Pancreatitis-associated acute lung injury: new insights

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Pancreatitis-Associated Acute Lung Injury*

New Insights

Catherine M. Pastor, MD, PhD; Michael A. Matthay, MD, FCCP; and Jean-Louis Frossard, MD

The ARDS is an important cause of mortality in critically ill patients. Its exact incidence is unknown but may be as high as 75 per 100,000 population in the United States.1 The risk factors for developing this syndrome include pneumonia, gastric aspiration, sepsis, shock, and multiple transfusions, as well as less common causes such as multiple trauma, multiple fractures, cardiopulmonary bypass, drug overuse, and acute pancreatitis. Although acute pancreatitis represents one of the less common clinical disorders associated with ARDS, severe attacks of pancreatitis are frequently associated with acute lung injury and respiratory failure.2

Acute pancreatitis is an inflammatory process that usually occurs in a normal organ and is diagnosed mainly by acute abdominal pain associated with a concomitant increase in the serum amylase and lipase concentrations.3,4 Gallstone migration into the common bile duct and alcohol abuse account for most of the etiologies of the disease in western countries.5,6 The injury is usually mild, but severe pancreatic injury develops in 20% of patients, and 15 to 25% of these patients will die.5,7

Studies have examined the clinical spectrum of lung injury associated with acute pancreatitis. Although these clinical reports have provided some insights into the pathogenesis of acute respiratory insufficiency associated with acute pancreatitis, several experimental studies have provided new understanding of the pathophysiology of acute pancreatitis-associated lung injury. The objective of this article is to review the clinical studies, including the original descriptions published >30 years ago, as well as the recent experimental findings that have used either pharmacologic blockade or genetically modified animals.

Pancreatitis-Associated Lung Injury in Humans

Pulmonary/Pleural Abnormalities in Acute Pancreatitis

The incidence of the pulmonary complications varies from 15 to 55%, and their severity varies from mild hypoxemia without clinical or radiologic abnormalities to severe ARDS (Fig 1, Table 1).8 Approximately 10% of patients show alveolar edema on the chest radiograph,23 and progressive hypoxemia develops in one third of patients, a finding that is evident within hours or may appear within 2 to 3 days. Pulmonary vascular resistance does not increase as an immediate consequence of pancreatitis, and the pulmonary edema results from an increase in lung microvascular permeability.23,24 In one study,12 published in 1972, 9 of 50 patients (18%) with acute pancreatitis had diffuse pulmonary infiltrates consistent with lung injury. Five patients (10%) died of the

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ARDS, and four survivors recovered with normal pulmonary function. In more recent studies, the incidence of abnormal chest radiographs was also high. For example, in 140 consecutive patients with acute pancreatitis, pulmonary infiltrates were found in 26% (9% bilateral and 16% unilateral) within 24 h after hospital admission.13 In a more recent study, 10 abnormal chest radiographic findings were present in 20% (106 of 539 patients); 6% had pulmonary infiltrates and 14% had pleural effusions (18 right sided, 25 left sided, and 34 bilateral). The mortality rate significantly correlated with the presence of pulmonary infiltrates and effusions. Logistic regression analysis showed that radiologic abnormalities were associated with a 15-fold increase in the mortality rate.10

Pleural effusions are often associated with acute pancreatitis. In one study, 3 to 17% of patients with acute pancreatitis acquire pleural effusions.11 Most effusions were left sided, although some were bilateral. Pleural fluid amylase concentration was increased up to 30 times over the simultaneous serum value and remained elevated even after the serum concentrations had returned to a normal level. Large pleural effusions were associated with subdiaphragmatic collections of fluid. The immobility of the diaphragm induced by local inflammation seems to be responsible in part for these pleural complications.25 Interestingly, in 25 patients with amylase-rich pleural effusions, 4 patients had evidence of either acute or chronic pancreatitis.26 In those patients, the pancreatic isoenzyme was dominant in the pleural fluid, while the salivary type predominated in the remaining 21 patients free of pancreatic disease.26

A reduced PaO₂ on hospital admission has been long regarded as a prognostic factor for the severity of acute pancreatitis. In 1973, Ranson et al2 reported that 58% of the patients hospitalized for acute pancreatitis had arterial hypoxemia within 48 h after admission. During this period, clinical signs were obvious in 5% and radiologic signs were seen in 8% of the patients. Arterial hypoxemia was not correlated with the severity of acute pancreatitis, serum amylase concentration, or fluid administration. In a subsequent study,27 43% of the patients with acute pancreatitis were moderately hypoxic on room air (PaO₂ ≤ 68 mm Hg).

