseline value.
† $P < 0.05$ *versus* control.

by gross examination and by measured lung weight gain. U46619 significantly increased pulmonary vascular resistance and both of its components (arterial and venous). U46619 significantly increased PAP and PCP but did not affect P_{isog} or Kf. PCP was not significantly different from P_{isog} at either baseline or final measurements in control lungs or at baseline in U46619 lungs. However, in U46619 lungs, PCP was significantly greater than P_{isog} ($P < 0.01$) after U46619 administration.

Discussion

In the control lungs, PCP during baseline and final conditions was approximately equal to P_{isog}, and pulmonary edema did not occur. U46619 increased PCP by 4–5 mmHg but did not affect Kf or P_{isog}. Thus, during U46619 administration PCP exceeded P_{isog}, and the lungs gained weight. The data therefore suggest that the major factor responsible for thromboxane-induced pulmonary edema formation is increased capillary hydrostatic pressure secondary to pulmonary venoconstriction. This conclusion is consistent with numerous studies in other models of pulmonary hypertension and pulmonary edema that have demonstrated that thromboxane produces pulmonary venoconstriction.

Many of these studies[3,16–21] used a model of acute respiratory failure in which endotoxin is administered to sheep. The pulmonary effects of endotoxin administration in sheep generally are considered to occur in two phases.[3] Phase 1 is associated with marked pulmonary hypertension and increased lung lymph flow. The lymph-to-plasma protein ratio is decreased during phase 1, suggesting increased pulmonary microvascular pressure as the major etiology of pulmonary edema. Pulmonary hypertension during phase 1 is due primarily to cyclooxygenase products of arachidonic acid, particularly thromboxane A_2.[3,16–19] After phase 1, PAP and lymph flow decrease. After the decrease, phase 2 occurs and PAP and lymph flow again increase; PAPs usually are only moderately elevated during phase 2. The lymph-to-plasma protein ratio is increased during phase 2, suggesting increased endothelial permeability as the major etiology of pulmonary edema in this phase. Phase 2 lasts from 2 to 6 h after endotoxin administration. Pulmonary hypertension and increased permeability during phase 2 are not primarily related to cyclooxygenase products of arachidonic acid but may be due to lipoxygenase products or other humoral or cellular mediators. The evidence suggesting that thromboxane A_2 is the major mediator of pulmonary hypertension and edema in phase 1 is compelling. Snapper *et al.*[17] demonstrated that meclofenamate significantly attenuated the pulmonary hypertension caused by endotoxin infusion. Schumacher *et al.*[19] showed that endotoxin-induced pulmonary hypertension was absent after pretreatment with selective thromboxane A_2-receptor antagonists. Winn *et al.*,[16] studying awake goats with lung lymph fistulae, demonstrated that selective inhibition of thromboxane synthesis with dazoxiben markedly attenuated the pulmonary hypertensive response. Similarly, Kubo and Kobayashi[18] showed that the early phase of endotoxin-induced pulmonary hypertension was blocked by OKY-046, a selective thromboxane synthetase inhibitor.

Using pulmonary artery occlusion pressure profile analysis in sheep, we have demonstrated that PCP is increased only during the 1st h after endotoxin administration.[20] Recently, Bradley *et al.*[21] analyzed the effects

of an endotoxin infusion in sheep using a two-pore mathematical model of the microvascular barrier that incorporated lymph, protein, pressure, and multiple indicator measurements. During phase 1, microvascular transmembrane pressure increased 2.4-fold. During phase 2, microvascular transmembrane pressure was similar to baseline, but the large pore size increased by 40%. These results, achieved through a different methodology to estimate microvascular pressure, again suggest increased PCP but unchanged vascular permeability during the thromboxane-dependent phase of endotoxin-induced pulmonary edema.

Similarly, thromboxane has been implicated as a mediator of the pulmonary hypertension and pulmonary edema due to arachidonic acid administration. Ogletree and Brigham[22] showed that arachidonate produced dose-related increases in PAP and lung lymph flow and corresponding decreases in the lymph-to-plasma protein concentration ratio. The lung lymph response was similar to that produced by LAP elevation. In addition, indomethacin inhibited the hemodynamic and lung lymph responses to arachidonate. Using methodology similar to the current study, Townsley *et al.*[23] studied the resistance distribution and Kf in canine lungs and found no increase in Kf with arachidonate administration. Other studies suggest that thromboxane produces pulmonary edema by a hydrostatic rather than a permeability mechanism after administration of A23187, oleic acid, or acetyl glycerol ether phosphorylcholine–stimulated human platelets to perfused lungs.[24–26]

