Eur Respir J
1988, 1, 297–301

EDITORIAL

Effective pulmonary capillary pressure

F.A. Grimbert

The adult respiratory distress syndrome (ARDS) is almost invariably accompanied by permeability pulmonary oedema, usually appearing in the first few hours [1, 2]. The extent and therefore the seriousness of this oedema is proportional to the filtration of fluid and proteins through the pulmonary vascular endothelium. The extreme sensitivity of this filtration to variations of capillary pressure should lead us to consider any lowering, however small, of the latter as an essential treatment of permeability pulmonary oedema [3, 4].

Permeability pulmonary oedema (resulting from an increase in pulmonary capillary permeability), contrasts with hydrostatic pulmonary oedema (resulting from an increase in hydrostatic pressure). The increase in capillary permeability is difficult to observe; we are therefore led to define permeability pulmonary oedema as an oedema with no increase in hydrostatic pressure. Recently, numerous experimental studies have questioned this dichotomy between hydrostatic and permeability pulmonary oedema. It has been shown in sheep that, in the development of pulmonary oedema, an increase in hydrostatic pressure can be followed by an increase in permeability [5]. Experimental studies on dogs have shown that a large increase in hydrostatic pressure can increase permeability [6]. Other studies have shown an increase in hydrostatic pressure and an increase in permeability to occur simultaneously [7]. Coincidence of an increase in hydrostatic pressure and an increase in permeability seems to be frequent. Does this coexistence within the same experimental or clinical model question the necessity of distinguishing between them? I think not.

Starling's equation

The appropriate treatment varies according to the relative extent of these two physiopathological mechanisms whatever the type of pulmonary oedema. To understand this, we must refer to Starling's equation which describes the relationship between the forces which govern the filtration of fluid from the intravascular to the extravascular compartment, excessive flow resulting in oedema:

$$Qfc \simeq Kfc\ (\Delta P - \sigma\ \Delta\pi)$$

Laboratory of Physiology, Faculté de médecine de Grenoble, 38700 - La Tronche, France.

The capillary filtration rate (Qfc) is a function of the hydrostatic (ΔP) and oncotic ($\Delta\pi$) pressure gradients on either side of the capillary wall, and of the capillary filtration coefficient (Kfc) which is the product of the exchange surface area and the coefficient of hydraulic conductivity. ΔP is the difference between intravascular and interstitial hydrostatic pressures. The intravascular pressure which intervenes in the filtration process in West's zone 3 is the intracapillary pressure [8], except perhaps in the case of microembolisation [9]. As for interstitial pressure, it hardly varies, with just a few exceptions (pulmonary oedema following either a tracheal obstruction [10] or the re-expansion of a collapsed lung). The variations of the term ΔP therefore depend almost wholly upon variations in capillary pressure.

The term $\sigma\ \Delta\pi$ is the product of the difference ($\Delta\pi$) between plasma and interstitial oncotic pressures, by factor σ, which is the protein reflection coefficient of the capillary wall. The importance of σ cannot be overemphasized: in fact, it expresses the protein permeability of the capillary wall. When the latter increases σ drops towards zero resulting in the diminution of $\sigma\ \Delta\pi$. It follows that the capillary lesion will usually either reduce or supress the oncotic counter-pressure. To this may be added an increase in the filtration coefficient Kfc, the whole process making the filtration rate very sensitive to any increase in capillary pressure. In dogs, we have been able to calculate that a rise of 3 mmHg of capillary pressure multiples the filtration rate by a factor of 8 in the areas affected by inhalation of acid, whereas this factor is only 2 in intact areas [11]. The sensitivity of injured lungs to an increase in capillary pressure is confirmed by measurements of lung extravascular water [11, 12].

