Pulmonary and extrapulmonary acute respiratory distress syndrome: myth or reality?

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Purpose of review

The pathogenesis of acute respiratory distress syndrome has been explained by the presence of a direct (pulmonary) or indirect (extrapulmonary) insult to the lung parenchyma. Evidence indicates that the pathophysiology of acute respiratory distress syndrome may differ according to the type of the insult. This article presents a brief overview of the differences between pulmonary and extrapulmonary acute respiratory distress syndrome, and discusses the interactions between lung functional, morphological aspects, and response to different therapies, both in experimental models and in patients with acute respiratory distress syndrome.

Recent findings

Many researchers recognize that experimental pulmonary and extrapulmonary acute respiratory distress syndrome are not identical when considering morpho-functional aspects, the response to positive end-expiratory pressure and recruitment manoeuvre, prone position and other adjunctive therapies. Contradictory results have been reported in different clinical studies, however, which may be attributed to the difficulty of classifying acute respiratory distress syndrome in one or the other category, and being confident of the onset, the phase and the severity of acute respiratory distress syndrome in all patients.

Summary

Heterogeneous acute respiratory distress syndrome patients are still considered to suffer from one syndrome, and are treated in the same way. Understanding the range of different pathways that lead to pulmonary dysfunction makes it possible to better target clinical treatment.

Keywords

acute lung injury, lung morphology, recruitment manoeuvre, static elastance

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Introduction

The American-European Consensus Conference (AECC) [1] defined two pathogenetic pathways leading to acute respiratory distress syndrome (ARDS): a direct (pulmonary) insult that directly affects lung parenchyma, and an indirect (extrapulmonary) insult that results from an acute systemic inflammatory response. Experimental pulmonary and extrapulmonary ARDS may differ morphologically, functionally, and therapeutically [2,3•]; however, contradictory results have been reported in different clinical studies [4–7,8••,9,10]. The present article presents a brief overview of the differences between pulmonary and extrapulmonary ARDS and discusses the interactions between lung mechanical and histological aspects, and responses to different therapies, both in experimental and clinical studies.

Epidemiology

The exact incidence of ARDS is difficult to measure, in part due to intrinsic problems related to the definition [11•], the lack of clinical diagnostic tests and also because ARDS remains largely undiagnosed [12]. Overall, approximately 7% of patients admitted to the ICU develop ARDS, and among mechanically ventilated patients with acute respiratory failure, the incidence varies from 11% to 23% [13]. The majority of recent studies report mortality to be in the 35–60% range when all patients who meet the AECC definitions are included [13]. Most available studies showed that the prevalence of pulmonary ARDS was higher compared with extrapulmonary ARDS [5,7,14,15], although Eisner *et al.* [16] identified an equal proportion of pulmonary and extrapulmonary ARDS patients. Pneumonia is the most frequent cause of direct lung injury, followed by aspiration of gastric contents and pulmonary trauma. Nonpulmonary sepsis, usually from Gram-negative infections, is the most prevalent and lethal cause of indirect injury. The mortality rate in pulmonary and extrapulmonary ARDS patients varies considerably. Suntharalingam *et al.* [17] showed a trend towards increased mortality in the direct aetiology group, while Eisner *et al.* [16] found no relationship between direct pulmonary insults and increased mortality. Angus *et al.* [18] measured quality-adjusted survival in the first year only in pulmonary ARDS patients, and observed that the quality of life in those who survived was markedly impaired. Recently, Parker *et al.* [19] found that the quality of life was similar in pulmonary and extrapulmonary ARDS patients at 3 months, but by 12 months patients with pulmonary ARDS had significantly better quality of life.

Pathophysiology

After a direct insult, the pulmonary epithelium is the primary injured structure. Epithelial damage leads to alveolar flooding [20], reduction in the removal of oedema fluid from the alveolar space [21], decrease in the production and turnover of surfactant [22], and fibrosis [23]. Efficient alveolar epithelial repair may reduce the development of fibrosis, since the presence of an intact alveolar epithelial layer suppresses fibroblast proliferation and matrix deposition [24]. Epithelial repair involves close coordination of several complex molecular mechanisms, including interactions between the alveolar type II cell and the matrix [25].

