

SERIES 'HIGHLIGHTS ON PULMONARY HYPERTENSION'

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Medical treatment of pulmonary hypertension in acute lung disease

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ABSTRACT: A moderate pulmonary hypertension is a hallmark of experimental, as well as clinical, acute lung injury. Pulmonary hypertension in acute lung injury, appears to be caused primarily by a partially reversible increase in extra-alveolar vascular closing pressure, the latter being modulated by vasodilating products of the cyclooxygenase pathway of arachidonic acid metabolism, as well as by an endogenous release of nitric oxide. Gas exchange in acute lung injury is improved by increased pulmonary vascular tone. However it is also improved by inhaled nitric oxide, which increases perfusion to the better aerated lung areas. Whether pharmacological interventions aimed at the prevention of right ventricular failure in acute lung injury improve right ventriculo-vascular coupling sufficiently to exert a favourable influence on outcome, remains to be shown.

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"En un mot, la physiologie doit être constamment appliquée à la médecine pour comprendre et expliquer le mécanisme des maladies et l'action des agents médicamenteux" (Claude Bernard, *Introduction à l'Etude de la Médecine Expérimentale*, 1866).

In 1967, ASHBAUGH *et al.* [1] reported on 12 previously healthy patients, who developed, in the course of other severe medical problems, dyspnoea, tachypnoea, cyanosis refractory to oxygen therapy, loss of lung compliance and diffuse alveolar infiltration on chest X-ray. The associated illnesses were major trauma, pancreatitis, drug overdose and suspected viral pneumonia. Positive end-expiratory pressure (PEEP) was found to be helpful in combating atelectasis and hypoxaemia. The authors speculated that this acute respiratory distress would be the adult counterpart of the infant respiratory distress syndrome, known to be caused by defective surfactant synthesis. This assumption (which was later proved to be erroneous) definitely coined the term "adult respiratory distress syndrome" (ARDS).

ASHBAUGH *et al.* [1] recognized that cases of "ARDS" had been reported previously, in association with shock states, fat embolism, epidemics of severe influenza, and inhalation of high concentrations of oxygen for prolonged periods. In fact, many descriptions of "ARDS", in the sense of a severe pulmonary oedema apparently caused by an increased capillary permeability, are to be found in the chronicles of major military conflicts, including reports on the "wet lung of trauma" and pulmonary oedema after phosgene inhalation during World War I. A review of this older literature by CAMERON [2], in 1948, did not mention pulmonary hypertension to be characteristic of high permeability pulmonary oedema. Clinical and experimental observations of pulmonary hypertension complicating endotoxaemia and extra-thoracic sepsis were published in the years 1950-1960 [3, 4]. With the rapidly expanding use of flow-directed pulmonary artery catheters, after the report by SWAN *et al.*

[5] in 1970, clinicians learned the routine differential diagnosis between "permeability oedema" and "hydrostatic oedema" [6], without realizing, however, that there was more involved than just a normal or an abnormal pulmonary artery occluded pressure (Ppo). In 1977, ZAPOL and SNIDER [7] demonstrated that pulmonary hypertension is a physiological hallmark of ARDS, as also are increased pulmonary shunt or decreased pulmonary compliance.

Pulmonary hypertension in patients with ARDS

In over 100 patients with ARDS, studied between 1-30 days after the onset of symptoms, whilst mechanically-ventilated with 5-40 cmH₂O PEEP, ZAPOL and co-workers [8] observed mean pulmonary arterial pressure (Ppa) to be around 22-28 mmHg in the absence of severe hypoxaemia, but higher, in the range of 28-35 mmHg or more, in severe hypoxaemia. The highest Ppa were seen in patients with the most advanced ARDS and clinical signs of right heart failure. These observations have been repeatedly confirmed by others, and suggest that a diagnosis of ARDS would be very unlikely in patients with a Ppa <20 mmHg and a cardiac index (\dot{Q}) above 2.5 l·min⁻¹·m⁻².

ZAPOL and co-workers described pulmonary haemodynamics in ARDS by pulmonary vascular resistance (PVR) calculations, and by Ppa *versus* \dot{Q} plots or PVR *versus* \dot{Q} plots. In addition to constantly elevated PVR or Ppa at given levels of \dot{Q} , they found an apparent independence of Ppa and \dot{Q} , contrasting with a hyperbolic decrease in PVR with increasing \dot{Q} (fig. 1). This striking behaviour of the pulmonary circulation in ARDS was evident when data from a large group of patients were pooled, as well as when data were obtained from individual patients in whom pulmonary blood flow was altered, either by vasoactive drugs or by a change in bypass flow during extracorporeal membrane oxygenation (ECMO) studies (fig. 2) [9].