In 1978, de Troyer et al9 reported that in 22 patients with uncomplicated acute pancreatitis (without clinical or radiologic evidence of pulmonary injury), the PaO₂ was < 75 mm Hg in only 4 patients. However, most patients had a marked decreased in the vital capacity and FEV₁. The functional residual capacity was normal and the total lung capacity was

<table>
<thead>
<tr>
<th>Table 1—Clinical Characteristics of Pancreatitis-Associated Lung Injury</th>
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<td>Characteristics</td>
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<tr>
<td>Hypoxemia</td>
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<tr>
<td>Chest radiograph</td>
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<tr>
<td>Pleural effusions</td>
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<td>Pulmonary infiltrates</td>
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<tr>
<td>Increased microvascular permeability</td>
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<tr>
<td>Pathogenesis</td>
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<tr>
<td>Phospholipase A₂</td>
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<tr>
<td>IL-8</td>
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<tr>
<td>TNF-α, IL-1, IL-6</td>
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<tr>
<td>Pancreatic enzymes</td>
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<tr>
<td>Treatments</td>
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<tr>
<td>Thoracic duct drainage</td>
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<tr>
<td>Octreotide</td>
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</table>

Figure 1. Pulmonary/pleural abnormalities in patients with acute pancreatitis. Top, A: mild left pleural effusion on day 2. Bottom, B: bilateral pulmonary infiltrates on day 5.
moderately decreased. By contrast, the pulmonary diffusing capacity for carbon monoxide was significantly reduced (78% of predicted values). Interestingly, an increase in lung vascular permeability to plasma proteins within 48 h after hospital admission (measured by the labeled transferrin technique) was present in the patients who later died (p < 0.01). The index remained within normal limits in the patients who survived. Although all patients with an abnormal index were hypoxemic, the PaO2 values did not reflect the extent of increased lung vascular permeability. Similar results were published more recently in another study. Thus, these studies provide reasonable evidence that the pulmonary infiltrates and pulmonary edema in most patients with acute pancreatitis can be attributed to an increase in lung vascular permeability.

Evolution of Pulmonary Injury Over Time

In severe acute pancreatitis, the early phase is associated with a systemic inflammatory response syndrome. One third of the deaths occurs during this early phase, and 50% of those deaths are associated with severe lung injury. The second phase of severe pancreatitis is closely related to the development of complications in the injured pancreas. These complications include fat necrosis, pseudocyst formation, and pancreatic abscess. Each of these complications can be related to the release of activated digestive enzymes. Release of lipase leads to adipose tissue injury and fat necrosis that usually takes place in peripancreatic tissue. The extraductal collection of pancreatic secretions, resulting from ductal rupture, forms a pseudocyst. The more severe complication is abscess, which is associated with substantial morbidity and mortality. Pancreatic abscess includes peripancreatic necrosis of connective tissue and contains both activated digestive enzymes and a mixed flora of bacteria. Local and systemic infections can contribute to the worsening or the persistence of preexisting ARDS. The delay between hospital admission and pulmonary complications was investigated by Berry et al. On hospital admission, radiologic abnormalities were present in 15% (5 of 33 patients) with acute pancreatitis. There were 71% additional patients (20 of 28 patients) with new radiologic abnormalities after day 5.

