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Controversies involving hypercapnic acidosis in acute respiratory distress syndrome

Controvérsias acerca da acidose hipercápnica na síndrome do desconforto respiratório agudo

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ABSTRACT

Acute respiratory distress syndrome is characterized by a diffuse inflammatory reaction of lung parenchyma induced by a direct insult to the alveolar epithelium (pulmonary acute respiratory distress syndrome) or an indirect lesion through the vascular endothelium (extrapulmonary acute respiratory distress syndrome). The main therapeutic strategy for acute respiratory distress syndrome is the ventilatory support. However, mechanical ventilation can worsen lung injury. In this context, a protective ventilatory strategy with low tidal volume has been proposed. The use of low tidal volume reduced the mortality rate in acute respiratory distress syndrome patients, but result in hypercapnic acidosis. The current article presents a literature review on the effects of permissive hypercapnia in acute respiratory distress syndrome. To that end, we carried out a systematic review of scientific literature based on established criteria for documental analysis including clinical and experimental articles, using as databases MedLine, LILACS, SciELO, PubMed, and Cochrane. Hypercapnic acidosis has been considered by some authors as an inflammatory process modulator in acute respiratory distress syndrome. However, clinical and experimental studies on hypercapnic acidosis effects have shown controversial results. Therefore it is important to better elucidate the role of hypercapnic acidosis in acute respiratory distress syndrome.

Keywords: Acute respiratory distress syndrome; Permissive hypercania; Hipercapinic acidosis; Inflammation

INTRODUCTION

The benefit of ventilating a patient with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) using protective ventilatory strategy is a consensus in the literature[1,2], because the inappropriate adjustment of ventilator may induce and/or exacerbate pulmonary and systemic inflammation[3,4] leading to multiple organ dysfunction[5,6] and contributing to a worse prognosis in ALI/ARDS patients. If on one hand, protective ventilatory strategy with low tidal volume of 6 ml/kg and limited plateau pressure (30-35 cmH_2O) reduces the stress, on the other hand it causes a condition referred to as permissive hypercapnia, with consequent respiratory acidosis.[1,2]

The effects of hypercapnic acidosis in ALI/ARDS are not completely understood. There are evidences that hypercapnic acidosis may, by itself,

reduce lung injury by modulating the inflammatory process.[7] However, experimental studies have shown controversial results, with some studies showing no improvement[8] and others presenting worsening of lung injury.[9] The controversies of the experimental studies may be attributed to: (1) the hypercapnia induction method, either by changing ventilatory parameters[8] or administration of a carbogenic gas mixture in the inspiratory extremity of the ventilator circuit;[7,9] and (2) the ALI/ARDS model used. In addition, it is important to emphasize that the human body tolerance to hypercapnic acidosis is so far unknown.

For years, hypercapnic acidosis was treated with sodium bicarbonate, being its use recommended by ADRSNet which describes the importance of buffering acidosis and partial hypercapnia correction for a better ALI/ARDS patients' survival.[2] However, the impact of the buffering hypercapnic acidosis with sodium bicarbonate in ALI/ADRS patients' mortality remains to be clarified.

This paper discusses controversies on hypercapnic acidosis as well as the possible therapeutic effects of ALI/ARDS buffering.

The CO_2 chemistry

The main ventilation function is to eliminate carbon dioxide (CO_2), the end-product of aerobic cell breath (Figure 1). CO_2 molecules are eliminated by the cell while hydrogen (H^+) molecules are captured by NAD molecules, which become $NADH_2$ (hydrogen ions carrier). In some reactions, ADP molecules are phosphorilated generating ATP molecules, in which a relevant portion of cellular energy is stored. The $NADH_2$ carrier delivers the H^+ ions to a cytochrome chain at the mitochondrial crest, releasing energy. The H^+ ions react with oxygen molecules (O_2) to form water (H_2O).

The CO_2 released by the cell into the extracellular environment is transported by blood to the lungs dissolved in the plasma with bicarbonate ions (HCO_3^-) and bound to hemoglobin (carbamino-hemoglobin) and other carbamin compounds. Only a minor portion of cells CO_2 (10%) is transported dissolved in the plasma, while most of it (90%) enters the erythrocytes. Inside the erythrocytes, CO_2 combines with water to form carbonic acid which dissociates into H^+ and HCO_3^-. Unlike plasma, this chemical reaction inside the erythrocyte is catalyzed by carbonic anhydrase (Figure 2).

