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EDITORIAL

We've never seen a patient with ARDS!

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Since the initial description by Ashbaugh et al. [1], it has been known that some forms of diffuse pulmonary edema are not primarily due to increased hydrostatic lung microvasculature pressures, which characterize left heart failure and/or fluid overload, but result from alterations in alveolar-capillary permeability. Acute respiratory distress syndrome (ARDS) is the clinical expression of this acute, non-hemodynamic lung edema, and is diagnosed by hypoxemia and bilateral lung infiltrates in the absence of increased capillary hydrostatic pressure (Fig. 1). ARDS is ubiquitous in the intensive care unit (ICU), representing almost a quarter of the ICU patients who require mechanical ventilation [2], and ubiquitous in the ICU literature. A quick search of PubMed revealed over 13,000 published articles on ARDS since 1967. Based on this, one would think that diagnosing a patient as having ARDS would really add something to improve that patient's outcome [3]; but does it?

The problem is that we generally tend to consider ARDS as a disease, forgetting that it is actually a syndrome associated with many possible pre-disposing factors ranging from pulmonary infections to heroin overdose, from intraabdominal abscess to intracranial bleeds. The attempt to distinguish between pulmonary and extrapulmonary sources–although initially promising—has not resulted in a major increase in our understanding of the disease process or in improvements in management.

So, is it important to diagnose ARDS? Before answering this question, we must recognize that there is no specific treatment for ARDS. Some years ago, we would have argued that the principal implication of an ARDS diagnosis was that it was a "prescription" for the use of small tidal volume ventilation. This recommendation followed observations from important multicenter randomized controlled trials indicating that using tidal volumes of 6 ml/kg rather than 12 ml/kg of predicted body weight (PBW) resulted in decreased mortality [4]. Other studies supported the concept of reducing ventilator-induced lung injury (VILI) by performing so-called 'protective ventilation', but it soon became apparent that this approach should not be limited to patients with ARDS. It is now well established that large tidal volumes should be avoided in *all* cases of mechanical ventilation [5] and even during major surgery [6]. This is similar to the concept that limiting fluid overload is a strategy applicable to all critically ill patients, not just those with ARDS.

There is little evidence to support the use of one mode of ventilation over another in patients diagnosed with ARDS, other than for high frequency ventilation, which is not recommended [7]. The place of recruitment maneuvers is also debated. Individual trials evaluating the effects of higher versus lower levels of positive end-expiratory pressure (PEEP) in patients with ARDS have largely been negative, although a meta-analysis demonstrated that higher PEEP was beneficial in patients with moderate or severe ARDS [8]. Although theoretically appealing, PEEP titration based on esophageal pressure measurements has not resulted in better outcomes [9].

A diagnosis of ARDS also does not suggest any specific pharmacologic therapies. The use of muscle relaxants should be individualized [10], and, if effective, they almost certainly act by decreasing VILI, not by treating the underlying disease process. Even administration of corticosteroids to all patients with ARDS is controversial, despite the recent report of a beneficial effect on duration of mechanical ventilation and mortality [11].

Getting back to the question of whether it is important to diagnose ARDS, the LUNG SAFE study [2] found that mild ARDS was missed by clinicians in

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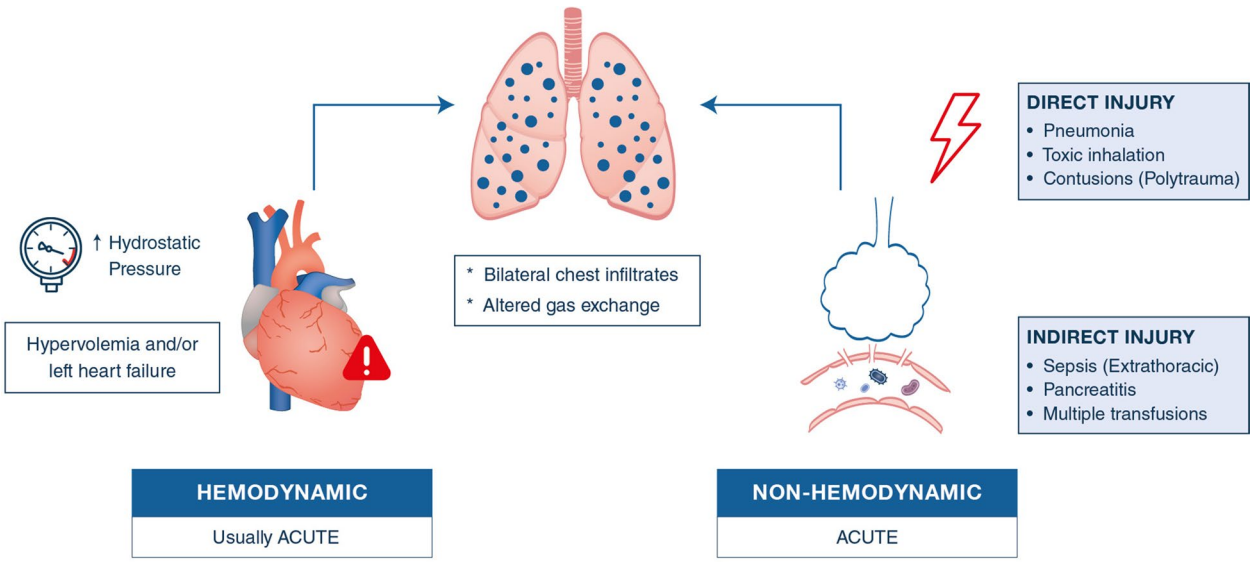

Fig. 1 The basic pathophysiologic approach to diffuse lung edema

about 50% of cases, and that severe ARDS was missed in over 20% of cases. But, given that we have no specific treatments, does it really matter? In the LUNG SAFE study, there was a minor impact on the tidal volume chosen [very slightly lower (~0.2 ml/kg PBW)] in those patients with a clinician diagnosis of ARDS, but there was an impact on the use of adjunctive measures (from ~22% to 44%).

Recent attempts to identify subgroups of patients with ARDS based on a relatively large number of clinical and laboratory variables have suggested that specific patient populations could benefit from specific therapies. In post hoc analyses of ARDS randomized trials, response to various treatments (level of PEEP, fluid therapy, and simvastatin) was dependent on whether the patients had a hypo- or hyper-inflammatory subphenotype [12]. Further development of parsimonious classifier models with relatively few (3 or 4) variables hopefully will help determine prospectively whether this approach will identify ARDS patients who will benefit from various therapies [13]. And perhaps a diagnosis of ARDS will not be necessary for the utility of such a scheme. Maybe in the future we will treat patients based on a diagnosis of hypo- or hyper-inflammatory lung failure [or some other defining phenotype(s)], rather than on the basis of having ARDS.

The COVID-19 pandemic has provided some interesting insights on this topic. Although COVID-19 related acute respiratory failure may often be ARDS, this is not always the case [14]. In any event, how would a label of ARDS help these patients? Management of COVID-19 related respiratory failure is the same whether we call it ARDS or not [15].

This reflects our key message: COVID-19 is a disease, and ARDS is a syndrome. ARDS usually has an underlying identifiable cause, and the cause can often result in a specific therapy, whether that is antimicrobials, surgery, corticosteroids, …. We do not need to "see" or diagnose ARDS to be able to treat it appropriately; the only benefit is that it may encourage us to search for a potentially treatable underlying condition, and it may encourage us to use lung protective ventilatory strategies.

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JLV drafted the manuscript; ASS revised the manuscript for critical content. Both authors read and approved the final manuscript.

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