Effective pulmonary capillary pressure

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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:

\[ Q_{fc} = K_{fc} (\Delta P - \sigma \Delta \pi) \]

The capillary filtration rate (Qfc) is a function of the hydrostatic (\(\Delta P\)) 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. \(\Delta P\) 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 \(\Delta P\) 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 \(\sigma\), which is the protein reflection coefficient of the capillary wall. The importance of \(\sigma\) cannot be overemphasized: in fact, it expresses the protein permeability of the capillary wall. When the latter increases \(\sigma\) drops towards zero resulting in the diminution of \(\sigma \Delta \pi\). It follows that the capillary lesion will usually either reduce or suppress 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 multiplies 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 a 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 Kf 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 Sarhald 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 (RC) of their resistance 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-naphthylthioleurea [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-naphthylthioleurea [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 during 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]. COPi 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 capillary 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.

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References

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