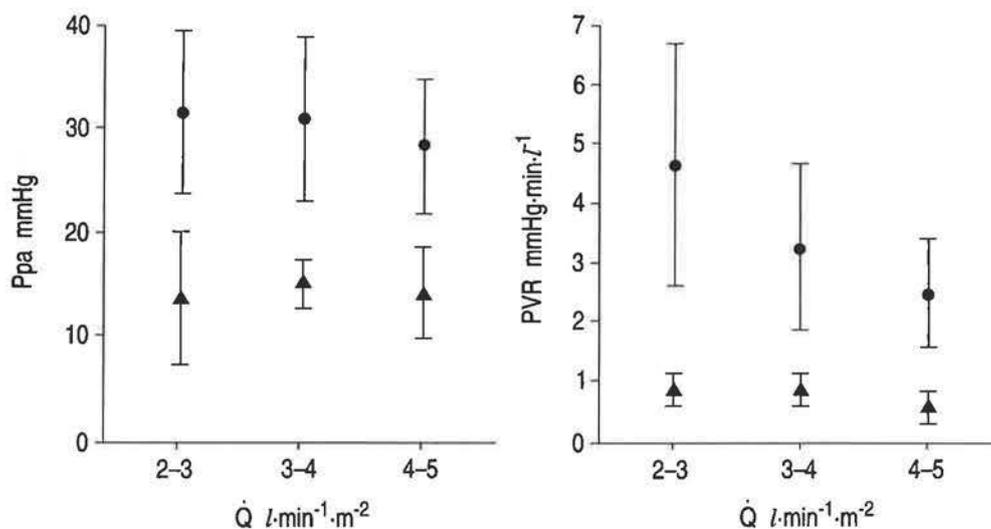


Fig. 1. — Mean \pm SD values of mean pulmonary artery pressure (Ppa) and pulmonary vascular resistance (PVR) as a function of cardiac index (\dot{Q}) for 30 patients with adult respiratory distress syndrome (ARDS), and for 33 normal controls. \bullet : ARDS patients; \blacktriangle : normals. (After reference [8]).

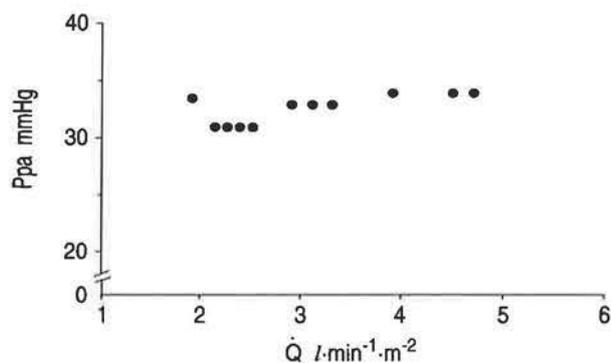


Fig. 2. — Absence of significant changes in mean pulmonary artery pressure (Ppa) in a patient with ARDS whose pulmonary blood flow (\dot{Q}) was altered by changes in bypass flow during extracorporeal membrane oxygenation and in infusion of isoprenaline. \dot{Q} : cardiac index. (After reference [9]).

A proposed explanation for these Ppa/\dot{Q} and PVR/\dot{Q} relationships was that pulmonary hypertension in ARDS would, in the main, be accounted for by an increased pulmonary vascular closing pressure [8, 9].

Pulmonary vascular pressure/flow relationships

In pulmonary haemodynamic studies, PVR, calculated classically as $(Ppa - Ppo)/\dot{Q}$ is usually taken either as an index of the forces that oppose flow in the pulmonary circulation, or as an index of the pulmonary arteriolar cross-sectional area. In clinical practice, pulmonary haemodynamic measurements are performed using Swan Ganz flow-directed, fluid-filled thermodilution catheters, which means that, because of an inherent methodological limitation, only valid numbers for mean Ppa and for mean \dot{Q} can be obtained. The calculation of PVR, thus, ignores the natural pulsatility of the pulmonary circulation. It has been shown that such a steady-flow haemodynamic approach underestimates the dynamic afterload of the right ventricle by 30–50% in normal subjects, and possibly by more in patients with pulmonary hypertension [10]. However, PVR

can be acceptable for the estimation of pulmonary arteriolar tone, by a transposition of Poiseuille's law to the pulmonary circulation, provided two major assumptions are taken into consideration. The first is that Ppa/\dot{Q} or $(Ppa - Ppo)/\dot{Q}$ plots are described by a linear approximation. The second is that the extrapolation of $(Ppa - Ppo)/\dot{Q}$ plots crosses the origin.

Pulmonary vascular pressure *versus* flow plots have been found to be well-described by a linear approximation over a physiological range of flows in healthy, as well as in diseased, lungs, *in vivo* as well as *in vitro*. In healthy well-oxygenated lungs perfused in zone 3, the extrapolation of a $(Ppa - Ppo)/\dot{Q}$ plot crosses the origin. However, when lungs are perfused in zone 2, hypoxic, or diseased, the extrapolated pressure intercept of $(Ppa - Ppo)/\dot{Q}$ plots may become positive. This means that pulmonary blood flow stops when the inflow pressure (Ppa) becomes equal to or lower than a closing pressure higher than left atrial pressure (estimated by Ppo). In these situations, Ppo becomes an apparent outflow pressure of the pulmonary circulation, of which the effective outflow pressure is pulmonary vascular closing pressure, and PVR is no more a constant number independent of the absolute levels of Ppa or of \dot{Q} . Because blood vessels are collapsible and have tone, most vascular systems present with a closing pressure higher than their venous pressure. As the flow of a waterfall is unaffected by its height, the flow within a vascular system is unaffected by changes in its apparent venous outflow pressure as long as the latter remains lower than its closing pressure [11].

