

Effects of hypercapnia in acute respiratory distress syndrome

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Abstract: In patients with acute respiratory distress syndrome (ARDS) hypercapnia is a marker of poor prognosis, however there is controversial information regarding the effect of hypercapnia on outcomes. Recently two studies in a large population of mechanical ventilation patients showed higher mortality associated independently to hypercapnia. Key roles responsible for the poor clinical outcomes observed in critically ill patients exposed to hypercapnia are not well known, two possible mechanisms involved are the effect of CO₂ on the muscle and the alveolar epithelium. Hypercapnia frequently coexists with muscle atrophy and dysfunction, moreover patients surviving ARDS present reduced muscle strength and decreased physical quality of life. One of the possible mechanisms responsible for these abnormalities could be the effects of hypercapnia during the course of ARDS. More over controversy persists about the hypercapnia role in the alveolar space, in the last years there is abundant experimental information on its deleterious effects on essential functions of the alveolar epithelium.

Keywords: Hypercapnia; acute respiratory distress syndrome (ARDS); alveolar epithelium; muscle dysfunction

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Mechanical ventilation with high tidal volumes can cause and worsen lung injury (1). Hickling *et al.* (2) reported that limitation of airway pressure to less than 30 cmH₂O, was associated with lower mortality in patients with acute lung injury, which reinforced the concept of lung protective strategy. In some patients ventilated with lower tidal volumes higher PaCO₂ values were observed (3), and the concept of permissive hypercapnia began to be accepted in acute lung injury patients allowing and purposefully increasing CO₂ levels (4). In the ARDS-network study (5), patients in the low tidal volume group had mild hypercapnia (35±8 vs. 40±10 mmHg) and better outcome. In a secondary analysis, where different categories of hypercapnic acidosis were defined (6), hypercapnic acidosis “in the first day of mechanical ventilation”, was associated

with a lower mortality rate only in the branch of patients receiving high tidal volume. In contrast, patients receiving low tidal volume and hypercapnic acidosis didn't have a protective or deleterious effect. In the same line, in a randomized clinical trial conducted in preterm infants the authors described that mild permissive hypercapnia was safe, but clinical benefits were not validated (7). On the contrary Laserna *et al.* reported that hypocapnia and hypercapnia were associated with higher mortality in patients with community-acquired pneumonia (8).

In experimental models, there were initial reports on the beneficial effects of hypercapnic acidosis in models of sepsis-induced acute lung injury (9,10). However, more recent studies reported that hypercapnia has harmful effects by impairing alveolar epithelial function, cell proliferation and importantly adverse effects on neutrophil function and innate immunity (11).

Recently a secondary analysis focusing on ARDS patients

receiving mechanical ventilation over 1-month periods in 1998, 2004, and 2010 from 927 intensive care units found that patients with severe hypercapnia (arterial $p\text{CO}_2 \geq 50$ mmHg) had higher rates of complications, organ failure, and poorer outcomes (12). After adjusting for age, SAPSII score, respiratory rate, PEEP, $\text{PaO}_2/\text{FiO}_2$ ratio, driving pressure, pressure/volume limitation strategy, corrected minute ventilation and presence of acidosis, severe hypercapnia was associated independently with increased risk of ICU mortality. In the same line, Tiruvoipati *et al.* (13) studying the effect of hypercapnia in a large population of mechanical ventilation patients (252,812 patients), shown that after adjusting for severity of illness, the adjusted odds ratio for hospital mortality was higher in hypercapnic acidosis patients and compensated hypercapnia when compared with patients with normocapnia and normal pH.

These last data question and warrant a re-evaluation of the current paradigm and the rationale for the use of “permissive hypercapnia” in mechanically ventilated patients.

Muscle response to hypercapnia

Hypercapnia frequently coexists with muscle atrophy and dysfunction in conditions such as ARDS and chronic obstructive pulmonary disease (COPD). During the last decade, concern has emerged regarding muscle compromise during and after ARDS. Patients surviving ARDS present reduced exercise capacity, limb muscle strength, maximal inspiratory pressure and physical quality of life, maintained years after hospital discharge (14). The mechanisms responsible for these abnormalities are unknown, although the presence of hypercapnia during the course of ARDS should be considered.

