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A new look at the pulmonary circulation in acute lung injury

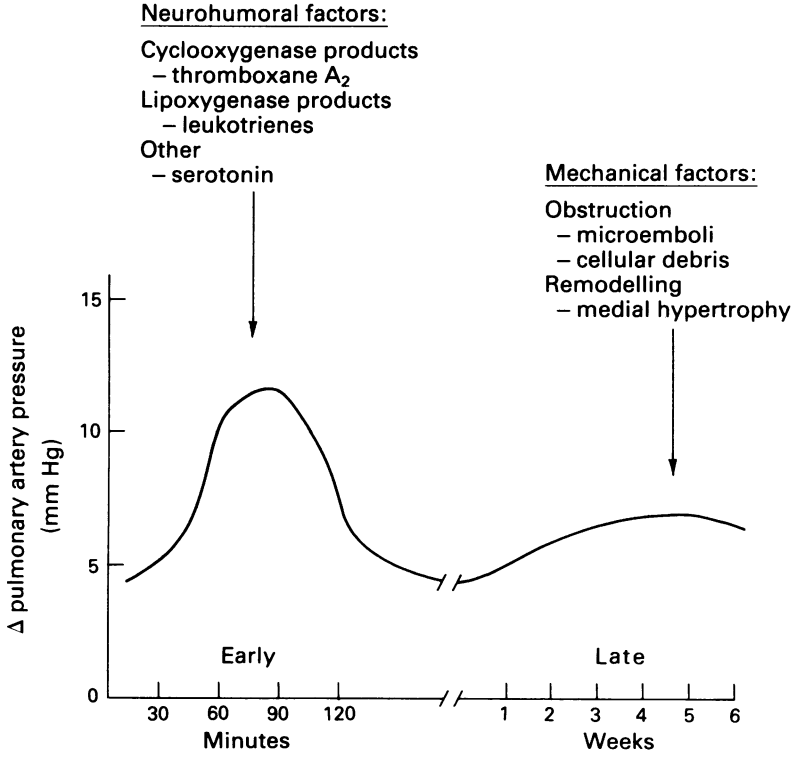
George A Fox, David G McCormack

AC Burton Vascular Biology Laboratory, Division of Respiratory Medicine, Department of Medicine, Victoria Hospital, 375 South Street, London, Ontario, Canada N6A 4G5
G A Fox
D G McCormack

Correspondence to:
Dr D G McCormack
(reprints will not be available)

Acute lung injury or the adult respiratory distress syndrome (ARDS) refers to the non-specific pulmonary response to various insults, acting either directly (for example, gastric acid aspiration, inhalation of toxic fumes, and oxygen toxicity) or indirectly (for example, sepsis syndrome, pancreatitis, and fat embolism syndrome).[1] The injury leads to reduced pulmonary compliance[2] and a defect in gas transfer,[3] both of which may occur in the absence of an appreciable increase in extravascular lung water.

After acute lung injury the pulmonary vasculature may be affected at various levels: (1) pulmonary resistance vessels may be stimulated to contract with a resultant increase in pulmonary artery pressure; (2) pulmonary vascular reactivity may be attenuated, causing increased ventilation-perfusion mismatching; and (3) the pulmonary microvascular endothelium may be disrupted with a consequent increase in permeability. The purpose of this article is to provide an update on new developments regarding the pulmonary circulation in acute lung injury and ARDS with reference to these abnormalities.



Pulmonary hypertension in acute lung injury.

Pulmonary hypertension

Clinically, pulmonary hypertension is a frequent complication of acute lung injury[4] and may be the result of an increase in pulmonary vascular resistance or cardiac output. In patients with ARDS the development of pulmonary hypertension is associated with increased mortality.[5] Many animal models of lung injury are complicated by pulmonary hypertension[6 7] and, although they do not exactly replicate the clinical syndrome, such models have been the focus of extensive research, resulting in a greater understanding of the pathophysiological mechanism of pulmonary hypertension in acute lung injury.

In the early stages of acute lung injury pulmonary hypertension is usually the result of neurohumoral mechanisms[8] (figure). Many vasoactive substances have been suggested as possible mediators of pulmonary hypertension in acute lung injury. The inflammatory eicosanoids are potent vasoactive compounds derived from the cyclooxygenase or lipoxygenase metabolism of arachidonic acid. Clinical studies have shown the increased levels of circulating prostanoids[9] and leukotrienes[10] in bronchoalveolar lavage fluid from patients with ARDS. Acute lung injury is associated with increased concentrations of circulating thromboxane A_2, a potent vasoconstrictor that may be responsible for the pulmonary hypertension associated with ARDS[11] and acute pneumonia.[12]

Intravenous infusion of endotoxin causes pulmonary artery pressure to rise within several minutes and remain raised for hours.[13] Serum levels of thromboxane B_2, the product of thromboxane A_2 metabolism, rise concurrently with pulmonary artery pressures both in animal models of ARDS[8] and in patients with pneumonia.[6] Pretreatment with cyclooxygenase inhibitors prevents the release of thromboxane A_2[6 8] and attenuates the rise in pulmonary artery pressure.[14] The source of thromboxane A_2 is unclear as neither neutrophil[15] nor platelet[16] depletion completely abolishes the associated pulmonary hypertension. Possible sources include the vascular endothelium and pulmonary macrophages.

