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Acute cor pulmonale in ARDS What's new?

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Author Comments:	Dear Editor in chief, As proposed by the editorial board of the journal, please find enclosed our contribution to the journal for the section "what's new" regarding ARDS and acute cor pulmonale. We hope that you will consider our manuscript acceptable for publication. Sincerely Antoine Vieillard-Baron
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Acute cor pulmonale in ARDS
What's new?

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In 1977 Zapol and colleagues reported that the pulmonary circulation was injured in patients with ARDS, leading to elevated pulmonary vascular resistance and pulmonary hypertension [1]. The investigators suggested that the pathogenesis was related to competition between alveolar distending pressure and blood flow in these patients who were ventilated with high airway pressure [2], as proposed by West et al. [3]. Pulmonary vascular remodeling also occurs with muscularization of normally non-muscularized arteries. Subsequently, using transesophageal echocardiography (TEE), Vieillard-Baron et al. reported 24 years later an incidence of acute cor pulmonale (ACP) of 25% during the first three days in 75 ARDS patients treated with lung protective ventilation [4]. A few years later, the same group reported a much higher incidence of 50% in more severe ARDS patients, all exhibiting a PaO_2/FiO_2 less than 100 mmHg [5]. The same group studied more than 300 patients and found that the incidence of ACP was strongly related to elevated plateau airway pressure with a safe limit for the right ventricle of 27 cmH_20 [6]. Since then several questions have been unresolved including: What is the actual incidence of ACP in a larger population? Which are the main variables associated with ACP? What is the impact of ACP on prognosis, if any? Should RV function be monitored, and if so how? Should clinicians adjust the ventilatory strategy to RV function? Recently published clinical studies provide answers to some of these questions.

In 2012, Guervilly et al. performed an evaluation of right ventricular (RV) function using TEE in a small series of 16 patients with persistent ARDS and a $PaO_2/FiO_2 < 150$ mmHg. Patients were ventilated in volume control mode with a mean tidal volume of 6.6 mL/kg, a mean plateau pressure of 25 cmH_20 and a mean PEEP of 13 cmH_20 [7]. They found that 56% of patients had RV dysfunction (isolated and moderate RV dilatation), whereas 25% had RV failure (major RV dilatation or paradoxical septal motion) [7].

More recently, Boissier et al. reported an incidence of ACP of 22% (95% confidence interval 16-27%) in a prospective single-center study of 226 patients using TEE within the first 3 days following diagnosis of ARDS [8]. All patients met the Berlin definition criteria for moderate to severe ARDS [9]. Patients were also ventilated in a volume control mode, with a tidal volume of 6 mL/kg, a plateau pressure < 30 cmH_20 and a PEEP of 8-9 cmH_20 [8]. In a multivariate logistic regression, independent factors associated with ACP were an infection as a cause of lung injury and the driving pressure (17 cmH_20 in patients with ACP versus 14 cmH_20 in the others) [8]. The driving pressure is the distending pressure related to tidal volume and then depends on tidal volume (i.e. the ventilatory strategy), and also on compliance of the respiratory system (i.e. the severity of injury). Infection as a factor associated with ACP is interesting. As discussed in the paper by Boissier et al., circulating cytokines may contribute to myocardial dysfunction [8]. In addition, inflammation, including infection, is an important component of vascular remodeling in chronic pulmonary hypertension. In the acute setting, vasoconstrictors may be more important, but inflammation may also enhance pulmonary vasoconstriction [10]. In the study by Boissier et al., the consequences of ACP on hemodynamics included a significant increase in heart rate, a decrease in systemic blood pressure and the need for hemodynamic support [8]. More importantly, ACP was independently associated with 28-day mortality and in-hospital mortality, as well as the McCabe and Jackson class, another cause of lung injury than aspiration, driving pressure (per cmH_20) and an elevated plasma lactate (per mmol/l) [8].