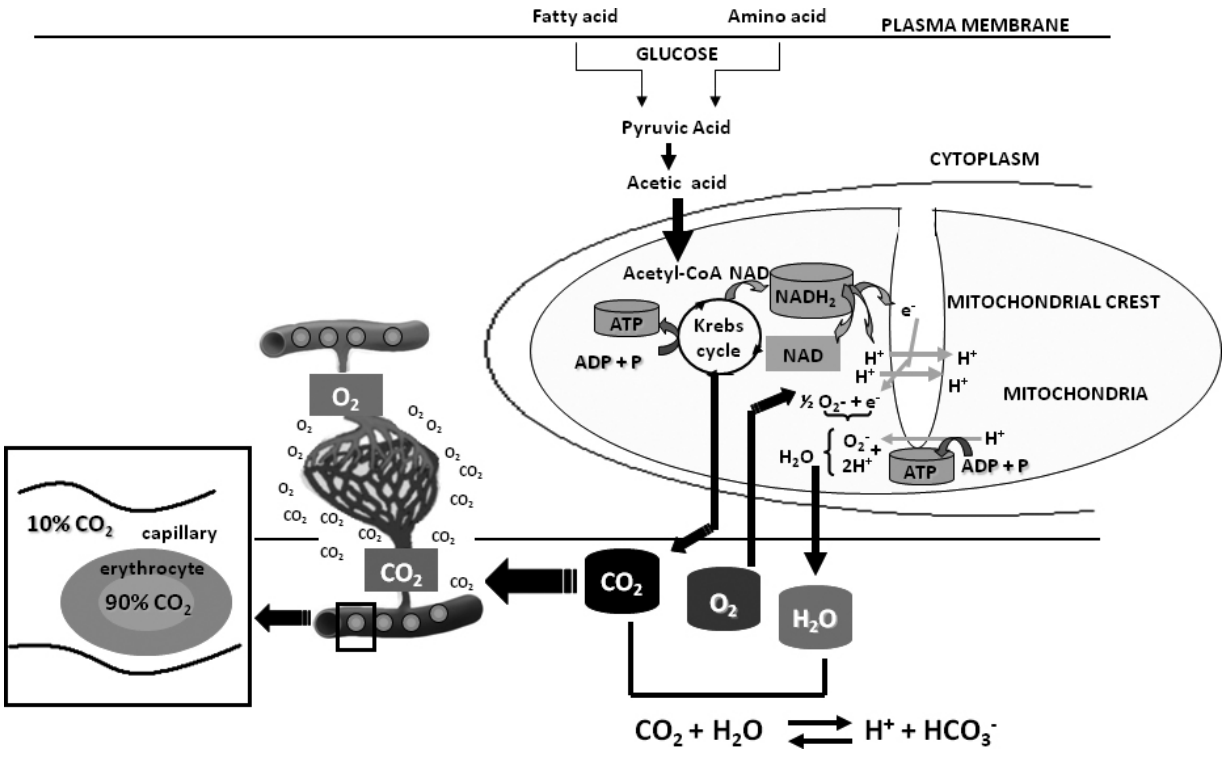

Figure 1 – Carbon dioxide and cellular breathing.

CO_2 is one of the final products of cellular respiration. The blood uptakes and transports the CO_2 produced by cells to the lung, where it takes part of gas exchange. A small portion of CO_2 released by the cells (10%) is dissolved in plasma, and most of it (90%) enters into the erythrocytes. CO_2 reacts with H_2O forming carbonic acid which rapidly dissociates producing HCO_3^- and H^+ ions. This reaction in the erythrocyte is catalyzed by carbonic anhydrase.

Usually, alveolar ventilation is adjusted to keep arterial carbon dioxide partial pressure ($PaCO_2$) around 35-45 mmHg. $PaCO_2$ changes are detected by central and peripheral chemoreceptors. When the alveolar ventilation is increased (hyperventilation) or decreased (hypoventilation) in relation to CO_2 production, there is a respiratory acid-base imbalance. When the CO_2 elimination is insufficient in relation to its tissue production rate, $PaCO_2$ increases, as well as the H^+ and HCO_3^- ions concentration, according to the Henderson-Hasselbalch equation, resulting in respiratory acidosis.[10]

