SUMMARY

BACKGROUND AND OBJECTIVES: The pathogenesis of acute respiratory distress syndrome (ARDS) has been described by the presence of direct (pulmonary) and/or indirect (extrapulmonary) insult to the lung parenchyma. Evidence indicates that the pathophysiology of ARDS may differ according to the type of primary insult. This article presents a brief overview of differences between pulmonary and extrapulmonary ARDS, and discusses the interactions between morpho-functional aspects and response to different therapies, both in experimental and clinical studies.

CONTENTS: This systematic review included clinical and experimental ARDS studies found in MedLine and SciElo databases in the last 20 years. Many researchers acknowledge that experimental pulmonary and extrapulmonary ARDS are not identical with regard to morpho-functional aspects, the response to positive end-expiratory pressure (PEEP), recruitment manoeuvre, prone position and other adjunctive therapies. However, contradictory results have been reported in different clinical studies, which could be attributed to the difficulty of classifying ARDS in one or the other category, and to the assurance regarding the onset, phase and severity of ARDS in all patients.

CONCLUSIONS: Heterogeneous ARDS patients are still considered as belonging to one syndrome, and are therefore treated in a similar manner. Thus, it is important to understand the pathophysiology of pulmonary and extrapulmonary ARDS in an attempt to better treat these patients.

Key Words: pulmonary histology, protective ventilation, recruitment manoeuvre, respiratory mechanics.
clínicos sobre SDRA incluídos nas bases de dados MedLine e SciElo nos últimos 20 anos. Muitos pesquisadores concordam, com base em estudos experimentais, que a SDRA pulmonar e a SDRA extrapulmonar não são idênticas no que diz respeito aos aspectos morfofuncionais, a resposta à pressão positiva ao final da expiração (PEEP), manobra de recrutamento alveolar, posição prona e outras terapias farmacológicas. Entretanto, os estudos clínicos têm descrito resultados contraditórios, os quais podem ser atribuídos à dificuldade de se classificar a SDRA em uma ou outra etiologia, e de se precisar o início, a fase e a gravidade da SDRA nos pacientes.

CONCLUSÕES: Pacientes com SDRA de etiologias distintas perduram sendo considerados como pertencendo a uma mesma síndrome e, assim, são tratados da mesma forma. Logo, é fundamental entender as diferenças fisiopatológicas entre a SDRA pulmonar e extrapulmonar para que a terapia seja mais bem direcionada.

Unitermos: histologia pulmonar, manobra de recrutamento alveolar, mecânica respiratória, ventilação protetora

INTRODUÇÃO

Acute lung injury (ALI) and its most severe form, the acute respiratory distress syndrome (ARDS) are characterized by acute respiratory failure, diffuse and bilateral pulmonary infiltrates seen at chest X-ray, reduced pulmonary compliance and the ratio between arterial oxygen partial pressure and fraction of inspired oxygen (P/F) \( \leq 300 \text{ mmHg} \) for ALI and \( P/F \leq 200 \text{ mmHg} \) for ARDS\(^1\). Various clinical and surgical conditions may lead to development of ALI/ARDS. There are two pathogenic pathways: direct injury (pulmonary) that directly affects the pulmonary parenchyma and indirect injury (extrapulmonary) resulting from a systemic inflammatory response\(^1\) (Chart 1). Experimental studies have disclosed morpho-functional and therapeutic differences between pulmonary and extrapulmonary ARDS\(^2,3,4-10\).

However, clinical findings are contradictory\(^4-10\). The purpose of this study was to carry out a critical analysis of the differences between pulmonary and extrapulmonary ARDS and to discuss interaction between respiratory mechanics, lung histology and response to different treatments.

EPIDEMIOLOGIA

Because of issues related to the definition\(^11\) and failure in the diagnostic tests\(^12\) it is difficult to assess incidence of ARDS. Approximately 7% of patients admitted in intensive care units (ICU) develop ARDS, with a mortality rate ranging from 35% to 60%\(^13\).

Various clinical studies attempted to demonstrate the incidence of pulmonary and extrapulmonary ARDS as well as identify the correlation between etiology and prognosis. Most studies disclosed a higher prevalence of pulmonary ARDS\(^5,7,14,15\), although Eisner et al.\(^16\) did not find a difference. Pneumonia is the more frequent cause of direct injury, while sepsis is the most prevalent and lethal cause of indirect injury. Suntharalingam et al.\(^17\) showed a higher mortality in pulmonary ARDS, whereas Eisner et al.\(^16\) had not found a correlation between the etiology of ARDS and mortality. Angus et al.\(^18\) observed that at the end of the first year, patients of pulmonary ARDS presented a worsening in quality of life. Parker et al.\(^19\) found that quality of life was similar in patients of pulmonary and extrapulmonary ARDS at three months, however after 12 months, patients with pulmonary ARDS presented a better quality of life.

