Pathophysiology of pulmonary hypertension in acute lung injury

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ACUTE LUNG INJURY (ALI) and acute respiratory distress syndrome (ARDS) are characterized by acute onset hypoxemia associated with increased pulmonary vascular permeability and the development of noncardiogenic pulmonary edema (5). These syndromes are defined by the severity of hypoxemia (according to the ratio of arterial to inspired oxygen: the P-to-F ratio), with the presence of bilateral infiltrates on chest radiography and the exclusion of cardiogenic pulmonary edema (143). Despite some evidence of improvements in mortality in selected centers over recent decades (1), ALI remains a major public health problem, with 28-day mortality in the region of 25–35% (84). ALI may develop after a diverse spectrum of causes. These associated conditions may be categorized according to the nature of the insult, with for example pneumonia causing a direct lung injury and pancreatitis and nonpulmonary sepsis causing indirect lung injury, often as part of a multiorgan dysfunction syndrome, the former being associated with a higher mortality (126).

These direct or indirect insults result in neutrophil- and platelet-dependent dysfunction of the alveolar-epithelial barrier. The resultant protein-rich pulmonary edema fluid floods alveoli and causes surfactant dysfunction, which results in collapse and consolidation of lung units. Severe refractory hypoxemia results from ventilation-perfusion mismatch due to impairment of hypoxic pulmonary vasoconstriction. In addition to hypoxemia, hypercapnia is also a feature of ALI. This reflects involvement of the pulmonary microcirculation, due both to the disease process itself, as well as relating to the effects of positive pressure ventilation. Involvement of the pulmonary microcirculation is important early in ALI. For example, the inability to excrete carbon dioxide in those areas of lung being ventilated but not perfused, which equates to ventilatory dead space, can be measured at the bedside and is associated with mortality (97).

CLINICAL PERSPECTIVE

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure of greater than 25 mmHg. According to this definition, PH is commonly found in patients who have developed ALI (149). However, this definition is largely used for patients with chronic PH. The World Health Organization further subclassified chronic PH into five groups, based on similar pathophysiology and anticipated responses to treatment (118). However, as yet there is no consensus definition of acute PH and it is difficult to assess how much information can be translated from the chronic setting to acute conditions like ALI/ARDS. As such, what may be of more clinical importance is the presence of right ventricular (RV) dysfunction or failure. Other factors may also contribute to reduced RV function in ALI including acute myocardial dysfunction, related to sepsis or a systemic inflammatory response. In the setting of ALI, RV failure with its nonspecific symptoms and signs is probably underdiagnosed. There are few studies documenting the progression of PH in patients with ALI, but a progressive increase in pulmonary pressures has been associated with a worse outcome (149). The incidence of acute RV failure appears to have fallen (from 22% to 50% to less than 10% in most studies) since the introduction of protective lung ventilation strategies (Table 1) (23, 26, 61, 62, 91, 100, 121, 135, 149).
The pathophysiological changes occurring within the pulmonary vasculature in ALI include: 1) endothelial dysfunction, 2) pulmonary vascular occlusion, 3) increased vascular tone, 4) extrinsic vessel occlusion, and 5) vascular remodeling, as summarized in Fig. 1.

**Endothelial Dysfunction**

Functions of healthy pulmonary endothelium include the control of appropriate local blood flow, coagulation, vascular tone, angiogenesis, and cell proliferation (7). Pulmonary endothelial cells (EC) synthesize and release a wide variety of products (Table 2), as well as metabolizing others [e.g., angiotensin I by pulmonary endothelial angiotensin converting enzyme (ACE)]. In health, ECs provide a smooth thromboreis- 
ting surface protecting the subendothelium from procoagulant factors and platelets (80). They form a tight monolayer that acts as a barrier to control water and solute transport, maintained through complex cytoskeletal tethering forces between and within each cell (85). The large surface area and proximity to the air space, however, make the pulmonary microvascular endothelium vulnerable to injury from both direct alveolar insult and circulating mediators (144). The resultant activation of the endothelium is followed by dysfunction. Endothelial dysfunction involves an imbalance between vasodilating and vasoconstricting mediators and a shift to a prothrombotic phenotype.