Thromboxane A_2 is an unstable compound that undergoes rapid spontaneous hydrolysis to the inactive compound thromboxane B_2. Attempts to study the direct effects of thromboxane A_2 on the pulmonary circulation therefore have required the use of stable thromboxane analogs. In sheep, U46619 administration increases lung lymph flow but decreases the lung lymph-to-plasma protein ratio, consistent with increased venous pulmonary vascular resistance and PCP.[27] Using pulmonary artery occlusion pressure profile analysis, we have demonstrated increased PCP due to pulmonary venoconstriction during U46619 administration in sheep.[28,29] Using methodology similar to that of the current study, Yoshimura *et al.*[30] demonstrated that the stable thromboxane analog 9,11-epithio-11,12-methano-thromboxane A_2 increases venous resistance and capillary pressure in the isolated buffer-perfused lung of the newborn lamb. In a subsequent study using the same thromboxane analog in the blood-perfused newborn-lamb lung,[31] those authors again demonstrated an increase in PAP and PCP as well as a 76% increase in Kf and a decrease in σ, the osmotic reflection coefficient. The authors therefore suggested that thromboxane increases both PCP and microvascular permeability. The reasons for the different conclusions in their study compared to the current study are not known but may be related to their use of a different thromboxane analog, a markedly higher PAP (52 *vs.* 26 mmHg), the addition of indomethacin to their perfusate, the use of blood instead of blood-free perfusate, species differences (lamb *vs.* rabbit), and age differences (newborn *vs.* adult).

One important limitation of the current study is that Kf reflects hydraulic conductance and is not a direct index of macromolecular permeability. However, as discussed above, experimental studies with lung lymph fistula models do not suggest increased macromolecular permeability with thromboxane. An additional limitation of Kf is that it represents the product of membrane surface area and membrane permeability per unit surface area. Thus, Kf may decrease if vasoconstriction decreases the perfused capillary surface area. The apparent lack of effect of U46619 on Kf could conceivably have resulted from a decrease in perfused capillary surface area combined with an increase in the permeability per unit perfused surface area. However, the entire lung was in zone III conditions during the measurement of Kf, and we are not aware of any data suggesting decreased capillary perfusion under the current study conditions.

Thromboxane may cause pulmonary edema by two mechanisms that were not evaluated in the current study—namely, a selective decrease in the osmotic reflection coefficient and a pressure-related alteration in membrane pore size. The measurement of Kf is independent of changes in the osmotic reflection coefficient. Although a decreased reflection coefficient generally is assumed to occur only in association with an increased Kf, selective decreases have been postulated to occur during acute lung injury.[32] However, such a decrease would produce high-protein lymph, a finding not commonly observed during thromboxane-mediated pulmonary hypertension. Increases in microvascular pressure may stretch membrane pores and thereby increase microvascular permeability.[33] In theory, such changes in pore size may be rapidly reversed when microvascular pressure is decreased and therefore may have been present during U46619 infusion but not during measurement of Kf. However, such changes are unlikely to have occurred in the current study because increases in Kf require microvascular pressures of > 41 mmHg in isolated dog lungs[34] and > 25 mmHg in isolated rabbit lungs.[35]

The current study demonstrated that a thromboxane analog does not increase vascular permeability in the isolated non–blood-perfused lung. The major implication of this finding is that thromboxane itself is not a direct mediator of increased capillary permeability. Extrapolation of our results to the clinical situation may be limited by the differences between the perfused lung preparation

and the living subject. The perfused lung is denervated, is isolated from the systemic circulation, and is perfused with a blood-free solution. Thromboxane may affect the lung indirectly *in vivo* by altering the neural input to the lung, activating systemic humoral mediators, or activating formed elements (*e.g.*, neutrophils) in the blood.