Pathophysiology of Pancreatitis-Associated Clinical Lung Injury

Two studies including a small number of patients showed that cytokine overproduction might participate to the pathogenesis of severe lung injury during acute pancreatitis. Among seven patients with acute pancreatitis at risk for acquiring the ARDS, lung injury developed in only one patient. In the BAL, the concentration of interleukin (IL)-8 was significantly higher on hospital admission in this single patient who acquired ARDS than in the six patients who did not. Because the thoracic duct drainage has been proposed as an alternative to remove proteolytic and lipolytic enzymes released by the injured pancreas, Montravers et al measured in plasma and thoracic duct the proinflammatory concentrations of cytokines on days 0 (24 h after the diagnosis of acute lung injury), 2, 4, and 8. There were high concentrations of tumor necrosis factor (TNF)-α, IL-1, IL-6, neutrophil enzymes, and pancreatic enzymes including amylase, lipase, and trypsin in plasma. A moderate increase in lymph-to-plasma gradient was observed for IL-6, lipase, and trypsin, while other mediators had similar concentrations in the plasma and lymph. Thus elevated concentrations of cytokines and pancreatic enzymes might be associated with the development of lung injury, but additional information is needed. Additionally, patients with acute pancreatitis and clinical lung injury had higher thrombocytopenia and prostacyclin concentrations in plasma than patients who did not acquire ARDS.

The relationship between phospholipase A2 and clinical lung injury has also been studied during acute pancreatitis. Two forms of the enzyme exist: type I originates from the pancreas, whereas type II is a mediator of the acute phase response. In the pancreas, phospholipase A2 induces cell necrosis by converting the lecithin of cellular membranes into the more toxic compound lysolecithin. Thus, phospholipase A2 may have predictive value for the development of lung injury, but additional information is needed. Similarly, other investigators reported that an elevated concentration of phospholipase A2 identifies patients with acute pancreatitis who will become hypoxemic. Thus, an elevated phospholipase A2 may have predictive value for the development of pulmonary complications. Additionally, lung injury has been attributed to the release of nitric oxide from alveolar macrophages and correlated to the serum C-reactive protein.

Treatment of Pancreatitis-Associated Lung Injury

Alveolar-capillary membrane injury may result from the pulmonary absorption of proteolytic en-
zymes and vasoactive substances released by the injured pancreas via the veins and lymphatic vessels that drain the pancreas and the peripancreatic tissues. Two studies\textsuperscript{20,21} investigated whether thoracic duct drainage might help to remove the pancreas-derived inflammatory mediators before they enter into the systemic circulation and whether the removal protects against lung injury. In six patients with the ARDS associated with acute pancreatitis and six hypoxemic patients at risk for acquiring acute lung injury, thoracic duct drainage was evaluated\textsuperscript{21}; interestingly, in this small study, thoracic duct drainage improved pulmonary gas exchange and decreased the duration of mechanical ventilation. The improvement was maintained after discontinuation of the thoracic duct drainage. However, in another study,\textsuperscript{20} there was no beneficial effect of thoracic duct drainage on gas exchange in six patients. Although thoracic duct drainage was longer in this last study, the beneficial outcome of the first study might be explained by the fact that 8 of 12 patients also had a peritoneal drainage. However, peritoneal lavage designed to remove pancreatic enzymes and exudate has failed to limit respiratory complications.\textsuperscript{8} It is impossible to draw any conclusion about the utility of thoracic duct drainage from such limited number of patients, and the thoracic duct drainage cannot be considered as a routine procedure.

Because octreotide is known to inhibit the endocrine and exocrine secretions of the pancreas, treatment with the long-acting synthetic analog of somatostatin, octreotide, has also been examined as a treatment to decrease the pulmonary complications during acute pancreatitis. In a study\textsuperscript{22} including 50 patients with acute pancreatitis, the incidence of acute lung injury (defined as tachypnea, PaO\textsubscript{2} \leq 60 mm Hg on room air, and diffuse interstitial infiltrates on the chest radiograph) was lower in patients who received octreotide (0.1 mg subcutaneously tid) than in those patients who did not. In the nontreated group, ARDS developed in 56% (14 of 21 patients), while in the group treated with octreotide, the ARDS developed in only 28% (7 of 21 patients).\textsuperscript{23} Because the pancreas had already been injured at the time of the treatment, the beneficial effect of octreotide might be also attributed to the immunomodulatory effects of somatostatin. Additionally, somatostatin reduces intestinal secretion and promotes intestinal water and electrolyte absorption. This effect could attenuate fluid losses. Importantly, the incidence of sepsis was also much lower in the patients treated with octreotide (24% vs 76% in the untreated group) and the mortality rate declined from 32 to 8%. No other study investigated the benefit of octreotide on lung injury during acute pancreatitis. Moreover, even the benefit of such treatment for pancreatitis is questioned.\textsuperscript{3,33}