**Evidence for endothelial dysfunction in acute lung injury.** Endothelial dysfunction is important early and late in the course of ALI (128, 129). Histological characteristics of injury include EC swelling, the presence of enlarged mitochondria, dilated endoplasmic reticulum adjacent to the capillary lumens (129), pinocytotic vesicle formation, and inter-endothelial cell separation (114). Additionally, there is evidence for altered production of endothelial-derived molecules including Von Willebrand’s factor (vWF), ACE, and angiotopoinet-2. vWF is a plasma glycoprotein produced by the endothelium considered to be a biomarker of EC activation and injury: plasma vWF levels were elevated in a

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**Table 1. Outcome studies of pulmonary hypertension and right ventricular dysfunction in patients with acute lung injury**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Period</th>
<th>No.</th>
<th>ALI Population</th>
<th>How Diagnosed</th>
<th>Pulmonary Hemodynamics</th>
<th>RVF (PH) Prevalence</th>
<th>Outcome Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zapol et al., 1977</td>
<td>1977</td>
<td>30</td>
<td>Mixed ALI</td>
<td>PAC</td>
<td>PAP, PAOP, PVR</td>
<td>All had PH</td>
<td>Not with initial but with persistent PH</td>
</tr>
<tr>
<td>Jardin et al., 1985</td>
<td>1985</td>
<td>23</td>
<td>Mixed ALI</td>
<td>TTE</td>
<td>RV size and systolic function</td>
<td>22% had RVF</td>
<td>Higher PAP &amp; RVSVI did worse</td>
</tr>
<tr>
<td>Squara et al., 1998</td>
<td>1998</td>
<td>586</td>
<td>Primary and secondary ALI</td>
<td>PAC</td>
<td>PAP, RVSVI</td>
<td>RVF did not contribute to increased mortality when Pplat low</td>
<td></td>
</tr>
<tr>
<td>Monchi et al., 1995</td>
<td>1992–1995</td>
<td>177</td>
<td>Direct and indirect ALI</td>
<td>PAC</td>
<td>RAP, PAOP</td>
<td>RVF not predictive; RVF reversible in survivors</td>
<td></td>
</tr>
<tr>
<td>Jardin et al., 1997</td>
<td>1997–1999</td>
<td>156</td>
<td>Mixed ALI; no limitation to ventilatory plateau pressure (Pplat)</td>
<td>TTE</td>
<td>RV size and function</td>
<td>56% had RVF when Pplat &gt;35 cmH2O</td>
<td>At higher Pplat, RVF increases mortality</td>
</tr>
<tr>
<td>Vieillard-Baron et al., 2001</td>
<td>2001</td>
<td>75</td>
<td>Mixed ALI (with pressure-limited ventilation)</td>
<td>TEE</td>
<td>sPAP, RV size, and function</td>
<td>25% had RVF</td>
<td>sPAP &amp; RV not predictive; RVF predictive of increased mortality</td>
</tr>
<tr>
<td>Cepkova et al., 2007</td>
<td>2007</td>
<td>42</td>
<td>Mixed ALI</td>
<td>TTE</td>
<td>sPAP, RV size, and function</td>
<td>7% had RV dysfunction</td>
<td>RV and SPAP dysfunction not predictive of increased mortality</td>
</tr>
<tr>
<td>Jardin et al., 2007*</td>
<td>2007–2008</td>
<td>196</td>
<td>Mixed ALI when ventilatory pressure limited (Pplat &lt;26 cmH2O)</td>
<td>TTE</td>
<td>RV size and function</td>
<td>13% had RVF when Pplat limited</td>
<td>RVF did not contribute to increased mortality when Pplat low</td>
</tr>
<tr>
<td>Osman et al., 2009</td>
<td>2009</td>
<td>145</td>
<td>Mixed ALI</td>
<td>PAC</td>
<td>PAP, PAOP, RVSVI</td>
<td>9.6% had RVF</td>
<td>mPAP and CVP&gt;PAOP predictive; Early RVF not predictive of mortality</td>
</tr>
<tr>
<td>Bull et al., 2010</td>
<td>2010</td>
<td>501</td>
<td>ARDSNET group</td>
<td>PAC</td>
<td>mPAP, PAOP, TPG, PVRI</td>
<td>12% had RVF; (73% had PH) Overall reduction in PH/RV dysfunction over time</td>
<td>High TPG predicted mortality Persistent PH associated with worse outcomes</td>
</tr>
</tbody>
</table>