An important consequence of the presence of an increased closing pressure within the pulmonary circulation is that Ppa/\dot{Q} plots are curvilinear, with a convexity to the pressure axis at low flows. The pulmonary circulation is then derecruited because of collapse of the vessels with the highest closing pressure. At higher flows, all of the pulmonary vessels are recruited, and an estimation of mean closing pressure can be obtained by the extrapolation of the linear portion of the Ppa/\dot{Q} plots. When the extrapolation of the linear portion of $(Ppa - Ppo)/\dot{Q}$ curves does not cross the origin, PVR calculations are misleading, as

illustrated in figure 3. The more the linear portion of a $(P_{pa} - P_{po})/\dot{Q}$ curve is parallel to the flow axis, the more PVR passively decreases with the slightest increases in \dot{Q} . Thus, when pulmonary hypertension is due to an increased closing pressure, PVR should not be calculated, and the functional state of the pulmonary circulation is better described by multipoint pulmonary vascular pressure *versus* flow curves.

Two methods can be used to show the presence of a closing pressure higher than the apparent outflow pressure within a vascular system [12]. The first is to measure vascular pressures at several levels of flow, preferably with the apparent outflow pressure kept low and constant, and to extrapolate the linear part of the pressure/flow curves obtained to the pressure axis. The linear part of these pressure/flow curves can be described by a slope, which is taken as the incremental PVR upstream to the site of

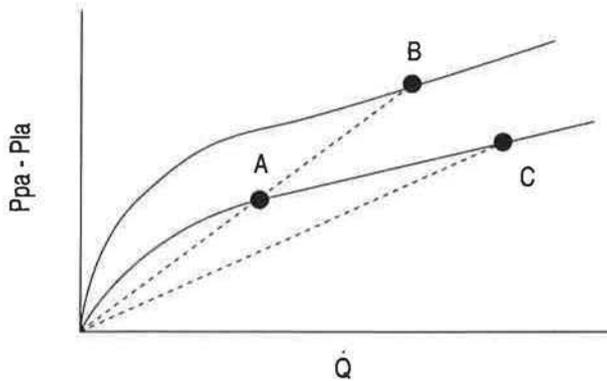


Fig. 3. - Misleading pulmonary vascular resistance (PVR) calculations shown on hypothetical mean pulmonary artery pressure (Ppa) minus left atrial pressure (Pla) *versus* pulmonary blood flow (\dot{Q}) plots, at two levels of pulmonary hypertension. A passive increase in Ppa due to an increase in \dot{Q} (from points A to C) is associated with a decrease in PVR, or slope of the dotted $(P_{pa} - P_{la})/\dot{Q}$ lines. An active pulmonary vasoconstriction (from points A to B) is associated with an unchanged PVR.

vascular closure, and by an extrapolated pressure intercept, which is taken as the mean closing pressure of the pulmonary vessels. The second is to increase the apparent outflow pressure with flow kept constant, and to record the level at which this manoeuvre results in an increase in the inflow pressure. Both methods are obviously technically difficult and would also be unethical in patients, necessitating investigation of experimental models of ARDS.

Pulmonary hypertension in experimental ARDS

We investigated the pulmonary circulation in anaesthetized dogs with oleic acid lung injury [13]. Oleic acid administration in dogs has been shown to induce a multifocal haemorrhagic pulmonary oedema, which bears close pathological and physiological similarities to the early stages of clinical ARDS [14].

In a first series of experiments, we manipulated venous return, which was either decreased by stepwise inflations of a balloon in the inferior vena cava, or increased by the opening of a femoral arteriovenous bypass, so as to measure Ppa over a wide range of \dot{Q} . Left atrial pressure (Pla) was kept constant by small inflations or deflations of a balloon inserted into the left atrium. Note that the P_{pa}/\dot{Q} plots obtained were linear before as well as after oleic acid administration. Before oleic acid, the extrapolated pressure intercept of the P_{pa}/\dot{Q} plots approximated Pla. Oleic acid administration shifted P_{pa}/\dot{Q} plots in parallel toward higher pressures (fig. 4a). In a second series of experiments, \dot{Q} was kept constant and Pla progressively increased. Before oleic acid, this induced a proportional increase in Ppa. After oleic acid, only the highest Pla resulted in an increase in Ppa (fig. 4b). We concluded that in experimental ARDS, closing pressure exceeds Pla, becomes the effective outflow of the pulmonary circulation and is responsible for pulmonary hypertension [13].