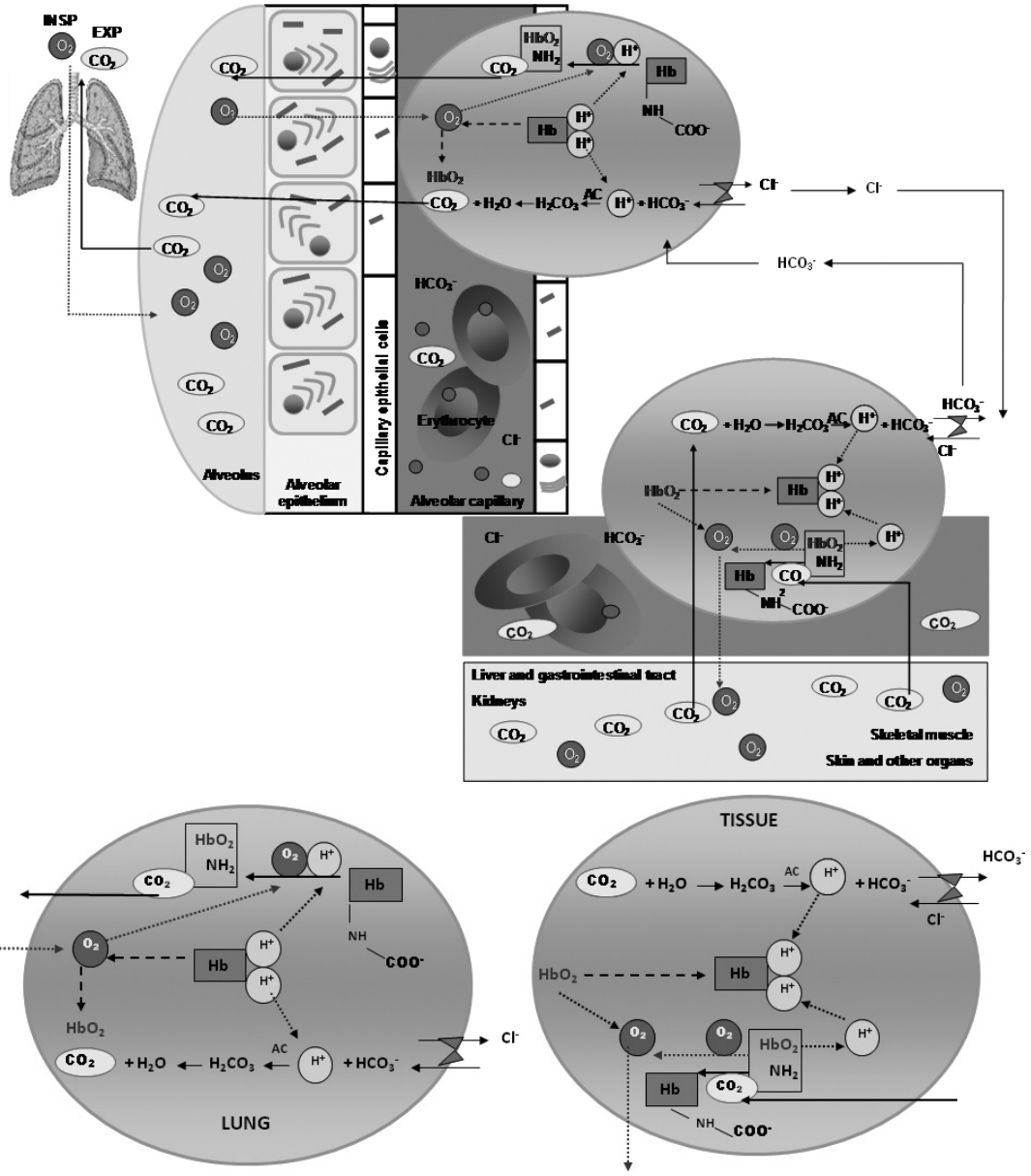

Figure 2 – Carbon dioxide transportation from tissues to lung.

Both in the periphery and in the lung, most of CO_2 transportation occurs within the erythrocyte, where there is carbonic anhydrase. In the periphery of body, the CO_2 diffuses from the tissues to capillaries. In the lungs, the CO_2 follows a reverse path spreading the pulmonary capillaries to the alveoli. In this context, the reactions are also contrary. In the periphery, the oxyhemoglobin (HbO_2) dissociates into reduced hemoglobin (Hb) and O_2. Hb buffers the H^+ ions released from the CO_2 and H_2O reaction as well as the H^+ ions released from the reaction of carbaminic compounds. O_2 goes to the tissues and peripheral organs. In the pulmonary capillaries, the reduced hemoglobin (Hb) dissociates from the H^+ ions and binds to O_2 forming HbO_2. The reoxygenation of Hb in the lungs is facilitated by intensive H^+ ions release, which are required in reactions with bicarbonate ions (HCO_3^-) and with carbaminic compounds. In periphery, about ¾ of HCO_3^- leaves the erythrocyte through a HCO_3^-/Cl^- transportation (chloride deviation) and the reverse mechanism takes place in lung capillary erythrocytes. HbO_2 = oxyhemoglobin; Hb = reduced hemoglobin; AC = carbonic anhydrase; EXP = expiration; INSP = inspiration.

Hypercapnia in ALI/ARDS: from the bench to clinical practice

Experimental studies

Experimental studies have reported controversial results regarding hypercapnia effects in ALI/ARDS. Hypercapnia-induced respiratory acidosis may improve, mitigate, and eventually worsen lung injury (Chart 1). Since the results differ according to the model used to induce ALI/ARDS, the exposed data will be initially discussed according to this line.

Chart 1 - Experimental studies on the effects of hypercapnic acidosis in acute pulmonary injury and ventilator-induced lung injury