Thromboxane A_2 is probably not the sole

mediator of pulmonary hypertension in lung injury because dazoxiben, a specific thromboxane synthase inhibitor, does not alter pulmonary artery pressures in patients with ARDS.[9] Furthermore, cyclooxygenase inhibitors block the acute pulmonary hypertension associated with endotoxin infusion but fail to prevent the subsequent rise in pulmonary artery pressure that occurs several hours later. In these circumstances it has been suggested that arachidonic acid metabolism may be shunted towards the lipoxygenase pathway, resulting in increased release of leukotrienes.[17]

Other possible mechanisms of pulmonary hypertension include obstruction of the pulmonary vasculature with microemboli, particulate matter or cellular debris,[18] and interstitial oedema, which may reduce the compliance of the pulmonary vasculature, causing a rise in pulmonary vascular resistance.[19] With lung injury of longer duration pulmonary hypertension is probably related to structural abnormalities within the pulmonary vasculature and may be consequent on the vascular remodelling that occurs with ongoing pulmonary injury and raised intravascular pressures.[20] Patients with prolonged ARDS have structural remodelling of the pulmonary vasculature, with medial hypertrophy and a reduction in luminal diameter.[21] These morphological changes are probably the result of protracted pulmonary hypertension and may contribute to the persistence of raised pulmonary artery pressures.

CLINICAL IMPLICATIONS

Pulmonary hypertension increases right ventricular afterload and may therefore impair right ventricular function and decrease cardiac output, leading to a reduction in systemic oxygen delivery. In the setting of ARDS and associated multiple organ dysfunction, this may further impair tissue oxygen utilisation and contribute to worsening organ dysfunction. Clinical studies have shown impaired right ventricular performance associated with sepsis and ARDS,[22] and pulmonary hypertension is associated with excess mortality in this setting.[5] This observation has led to numerous clinical trials evaluating the effect of pulmonary vasodilators in acute lung injury.

Therapeutic manoeuvres in ARDS are directed towards increasing tissue oxygen delivery. If cardiac function is limited as a result of increased right ventricular afterload, reductions in pulmonary vascular resistance may prove beneficial. Nevertheless, although clinical trials using vasodilators such as nitroprusside[23] and nitroglycerin[24] in acute lung injury have been shown to decrease pulmonary artery pressure, increases in cardiac index and oxygen delivery are not observed consistently (table). Furthermore, the use of vasodilators in ARDS may reduce systemic oxygen delivery[25] as a result of diminished right and left ventricular preload[26] or impaired ventilation-perfusion matching.

Several recent clinical trials have evaluated the effect of an infusion of the vasodilator prostaglandin PGE_1 in patients with ARDS. Unfortunately, results have been disappointing. In a double blind study the effects of a continuous seven day infusion of prostaglandin E_1 (PGE_1) were examined.[27] In 41 patients randomly allocated to the PGE_1 or the placebo group significant reduction in mortality at 30 days was observed in patients assigned to the treatment arm. Although the overall survival was not significantly improved, subgroup analysis showed that in those patients free of severe organ dysfunction at the time of entry there was an absolute reduction in mortality of 60%. The average ratio of arterial oxygen tension to fractional inspired oxygen concentration (Pao_2/FIo_2) improved significantly in patients receiving PGE_1, though several patients had an early decline in gas exchange, presumably secondary to the inhibition of hypoxic pulmonary vasoconstriction. In a similar study Melot *et al*,[28] using the multiple inert gas elimination technique, found that PGE infusion increased intrapulmonary shunt from 21% to 32%, with a concomitant fall in arterial oxygen saturation. Finally, PGE_1 infusion has been shown not to influence survival in patients with ARDS, despite improving systemic oxygen delivery and reducing pulmonary vascular resistance.[29] Thus, although PGE_1 does increase systemic oxygen delivery, its potentially adverse effects, on systemic blood pressure, cardiac rhythm, and gas exchange limit its use as a pulmonary artery vasodilator in ARDS.

Although there are intuitive reasons for supporting the use of vasodilators in the management of patients with acute lung injury and ARDS, we must conclude that this treatment has not been proved to be of benefit. Systemic side effects preclude its use in the clinical setting, but agents acting selectively on the pulmonary circulation would theoretically reduce right ventricular afterload and improve cardiac function without causing systemic hypotension in patients with ARDS. Unfortunately, such an agent has not so far been developed.

