Right heart function during acute respiratory distress syndrome

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Abstract: Acute respiratory distress syndrome (ARDS) is burdened with significant mortality, mainly in connection with circulatory failure. The right ventricle (RV) is the weak link of hemodynamic stability among ARDS patients and its failure, also named “severe” acute cor pulmonale (ACP), is responsible for excess mortality. Driving pressure ≥18 cmH2O, PaCO2 ≥48 mmHg and PaO2/FiO2 <150 mmHg are three preventable factors recently identified as independently associated with ACP, on which ventilator strategy designed to protect the RV has to focus. This is largely achieved by the use of early and extended sessions of prone positioning (PP) and by daily monitoring of the RV by echocardiography.

Keywords: Acute respiratory distress syndrome (ARDS); right ventricle (RV); acute cor pulmonale (ACP); driving pressure; hypercapnia; oxygenation

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Historical and physiological background

Acute respiratory distress syndrome (ARDS) is still associated with high mortality (1) and long-term disability (2). This poor outcome is probably more the consequence of circulatory failure than hypoxemia per se (3). In ARDS, septic shock is responsible for circulatory failure in half of patients (4), but awareness of its management is high worldwide (5). On the other hand, for the other half of patients, hemodynamic instability is directly related to ARDS as a result of pulmonary circulation dysfunction and its consequence, which is right ventricular (RV) failure. The RV is now consensually considered as the weakest link during ARDS, and its failure, in the most severe form, is named acute cor pulmonale (ACP) (6). The RV acts as a passive crescent chamber promoting venous return from the systemic circulation to the pulmonary one (8). Without any contractile reserve (9), the RV has no adaptive mechanism other than its dilatation when its afterload is increased, even a little. Any ventriculo-arterial uncoupling between the RV and the pulmonary circulation leads to RV dilatation, which is responsible for LV compression on the one hand and an ischemic vicious circle for itself on the other hand. ARDS is also a disease of RV afterload resulting in ventriculo-arterial uncoupling as a consequence of the increase in pulmonary vascular resistance (10-12). But pulmonary arterial hypertension is generated by numerous factors that can be schematically classified as “intrinsic”, resulting from alveolar and capillary injuries (12), actions on which are limited, and “extrinsic”, which are mainly the consequences of mechanical ventilation, on which the ventilator strategy has to focus (13). Severe ACP, as well as...
pulmonary dysfunction, has been shown to independently increase mortality during ARDS (14,15), showing that uncoupling between the RV and the pulmonary circulation is at the core of the prognosis. Here we will briefly describe the main known risk factors for ACP in ARDS and will then propose another reading of recent ARDS studies, mainly based on their potential protective effect on the RV. This will help us to propose testing of an RV protective approach as a new respiratory strategy in ARDS.

**Risk factors for ACP in ARDS**

Besides pneumonia as the cause of ARDS, 3 parameters have recently been demonstrated as independently associated with ACP (15): driving pressure ≥18 cmH₂O, PaCO₂ ≥48 cmH₂O and PaO₂/FiO₂ ratio <150 mmHg.

Driving pressure, which is the difference between the end-inspiratory alveolar pressure and the total positive end-expiratory pressure (PEEP), reflects the pressure induced by tidal ventilation. It is, then, related to the respiratory strategy (in which tidal volume is increased) and to the severity of ARDS (how depressed the respiratory compliance is). In clinical practice, esophageal pressure is usually not measured and driving pressure is used as a surrogate of transpulmonary pressure, at least in patients without significant depression in chest wall compliance. For nearly 50 years, it has been well known that transpulmonary pressure exponentially increases pulmonary vascular resistance (16,17). High transpulmonary pressure participates in pulmonary hypertension and is responsible for cyclic alteration of RV function during tidal ventilation (18). Interestingly, it has recently been shown that a driving pressure >18 cmH₂O is associated with increased mortality (19). Very recently, Villar et al. also nicely demonstrated that for a plateau pressure maintained below 30 cmH₂O, survival decreased when driving pressure was equal to or higher than 19 cmH₂O (20). Unfortunately, no RV evaluation was proposed in these studies, but one can assume that the impact of driving pressure on prognosis could be explained in part by its impact on the RV.

