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Acute Cor Pulmonale in ARDS
Rationale for Protecting the Right Ventricle

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The ventilatory strategy for ARDS has been regularly amended over the last 40 years as knowledge of the pathophysiology of ARDS has increased. Initially focused mainly on the lung with the objectives of "opening the lung" and optimizing arterial oxygen saturation, this strategy now also takes into account pulmonary vascular injury and its effects on the right ventricle and on hemodynamics. Hemodynamic devices now available at the bedside, such as echocardiography, allow intensivists to evaluate respiratory settings according to right ventricular tolerance. Here, we review the pathophysiology of pulmonary vascular dysfunction in ARDS, consider the beneficial and deleterious effects of mechanical ventilation, describe the incidence and meaning of acute cor pulmonale based on recent studies in large series of patients, and propose a new, although not strictly validated, approach based on the protection of both the lung and right ventricle. One of our conclusions is that evaluating the right ventricle may help intensivists to assess the balance between recruitment and overdistension induced by the ventilatory strategy. Prone positioning with its beneficial effects on the lung and also on hemodynamics (the right ventricle) is a good illustration of this. Readers should be aware that most of the information given in this article reflects the point of view of the authors. Although based on clinical observations, clinical studies, and well-known pathophysiology, there is no evidence-based medicine to support this clinical commentary. Other approaches may be favored, in which case our article should be read as another attempt to help intensivists to improve management of ARDS.

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ABBREVIATIONS: ACP = acute cor pulmonale; HFOV = high-frequency oscillatory ventilation; LV = left ventricular; PAC = pulmonary artery catheter; PEEP = positive end-expiratory pressure; RV = right ventricular

In 1975, a study by Suter et al[1] defined the best ventilatory strategy in ARDS as the one which allows the best oxygen delivery. In particular, the authors reported that the "best" positive end-expiratory pressure (PEEP) was the best compromise between improvement in respiratory system compliance and dead space and oxygen transport. From PEEP zero to PEEP 7 cm H_2O, compliance increased in parallel with oxygen transport and dead space decreased, whereas from PEEP 7 cm H_2O to PEEP 13 cm H_2O, compliance decreased in parallel with a decrease in oxygen transport and an increase in dead space.[1] At that time, this strongly suggested the link between

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lung and hemodynamics, with the impact of respiratory settings. Unfortunately, since this study, most guidelines on respiratory management have for many years been focused mainly on the lung, forgetting hemodynamics, with the aim of "opening the lung" and optimizing arterial oxygen saturation, as illustrated, for instance, by the PEEP/F_{IO_2} scale proposed in different randomized controlled studies.[2] A new area may be emerging, also taking into account pulmonary vascular injury, its effects on the right ventricle, and, finally, the hemodynamic issue. This is largely due to the development of new tools available at the bedside, allowing intensivists to apply the well-known pathophysiology of pulmonary hypertension in ARDS and then to evaluate accurately and noninvasively right ventricular (RV) function at baseline, but also after adaptation of respiratory settings.

In this article we briefly review the pathophysiology of pulmonary vascular dysfunction in ARDS, the impact of the open-lung approach, and the incidence and diagnosis of acute cor pulmonale (ACP) and its consequences for hemodynamics and prognosis. Lastly, we propose an "RV protective approach" to ventilation.

Rationale

Defined more than one-half a century ago, ARDS involves heterogeneous pathophysiologic mechanisms in great part responsible for different degrees of severity. The most hypoxemic patients have a high mortality rate,[3,4] even though the severity of hypoxemia per se has not been reported as a reliable predictor of outcome.[5] ARDS affects not only alveoli but also the pulmonary circulation, as reported by Zapol and Snider[6] in their landmark study showing significant elevation of mean pulmonary artery pressure, magnified by the application of a PEEP. This is in part the consequence of structural alteration of the pulmonary circulation, with inflammation, vasoconstriction, edema, thrombi, and vascular remodeling, that is, muscularization of normally nonmuscularized pulmonary arteries.[7] But in some cases it is also due to unadapted positive pressure ventilation inducing a deleterious competition between the distending pressure of alveoli and the flow into pulmonary capillaries.[8,9] Zapol et al[10] also suggested this effect by reporting an unexpected inverse relation between pulmonary vascular resistance and cardiac output. Jardin et al[11] showed that the relationship between left ventricular (LV) end-diastolic pressure and pulmonary artery occlusion pressure was not preserved after applying a PEEP $>$ 10 cm H_2O, the latter systematically overestimating the first. Clinical studies provide evidence of this deleterious effect of unadapted positive pressure ventilation. In a first randomized controlled study, high-frequency oscillatory ventilation (HFOV) increased mortality.[12] In the HFOV group, more patients required vasopressors and received them for a longer period.[12] In another observational study using transesophageal echocardiography, Guervilly et al[13] showed that HFOV induces a significant increase in RV dysfunction and failure. Although very different from conventional modes, HFOV can be understood as an open-lung approach mode, its aim being to keep the lung open. As a consequence, a high level of mean airway pressure is maintained throughout the respiratory cycle, which may lead to impairment of pulmonary circulation, as briefly described previously. Taken together, these studies suggest that some ventilatory strategies may alter pulmonary vascular circulation, RV function, and finally prognosis. This is mainly mediated by lung stress, that is, the transpulmonary pressure (which is the alveolar pressure minus the pleural pressure), as shown $>$ 35 years ago in dogs[14] and more recently in humans by our group.[15]