PATHOPHYSIOLOGIA

In pulmonary ARDS the alveolar epithelium is the first structure injured. Injury to the epithelial barrier induces:
alveolar edema\textsuperscript{20}, reduction of edema depuration\textsuperscript{21}, decrease in the production and turnover of surfactant\textsuperscript{22} and fibrosis\textsuperscript{23}. Efficient alveolar epithelial repair can minimize formation of fibrosis as the intact epithelial layer suppresses proliferation of fibroblasts and deposits of the extracellular matrix (ECM)\textsuperscript{24}. Epithelial repair involves various molecular mechanisms including interaction between type II pneumocites and the ECM\textsuperscript{25}. In extrapulmonary ARDS, the endothelial cell is first injured\textsuperscript{26} by circulating inflammatory mediators released by the extrapulmonary focus (i.e. peritonitis, pancreatitis). Pulmonary endothelium is a highly specialized tissue having physiological and immunological functions, in addition to storing numberless enzymes, receptors and transduction molecules that interact with one another and with the components of the capillary wall and circulating blood cells\textsuperscript{27}. The alveolar-capillary barrier plays a decisive role in repair and remodeling\textsuperscript{27}.

**HISTOLOGY**

In pulmonary ARDS, involvement of the pulmonary parenchyma is multifocal, whereas in the extrapulmonary, change is more diffuse and uniform due to the hematogenic distribution of inflammatory mediators. Morphological differences between pulmonary and extrapulmonary ARDS were evaluated in autopsies\textsuperscript{8} observing the prevalence of alveolar collapse, fibrinous exudate and alveolar wall edema in patients with pulmonary ARDS. Negri et al.\textsuperscript{28} found a higher number of collagen fibers in the pulmonary parenchyma of patients with pulmonary ARDS when compared with the extrapulmonary, suggesting that remodeling of ECM depends on the initial site of the injury.

**MORPHOLOGY**

Various studies described the morphological difference at CT scan in patients with pulmonary and extrapulmonary ARDS\textsuperscript{5,28-31}. However, Desai et al.\textsuperscript{7} reported that there is no tomographic characteristic able to predict the etiology of the injury. Studies with CT scan presented the following limitations: 1) small number of patients; 2) the group with extrapulmonary ARDS includes patients with abdominal sepsis and postoperative of heart surgery that usually progress with left lower lobe collapse and 3) direct and indirect injuries can coexist, making interpretation of the morphological pattern more difficult.

**RESPIRATORY MECHANICS**

Respiratory mechanics also seems to vary according to the etiology of the injury. Gattinoni et al.\textsuperscript{5} described that although static elastance of the respiratory system is similar in pulmonary and extrapulmonary ARDS, static elastance of the lung was greater in pulmonary ARDS, while static elastance of the thoracic wall was greater in the extrapulmonary. In this framework Albaiceta et al.\textsuperscript{33} further demonstrated the role of the thoracic wall in the mechanics of the respiratory system of patients with extrapulmonary ARDS. Therefore, to better characterize the pathophysiological process, an analysis of the respiratory system and of its components, the lung and thoracic wall, becomes essential.

**RESPONSE TO THE DIFFERENT VENTILATORY AND PHARMACOLOGICAL THERAPIES**

**Experimental Studies**

In pulmonary and extrapulmonary ARDS therapeutic responses presented contradictory outcomes, probably because of the possible coexistence of direct and indirect injuries in the same patients\textsuperscript{5,34}. To avoid such limitations, experimental models of pulmonary and extrapulmonary ARDS have been developed. In this context Menezes et al.\textsuperscript{2} developed with mice, models of pulmonary and extrapulmonary ALI induced by intratracheal and intraperitoneal administration of \textit{E. coli} lipopolysaccharides, respectively with similar levels of mechanical changes at the early stage. They found that the direct injury provoked a more accentuated inflammatory response than the indirect\textsuperscript{2}, notwithstanding that the amount of collagen fibers had been similar in both models. Santos et al.\textsuperscript{3} when making a temporal study of pulmonary parenchyma remodeling, in these models of pulmonary and extrapulmonary ALI observed that direct injury caused fibroblastogenesis, whereas indirect injury only brings about an early fibrosis that was repaired. Therefore, the balance between alveolar epithelial inflammation and/or endothelial injury and the repair mechanisms, apparently determines the prognosis of ALI/ARDS. Since inflammatory response was different between pulmonary and extrapulmonary ALI, Rocco et al.\textsuperscript{35} analyzed the role of corticosteroids in these models and found that the steroid (methylprednisolone) attenuated morphological changes as well as pulmonary inflammatory response, only in the group of pulmonary ALI but avoided changes in the content of collagen fibers in both groups.
Effects of recruitment maneuvers (RM) or positive expiratory end pressure (PEEP) in the pulmonary function and gas exchange also have been studied in different models of ALI. Most studies reported that RM are more beneficial in extrapulmonary ALI, than in the pulmonary. Kloot et al. observed that high levels of PEEP caused a more effective recruitment in the ALI model induced by oleic acid (extrapulmonary) than in that produced by bacteria (pulmonary). Recently, Riva et al. investigated the effects of RM on pulmonary mechanics and histology and oxygenation in experimental models of pulmonary and extrapulmonary ALI with similar transpulmonary pressures. They observed that RM improved oxygenation and pulmonary mechanics and decreased alveolar collapse more effectively in extrapulmonary ALI than in the pulmonary; suggesting that efficacy of RM differs according to the injury’s etiology.