During the first twenty years of ARDS ventilatory support, one of the main objectives was to maintain carbon dioxide in the normal range. At the beginning of the 1990s, the application of a lung protective approach with permissive hypercapnia opened up a new era during which the main objective was to limit tidal volume, so as to decrease the phenomenon of volume-induced lung injury (21). The enthusiasm associated with this concept was strengthened by the description of the pleomorphic beneficial effect of carbon dioxide (22), and some authors proposed enlarging the concept of permissive hypercapnia to one of “therapeutic” hypercapnia (23). However, hypercapnia was also described as a powerful vasoconstrictor of the pulmonary circulation (24), and its deleterious effects have been more deeply understood since the beginning of the 2000s. Some authors nicely showed very recently that severe hypercapnia, defined as a PaCO₂ ≥50 mmHg, is independently associated with mortality in moderate to severe ARDS (25). A few years ago, before showing that a PaCO₂ ≥48 mmHg was associated with ACP in a large cohort of ARDS patients (15), we reported in a small number of patients with severe ARDS that an abrupt increase in PaCO₂ applied for only one and a half hours, even associated with a decreased driving pressure, is responsible for severe ACP and hemodynamic alterations (26). Once again, putting these data together, we might understand the deleterious effect of severe hypercapnia on prognosis as the consequence of its effect on the pulmonary circulation and the RV, even though no study has directly reported such a link.

The PaO₂/FiO₂ ratio is routinely used to evaluate the severity of lung injury, while many confounding factors have been reported, as changes in cardiac output (27) and low PvO₂ effect (28). A ratio below 150 mmHg is also associated with ACP (15). The effect of low oxygen levels on the pulmonary circulation has long been known. Enson et al. reported that the greater the oxygen unsaturation, the higher the mean pulmonary arterial pressure (29). And this is obviously true whatever the cause of such a decrease in oxygenation, i.e., severe lung injury or associated compromised hemodynamics. It is interesting to note that the only study on prone positioning (PP) that reported a significant increase in survival is the one which included patients with a PaO₂/FiO₂ ratio below 150 mmHg (30). In this study, PP very significantly increased survival as well as the number of days free from cardiovascular dysfunction, and decreased the number of cardiac arrests (30), suggesting that hemodynamics plays a major role in the effect of PP on survival. Indeed, PP is also well known to unload the RV (31,32) and we can reasonably assume that improvement in RV function during PP could be one of the main mechanisms explaining the amelioration of survival. PP has very few limitations and can also be proposed for obese patients (33) and after abdominal surgery (34).
How to protect the RV?

As suggested above, the RV protective approach is intended to control the three main factors associated with RV failure, so as to alleviate RV afterload and, as a consequence, decrease mortality (Figure 1). This ventilatory strategy relies on a triptych associating increase in PaO$_2$/FiO$_2$ >150 mmHg, decrease in driving pressure <18 cmH$_2$O and control of PaCO$_2$ under 48 mmHg (35). PP is the cornerstone of this strategy (36), since it increases oxygenation (without increasing PEEP) and decreases PaCO$_2$ and driving pressure (37), which explains its beneficial effects on the RV (31).

To apply an RV protective approach, daily monitoring of the RV by echocardiography is essential (38). If echocardiography is not available 24/24, experts recently proposed an algorithm for hemodynamic monitoring based on pulse pressure respiratory variations (39). Pulse pressure variations have to be considered as a signal which obliges intensivists to look for hypovolemia, but mostly for RV failure (39) confirmed by an echocardiogram simply showing RV dilatation and paradoxical septal motion (40). Detecting RV failure by daily echocardiography could help intensivists to control risk factors better and to apply PP whatever the PaO$_2$/FiO$_2$ ratio. Further research would help determine whether other treatments designed to correct pulmonary capillary dysfunction, such as sevoflurane (41) or cell-based therapy (42), are synergistic with PP.

Conclusions

ARDS is associated with a poor outcome, in which RV failure plays a major role. The RV appears to be the weak link and correction of the ventriculo-arterial uncoupling between the RV and the pulmonary arterial circulation could be at the core of the ventilatory strategy. The RV protective strategy, which relies on PP and RV monitoring by echocardiography, could be promising and should be further evaluated in a randomized control trial.
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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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