In conclusion, a thromboxane analog (U46619) produced pulmonary edema in the isolated perfused rabbit lung by increasing capillary hydrostatic pressure without altering the filtration coefficient. Similar effects have been described with histamine and leukotriene administration in perfused lungs.[36-38] Thus, pulmonary venoconstriction alone without change in permeability may produce pulmonary edema. In addition, in the setting of increased permeability, small increases in PCP due to pulmonary venoconstriction dramatically exacerbate pulmonary edema.[39,40] Thromboxane has been implicated as a mediator of pulmonary hypertension and edema in diverse settings.[2-8] Although thromboxane may not be a direct mediator of altered capillary permeability, inhibition of thromboxane release or its effects in order to decrease PCP and thereby decrease pulmonary edema may be an appropriate consideration in these situations.[41]

References

1. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476–480, 1977
2. Slotman GJ, Yellin SA, Handy JR, Hulstyn M, Husain SE, Gann DS: Thromboxane A_2 mediates hemodynamic and respiratory dysfunction in graded bacteremia. Surgery 100:214–221, 1986
3. Brigham KL, Meyrick B: State of the art: Endotoxin and lung injury. Am Rev Respir Dis 133:913–927, 1986
4. Gee MS, Perkowski SZ, Tahamont MV, Flynn JT, Wasserman MA: Thromboxane as a mediator of pulmonary dysfunction during intravascular complement activation in sheep. Am Rev Respir Dis 133:269–273, 1986
5. Loyd JE, Newman JH, English DE, Ogletree ML, Meyrick BO, Brigham KL: Lung vascular effects of phorbol myristate acetate in awake sheep. J Appl Physiol 54:267–276, 1983
6. Malik AB: Pulmonary microembolism. Physiol Rev 63:1114–1207, 1983
7. Morel DR, Zapol WM, Thomas SJ, Kitain EM, Robinson DR, Moss J, Chenoweth DE, Lowenstein E: C5a and thromboxane generation associated with pulmonary vaso- and broncho-constriction during protamine reversal of heparin. ANESTHESIOLOGY 66:597–604, 1987
8. Ganey PE, Roth RA: 6-keto prostaglandin $F_1\alpha$ and thromboxane B_2 in isolated, buffer-perfused lungs from monocrotaline pyrrole-treated rats. Exp Lung Res 12:195–206, 1987
9. Malmsten C: Some biological effects of prostaglandin endoperoxide analogues. Life Sci 18:169–176, 1976
10. Coleman RA, Humphrey PPA, Kennedy I, Levy GP, Lumley P: Comparison of the actions of U-46619, a prostaglandin H_2-analogue, with those of prostaglandin H_2 and thromboxane A_2 on some isolated smooth muscle preparations. Br J Pharmacol 73:773–778, 1981
11. Shasby DM, Vanbenthuysen KM, Tate RM, Shasby SS, McMurtry I, Repine JE: Granulocytes mediate acute edematous lung injury in rabbits and in isolated rabbit lungs perfused with phorbol myristate acetate: Role of oxygen radicals. Am Rev Respir Dis 125:443–447, 1982
12. Townsley MI, Korthuis RJ, Rippe B, Parker JC, Taylor AE: Validation of double vascular occlusion method for Pc,i in lung and skeletal muscle. J Appl Physiol 61:127–132, 1986
13. Dawson CA, Linehan JH, Rickaby DA: Pulmonary microcirculatory hemodynamics. Ann NY Acad Sci 384:90–106, 1982
14. Linehan JH, Dawson CA, Rickaby DA: Distribution of vascular resistance and compliance in a dog lung lobe. J Appl Physiol 53:158–168, 1982
15. Drake R, Gaar KA, Taylor AE: Estimation of the filtration coefficient of pulmonary exchange vessels. Am J Physiol 234:H266–H274, 1978
16. Winn R, Harlan J, Nadir B, Harker L, Hildebrandt J: Thromboxane A_2 mediates lung vasoconstriction but not permeability after endotoxin. J Clin Invest 72:911–918, 1983
17. Snapper JR, Hutchison AA, Ogletree ML, Brigham KL: Effects of cyclooxygenase inhibitors on the alterations in lung mechanics caused by endotoxemia in the unanesthetized sheep. J Clin Invest 72:63–76, 1983
18. Kubo K, Kobayashi T: Effects of OKY-046, a selective thromboxane synthetase inhibitor, on endotoxin-induced lung injury in unanesthetized sheep. Am Rev Respir Dis 132:494–499, 1985
19. Schumacher WA, Adams HD, Ogletree ML: Effect of the thromboxane A_2-receptor antagonists, SQ 29,548 and SQ 28,668, on the pulmonary hypertensive response to endotoxemia in swine. Pharmacology 34:301–308, 1987
20. Baer ER, Pearl RG, Siegel LC, Rice SA: Longitudinal distribution of pulmonary vascular resistance during endotoxin-induced pulmonary hypertension in sheep. (Abstract) ANESTHESIOLOGY 69:A860, 1988
21. Bradley JD, Roselli RJ, Parker RE, Harris TR: Effects of endotoxemia on the sheep lung microvascular membrane: A two-pore theory. J Appl Physiol 64:2675–2683, 1988
22. Ogletree ML, Brigham KL: Arachidonate raises vascular resistance but not permeability in lungs of awake sheep. J Appl Physiol 48:581–586, 1980
23. Townsley MI, Korthuis RJ, Taylor AE: Effects of arachidonate on permeability and resistance distribution in canine lungs. J Appl Physiol 58:206–210, 1985
24. Littner MR, Lott FD: Edema from cyclooxygenase products of arachidonic acid in isolated lung. J Appl Physiol 67:846–855, 1989
25. Selig WM, Patterson CE, Rhoades RA: Cyclooxygenase metabolites contribute to oleic acid-induced lung edema by a pressure effect. Exp Lung Res 13:69–82, 1987
26. Heffner JE, Shoemaker SA, Canham EM, Patel M, McMurtry IF, Morris HG, Repine JE: Acetyl glyceryl ether phosphorylcholine-stimulated human platelets cause pulmonary hypertension and edema in isolated rabbit lungs: Role of thromboxane A_2. J Clin Invest 71:351–357, 1983
27. Bowers RE, Ellis EF, Brigham KL, Oates JA: Effects of prostaglandin cyclic endoperoxides on the lung circulation of unanesthetized sheep. J Clin Invest 63:131–137, 1979
28. Wakerlin G, Flavin T, Siegel LC, Benson GV, Pearl RC: Pulmonary capillary pressure measurement from pulmonary artery occlusion pressure profile analysis (abstract). ANESTHESIOLOGY 73: A1163, 1990
29. Pearl RG, Siegel LC, Baer ER: Vasodilators and the longitudinal distribution of pulmonary vascular resistance (abstract). ANESTHESIOLOGY 69:A154, 1988

