Editorial

Hypercapnia during acute respiratory distress syndrome: the tree that hides the forest!

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Introduction

Nin and coworkers recently published an article that examines whether hypercapnia has an impact on mortality in patients with moderate or severe acute respiratory distress syndrome (ARDS) (1). To answer this important question, they conducted a post-hoc analysis of three prospective non-interventional international cohort studies focusing on ARDS (2-4). Among the 18,302 mechanically ventilated patients included (2-4), 1,899 were ventilated for more than 24 h because of ARDS or developed ARDS after the first 24 h of mechanical ventilation (1). The study population was exclusively composed of patients with moderate or severe ARDS according to the Berlin definition (5). Severe hypercapnia was defined as a highest $PaCO_2$ within 48 h after the diagnosis of ARDS ≥50 mmHg (≥85th percentile of the distribution of $PaCO_2$ values). The main result of the study is that severe hypercapnia is associated with higher ICU mortality and more organ failure (including hemodynamic failure), even after adjustment for possible confounders such as age, SAPS II, PaO_2/FiO_2, positive end-expiratory pressure (PEEP), driving pressure, respiratory rate (RR), acidosis, corrected minute ventilation (a surrogate of dead space), the use of pressure/volume limitation strategy (PLS) and the period of the study. The authors also nicely reported that the incidence of severe hypercapnia increased significantly with the time period (1998, 2004 and 2010) (1), as a consequence of different respiratory strategies and the feeling of many intensivists that hypercapnia is beneficial (6). Regarding the association between severe hypercapnia and hemodynamic failure, it is of note that the occurrence of sepsis did not differ between patients with or without severe hypercapnia (1), suggesting that it could be related to the deleterious effects of $PaCO_2$ on the pulmonary circulation and the right ventricle. This article by Nin and coworkers strongly suggests that hypercapnia can no longer be considered as a supporting or a therapeutic factor in ARDS, but more as a (deleterious) consequence of the respiratory strategy that should be limited. This is what we discuss here.

The impact of hypercapnia in ARDS

The impact of hypercapnia has not been clearly elucidated and is still controversial given its disparate effects (7,8). Nevertheless, it has come to be seen as a major factor in ARDS and its pivotal role has emerged from the historical evolution of ventilator strategies (*Figure 1*). During the first 20 years following the characterization of ARDS, the ventilatory strategy relied on “high” tidal volume to normalize $PaCO_2$; hypercapnia almost did not exist. Carbon dioxide (CO_2) has become a noticeable factor since the early 1990s with the work from Hickling *et al.*, who demonstrated in two observational uncontrolled studies that mechanical