PAC, pulmonary artery catheterization; Pplat, plateau pressure; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; SPAP, systolic pulmonary arterial pressure; PH, pulmonary hypertension; ALI, acute lung injury; RVSVI, right ventricular stroke work index; RVF, right ventricular failure; TPG, transpulmonary gradient; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance; CVP, central venous pressure.
primate model of lung inflammation induced by intravenous bacterial lipopolysaccharide even before significant EC damage (111). Furthermore, elevated plasma levels predict the onset and increased mortality of patients with ALI (110, 139). Pulmonary endothelial ACE is responsible for regulation of vascular tone, hydrolysis of angiotensin I, and deactivation of bradykinin. Circulating levels fell early in experimental ALI before deterioration in respiratory parameters (25). Clinical indicator dilution studies suggest that pulmonary capillary endothelium-bound ACE is a good biomarker of endothelial dysfunction and ALI severity (98). Angiopoietin-2 may represent another biomarker of endothelial activation: it is produced by epithelial cells to activate EC, and levels are elevated in patients with ALI (14). Markers of endothelial injury have been associated with pulmonary dead space fraction in experimental lung injury (39) as well as with raised pulmonary vascular pressures (24).

**Initiation of endothelial dysfunction in acute lung injury.** Factors responsible for activating EC in ALI include microbes, immune complexes, drugs, toxins, reactive oxygen species, cytokines, microemboli, and activated leukocytes (99), as well as mechanical forces (for example strain associated with mechanical ventilation or increased shear). These stimuli may initiate innate and adaptive immune responses. In the former, recognition of conserved components of pathogens or of endogenous ligands released by injured tissue occurs through Toll-like receptors present on vascular cells. For example, following activation of Toll-like receptor-4 on EC by gram-negative bacterial endotoxin, transcription factors such as NF-κB lead to the expression of inflammatory mediators (4). The process of endothelial activation and dysfunction is illustrated in Fig. 2 and discussed below.

**Components of endothelial dysfunction in acute lung injury.**

**ENDOTHELIAL CELL–LEUKOCYTE INTERACTIONS (FIG. 2, POINT 1).** Activation of pulmonary microvascular endothelium in ALI generates expression of the EC-derived adhesion molecules (E- and P-selectins and ICAM-1) and the expression of corresponding neutrophil ligands (for example, L-selectin and β2-integrins such as CD11/CD18) (125, 130). These interactions result in the rolling and adhesion of neutrophils on the endothelium, as well described in the systemic endothelium (73). In addition to the upregulation of these adhesion molecules, slowing of neutrophil traffic also reflects important cytoskeletal alterations to neutrophils and a difference in their anatomical exit from the pulmonary compared with the systemic circulation (see **Microvascular cell sequestration**). Subsequent neutrophil extravasation through pulmonary capillaries and alve-
Table 2. Examples of endothelial cell products

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombomodulatory</td>
<td></td>
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<tr>
<td>Thrombomodulin</td>
<td></td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td></td>
</tr>
<tr>
<td>Ecto ADPases</td>
<td></td>
</tr>
<tr>
<td>TF</td>
<td></td>
</tr>
<tr>
<td>Vasoactive</td>
<td></td>
</tr>
<tr>
<td>Prostacyclin, thromboxane, and other prostanoids</td>
<td></td>
</tr>
<tr>
<td>Endothelins</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td></td>
</tr>
<tr>
<td>E-selectin</td>
<td></td>
</tr>
<tr>
<td>ICAM 1 and 2</td>
<td></td>
</tr>
<tr>
<td>VCAM</td>
<td></td>
</tr>
<tr>
<td>Inflammatory molecules</td>
<td></td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td></td>
</tr>
<tr>
<td>Cytokines: IL-6, IL-8, MCP-1</td>
<td></td>
</tr>
<tr>
<td>Class II MHC molecules</td>
<td></td>
</tr>
</tbody>
</table>

- MCP, monocyte chemoattractant protein; MHC, major histocompatibility class; TF, tissue factor.

... intravenous streptokinase to these patients led to angiographic clearance of the obstructions as well as increased microvascular filling, improved cardiac output, and oxygenation (48).