Capillary pressure and filtration rate

One of the standard methods of testing capillary permeability in experimental models of pulmonary oedema uses this sensitivity of filtration rate to variations in capillary pressure. The method compares the increase in protein filtration for the same increase in capillary pressure in intact and injured lungs. In certain protocols where the maximum protein filtration rate is approached [7, 11, 13–15], the increases in protein clearance are compared. The interpretation of

the protein clearance increases is not unequivocal and has recently been discussed in some general reviews [16, 17], regarding their meaning: an increase in capillary permeability and/or capillary exchange surface area. However, if the increase in capillary pressure allows maximum protein filtration rate to be reached, it should be possible to calculate σ directly [17, 18]. This technique has been used in certain experimental protocols [19, 20] and is presently the method of choice for measurement of capillary protein permeability. It is worth noting that the increases in capillary pressure also cause gravimetric variations of the lung from which Kfc can be measured [21, 22]. In man, clearance of plasma albumin into alveolar fluid (sampled by bronchoalveolar lavage) has been estimated in hydrostatic or permeability pulmonary oedemas by Sibbald *et al.* These authors have shown that protein clearance increases proportionally to pulmonary capillary pressure. The slope of the albumin clearance/capillary pressure relationship is fourteen times greater in a patient affected by ARDS than in one with hydrostatic pulmonary oedema [23].

An increase in pulmonary capillary permeability is more often than not secondary to inflammatory phenomena. It is difficult to judge the right moment for anti-inflammatory treatment, given the frequency of superinfections in these patients [24] and the absence of satisfactory methods of measuring permeability in man. On the other hand, an increase in capillary pressure is easier to measure and correct; above all, lowering the pressure is always effective, whether or not permeability is increased. The beneficial effect of lowering pulmonary capillary pressure has been demonstrated in experimental studies using several models of permeability oedema, either after injections of pseudomonas [25], endotoxin [26, 27], gaseous emboli [28], oleic acid [29–32], or inhalation of acid [33–37]. Arguments in favour of a time-limited depletive therapy have been provided by a recent experimental study where a temporary lowering of hydrostatic pressure allowed the stabilization of a permeability oedema resulting from an injection of oleic acid [38].

Definition of effective pulmonary pressure

Having established the importance of pulmonary capillary pressure, how can it be measured at the patients' bedside? Permeability oedema is often accompanied by an increase in pulmonary arterial pressure, whilst pulmonary venous pressure hardly changes; which means for an identical pulmonary blood flow an increase in pulmonary vascular resistance. The distribution of this increase in vascular resistance determines the value of capillary pressure. If the increase in vascular resistance occurs on the arterial side, capillary pressure does not change. Conversely, if it occurs on the venous side, capillary pressure approaches the value of pulmonary arterial pressure. In either case, capillary filtration pressure cannot be estimated by pulmonary capillary wedge pressure obtained after inflation of the balloon of a Swan-Ganz catheter. This is due to the fact that the balloon interrupts the blood flow in one pulmonary segment and suppresses any pressure difference through that segment. Pulmonary capillary wedge pressure measured by the catheter below the balloon is the pressure found in the pulmonary veins if the end of the catheter is situated in zone 3; it should ideally correspond to the end-diastolic pressure in the left ventricle. Capillary wedge pressure thus depends on the left ventricular end-diastolic pressure but is not capillary filtration pressure. In order to avoid semantic confusion between pulmonary capillary wedge pressure and pulmonary capillary filtration pressure, the name *effective pulmonary capillary pressure* [39] has been suggested and we shall use it from now on.

Measurement

Since *effective pulmonary capillary pressure* is not the same as pulmonary capillary wedge pressure, how can it be measured? Measurement may be obtained experimentally using various techniques. A direct measurement may be performed by micropuncture of sub-pleural capillaries of isolated perfused lungs [40], or by catheters introduced into pulmonary arteries and veins of small diameter [41]. An indirect technique, known as the isogravimetric method using isolated perfused lungs, measures pressure in vessels where filtration takes place [42]. If pulmonary arterial pressure is increased in stages, while pulmonary venous pressure is simultaneously reduced, without allowing the weight of the lungs (or their fluid content) to change, straight lines can be drawn between arterial and venous pressures at each stage. Their intersection is at the level of *effective capillary pressure.* Gaar's equation, obtained from the measurement of isogravimetric pressure in normal lung, evaluates venous resistance as about 40% of total resistance. Normal *effective capillary pressure* can then be calculated as venous pressure plus 40% of the arterio-venous pressure gradient.

Another method for measuring capillary pressure has been developed recently [43]. It uses an analysis of pulmonary arterial and venous occlusion pressure profiles and has made possible the study of longitudinal distribution of compliance and resistance in the pulmonary circulation. Pulmonary vascular compliance is mostly distributed in the median or capillary compartment and pulmonary vascular resistance is mostly, but not exclusively, distributed on either side of the capillary compartment *i.e.* in arterial and venous compartments. Used firstly in isolated perfused canine lungs [8, 43–45], the technique of analysis of arterial and venous occlusion pressure profiles was later applied, to canine lungs *in situ*, by means of a Swan-Ganz balloon catheter [39]. Measurements in intensive care patients rapidly followed [46–48], using pulmonary arterial occlusion pressure profile analysis, which is easier to obtain.