Animal	Lung injury model	Hypercapnia	Results	$PaCO_2$ (mmHg)	pH	Time
Rabbits *ex vivo* [11]	1. ALI induced by purine and xhantine oxydase addition.	addition of $FiCO_2$ = 5% or 25%	Attenuation of lung injury, possibly by endogenous xhantine-oxydase inhibition.	~32 (5%) e ~120.2 (25%)	~7.39 (5%) e ~6.84 (25%)	25 min
	2. ALI induced by ischemia-reperfusion			~31 (5%) e ~113 (25%)	~7.44 (5%) e ~6.89 (25%)	3 h
Rabbits *ex vivo* [7]	ALI induced by ischemia-reperfusion	addition of $FiCO_2$ = 25%	Pulmonary function improvement and reduced alveolar-capillary membrane permeability.	~110	~7	40 min
Rabbits *in vivo* [12]	ALI induced by ischemia-reperfusion	addition of $FiCO_2$ = 12%	Preservation of lung mechanics, attenuation of lung inflammation, and reduction of damage induced by free radicals.	~101	~7.1	1 h e 45 min
Rabbits *ex vivo* [24]	VILI induced by barotrauma	addition of CO_2 to achieve a $PaCO_2$ = 70-100 mmHg	Reduction of VILI severity, attenuating the barotrauma-induced increment of NO production, weight gain, capillary filtration coefficient and BALF protein and hemoglobin.	~105	~6.93	60 min
Rabbits *in vivo* [25]	VILI induced by volutrauma	addition of de $FiCO_2$ = 12%	Reduction of VILI severity, attenuating the increment of lung wet-to-dry weight ratio, BALF protein concentration, and lung injury.	80-100	~7.1	4 h
Rats *in vivo* [13]	ALI induced by ischemia-reperfusion	addition of $FiCO_2$ = 2,5%, 5%, 10%, and 20%	Lung mechanics preservation, attenuation of protein leakage and oxygenation improvement. Protection both prophylactic (15 min before) and therapeutic (15 min after reperfusion), which was dose-dependent with better protective effect with $FiCO_2$ above 5%.	57.4 - 62.5	7.11 - 7.19	?
Rats *in vivo* [15]	ALI induced by intratracheal instillation of E. coli	addition of CO_2 = 12% before (prophylactic) or 30 min after (therapeutic) instillation	Hypercapnic acidosis attenuated endotoxin-induced ALI, with both prophylactic and therapeutic efficacy. Its beneficial actions were not mediated by the inhibition of peroxy-nitro induced proteins nitration.	70-80	~ 7.1	4 h prophylactic 6 h therapeutic

Continued

Chart 1 - Continuation

Animal	Lung injury model	Hypercapnia	Results	$PaCO_2$ (mmHg)	pH	Time
Rats *ex vivo* [28]	VILI induced by volutrauma	addition of FiCO2 = 12%	Compared to normocapnia, hypercapnic acidosis reduced the lung cells capacity to repair cytoplasm membrane injury.	119	7.01	20 min
Rabbits *in vivo* [9]	ALI induced by intravenous administration of *E. coli* LPS	respiratory rate reduction	The increment of BALF protein and cells content, NO synthase expression, NO metabolites formation, and the lung wet-to-dry weight ratio, in addition to worsening of histological changes.	~ 60	~7.17	6 h
Rabbits *in vivo* [26]	VILI induced by barotrauma	addition of CO2 to achieve a PaCO2 = 65-75 mmHg	VILI protection, with no change in oxygenation, BALF cytokines contents, lung wet-to-dry weight ratio and histology.	65 - 75	~ 7.25	6 h
Rats *in vivo* [8]	ALI induced by intratracheal instillation of *E. coli*	addition of $FiCO_2$ = 5%	Hypercapnic acidosis did not change the ALI severity induced by intratracheal instillation of *E. coli* either with our without antibiotics.	~64	~7.17	6 h
Rats *in vivo* [16]	ALI induced by intratracheal instillation of *E. coli*	addition of $FiCO_2$ = 5%	Worsening of ALI induced by bacterial infection, suggesting immunosuppressive effect	~55.6	~7.36	2 days
Rats *in vivo* [18]	ALI induced by intratracheal instillation of *E. coli*	addition of $FiCO_2$ = 5%	Attenuation of airway pressure increase and the reduction of pulmonary compliance reduction and PaO_2, being this action neutrophil-independent.	~61.5	~7.13	6 h
Rabbits *in vivo* [19]	ALI induced by intratracheal instillation of E. coli	respiratory rate reduction	Increment of nitrogen reactive species, BALF neutrophil and myeloperoxydase contents, and neutrophil adhesion via increased adhesion molecules expression.	55–65	?	4 h
Piglets *in vivo* [39]	Normal animals	addition of CO2 to achieve a $PaCO_2$ = 35-45, 50-60, 60-70, 90-100 e 110-120 mmHg	A short term exposure to respiratory acidosis reduces the diaphragm contractility proportional to the hypercapnia degree, and this change was partially reverted 60 minutes after exposure discontinuation.	~40. ~54. ~68. ~95 e ~116. respectively	~7.46. ~7.34. ~7.27. ~7.03 e ~6.98. respectively	~15 min at each $PaCO_2$ level
Rats *in vivo* [20]	ALI induced by early sepsis (6 h) or prolonged sepsis (96 h) resulted from CLP	addition of $FiCO_2$ = 5%	In early sepsis, attenuation of hypotension severity development, and reduction of lactate accumulation and central venous oxyhemoglobin levels, BALF neutrophil infiltration and lung wet-to-dry weight ratio. In prolonged sepsis, lung injury scores reduction.	~60	7.10 - 7.30	3 h

ALI – acute lung injury; $FiCO_2$ – inspired fraction of carbon dioxide; NO – nitric oxide; BALF – bronchoalveolar lavage fluid; CLP - cecal ligation and perforation.

Hypercapnia in ALI/ARDS induced by ischemia-reperfusion

Some experimental studies on ALI induced by ischemia-reperfusion showed a protective effect of hypercapnic acidosis.[7,11] However, there are some doubts related to the protective role of hypercapnic acidosis, i.e., if the beneficial effects were related to CO_2 or to the acid pH, as hypercapnic acidosis buffering did not protect the lungs from ischemia-reperfusion induced ALI[7] Furthermore, these studies were performed *ex vivo*, thus limiting the understanding of the role of systemic hypercapnic acidosis.