In the case of extrapulmonary ARDS, the insult is indirect and pulmonary lesions are caused by circulating mediators released from extrapulmonary foci into the blood (e.g. peritonitis, pancreatitis). The main target for damage is the pulmonary endothelial cell [26,27]. The vascular endothelium is a highly specialized metabolically active organ that possesses numerous physiological, immunological, and synthetic functions. The endothelium also holds numerous enzymes, receptors, and transduction molecules, which interact with other vessel wall constituents and circulating blood cells [28,29]. The lung endothelium, in concert with the epithelial barrier, mediates the initial change in permeability and is also critical for the repair and remodelling of the alveolar capillary membrane [28].

Histology

Since pulmonary and extrapulmonary ARDS have two different pathogenetic pathways, multifocal involvement of the lung parenchyma is expected in pulmonary ARDS, whereas with extrapulmonary ARDS, a more diffuse and uniform parenchymal alteration due to haematogenous distributed mediators may be observed. The morphological differences between pulmonary and extrapulmonary ARDS were studied using biopsy tissues from ARDS patients [4] and there was a predominance of alveolar collapse, fibrinous exudate and alveolar wall oedema in patients with pulmonary ARDS. Furthermore, Negri *et al.* [30] observed that the amount of collagen fibres in lung parenchyma was higher in pulmonary than in extrapulmonary ARDS, suggesting that extracellular matrix remodelling depends on the site of initial insult.

Morphology

Several studies described that the morphological computed tomography (CT) patterns in pulmonary and extrapulmonary ARDS are different [6,31–33,34••]. Conversely, Desai *et al.* [7] described that the differentiation of pulmonary and extrapulmonary ARDS is not assured on the basis of CT scan alone: no single CT isolated feature can accurately predict whether ARDS is of pulmonary or extrapulmonary type. Unfortunately, these studies presented some limitations: a small number of patients; the extrapulmonary ARDS group included patients with abdominal disease and patients after cardiac surgery, when left lower lobe collapse is a frequent finding; and direct and indirect insults may coexist, making the morphologic pattern difficult to interpret.