The course of the pulmonary arterial pressure curve after occlusion with a Swan-Ganz catheter balloon is characteristic. Immediately after occlusion, the curve de-

creases according to a first exponential whose slope is steep enough to be confused with a straight line. This profile reveals the rapid emptying of the uncompliant arterial compartment through the pulmonary vascular resistance. The curve then changes into a second exponential whose slope is less steep, until it reaches the level of pulmonary capillary wedge pressure. This second exponential reveals the slow emptying of the capillary compartment which is very compliant, through the venous resistance. For each of these compartments, the initial slope of the drop in pressure (dP/dt) is inversely proportional to their time constant, *i.e.* to the product (R·C) of their resitance and compliance. Once the initial slope and the amplitude of the drop in pressure in each of these compartments are known, compliance and resistance can be calculated. Capillary pressure is the pressure existing in the capillary compartment immediately before it empties, and can be estimated either by extrapolating the second exponential at the moment of occlusion, or by identifying the inflexion point of the arterial occlusion curve (after filtering) corresponding to the pressure level where the curve profile changes from a quasilinear appearance to that of an exponential. HOLLOWAY's study on lungs *in situ* [39] showed the existence of a good correlation between these two methods of measurement, namely extrapolation at the moment of occlusion and identification of the point of inflexion. The first method is more precise, but in practice necessitates computerized processing of the signal. The second can be carried out with no more than a graphic recorder.

Does this so-called capillary pressure, obtained from arterial occlusion pressure profiles, represent *effective capillary filtration pressure?* Studies carried out on isolated perfused canine lungs show that the point of inflexion of the arterial occlusion pressure profile overestimates to a greater or lesser extent *effective capillary pressure* measured by the isogravimetric method as a reference [49]. The overestimation is proportional to capillary compartment resistance, which increases with pulmonary alveolar volume [50, 51], hypoxia [52, 53], haematocrit [54] and permeability oedema caused by a toxic, alpha-naphthylthiourea [55]. Conversely, pressure increases in the pulmonary circulation, whether caused by a rise in blood flow [43, 56], venous pressure [43] or a simultaneous rise in arterial and venous pressures [49], cause a relative drop in capillary resistance, resulting in a better evaluation of *effective capillary pressure* from the arterial occlusion pressure profile.

As for measurements *in vivo*, they can only be compared to values calculated in intact lungs according to Gaar's equation [42]. The only isogravimetric measurements *in vivo* available are those of GABEL and DRAKE [57] and give values which hardly differ from those obtained using Gaar's equation. However, it must be remembered that experimental data concerning the validity of Gaar's equation applied to hydrostatic or permeability oedema are still sparse. In isolated perfused lungs [55, 58] or lungs *in situ* [57], hydrostatic oedema results in few modifications of the arterial or venous partition of pulmonary vascular resistance. This does not apply to permeability pulmonary oedema. According to experimental models, the venous resistance/total resistance ratio, and therefore *effective capillary pressure*, can either increase, as it does after an injection of oleic acid or endotoxin [59, 60]; remain unchanged, as after an injection of alpha-napthylthiourea [55], or diminish, as after microembolisation [61]. Thus, there is a clear need for studies showing a comparison between several different methods of estimating *effective capillary pressure* in various experimental models of permeability oedema.

For canine lungs *in situ*, there is good correlation between capillary pressure estimated by the inflexion point of the arterial occlusion pressure profile and that calculated by Gaar's equation [39, 62]. In man, in the immediate post-operative period following major surgery, measured capillary pressure is slightly lower than that calculated by Gaar's equation [47, 48]. In ARDS, where pressures existing in the pulmonary circulation are high, measured values are practically identical with those calculated from Gaar's equation [46, 48]. It is noteworthy that in ARDS pulmonary capillary wedge pressure can underestimate *effective capillary pressure* by at least 10 mmHg [46, 48], whether the latter is measured or calculated.