In summary, acute lung injury is a frequent complication of acute pancreatitis, although the exact incidence has not been clearly established. Arterial hypoxemia is common, and although its severity is not correlated to the severity of pancreatic injury itself, it is a primary criterion for evaluating the prognosis of the disease. Pulmonary infiltrates and pleural effusions on the chest radiograph are also frequent. Even when oxygenation remains normal, an increase in alveolar-capillary membrane permeability can be detected. Acute lung injury with pulmonary edema is a cause of fatal complications within the first week, whereas infection and sepsis are the major serious complications later in the course of the disease. The pathophysiology of clinical lung injury is incompletely understood, but phospholipase A\textsubscript{2} has been implicated in the pathogenesis of ARDS. A single study\textsuperscript{21} showed that thoracic duct drainage improves pulmonary gas exchange. The potential therapeutic benefit of octreotide deserves further study. However, as discussed in the next section, recent experimental work in animal models has increased our knowledge of the pathophysiology of pulmonary injury in acute pancreatitis, and may suggest novel therapeutic strategies for the treatment of the clinical lung injury associated with acute pancreatitis.

\section*{Pathogenesis of Experimental Pancreatitis-Associated Lung Injury}

Because of the inaccessibility of human pancreas during the early phases of pancreatitis, most of our knowledge of the pathophysiology of the disease is derived from experimental studies. Several models have been described with variable severity and mortality rates. Intraperitoneal administration of supramaximal doses of cerulein (the cholecystokinin analog) induces a mild edematous form of pancreatitis,\textsuperscript{34} while administration of a cholin-deficient/ethionine-supplemented diet to young female mice induces an acute, hemorrhagic, necrotizing pancreatitis with death occurring within 5 days.\textsuperscript{35} In the taurocholate model, the disease induced by intraductal injection of taurocholate is severe, with a high mortality within hours of injection.\textsuperscript{36} The main features of these models include activation and release of pancreatic enzymes in the interstitium, the autodigestion of the pancreas, and multiple organ dysfunction following the release of mediators into the systemic circulation.\textsuperscript{5,37–39} However, none of these models mimic the two major causes of human pancreatitis, \textit{ie}, alcohol...
and gallstone migration. The common bile duct ligation in the opposum is another experimental model of gallstone-induced acute pancreatitis.40

Interestingly, in the rat taurocholate injection model, Milani et al41 found that the mechanical and morphologic alterations of the lung in pancreatitis-associated pulmonary injury were similar to those observed in patients. However, no other studies have yet investigated the mechanisms and mediators involved in this interesting model.

The initial phase of the pancreatic injury may originate from the activation of trypsinogen to active trypsin within the acinar cells, which in turn activates other pancreatic enzymes including elastase and phospholipase A2, as well as complement and kinins. Convincing experimental studies also indicate that synthesis and release of proinflammatory cytokines and chemokines are responsible for the local injury and the systemic dispersion of the inflammation. Inflammatory mediators produced within the gland increase the pancreatic injury and may spread to distant organs, transforming local inflammation into systemic disease (Fig 2). These recent experimental findings are summarized in the following sections.

