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JA SYMPOSIUM

# Therapeutic strategy for acute respiratory distress syndrome: recent understanding of the pathophysiology of the disease

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## The pathogenesis of acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) features acute onset, severe hypoxemia, bilateral infiltrates documented by chest radiograph, and the absence of left atrial hypertension. Factors that lead to this syndrome vary from direct lung damage, including respiratory infection, aspiration, inhalation of chemical or poisonous gas, pulmonary contusion, and pulmonary ischemia–reperfusion, to indirect causes including sepsis, acute pancreatitis, severe trauma, cardiopulmonary bypass, and transfusion.

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## Epidemiology of ARDS

In the United States, more than 200,000 patients annually develop ARDS [1]. The mortality rates of ARDS are reported to be 30–60% and may not be ignored. A randomized controlled trial (RCT), the ARMA trial, demonstrated reduced mortality rate with lower tidal volume ventilation as compared with conventional tidal volume ventilation (31% vs. 40%, respectively) [2].

## Therapy for ARDS

### Therapies at present

The cause of death in ARDS patients is mostly the progression of the disease to multiorgan dysfunction syndrome or sepsis rather than respiratory failure. Therefore, molecules targeting systemic inflammation or coagulation-fibrinolysis may be among the candidates for therapeutic drugs. Multiple molecules including steroids, elastase inhibitors, activated protein C, anticoagulation agents, and antithrombin have been tested; however, there is no established therapy for ARDS at present.

### Experimental verification of lung damage caused by systemic inflammation

We have demonstrated that the combination of systemic inflammation caused by liver ischemia–reperfusion and higher tidal volume ventilation caused elevation of inflammatory cytokine concentration in the airspace, infiltration of polymorphonuclear cells into the airspace, reduction in lung compliance, and pulmonary edema, whereas liver ischemia–reperfusion or higher tidal volume

ventilation alone did not cause such pathology [3]. The study indicated that ARDS is caused by multiple factors including systemic inflammation.

### Experimental verification of systemic inflammation caused by lung injury

We have demonstrated that proinflammatory cytokines produced in the airspace in pneumonia spread into systemic circulation when bacterial toxins damage the biological barrier in the lungs [4]. The systemic inflammation further advanced into septic shock, although systemic administration of anti-tumor necrosis factor (TNF)-α antiserum or recombinant interleukin (IL)-10 ameliorated septic physiology and decreased mortality. In the study, proinflammatory cytokines in the lungs of rabbits instilled with noncytotoxic strain of bacteria were as high as those instilled with parental, cytotoxic strain of bacteria. However, when animals were infected with noncytotoxic strain of bacteria, they did not exhibit shock physiology because alveolar epithelia were not injured and translocation of TNF-α from airspace to systemic circulation was limited.

## Future therapy for ARDS

Previous findings suggest that the airway barrier is important to limit the translocation of biologically active molecules between pulmonary and systemic compartments. We have demonstrated that an adenovirus vector expressing keratinocyte growth factor (KGF) induced proliferation of type II pneumocytes and ameliorated hyperoxia-induced acute lung injury [5]. Strategies promoting proliferation of pneumocytes are expected to be a novel therapy for acute lung injury in restoring gas-exchange units as well as the alveolar epithelial barrier to compartmentalize biologically active molecules.

## Conclusion

ARDS is usually caused by a combination of factors. There is no established therapy for ARDS, despite its high mortality rate. Therapies targeting sepsis or restoring injured alveolar epithelium are expected to be the focus for ARDS treatments.

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