Permissive and Non-permissive Hypercapnia: Mechanisms of Action and Consequences of High Carbon Dioxide Levels

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ABSTRACT

Acute lung injury is a disease with high mortality, which affects a large numbers of patients whose treatment continues to be debated. It has recently been postulated that hypercapnia can attenuate the inflammatory response during lung injury, which would assign it a specific role within lung protection strategies during mechanical ventilation. In this paper, we review current evidence on the role that high levels of CO2 in the blood play in lung injury. We conclude that, although there are reports that show benefits, the most recent evidence suggests that hypercapnia can be harmful and can contribute to worsening lung damage.

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Hipercapnia permisiva o no permisiva: mecanismos de acción y consecuencias de altos niveles de dióxido de carbono

RESUMEN

La lesión pulmonar aguda es una enfermedad con alta mortalidad, que afecta a gran cantidad de pacientes y cuyo tratamiento continúa en debate. Recientemente, se ha postulado que la hipercapnia podría atenuar la respuesta inflamatoria durante la lesión pulmonar, lo que le otorgaría un papel específico dentro de las estrategias de protección pulmonar durante la asistencia respiratoria mecánica. En el presente trabajo revisamos la evidencia actual sobre el papel que altos niveles de CO2 en sangre desempeñan en la lesión pulmonar. Concluimos que, si bien existen reportes que demuestran beneficios, evidencia más reciente sugiere que la hipercapnia puede ser nociva, contribuyendo a agravar el daño pulmonar.

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Introduction

Fifteen hundred million years have passed since the origin of the universe and since then the universe has been expanding and cooling. On the other hand, evidence has been building in recent years regarding the upward trend in the temperature of our planet, which is correlated with an increase in the atmospheric levels of CO2, known as the “global warming” phenomenon.

This increase, which is directly related to the emission of gases generated by industrial activity, has already been identified as the source of harmful effects both on vegetation and the oceans, two of the fundamental components in nature’s CO2 cycle.

Mammals, particularly humans, have a need to generate high-energy compounds that consume oxygen and produce, in return, carbon dioxide. The production of CO2 is a reflection of cellular metabolic activity and, as a result, varies as a function of the organ being studied. Regardless of these differences, the CO2 plasma level is maintained within a narrow range (40 ± 5 mmHg). Moreover, its accumulation rapidly changes the acid-base balance, and therefore there are multiple mechanisms for maintaining CO2 plasma levels in this physiological range. In general, CO2 transport...
from mitochondrial production until its removal in the pulmonary alveolar space involves the action of two mechanisms: simple diffusion and facilitated diffusion due to the action of carbonic anhydrase that allows for the parallel transport of bicarbonate.\(^6\) Within this context, the concept has prevailed for decades that CO\(_2\) constitutes a waste element that must be eliminated depending on the acid-base disturbances it causes, and that in of itself CO\(_2\) is not a harmful element for the body. In this way, it has been classically associated with respiratory pathologies in which there is a decrease in the renewal of the alveolar gas (muscle weakness, chronic obstructive pulmonary disease, acute asthma attack, to name a few). However, in recent years carbon dioxide has been linked with various biological processes that differ from the balance between acids and bases and, as a result, a significant amount of new information about this issue has emerged.

Acute lung injury is a severe situation that requires a complex system of care and monitoring. Its production mechanisms and therapeutic strategies are constantly being revised and, recently, CO\(_2\) has been proposed as a possible therapeutic tool.\(^7\)

In the present study, we review scientific evidence on the effects of CO\(_2\) during acute lung injury.

**Permissive Hypercapnia**

The deleterious effect of alveolar overdistension during mechanical ventilation was published in the 1960s\(^8\) although it was not recognised as a clinical problem at the time. Later, the use of lung CT images helped develop the concept of baby lung\(^9\) and demonstrated the irregularity of the distribution of the lung injury. In the mid-1980s the term "volutrauma" arose, which ranked the role of maximum pulmonary volume (and not the maximum pulmonary pressure) as the most equivalent to mechanical stress and, therefore, generator of the parenchymal lesion.\(^10,11\) It wasn’t until the end of the 1990s that the idea of "biotrauma" came about as a overall mechanism for lung injury associated with mechanical ventilation\(^12\) and, consequently, the need for optimising the ventilation pattern as a “protective” strategy for lung tissue.

