

# Lung injury in acute pancreatitis: mechanisms, prevention, and therapy

Conor J. Shields, MB, BCh, AFRCSI, Desmond C. Winter, MD, FRCSI, and H. Paul Redmond, BSc, MCh, FRCSI

Lung injury is the most pertinent manifestation of extra-abdominal organ dysfunction in pancreatitis. The propensity of this retroperitoneal inflammatory condition to engender a diffuse and life-threatening lung injury is significant. Approximately one third of patients will develop acute lung injury and acute respiratory distress syndrome, which account for 60% of all deaths within the first week. The variability in the clinical course of pancreatitis renders it a vexing entity and makes demonstration of the efficacy of any specific intervention difficult. The distinct pathologic entity of pancreatitis-associated lung injury is reviewed with a focus on etiology and potential therapeutic maneuvers. *Curr Opin Crit Care* 2002, 8:158–163 © 2002 Lippincott Williams & Wilkins, Inc.

Department of Academic Surgery, Cork University Hospital, and National University of Ireland, Cork, Ireland.

Correspondence to: H. Paul Redmond, BSc, MCh, FRCSI, Department of Academic Surgery, Cork University Hospital, Wilton, Cork, Ireland; e-mail: profredmond@eircom.net

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## Abbreviations

<b>ALI</b>	acute lung injury
<b>ARDS</b>	acute respiratory distress syndrome
<b>ICAM-1</b>	intercellular adhesion molecule-1
<b>MAP</b>	mitogen-activated protein
<b>PMN</b>	polymorphonucleocyte (neutrophil)
<b>TNF</b>	tumor necrosis factor

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Acute pancreatitis is thought caused principally by auto-digestion of the pancreas, with extravasation of proteolytic enzymes and vasoactive mediators leading to inflammation of contiguous tissues [1]. Entry of these noxious substances into the systemic circulation results in multiorgan complications [2]. The mechanisms that initiate progression to end-organ injury in pancreatitis remain ill defined [1]; however, excessive neutrophil cytotoxicity is convincingly implicated in the development of lung injury, the most pertinent manifestation of extra-abdominal organ dysfunction in pancreatitis [3].

Approximately one third of patients will develop acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [2], which account for 60% of all deaths within the first week [2]. Improved supportive and ventilatory treatment of these critically ill patients has resulted in a modest decline in the overall mortality rate; however, the underlying inflammatory process remains unchecked by medical intervention [4•]. Various therapeutic endeavors have been proposed, but few exhibit pertinence in the clinical setting [5]. Supportive care, including mechanical ventilatory support, remains the principal determinant of outcome, but disappointingly, mortality in this cohort exceeds 75% [6].

## Mechanisms of lung injury

Increased pulmonary microvascular permeability with protein-rich transudate spilling into the alveolar spaces and decreased lung compliance are the hallmarks of ALI. These manifest clinically as progressive hypoxemia with radiologic evidence of diffuse infiltrations. Physicochemical alterations in the pulmonary vascular barrier are mediated by the local release of cytotoxic and vasoactive substances [7]. Evidence for the central role of these alterations in vascular permeability is derived from studies demonstrating increased bronchoalveolar lavage protein levels and lung wet to dry weight ratios [8,9•] in models of ALI. Experimental pancreatitis also induces intra-alveolar edema, distal airway contraction [10], endothelial cell damage, and leukocyte sequestration [11], as evidenced by pulmonary myeloperoxidase activity [8,9•].

The propensity of a heterogenous group of extrapulmonary pathologies to engender a diffuse and frequently life-threatening lung injury is predicated on the complex

interplay of endogenous proinflammatory and anti-inflammatory mediators liberated as a consequence of a distant insult. Given the retroperitoneal origin of this inflammatory process, attention has focused on explaining the induction of respiratory dysfunction. Recent studies suggest that the liberation of the pancreatic enzyme elastase may lead to systemic activation of inflammatory cells [12•,13]. The agent of tissue destruction is the neutrophil, a cell with considerable cytotoxic potential. Unrestrained activation of neutrophils has been strongly implicated in the development of ALI [9•]. The sequence of events leading to lung injury culminates in the inappropriate entrapment of neutrophils within lung tissue [3].

### Neutrophil recruitment

Teleologically, neutrophil activation and transmigration equip the host to withstand and combat septic challenge and are integral to the successful functioning of the innate immune system. However, in states of immunologic disarray, the unleashing of their potent destructive faculties results in unnecessary tissue damage. The pivotal importance of neutrophil accumulation in the instigation of pulmonary injury is substantiated by the findings of studies using agents to attenuate or abrogate neutrophil cytotoxicity [14].