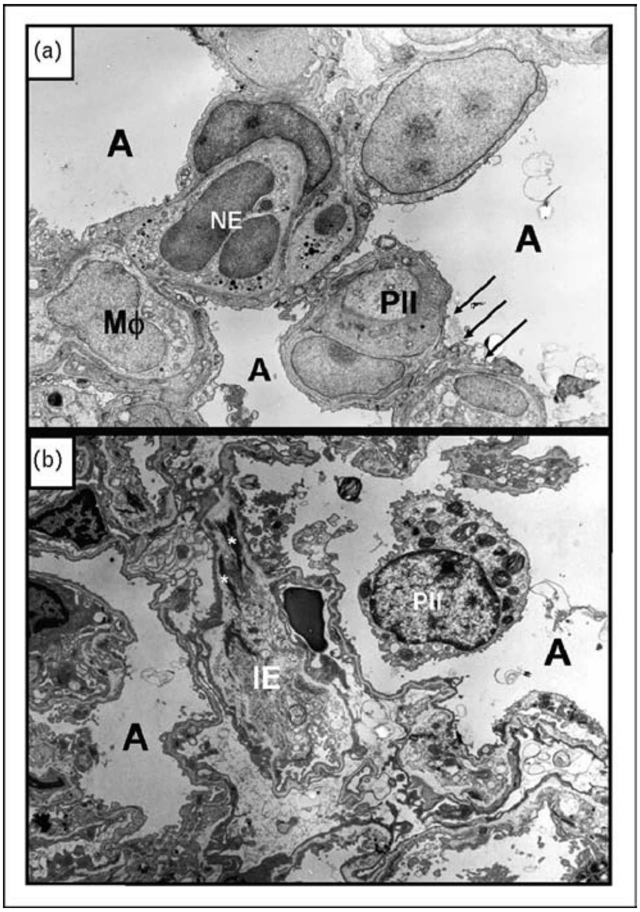
Respiratory mechanics

Gattinoni *et al.* [5] observed different respiratory mechanical data in pulmonary and extrapulmonary ARDS. They reported that even though respiratory system static elastance was similar in both groups, lung static elastance was markedly higher in pulmonary than in extrapulmonary ARDS patients, whereas chest wall static elastance was abnormally increased in the extrapulmonary ARDS group. In this line, Albaiceta *et al.* [35] also showed that the chest wall has an impact on respiratory system mechanics in extrapulmonary ARDS. In other situations such as cardiac surgery, trauma, near drowning, or aspiration, the precise identification of the pathogenetic pathway is somewhat questionable. Furthermore, it is difficult to be confident of the onset of ARDS, the phase and the severity of the lesion in all patients.

Experimental studies

There is a general belief that ARDS is the extreme form of a spectrum of lung injury caused by a uniform mechanism that is independent of the precipitating disease. Unfortunately, most studies report late or terminal events, and pathologic features of early phases of ARDS, such as interstitial oedema and alveolar collapse, are not easily recognized. There are several limitations in assessing the possible differences between ARDS resulting from pulmonary and extrapulmonary diseases: the determination of the severity of the lung injury, making comparison between the two conditions unwarranted; and it is possible that direct and indirect insults coexist in the same patient, making it difficult to separately evaluate these two entities [9,36]. Thus, to better elucidate the pathophysiology of pulmonary and extrapulmonary acute lung injury (ALI), experimental models have been used. Menezes *et al.* [2] developed murine models of pulmonary and extrapulmonary ALI induced by intratracheal or intraperitoneal injection of *Escherichia coli* lipopolysaccharide, respectively, with similar degrees of lung mechanical changes, and reported that direct insult yielded more pronounced inflammatory responses. The pulmonary ALI group presented a three-fold increase in keratinocyte-derived cytokine and interleukin (IL)-10 compared with the extrapulmonary group, whereas IL-6 was doubled in pulmonary ALI [2]. These inflammatory changes resulted in ultrastructural modifications (Fig. 1). Rocco *et al.* [37] tested the hypothesis that corticosteroids may act differently depending on the aetiology of the ALI and observed that one low-dose steroid therapy early in the course of lung injury attenuated lung mechanics and morphometric changes, cytokine levels in bronchoalveolar lavage fluid only in pulmonary ALI, but avoided changes in collagen fibre content in both ALI groups. Although an exaggerated inflammatory response underlies the pathogenesis of pulmonary ALI at the early phase, the amount of collagen fibre was similar in both ALI models, suggesting that inflammation and fibrosis could be dissociated [2]. Menezes *et al.* analysed the morphofunctional changes only 24 h after the induction of lung injury, but could not assert whether a progressive fibrosis occurred without an increase in lung inflammation [38]. To further clarify this issue, Santos *et al.* [3•] studied the time course of lung parenchyma remodelling in murine models of pulmonary and extrapulmonary ALI and with similar degrees of mechanical compromise and observed that the insult to pulmonary epithelium yielded fibroelastogenesis, while extrapulmonary ALI mice developed only fibrosis that was repaired early in the course of lung injury. The conciliating concept to determine the outcome may be the balance between alveolar epithelial inflammation or vascular endothelial injuries and their repair mechanisms [39] (Table 1).

Figure 1 Electron microscopy of lung parenchyma in *Escherichia coli* lipopolysaccharide intratracheally instilled (10 μg) (a) and intraperitoneally injected (125 μg) (b)



In (a) note the injury of alveolar epithelium (arrows), swollen type II cells, intact capillary endothelium, and apoptotic neutrophils in electron microscopy. (b) Depicted interstitial oedema formation and preservation of lung epithelial layers. Type III collagen fibre appeared early in the course of pulmonary and extrapulmonary acute lung injury groups. A, alveolar space; IE, interstitial oedema; NE, neutrophil; Mϕ, macrophage; PII, type II pneumocyte; ∗, collagen fibre.