To overcome such limitations, Laffey et al. done *in vivo* studies using ALI models induced by ischemia-reperfusion.[12,13] They initially evaluated in rabbits the effects of mechanical ventilation with a N_2 balanced 12% CO_2 and 75% O_2 gas mixture for 90 minutes in a experimental pulmonary ischemia-reperfusion.[12] They observed an improvement in lung function and a reduction in alveolar-capillary permeability, suggesting a beneficial effect of hypercapnic acidosis. They also evaluated the effects of therapeutic hypercapnia (increase in inhaled CO_2) in an ALI model induced by mesenteric ischemia-reperfusion and showed that pulmonary microvascular permeability, compliance and oxygenation changes were mitigated, but the results were not significant.[13] Based on these results, we can speculated that mechanical and gas exchange parameters might not be ideal for assessing the effects of CO_2, especially if its action was more at the cellular and molecular levels. Despite this, it should be highlighted that this experimental model is highly relevant for the clinical context since extrapulmonary ALI/ARDS presents high mortality rate.[14] It is important to say that, in none of these *in vivo* ALI/ARDS models induced by ischemia-reperfusion, hypercapnic acidosis buffering was used in order to separate CO_2 and pH effects, thus, determining which parameter is responsible for the protective effect.

Hypercapnia in ALI/ARDS induced by pneumonia (pulmonary ALI/ARDS) and sepsis (extrapulmonary ALI/ARDS)

In a model of ALI induced by intratracheal instillation of *E. coli* lipopolysaccharide (LPS), hypercapnia induced by inhalation of a high CO_2 concentration-containing gas mixture yielded gas exchange improvement and lung inflammation reduction associated with a decrease in nitric oxide (NO) end-products, nitrite and nitrosothiol in the bronchoalveolar lavage fluid (BALF) and lung tissue.[15] In contrast, in an *E. coli* LPS ALI model, Lang et al. evidenced that hypercapnia induced by changes in respiratory frequency worsened lung injury, increasing BALF cells and proteins content, and lung wet-to-dry weight ratio.[9] In addition, NO synthase expression and NO metabolites formation were higher in LPS groups under hypercapnic conditions. Although both studies differ according to animal model and hypercapnia induction method, these data requires careful analysis.

Since 2005 Laffey's group carried out some studies to better understand the mechanisms of hypercapnic acidosis induced by CO_2 inhalation in an ALI model induced by *E. coli* intratracheal instillation[8,16-18], however their results were also controversial.

Laffey's group also evaluated the influence of antibiotic therapy (100 mg/kg of intravenous ceftriaxone). In contrast to his findings in experimental ALI induced by *E. coli* LPS[15], when ALI was induced by intratracheal instillation of living bacteria, the severity of lung injury was not modulated by hypercapnic acidosis, neither in the presence nor absence of antibiotics.[8] These differences could be attributed to the experimental model used. Furthermore, it is important to highlight that the degree of lung injury in the study of O'Croinin et al. may have not been severe enough to allow hypercapnic acidosis effects.

In 2008, the same researchers analyzed the effects of 5% CO_2 inhalation during 48 hours in an ALI model induced by intratracheal instillation of *E. coli*.[16] They observed that hypercapnic acidosis worsened lung injury and increased bacterial colonies count.[16] Although the interleukin (IL)-1β levels in BALF and the content of macrophages and neutrophils in the lung were similar both in normo- or hypercapnia ALI groups, neutrophil phagocytic function was significantly worsened in the hypercapnic group. The use of antibiotics in the presence of hypercapnia reduced the bacterial colonies count,

as well as the infection extension and inflammatory mediators' levels compared to those seen in normocapnic animals. Therefore, prolonged hypercapnic acidosis may be immunosuppressive and worsen the bacterial pneumonia if not treated. This brings up a dilemma for clinicians as, if on one hand the protective ventilatory strategies with tidal volume reduction and permissive hypercapnia are indicated for ALI/ARDS, on the other hand, the benefits that it provides are uncertain. Attention should be paid to the fact that the studies O'Croinin et al.[8,16] showed that hypercapnic acidosis may compromise the host response to bacterial invasion, allowing a greater bacterial growth and worsening lung injury. However, it is important to say that the duration of therapeutic hypercapnia also needs to be better investigated, in order to be safely used in clinical practice, since longer exposure periods (2 days)[16] led to adverse effects, worsening lung injury and increasing bacterial growth.

Undoubtedly, the studies of Ni Chonghaile et al. have contributed to a better comprehension of the effects of the interaction between the antibiotic and hypercapnic acidosis in ALI/ARDS.[17,18] Using the same ALI model induced by intratracheal instillation of *E. coli*, they demonstrated that, without antibiotic therapy, hypercapnic acidosis reduced lung peak pressure and compliance. However, with antibiotic therapy, which substantially reduces the content of bacteria in the lung, hypercapnic acidosis significantly attenuated the extent of histological injury induced pneumonia.[17] This study showed the therapeutic potential of hypercapnic acidosis, since the effects of therapeutic hypercapnia were evaluated after pneumonia be installed (6 hours after intratracheal instillation of *E. coli*). This is important because in the clinical practice therapeutic intervention occurs only after the lung disease is established.