The mediation of neutrophil entrapment within the lung is a consequence of complement activation, cytokine production, and stimulation of adhesion molecule expression and alveolar macrophages [15]. Secretion of chemoattractant substances, including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-8, fMet-Leu-Phe (a bacterial wall product), and complement factor C5a, results in enticement of neutrophils to the pulmonary microvasculature. Exposure of neutrophils to these endogenous inflammatory mediators leads to an upregulation of  $\beta$ -2-integrin expression and an enhanced adhesive potential.

The signaling molecule TNF- $\alpha$ , discharged from activated macrophages, exerts a considerable amplifying influence on the systemic inflammatory response. The severity of pancreatitis has been shown to correlate with TNF- $\alpha$  activity [16], and high concentrations can be found in ascitic fluid [17]. After the onset of pancreatitis, TNF- $\alpha$  production within lung parenchyma reaches significant levels [18], and large quantities of cytokines, including TNF- $\alpha$ , are released from macrophages via a p38 mitogen-activated protein (MAP)-kinase activated pathway [19].

The predominant role of monocyte-derived inflammatory cytokines in promoting neutrophil recruitment, adherence, and extravasation is further emphasized by the observation of a positive correlation between clinical severity and serum concentration of IL-8 in pancreatitis.

IL-8 is a potent chemoattractant and a leukocyte and T-cell activator [20]; IL-8 found in the air spaces of patients with ARDS is associated with high mortality [21]. IL-8 may also play a role in promoting polymorphonuclear leukocyte (PMN) traffic into lung tissue via a CD18 independent pathway [22,23], because inhibition of CD18 expression results in merely a 40% reduction in PMN accumulation [24•].

### Neutrophil adhesion

The cytokine-driven inflammatory response results in upregulation of intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells, and the ligand  $\beta$ -2-integrin (CD11b/CD18) expression on leukocytes. This facilitates neutrophil-endothelial cell interaction, ultimately engendering endothelial hyperpermeability. The initial step in a process culminating in firm neutrophil-endothelial cell adherence is neutrophil rolling, involving L-selectin and P-selectin and mediated by the neutrophil-endothelial interactions.

The detection of elevated circulating levels of ICAM-1, an inducible endothelial cell surface protein, in patients with pancreatitis [25] has led to speculation that this ligand for  $\beta$ -2-integrin may be a major determinant of leukocyte adhesion [26]. This notion is supported by the finding that pulmonary expression of ICAM-1 is increased in pancreatitis [27,28], and that ICAM-1-deficient mice with pancreatitis evince less lung injury [27] than their disease-free counterparts.

In addition to alterations in the adhesive qualities of neutrophils, conformational changes in the actin cytoskeleton may further enhance accumulation of leukocytes in vascular beds. Polymerization of F-actin filaments in activated neutrophils may render cytoskeletal structure more resolute and less inclined to deform [29], resulting in an entrapment of activated leukocytes within alveolar capillaries. Phagocytosis of entrapped apoptotic neutrophils at the site of inflammation limits neutrophil-mediated tissue insult [3]. Dysfunction of this regulatory mechanism is a pivotal component in the propagation of the massive inflammatory response evident in systemic inflammatory response syndrome.

### Neutrophil activation

Although the onset of endothelial hyperpermeability parallels the accumulation of leukocytes within the lung, mere sequestration does not engender endothelial leak, but rather the subsequent adhesion and activation of the entrapped neutrophils [30,31]. The infiltration of activated and adherent neutrophils into the lung parenchyma and their ultimate degranulation with release of proteolytic enzymes and reactive oxygen species result in the stigmata of lung injury. Some of the cellular products that play a role in the pulmonary damage include nitric oxide, a potent vasoregulatory mediator, and arachidonic acid metabolites [32,33]. Nitric oxide, released

by alveolar macrophages, has been implicated in the development of microvessel permeability, possibly through the generation of free radicals [34]. Enhanced nitric oxide synthesis has been implicated in pancreatitis induced by a range of experimental protocols and appears to be a central event [35].

Neutrophil-derived reactive oxygen species are believed to be a product of the nicotinamide adenine dinucleotide phosphate oxidase complex, and inhibition of this pathway results in an attenuation of lung injury [36]. The unleashing of proteases such as elastase by PMNs further contributes to pulmonary injury [37]. Recent studies have demonstrated that migration of leukocytes through the basement membrane is associated with the release of matrix metalloproteinases, whereas their inhibition correlates with limited transendothelial transport [38].