The effects of hypercapnia over skeletal muscle are still a matter of debate. The number of studies designed to address this specific topic is scarce, and the results in many cases contradictory. Nevertheless, elevated $p\text{CO}_2$ is considered to have deleterious consequences for striated muscle.

Respiratory muscles

The respiratory muscles represent the pump that ventilates the lungs during spontaneous breathing. Controlled by the central nervous system (CNS), their activity must adapt to different physiologic and pathologic situations in order to maintain adequate gas exchange. Respiratory muscle

dysfunction causes alveolar hypoventilation, which leads to carbon dioxide retention. On the other hand, elevation of arterial $p\text{CO}_2$ constitutes a major stimulus for the CNS to increase minute ventilation, and thus rising respiratory muscles work. In line with this, some authors propose that in certain cases of increased respiratory loading patients “choose” to breathe at a lower minute ventilation, at the expense of developing hypercapnia, in order to prevent muscle fatigue due to excessive respiratory work (15). Either in spontaneous breathing or in mechanical ventilation, increased respiratory drive might have deleterious consequences for the diaphragm. In one way or another, there is a close relation between high $p\text{CO}_2$ and respiratory muscles. However, the effect that hypercapnia has over respiratory muscles structure and function is not fully understood, as many reports are contradictory.

Juan *et al.* studied diaphragm performance in healthy volunteers while breathing CO_2 -enriched gas (16). The authors demonstrated decreased diaphragm contractility and fatigue resistance during acute respiratory acidosis. Reduction of human diaphragm force immediately after a fatigue protocol has also been reported in hypercapnic conditions (17). On the contrary, other authors have been unable to demonstrate any effects of hypercapnia on diaphragm contractility in humans (18). While clinical research has focused on acute hypercapnia, in the laboratory setting the effects of acute and chronic respiratory acidosis over diaphragm have been investigated. Different authors have consistently demonstrated a reduction of diaphragm contractile force during acute hypercapnia in mechanically ventilated animals (19). Impaired *in vitro* contractility has also been reported when normal diaphragms are studied under hypercapnic conditions (20). Chronic hypercapnia (generated by prolonged exposure to CO_2 in rats) was associated with a decreased diaphragmatic *in vitro* contractility and increased fatigue tolerance (21). Consistent with this last finding, diaphragm of rats chronically exposed to CO_2 presented an increase in the proportion of type I (slow-twitch, fatigue-resistance) fibers (21,22). In parallel, a reduction in the size of type IIb (fast-twitch) fibers and the presence of degenerative changes was observed (21,22). While hypercapnia seems deleterious to diaphragm contractility in every studied condition, the switch to a more fatigue-resistant fiber type conformation might represent an adaptive mechanism to overcome the sustained load imposed by hypercapnia. Interestingly, two recent publications suggest that hypercapnia might protect against ventilator-induced diaphragmatic dysfunction (23).

Limb muscles

Unlike the diaphragm, peripheral muscles are not overloaded by hypercapnia. Nevertheless, respiratory acidosis also affects limb muscle structure and function. Acute hypercapnia depresses limb muscle contractility and increases muscle fatigue induced by exercise in healthy subjects (18-24). However, acute respiratory acidosis did not affect gastrocnemius muscle *in vivo* contractility in mechanically ventilated dogs (25). Chronic hypercapnia in rodents was associated with decreased limb *in vitro* contractility (more evident in fast-twitch muscles) and grip strength (21,26). No effect was seen over fatigue tolerance, either in fast- or slow-twitch muscles (21). Structural changes have been observed in peripheral muscles of animals chronically exposed to CO₂, although some findings are contradictory. Jaitovich *et al.* and Shiota *et al.* demonstrated atrophy of various hind limb muscles in rodents with chronic respiratory acidosis, while Kumagai *et al.* did not find atrophy in the quadriceps femoralis muscle (21,22,26). In terms of fiber type composition, an increase in slow-twitch fibers was reported in one specific muscle, but this was not confirmed in others (21,22,26). An increase in myonuclear centralization was observed in soleus muscle of chronically hypercapnic mice, likely representing tissue response to injury (27).