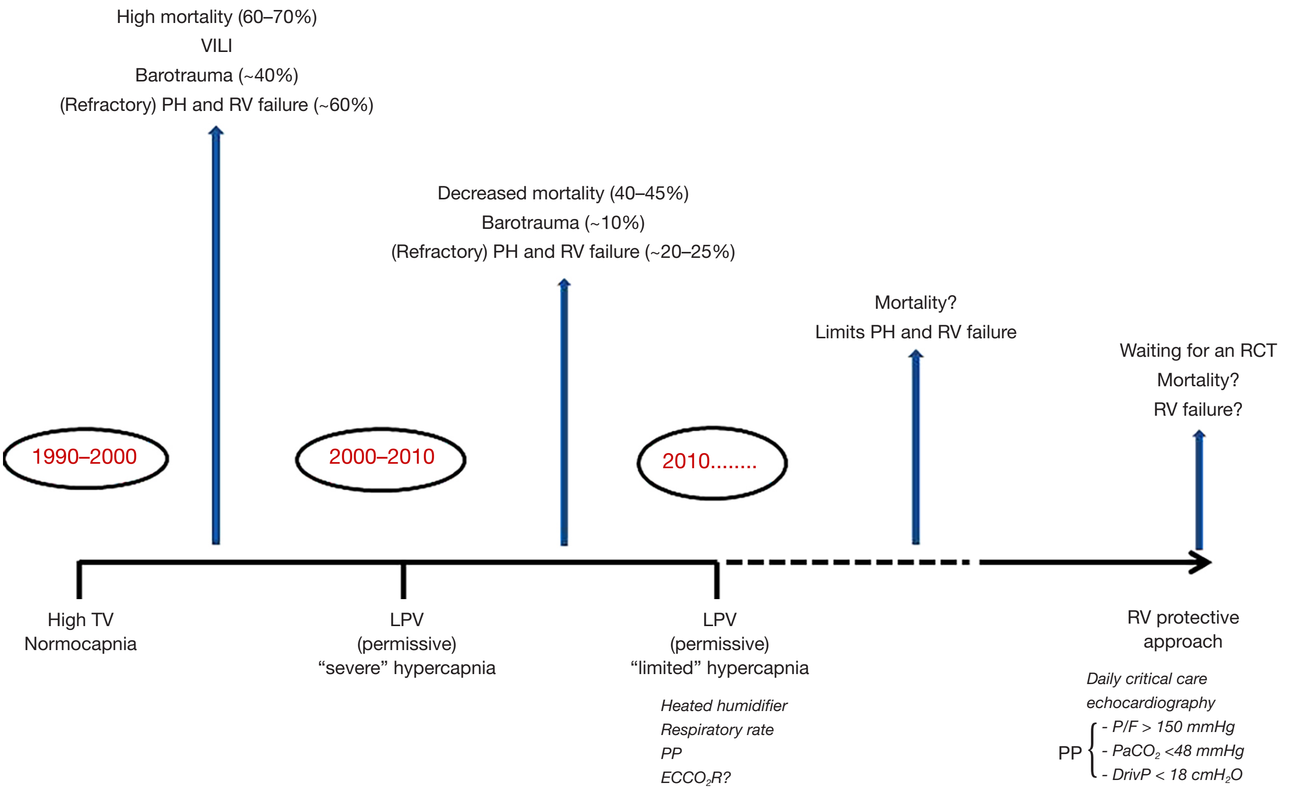

Figure 1 Timescale of the evolution of therapeutic strategies in ARDS and their link with observed mortality, $PaCO_2$ and right ventricular failure. ARDS, acute respiratory distress syndrome; drivP, driving pressure; $ECCO_2R$, extra-corporeal CO_2 removal; LPV, lung protective ventilation; PH, pulmonary hypertension; PP, prone position; RCT, randomized controlled trial; RV, right ventricle; TV, tidal volume; VILI, volume induced lung injury.

ventilation with low volume and low pressure, along with an increase in $PaCO_2$, was associated with better outcome (9,10). The concept of "permissive hypercapnia" was born (10). At that time, this new paradigm was strengthened by experimental studies demonstrating the beneficial effects of CO_2 on inflammation (11), even though the effect of hypercapnia in the immuno-inflammatory response to sepsis remains controversial (11-13). More than 10 years of "permissive hypercapnia" ventilatory strategy even led some authors to propose the concept of "therapeutic hypercapnia" (6). Nevertheless, more recent studies have tempered such an enthusiasm by demonstrating harmful effects of CO_2 on the lung on the one hand (14,15), and on the pulmonary circulation and the right ventricle on the other hand (16,17).

Effect of CO_2 on the pulmonary circulation and the right ventricle

The effects of CO_2 on the circulatory system are multimodal and can be schematically classified in three categories: a depression of the left ventricle contraction secondary to an acute increase in $PaCO_2$ responsible for intra-cellular acidosis (18), an increase in cardiac output relying on a peripheral reduced vasomotor tone which may counterbalance the depressant effect of CO_2 on the left ventricle (19), and finally an increase in right ventricular afterload linked to pulmonary arterial vasoconstriction (20,21). In ARDS, the main effect of hypercapnia is exerted on the right ventricle, because of the huge increase in pulmonary arterial resistance, leading to right ventricular failure, named acute cor pulmonale (ACP) (22). Pulmonary arterial hypertension is constant in ARDS and was observed before the area of permissive hypercapnia, as the consequence of the high transpulmonary pressure, which compresses the pulmonary capillaries (23), and alteration of the capillary pulmonary circulation mediated by inflammatory and procoagulant phenomena (24,25). The speed of CO_2 augmentation probably plays an

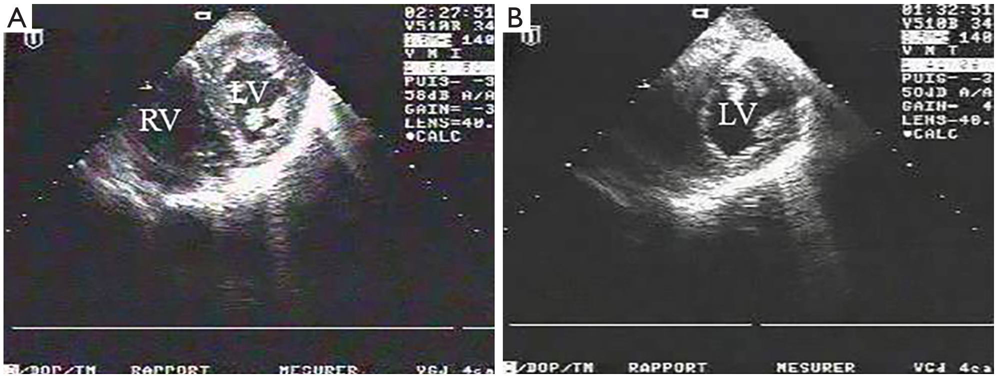

Figure 2 Effect of a fast change in $PaCO_2$ (90 minutes) on the right ventricle in a patient ventilated for severe ARDS. Note that between the 2 conditions, one with very severe hypercapnia (panel A), the other with a limited hypercapnia, plateau pressure, as well as oxygenation, were the same and driving pressure was lower in panel A. In panel A, a short axis view of the left ventricle by a transgastric approach visualized a dilated right ventricle with a septal flattening while in panel B no more RV failure is observed. ARDS, acute respiratory distress syndrome; LV, left ventricle; Pplat, plateau pressure; RV, right ventricle.

important role in the occurrence of right ventricular failure. Mekontso-Dessap *et al.* showed that an increase in $PaCO_2$ to around 70 mmHg although associated with a decrease in tidal volume and in driving pressure, was responsible for right ventricular failure (17) (*Figure 2*). Two specific points were discussed in this study. First, the short time course (no more than 1.5 h) of $PaCO_2$ changes. Whether a more progressive increase in $PaCO_2$ could be responsible for the same right ventricular failure remains to be elucidated. Second, the study did not differentiate between the effects of hypercapnia itself and the induced respiratory acidosis. Interestingly, the effect of severe hypercapnia in the study by Nin *et al.* was independent of pH (1) .

