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Why improved PF ratio should not be our target when treating ARDS

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Running title: PF ratio and the outcome of ARDS

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The use of PF ratio as a bedside physiological target: evidences from clinical trials and meta-analyses

Despite decades of research investigating etiopathogenetic treatments and supportive therapies, very few strategies proved effective in decreasing mortality of patients with the acute respiratory distress syndrome (ARDS). These disappointing results are confirmed by the meta-analysis performed by Longobardo et al. in this issue of Minerva Anesthesiology.[1] The authors focused on therapeutic strategies readily available in non-specialized general intensive care units (ICU): corticosteroids, fluid restriction, higher positive end-expiratory pressure (PEEP), low tidal volume, neuromuscular blockade, prone position and recruitment maneuvers. Through accurate meta-analyses, they reported that only low tidal volume and prolonged prone position improve survival of ARDS. But this may not be the only clinically relevant finding of the study. Corticosteroids, higher PEEP, neuromuscular blockade and recruitment maneuvers improved oxygenation (i.e., the PF ratio) without decreasing mortality. Conversely, the survival benefit of low tidal volume ventilation and prone position was not preceded by an improvement in oxygenation. By putting in evidence the nearly complete dissociation between the effect of treatments on reducing mortality (primary outcome) vs. the improvement in the PF ratio (secondary physiological outcome), this series of meta-analyses provides a matter for reflection on what should be our target in the clinical management of ARDS.

Oxygenation impairment is a cornerstone of the definition of ARDS and low PF ratio is the most alarming sign for clinicians taking care of ARDS patients (e.g., rescue treatments such as extracorporeal support are usually reserved for the most hypoxemic patients). Therefore, it is tempting to use improved oxygenation as a daily bedside endpoint when assessing the effects of our treatments. But if the short-term effect on oxygenation is dissociated from the improvement of clinical outcomes, this approach may be misleading.

Physiological mechanisms underlying the dissociation between improved PF ratio and clinical outcomes

When looking at the causes of death in ARDS patients, it is striking to note that hypoxemia and "unsupportable" respiratory failure are very rare. Indeed, observational studies showed that ARDS patients die as a consequence of hemodynamic decompensation and of the complications of prolonged ventilation and ICU stay, usually super-infections causing refractory shock with multiple organs failure[2]. Interestingly, most therapeutic strategies that improve oxygenation might adversely

affect hemodynamics and delay weaning from mechanical ventilation, eventually increasing the risk of infections, organs failure and poor outcome.

Detrimental effects on hemodynamics could derive from use of higher PEEP, recruitment maneuvers and failure to apply restrictive fluid management. The use of higher PEEP potentially induces a reduction of venous return due to the elevated intrathoracic pressure and an increase in right ventricular afterload due to increased pulmonary vascular resistance[3]. The resulting decrease in cardiac output could further aggravate right ventricular failure and induce shock. The effects of PEEP are highly variable among ARDS patients and preliminary assessment of recruitabilty may be the best way to predict the balance between benefits and risks of higher PEEP: recruitment is poorly correlated with improved PF ratio; at the opposite decreased cardiac output may lead to decreased intrapulmonary shunt[4]. Similar mechanisms may explain the pitfalls linked to indiscriminate application of recruitment maneuvers, which transiently increase airway pressure to very high values. Since these adverse cardiocirculatory effects are counteracted by hypervolemia, use of higher PEEP and recruitment maneuvers may hinder the applicability of conservative fluid strategy. Hypotension, positive fluid balance and increased use of vasopressors are the price paid when high PEEP and recruitment maneuvers are applied to unselected patients and might explain the lack of effect on mortality[5].

The impact of complex drugs such as corticosteroids and neuromuscular blocking agents cannot be accurately estimated by their effect on oxygenation. Corticosteroids might increase the risk of infections and of muscular weakness[6]. Use of neuromuscular blockade usually requires deeper sedation and causes muscular weakness[7]. Thus, both drugs potentially prolong the duration of mechanical ventilation and the risk of multi-organs failure.

In summary, therapeutic strategies that are intended to improve outcome have complex interactive effects with potential harm. Improvement in the PF ratio is a single, limited measurement of the effect of these therapeutic strategies and does not accurately reflect lung protection and even less patient protection.

If not PF ratio, then what?

Individualized treatment is the only way we have to apply therapeutic strategies to selected patients in whom preliminary physiologic tests indicate the potential for a favorable balance between beneficial and detrimental effects.

Intensivists could integrate data available at the bedside to characterize the ARDS phenotype expressed by individual patients in order to predict the effects of each therapeutic strategy. Differences in clinical, physiological, radiological and biological variables distinguish ARDS phenotypes[8] and may guide personalized treatments based on the predicted patient-specific benefits (Table 1). Bedside targets to evaluate the physiological benefits of each intervention will be those most closely reflecting the relevant mechanisms (e.g., recruitment after application of higher PEEP or decreased hyper-inflammation after pharmacological modulation).

While our ability to characterize ARDS continues to improve, randomized controlled trials in unselected patients become less and less adequate as a method to obtain useful evidences on the effects of treatments. Machine learning algorithms to identify ARDS phenotypes[9] and enrichment strategies for informing clinical trials[10] will hopefully reduce this gap in the future. In the meantime, we can apply clinical reasoning and bedside physiological measures to provide personalized care aimed at restoring well-balanced physiology. And we should keep in mind that accepting lower oxygenation may be more patient-protective than aggressive efforts improve PF ratio.

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Notes

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Table 1. Specific variables and mechanisms identifying ARDS phenotypes

Specific variables	Specific mechanisms affecting therapeutic strategies
Clinical	
• **Etiology**	Different etiologies influence respiratory mechanics, mechanisms of hypoxia, lung morphology, need for specific etiologic treatments
• **Days since diagnosis**	Opposite pathophysiology despite similar measures (decreased compliance due to acute inflammation vs. fibrosis)
• **Site of original inflammatory insult**	Different pathophysiology for extrapulmonary vs. primary origin (recruitability, heterogeneity)
Physiological	
• **Respiratory mechanics**	Compliance reflects the size of baby lung. The ratio between lung and respiratory system elastances affects the hemodynamic consequences of PEEP
• **Mechanisms of hypoxemia**	Alveolar collapse is the prerequisite for recruitability as opposed to ventilation/perfusion maldistribution
• **Dead Space**	High dead space implies risk of hypercapnia with low Vt; high PEEP might increase dead space and overdistension
• **Recruitability**	protective role of higher PEEP on the lung and less impact on hemodynamics
• **Cardiocirculatory shock**	Hypovolemia and poor cardiac function amplify the adverse effects of PEEP and recruitment maneuvers
Radiological	
• **Spatial distribution of infiltrates**	Focal ARDS may benefit from lower PEEP strategy that minimizes overdistension combined with prone position to improve lung homogeneity; non-focal ARDS may benefit from higher PEEP to maximize recruitment
Biologic	
• **Biomarkers**	Hyperinflammatory phenotype benefits from more aggressive PEEP strategy and fluid restriction, the opposite for hypoinflamed patients. Steroids may be indicated for hyper-inflamed phenotype.