Mechanisms underlying muscle compromise

The mechanisms by which hypercapnia affects skeletal muscle are complex and poorly understood. First of all, it must be considered that hypercapnia usually coexists with decreased oxygen content and/or pH, both conditions capable of impairing muscle function. Reduced intracellular pH is the most accepted mechanism for depressed muscle contractility during hypercapnia (19). Other suggested explanations involve abnormalities in calcium homeostasis, oxidative stress and reduced glycolysis and ATP production (17). Of note, mitochondrial dysfunction has been reported in diaphragm of rats after seven days of CO₂ exposure (27). Direct effects of respiratory acidosis on neuromuscular transmission cannot be ruled out, although it seems unlikely considering the results from *in vitro* contractility experiments (20,27). Recently, it was demonstrated that hypercapnia triggers muscle atrophy (*in vivo* and *in vitro*) mediated by the ubiquitin-proteasome system, through a pathway that involves AMPK α 2, FoxO3a and MuRF1 (28). Finally, whether hypercapnia has any

effect over skeletal muscle regeneration process is yet to be studied.

Alveolar epithelium and hypercapnia in ARDS

The alveolar epithelium is essential in many lung functions. From a histological point of view, it is a confluent mosaic of two different cellular types with close anatomical contact and a complex functional interaction: alveolar type I (AT1) and type II (AT2) cells. AT1 cells are large, squamous cells covering up to 95% of the lung alveoli. The other 5% is covered by AT2 cells, which are cuboidal and specialized in pulmonary surfactant synthesis. Over the last years, it has become clear that the alveolar epithelium is much more than “just a barrier”, and is increasingly appreciated to play an important role in gas exchange, surfactant secretion and alveolar fluid clearance (28).

Several respiratory disorders (ARDS, COPD, cystic fibrosis) frequently develop abnormalities in gas exchange with hypercapnia. However, the effects of high pCO₂ contributing to these disease states and the lung epithelium have not been fully elucidated. In general, the CO₂ produced by cell metabolisms is removed in the pulmonary alveolar space directly interacting with the alveolar epithelium. In that sense, the carbon dioxide diffusion could be facilitated by specific alveolar structures like aquaporin-5, which, within distal lung epithelium, is selectively expressed in AT1 cells (29). However, is this the only interaction between CO₂ and the epithelium? It is generally accepted that gases, such as CO₂, cross cell membranes by dissolving in the membrane lipid, activate intracellular pathways and generate specific responses.

Based on recent reports, high CO₂ levels are detrimental for at least two key functions of the alveolar epithelium: the alveolar fluid reabsorption (AFR) (10) and the tisular repair capacity (11). Both functions are consistently reported as major problems in patients with ARDS.

ARDS scenario: the combination of injury/repair and the battle for survival

Despite the controversies about ARDS definitions among the last 50 years, most experimental models of lung injury (and the majority of ARDS patients admitted to ICU) have a combination of hypoxia, hypercapnia, ATP release, inflammation and mechanical stress (30). Each one of these components is involved in AFR deterioration in experimental (31) and clinical reports. Previous studies

have reported that active Na⁺ transport and lung edema clearance are impaired in the majority of patients with ARDS, and that edema needs to be cleared by the alveolar epithelium for the ARDS patient to survive (32).

Alveolar fluid reabsorption

AFR is a regulated process, mostly involving apical Na⁺ channels and basolateral Na,K-ATPase (33). The Na,K-ATPase provides the basis for active Na⁺ transport (34) thus, its regulation represents an important mechanism by which fluid clearance from the alveolar epithelium occurs. We and other investigators have reported that increases or decreases in Na,K-ATPase activity are associated with parallel changes in alveolar fluid clearance (10,31).