Role of Pancreatic Enzymes in the Initiation of Lung Injury

The potential role of phospholipase A2 has been tested in experimental studies. Although both pancreatic and nonpancreatic isoenzymes are increased in serum during acute pancreatitis, the nonpancreatic isoenzyme seems to be the only one responsible for the complications in the pancreas itself and...
Phospholipase A2 releases arachidonic acid, thromboxanes, kinins, and platelet-activating factor. In the lungs, dipalmitoylcholine, a major component of surfactant, is a target of activated phospholipase A2. Interestingly, the intratracheal instillation of the nonpancreatic phospholipase A2 induced lung injury with interstitial and alveolar edema and accumulation of inflammatory cells. Thus, there is evidence for a pathogenic role of phospholipase A2 in both experimental and clinical studies (Table 2). Other digestive enzymes that may be important in the pathophysiology of lung injury are pancreatic elastase and trypsin, which are released systematically during pancreatitis. Jaffray et al found that the systemic injection of pancreatic elastase to mice induces pulmonary damage through nuclear factor-κB activation and TNF-α gene expression with subsequent neutrophil infiltration into the lungs and an increase in lung vascular permeability. IV infusion of trypsin in sheep also increased the pulmonary transvascular protein clearance, an effect that was prevented by pretreating the animals with the antiprotease, aprotinin. Finally, Hartwig et al found that pulmonary injury induced by protease infusions was dose dependent in two experimental models of pancreatitis.

These studies indicate that specific pancreatic enzymes administered either systemically or intrabronchially may precipitate acute lung injury in the absence of concomitant pancreatitis. Similarly, ascites collected from rats with pancreatitis and injected in normal animals induced a direct lung injury associated with an increased pulmonary TNF-α, IL-1β and IL-6 gene expression.

Table 2—Relationship of Pancreatic Enzymes to Lung Injury in Experimental Studies

<table>
<thead>
<tr>
<th>Pancreatic Enzymes</th>
<th>Mode of Administration</th>
<th>Pancreatic Injury</th>
<th>Lung Injury</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipase A2</td>
<td>Intratracheal</td>
<td>0</td>
<td>Yes</td>
<td>Edelson et al</td>
</tr>
<tr>
<td>Elastase</td>
<td>IV injection</td>
<td>0</td>
<td>Yes</td>
<td>Jaffray et al</td>
</tr>
<tr>
<td>Trypsin</td>
<td>IV injection</td>
<td>0</td>
<td>Increased vascular permeability</td>
<td>Tahamont et al</td>
</tr>
<tr>
<td>Ascites from pancreatic rat</td>
<td>IV injection</td>
<td>0</td>
<td>Yes</td>
<td>Denham et al</td>
</tr>
</tbody>
</table>

Role of Inflammatory Cells

During acute pancreatitis, the lung injury is associated with the accumulation of neutrophils within the interstitial and alveolar spaces, a finding common to clinical and experimental studies (Fig 2, Table 3). Activation of these neutrophils may mediate the pulmonary injury. In the cholin-deficient/ethionine-supplemented diet model of pancreatitis, administration of antineutrophil serum reduced the severity of pancreatitis and completely prevented the development of lung injury as evidenced by the absence of sequestered intrapulmonary neutrophils and normal pulmonary microvascular permeability.

Leukocyte sequestration within an inflamed area is a multistep process that begins with leukocyte activation, followed by the rolling of inflammatory cells and the adhesion of circulating activated inflammatory cells to the endothelium via adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1). Under physiologic conditions, ICAM-1 is not constitutively expressed or is expressed only at low levels, but it is markedly upregulated during inflammation, leading to the interaction of ICAM-1 with CD11a/CD18.

Table 3—Pathophysiology of Acute Lung Injury in Experimental Studies*

<table>
<thead>
<tr>
<th>Models of Pancreatitis</th>
<th>Pharmacologic and Genetic Manipulations</th>
<th>Pancreatic Injury</th>
<th>Lung Injury</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDE diet</td>
<td>Antineutrophil antibody</td>
<td>Decreased</td>
<td>Prevented</td>
<td>Bhatia et al</td>
</tr>
<tr>
<td>Cerulein and CDE diet</td>
<td>ICAM-1 knockout mice</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Frossard et al</td>
</tr>
<tr>
<td>Cerulein and taurocholate</td>
<td>Anti-ICAM-1 antibody</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Werner et al</td>
</tr>
<tr>
<td>Cerulein</td>
<td>II-1 CE knockout mice</td>
<td>Prevented</td>
<td>Prevented</td>
<td>Norman et al</td>
</tr>
<tr>
<td>CDE diet</td>
<td>IL-10 knockout mice</td>
<td>No effect</td>
<td>Increased</td>
<td>Gloor et al</td>
</tr>
<tr>
<td>Cerulein</td>
<td>CCR-1 knockout mice</td>
<td>No effect</td>
<td>Decreased</td>
<td>Gerard et al</td>
</tr>
<tr>
<td>Cerulein</td>
<td>Anti-CINC antibody</td>
<td>Approximately no effect</td>
<td>Decreased</td>
<td>Bhatia et al</td>
</tr>
<tr>
<td>Cerulein and CDE diet</td>
<td>NK, R knockout mice</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Bhatia et al</td>
</tr>
<tr>
<td>Cerulein</td>
<td>C5 and C5a receptor knockout mice</td>
<td>Increased</td>
<td>Increased</td>
<td>Bhatia et al</td>
</tr>
<tr>
<td>Cerulein</td>
<td>CD40 ligand knockout mice</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Frossard et al</td>
</tr>
</tbody>
</table>

