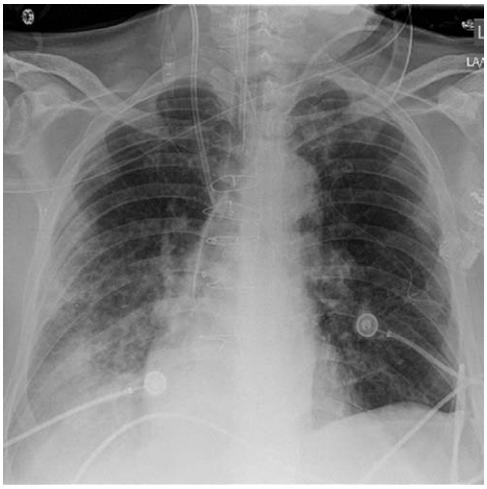
Targeting Aspiration Pneumonitis

ASPIRATION of gastric acid contents is recognized as a complication of general anesthesia occurring in about 1 in every 2,000–3,000 cases. It is also a problem that affects critical care patients who have altered levels of consciousness from trauma, cerebral vascular ischemia, and metabolic encephalopathies. The inhalation of low-pH gastric fluid and/or particulate food material leads to an initial pneumonitis and the development of acute respiratory distress syndrome (ARDS), which may or may not become complicated by subsequent bacterial pneumonia. The problem can also be insidious in its presentation occurring silently in the ambulatory population causing chronic cough and exacerbating/mimicking asthma.[1] Therapy is at best supportive, including mechanical ventilation with low tidal volume ventilation or the open-lung approach, which uses low tidal volume ventilation with higher positive end-expiratory pressure to aid with oxygenation. Currently, there are no interventions that target the etiology of this disease. The study by Richter *et al.*[2] in this issue of Anesthesiology provides new and important information regarding the regional distribution of pulmonary blood flow and histological damage that occurs early in the disease using a rat model of acid pneumonitis. More importantly, however, this study opens the door to some exciting new possibilities on treatment to this devastating disease.



"The findings of this study ... point to some exciting new treatment options that could target the mechanisms of the lung inflammation associated with acid aspiration."

During the last 20 yr, there has been a growing body of experimental work to characterize lung injury caused by the aspiration of gastric content and to determine the molecular mechanisms that are responsible for the development of ARDS. Extensive work from Dr. Knight's laboratory has shown that acid or small nonacidified gastric particles can cause aspiration pneumonitis and that the combination of both has a synergistic injurious effect on the lung.[1] Experimental work has also shown that aspiration of gastric content is characterized by a biphasic response comprising an early insult that is characterized by stimulation of capsaicin-sensitive neurons and direct caustic actions of low pH on airway epithelium followed by an acute neutrophilic inflammatory response after 4–6 h.[3] The mechanistic role of neutrophils in aspiration pneumonitis has been shown by several experimental studies. It is known that as early as 1 h after injury, neutrophils are increased in the blood and by 4 h, there is a peak in the number of marginated neutrophils in the lung vasculature. Finally, at 24, h there is a peak in the number of alveolar neutrophils, whereas there was a decrease in marginated and interstitial neutrophils.[4] Several experimental studies have demonstrated the mechanistic role of neutrophils in causing injury to the alveolar–capillary barrier. For example, in a rabbit model of acid aspiration pneumonitis, acid-induced abnormalities in oxygenation and cell damage to the lung endothelium and alveolar epithelium were significantly attenuated in the animals that were pretreated with an interleukin-8 monoclonal antibody.[5,6] Furthermore, neutrophil sequestration in the lungs after acid aspiration in mice was partially mediated by the chemokine receptor CXCR2.[7] Finally, more recent experimental work supports an important role for interactions between neutrophils and platelets in the development of lung injury associated with acid aspiration pneumonitis. Indeed, acid aspiration induced platelet-derived P-selectin–dependent platelet–neutrophil interactions in blood and lung capillaries. Reducing platelet number or blocking P-selectin improved gas exchange, reduced neutrophil recruitment into the alveolar space, and decreased the formation of pulmonary edema after acid aspiration in mice.[8,9] Taken together, these experimental studies demonstrate an important role

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◆ This Editorial View accompanies the following article: Richter T, Bergmann R, Knels L, Hofheinz F, Kasper M, Deile M, Pietzsch J, Ragaller M, Koch T: Pulmonary blood flow increases in damaged regions directly after acid aspiration in rats. Anesthesiology 2013; 119:890–900.

for neutrophils and platelets in the development of ARDS after acid aspiration. However, despite these important progresses in our understanding of the pathophysiology of the lung injury associated aspiration pneumonitis, the effect of acid aspiration on the regional distribution of the pulmonary blood flow, which greatly affects gas exchange early after onset of the disease, is still unknown.

As Richter *et al.* point out in their article, previous studies using experimental lung injury models of surfactant depletion, smoke inhalation, and exposure to oleic acid or endotoxin have reported the effects of these injurious mechanisms on pulmonary blood flow later in the course of the disease and were not designed to examine pulmonary blood flow soon after insult.[10–13] In contrast, the study by Richter *et al.* examines the early effect of acid aspiration on pulmonary blood flow measured by positron emission tomography after injection of microspheres and correlate these results with the effect of acid aspiration on lung densities measured by computed tomography scans. As early as 10 min after acid aspiration, computed tomography scans revealed that increased lung densities colocalized with areas of increased blood flow and areas of histological lung damage. Although hyperperfusion, as a single factor, has been shown not to increase lung vascular permeability,[14] it has been associated with alveolar damage after one-lung ventilation in pigs.[15] Thus, the results of the study by Richter *et al.* may provide a new explanation for the profound hypoxemia observed at times after massive gastric content aspiration in humans. The findings of this study also point to some exciting new treatment options that could target the mechanisms of the lung inflammation associated with acid aspiration. Indeed, these results suggest that the injured areas of the lungs could be preferentially targeted by the intravenous administration of drugs specifically designed to inhibit platelet–neutrophil interactions that appear to be critical for the development of ARDS induced by acid aspiration.[8,9] This approach could inhibit the recruitment of neutrophils into the lung parenchyma and thus significantly decrease the severity of lung damage caused by acid aspiration.

The study by Richter *et al.* has some limitations that are inherent to the techniques used to measure pulmonary blood flow and lung damage after acid aspiration; however, these limitations do not decrease the importance of the results summarized in this study. Computed tomography scans, pulmonary blood flow measurements, and histological data were not obtained simultaneously on the same specimens. Therefore, there may have been some advancement in the histological measureable damage from the time of computed tomography scan and pulmonary blood flow measurements to preparation of the samples. There is also the possibility that the differences in measured pulmonary blood flow could be in part due to attenuation of the signal over the time that is required for acquisition of the emission image, although the investigators have provided evidence that the acquisition time for the positron emission tomography scan was adjusted to obtain optimal activity count rate.

In summary, Richter *et al.* have provided a fascinating new insight into the early inflammatory phase of acid-induced lung injury. Furthermore, the results of this study suggest that drugs administered intravenously have the potential to preferentially target injured lung areas within minutes after onset of aspiration of gastric content and thus prevent the development of severe ARDS. The experimental model developed by Richter *et al.* should also provide the opportunity to better understand the effects of interactions between neutrophil, platelet, and endothelial cell early after acid aspiration. Finally, this new experimental model may help to develop new causal therapeutic approaches that could attenuate the severity of lung damage caused by aspiration pneumonitis, and the days of treating aspiration pneumonitis solely with protective ventilation strategies will be long-forgotten memories best left to historians.

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