The AFR impairment induced by CO₂ have been partially elucidated at the cellular level in the past years (10,35). Based on that evidence, high CO₂ levels promote the endocytosis of the Na,K-ATPase by the phosphorylation of its α1 subunit at Ser 18 residue in a pathway regulated by the activation of protein kinase C-α, AMP kinase, protein kinase kinase-β (a calcium/calmodulin-dependent protein kinase) and extracellular regulated kinase (ERK). Although this evidence strongly supports the role of CO₂ in the inhibition of AFR, it is not sufficient to ensure that the same effect occurs in the patient with ARDS. However, the central role of calcium in the deterioration of CO₂-induced AFR was also explored in a model of lung injury (10). In that report, ventilator-induced lung injury determined the release of ATP into the intracellular space, which amplified the CO₂-induced calcium signal, promoting a further deterioration of AFR. Following this reasoning, when a patient is admitted to ICU suffering from ARDS their epithelium released ATP alveolar space as a sign of stress and is subjected to varying levels of hypercapnia. This combination (cellular damage, ATP release and hypercapnia) is likely to lead to marked deterioration of AFR and further formation of pulmonary edema.

Surfactant

Pulmonary surfactant secretion is another essential function of the alveolar epithelium from the fetal stage throughout life. It is a primary function of AT2 cells and is severely affected in patients with ARDS. Specifically, a reduction in surfactant secretion has been identified along with phospholipid degradation probably induced by phospholipase 2.

At the same time, exposure of epithelial cells to mechanical stress and hypercapnia revealed a reduction in surfactant secretion (36), suggesting that the combination of ARDS and permissive hypercapnia could further inhibit the secretion of surfactant and further reduce pulmonary compliance by alveolar collapse.

This is an essential point because persistent alveolar collapse increases the chances of amplifying ventilator-induced lung injury, which represents a significant proportion of patients with non-DAD lung injury in post-mortem samples (37). In this sense, it is reasonable to think that persistently elevated CO₂ values in ventilated patients could lead to poor mechanical performance and increased lung injury induced by mechanical ventilation, both due to decreased pulmonary edema reabsorption and inhibition of secretion of pulmonary surfactant.

Immune response

Many *in vitro* studies report that hypercapnia is able to modulate the innate immune response. Elevated levels of CO₂ “per se” promote cytokine suppression, phagocytosis and activation of NF-κB dependent pathways (33). On the other hand, hypercapnic acidosis impairs the cellular immune response. In this way, both through pH and CO₂, hypercapnia affects the response to pathogens (38). Although this effect could reduce the inflammatory response detrimental to the patient with ARDS, it constitutes a high risk of death related to pathogens that are at the beginning of the ARDS or throughout the stay of the patient in ICU.

Wound healing

The epithelium-endothelium barrier is a complex structure that must meet the mechanical requirements of lung tissue while ensuring optimal ventilation/perfusion ratio for gas exchange (28). Clearly this balance is altered during ARDS and the inflammatory response must be continued by an efficient tissue repair process. However, it has been reported that high CO₂ levels directly affect the two main components of the repair process: (I) phagocytosis of intra-alveolar macrophages and (II) cell growth. In this way the elimination of cellular debris from the alveolar space is prevented and the AT1 decrease its growth rate slowing the process of epithelial mosaic recovery (39).

Based on these reports, one of the key elements of this CO₂ effect is mitochondrial dysfunction that down-regulates the TCA cycle and should be further investigated

in the future.

The future

In the near future there are two interesting strategies to reduce the impact of hypercapnia on lung tissue. One of them is the removal of CO₂ with or without external oxygenation that will allow to maintain a low level of mechanical stress in the lungs (ultraprotective ventilation), minimizing the accumulation of CO₂ by hypoventilation. The other strategy is the use of mesenchymal stromal cells for their differentiation capacity and reduction of the local inflammatory response. This could regenerate the epithelial barrier and recover all its functions in a shorter period of time.

Analyzing the current evidence, it is quite clear that the use of high levels of CO₂ in patients with ARDS as a therapeutic strategy does not seem to be the best option to date. Although controversy persists about its role in the alveolar space and if there is a CO₂ sensor at that level, there is abundant experimental information on its deleterious effects on essential functions of the alveolar epithelium. In fact, these effects surely play a key role in poor clinical outcomes observed in critically ill patients exposed to hypercapnia and should be investigated in the future.

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Footnote

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

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