### **Signal transduction pathways**

Neutrophil activation leads to a redistribution of various cytoskeletal proteins and is associated with tyrosine kinase activation [39], increasing integrin binding avidity through the initiation of complex intracellular signal transduction pathways. Phosphorylation of various protein tyrosine kinases, including the lipid kinase phosphatidyl inositol 3-kinase [40], protein kinase-C [41], Src-kinases, and the MAP-kinases such as p38 MAP-kinase, extracellular signal-related kinase, and Jun N-terminal kinase [42], is a recurrent theme in signal transduction. The activation of p38 MAP-kinase by, among others, lipopolysaccharide [43] augments neutrophil cytotoxic potential by causing an escalation in the liberation of free radicals, enhancing integrin adhesive qualities [44], and regulating the synthesis of proinflammatory cytokines [4•].

The induction of the local transcription factor nuclear factor- $\kappa$ B and the consequent expression of multiple rapid response inflammatory genes, culminating in the release of IL-6 and IL-8, TNF- $\alpha$ , and cyclo-oxygenase-2, has been described in a variety of inflammatory and autoimmune conditions, including inflammatory bowel disease [45], rheumatoid arthritis [46], and endotoxin-induced lung inflammation [47], in which a temporal correlation has been observed between nuclear factor- $\kappa$ B activation in lung and the expression of cytokine mRNA [48]. Not surprisingly, expression of this dimeric transcription factor has also been described in acute pancreatitis [12•,49,50•]. Transcriptional upregulation within pulmonary vascular endothelium of IL-6 and IL-8 production has been observed after exposure to pancreatic ascites [51], whereas the systemic administration of pancreatic elastase results in pulmonary activation of nuclear factor- $\kappa$ B [12•].

### **Type II pneumocytes**

The association between quantitative and qualitative deficiencies in surfactant production and lung injury has long been established. After an inflammatory insult, type

II cells differentiate into type I cells [52], further compromising pulmonary phospholipid synthesis.

### **Prevention and treatment**

The seeming unresponsiveness of pancreatitis-associated lung injury to intervention renders this condition a vexing entity and makes demonstration of the efficacy of any specific intervention difficult. Treatment remains largely nonspecific. Although there is good evidence for the use of antibiotics [53] and nutritional support [53,54•] in severe pancreatitis, paradigms of treatment based on antisecretory agents have been profoundly disappointing [55]. Once a decrease in lung compliance and an impairment of gas exchange become clinically manifest, the progression to ARDS and, ultimately, multiple organ dysfunction syndrome is well established, frequently rendering prevention unattainable. Ventilation is the principle therapeutic maneuver, although recent interest has focused on suppressing the overly exuberant inflammatory response. Attempts to influence the interplay between proinflammatory and anti-inflammatory cytokines may offer the best prospect of diminishing pulmonary involvement. However, there are few accepted therapeutic endeavors in this regard.

Inhibition of nuclear factor- $\kappa$ B expression or signaling is immunosuppressive and modulates cytotoxicity, and has been shown to reduce lung injury and mortality rate in experimental models of pancreatitis [56,57]. Although nitric oxide has been implicated in the progression and amplification of the systemic response, its exact role is disputed, because some authors have found it protective when administered pharmacologically [11]. In contrast, some therapeutic success in improving local and systemic injury has been achieved by inhibiting nitric oxide synthesis in animal models [33,58]. Excessive nitric oxide production is associated with diaphragmatic dysfunction [59], which may be attenuated by an inducible nitric oxide synthase inhibitor [60].

Other strategies to attenuate pulmonary injury in pancreatitis have focused on reducing neutrophil and macrophage influx or function. These are attractive proposals because the lung damage is largely cell-mediated [61,62]. Inhibition of neutrophil L-selectin and pulmonary ICAM-1 expression has been shown to prevent leukocyte microvascular sequestration and results in an attenuation of end-organ damage [63•,64–66]. Treatment of rats with a neutralizing antibody against cytokine-induced neutrophil chemoattractant offers protection from pancreatitis-associated ALI [61,67], whereas blockade of p38 MAP-kinase attenuates pulmonary TNF- $\alpha$  and nitrite production, impacting lung injury favorably [4•]. Another target of monoclonal antibody therapy is IL-8, which plays a predominant role in neutrophil chemotaxis. Anti-IL-8 suppresses serum IL-8 and TNF- $\alpha$  and pulmonary expression of  $\beta$ -2-integrin, resulting in