The method of measurement of *effective capillary pressure* by arterial occlusion pressure profile has a number of limitations. Some are inherent in the principle of the method: as seen above, a large increase in capillary resistance [50–55] results in an overestimation of *effective pulmonary capillary pressure*. Permeability oedemas are sometimes distributed very irregularly, and one cannot extrapolate one segmental measure to the whole lung.

There are also practical limitations: 1) it is sometimes impossible to measure occlusion pressure above a pulmonary embolism [63]; 2) the occlusion has to be made between two respiratory excursions [64] but in practice this is not always possible; 3) occlusion by the balloon can occur during the systolic or diastolic phase of the pulmonary arterial pressure curve thus resulting in variability of the estimated *effective capillary pressure*; 4) finally, important modifications of arterial or capillary resistance and compliance and the appearance of a resistance between the pulmonary veins and the left atrium can interfere with the processing of the pressure signal.

Clinical application

What is the clinical application of the measurement of *effective capillary pressure?* It is essential to measure *effective capillary pressure* in cases where there is a considerable difference between pulmonary arterial and venous pressure since the effects of a possible change in the venous resistance/total resistance ratio are then amplified. This occurs in a number of hydrostatic pulmonary oedemas. Similarly, during the phase of permeability oedema in ARDS, there is not only a considerable arterio-venous pressure gradient but also extreme sensitivity of capillary filtration to

variations in capillary pressure. Permeability pulmonary oedema in both its diagnosis and treatment, appears to be one of the fields in which the measurement of *effective capillary pressure* has been shown to be most useful.

According to our study [48], therapeutic techniques currently applied in intensive care can modify the venous resistance/total resistance ratio and hence *effective capillary pressure* both in the post-operative period and durings ARDS. These observations confirm that it is possible to modify the longitudinal distribution of pulmonary vascular resistance and therefore of *effective capillary pressure* by drugs [65]. COPE *et al.* [47] have shown in canine lungs *in situ* that perfusion of serotonin lowers the venous resistance/total resistance ratio from 34 to 21%, resulting in an increase of 1 mmHg in effective capillary pressure whilst pulmonary arterial pressure rises by 7 mmHg. In the same experimental conditions, histamine brings about a rise of 2 mmHg in pulmonary arterial pressure but *effective capillary pressure* increases by 3 mmHg as the venous resistance/total resistance ratio rises from 34 to 40%. Serotonin and histamine, like arachidonic acid, are among those vasoactive substances whose involvement in the inflammatory process of ARDS has been suggested [66–69]. These examples are cases where the calculation of *effective capillary pressure* by Gaar's equation is invalid. These observations confirm the importance of developing an on line treatment of the arterial occlusion pressure signal, allowing clinicians to measure *effective pulmonary capillary pressure* rapidly and to evaluate the effects of therapy during the critical phase of permeability oedema in ARDS.

The measurement of *effective pulmonary capillary pressure* in ARDS has so many advantages over that of pulmonary capillary wedge pressure or even its estimation by Gaar's equation that it should be made despite the limitations described above.

In all conditions *effective pulmonary capillary pressure* is the determining factor in pulmonary capillary filtration. Its increase is the first cause of hydrostatic pulmonary oedema [70] and considerably accentuates permeability oedema. The lowering of *effective pulmonary capillary pressure*, as a recent editorial pointed out [16], remains the cornerstone of any treatment for pulmonary oedema, including permeability pulmonary oedema. The dangers to the systemic circulation resulting from treatments designed to lower pulmonary capillay pressure (water restriction, diuretics, vasodilators, etc...) can be lessened if these are administered only during the phase, sometimes very brief, when permeability oedema is predominant in ARDS.

Acknowledgements: I wish to thank P. Baconnier, G. Benchetrit, D. Martin, C. Perret for their help in preparing this editorial.