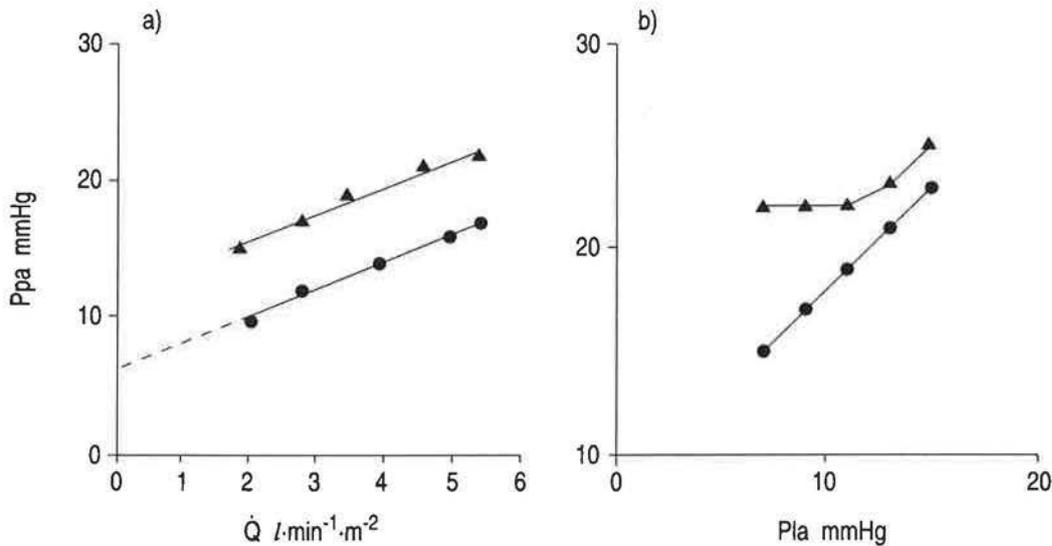


Fig. 4. - a) Mean pulmonary artery pressure (Ppa) *versus* pulmonary blood flow (\dot{Q}) at constant left atrial pressure (Pla = 6 mmHg); and b) Ppa *versus* Pla at constant blood flow ($\dot{Q} = 3.05 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$), in a dog before and after induction of an acute oleic acid lung injury (OA). Oleic acid lung injury was associated with an increased extrapolated pressure intercept of the P_{pa}/\dot{Q} plot, and with a functional dissociation between Ppa and Pla, both suggestive of an increased closing pressure accounting for pulmonary hypertension in this model of experimental ARDS. —●—: baseline; —▲—: OA. ARDS: adult respiratory distress (After reference [13]).

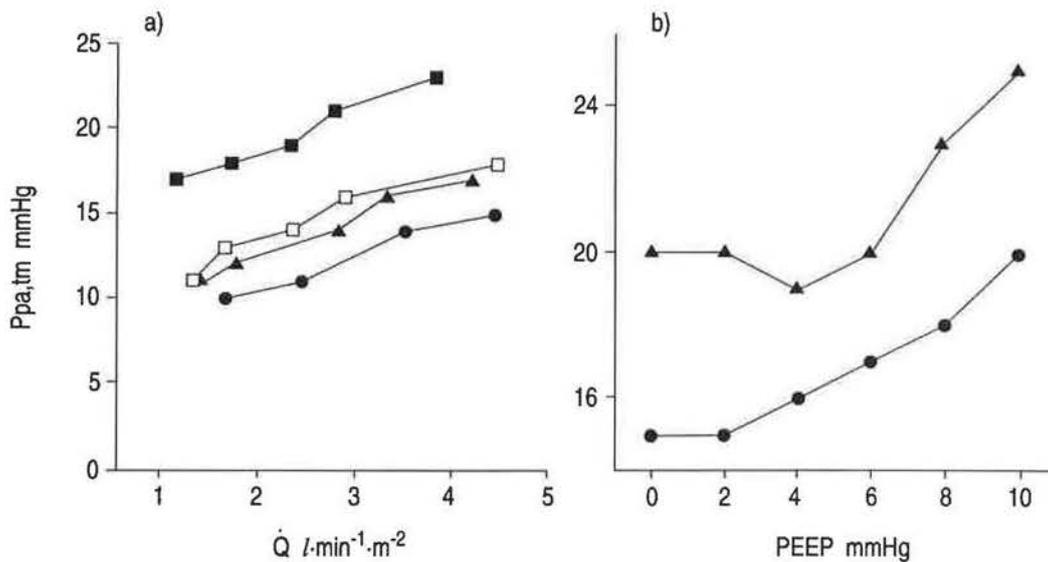


Fig. 5. — a) Transmurial mean pulmonary artery pressure ($P_{pa,tm}$) versus pulmonary blood flow (\dot{Q}); and b) $P_{pa,tm}$ versus PEEP at constant \dot{Q} in a dog before and after induction of an acute oleic acid lung injury (OA) and treated with progressively increased levels of PEEP. Only the highest level of PEEP shifted the $P_{pa,tm}/\dot{Q}$ plot to higher pressures. An increase in $P_{pa,tm}$ occurred only after the highest levels of PEEP. This functional dissociation between P_{pa} and PEEP suggests an extra-alveolar site for increased pulmonary vascular closing pressure in this model of experimental ARDS. —●—: baseline; —▲—: OA; —□—: OA+PEEP 4 mmHg; —■—: OA+PEEP 10 mmHg. PEEP: positive end-expiratory pressure; ARDS: adult respiratory distress syndrome (After reference [15]).

