Pulmonary hypertension in ARDS: inflammation matters!

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The recognition of pulmonary vascular complications in acute respiratory distress syndrome (ARDS) spans more than 40 years. Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure of ≥25 mm Hg at right heart catheterisation. PH is a recognised consequence of ARDS, with a high prevalence in early studies. The pathogenesis of PH in ARDS is likely to be multifactorial and disease stage-dependent. Further to the modifiable effects of positive pressure ventilation,[1] potential underlying mechanisms of PH in ARDS include vessel obliteration, microthrombosis and pulmonary vasoconstriction due to hypoxia, hypercapnia and vasoactive mediator imbalance. Pulmonary vascular remodelling occurs later.[2] Sepsis-related right-sided and also left-sided ventricular myocardial dysfunction may also contribute. Whatever the cause of PH, the resulting right ventricular (RV) dysfunction is associated with increased morbidity and mortality,[3 4] although it is not actually proven that RV failure is a mode of death in ARDS. Trials of pulmonary vasodilators, such as inhaled nitric oxide and prostacyclin, have met with disappointment in terms of outcomes, although there is fair criticism of the design of the studies and the heterogeneity of the populations involved. Notably, these studies targeted oxygenation rather than pulmonary haemodynamics; so, any potential contribution of improved RV function to better outcomes is untested. What is clear is that outcome has improved in ARDS with a parallel apparent reduction in prevalence of PH and RV dysfunction. Both may be due to changes in ventilation practice following the landmark protective ventilation studies, as limiting ventilator airway pressures directly reduces RV dysfunction through physiological mechanisms.[5] However, even with the use of 'modern era' lower airway pressures, RV dysfunction remains in the region of 20%–25%[3 4] and interestingly appears to be associated with sepsis.[3] So, what is the role of sepsis and, indeed, non-sepsis related inflammation to the pathogenesis of PH and RV dysfunction in the context of ARDS? We know that ARDS is, by its very nature, an inflammatory condition. It is associated with endothelial cell injury and dysfunction,[6 7] events that may trigger acute pulmonary vasoconstriction, and also later remodelling processes. We also know that mechanical ventilation is bad for lungs, through processes such as ventilator-induced lung injury (VILI). High ventilatory pressures and flow increase lung cytokine levels, including interleukin (IL)-6 in man[8] and also in relevant animal models of VILI,[9] with levels falling as airway pressures are lowered.[8 9] In addition, pulmonary arterial myography in rats ventilated with high tidal volumes demonstrates reduced α-adrenergic induced vasoconstriction and reduced endothelium-dependent vasodilatation.[10] It therefore seems likely that the increase in inflammation inherent to ARDS and also secondary to VILI drives the pulmonary vascular injury observed in this condition.

The article by Pandolfi and coworkers[11] adds to the evidence that inflammatory mechanisms contribute to the pathogenesis of PH in ARDS. In particular, their study addresses whether IL-6 and acid sphingomyelinase (aSMase) contribute to pulmonary vascular dysfunction in a rat model of inhaled lipopolysaccharide (LPS)-induced ARDS. They demonstrate that LPS induces both IL-6 and ceramide production in rat pulmonary artery smooth muscle cells (PASMC) via an aSMase and transforming growth factor β-activated kinase-1 dependent pathway, and that LPS increases serotonin-induced pulmonary vasoconstriction, also mediated by aSMase and IL-6. They show in vivo that pulmonary IL-6, IL-1β and endothelin (ET)-1 levels correlate with LPS-induced increases in pulmonary artery pressure, but interestingly that plasma levels of these cytokines, although also raised (but to a lesser degree), did not. aSMase inhibition using D609 prevented LPS-induced PH and reduced markers of inflammation in bronchoalveolar lavage, as well as IL-6 plasma levels. Specific IL-6 blockade was not used in vivo, but lung tissue IL-6 (and IL-1β) levels were suppressed by aSMase, suggesting their predominant production and target are in the lungs. Conversely, ET-1 levels were increased in both lung and plasma, but were not affected by aSMase.