Sickle cell chest crises are a rare cause of ALI, often associated with severe PH. These are characterized by pulmonary microvascular occlusion due to adherent sickled erythrocytes, leukocytes, and infarcted bone marrow-derived emboli (134), as well as larger vessel thrombi in up to 20% of patients (32a). These patients have endothelial dysfunction with increased adhesiveness of erythrocytes to EC (117) and increased circulating levels of endothelin-1 (104).

The overlapping components of microvascular occlusion in ALI include sequestration of cells within the pulmonary microcirculation and the onset of intravascular coagulation. These are discussed in turn.

**Microvascular cell sequestration.** Neutrophils and platelets are likely to contribute to the occlusion of small vessels in ALI. Studies illustrate intrapulmonary trapping of neutrophils upon first-pass through the lung (77, 105) preceding their migration into the lung parenchyma. This is probably due to both to a mechanical obstruction [since neutrophil migration occurs at the level of the pulmonary capillaries, rather than at the level of the postcapillary venules as in the systemic circulation (33)] and to a morphological change in the neutrophils; in the latter, their cytoskeletal stiffness increases, reducing their deformability, thereby trapping them and arresting them at sites of inflammation. Perhaps surprisingly this does not appear to depend on classic adhesion molecules including L-selectin and CD11b-CD18 (146).

Despite the obvious importance of the neutrophil, ALI also occurs in neutropenic patients (115). It is interesting that neutropenic sheep had a blunted acute pulmonary hypertensive response following infused endotoxin compared with normal sheep, associated with lower plasma thromboxane levels (59). Leukocyte-dependent platelet microvascular sequestration was also demonstrated in a model of transfusion-related lung injury forming leukocyte-platelet aggregates. In this model, ALI severity was attenuated by platelet depletion or inhibition with aspirin (76).

**Intravascular coagulation.** An important shift to a procoagulant antiﬁbrinolytic state occurs in ALI. This was suggested over 30 years ago when a thrombin infusion led to respiratory insufficiency in dogs (112) and fibrin microthrombi were found postmortem (17). Changes in measureable procoagulant and antifibrinolytic factors are summarized (Table 3). For example, increased fibrin deposition is reflected by increased bronchoalveolar lavage levels of procoagulant mediators (ﬁbrinopeptide A, factor VII, and d-dimer) and reduced fibrinolytics [e.g., reduced urokinase and increased plasminogen activator inhibitor (PAI)] (13, 60). A reduction in the natural anticoagulant protein C occurs, suggestive of intravascular coagulation, associated with worse clinical outcomes (83). In lung injury models, administration of recombinant activated protein C (aPC) improved both lung edema and attenuated the increase in pulmonary artery pressure (136). In a large clinical trial where aPC was given to selected patients with ALI, it is noteworthy that despite no apparent beneﬁts in terms of ventilator free days or 60-day mortality, there was an improvement in dead space fraction (74). However, given the recent negative outcome from the PROWESS-shock trial (37a) and subsequent withdrawal of Xigris, it is unlikely that any potential beneficial...
effects of aPC on the pulmonary circulation will be investigated further.

Coagulation and inflammation. Activation of coagulation overlaps with inflammatory processes at the EC surface as illustrated in Fig. 4. For example, IL-6 upregulates tissue factor (TF) expression on EC (113), and tumor necrosis factor (TNF)-α attenuates fibrinolysis by stimulating the release of inhibitors of plasminogen activators (72). Exposure of TF activates the extrinsic pathway, resulting in thrombin release, fibrinogen cleavage to produce fibrin, and activation of platelets by binding protease-activated receptors (28). Release of vWF is also increased from EC in response to fibrin (107). In an attempt to balance increased intravascular coagulation, anticoagulant mechanisms are in place: thrombin binds to the
surface anticoagulant thrombomodulin and the surface endothelial protein C receptor (EPCR) releases aPC that degrades thrombin. Furthermore, there is a concurrent increase in tissue factor pathway inhibitor, although this is deemed insufficient to match the increase in TF in patients with ALI (42). Finally, inhibition of fibrinolysis is characteristic in ALI, which at least in part leads to a reduction in PAI-1 (13). The linkage of inflammation and intravascular coagulation is further supported by studies where prevention of vascular injury by aPC is dependent on inhibition of leukocyte activation (132).