In order to obtain a deeper insight into the functional state of the pulmonary circulation in experimental ARDS, we studied the effects of an increased alveolar positive end-expiratory pressure (PEEP) on P_{pa}/\dot{Q} plots at constant transmurial P_{la} , and on P_{pa} at constant \dot{Q} and transmurial P_{la} , in dogs before and after induction of oleic acid lung injury. Following oleic acid, P_{pa}/\dot{Q} plots were unaffected by a PEEP of 4 mmHg, but were shifted toward higher pressures by a PEEP of 10 mmHg. Increasing PEEP from 0 to 10 mmHg at constant \dot{Q} led to an almost linear increase of P_{pa} before oleic acid, but did not affect P_{pa} after oleic acid until a PEEP of 8 mmHg. These functional dissociations between P_{pa} and PEEP, illustrated in figure 5, suggested to us that the site of vascular closure responsible for pulmonary hypertension in experimental ARDS would be extra-alveolar. If, indeed, the site of vascular closure had been alveolar, direct additive effects of PEEP and of oleic acid lung injury should have been apparent on P_{pa}/\dot{Q} and on $P_{pa}/PEEP$ plots at all levels of PEEP [15]. In all of these canine studies, P_{po} and P_{la} remained virtually identical in all experimental circumstances [13, 15]. ZAPOL and co-workers [8] had also noted that PEEP up to 20 cmH₂O (14.7 mmHg) had little or no effect on P_{pa} or P_{po} in patients with severe ARDS.

Mechanisms of pulmonary hypertension in ARDS

Possible mechanisms for increased P_{pa} in ARDS are active vasoconstriction, lumen compression by extravascular events (alveolar and interstitial haemorrhage, interstitial cell swelling, interstitial fibrosis), lumen compression by alterations of the vascular wall (endothelial cell hypertrophy and or swelling, medial hypertrophy and extension), intra-

vascular thrombosis/embolism (fibrin clot and cellular obstruction), and reduced lung volume [8]. Pulmonary artery filling defects correlating with the severity of pulmonary hypertension have been demonstrated, using a technique of balloon occlusion angiography in patients with ARDS [16]. Microscopic studies of lungs of patients with ARDS have shown various combinations of all the above mentioned structural changes [17–19]. Interstitial pulmonary oedema, whether lesional or hydrostatic, may not suffice to significantly increase P_{pa} at a given level of \dot{Q} , as long as there is no alveolar flooding [20]. Active vasoconstriction has been demonstrated by a partial reversibility of pulmonary hypertension in patients with ARDS after the administration of vasodilators, such as isoproterenol [8], nitroprusside [8, 21], ketanserin [21], diltiazem [22], and prostaglandin E₁ [23]. All of these agents decreased PVR, but this was not only due to an increased \dot{Q} . As illustrated in figure 6, a reduction in pulmonary vascular tone is unequivocal when a decrease in P_{pa} occurs in spite of an increase in \dot{Q} .

Many vasodilators have been reported to decrease PVR in experimental ARDS. We investigated the effects of prostaglandin E₁ and of nitroprusside in dogs with oleic acid lung injury, using the P_{pa}/\dot{Q} plot method [24]. Nitroprusside, at a dose associated with an inhibition of canine hypoxic pulmonary vasoconstriction (HPV) [25], was ineffective, whilst prostaglandin E₁, at a dose associated with only a slight inhibition of canine HPV [26], induced a 50% reversal of oleic acid pulmonary hypertension (fig 7). These findings led us to conclude that at least 50% of the shift of P_{pa}/\dot{Q} curves to higher pressures is functional in experimental ARDS. Prostaglandin E₁ appears to specifically inhibit vasoconstrictor mediators (leukotrienes?) likely to differ from those potentially involved in the mediation of hypoxic pulmonary hypertension. Most recently, in studies on the

effects of the acid-base status on pulmonary circulation and gas exchange in canine oleic acid lung injury, we observed a quasi-complete reversal of pulmonary hypertension by severe metabolic alkalosis (arterial pH 7.6, arterial carbon dioxide tension (P_{aCO_2}) 40 mmHg (5.3 kPa)) [28]. Alkalosis might, thus, be associated with a release of pulmonary vasodilating mediators more potent than the pharmacological agents tested until now, and almost all of the increase in Ppa in experimental ARDS would be due to active vasoconstriction. Whether this finding might be transposed to early stages of clinical ARDS remains to be investigated.