In fact, neutrophils are fundamental in ALI/ARDS pathogenesis. In this line, recently, Ni Chonghaile et al.[18] reported that in the absence of neutrophil depletion, hypercapnic acidosis protected against pneumonia-induced ALI, attenuating the increase in airway pressure and the reduction in lung compliance and arterial oxygen partial pressure (PaO_2), without changing the histological lesion. The lack of some other parameters as mean airway pressure, inspiratory flow, and inspiratory:expiratory times rate has limited the understanding of the functional effects. Furthermore, the use of a 2 cmH_2O PEEP does not appropriately reflects the clinical scenario, because these patients need higher PEEP levels.

The negative findings of Laffey et al. regarding therapeutic hypercapnia in ALI induced by intratracheal instillation of *E. coli* LPS[15] were contrary to those of Liu et al.[19] who submitted rabbits, instead of rats, to mechanical ventilation during 4 hours with moderate hypercapnia (~55-60 mmHg). They observed that lung injury worsens with an increase in reactive nitrogen species and neutrophil content in BALF. Furthermore, hypercapnia also increased *in vitro* and *in vivo* neutrophil adhesion associated with a raise in vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and chemokines. It is important to highlight that these studies[15,19] differ according to the method to induce hypercapnia, since in the study of Laffey et al.[15] hypercapnia was induced by increasing the CO_2 inspired fraction, and in the Liu et al.[19]'s study by the respiratory rate reduction.

Finally, more recently, Costello et al. published a study investigating whether acute hypercapnic acidosis induced by adding CO_2 to the inspired air would protect against the pulmonary and systemic organ lesions induced by severe sepsis induced by cecal ligation and perforation.[20] In early sepsis, hypercapnic acidosis, when compared to normocapnia, attenuated the hypotension development and severity, and reduced the lactate accumulation, the central venous oxyhemoglobin levels, neutrophil infiltration and the lung wet-to-dry weight ratio. In prolonged sepsis, hypercapnic acidosis reduced the histological scores of lung injury. Despite the positive findings, hypercapnic acidosis did not change the pulmonary and systemic bacterial load, both in early and late sepsis.

The high relevance of these studies comes, mostly, from the use of *in vivo* animal models. Each study has its particular relevance, as the findings add and complete each other aiming to complete the hypercapnic acidosis regulating mechanisms puzzle, a still very controversial subject in the literature.

Hypercapnia in ventilator-induced lung injury

Ventilator-induced lung injury (VILI), reviewed by Nardelli et al.[21] is an important component of ALI/ARDS pathogenesis, and may contribute to the high mortality rate.[22] The protective strategy with low tidal volume and pressure limitation had a positive impact on mortality rate reduction,[1,2] but it may cause a CO_2 increase leading to a hypercapnic acidosis. Moreover, during mechanical ventilation, airway and alveoli epithelial cells and other lung parenchyma cells as fibroblasts and macrophages, undergo a variety of mechanical forces that activate several cell signaling cascades (revised by Garcia et al.),[23] some of which show pH or PCO_2 dependence. To better understand the role of hypercapnic acidosis in VILI, Broccard et al. evaluated, in isolated rabbit lungs, the effects of two distinct gas mixtures administration: the first with 5% CO_2 and the second with 25% CO_2.[24] They observed a reduction in the severity of VILI associated with a decrease in BALF protein concentration. In addition, high pressures mechanical ventilation increased the BALF nitric oxide (NOx) end-products contents, which were attenuated by hypercapnia. Although Broccard et al.[24]'s study is an *ex vivo* model, the results showed that hypercapnic acidosis has a protective effect in VILI. *In vivo* studies have corroborated Broccard et al.[24]'s findings, showing that hypercapnic acidosis is protective in VILI.[25,26]

In these VILI models, it is also unknown if the hypercapnic acidosis protective effect [24-26] is related to either low pH or increased CO_2. In this context, Caples et al. evaluated the effects of buffering hypercapnic acidosis with bicarbonate or tris-hydroxymethyl aminomethane (THAM) in isolated rat lungs under non-protective mechanical ventilation.[27] The authors found worsening of repair process under hypercapnia acidosis, confirming the previous findings by Doerr et al.[28] Hypercapnic acidosis buffering, both with bicarbonate or TAM, protected against mechanical ventilation-associated pulmonary cell damage, suggesting a pH-dependent protective mechanism.

Hypercapnia effects in the microcirculation

Hypercapnia may affect the local and systemic arterial blood flow distribution, as well as blood oxygenation and tissues oxygen uptake, since respiratory acidosis: 1) right-shifts the hemoglobin dissociation curve, increasing the venous blood partial pressure of oxygen (PvO_2) and, consequently, the O_2 uptake in ischemic tissues, 2) reduces the intrapulmonary shunt by potentiating the hypoxic pulmonary vasoconstriction and directly acting on airways, and 3) increases the cardiac output, further increasing the PvO_2 and venous blood oxygen content (CvO_2).[29]

Hypercapnia effects on microcirculation appear to be pH-dependent. In this context, Cardenas et al. showed that the changes in the cardiac output, organs blood flow and intracranial pressures during hypercapnia may be attenuated by acidosis correction with sodium bicarbonate, with no adverse hemodynamic effects.[30]

Additionally, the time of hypercapnia exposure also appears to modulate the effects on the microcirculation, since Kiefer et al. demonstrated that acute PCO_2 changes have no relevant effects on splanchnic perfusion and metabolism.[31]

It is important to better understand the effects of hypercapnia on the microcirculation since microcirculatory disorders may compromise tissues nutrients and oxygen supply, leading to organ failure.