References

1. Andreadis N, Petty TL. – Adult respiratory distress syndrome: problems and progress. *Am Rev Respir Dis*, 1985, 132, 1344–1348.
2. Lemaire F, Matamis D, Lange F. – Description du syndrome de détresse respiratoire aigüe de l'adulte. In: Le syndrome de détresse respiratoire aigüe de l'adulte. F. Lemaire ed., Masson, Paris, 1984, pp. 53-68.
3. Molloy DW, Ducas J, Dobson K, Girling L, Prewitt RM. – Hemodynamic management in clinical acute hypoxemic respiratory failure: dopamine *vs* dobutamine. *Chest*, 1986, 89, 636–640.
4. Wood LDH, Prewitt RM. – Cardiovascular management in acute hypoxemic respiratory failure. *Am J Cardiol*, 1981, 47, 963–972.
5. Brigham KL, Woolverton WC, Blake LH, Staub NC. – Increased sheep lung vascular permeability caused by pseudomonas bacteremia. *J Clin Invest*, 1974, 54, 792–804.
6. 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: Respirat Environ Exercise Physiol*, 1984, 57, 233–239.
7. Martin DJ, Baconnier P, Benchetrit G, Royer F, Grimbert FA. – Effect of acute hypoxia on lung fluid balance in the prerecruited dog lung. *Bull Eur Physiopathol Respir*, 1986, 22, 335–340.
8. Parker JC, Kvietys PR, Ryan KP, Taylor AE. – Comparison of isogravimetric and venous occlusion capillary pressures in isolated dog lungs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 55, 964–968.
9. Staub NC, Schultz EL, Albertine KH. – Leucocytes and pulmonary vascular injury. *Ann NY Acad Sci*, 1982, 384, 332–343.
10. Loyd JE, Nolop KB, Parker RE, Roselli RJ, Brigham KL. – Effects of inspiratory resistance loading on lung fluid balance in awake sheep. *J Appl Physiol* , 1986, 60, 198–203.
11. Grimbert FA, Parker JC, Taylor AE. – Increased lung microvascular permeability following acid aspiration. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1981, 51, 335–345.
12. Huchon GJ, Hopewell PC, Murray JF. – Interactions between permeability and hydrostatic pressure in perfused dogs' lungs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1981, 50, 905–911.
13. Bernard GR, Snapper JR, Hutchinson AA, Brigham KL. – Effects of left atrial pressure elevation and histamine infusion on lung lymph in awake sheep. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1984, 56, 1083–1089.
14. Jones TA, Townsley MI, Weidner WJ. – Effects of intracranial and left atrial hypertension on lung fluid balance in sheep. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 52, 1324–1329.
15. Landolt CC, Matthay MA, Albertine KH, Roos PJ, Wiener-Kronish JP, Staub NC. – Overperfusion, hypoxia and increased pressure cause only hyrostatic pulmonary edema in anesthetized sheep. *Circ Res*, 1983, 52, 335–341.
16. Staub NC. – The hemodynamics of pulmonary edema. *Bull Eur Physiopathol Respir*, 1986, 22, 319–322.
17. Taylor AE, Granger DN. – Exchange of macromolecules across the microcirculation. *In*: Handbook of Physiology - The cardiovascular system IV. E.M. Renkin and C.C. Michel eds., Am Physiol Soc, Bethesda, MD. 1985, pp. 467–520.
18. Parker JC, Parker RE, Granger DN, Taylor AE. – Vascular permeability and transvascular fluid and protein transport in the dog lung. *Circ Res*, 1981, 48, 549–561.
19. Gabel JC, Butler BD, Scott RL, Drake RE. – Pulmonary microvascular permeability after coronary arterial ligation in dogs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 55, 866–869.
20. Rutili G, Kvietys P, Martin D, Parker JC, Taylor AE. – Increased pulmonary microvascular permeability induced by alpha-naphthylthiourea. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 52, 1316–1323.
21. Drake R, Gaar KA, Taylor AE. — Estimation of the filtration coefficient of pulmonary exchange vessels. *Am J Physiol*, 1978, 234, H266–H274.
22. Drake RE, Gabel JC. – Effect of histamine and alloxan on canine pulmonary vascular permeability. *Am J Physiol*, 1980, 239, H96–H100.
23. Sibbald WJ, Dreidger AA, Wells GA. – The synergistic influence of the intravascular Starling forces on pulmonary microvascular solute flux in human ARDS. *J Surg Res*, 37, 123–132.
24. Hyers TM, Fowler AA. – Adult respiratory distress syndrome: causes, morbidity and mortality. *Fed Proc*, 1986, 45, 25–29.