While the effects of LPS, aSMase and IL-6 were to *augment* PH and vasoconstriction (in vitro and in vivo), the authors demonstrate in an isolated perfused rat pulmonary artery model that LPS-induced hypoxic pulmonary vasoconstriction (HPV) failure was also mediated by IL-6 and aSMase. In this model, LPS inhibited pulmonary vasoconstriction induced by hypoxia and phenylephrine, and acetylcholine-induced vasodilatation was blunted (although ET-1-induced contraction was unaffected). Signalling pathways were carefully dissected to show that LPS-induced HPV impairment via phenylephrine was mediated by inhibition of inducible nitric oxide synthase (iNOS), but not aSMase or IL-6, and that LPS-induced blunting of acetylcholine-induced relaxation was mediated via aSMase and iNOS inhibition, but not IL-6 blockade. The hyper-responsiveness of LPS to serotonin persisted despite iNOS inhibition. This suggests that HPV failure is complex and acts through IL-6 and aSMase-dependent mechanisms, and is not simply related to excess NO production by iNOS, which had been previously shown to be the case in a model of PH following intravenous microparticle injection in broiler chickens.[12] In addition, the potent vasoconstrictor ET-1 and the LPS-induced hyper-responsiveness to serotonin must contribute to the overall increase in PH that, paradoxically, coexists with HPV failure. That aSMase inhibition using D609 could potentiate the vasoconstrictor response to hypoxia in these rat myography experiments was confirmed in human studies. The authors also nicely demonstrate in a rat model of partial airway occlusion that the LPS-induced delay in blood redistribution from unventilated alveoli was prevented by aSMase inhibition. The finding that the aSMase and IL-6 pathways contribute to HPV failure in this setting adds to the fascinating story of opposing vasoactive response between pulmonary and systemic vessels in relation to hypoxia, and to sepsis and endotoxinaemia, depending on the prominent vasoactive factor at play. Indeed, sphingolipids have been shown to mediate oxygen sensing and have opposing effects on vessels depending on the vascular tissue involved,[13] with hypoxic vasoconstriction occurring in pulmonary arteries through inhibition of voltage-gated K(+)

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(K(v)) channels and activation of neutral SMase.[14]

What do we already know about these mediators? There is evidence that sphingolipids are important in lung injury, sepsis, HPV and chronic lung diseases including COPD, idiopathic pulmonary fibrosis and pulmonary arterial hypertension (PAH) as well as many types of cancer cells. For example, ceramide induces apoptosis in murine emphysema,[15] susceptibility to bacterial infections in cystic fibrosis[16] and IL-6 release from human lung fibroblasts.[17 18] In human PAH and rodent hypoxic PH, sphingosine kinase 1 is increased in the lungs and PASMC. SphK1 inhibition prevents hypoxic PH, and overexpression promotes PASMC proliferation.[19] Further to pro-proliferative effects, the proinflammatory role of sphingolipids may be relevant in PAH, where dysregulated inflammation is recognised. The endotoxin-induced ceramide release from PASMC in this study[11] is relevant to PH in ARDS and also chronic respiratory diseases, where acute exacerbations are characterised by a reversible increase in pulmonary arterial pressure, which is related to acute hypoxia (eg, in COPD). Chronic repeated inflammation is likely also to cause progressive pulmonary vascular remodelling and PH,[20] as suggested in patients with frequent COPD exacerbations.[21]

Hypoxia-inducible factor (HIF) regulation of cellular responses is likely to be relevant in this model of pulmonary vascular inflammation. Further to the response to cellular hypoxia, cytokines (including IL-6) and LPS can synergistically regulate HIF transcription. Through HIF-1α binding, hypoxia activates nuclear factor (NF)-κB expression, providing crosstalk between HIF and NF-κB pathways with resulting bidirectional signalling.[22] Downstream, HIF-1α induces macrophage release of tumour necrosis factor-α, IL-1β and vascular endothelial growth factor.[22] This is likely to contribute to the acute pulmonary vasoactive effects described in this paper, as well as more chronic effects on pulmonary vascular cell proliferation with the onset of hypoxic vascular remodelling.[23] In terms of relevance for sphingolipids, studies in hypoxic mouse myocardium suggest the conversion of ceramide from its precursor is hypoxia-related;[24] so, it is likely that HIF signalling is implicated in sphingolipid biology.

Overall, the study by Pandolfi *et al* supports the importance of inflammation and in particular IL-6 in endotoxin-induced endothelial dysfunction, failure of HPV and PH. They provide a novel 'acute' pulmonary vascular action of IL-6, which adds to the well-studied chronic effects of IL-6 in hypoxia-driven PH and PAH, as a key inflammatory and pro-proliferative mediator, as discussed by the authors. It may help to explain why protective ventilator strategies improve outcome, through lowering of IL-6 and other cytokines, mediated through an improvement in pulmonary vascular function, and suggests an era of targeting the vasculature in ARDS. Further studies of aSMase and IL-6 inhibition in VILI models would be of interest, as would unravelling how IL-6 acutely alters pulmonary vascular tone. Even more intriguing would be whether the inhibition of IL-6 and aSMase in human ARDS would improve pulmonary vascular dysfunction (and outcome), and also the relevance of this axis to the acute worsening of PH in patients with acute exacerbations of chronic lung disease.

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