Pulmonary vascular dysfunction is nowadays studied much more in this field and is well characterized. In one study, Bull et al[16] reported a 73% incidence of such dysfunction in 475 patients with ARDS monitored with a pulmonary artery catheter (PAC). This dysfunction, defined by an elevated transpulmonary pressure gradient (pulmonary artery diastolic pressure minus pulmonary capillary wedge pressure) (Fig 1), occurred in $>$ 70% of cases and was independently related to increased mortality, suggesting a strong link between both.[16] Because the right ventricle acts as a "passive conduit" in normal conditions,[17] pulmonary vascular dysfunction, leading to an abrupt increase in pulmonary artery pressure, may induce ACP. In a large series of patients with ARDS submitted to protective mechanical ventilation, ACP was shown to be independently associated with mortality.[18] At the beginning, cor pulmonale was described as a clinical entity, illustrating close heart-lung interactions.[19] Later on, cor pulmonale was reported as an acute phenomenon, in particular in pulmonary embolism.[20] Since the 1980s, we have known that it may also occur in ARDS.[21]

Diagnosis, Incidence, and Consequences of ACP

In the past, ACP was mainly suggested using a PAC, as a central venous pressure higher than the pulmonary artery occlusion pressure,[22,23] where such an inverse pressure gradient was also associated with increased

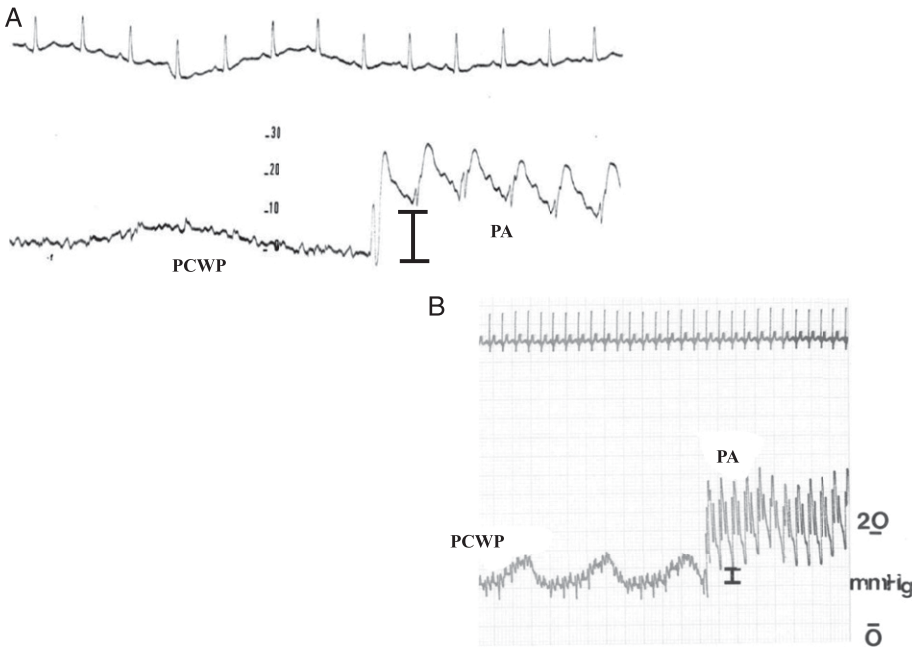

Figure 1 – *A-B, Illustration of a high transpulmonary pressure gradient (marker) in a patient ventilated for ARDS (A), compared with a patient with a normal gradient (B). PA = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.*