Effects of $PaCO_2$ on mortality: making the link with the right ventricle

Many recent studies suggest that right ventricular protection is at the core of the effect of different ventilatory strategies on prognosis. Pulmonary hypertension and pulmonary vascular dysfunction have been shown to be associated with poor outcome in ARDS (26). Lhéritier *et al.* demonstrated that a $PaCO_2$ >60 mmHg was an independent risk factor for ACP and this was strongly confirmed by Mekontso-Dessap *et al.* in a large cohort of 752 patients with moderate or severe ARDS. In this latter study, a $PaCO_2$ ≥48 mmHg, a value very close to that reported by Nin *et al.*, was an independent risk factor for ACP with an odds ratio of 2.9 and severe ACP was independently associated with hospital mortality in moderate to severe ARDS (27). Severe hypercapnia is associated with more circulatory failure not related to sepsis, and with higher ICU mortality (1). Interestingly, prone position, a strategy well known to decrease $PaCO_2$ (28) and to improve right ventricular function (29), has been reported to improve prognosis (30).

How to protect the right ventricle from hypercapnia

Based on this literature analysis, we can suggest that control of permissive hypercapnia during the PLS may come to be at the core of the ventilatory strategy. It has been suggested that the positive results of the ARMA study (31) could at least in part be explained by the effort to correct hypercapnia by increasing RR (32,33). Nevertheless, high RR exposes ARDS patients to the risk of dynamic hyperinflation, which dramatically impairs right ventricular ejection (34). This is why the RR must be cautiously increased by verifying with a 4-second end-expiratory pause that no intrinsic PEEP has been generated (35). To avoid such a side effect of too high a RR, Prin *et al.* reported that the use of heated humidifiers significantly decreased the level of $PaCO_2$ in moderate or severe ARDS, as compared with the use of heat and moisture exchangers (36). Aguirre-

Bermeo *et al.* recently demonstrated in 13 ARDS patients that end-inspiratory pause prolongation from 0.1–0.2 to 0.7 s induced a significant decrease in $PaCO_2$ from 54±9 to 50±8 mmHg (37). They showed that this decrease in $PaCO_2$ was correlated with the drop in physiological dead space (37). However, it has also been reported that ventilation with inverted I/E ratio could have deleterious hemodynamic effects (38). As briefly discussed above, prone position is another very pertinent way to limit hypercapnia and to increase oxygenation without increasing PEEP, tidal volume and RR, by recruiting the lung and decreasing its heterogeneity (28,39). Even though this was not reported in the study by Nin *et al.*, it is key to improving both $PaCO_2$ and PaO_2/FiO_2, since hypoxia may magnify the deleterious effect of hypercapnia on the pulmonary circulation (40). There are preliminary data on the use of extracorporeal CO_2 removal (ECCOR) to limit hypercapnia and then to alleviate right ventricular overload by controlling the CO_2 level. In an experimental model of ARDS conducted in pigs, veno-venous CO_2 removal therapy enabled protective ventilation while maintaining normocapnia, with decreased pulmonary hypertension, and improved right ventricular function (41). Whether such approach, combining a lung protective (or even ultra protective) approach and ECCOR, could improve right ventricular function or prevent right ventricular failure remains to be studied, even though it may probably be applied in critical situations (42).

It is high time to evaluate the right ventricular protective approach

Nowadays, the right ventricle is definitively the weak link in ARDS and one of the main objectives of management is to prevent right ventricular failure or to support right ventricular function. The right ventricular protective strategy has recently been proposed (43) and relies mostly on the control of right ventricular overload, by controlling hypoxemia, driving pressure and hypercapnia (44). The cornerstone of such a strategy is probably the early and prolonged use of prone position for the most severe cases in terms of oxygenation (30) or for patients who develop right ventricular failure despite lung protective ventilation. In this strategy, severe hypercapnia, as defined by Nin *et al.*, has to be avoided, PaO_2/FiO_2 optimized and driving pressure decreased. $PaCO_2$ is controlled and maintained <48–50 mmHg with cautious increases in RR, while checking that no intrinsic PEEP has been generated, and with the use of heated humidifiers. During the whole ventilator support of such patients, the right ventricle has to be rigorously monitored by at least daily critical care echocardiography during the first 3 days, in order to detect early right ventricular dysfunction, which would motivate adaptation of treatment. Based on the cumulative information that the right ventricle is at the core of respiratory strategy, the right ventricular protective approach has yet to be 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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