Hypercapnia effects in the diaphragm

Patients with respiratory failure may have hypercapnic acidosis in two main circumstances: short term (acute) or chronic. Hypercapnic acidosis that occurs in acute respiratory failure can be result from any injury to the lung parenchyma (pulmonary edema and massive pulmonary embolism),[32] airway,[33] pleura, chest wall, neuromuscular (spinal cord injury) or central nervous system (drug overdose).[34] Chronic hypercapnic acidosis is seen in mechanically ventilated patients with limited plateau pressure and tidal volume ("protective strategy").[35,36] Although hypercapnia effects on pulmonary function[35] and hemodynamics[30] have being evaluated, few studies evaluated *in vivo* hypercapnia effects on diaphragm function.[37,38] It was observed that hypercapnic acidosis caused a reduction in diaphragm strength, however no study evaluated the recovery of diaphragm contractile properties, fundamental for the weaning process. Recently, Jaber et al. evalu-

ated the diaphragm contractility under hypercapnic conditions and after $PaCO_2$ normalization.[39] The authors showed that a short-term exposure to hypercapnic acidosis reduced diaphragm contractility proportionally to the level of hypercapnia, being this change partially reverted 60 minutes after the exposure was discontinued. This is an interesting finding, because it may explain why asthmatic patients or compensated obstructive pulmonary disease did not recover immediately their diaphragm strength after a respiratory failure episode. However, caution should be taken into account to extrapolate these results to a real setting, since the study was only performed on healthy diaphragms.

Clinical trials

Since 2000, the randomized multicenter trial comparing ventilated patients with 12 ml/kg versus 6 ml/kg tidal volume has been the mainstay for successive experimental studies regarding mechanical ventilation in ALI/ARDS.[2] Tidal volume reduction induces the increment of $PaCO_2$ leading to permissive hypercapnia. This hypercapnic acidosis, according to the ARDSNet protocol, was buffered by sodium bicarbonate, suggesting that this buffering was fundamental for these patients improved prognosis. In this context Kregenow et al. performed multiple logistic regression using the ARDSNet trial data, and found that hypercapnic acidosis was associated to reduced mortality in the high tidal volume patients group.[40] A meta analysis of six trials involving 1297 adult ALI/ARDS patients compared low volume or low airway pressure ventilation versus ventilation with tidal volumes between 10 and 15 ml/kg. The clinical heterogeneity and the differences between follow-up time and the degree of plateau pressures in the two trials make interpreting trial results more difficult. The long term effects on mortality are unknown, however the clinical benefit of hypercapnic acidosis may not be ruled out.[41]

Hypercapnia buffering

Several buffers are responsible for maintaining body pH, among them the bicarbonate buffer which is highly relevant not only for buffering H^+ ions, but also for the components concentration being independently changeable: [CO_2] by respiration, and [HCO_3] by liver and kidneys, being thus called a "open buffer system". CO_2 is a conjugate acid which is membrane permeable and, by diffusion, overcomes the lipid layer; HCO_3^- is a base which moves through membrane only helped by specific transporter proteins.

Some experimental protocol mentioned on this review did not include the hypercapnic acidosis buffering, thus leading to doubt regarding if the protective effects seen were due to the increased CO_2 or the pH drop. There is one single *ex vivo* study conducted in rabbits, ventilated with 5% CO_2 and 95% O_2, where the authors performed a bicarbonate hypercapnic acidosis buffering. The authors concluded that hypercapnic acidosis entailed beneficial effect, and that buffering attenuated these effects, suggesting that the protective effect is related to the acidosis and not to CO_2.[7] This finding is very interesting considering pulmonary vascular tonus, since hypercapnia, itself, is a potent vasodilator, while acidosis acts as a pulmonary vasoconstrictor. Hypercapnic acidosis results in pulmonary vasoconstriction, showing that the pulmonary vascular tonus is more sensitive to pH than to CO_2. This may suggest that direct pH and PCO_2 effects are independent. Since it was an *ex vivo* study[7] it neglects the hemodynamic changes from systemic circulation limiting the understanding of these data. Therefore, *in vivo* studies are required.

In a critical patient, acidosis promotes systemic changes, and the main organism defense is constituted by bicarbonate/carbonic acid buffering system (Figure 3). Bicarbonate links to excessive hydrogen producing CO_2 which reaches the lungs to be eliminated; this process would continue until pH is normalized, if not limited by progressive bicarbonate levels reduction. Cavaliere et al. studied the acid-base balance changes and the CO_2 elimination induced by bicarbonate infusion in 10 patients, and found that during bicarbonate infusion the doses used increased the total CO_2 blood contents, while no tissue retention was found, since hemodynamics remained steady as well as the arterial-venous TCO_2 difference.[42] In the venous blood, bicarbonate infusion increased the CO_2 transportation capacity, probably by the pH increment effect. CO_2 elimination only increased after a given bicarbonate amount was infused.