diminished pulmonary damage [68]. Pretreatment of rabbits with a synthetic IL-10 agonist reduces the stigmata of lung injury [69]; however, a recent randomized trial exploring the potential of IL-10 for prophylaxis in humans failed to show any benefit associated with this potent anti-inflammatory cytokine [70]. The platelet activating factor antagonist acetyl hydrolase is currently in clinical trial after promising anti-inflammatory results in an animal model [71]. Animal models of pancreatitis have a propensity for responding to manipulation of cytokine pathways, but, lamentably, this response rarely translates into a demonstrable clinical effect in human trials. Furthermore, the pharmacodynamics or toxicity of these agents may limit their value in critically ill patients with multiple organ dysfunction syndrome.

The immunomodulatory effects of hypertonic saline infusion provide potential strategies for attenuating inappropriate neutrophil activation. Significant attenuation of end-organ injury has been demonstrated in an animal model of pancreatitis with intravenous hypertonic resuscitation [8]. The benefits of transient hyperosmolar resuscitation extend to the attenuation of receptor-mediated PMN functions, including the downregulation of neutrophil oxidative burst activity and adhesion molecule expression, and the suppression of PMN activation [72].

Selective reduction of hyperresponsive inflammatory infiltrates may also be achieved in the lung through the tracheobronchial route. Aerosolized hypertonic saline is as successful as intravenous infusion in ameliorating pulmonary infiltration and damage in experimental pancreatitis [8,9•]. The advantages of this route include anatomic specificity and potential safety in the presence of renal, biochemical, or cardiac abnormalities. Furthermore, it avoids potential central nervous system damage with intravenous solutions of varying tonicity [73].

### Ventilation strategies

Current critical care stratagems attempt to improve lung mechanics and oxygenation in patients with ARDS by optimizing alveolar recruitment and maintaining lung volume. Persistently atelectatic lung predisposes to superimposed infection and necessitates use of increased airway pressure, increasing the potential for ventilation-induced alveolar injury. Sustaining lung recruitment is critical to prevent lung injury arising from the subjection of lung units to repeated shear stress. Recent data have demonstrated that low tidal volume ventilation (approximately 6 mL/kg) reduces mortality [74•,75] and, when combined with positive end-expiratory pressure, induces as little lung damage as high frequency oscillation ventilation [76].

A number of novel ventilation strategies are under consideration. A significant reduction in pulmonary shunt in

patients with ALI and ARDS was observed with prone positioning [77], resulting in a decrease in hypoxemia [78]. Numerous animal studies have shown improved ventilation mechanics after the intra-alveolar administration of perfluorocarbons, and the potential adjunctive role of liquid ventilation has aroused considerable interest [79]. The dense and inert nature of perfluorocarbons facilitates distribution to collapsed and dependent lung units, where a reduction in surface tension results, and augments lung recruitment. The deleterious effects of heightened alveolar surface tension caused by surfactant depletion underlie partial liquid ventilation and the therapeutic instillation of exogenous surfactant. Administration of surfactant has been shown to attenuate ventilation-induced lung injury in animal models [80]. Preservation of surfactant producing type II cells may facilitate recovery from lung injury.

### Nutrition

Severe pancreatitis induces a state of profound catabolism, necessitating nutritional support. Traditionally, total parenteral nutrition has been used to provide exogenous nutrients; however, enteral nutrition offers several putative benefits: restitution and preservation of gut barrier integrity, and less septic complications. Furthermore, induction of ICAM-1 expression has been noted subsequent to parenteral feeding [27]. A recent meta-analysis of trials noted a trend toward less adverse outcomes with enteral feeding [81], and another study observed the induction of a more benign immunologic profile [82].

### Conclusions

Future attempts to devise effective treatment regimes for this frustrating disease are likely to focus on interrupting the propagation of the inflammatory cascade at the cellular level. Regulators of cellular signal transduction pathways such as p38 MAP-kinase and nuclear factor- $\kappa$ B inhibitors provide potential pharmacologic targets for suppressing unchecked and unrestrained inflammation. Inhalational therapy with nitric oxide, aerosolized hypertonic saline, or pharmacologic agents may represent the most plausible interventions to improve outcome in patients with pancreatitis-induced ARDS. Clinical trials are warranted.

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