Clinical Studies
Results of RM on patients with ARDS remain controversial.Gattinoni et al. report that for recruitment of collapsed alveoli PEEP was less efficient in the pulmonary ARDS. Likewise, Pelosi et al. observed beneficial effects of three breaths per minute with a plateau pressure of 45 cmH₂O in extrapulmonary ARDS. Lim et al. to substantiate these findings showed that a better oxygenation obtained through alveolar RM in extrapulmonary ARDS was about five times greater than in the pulmonary. Tugrul et al. observed that although, lung insufflation sustained at 45 cmH₂O for 30 seconds, associated to application of PEEP after insufflation of approximately 16 cmH₂O improved extrapulmonary and pulmonary ARDS oxygenation, whereas static compliance increased only in the extrapulmonary ARDS.

On the other hand, Estenssoro et al. found responses similar to alveolar recruitment in patients with pulmonary and extrapulmonary ARDS. To substantiate such results Thille et al. conducted a multicentric study and proved that the response to alveolar recruitment with PEEP was no different between pulmonary and extrapulmonary ARDS. This suggests that injury etiology does not influence the recruiting capacity of the alveoli. However, this study measured the pressure of the airways instead of the transpulmonary pressure. In extrapulmonary ARDS, for the same pressure in the airways, due to the high intra-abdominal pressure transpulmonary pressure is low, favoring alveolar recruitment. On the other hand in pulmonary ARDS there is a predominance of alveolar consolidation. As such, for the same airways pressure, transpulmonary pressure is relatively high with a low recruitment potential (Figure 1). Within

![Figure 1 – Pathophysiology and Response to Alveolar Recruitment Strategies in the Pulmonary and Extrapulmonary Acute Respiratory Distress Syndrome.](image-url)
this framework, Grasso et al. reported that efficacy of recruitment maneuvers would be influenced by the elastic properties of the lung and of the thoracic wall, independent of ARDS etiology.

Functional response of extrapulmonary and pulmonary ARDS also differs because of the patient’s position in bed. Various authors observed that the ventral decubitus (prone position) produced better oxygenation in the pulmonary than in the extrapulmonary ARDS. This beneficial effect ceased when patients were placed in dorsal decubitus. Pachl et al., when assessing the effects of HFOV (high-frequency oscillatory ventilation) suggested that patients with pulmonary ARDS have less recruitable pulmonary tissue. Although response to recruitment maneuvers and to the prone position remain controversial, there is consensus that the ventilatory strategy with low tidal volume must be used in ALI/ARDS independent of the injury’s etiology.

Response to pharmacological therapies also differs for pulmonary and extrapulmonary ARDS. Rialp et al. observed that the prone position brought about better oxygenation in the pulmonary than in the extrapulmonary ARDS. The controversies in different clinical studies may be ascribed to: 1) difficulty in separating the two types of direct and indirect injuries that may coexist; 2) different stages of injury; 3) different transpulmonary pressures; 4) use of vasoactive drugs that may affect cardiac output and gas exchange; 5) type of RM applied; 6) position adopted (supine, superolateral and prone) during the study; 7) method for measuring beneficial effects of pulmonary recruitment; 8) different causes of pulmonary and extrapulmonary ARDS and 9) clinical and ventilatory handling at the time of the study. That is why well controlled experimental studies with animals are important to standardize and clarify such controversial matters. Certainly experimental data cannot be directly extrapolated to a clinical scenario, yet they can be extremely useful to design appropriate clinical studies.

CONCLUSION

ARDS can be divided into pulmonary or extrapulmonary if the primary injury is epithelial or endothelial. Results of pharmacological and ventilatory treatment of pulmonary and extrapulmonary ARDS continue to be controversial. However, use of adequate methods for assessment of respiratory mechanics and pulmonary histology may reduce the existing controversies about response to ventilatory and pharmacological therapies. To enhance clinical handling and increase survival of ARDS patients, it might be necessary to differentiate not only pulmonary and extrapulmonary ARDS, but also the different etiologies of ARDS.

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