*CDE = cholin-deficient/ethionine; CE = converting enzyme; CINC = cytokine-induced neutrophil chemoattractant; CCR-1 = chemoattractant cytokine receptor-1; NK, R = neurokinin-1 receptor.
CD18 and CD11b/CD18 located on lymphocytes and neutrophils. This interaction is a determinant of leukocyte adhesion to the endothelium and leads to transmigration of leukocytes into the inflamed area. In two models of experimental pancreatitis, ICAM-1 concentrations were increased over normal in the serum (1.3), pancreas (9.6), and lungs (2.4). ICAM-1–deficient mice had less severe pancreatitis and lung injury. Neutrophil depletion with an antineutrophil antibody also reduced the severity of the disease. Finally, treatment of severe pancreatitis with monoclonal antibodies directed against ICAM-1 also decreased both the pancreatic and lung injury. Taken together, these observations suggest that ICAM-1 is an important determinant of neutrophil-mediated lung injury during acute pancreatitis. Additionally, the activation of matrix metalloproteinase-9 in the rat lung during acute pancreatitis promotes the transmigration of neutrophils and the increased alveolar-capillary permeability.

Role of Cytokines and Chemokines

There is evidence linking IL-1β and TNF-α in the pathogenesis of acute pancreatitis. Inhibition of IL-1β with the receptor antagonist, IL-1 receptor antagonist, or the genetic deletion of IL-1β reduce the severity of experimental pancreatitis. Interestingly, in the double IL-1β and TNF-α receptor knockout mice, the IV administration of sterile, cytokine-free ascitic fluid collected from rats with pancreatitis failed to induce lung injury as observed in wild-type animals, emphasizing an important role for IL-1β and TNF-α in acute lung injury. In a similar model, the IV administration of pancreatic ascites to healthy rats increased leukocyte within the BAL and injured lung tissue. Protein concentrations in the BAL had a twofold increase. Inhibition of the p38 mitogen-activated kinase, which is responsible for production of TNF-α and nitric oxide, reduced the severity of lung injury. Thus, an unknown component in pancreatic ascites apart from endotoxin, cytokines, or bacteria is capable of inducing lung injury in healthy rats through a mechanism that involves nitric oxide, TNF-α, and the p38 mitogen-activated kinase. Finally, mice who lack IL-1β converting enzyme, which is responsible for the cellular export of mature IL-1β, cannot secrete IL-1β and do not develop acute pancreatitis and concomitant lung injury.

Many investigators believe that the severity of pancreatitis and pancreatitis-associated lung injury results from the ratio between proinflammatory and anti-inflammatory mediators. Among the anti-inflammatory mediators, IL-10 inhibits the release of proinflammatory cytokines from macrophages. In the model of cholin-deficient/ethionine-supplemented diet-induced pancreatitis, the severity of lung injury was greater in the IL-10 knockout mice than in the wild-type mice, whereas the severity of pancreatitis was similar in both groups. Thus, endogenous IL-10 seems important in linking the pancreas and acute pulmonary injury.