The effect of recruitment manoeuvres or increased positive end-expiratory pressure (PEEP) on lung function and gas exchange was studied in different models of ARDS [40–42]. Overall, the authors reported more beneficial effects with recruitment manoeuvres on oxygenation and lung mechanics in extrapulmonary than in pulmonary ARDS. Van der Kloot *et al.* [40] found that the pneumonia model of intratracheal instillation of bacteria (more similar to pulmonary ARDS) was less responsive to PEEP than the oleic acid model (more similar to extrapulmonary ARDS). Recently, Rocco *et al.*

Table 1 Differences in experimental models of pulmonary acute respiratory distress syndrome (ARDSp) and extrapulmonary ARDS (ARDSexp) early and late in the course of lung injury

	Early		Late	
	ARDSp	ARDSexp	ARDSp	ARDSexp
Lesion of type I and II cells	↑Damage	Damage	Damage	Normal
Lesion of endothelial cell	Damage	↑Damage	Normal	Normal
Neutrophilic apoptosis	Prevalent	Rare	Rare	Rare
Increased number of alveolar neutrophils	Prevalent	Rare	Rare	Rare
Alveolar collapse	Prevalent	Prevalent	↓Prevalent	Rare
Increased cytokines in the BALF	↑Prevalent	Prevalent	↓Prevalent	Rare
Collagen fibre	Increased	Increased	↑Increased	Normal
Elastic fibre	Normal	Normal	↑Increased	Normal

BALF, bronchoalveolar lavage fluid.

[43] investigated the effects of recruitment manoeuvres on lung mechanics and histology and arterial oxygen partial pressure in experimental models of pulmonary and extrapulmonary ARDS with similar transpulmonary pressures. They found that recruitment manoeuvres were associated with a greater improvement in oxygenation and lung mechanics and reduction in the amount of atelectasis in extrapulmonary ARDS compared with pulmonary ARDS, suggesting that recruitment manoeuvres affected the lung in a different manner [43].

Clinical studies

Although experimental studies described recruitment manoeuvres having more beneficial effects on oxygenation and lung mechanics in extrapulmonary ARDS compared with pulmonary ARDS, clinical data are controversial. Gattinoni *et al.* [5] reported that the efficacy of PEEP in recruiting collapsed alveoli is lower in pulmonary ARDS than in extrapulmonary ARDS patients [44]. Similarly, Pelosi *et al.* [45] observed beneficial effects of three sighs per minute at 45 cmH_2O plateau pressure on oxygenation and recruitment in extrapulmonary ARDS. Supporting these observations, Lim *et al.* [46] showed that the mean improvement in PaO_2 achieved by the alveolar recruitment manoeuvre in extrapulmonary ARDS was approximately five-fold than in pulmonary ARDS. Tugrul *et al.* [47] observed that a sustained inflation of 45 cmH_2O for 30 s and application of a postinflation PEEP of approximately 16 cmH_2O could improve arterial oxygenation in both ARDS groups. Static compliance, however, increased only in patients with extrapulmonary ARDS in response to their ventilation strategy.

Prone positioning is also helpful in recruitment and its response is different in pulmonary and extrapulmonary ARDS. Pelosi *et al.* [48] observed better oxygenation in extrapulmonary ARDS in comparison to pulmonary ARDS after 6 h in the prone position, but the beneficial effects of oxygenation during prone positioning do not persist when patients are turned supine. Additionally, Lim *et al.* [49] found that in the prone position the response in oxygenation was more marked in extrapulmonary ARDS than in pulmonary ARDS, the kinetic of the increase in oxygenation was slower in pulmonary ARDS, the decrease in respiratory system compliance was greater in extrapulmonary ARDS, and the densities determined on chest radiography decreased to a greater degree in extrapulmonary ARDS. In this line, Demory *et al.* [50•] observed that the sequence prone positioning followed by high-frequency oscillatory ventilation (HFOV) maintained the improvement in oxygenation, whereas there was no persistent improvement when the prone position was followed by a 12 h period of supine positioning with conventional ventilation. On evaluating HFOV effects Pachl *et al.* [51] also suggest that patients with pulmonary ARDS have less recruitable lung tissue than those with extrapulmonary ARDS.