This concept has been further consolidated with the results provided by the ARDSnet in relation to mortality as a function of the current volume used.\(^13\)

With this vision of mechanical protection of lung tissue, ventilation with current volume close to 6 ml/kg of ideal weight resulted in a reduction in alveolar ventilation and the retention of variable levels of CO\(_2\) in plasma. The discussions following this multicentric trial were focused on revealing the mechanisms involved in the reduction of mortality beyond the reduction of current volume. There are many areas of uncertainty about the role played by the inflammatory response on pulmonary micromechanics, the capacity of cellular repair and the preservation of the alveolar epithelium-endothelium interaction in this context. Hypercapnia and the acidosis it implies have been two of the most intensely evaluated candidates responsible for both damage and protection, and the results are inconclusive this far.

**Inflammation and CO\(_2\)**

Inflammation leads to sharp charges at the cellular level and often the therapeutic actions cause contradictory and unexpected responses. One of the most widely studied mechanisms is the generation of reactive oxygen species due to its involvement in the response to agression, repair and cell death.\(^14\)

Carbon dioxide reacts with both reactive oxygen species and nitrogen-derived species. In aqueous media, this reaction is presented as protective and reduces oxidative damage. However, in a non-polar biological membrane environment, CO\(_2\) is part of the mechanism leading to protein nitration and oxidative damage.\(^15\) This dual role may explain the apparent contradiction between publications that attribute to CO\(_2\) both a protective\(^16\) and a damaging\(^17\) role in experimental models of lung damage.

The mediators of the inflammatory response, particularly cytokines, have been the subject of multiple studies both on the origin\(^18,19\) and treatment\(^20\) of systemic inflammation states.

There is fairly widespread agreement that initially cytokines are released by the alveolar epithelium which command the activation and recruitment of neutrophils into the alveolar space, altering endothelial permeability, amplifying the local inflammatory response and initiating the phase of clinically apparent pulmonary edema.\(^20\) While there is considerable evidence of its immunosuppressive effect (or at least immunomodulatory),\(^21\) carbon dioxide has also been reported to be part of a mechanism of activation of immune response.\(^22\) Although its role as an inhibitor of immune response has been largely accepted, this does not solve the dilemma because maintaining a state of immune weakness seems the most reasonable strategy for a disease with a major infectious component.\(^23\)

At the other extreme, on confirming its pro-inflammatory role, the consequences of hypercapnia on acute lung injury would be a greater anatomic and functional deterioration of the lung tissue.

**Cellular Repair and CO\(_2\)**

Innumerable publications are available on the mechanisms of cellular damage.\(^24-26\) repair\(^27\) and tissue fibrosis\(^28\) during pulmonary injury. However, the role of CO\(_2\) in these mechanisms has been poorly studied.

In vitro studies have shown that elevated levels of CO\(_2\) inhibit cell growth.\(^29\) Moreover, it has been speculated that intracellular accumulation of certain amino acids would be a protective mechanism against hypercapnia.\(^30\) This inhibition of cell growth has led to exploring, among other phenomena, the effect of CO\(_2\) on the repair capacity of the epithelial-endothelial barrier.\(^31\)

In this respect, experimental evidence is growing regarding the reduction in the capacity for endothelial\(^32\) and epithelial\(^33\) repair in the face of agression in the presence of high levels of carbon dioxide.

Most authors consider that the “sine qua non” condition for remodeling and tissue repair is apoptosis.\(^34\) This mechanism of cell death is inhibited during the exudative stage of distress, allowing the infiltration of neutrophils to be prolonged in lung tissue.\(^34\) At the same time, there is a stimulus of apoptosis of alveolar epithelial cells\(^35,36\) resulting in a histopathologic image of distress described many years ago and characterised by persistent inflammatory infiltrate with loss of alveolar epithelium.\(^37\) For example, in an experimental model of lung injury by inhalation, the removal of CO\(_2\) accumulated by the application of a protective ventilatory pattern reduced the histological changes and decreased levels of cell apoptosis.\(^38\) This evidence, although limited and experimental, brings together in one animal model part of the information previously provided on the role of carbon dioxide in the injury and repair processes that take place throughout respiratory distress. Moreover, it opens an interesting question about the usefulness of extracorporeal CO\(_2\) removal systems associated with a strategy for lung protection in patients with distress as a future possibility.

**Pulmonary Odema and CO\(_2\)**

Pulmonary oedema is one of the most common characteristics of acute lung injury and respiratory distress.\(^39\) In its origin, there is an increase in capillary permeability, although increasing evidence points to a predominant role of alveolar epithelial dysfunction. While capillary endothelial dysfunction is responsible for the leak of fluid from the vascular space, the dysfunctional epithelium is responsible...
for the reduction in the reabsorption of alveolar liquid and the impairment of pulmonary surfactant.

There are experimental data that support the beneficial effects of CO₂ on pulmonary and systemic vasculature. However, an alteration in the ventilation-perfusion ratio has been observed that, together with the deterioration in endothelial repair capacity, casts doubt on whether CO₂ determines a better gas exchange during lung injury.