In another large prospective multicenter study of 200 patients with moderate to severe ARDS, Lhéritier et al. found a similar incidence of ACP (23%, 95% confidence interval 17-29%) [11]. The only factor independently associated with ACP was a $PaCO_2 \geq 60$ mmHg. Data on the driving pressure was not available [11]. This result is also interesting because a few years ago Mekontso-Dessap et al. suggested in a small series of very severe ARDS

patients that increased $PaCO_2$ had a major deleterious effect on RV function [12]. Vieillard-Baron et al. also suggested the same result in 2001 [4]. Hypercapnia is a vasoconstrictor of the pulmonary circulation [13]. Elevated $PaCO_2$ can be a consequence of the ventilatory strategy and severity of lung injury, as suggested by the strong impact of an elevated pulmonary dead space fraction on prognosis [14]. Also, based on the results of the study by Lhériter et al., monitoring RV function by transesophageal echocardiography was much more effective than transthoracic echocardiography [11]. Finally, this study indicated that ACP was not associated with mortality [11]. Why were the results of this study different than results of the study by Boissier et al? In the study by Lhéritier et al., almost half of the patients with ACP were ventilated in the prone position, compared to only 32% of patients without ACP [11]. It has been clearly reported that lung protective ventilation in the prone position decreases plateau airway pressure [15]. In a cohort of more than 300 patients Jardin et al. suggested that effect of ACP on prognosis depends in part on plateau airway pressure with a safe limit at 27 cmH_20 [6].

These results prompt us to recommend that clinicians consider monitoring RV function using TEE in moderate to severe ARDS patients and to adapt the therapeutic lung protective ventilation strategy according to the function of the right ventricle. This can be considered an “RV protective approach” - as illustrated in the Figure. Recently, in a randomized clinical trial comparing supine to prone positioning (PROSEVA), Guerin et al. reported a large beneficial effect of prone position on reducing mortality in severe and persistent ARDS with a $PaO_2/FiO_2 < 150$ mmHg [16]. The prone positioning may have been effective in part because of the beneficial effects on the pulmonary circulation and the right ventricle. Prone position may be an ideal protective approach for improving the function of the RV because it corrects hypoxemia without increasing PEEP and it decreases the $PaCO_2$ and plateau airway pressure by recruiting collapsed lung zones. This result can be contrasted

with the “open-lung” approach, as represented by high-frequency oscillation ventilation (HFO), which worsened mortality, with more circulatory failure and a higher vasopressor requirement [17], perhaps reflecting increased RV dysfunction and failure, as shown by Guervilly et al. [7]. In HFO ventilation, airway pressure remains significantly elevated during all the respiratory cycle.

However, some issues remain unclear. Do we need to turn patients to the prone position with ACP, even though PaO_2/FiO_2 is still > 150 mmHg? Could inflammation-driven pulmonary vasoconstriction be a therapeutic target to reduce injury to the pulmonary microcirculation, for example with novel therapeutics such as mesenchymal stromal cells or other anti-inflammatory therapies such as statins [18]? What is the effect of isolated RV dilatation without paradoxical septal motion and is it predictive of imminent ACP/RV failure? How should the level of PEEP be adjusted in individual ARDS patients, providing that the plateau airway pressure is maintained below 27 cmH_2O? Some preliminary data suggest that the effect of PEEP on the pulmonary circulation and RV function depends on the balance between recruitment and overdistension induced by application of PEEP [12]. And finally, would the RV protective approach, as presented in the Figure, have a beneficial survival effect compared to a more conventional approach? Further clinical and experimental studies will be needed to address these questions.

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Legend for the Figure: Proposed approach to preventing acute cor pulmonale and limiting its consequences: a right ventricular protective approach.

RR: respiratory rate; RV right ventricular; HME: heat and moisture exchanger; PP: prone positioning; PEEP: positive end-expiratory pressure

* avoid any intrinsic PEEP

** replace HME by a heated humidifier

Figure