

Clinical and Biological Heterogeneity in Acute Respiratory Distress Syndrome Direct Versus Indirect Lung Injury



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KEYWORDS

• Direct lung injury • Indirect lung injury • Acute respiratory distress syndrome • Acute lung injury

KEY POINTS

- Acute respiratory distress syndrome (ARDS) is caused by both direct (pulmonary, primary) and indirect (extrapulmonary, secondary) causes.
- Direct ARDS causes epithelial injury and indirect ARDS causes endothelial injury.
- There are important clinical differences between direct ARDS and indirect ARDS in pathologic abnormality, radiography, respiratory mechanics, response to treatment, and outcomes.
- Animal models of direct and indirect lung injury highlight different mechanisms of injury, particularly early in disease.
- Greater understanding of the mechanisms of direct and indirect ARDS in humans and in animal models is needed for development and testing of new therapeutics.

INTRODUCTION

Twenty years ago, the American-European Consensus Conference on ARDS emphasized the complexity of the pathogenesis of acute respiratory distress syndrome (ARDS) and suggested that separation of ARDS patients into more homogeneous subgroups could be a useful strategy to facilitate understanding of this syndrome. The consensus panel authors proposed 2 broad groups of patients with ARDS: those with direct injury to the lung parenchyma and those with indirect lung injury in the setting of systemic inflammation.¹ These 2 categories are appealing because they are based solely on clinical information readily available at the patient's bedside, and it is reasonable to

hypothesize that direct lung insults may be distinct from bystander lung damage. However, it is important to note that there are many alternative ways to separate patients into groups. For example, patient groups could be defined using panels of recently identified biomarkers, by severity of disease (mild, moderate, or severe by Berlin definition²), or by more specific inciting cause, such as trauma or sepsis. As emphasized by the consensus panel authors, distinct mechanisms underlying lung injury may affect clinical response to therapeutics and impact clinical trial design. For the purposes of this review, comparisons between direct and indirect causes of ARDS have been chosen to be the focus.

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The underlying causes of ARDS are summarized in [Table 1](#). Direct (pulmonary or primary) lung injury results in local damage to the lung epithelium, whereas indirect (extrapulmonary or secondary) lung injury occurs in the setting of systemic disorders that diffusely damage the vascular endothelium. Pneumonia and aspiration of gastric contents account for most direct lung injury, while sepsis is the major cause of indirect injury.^{3,4} Although there is substantial overlap, studies estimate that approximately 55% of ARDS is caused by direct lung injury.⁵ Although a direct cause of ARDS from pneumonia may be the initiating factor, almost 80% of patients with ARDS have sepsis, with 46% resulting from a direct pulmonary infection and the remainder resulting from extrapulmonary sources.⁴

Many patients have multiple potential contributors to ARDS. In one study, up to 21% of ARDS patients had mixed causes of lung injury.⁵ Furthermore, even with illness restricted to the thoracic cavity, there may be elements of both direct and indirect injury. For example, a direct injury from lobar pneumonia may have indirect inflammatory effects in the contralateral lung. This type of clinical heterogeneity makes it difficult to focus clinical trials on defined nonoverlapping subgroups and presents challenges to interpretation of data from experimental animal models of ARDS. Nonetheless, separation of underlying causes of ARDS into direct and indirect causes provides a useful framework for understanding the pathogenesis of lung injury and for explaining some of the clinical

heterogeneity seen in patients. In addition, the distinction between direct and indirect lung injury allows for improved study design in animal models and more specific therapeutic trials in subsets of patients with ARDS.

This review focuses on the distinctions between ARDS from direct or indirect causes in both human patients and experimental lung injury models. Because of variability in study design and outcome measures, the authors have chosen to limit their discussion to studies that separated patients according to the underlying cause of ARDS (direct vs indirect) and to those mechanisms that have been studied specifically in both direct and indirect injury models, with an emphasis on studies that tested both types of models in a single study.

CLINICAL DIFFERENCES BETWEEN DIRECT AND INDIRECT ACUTE RESPIRATORY DISTRESS SYNDROME

The Berlin definition of ARDS defines this syndrome as acute onset respiratory failure associated with bilateral pulmonary infiltrates and hypoxemia that is not fully explained by cardiac disease or fluid overload.² In this section, the existing clinical evidence that outlines important differences between direct and indirect ARDS in humans is summarized. [Table 2](#) is designed to highlight distinctions between these 2 groups of ARDS patients, recognizing that there may be significant overlap between direct and indirect ARDS with more subtle differences between these groups.

Pathologic Findings

When examined pathologically, lung biopsies from patients with ARDS from direct and indirect causes show different properties.⁶ One retrospective study showed that direct ARDS had significantly more alveolar collapse, fibrin deposition, and alveolar wall edema than ARDS from indirect causes.⁷ Increased amounts of collagen, but not elastin, were present in early ARDS from direct injury but not in ARDS from indirect injury.⁸ Lamy and colleagues⁹ demonstrated that patients with limited response to positive end-expiratory pressure (PEEP) had more severe tissue injury with greater alveolar hemorrhage and exudate on lung biopsy. An elegant study of patients by Peres and colleagues² described the hyaline membranes seen in direct and indirect ARDS in great detail ([Fig. 1](#)). In direct ARDS, hyaline membranes were discontinuous and thickly deposited, whereas the hyaline membranes in indirect ARDS were thin and more evenly distributed. Indirect ARDS had reduced expression of factor VIII, consistent with endothelial injury, and increased expression of

Table 1 Causes of acute respiratory distress syndrome	
Direct Lung Injury	Indirect Lung Injury
Pneumonia (bacterial, viral, fungal)	Sepsis syndrome
Aspiration	Nonthoracic trauma
Mechanical ventilation (barotrauma, volutrauma)	Transfusion
Lung contusion	Cardiopulmonary bypass
Inhalation injury	Pancreatitis
Near-drowning	Drug overdose
Fat emboli	Burn injury
Reperfusion injury	

Adapted from Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):821; and Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1338.

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