mortality.[23] With the development of critical care echocardiography, echocardiography now appears as the "gold standard."[24] Even though the transesophageal approach is considered to be more effective,[25] both approaches, transesophageal and transthoracic, can be used. In a suggestive clinical context, ACP is defined as the association of RV dilatation with a paradoxical septal motion at end-systole[26] (Fig 2). Thus, ACP combines RV systolic and diastolic overload. Whereas in the 1990s the reported incidence of ACP was very high, around 60%, in patients ventilated with high tidal volume and with high lung stress,[21] many studies in patients on protective mechanical ventilation, that is, with limited lung stress, have reported an incidence of 20% to 25%[18,25,27] (Table 1).[28-32] In this modern area of protective ventilation, three parameters appear especially related to the occurrence of ACP: plateau pressure[33] (a surrogate of lung stress, especially in patients with normal chest wall compliance), driving pressure[18] (which is actually the lung stress induced by tidal volume), and $Paco_2$.[25]

ACP may cause or precipitate circulatory failure. In 81 patients with ARDS, we found that 13 had moderate ACP (RV end-diastolic area/LV end-diastolic area between 0.6 and 1).[34] Cardiac index was lower in this group (3.1 L/min/m^2 vs 2.8 L/min/m^2). We also found that six patients had "severe" ACP (RV end-diastolic area $\geq$ LV end-diastolic area) in which cardiac index

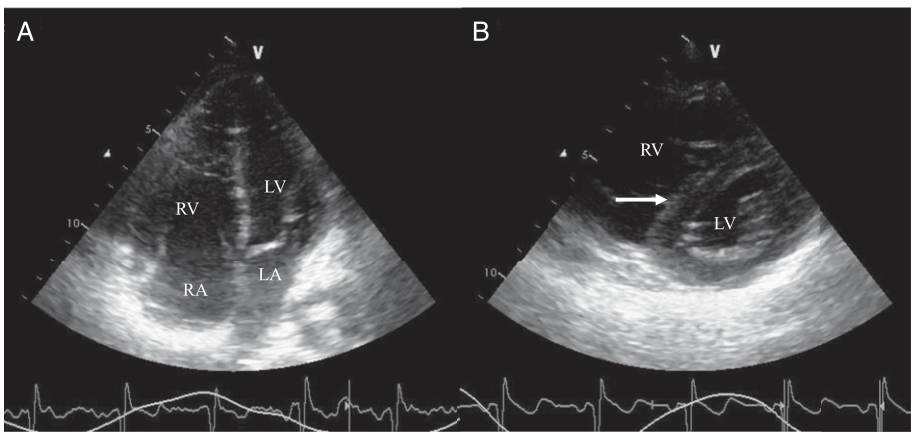

Figure 2 – *Acute cor pulmonale by a transthoracic approach in a patient ventilated for ARDS. A, Apical four-chamber view demonstrating right ventricular dilatation with an RV bigger than the left. B, Parasternal short-axis view of the LV demonstrating paradoxical septal motion (arrow, D-shape). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.*

TABLE 1] Incidence of ACP in Studies Using Echocardiography in Patients With ARDS Submitted to Protective Mechanical Ventilation

Study	No. of Patients	Year of Publication	Incidence of ACP, %
Vieillard-Baron et al[27]	75	2001	25
Page et al[28]	110	2003	24.5
Vieillard-Baron et al[29]	42	2007	50
Fougères et al[30]	21	2010	14
Brown et al[31]	19	2011	32
Mekontso Dessap et al[32]	33	2011	33
Boissier et al[18]	226	2013	22
Lhéritier et al[25]	200	2013	23

ACP = acute cor pulmonale.

decreased to 2 L/min/m^2.[34] Similar results were found by Boissier et al[18] in 226 patients. ACP was associated with a higher heart rate, a lower systolic and mean arterial pressure, and a higher incidence of shock.[18] In another study in 200 patients with ARDS, 64% of patients with ACP required norepinephrine infusion, compared with 49% of patients without ACP.[25]

For a long time, intensivists considered that ACP was only a marker of severity and had no direct impact on prognosis. This was mainly due to our landmark study in which we did not observe any difference in mortality between patients with or without ACP.[27] But, as explained in this study, we applied a systematic adaptation of respiratory settings by decreasing plateau pressure and $Paco_2$ more and by using prone position more frequently in patients with ACP.[27] As discussed in the RV Protective Approach section, this may explain this absence of difference in mortality. Lhéritier et al[25] also reported no difference in mortality, but patients with ACP had more inhalation of nitric oxide and particularly more proning than the others. Conversely, in the study by Boissier et al,[18] ACP was independently associated with mortality, like in the pure observational study of Osman et al[23] using a PAC. This is in accordance with the observation that ACP has a significant impact on hemodynamics, as described previously. Although not definitely proven, these results suggest that ACP may alter prognosis and so should lead to adaptation of respiratory settings to limit pulmonary vascular dysfunction and protect the right ventricle.