Alterations in Pulmonary Vasomotor Tone

Rather than overt pulmonary vasoconstriction per se, increased pulmonary vascular resistance seen in ALI may reflect a loss of control of vascular tone, with an excess of pulmonary vasoconstrictor over vasodilator substances (Table 4). In animal models, direct injection of endotoxin leads to acute rises in pulmonary vascular resistance, probably through inhibition of nitric oxide (NO) (94), a phenomenon that may be mediated by endothelin B receptors (109). Derangements in acid-base balance also influence pulmonary vascular resistance (PVR) in patients with ALI (41, 86). The role of hypoxic pulmonary vasoconstriction in ALI is discussed, followed by a brief description of potential roles of relevant vasoactive mediators.

Hypoxic pulmonary vasoconstriction. Hypoxic pulmonary vasoconstriction (HPV) is a dynamic process predominantly mediated by precapillary arterioles (21) that promotes ventilation-perfusion matching by diverting blood flow away from poorly ventilated (diseased) and therefore hypoxic lung units. Although the mechanism of action of HPV is not fully understood, it is likely to involve inhibition of oxygen-sensitive K channels on vascular smooth muscle, leading to activation of voltage-gated calcium channels, Ca\(^{2+}\) influx and vasoconstriction (147). Basal NO release is likely to be important in limiting HPV (75), whereas reduced NO levels maintain it (93).

Table 3. Principle coagulation and fibrinolytic factors and their function in ALI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Location</th>
<th>Biological Function</th>
<th>Levels in ALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF</td>
<td>Constitutively expressed subendothelium (away from plasma coagulation factors)</td>
<td>Complexes with FVIIa to initiate extrinsic pathway to form thrombin (from prothrombin) and fibrin</td>
<td>Increased BAL levels in ALI (60)</td>
</tr>
<tr>
<td></td>
<td>Upregulated on platelets, monocytes, macrophages, and EC in response to cytokines</td>
<td>In ALI, generation of alveolar thrombin is mediated by TF (72)</td>
<td>Increased staining in lung tissue in ALI (in hyaline membranes, alveolar epithelial cells and macrophages) (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BAL contains elevated thrombin and fibrin (TF-induced) (60).</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>Procoagulant amino acid/protein on EC</td>
<td>Binds to other proteins, especially factor VIII; important in platelet adhesion</td>
<td>Increased in ALI (111)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF pathway inhibitor</td>
<td>Anticoagulant protein</td>
<td>Natural anticoagulant for extrinsic pathway: inactivates TF-FVIIa complexes after binding to Xa</td>
<td>Increased in ALI after endothelial injury (but not to match TF increase) (42)</td>
</tr>
<tr>
<td></td>
<td>Made by EC</td>
<td>Attenuates LPS-induced inflammatory responses in rats by inhibiting TNF-(\alpha) production by monocytes</td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td>15% Secreted into blood</td>
<td>1) Natural anticoagulant</td>
<td>Low plasma levels in ALI (140), associated with worse outcomes (83)</td>
</tr>
<tr>
<td></td>
<td>Serine protease inactive zymogen on EC surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activated (to aPC) by thrombin /thrombomodulin complex</td>
<td>aPC initiates FVa and FVIIIa so reducing downstream thrombin generation 2) Anti-inflammatory—e.g., aPC inhibits TNF production via NF-(\kappa)B and AP-1 signaling</td>
<td></td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>EC surface protein that binds thrombin</td>
<td>Anticoagulant cofactor in the thrombin-induced activation of protein C</td>
<td>Increased in edema fluid in ALI, associated with worse outcomes (140)</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor type-1</td>
<td>Produced by EC</td>
<td>Main inhibitor of tPA and urokinase: inhibits fibrinolysis</td>
<td>BAL levels reduced (13)</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Plasma glycoprotein inhibitor of thrombin</td>
<td>Anticoagulant; shown to prevent LPS-induced vascular injury and promotes endothelial release of prostacyclin (131)</td>
<td>Reduced in ALI (101)</td>
</tr>
</tbody>
</table>

EC, endothelial cell; LPS, lipopolysaccharide; tPA, tissue plasminogen activator; aPC, activated protein C.
Disordered, inhomogeneous HPV is a potential contributor to high altitude pulmonary edema, a condition also characterized by pulmonary hypertension, which may have parallels to ALI (8). The resulting uneven distribution of pulmonary blood flow with exaggerated hypoxic pulmonary vasoconstriction in turn exposes some pulmonary capillaries to high pressure (79) thought to induce endothelial stress failure (142).