25. Foy T, Marion J, Brigham KL, Harris TR. – Isoproterenol and aminophylline reduce lung capillary filtration during high permeability. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1979, 46, 141–151.
26. Allen S, Laine G, Drake R, Gabel J. – Reduction of pulmonary artery pressure and systemic venous pressure decreases pulmonary edema formation in endotoxinemia. *Fed Proc*, 1986, 45, 283.
27. Ogletree ML, Brigham KL. – PGE 1 reduces lung transvascular filtration during endotoxin-induced high permeability in sheep. *Clin Res*, 1979, 27, 402A.
28. Culver PL, Rao WH, Dodek P, Roos P, Staub NC. – Effect of beta-receptor stimulation on lung fluid balance during air emboli in awake sheep. *Fed Proc*, 1983, 42, 1271.
29. Ali J, Chemicki W, Wood LDH. – Effect of furosemide in canine low-pressure pulmonary edema. *J Clin Invest*, 1979, 64, 1494–1504.
30. Dauber IM, Weil JV. — Lung injury edema in dogs: influence of sympathetic ablation. *J Clin Invest*, 1983, 72, 1977–1986.
31. Molloy WE, Lee KY, Girling L, Prewitt RM. – Treatment of canine permeability pulmonary edema: short-term effects of dobutamine, furosemide, and hydralazine. *Circulation*, 1985, 72, 1365–1371.
32. Prewit RM, McCarthy J, Wood LDH. – Treatment of acute low pressure pulmonary edema in dogs: relative effects of hydrostatic and oncotic pressure nitroprusside, and positive end-expiratory pressure. *J Clin Invest*, 1981, 67, 409–418.
33. Broe PJ, Toung TJK, Permutt S, Cameron JL. – Aspiration pneumonia: treatment with pulmonary vasodilators. *Surgery*, 1983, 94, 95–99.
34. Gottlieb SS, Hansen DH, Wood LDH, Long GR. – The effect of nitroprusside on edema and O_2 delivery (QO_2) in canine hydrochloric acid (HCl) aspiration. *Am Rev Respir Dis*, 1984, 129, A94.
35. Mizus I, Summer W, Farrukh I, Micheal JR, Gurtner GH. – Isoproterenol or aminophylline attenuate pulmonary edema after acid lung injury. *Am Rev Respir Dis*, 1985, 131, 256–259.
36. Sznajder JI, Zucker AR, Wood LDH, Long GR. – The effects of plasmapheresis and hemofiltration on canine acid aspiration pulmonary edema. *Am Rev Respir Dis*, 1986, 134, 222–228.
37. Utsunomiya T, Krausz MM, Dunham B, Valeri CR, Levine L, Shepro D, Hechtman HB. – Modification of inflammatory response to aspiration with ibuprofen. *Am J Physiol*, 1982, 243, H903–H910.
38. Oppenheimer L. – Manipulation of tissue forces in treating the adult respiratory distress syndrome. *Can J Surg*, 1985, 28, 326–328.
39. Hooloway H, Perry M, Downey J, Parker J, Taylor A. – Estimation of effective pulmonary capillary pressure in intact lungs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 54, 846–851.
40. Bhattacharya J, Staub NC. – Direct measurement of microvascular pressures in the isolated perfused dog lung. *Science*, 1980, 210, 327–328.
41. Michel RP, Hakim TS, Chang HK. – Pulmonary arterial and venous pressure measured with small catheters in dogs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1984, 57, 309–314.
42. Gaar KA Jr, Taylor AE, Owens LJ, Guyton AC. – Pulmonary capillary pressure and filtration coefficient in the isolated perfused lung. *Am J Physiol*, 1967, 213, 910–914.
43. Hakim TS, Michel RP, Chang KH. – Partitioning of pulmonary vascular resistance in dogs by arterial and venous occlusion. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 52, 710–715.
44. Hakim TS, Dawson CA, Linehan JH. – Hemodynamic responses of dog lung lobe to lobar venous occlusion. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1979, 47, 145–152.
45. Linehan JH, Dawson CA, Rickaby DA. – Distribution of vascular resistance and compliance in a dog lung lobe. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 53, 156–168.
46. Collee GG, Lynch KE, Hill RD, Zapol WM. – Bedside measurement of pulmonary capillary pressure in patients with acute respiratory failure. *Anesthesiology*, 1987, 66, 614–620.
