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Editorial

Protecting the Right Ventricle in ARDS: The Role of Prone Ventilation

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is associated with high mortality (up to 46%) despite best standards of supportive care.[1] One of the major determinants of mortality in severe ARDS is hemodynamic instability, in particular pulmonary vascular dysfunction and right ventricular (RV) dysfunction/failure[2,3]; however, cardiopulmonary interactions in the context of ARDS are not understood fully. In most ARDS studies, RV failure is defined as "acute cor pulmonale" (ACP), which refers to an abrupt increase in RV afterload. On echocardiography, this is characterized by septal dyskinesia and RV dilatation with a ratio of RV end-diastolic area (RVEDA) to left ventricular end-diastolic area (LVEDA) > 0.6 and > 1 for severe ACP.[4,5] A recent risk score developed for the prediction of ACP in ARDS demonstrated several important clinical and physiologic parameters: (a) pneumonia as a cause of ARDS, (b) ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/F_iO_2) < 150 mmHg, (c) arterial carbon dioxide partial pressure ($PaCO_2$) ≥ 48 mmHg, and (d) driving pressure ≥ 18 cm H_2O.[5] The aforementioned variables have a statistically significant correlation with development of ACP with a reported incidence of 19%, 34%, and 74% in ARDS patients with risk scores of 2, 3, and 4, respectively.[5]

Pathophysiology of RV Injury in ARDS

Pulmonary vascular dysfunction and RV injury are characterized by increased pulmonary vascular resistance (PVR), pulmonary hypertension, and uncoupling between the RV and pulmonary circulations. ARDS-related pathophysiologic factors contributing to this include the following: hypoxic/hypercapnic pulmonary vasoconstriction, imbalance of vasoactive mediators (eg, increased endothelin-1 levels) and increased vasomotor tone, development of intravascular microthrombi, extrinsic vessel compression (due to reduction in lung volume, interstitial edema, and atelectasis), and pulmonary vascular remodeling.[6–8] These factors are related to mechanical ventilation and pulmonary mechanics with a negative impact on RV function in ARDS (alveolar vessel collapse leading to increased RV afterload): extremes of lung volume and imbalance between overdistension and recruitment,[9–13] plateau pressure (alveolar end-inspiratory pressure) > 27 cm H_2O,[13] and driving pressure (plateau pressure minus total positive end-expiratory pressure) > 18 cm H_2O.[3,5]

RV Function during Prone Ventilation—Evaluating the Evidence

Correction of hypoxemia/hypercapnia along with pressure and volume-limited mechanical ventilation potentially could minimize the adverse heart–lung interactions in ARDS. Prone mechanical ventilation has been used as a strategy to improve oxygenation and respiratory mechanics in the most severe form of ARDS ($PaO_2/F_iO_2 < 150$ mmHg) when conventional modes of ventilation fail. Early randomized trials showed a consistent association between prone ventilation and improvement in gas exchange, but no clear mortality benefit.[14–16] One might argue that this is because the proning sessions were of short duration (6-8 hours), ventilatory strategies used were nonprotective, and there was supine/prone crossover.[14–16]

Vieillard-Baron et al. examined the effect of prone ventilation on RV function, using transesophageal echocardiography (before and after the first 18-hour session of proning) in 42 patients with severe ARDS (defined as $PaO_2/F_iO_2 < 100$ mmHg).[17] Acute cor pulmonale was present in 50% of the cohort, and prone position ventilation was associated with a significant reduction in plateau pressure and $PaCO_2$, with associated improvement in RV function (reduced RVEDA/LVEDA ratio and septal dyskinesia).[17] Joswiak et al. showed that in patients with moderate to severe ARDS receiving pressure-limited low-tidal-volume ventilation, who are preload dependent, proning was associated with a decrease in RV afterload, increased cardiac index, and significant reduction in RVEDA/LVEDA ratio.[18] The PROSEVA (Proning Severe ARDS patients) randomized controlled trial demonstrated that prone positioning patients with a $PaO_2/F_iO_2 < 150$ mmHg subjected to low-tidal-volume ventilation and neuromuscular blockade confers significant mortality benefit (16.8% absolute

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reduction in 28-day all-cause mortality compared to the supine group).[19] The "prone ventilation" arm of PROSEVA had fewer cardiac arrests and more cardiac failure-free days at 28 days after recruitment, which could suggest that the RV-protective effect of prone positioning may contribute to survival benefit.

Five systematic reviews and meta-analyses based on individual or grouped data from randomized controlled trials (including PROSEVA) have shown that patients with moderate to severe ARDS are likely to benefit from early prone positioning; none of the studies, however, explored cardiovascular outcomes.[20–24] The recently published APRONET (ARDS Prone Position Network)[25] study is the first multicenter international prospective prevalence study dedicated specifically to the use of prone positioning. APRONET enrolled 735 ARDS patients (Berlin Definition)[26] from 20 countries (141 intensive care units) and showed that 32.9% of severe ARDS patients are being prone positioned. Prone ventilation is associated with significant improvement in gas exchange and a decrease in driving pressure, known to be a risk factor for ACP and an independent predictor of mortality in ARDS.[1,5,27] Of note, the 2 main reasons for not prone positioning patients in the APRONET study were (1) hypoxemia being not severe enough to justify prone positioning, based on the clinicians' judgment ($PaO_2/F_iO_2 < 150$ mmHg had the lowest odds ratio for predicting the risk for not prone positioning); and (2) hemodynamic instability.[25] The latter suggests that intensive care specialists may not be aware that changes in cardiovascular physiology associated with prone position in ARDS are advantageous, in particular reversal of RV-pulmonary artery (PA) uncoupling, and RV unloading during prone positioning could confer a mortality benefit.[17,18] However, a major concern remains: It may be difficult for intensivists to distinguish between ACP and other potential mechanisms of circulatory failure, such as vasodilatory shock as seen in sepsis. This dilemma highlights the value of critical care echocardiography in this setting.