**Pulmonary vasoactive mediators.** In the setting of pulmonary arterial hypertension (PAH), of many potential mediators, reduced NO and cyclooxygenase (COX) pathway signaling, and increased endothelin (ET)-I signaling occur. The resultant excessive pulmonary vasoconstriction and promotion of vascular cell proliferation are well recognized to contribute to the pathophysiology of PAH (58). Whether the same or similar mediators are responsible for the increase in pulmonary vascular tone and/or the pulmonary vascular remodeling in ALI is uncertain. The possible contribution of the COX, ET-1, and NO pathways to increased vasomotor tone in ALI is discussed.

**COX PATHWAY.** Arachidonic acid is metabolized by isoforms of the COX enzyme to prostaglandins, prostacyclin, and thromboxane. Some of these products are vasoactive and may be implicated in dysregulated vascular tone in ALI. For example, raised levels of prostacyclin and thromboxane-A2 were seen in models of sepsis and ALI (12), and reduced removal of prosta-
Table 4. Local factors that may increase pulmonary vascular tone in acute lung injury

<table>
<thead>
<tr>
<th>Local Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low mixed venous P\textsubscript{O}2: hypoxic vasoconstriction</td>
</tr>
<tr>
<td>Acidosis (hypercapnia)</td>
</tr>
<tr>
<td>Increased sympathetic tone</td>
</tr>
<tr>
<td>High airway pressure</td>
</tr>
<tr>
<td>Vasoconstrictor: vasodilator imbalance</td>
</tr>
<tr>
<td>Excess ET-1, TXA-1, 5-HT</td>
</tr>
<tr>
<td>Reduced nitric oxide, prostanoids</td>
</tr>
<tr>
<td>Effects of endotoxin</td>
</tr>
</tbody>
</table>

5-HT, serotonin; ET-1, endothelin-1; P\textsubscript{O}2, partial pressure of oxygen; TXA-1, thromboxane A1.

Endoglin E1 was demonstrated in dilution studies in patients with ALI (47). Thromboxane-A2 release from leukocytes following endotoxin challenge is likely to contribute to the acute elevation in pulmonary artery pressure, as demonstrated in a sheep model of ALI (59).

ET-1. ET-1 is a potent naturally occurring vasoconstrictor peptide and smooth muscle mitogen. It is produced predominantly by EC, and also by the more numerous PASMC (and fibroblasts). Stimuli for ET-1 production include hypoxia, endotoxin, and cytokines, via NF-\textit{kB}–dependent signaling (145). There is evidence for upregulation of ET-1 in models of direct lung injury (68, 116) and in patients with ALI (34), where circulating levels are elevated and fall in association with clinical improvement and a fall in PVR (69). Treatment with an endothelin receptor antagonist in an oleic acid model suggested that ET-1 contributes to the early increase in PVR in ALI (56).

NO. NO is an endogenous pulmonary vasodilator. It is produced by EC and other cells and acts via soluble guanylate cyclase to produce cGMP in vascular smooth muscle. In addition to basal vasodilatation, NO inhibits platelet and leukocyte adhesion, platelet aggregation, and smooth muscle cell proliferation (102, 122). In PAH, expression of pulmonary endothelial NO synthase is decreased (46). It is not known whether this is the case in ALI, where NO levels may even be increased. In a rodent lipopolysaccharide-induced model of severe sepsis, NO synthase was induced in both systemic and pulmonary vessel walls leading to the production of large quantities of vasoactive NO (50). Rather than increasing vasodilatation, however, these high NO levels may combine with reactive oxygen species to form the highly damaging reactive nitrogen species peroxynitrite (40, 124). Finally, there is evidence for decreased exhaled NO in ALI (18), although the relevance of this to the vasculature is uncertain.