47. Cope DK, Allison RC, Parmentier JL, Miller JN, Taylor AE. – Measurement of effective pulmonary capillary pressure using the pressure profile after pulmonary artery occlusion. *Crit Care Med*, 1986, 14, 16–22.
48. Royer F, Anglade D, Peyrin JC, Gelas P, Martin D, Grimbert F. – Estimation of effective pulmonary capillary pressure (EPCP) in intensive care patients. *Bull Eur Physiopathol Respir*, 1986, 22, 92S.
49. Rippe B, Parker JC, Townsley M, Mortillaro NA, Taylor AE. – Segmental vascular resistances and compliances in the dog lung. *J Appl Physiol*, 1987, 62, 1206–1215.
50. Hakim TS, Michel RP, Chang KH. – Effect of lung inflation on pulmonary vascular resistance in dogs by arterial and venous occlusion. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 53, 1110–1115.
51. Hakim TS, Chang HK, Michel RP. – The rectilinear pressure-flow relationship in the pulmonary vasculature: zone 2 and 3. *Respir Physiol*, 1985, 61, 115–123.
52. Hakim TS, Michel RP, Chang KH. – Site of pulmonary hypoxic vasoconstriction studied with arterial and venous occlusion. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 54, 1298–1302.
53. Rock P, Patterson GA, Permutt S, Sylvester JT. – Nature and distribution of vascular resistance in hypoxic pig lungs. *J Appl Physiol*, 1985, 59, 1891–1901.
54. Julien M, Hakim TS, Vahi R, Chang KH. – Effect of hematocrit on vascular pressure profile in dog lungs. *J Appl Physiol*, 1985, 58, 743–748.
55. Wang CG, Hakim TS, Michel RP, Chang HK. – Segmental pulmonary vascular resistance in progressive hydrostatic and permeability edema. *J Appl Physiol*, 1985, 59, 242–247.
56. Shepard JM, Gropper MA, Bhattacharya J. – Effect of blood flow on segmental pulmonary vascular resistance determined by micropunture. *Fed Proc*, 1986, 45, 556.
57. Gabel JC, Drake RE. – Pulmonary capillary pressure in intact dog lungs. *Am J Physiol*, 1978, 235, H569–H573.
58. Raj JU, Bland RD, Lai-Fook SJ. – Microvascular pressures measured by micropipettes in isolated edematous rabbit lungs. *J Appl Physiol*, 1986, 60, 539–545.
59. D'Orio V, Halleux J, Rodriguez LM, Wahlen C, Marcelle R. – Effects of *Escherichia coli* endotoxin on pulmonary vascular resistance in dog. *Crit Care Med*, 1986, 14, 802–806.
60. Hofman WF, Ehrhart IC. – Methylprednisolone prevents venous resistance increase in oleic acid injury. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 54, 926–933.
61. Ehrhart IC, Granger WM, Hofman WF. - Effect of arterial pressure and edema after microembolism. *J Appl Physiol*, 1986, 60, 133–140.
62. Grimbert F-A, Martin DJ, Parker JC, Taylor AE. – Pulmonary blood flow *vs* microvascular pressure effects on lung lymph flow in dogs. Submitted for publication.
63. Traeger SM. – "Failure to wedge" and pulmonary hypertension during pulmonary catheterization: a sign of totally occlusive pulmonary embolism. *Crit Care Med*, 1985, 13, 544–547.
64. Schuster DP, Seeman MD. – Temporary muscle paralysis for accurate measurement of pulmonary artery occlusion pressure. *Chest*, 1983, 84, 593–597.
65. Dawson CA. – Role of pulmonary vasomotion in physiology of the lung. *Physiol Rev*, 1984, 64, 544-616.
66. Bernard GR, Brigham KL. – The adult respiratory distress syndrome. *Ann Rev Med*, 1985, 36, 195–205.
67. Lindenschmidt RC, Selig WM, Patterson CE, Verburg KM, Henry DP, Forney RB, Rhoades RA. – Histamine action in paraquat-induced lung injury. *Am Rev Respir Dis*, 1986, 133, 274-278.
68. Selig WM, Patterson CE, Henry DP, Rhoades RA. – Role of histamine in acute oleic acid-induced lung injury. *J Appl Physiol*: Respirat Environ Exercise Physiol, 1986, 61, 233-239.
69. Townsley MI, Korhuis RJ, Taylor AE. – Effects of arachidonate on permeability and resistance distribution in canine lungs. *J Appl Physiol*, 1985, 58, 206–210.
70. Guyton AC, Lindsey AW. – Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ Res*, 1959, 7, 649–657.