The activation and trafficking of activated inflammatory cells involves a multigene family of chemoattractants termed chemokines. The chemokine system is characterized by redundancies of ligand and receptors that complicate the investigation of chemokine-regulated events. The role of the chemoattractant chemokine receptor-1, one of the 18 known chemokine receptors, was examined in the model of cerulein-induced acute pancreatitis by using chemoattractant chemokine receptor-1-deficient mice. Although the severity of pancreatitis was similar in these and wild-type mice, the lung injury was significantly reduced in the knockout mice. This finding raises the hypothesis that pancreatic injury produces and releases chemokines into the systemic circulation that can activate circulating inflammatory cells subsequently sequestered within the lung microvasculature. Because pancreatic injury was not modified in mice lacking chemoattractant chemokine receptor-1 while lung injury was decreased, chemoattractant chemokine receptor-1 may play an important role in disseminating the injury from the pancreas to the lungs.

To evaluate the effects of blocking the cytokine-induced neutrophil chemoattractant, analogous in rodents to IL-8 in humans, antibody directed against cytokine-induced neutrophil chemoattractant was administered either before or after starting cerulein injection in mice. Although cytokine-induced neutrophil chemoattractant blockade had little effect on the pancreatic damage, it reduced the cerulein mediated acute lung injury when administered either prophylactically or therapeutically.

Finally, several reports indicate that platelet-activating factor is involved in the pathogenesis of acute pancreatitis. Platelet-activating factor is a proinflammatory phospholipid that promotes the recruitment and the activation of inflammatory cells, the production of chemokines and cytokines, and alters microvascular permeability. Pancreatic concentrations of platelet-activating factor increased during experimental pancreatitis and platelet-activating factor antagonists reduced the severity of experimental acute pancreatitis by 37%. Moreover, the administration of the human recombinant enzyme, platelet-activating factor acetylhydrolase that hydrolyzes platelet-activating factor and terminates its action, has been successful in partially preventing the development of

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experimental pancreatitis-associated lung injury in the opossum model. Importantly, the treatment was effective when administrated after the beginning of pancreatic injury.

Substance P

The neuropeptide substance P, which is released from nerve endings and binds to the neurokinin-1 receptors, can mediate the abnormal vascular permeability during acute inflammation. In the cerulein model of pancreatitis, neurokinin-1 receptor and substance P are both expressed in the pancreas. Deletion of the neurokinin-1 receptor gene reduces both pancreatitis and pancreatitis-associated lung injury compared to control mice. Interestingly, the increase in lung microvascular permeability associated with acute pancreatitis is strongly attenuated in the absence of neurokinin-1 receptor. This result was confirmed in the diet-induced hemorrhagic pancreatitis in mice. These results emphasize the role of substance P acting on endothelial cells via neurokinin-1 receptors, increasing lung vascular permeability and promoting edema formation in the surrounding tissues. This hypothesis is supported by the finding that the concentration of substance P was twofold higher in the pulmonary edema fluid of patients with ARDS than in the edema fluid of control patients with congestive heart failure.

Complement Factor C5a and CD40

C5a, which acts via the C5a receptor, is an anaphylatoxin and a chemoattractant that exerts proinflammatory effects by increasing blood flow and by promoting vascular permeability. In genetically modified mice that lack C5 or C5a receptor, the severity of pancreatitis and lung injury was surprisingly greater than the injury observed in wild-type mice. The explanations for such finding remain puzzling.

The CD40 receptor is a 50-kd protein expressed on the membranes of B lymphocytes, monocytes, dendritic cells, and biliary epithelial cells. The CD40 ligand is expressed on the surface of activated T lymphocytes. The CD40 ligand binds to the receptor and mediates major immunoregulatory signals and participates in organ-specific autoimmune diseases, graft rejection, and development of atherosclerosis. In a model of antigen-induced airway inflammation, CD40 ligand-deficient mice were protected, while the disruption of the CD40-CD40 ligand interaction prevented the pulmonary lesions induced by the high fraction of inspired oxygen. In the cerulein model of pancreatitis, mice deficient for the CD40 ligand had a marked decrease in the severity of both pancreatic and lung damage. Interestingly, both CD40 and the CD40 ligand were expressed at the acinar cell surface, suggesting that therapeutic interventions designed to prevent CD40 ligation may have clinical value in reducing the severity of pancreatitis and the associated acute lung injury.