Table 5. Conditions that may inhibit hypoxic pulmonary vasoconstriction in acute lung injury

<table>
<thead>
<tr>
<th>Pathological</th>
<th>Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin (59)</td>
<td>\beta-Adonists, \alpha-adrenoceptor antagonists, nitro-glycerine, prostacyclin (82)</td>
</tr>
<tr>
<td>Alkalosis (22)</td>
<td>Volatile anesthetic agents (88)</td>
</tr>
<tr>
<td>Hypothermia (10)</td>
<td>Calcium channel blockers (65)</td>
</tr>
<tr>
<td>Postural effects (138)</td>
<td>Nitroprusside (63)</td>
</tr>
<tr>
<td>Raised left atrial pressure (70)</td>
<td>Increased positive end-expiratory pressure (71)</td>
</tr>
</tbody>
</table>

Fig. 5. Increased pulmonary vascular resistance at extremes of lung volumes. This figure represents measurements made in an animal lobe preparation in which the transmural pressure of the capillaries is held constant. It illustrates, at least in noninjured lungs, that at low lung volumes (as may occur with atelectasis), extra-alveolar vessels become narrow, and smooth muscle and elastic fibers in these collapsed vessels increase PVR. At high lung volumes, as alveolar volumes are increased and walls are thinned, capillaries are stretched, reducing their caliber and also increasing PVR (adapted from \textit{John West's Essential Physiology}, 8th edition, Philadelphia: Lippincott & Williams, with permission) (141).

Extrinsic Vessel Compression

Several factors causing mechanical compression of pulmonary capillaries and veins may increase intravascular pressure in ALI (Fig. 1). In areas of lung with high alveolar volumes, alveolar pressure exceeds intra-capillary pressure (West zone 1), which through compression of capillaries may increase PVR (Fig. 5). This is demonstrated in patients following a Fontan procedure, where venous blood is shunted from the right atrium to the pulmonary arteries, and pulmonary blood flow is directly dependent on venous return to the right heart: pulmonary blood flow is reduced by positive pressure ventilation and augmented by negative pressure ventilation (103). In some patients with ALI elevated PVR, the resulting RV dysfunction may be rapidly reversed by reducing the airway pressure (135). At low lung volumes, such as in areas of atelectasis, PVR may also be increased through increased tone in extra-alveolar muscular vessels (Fig. 5) (141). Pulmonary veins may also be compressed by edema or areas of atelectasis, which in theory will also increase capillary pressure and pulmonary arterial pressure, as well as increasing vascular inflammation (66). Finally, the overall reduction in total lung volume will increase PVR, which may at least in part be due to compressive effects.

Pulmonary Vascular Remodeling and Neomuscularization

Evidence for structural changes to small pulmonary vessels including fibrous intimal proliferative lesions was derived from postmortem studies in the era when higher airway pressures and inspired oxygen fraction were deemed to be acceptable.
(129). In intermediate and late cases (beyond 18 days’ duration) smooth muscle hypertrophy and neomuscularization of previously nonmuscular vessels were evident, with morphometric analysis revealing thrombosis, medial thickening, and decreased vascular density of pre- and intra-acinar vessels (120, 129). Proposed mechanisms may be similar to other causes of PH associated with chronic respiratory disease, where hypoxia is an important precipitant, and also likely to reflect the smooth muscle mitogenic effects of ET-1 as well as inflammation itself. For example, cytokines such as IL-6 are implicated in vascular remodeling in PAH (123). It has indeed been shown that repeated lung injury induced by 10–14 wk of endotoxin injection can lead to PH associated with remodeling (90).

Diagnosis of PH in ALI

The diagnosis of PH and RV dysfunction in ALI may be difficult since clinical signs may be nonspecific. Potential aides to clinical diagnosis include biomarkers such as brain natriuretic peptide (BNP), a marker of ventricular stretch and biomarkers reflecting endothelial dysfunction (see Table 3). These are, however, not validated in patients with pulmonary vascular dysfunction in ALI and likely to be very difficult to interpret. One study investigated BNP as a potential biomarker of RV dilatation early in ALI: serum BNP levels were found to be increased in the cohort overall, and RV dilatation on echocardiography was seen in 11 (26%) of patients. However, no correlation was found between elevated BNP and RV dilatation, although there was a moderate correlation between BNP and pulmonary dead space (27). It would be of interest to assess potential correlation of BNP with RV dysfunction, but this would require a much larger number of patients. The use of pulmonary artery catheters for invasive hemodynamic monitoring was previously commonplace in the management of ALI. We are not suggesting this practice is resumed, but given the adverse prognostic association of pulmonary vascular dysfunction with survival, consideration of the vascular component of ALI is indicated. Echocardiography is a very useful first-line diagnostic tool and is frequently used; however, it does have some limitations. These might include difficult visualization of the RV during trans-thoracic echocardiographic studies, and the nonsymmetrical shape of the RV, making it hard to reproducibly assess RV contractility or volume (53). Pulmonary arterial catheterization remains the gold standard for assessment of PH in other settings, and it may be useful both as a diagnostic and monitoring tool in ALI in the setting of RV dysfunction secondary to pulmonary hypertension. Cardiac output can be measured by several indicator dilution techniques and by oesophageal Doppler, but none of these provide a measure of PH and RV afterload, which therapies may manipulate directly or indirectly.