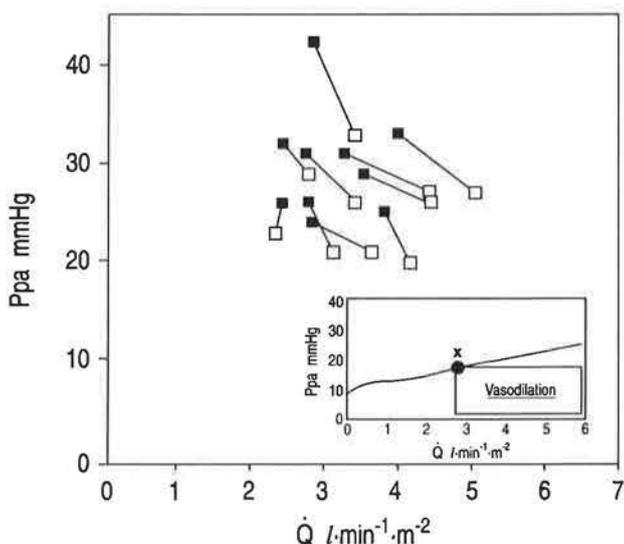


Fig. 6. - Mean pulmonary artery pressure (Ppa) and pulmonary blood flow (\dot{Q}) in 10 patients with ARDS before and after an infusion of prostaglandin E_1 (PGE_1). Prostaglandin E_1 induced a pulmonary vasodilatation, as suggested by a decreased Ppa in all of the patients, whilst \dot{Q} increased in nine of them. —■— : baseline; —□— : PGE_1 . ARDS: adult respiratory distress syndrome. (Six of the patients are reported in ref. [23]).

Pulmonary vascular tone and gas exchange in ARDS

Attempts at pharmacological pulmonary vasodilatation in ARDS have been justified by concern about a risk of excessively rapidly increasing right ventricular afterload in some patients [8], and by the speculation that associated increased oxygen delivery (by means of an increased \dot{Q}) and decreased pulmonary capillary pressures would be helpful [29]. Until now, however, no vasodilator has been shown to exert a favourable influence on the outcome of patients with ARDS. Moreover, vasodilators cause a deterioration in gas exchange. More or less important increases in shunt have been reported in patients with ARDS after nitroprusside [8, 21], isoproterenol [8], diltiazem [22], prostacyclin [30] and prostaglandin E_1 [23]. Postulated mechanisms of vasodilator-induced increases in pulmonary shunt are an increase in pulmonary blood flow, which promotes vascular recruitment in non-ventilated lung units, increases alveolar oedema or blunts HPV by means of an increased mixed venous oxygen tension (P_{O_2}), or an impairment of hypoxic regulation of the distribution of pulmonary perfusion by a direct inhibition of HPV [23]. Most recently, inhaled nitric oxide was shown, in patients with ARDS, to decrease both Ppa and shunt, which was explained by a preferential vasodilation in the better aerated and less diseased lung areas, leading to an improved ventilation/perfusion matching [30]. This interesting observation may open new perspectives in the treatment of pulmonary hypertension secondary to ARDS.

Anecdotal clinical observations of inadvertent airway disconnection from mechanical ventilation in patients with ARDS suggest that their pulmonary vessels retain the capability to constrict in response to hypoxia [8]. However, HPV may be insufficient in injured lungs. Cyclooxygenase inhibitors, well-known to enhance or to restore HPV [25, 31], have been reported to reduce pulmonary shunt in lobar atelectasis [32], lobar pneumonia [33] and lobar oleic acid lung injury [34]. We administered acetylsalicylic acid