In contrast, Estenssoro *et al.* [52] found similar responses to PEEP-induced alveolar recruitment in pulmonary and extrapulmonary ARDS patients, as assessed by oxygenation. Recently, a multicentre study by Thille *et al.* [53••] reported that PEEP-induced alveolar recruitment does not differ between patients with pulmonary and extrapulmonary ARDS, suggesting that the origin of ARDS does not influence the recruitability of the lungs; however, this study measured airway pressure instead of transpulmonary pressure. In pulmonary ARDS, the amount of atelectasis is scarce, and the predominant damage is the consolidation of alveolar units. Thus, for a given applied airway pressure, the average change in transpulmonary pressure is relatively high with low potential for recruitment. By contrast, in extrapulmonary ARDS patients with higher intra-abdominal pressures, considering similar airway pressures (inspiratory and expiratory), transpulmonary pressure remains low, and the lungs seem more amenable to recruitment strategies. Therefore, since the alveolar recruitment at CT scan was comparable in both ARDS groups [32,34••,54], it is likely that the potential for recruitment was higher in extrapulmonary than in pulmonary ARDS. In this context, Grasso *et al.* [55] examined the hypothesis that the effectiveness of a recruiting manoeuvre to improve oxygenation in patients with ARDS would be influenced by the elastic properties of the lung and chest wall independent of the aetiology of ARDS. They observed that application of recruiting manoeuvres improved oxygenation only in patients with early ARDS, who showed no impairment of chest wall mechanics and presented a large potential for recruitment, as indicated by low values of lung static elastance. Thus, the potential for alveolar recruitment is probably related to changes in lung and chest wall mechanics, unlike the underlying disease responsible for ARDS. Although the response of recruitment manoeuvres remains controversial in both ARDS groups, there is a consensus that low tidal volume strategy should be broadly applied to patients with ALI/ARDS despite the aetiology of lung injury [16].

Besides ventilatory strategies there are several other potential therapeutic strategies for ARDS patients. Rialp *et al.* [56] observed that prone position was associated with a marked improvement in oxygenation, irrespective of the causes of ARDS, and the additive effects of nitric oxide inhalation were mainly seen in patients with pulmonary ARDS [56]. Conversely, Gerlach *et al.* [57] showed that the effects of nitric oxide inhalation on oxygenation were not different between the two ARDS groups. Domenighetti *et al.* [58] reported that considering the group of ARDS patients as a whole, mean pulmonary artery pressure decreased during nebulized prostacyclin nebulization, but oxygenation did not change significantly. Additionally, all extrapulmonary ARDS patients responded to prostacyclin on oxygenation, whereas all pulmonary ARDS patients (plus one extrapulmonary ARDS patient) were nonresponders. No pharmacological treatment has been found to be effective in the reduction of mortality in ARDS. It seems likely that success will be determined by the stage of ARDS to which treatment is applied (early or late) and based on the aetiology of lung injury.

The differences among these clinical studies could be attributed to several reasons: difficulty at separating both types of injury, which may coexist [59]; different baseline characteristics of patients, like the severity of injury at the onset of ALI/ARDS; different transpulmonary pressures reached during tidal breathing and after PEEP due to different chest wall mechanical properties; the use of vasoactive drugs, which may affect cardiac output and gas-exchange response at different mean airway pressures; the type of recruitment manoeuvres applied; supine, upright or prone positioning during the study; the method of measuring lung recruitment; the different causes of pulmonary and extrapulmonary ARDS; and the ventilatory and clinical management at the moment of the study. Thus, controlled animal studies are important to standardize and clarify these controversies. Certainly, experimental data should not be directly extrapolated to the clinical scenario, but can be extremely helpful to design appropriate clinical studies.

Conclusion

The distinction between pulmonary and extrapulmonary ARDS is not simple and clear, and the observation of some pathogenetic overlapping mechanisms and morphological interaction may be frequent impairing the understanding of different pathways. Additionally, the use of adequate methods to evaluate lung function and pathology may reduce controversies over the values of certain therapeutic measures. We believe there is the need to distinguish not only pulmonary and extrapulmonary ARDS, but also different aetiologies to improve clinical management and survival.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 109–110).

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