RV Protective Approach

Although not yet validated in a randomized controlled study, an RV protective approach has recently been formalized as a step-by-step approach to the ventilatory strategy, putting the pulmonary circulation and the right ventricle at the center of the decision-making process.[35] Briefly, this approach is based first on strictly limiting plateau pressure to below 27 cm H_2O[33] and driving pressure to below 17 cm H_2O,[18] second on limiting $Paco_2$ to below 60 mm Hg,[25] third on PEEP settings according to RV function, and finally on the use of prone position in the patients with the most severe ARDS. Plateau pressure is only a surrogate of lung stress and transpulmonary pressure. Whereas both are closely related in patients with normal chest wall compliance and with pleural pressure that is not so positive, it is not true in the other cases, especially in obese patients for instance.[36] In this latter situation, plateau pressure may significantly overestimate transpulmonary pressure and then lung stress.

This ventilatory approach could be summarized as "what is good for the lung is good for the right ventricle" and vice versa. RV function could be considered as the cornerstone to establishing the balance between lung recruitment and lung overdistension (Fig 3A), since the gold standard CT scan is not routinely available. A collapsed lung has been reported to induce RV overload in an experimental model of atelectasis, whereas RV function is greatly improved after reaeration of the lung.[37] We reported in a few patients with severe ARDS that a strategy based on increased PEEP, when not inducing significant lung recruitment (and so probably considerable overdistension), led to a huge decrease in RV stroke volume, whereas RV function was preserved providing that significant recruitment occurred.[38] This may help us to demonstrate in humans the relation reported 50 years ago between pulmonary vascular resistance and lung stress or transpulmonary pressure[39]

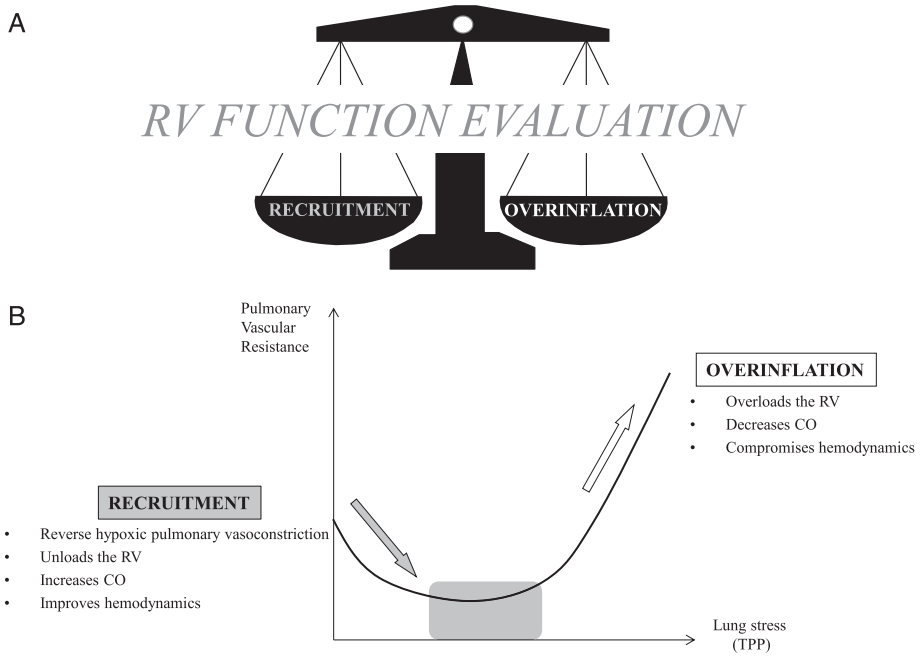

Figure 3 – *Value of RV function in evaluating the balance between overdistension and lung recruitment and its effect on pulmonary vascular resistance. A, Graphic representation of the value of RV function in evaluating the balance between overdistension and recruitment induced by the ventilatory strategy. B, U-shaped relationship between pulmonary vascular resistance and lung stress as described by Niden.[39] The goal of the ventilatory strategy is to ventilate the patient on the flat part of the curve. The shaded area represents the target stress volume operating area. CO = cardiac output; TPP = transpulmonary pressure (alveolar pressure minus pleural pressure). See Figure 2 legend for expansion of the other abbreviation.*

(Fig 3B). So, RV evaluation may be understood as a way to know where the ventilatory strategy is located on this relation in a given patient, the goal being to be on the flat part (Fig 3).