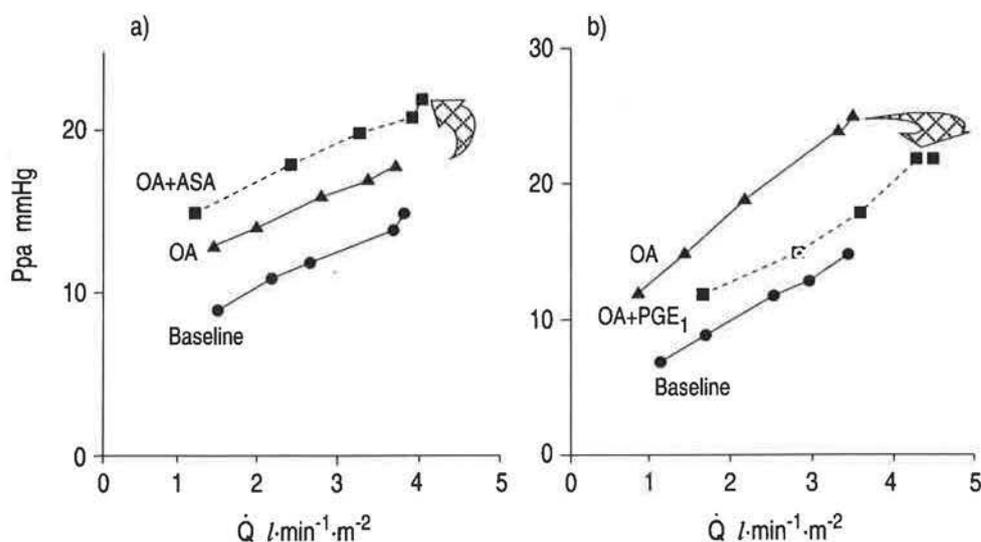


Fig. 7. - Mean pulmonary artery pressure (Ppa) versus pulmonary blood flow (\dot{Q}) plots: a) in a dog given successively oleic acid (OA) and acetylsalicylic acid (ASA); and b) in another dog given successively OA and an infusion of prostaglandin E_1 (PGE_1). Pulmonary hypertension in this model of experimental ARDS is at least in part functional. ARDS: adult respiratory distress syndrome. (After references [24] and [27]).

and indomethacin, two structurally dissimilar cyclooxygenase inhibitors, in dogs with oleic acid ARDS [27]. Both drugs increased Ppa at all levels of \dot{Q} studied (fig. 7), indicating an increase in pulmonary vascular tone, and at the same time increased arterial oxygen tension (P_{aO_2}) and decreased pulmonary shunt. Similar findings were also reported after the administration of meclofenamate, another cyclooxygenase inhibitor, in dogs with oleic acid lung injury [35]. However, other mediators than the cyclooxygenase products of arachidonic acid metabolism, such as nitric oxide [36], may affect the hypoxic regulation of pulmonary vascular tone and gas exchange in ARDS.

Almitrine, a peripheral chemoreceptor agonist, that has been shown to improve ventilation/perfusion matching in patients with chronic obstructive pulmonary disease, presumably through an enhancement of HPV [37], has recently been reported to improve gas exchange in patients with ARDS [38]. We found that in dogs with oleic acid lung injury, almitrine increased pulmonary vascular tone to the same extent as cyclooxygenase inhibitors, but actually deteriorated gas exchange [27]. We interpreted these conflicting findings by the fact that in dogs the pulmonary vascular effects of almitrine may be dependent on pre-existing tone, as well on the dose administered [39]. Whether such dose- and tone-dependent effects of almitrine occur in patients with ARDS is unknown. To our knowledge, there has been no double-blind controlled study on the effects of almitrine on gas exchange and pulmonary haemodynamics in patients with ARDS.

Ventriculo-vascular coupling in ARDS

Pulmonary arterial pulse pressure represents about half of the mean Ppa, in contrast to aortic pulse pressure, which represents only about 20% of mean aortic pressure. Pulsatile hydraulic power output is, therefore, a proportionally more important part of total hydraulic power output of the right ventricle than of the left ventricle, about 40% and 10%, respectively [10]. If systolic pressure increases in the face of an unchanged mean pressure, which occurs for example because of a decreased vascular compliance or an increase in wave reflections, pulse pressure and ventricular afterload are increased. The forces that oppose ventricular ejection result from a dynamic interplay between arteriolar resistance, closing pressure, vascular compliance and reflected waves. All these determinants of total ventricular afterload can be quantified by an analysis of vascular pressure and flow waves in the frequency domain rather than in the time domain [10].

For the study of pulsatile pulmonary haemodynamics, it is mandatory to measure instantaneous Ppa (by a high-fidelity micromanometer-tipped catheter), and instantaneous \dot{Q} (by an echographic or electromagnetic flowmeter). Pulmonary arterial flow and pressure waves are separated into their respective sums of harmonics using a Fourier analysis, and pulmonary vascular impedance (PVZ) is calculated. Pulmonary vascular impedance is defined as the ratio of pressure to flow oscillations [10]. The results are expressed as a spectrum of PVZ, which is the ratio of pressure and flow moduli *versus* frequency, and the phase

angle *versus* frequency (fig. 8). Pulmonary vascular impedance at 0 Hz (Z_0) corresponds to PVR calculated as Ppa/\dot{Q} ("total PVR"). It decreases rapidly to a first minimum at 2–3 Hz and increases again a little to a first maximum at 5–6 Hz. At low frequencies the phase angle is negative, which means that flow leads pressure.

Possible changes in an impedance spectrum are the following. An increase in the ratio of P and \dot{Q} moduli at all frequencies is a sign of reduced distensibility, or stiffening of the large arteries. A shift of the frequency at which minima and maxima appear signals a change in either wave velocity or in the dominant reflection sites. A more negative phase angle at low frequencies indicates an increased influence of reflected pressure waves on systolic pressure. Flow normally leads pressure, because of reflected pressure waves at the main site of increased pulmonary arteriolar resistance.