The reabsorption of pulmonary edema is one of the major mechanisms that keeps the alveolar space “dry”. It is also the consequence of active transport of sodium through the epithelial barrier due to the action of the Na, K-ATPase. It has been well documented how the reduction in reabsorption capacity of alveolar fluid determines the mortality of patients with pulmonary oedema. Many of the elements present during the pulmonary injury and distress impair reabsorption of alveolar fluid as do, for example hypoxia, endothelial activation and mechanical stress. Furthermore, hypercapnia, independently of acidosis, impairs the reabsorption of alveolar fluid stimulating the endocytosis of Na, K-ATPase.

From the mechanical point of view, the presence of pulmonary surfactant is key to reducing superficial tension, increasing the alveolar exchange surface and reducing the tendency for the lung tissue to collapse at the end of expiration.

Its synthesis, secretion, and assembly in the alveolar space are complex processes that require energy consumption and that put in motion various intracellular signaling routes. In various studies, both basic and clinical, the loss of its tensioactive ability has been linked to pulmonary injury and to respiratory distress. However, its replacement with semisynthetic agents has not been shown to be effective in respiratory pathology in adult patients.

In relation to hypercapnia, the presence of high levels of CO₂ in experimental models reduces the secretion of surfactant without reducing cellular metabolism. This suggests that the reduction of its production does not obey a mechanism that is protective of cellular viability through a reduction in energetic consumption, but rather which adds a new mechanism of mechanical stress to lung tissue. Furthermore, when epithelial tissue turns to conservation and energetic compensation in response to hypoxia, the synthesis of carbonic anhydrase IX, which increases hydration of CO₂ and

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**Figure 1.** Diagram of the main mechanisms of lung injury in which CO₂ has been linked. 1) Endocytosis of Na, K-ATPase with decreased reabsorption of alveolar fluid. 2) Decreased inflammatory response with less capacity for tissue repair and increase in the risk of infection. 3) Increase in tissue damage mediated by O₂ reactive species.
stimulates the production of bicarbonate, as a regulator of intracellular Ph.51

Although hypercapnia has shown promise as an immunomodulator able to mitigate some markers of lung injury, the combination of mechanical injury, hypoxia and inflammatory activation as a praeule to hypercapnia as a therapeutic strategy has led some authors, promoters of its use, to see the need to explore further before beginning clinical trials.7

Clinical Trials and CO2

At the present time, we have no human studies in which the effect of high levels of CO2 is evaluated during acute lung injury with protocols specifically designed for this purpose.

Current evidence comes from animal models in which there is an attempt to reproduce the clinical setting, with mixed results, as we have mentioned earlier. In any case, promoters of its use as a therapeutic tool are supported by indirect evidence provided by the ARDSnet.12 In this study the authors carried out a detailed statistical analysis of the factors associated with mortality in the groups originally distributed according to the tidal volume used. They ultimately concluded that hypercapnic patients ventilated with a tidal volume of 12 mL/kg reported lower mortality than those with normal levels of CO2 and the same ventilatory pattern. While statistically this is correct, in the group of patients ventilated with 6 mL/kg no differences were observed in terms of their plasma CO2. This makes it difficult to separate, in this experimental design not created for this purpose, whether the high levels of CO2 may benefit patients with respiratory distress beyond the protection provided by the low tidal volume.

On the other hand, hypercapnia has been reported to be an adverse factor in patients with chronic obstructive pulmonary disease,13 lung injury,41 and in newborns.14

Future Directions

The interaction of CO2 with minerals, plants and mammals has induced dramatic changes in nature.52 Indeed, accepting that such “universal” mechanism that recognizes the variations in levels of carbon dioxide, this structure or CO2 “sensor” has not yet been identified but the data provided by basic research are very interesting.

Specifically, experimental models have been used with Caenorhabditis elegans53 and Drosophila54 that have identified immune changes, of development and survival in these species, suggesting the existence of high impact biological mechanisms influenced by CO2.55 Unfortunately, they still have not defined the mechanisms regulating these changes.

In recent years it has been recognized that carbon dioxide is much more than a waste product of cellular metabolism. Indeed, multiple effects of its interaction with structures and intracellual routes have been identified, some of which are downright harmful to lung tissue (fig. 1).

Along these lines there are different stages: from permissive hypercapnia to treatment and from protection to injury mediated by CO2. Is this the stage of non-permissive hypercapnia?

Without doubt, the role of carbon dioxide in the process of lung injury is not yet defined. However, in terms of its importance at the level of the biosphere and its capacity to modulate intracellular signalling, future research in this area is assured.

Conflicts of Interest

The authors affirm that they have no conflicts of interest.

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