30. Yoshimura K, Tod ML, Pier KG, Rubin LJ: Role of venoconstriction in thromboxane-induced pulmonary hypertension and edema in lambs. J Appl Physiol 66:929–935, 1989
31. Yoshimura K, Tod ML, Pier KG, Rubin LJ: Effects of a thromboxane A_2 analogue and prostacyclin on lung fluid balance in newborn lambs. Circ Res 65:1409–1416, 1989
32. Permutt S: The role of pulmonary arterial pressure in experimentally induced acute lung injury, Acute Respiratory Failure. Edited by Zapol WM, Falke KJ. New York, Marcel Dekker, 1985, pp 227–239
33. Shirley HH Jr., Wolfram CG, Wasserman K, Mayerson HS: Capillary permeability to macromolecules: Stretched pore phenomenon. Am J Physiol 190:189–193, 1957
34. Rippe B, Townsley M, Thigpen J, Parker JC, Korthuis RJ, Taylor AE: Effects of vascular pressure on the pulmonary microvasculature in isolated dog lungs. J Appl Physiol 57:233–239, 1984
35. Nicolaysen G, Waaler BA, Aarseth P: On the existence of stretchable pores in the exchange vessels of the isolated rabbit lung. Lymphology 12:201–207, 1979
36. Albert RK, Lamm WJE, Henderson WR, Bolin RW: Effect of leukotrienes B_4, C_4, and D_4 on segmental pulmonary vascular pressures. J Appl Physiol 66:458–464, 1989
37. Albert RK, Greenberg G, Guest RJ, Luchtel D, Henderson WR: Leukotrienes C_4 and D_4 do not increase filtration coefficient of excised perfused guinea pig lungs. J Appl Physiol 62:1–9, 1987
38. Rippe B, Allison RC, Parker JC, Taylor AE: Effects of histamine, serotonin, and norepinephrine on circulation of dog lungs. J Appl Physiol 57:223–232, 1984
39. Allen SJ, Drake RE, Katz J, Gabel JC, Laine GA: Lowered pulmonary arterial pressure prevents edema after endotoxin in sheep. J Appl Physiol 63:1008–1011, 1987
40. Prewitt RM, McCarthy J, Wood LDH: Treatment of acute low pressure pulmonary edema in dogs. J Clin Invest 67:409–418, 1981
41. Goldstein G, Luce JM: Pharmacologic treatment of the adult respiratory distress syndrome. Clin Chest Med 11:773–787, 1990