A useful number is characteristic impedance (Z_c), defined as the input impedance without wave reflection. Characteristic impedance can be visually estimated as PVZ averaged for the higher frequencies above the first minimum, or calculated as a PVZ at a frequency equal to the infinite. Characteristic impedance is dependent on the ratio of inertial elements to compliant elements of the pulmonary vascular system. The extent to which Z_0 differs from Z_c can be used to quantify wave reflection. The proportion of forward wave that is reflected back is expressed as a reflection coefficient (R_c) which can be estimated from the equation:

$$R_c = (1 - Z_c/Z_0)/(1 + Z_c/Z_0)$$

Changes in the spectrum of PVZ that occur in acute canine microembolic pulmonary hypertension, another experimental ARDS model characterized by more severe pulmonary hypertension than in oleic acid lung injury, are illustrated in figure 8. An increase in Ppa induced by the injection of 150 μ m glass beads in dogs increased Z_0 , indicating an increased pulmonary arteriolar resistance, shifted the first minima and maxima of the impedance moduli to higher frequencies, suggesting increased wave speed and wave reflections, increased the negativity of the phase angle at low frequencies, suggesting also increased wave reflections, and somewhat surprisingly decreased Z_c [40]. The latter was explained by a marked (possibly active) dilatation of the proximal pulmonary vascular tree in the face of unchanged or decreased pulmonary arterial compliance.

Previous studies have shown that a more proximal pulmonary vascular obstruction, induced by a banding of the main pulmonary artery, increases both Z_0 and Z_c [41, 42]. A reduction in Z_c results in a decrease in the pulsatile component of the hydraulic load imposed upon the right ventricle, or, in other words, a decrease in the forces that oppose right ventricular ejection [40–42]. An intriguing hypothesis is that such vascular changes, obviously undetected by steady-flow haemodynamic studies, could be of adaptive value, and possibly amenable to pharmacological interventions [40–42].

More experimental and clinical studies on pulsatile pulmonary haemodynamics may show us whether right

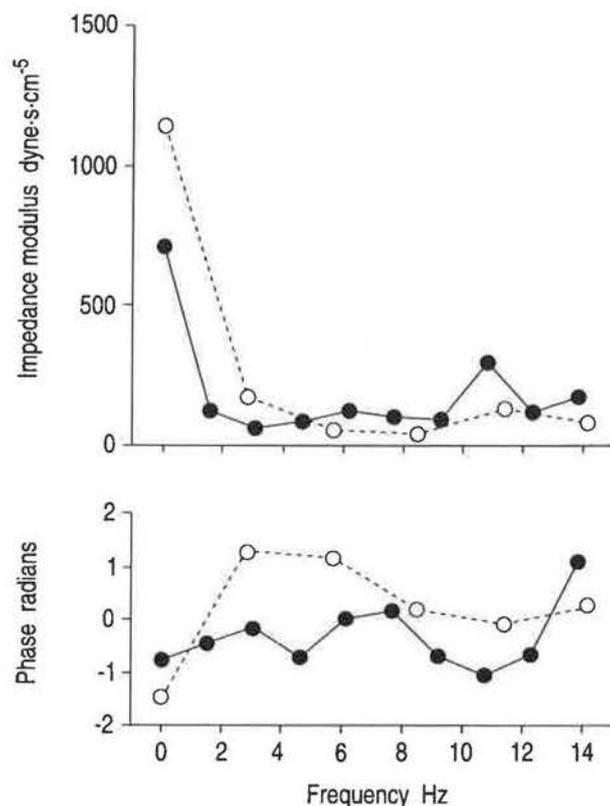


Fig. 8. - Spectrum of pulmonary vascular impedance in a dog before (mean pulmonary artery pressure (Ppa) 15 mmHg) and after (Ppa 35 mmHg) induction of an acute microembolic lung injury by injection of 150 μ m glass beads. Pulmonary hypertension in this model of experimental ARDS is characterized by an increased 0 Hz impedance, a shift of the first minimum and maximum of the impedance moduli to higher frequencies, a decrease in characteristic impedance and a more negative phase angle at the lowest frequencies. —●—: Ppa 15 mmHg; -○- : Ppa 35 mmHg. ARDS: adult respiratory distress syndrome. (After reference [40]).

ventricular-vascular coupling can be improved, and whether this may prevent or treat right ventricular failure in patients with pulmonary hypertension secondary to the adult respiratory distress syndrome.

Conclusions

In summary: 1) pulmonary hypertension is a hallmark of ARDS; 2) pulmonary hypertension in ARDS is essentially caused by an increased closing pressure of extra-alveolar lung vessels; 3) increased pulmonary vascular closing pressure in ARDS is, at least in part, due to active vasoconstriction; 4) increased pulmonary vascular tone improves gas exchange in ARDS; however, a decreased vascular tone in the better aerated lung areas by the inhalation of nitric oxide also improves gas exchange in ARDS; 5) pharmacological manipulations of pulmonary vascular tone are feasible in ARDS, but without any proven clinical benefit reported until now; 6) improvements in the results of pharmacological interventions, aimed at the prevention or the treatment of right ventricular failure in ARDS, will probably result from a better understanding of pulsatile pulmonary haemodynamics.

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