招 1 The Acute Respiratory Distress Syndrome: Pathogenesis and Treatment

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Considerable progress has been made in developing uniform definitions for acute lung injury and the acute respiratory distress syndrome which have facilitated the conduct of several clinical trials to evaluate new treatment strategies. In addition, clinical research, combined with clinically relevant animal models of acute lung injury, have provided remarkable new insights into the pathogenesis and pathophysiology of acute lung injury.

Definitions

Acute lung injury is defined as a PAO_2/FiO_2 < 300 with bilateral opacities on the chest radiograph that need not be symmetrical or extensive in the presence of a pulmonary arterial wedge pressure < 18 mmHg or the absence of clinical evidence of left atrial hypertension. The acute respiratory distress syndrome is defined by the same criteria except the PAO_2/FiO_2 ratio is < 200 .

Pathogenesis/Pathophysiology

It is clear that there are several neutrophil dependent and independent mechanisms that can precipitate acute lung injury. Injury to the lung endothelial barrier is a prerequisite for the development of protein rich, increased permeability pulmonary edema. In addition, it is also clear that structural and functional injury to the alveolar epithelial barrier is associated with a more prolonged clinical course, longer duration of mechanical ventilation, and higher mortality. Classic morphologic studies in the late 1970's demonstrated that patients who died with ARDS had extensive injury to the alveolar epithelium . Recent clinical studies have also demonstrated that the inability to remove edema fluid from the airspaces of the lung early in the clinical course of acute lung injury is associated with a more prolonged clinical course and a higher mortality . There are several mechanisms that may be responsible for injury to the alveolar epithelial barrier including mechanical injury from overdistension, oxidant mediated injury, neutrophil dependent injury, as well as direct injury from bacteria or viruses.

Treatment

Although several experimental studies and some clinical trials have evaluated a variety of anti-inflammatory therapies, none of these approaches has been proven unequivocally to reduce mortality. However, interestingly, a lung protective ventilatory strategy with 6 ml/kg ideal body weight and a plateau pressure limit of $30cmH_2O$ has proven to be efficacious in reducing mortality in a large randomized clinical trial of 861 patients .

This clinical trial provided the first evidence that mortality can be substantially reduced with any intervention. The trial demonstrated that absolute mortality was reduced from 39 to 31% with a relative reduction of mortality of 22%. Interestingly, there is also evidence that this clinical trial was associated with a reduction in interleukin-6 levels in the plasma, suggesting that part of the mechanism for the beneficial effect was related to reduced inflammation of the lung. Also, there was evidence of reduced non-pulmonary organ failure in the patients treated with the low tidal volume strategy. A new trial is currently underway in the United States to evaluate the potential benefit of a higher level of positive end-expiratory pressure in patients treated with the low tidal volume, plateau pressure limited strategy. This trial has enrolled 400 patients to date and is scheduled to enroll a maximum 750 patients. The results of this trial will provide new information regarding the potential value of elevated levels of positive end-expiratory pressure in treating patients with acute lung injury and the acute respiratory distress syndrome. Other strategies that are being evaluated currently include the potential value of prone positioning, high frequency ventilation, high dose glucocorticoids for persistent late onset ARDS, as well as the value of the pulmonary arterial catheter versus the central venous catheter in administering specific intravascular volume fluid strategies.