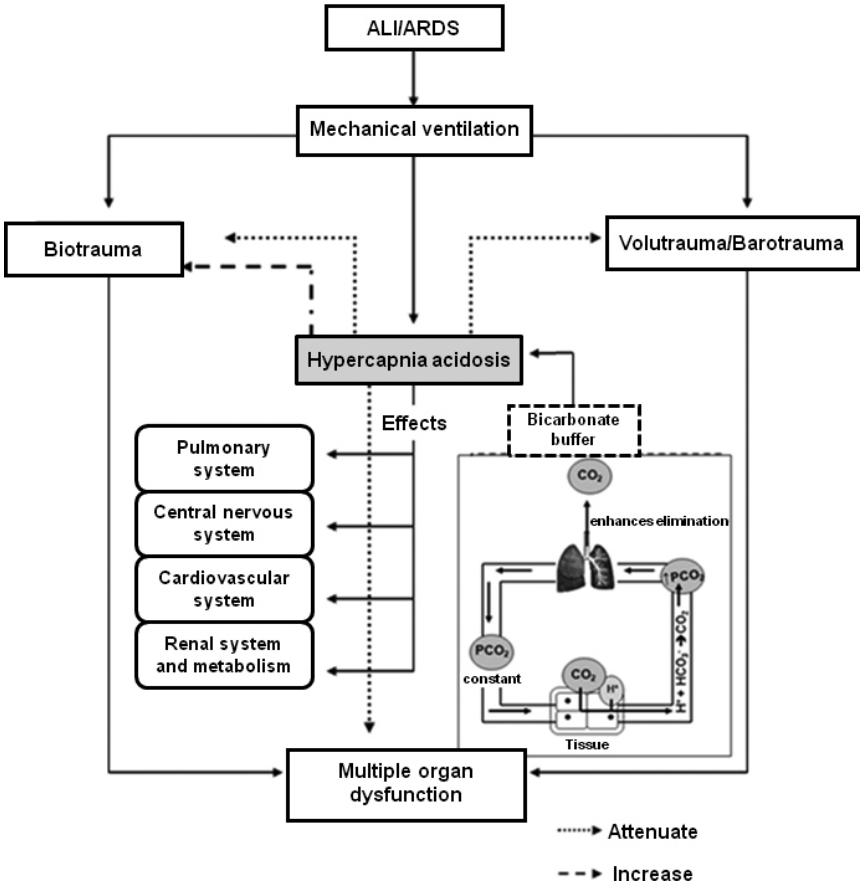

Figure 3 – Mechanical ventilation may contribute to acute lung injury (ALI) by causing direct structural damage (baro/volutrauma) to the lung and activating the inflammatory response (biotrauma) leading to multiple organ dysfunction.

Low tidal volume ventilation minimizes barotrauma, volutrauma and biotrauma, however promotes hypercapnic acidosis which acts on several organ systems. This hypercapnic acidosis may attenuate lung physical and inflammatory injuries; however, in some cases it increases infammation. In critically ill patients acidosis is usually buffered with bicarbonate (Figure modified from Laffey et al., 2004[15]).

COMMENTS

Permissive hypercapnia has been tolerated and used in ALI/ARDS. Therefore, it is essential to better understand the effects of hypercapnic acidosis, as well as CO_2 and/or pH levels separately. There is still insufficient knowledge on hypercapnic acidosis benefits on respiratory system and distal organs to allow it to be consolidated in the therapeutic arsenal of ALI/ARDS. Additionally, it is unclear whether hypercapnic acidosis should or not be buffered, and additional studies are necessary to clarify this issue.

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RESUMO

A síndrome do desconforto respiratório agudo é caracterizada por uma reação inflamatória difusa do parênquima pulmonar induzida por um insulto direto ao epitélio alveolar (síndrome do desconforto respiratório agudo pulmonar) ou indireto por meio do endotélio vascular (síndrome do desconforto respiratório agudo extrapulmonar). A principal estratégia terapêutica da síndrome do desconforto respiratório agudo é o suporte ventilatório. Entretanto, a ventilação mecânica pode agravar a lesão pulmonar. Nesse contexto, uma estratégia ventilatória protetora com baixo volume corrente foi proposta. Tal estratégia reduziu a taxa de mortalidade dos pacientes com síndrome do desconforto respiratório agudo, porém acarretou acidose

hipercápnica. O presente artigo apresenta uma revisão da literatura acerca dos efeitos da acidose hipercápnica na síndrome do desconforto respiratório agudo. Para tal, realizou-se uma revisão sistemática da literatura científica conforme critérios já estabelecidos para análise documental incluindo artigos experimentais e clínicos sobre o tema, usando-se como bases de dados MedLine, LILACS, SciElo, PubMed, Cochrane. A acidose hipercápnica é defendida por alguns autores como moduladora do processo inflamatório da síndrome do desconforto respiratório agudo. Entretanto, estudos clínicos e experimentais acerca dos efeitos da acidose hipercápnica têm demonstrado resultados controversos. Logo, é fundamental a realização de mais pesquisas para elucidar o papel da acidose hipercápnica na síndrome do desconforto respiratório agudo.

Descritores: Síndrome do desconforto respiratório agudo; Hipercapnia permissiva; Acidose hipercápnica; Inflamação

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