Potential Therapeutic Strategies

RV dysfunction in ALI may prevent the cardiac output rising appropriately or only doing so at the expense of systemic venous hypertension. This may limit oxygen delivery and contribute to other organ dysfunction and worse outcomes. Therapies can be directed at reducing PH directly. The systemic administration of vasodilators to patients with ALI may, however, worsen oxygenation due to blunting of HPV (29), as seen in the setting of PH in chronic hypoxic lung disease (44). Mechanical ventilation may also have profound effects on RV afterload and function with reductions in airway pressures improving RV function and hemodynamic stability (62, 135).

Inhaled NO. Inhaled NO is a potent selective pulmonary vasodilator, which reduced PVR and improved cardiac output in patients with acute RV failure in the setting of ALI (11, 15, 16, 38, 108). Beneficial effects on the RV probably require higher doses of NO than those required to improve oxygenation (54). Continuous administration of NO is needed to reduce PVR, and oxygenation may worsen at high doses (43). A reduction in RV afterload, however, does not appear to correlate with any clinical outcome benefits in ALI (19, 32, 127), and its use is largely confined. Potential limitations of NO include its expense, an association with acute kidney injury (2), and accumulation of toxic metabolites, although this is not usually a clinically significant problem (49). Rebound PH with RV dysfunction on weaning from NO may be reduced with phosphodiesterase type 5 inhibitors (45).

Other pulmonary vasodilators. Intravenous prostacyclin also reduced PVR and improved RV function in studies of ALI, although at the expense of increased intrapulmonary shunt (106). Inhaled administration of prostacyclin (133, 137, 151) and inhaled prostaglandin E1 (89) improved oxygenation and reduced PVR in ALI with minimal effects on SVR: further studies of prostacyclin and iloprost in patients with PH and ALI (3, 117a, 133a) are ongoing. NO and intravenous prosta-
cyclin have been combined in ALI with effective reduction of PVR without adverse effects (67). Levosimendan is a calcium-sensitizing agent that also vasodilates the pulmonary, systemic, and coronary vessels by activating adenosine triphosphate-sensitive potassium channels. In a preliminary study of 35 patients, a 24-h infusion of leovsimendan increased RV ejection fraction and cardiac output compared with placebo (92). Agents such as sildenafil and bosentan have not been investigated formally in ALI (96).

Potential future therapies. Potential ALI therapies such as those targeting intravascular coagulation, neomuscularization, or endothelial/epithelial function may limit PH. There are no data about their concomitant effects on PH and RV function. For example, prior treatment with antiplatelet therapy may protect patients from ALI (37) but the effects on PH are unknown. The effects of other potential agents such as interferon-β, anti-tissue factor, anti-VEGF, HMG-CoA reductase inhibitors, and neuromuscular blockade are also unknown.

CONCLUSION

In ALI, the presence of significant PH is associated with increased mortality, although the incidence of acute RV failure does appear to have fallen over the last few decades probably in relation to use of lung protective ventilation strategies. Although PH may simply be a surrogate for the extent of pulmonary damage, it is possible also that the associated right ventricular dysfunction and systemic venous hypertension contribute significantly to further organ dysfunction. Moreover, the reduced gas transfer factor in patients who survive ALI suggests that pulmonary vascular dysfunction persists, at least in a selection of patients.
Several mechanisms may contribute to PH in ALI, including endothelial dysfunction, microvascular occlusion, an imbalance of vasoactive mediators, extrinsic compression of small vessels, pulmonary vascular neomuscularization, and remodeling. Whether these processes could be targeted to reduce PH and thereby modify acute outcome or even longer term cardiovascular performance is not known, but represent strategies that are largely untested.

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PULMONARY HYPERTENSION IN ACUTE LUNG INJURY