Finally, the use of prone position deserves a few words because data strongly support its use and very well illustrate our demonstration. By its ability to increase Pao_2 without PEEP elevation, and to decrease $Paco_2$ and plateau pressure by recruiting the lung, prone position is expected to preserve the pulmonary circulation and to unload the right ventricle[40] (Fig 4). This is exactly what we showed a few years ago using echocardiography in a population of 42 patients with severe ARDS, one-half of them with ACP.[29] After a first session of proning, lasting 18 h, we reported a complete normalization of RV function, with a decrease in heart rate and an increase in cardiac output in patients with a previous ACP.[29] A study in 18 patients combining echocardiography and PAC confirmed our results.[41] Guérin et al,[42] in a large randomized controlled study, demonstrated a huge decrease in mortality in the interventional group (patients submitted to prone position) compared with the control group. Interestingly, in the interventional group, PEEP was < 9 cm H_2O and lower than in the control group, plateau pressure was below 25 cm H_2O, and $Paco_2$ around 50 mm Hg.[42] One can say that this is a perfect RV protective approach and that it could actually explain in part the very positive results.

Unresolved Issues

However, several questions are still debated. First, as discussed previously, whether ACP has an impact on outcome remains controversial and needs to be definitively ascertained. In particular, it is not totally clear whether RV failure is the cause of death or only a cotraveler. However, whatever the linkage between

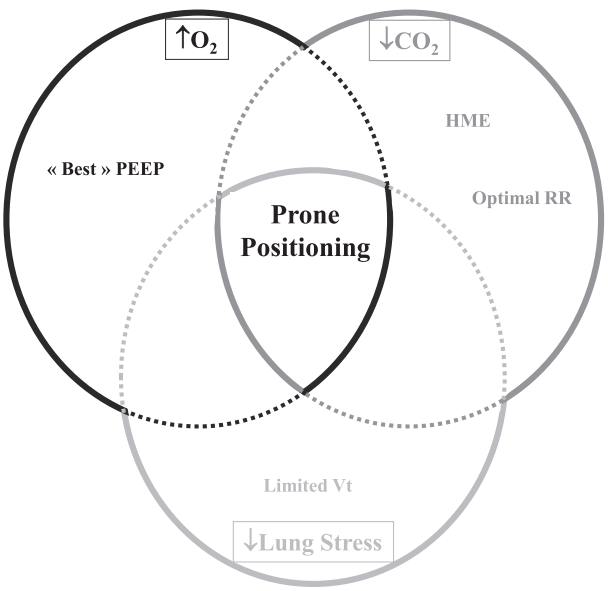

Figure 4 – *Main mechanisms of the beneficial effect of prone position in unloading the right ventricle. HME = heat and moisture exchanger; O_2 = oxygen; PEEP = positive end-expiratory pressure; RR = respiratory rate; Vt = tidal volume.*

RV failure and death, there is no benefit in damaging the lungs, and what better way of avoiding this than to assess RV function? Another related issue is whether we should distinguish between RV dysfunction and RV failure, and, if so, how. For instance, the meaning of isolated RV dilatation without paradoxical septal motion is still unclear. Is it a warning signal that something will happen? Finally, the most interesting question is whether our proposal based on clinical studies and pathophysiology is really effective. For that, it is clear that we lack a randomized controlled study, especially regarding the setting of PEEP, for which randomized controlled studies have been already published.

Conclusions

The right ventricle now appears as a key factor in adapting the ventilatory strategy in patients with ARDS, especially thanks to the development over the last few years of critical care echocardiography, which allows intensivists to evaluate RV function easily at the bedside. Forty years after Peter Suter,[1] the RV protective approach that we propose represents a complete switch in the thinking of how to ventilate patients with ARDS. This approach keeps the right ventricle and the lung connected and is perfectly illustrated by the adage that "what is good for the lung is good for the right ventricle."

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