In cases of ARDS complicated by refractory hypercapnia despite prone ventilation, extracorporeal devices could be considered to mitigate the deleterious effects of hypercapnia on the RV (increased RV afterload and RV-PA uncoupling). In particular, venovenous extracorporeal CO_2 removal ($ECCO_2R$) offers CO_2 clearance and facilitates ultraprotective ventilation (tidal volume of 4 mL/kg predicted body weight and reduction in plateau pressure).[28] In an experimental porcine ARDS model, Morimont et al. showed that institution of $ECCO_2R$ effectively reduced hypercapnia during protective ventilation, reduced PVR and mean PA pressure, and improved RV-PA coupling.[29] However, given the experimental and observational nature of current evidence pertaining to the use of $ECCO_2R$, it cannot be recommended as an accepted therapeutic measure or routine adjuvant therapy to prone ventilation in ARDS and RV protection at this time.[30]

Feasibility and safety of prone positioning for ARDS in the context of cardiothoracic surgery has not been tested in randomized controlled trials. In fact, 2 of the PROSEVA trial exclusion criteria were recent sternotomy and lung transplantation.[19] Retrospective data suggest that prone positioning can be applied safely as a bridge to recovery in lung transplantation recipients with refractory hypoxemia secondary to primary graft dysfunction, and it is associated with a decrease in vasoactive drug support.[31] A proportion of lung transplant candidates have preoperative RV dysfunction/failure secondary to chronic lung disease, which may be worsened by perioperative ARDS.[32] It is therefore reasonable that prone ventilation be considered in this cohort of patients.

Mechanisms of RV Unloading During Prone Positioning in ARDS

The physiological effect of prone positioning on the RV and pulmonary circulation can be explained by the following potential mechanisms:

Reduction in Pulmonary Vascular Tone

The ventral–dorsal transpulmonary pressure difference is reduced during prone positioning, and as ventilation becomes more homogeneous and the distribution of perfusion remains constant (in supine and prone positions), intrapulmonary shunt decreases and oxygenation improves.[33] The homogenous pulmonary aeration during prone positioning leads to reduced regional stress and strain and better carbon dioxide clearance.[33] The reduction in hypoxic/hypercapnic pulmonary vasoconstriction results in decreased PVR, a decrease in RV afterload, and improved RV-PA coupling.[33,34]

Reduction in Driving Pressure

Driving pressure, a surrogate currently used for dynamic lung stress, can be calculated as the difference between plateau pressure (end-inspiratory alveolar pressure) and total positive-end expiratory pressure (PEEP), and reflects the pressure generated in the respiratory system by the tidal volume.[27,35] It has been shown that when high PEEP is applied during prone ventilation, the associated reduction in tidal hyperinflation and alveolar cyclic recruitment/derecruitment results in a reduction in driving pressure,[36] a reduction in pulmonary capillary and extra-alveolar vessel compression, and a drop in PVR.[12]

Increase in Central Blood Volume

During prone ventilation there is an increase in central blood volume due to the shift of blood from the splanchnic into the thoracic circulation, which may induce recruitment of pulmonary microvasculature, increase in pulmonary capillary wedge pressure, and reduction in PVR and RV afterload.[18,33] This probably is true especially in patients with preliminary relative or absolute hypovolemia.

Protection Against Ventilator-Induced Lung Injury

Injurious mechanical ventilation can further exacerbate RV dysfunction in ARDS. It is assumed that cyclic interruption

and exaggeration of pulmonary blood flow during high-pressure ventilation may cause pulmonary microvascular injury, leading to cor pulmonale.[36] Recent data suggest that not only is the RV dysfunction the consequence of VILI, but also it could promote in part such a ventilator-induced lung injury (VILI).[37,38] The protective effect of prone positioning against VILI potentially could be explained by ventilatory homogeneity, a decrease in tidal hyperinflation, and homogenous distribution of strain.[33–37]

In conclusion, a substantial body of evidence supports the pivotal role of prone positioning in reducing mortality outcomes in severe ARDS. RV failure is a predictor of mortality in ARDS, and therefore monitoring and protecting the RV should be made an integral part of a heart and lung protective strategy in severe ARDS. The recommended RV-protective ventilatory goals (driving pressure < 18 cm H_2O, $PaCO_2 < 48$ mmHg, and $PaO_2/F_iO_2 > 150$ mmHg)[5,11] could be met with prone ventilation and no need for recruitment maneuvers and titrated high PEEP, recently found to be associated with mortality.[39] Adequately powered and well-designed randomized controlled trials should test the hypothesis that prone positioning ARDS patients with severe RV dysfunction regardless of PaO_2/F_iO_2 ratio improves patient-centred outcomes.

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