Potential New Treatment Strategies for Acute Pancreatitis-Associated Lung Injury

Severe attacks of acute pancreatitis are frequently associated with acute lung injury. Arterial hypoxemia, pulmonary infiltrates, and pleural effusions, as well as the ARDS, may develop as a complication of acute pancreatitis. Within the first few days following the onset of severe acute pancreatitis, lung injury develops as a consequence of the acute pancreatitis, whereas sepsis is a dominant cause of lung injury and mortality in the later phase of the disease. Consequently, besides standard supportive therapy, including lung protective ventilation, hemodynamic management, and nutrition, the anti-inflammatory strategies and the management of infections are important to consider in the treatment of acute pancreatitis-associated lung injury.

Following the onset of acute pancreatitis, clinical trials that target mediators involved in the pathogenesis of acute pancreatitis have been disappointing. Several prospective randomized clinical trials designed to treat acute pancreatitis with protease inhibitors, such as aprotinin and gabexate mesylate, have not shown benefit in patients with severe acute pancreatitis. Although specific inhibitors targeting phospholipases A2 improved the course of experimental acute pancreatitis, these treatments have not been tested in humans. To date, controlled clinical trials have failed to demonstrate the therapeutic efficacy of antioxidants. When patients with severe acute pancreatitis were treated with the potent platelet-activating factor receptor antagonist, lepirudin, for up to 3 days or 7 days, the severity score for all organ dysfunction was lower in this group than in the group of patients treated with saline solution. However, a study including 290 patients with acute pancreatitis definitively reported no efficacy of lepirudin in decreasing the severity of the disease, including multiple organ failure. Unfortunately, in these studies, lung injury was not specifically studied. Platelet-activating factor acetylhydrolase has been successful in preventing the development of experimental pancreatitis and pancreatitis-associated lung injury, but has not been tested in clinical trials. Antineutrophil antibodies were efficient in preventing the lung injury in experimental models but were not tested in humans. Finally, ketoconazole, a potent inhibitor of thromboxane and leukotriene synthesis, pentoxifylline,
anti–IL-8 therapy, and prostaglandin E₁, which have been tested in ARDS of diverse etiologies, has not been specifically evaluated in patients with acute pancreatitis. Thus, to date, the only treatment that improved acute pancreatitis-associated lung injury was thoracic duct drainage, but this treatment has not been tested in a large clinical trial.

The second phase of severe acute pancreatitis is closely related to the development of pancreatic and peripancreatic infection. Some of the infectious complications are likely to originate from blood (catheter-related sepsis) or from the GI tract (bacterial translocation) because patients with acute pancreatitis have an increase in intestinal epithelial permeability. Thus, selective decontamination of the GI tract and prophylactic antibiotherapy have decreased the incidence of septic complications and mortality in acute necrotizing pancreatitis. However, the evolution of lung injury in these clinical studies was not described.

In conclusion, acute lung injury is a frequent complication of acute pancreatitis, although the exact incidence has not been clearly established. The pathophysiology of clinical lung injury is incompletely understood, but recent experimental work in animal models has significantly increased our understanding of the mechanistic links between acute pancreatitis and lung injury. Acute lung injury with pulmonary edema is a cause of fatal complications within the first few days, whereas infection and septicemia are the major serious complications later in the course of the disease. Consequently, beside standard supportive therapy, including lung protective ventilation, hemodynamic management, and nutrition, the anti-inflammatory strategies and the management of infections are important to consider in the treatment of acute pancreatitis-associated lung injury. Specific treatments that have targeted the pancreatic injury itself have not been successful in decreasing the severity of the disease. To date, the only treatment that improved acute pancreatitis-associated lung injury was thoracic duct drainage, but this treatment has not been tested in a large clinical trial. To decrease the incidence of septic complications and mortality in acute necrotizing pancreatitis in the later course of the disease, selective decontamination of the GI tract, enteral nutrition and prophylactic antibiotherapy have been successfully tested. Because several treatments have been effective in treating experimental acute pancreatitis-associated lung injury, human studies are now needed.

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