Results of vasodilator treatment in acute lung injury in published studies

Vasodilator (with reference)	*CI*	*$\dot{Q}o_2$*	*$\dot{V}o_2$*	*PAP*	*PVR*	*Pao_2*	*$\dot{Q}s/\dot{Q}t$*	*Survival*
Nitroprusside[23]	↑	↓	↔	↓	↓	↓	↑	NR
Diltiazem[32]	↔	NR	↔	↓	↓	↓	↑	NR
Prostaglandin E_1[27]	NR	NR	NR	NR	NR	↑	NR	↑
Prostaglandin E_1[29]	↑	↑	↑	NR	↓	NR	NR	↔
Prostaglandin E_1[28]	↑	NR	↔	↓	NR	↓	↑	NR

CI—cardiac index; $\dot{Q}o_2$—systemic oxygen delivery; $\dot{V}o_2$—systemic oxygen consumption; PAP—pulmonary artery pressure; PVR—pulmonary vascular resistance; Pao_2—partial pressure of oxygen; $\dot{Q}s/\dot{Q}t$—shunt fraction; NR—not reported; ↑—increased; ↓—decreased; ↔—no change.

Ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance

Although the defect in gas exchange associated with acute lung injury is undoubtedly related to pulmonary oedema,[11] the true aetiology of arterial hypoxaemia is more complex. Thus the lung's extravascular water content does not correlate with the degree of hypoxaemia in either experimental animals[13] or patients.[30] In sheep the hypoxaemia that develops after the infusion of endotoxin precedes the accumulation of water in the lung.[13] Similarly, in man hypoxaemia frequently occurs in the absence of radiographic evidence of pulmonary oedema.

Dantzker *et al*,[31] however, have shown that hypoxaemia in ARDS is primarily the result of intrapulmonary shunting. Using the multiple inert gas elimination technique, they showed that this was related to perfusion of lung units characterised by a low ventilation ($\dot{V}$)-perfusion ($\dot{Q}$) ratio. Furthermore, the use of vasodilators exacerbates the arterial hypoxaemia and increases intrapulmonary shunting in patients with ARDS (see above), which supports the hypothesis that abnormal vascular tone may result in $\dot{V}/\dot{Q}$ mismatch.[32]

In normal conditions hypoxic pulmonary vasoconstriction develops in response to alveolar hypoxia, resulting in a redirection of pulmonary blood flow away from non-ventilated lung segments, improving $\dot{V}/\dot{Q}$ matching. The attenuation of hypoxic pulmonary vasoconstriction has been reported in various forms of lung injury, including that consequent on endotoxin infusion,[33] and acute[34] and chronic[6] pneumonia. Although the exact mechanism underlying hypoxic pulmonary vasoconstriction remains uncertain, it has been suggested that the blunted response observed in ARDS may be due to the excessive release of endogenous vasodilator substances, such as prostacyclin,[35] endothelium derived relaxant factor,[36] and platelet activating factor.[37] Thus in a rat model of chronic *Pseudomonas* pneumonia the attenuated hypoxic pulmonary vasoconstriction can be reversed with meclofenamate, a specific cyclooxygenase inhibitor.[6] Similarly, the fall in the hypoxic pressor response that follows endotoxin infusion in sheep can be prevented with cyclooxygenase inhibitors.[17] Although the excessive release of vasodilator prostaglandins may partially explain the altered vascular reactivity following endotoxin exposure, other investigators have been unable to confirm these results,[38] and other causes of altered pulmonary vascular reactivity are under investigation.

The vascular endothelium produces a nitric oxide like substance (endothelium derived relaxant factor) that acts locally to cause smooth muscle relaxation.[39] Endothelium derived relaxant factor is probably important in the regulation of vascular smooth muscle tone and may modulate the normal hypoxic pressor response.[40] It has been suggested that production of excess endothelium derived relaxant factor occurs in lung injury and may contribute to the attenuated hypoxic pressor response of the pulmonary vasculature,[41] though recent work from our laboratory does not support this hypothesis (unpublished data).

The finding of non-adrenergic, non-cholinergic (NANC) relaxation in systemic[42] and pulmonary[43] blood vessels suggests that NANC nerves may have a role in the control of vascular tone. The neurotransmitters in the NANC nervous system have not been conclusively identified, but likely candidates include the sensory neuropeptides substance P and calcitonin gene related peptide,[44] both of which have been shown to be potent pulmonary vasodilators. Neuropeptides may be released from unmyelinated C fibre sensory nerve endings when these are stimulated, though whether these peptides contribute to the abnormal vascular contractility found in disease is not known.

Thus the pathophysiological mechanism underlying abnormal vascular reactivity and the attenuation of the hypoxic pressor response and $\dot{V}/\dot{Q}$ imbalance are still the subject of intense laboratory and clinical research. With a better understanding of the underlying mechanisms specific therapeutic measures are likely to be developed to improve arterial hypoxaemia associated with acute lung injury.

Increased pulmonary microvascular permeability

The acute lung injury associated with ARDS is characterised by increased pulmonary microvascular permeability.[1] Interstitial and alveolar oedema typically occur in the presence of normal hydrostatic pressures.[45] Fluid flux across the pulmonary microvascular bed may be defined by the modified Starling equation,[45] which describes the balance between hydrostatic and osmotic factors related to the pathogenesis of pulmonary oedema. An increase in either hydrostatic forces or membrane permeability can therefore lead to the accumulation of extravascular lung water.[45] Abnormalities in the balance between osmotic pressure gradients or diminished lymphatic drainage also make a contribution.[45]

Many studies, both in the laboratory and in the clinical setting, have shown that an increase in the microvascular permeability of the lung occurs with acute lung injury[46–48]; after infusion of endotoxin,[49] live bacteria,[50] and tumour necrosis[51]; and in association with oleic acid injury,[52] peritoneal sepsis,[53] and various other insults.

There is mounting evidence that granulocytes are essential participants in the microvascular permeability associated with lung injury. Clinical studies have shown the accumulation of neutrophils in the lungs of patients with ARDS.[54] Others have produced morphological evidence of pulmonary neutrophil sequestration in animal models of acute lung injury.[49]

Margination of neutrophils and their migration between endothelial cells into the interstitial space follows endotoxin infusion.[49] In neutrophil depletion studies using hydroxyurea the accumulation of extravascular water in the lung in acute lung injury was significantly reduced.[55] Laboratory data suggest that neutrophil sequestration occurs at the microvascular level,[56] and may therefore

predispose the capillary endothelial cells to injury from activated neutrophils; endothelial cell injury with associated cellular contraction, ruffling of the surface membrane, and dilatation of intracellular junctions has been observed in clinical[57] and laboratory studies[7] of ARDS.

Polymorphonuclear leucocytes contain lysosomal enzymes, proteases, and reactive oxygen species, which have been implicated as possible mediators of acute microvascular lung injury.[58] Neutrophils elaborate other factors responsible for tissue injury and inflammation, including platelet activating factor,[59] cyclo-oxygenase and lipoxygenase metabolites of arachidonic acid,[60 61] and various chemotactic factors,[62] all of which may have a role in initiating and perpetuating the inflammatory injury. Endotoxin may directly injure endothelial cells, even in the absence of circulating neutrophils; and endothelial cell retraction, pyknosis, and increased release of lactate dehydrogenase and prostacyclin have followed the incubation of endothelial cells with endotoxin in culture.[63] Endotoxin induced injury to the vascular endothelium is likely to be initially a direct effect, but activated complement and granulocytes exaggerate the injury by their interaction with the altered endothelial cells.[64]

CLINICAL IMPLICATIONS

Therapeutic attempts to reduce the hydrostatic influences on the accumulation of extravascular water in the lung in ARDS have shown encouraging results,[48] though intravascular volume depletion is potentially deleterious in the setting of sepsis and ARDS, where decreased perfusion of non-pulmonary organs may lead to impaired tissue oxygenation.[65]

Unfortunately, clinical trials of treatments directed towards diminishing the permeability defect in acute lung injury have been disappointing. For example, although oxygen radical scavengers have been shown to decrease permeability in the laboratory setting,[66] these results have not been duplicated in clinical trials. Methylprednisolone blocks the acute permeability defect associated with an infusion of endotoxin in sheep[67] but did not improve overall survival in a multicentre trial of patients with ARDS.[68] The current management of patients with non-cardiac pulmonary oedema therefore includes ventilatory support, treatment of the precipitating or underlying condition, and the maintenance of systemic oxygen delivery, and avoidance of excessive microvascular hydrostatic pressures caused by volume overload. Unfortunately, the current modalities of ventilatory support for these patients include high fractional inspired oxygen concentrations and positive end expiratory pressure, both of which may have detrimental effects. Thus newer treatments are desperately needed that specifically attenuate the permeability defect found in acute lung injury.

Summary

Acute lung injury affects the pulmonary circulation at many levels, being associated with pulmonary hypertension, impaired regulation of ventilation-perfusion matching, and increased lung permeability. The interplay of these factors contributes to the significant morbidity and mortality associated with ARDS. For example, as outlined above, treating pulmonary hypertension with vasodilators will worsen the already abnormal ventilation-perfusion relationships of acute lung injury and cause significant side effects. As research proceeds, new treatments will become available for dealing with acute lung injury. We will need to assess new therapeutic modalities, using the knowledge that many factors interact to affect outcome in this clinical problem.

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