Hypercapnia and hypercapnic acidosis in sepsis: harmful, beneficial or unclear?

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ABSTRACT

Mortality related to sepsis among critically ill patients remains high. Recent literature suggests that hypercapnia may affect the pathophysiology of sepsis. The effects of hypercapnia on sepsis are largely related to the direct effect of hypercapnic acidosis on immune function and, as a consequence, of increased cardiac output that subsequently leads to improved tissue oxygenation. Appropriate management of hypercapnia may aid in improving the outcomes of sepsis. Our aim was to review the effects of compensated hypercapnia and hypercapnic acidosis on sepsis, with a specific focus on critically ill patients.

Hypercapnic acidosis has been extensively studied in various in vivo animal models of sepsis and ex vivo studies. Published data from animal experimental studies suggest that the effects of hypercapnic acidosis are variable, with benefit shown in some settings of sepsis and harm in others. The effects may also vary at different time points during the course of sepsis. There are very few clinical studies investigating the effects of hypercapnia in prevention of sepsis and in established sepsis. It appears from these very limited clinical data that hypercapnia may be associated with adverse outcomes. There are no clinical studies investigating clinical outcomes of hypercapnic acidosis or compensated hypercapnia in sepsis and septic shock in critical care settings, thus extrapolation of the experimental results to guide critical care practice is difficult. Clinical studies are needed, especially in critically ill patients, to define the effects of compensated hypercapnia and hypercapnic acidosis that may aid clinicians to improve the outcomes in sepsis.

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Sepsis is one of the most common reasons for admission to the intensive care unit (ICU).[1] Improvement in mortality due to sepsis and septic shock was reported over the course of the past few years, but it remains high.[2-4] Some of the factors important in reducing mortality are early diagnosis, source control[5] and early administration of antibiotics.[6]

Studies investigating the effects of hypercapnia in sepsis suggest that hypercapnia may have an impact on pathophysiology in sepsis.[7,8] The effects of hypercapnia in sepsis may vary depending on the presence of acidosis (hypercapnic acidosis) or lack of acidosis (compensated hypercapnia).[9,10] Hypercapnia in the setting of sepsis was shown to have a direct effect on immune function.[11] The effects of hypercapnia were reported to vary at different stages during evolution, progress and the source of sepsis.[7,12-14] Studies reporting on the effects of hypercapnia show conflicting results, with some studies showing beneficial effects and others showing harmful effects.[15,16] In addition to affecting immunity, hypercapnia and acidosis increase the proliferation of bacteria.[17] Hypercapnia was also shown to improve cardiac output and tissue oxygenation in sepsis;[18-20] this improvement in tissue oxygenation was considered to reduce the development of surgical site infections.[21,22] Some of the studies have shown that hypercapnia in the setting of sepsis can impair vascular reactivity in cerebral circulation.[23,24]

A clear understanding of the basic science and the effects of hypercapnia and hypercapnic acidosis in the clinical setting of sepsis may help clinicians in developing attractive strategies to improve the outcomes of critically ill patients with sepsis. Hypercapnic acidosis, if proven to be safe and effective, can be applied in patients with sepsis who are mechanically ventilated. On the other hand, if it is proven to be harmful, hypercapnic acidosis could be avoided or actively corrected to ensure normocapnia in patients with sepsis.

We reviewed the literature with an aim to identify the effects of hypercapnia and hypercapnic acidosis on sepsis, with a specific focus on clinical studies investigating the effects of hypercapnic acidosis and hypercapnia in critically ill patients with sepsis.

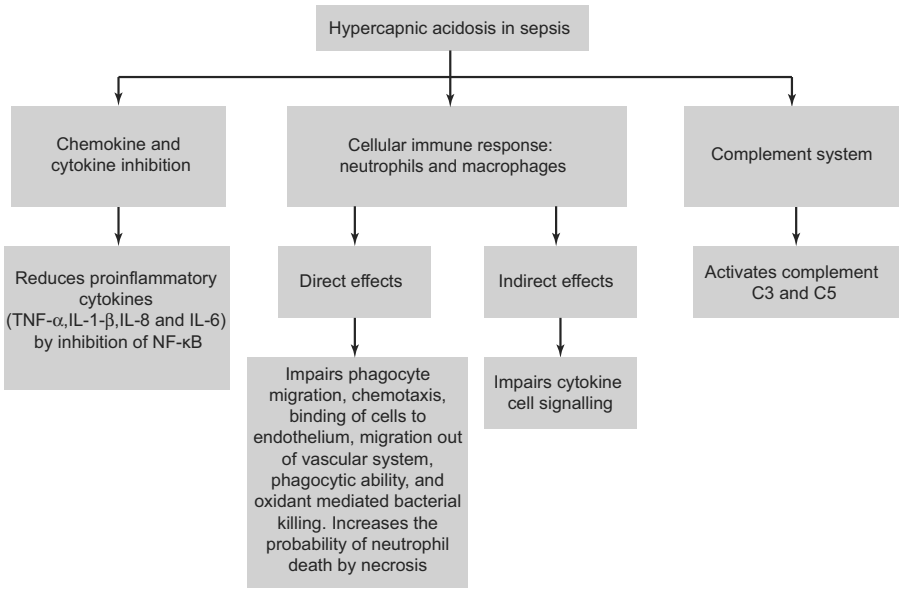
MEDLINE via PubMed (from inception to June 2017) and EMBASE (from inception to June 2017) were systematically searched. The search was performed using the following exploded medical subject headings and text words: "carbon dioxide", "hypercarbia", "hypercapnia", "acidosis", "sepsis", "septicaemia", "blood stream infection", "septic shock", "endotoxic shock", "toxic shock", "severe sepsis", "critically ill" or "critical care" in isolation and in combination without restrictions. We also

searched bibliographic references of relevant studies, irrespective of study design, with the intention of finding relevant studies to be included in this review.

Biological effects of hypercapnia and hypercapnic acidosis in sepsis

The reported effects of hypercapnia and hypercapnic acidosis in septic settings are attributed mainly to a direct effect of hypercapnia on immune function, and an indirect effect of hypercapnia and hypercapnic acidosis on cardiac output, tissue oxygenation, cerebral vascular reactivity and autoregulation.

Figure1. Effects of hypercapnic acidosis on immune function



IL = interleukin. NF-κB = *nuclear factor*-κB. TNF = tumour necrosis factor.

Effect of hypercapnia and hypercapnic acidosis on immune function

Hypercapnia and hypercapnic acidosis are well known to influence innate immunity in various animal models of sepsis, whereas data regarding impact on adaptive immune function are sparse. This influence appears to be mediated through various mechanisms, including its effect on cytokines, neutrophils, macrophage function and complements activation. The overall effect may be harmful or beneficial based on the stages during evolution, progress, source of sepsis and the duration of hypercapnia. A summary of the effects of hypercapnic acidosis on immune function[7] in sepsis is presented in Figure 1.

Harmful effects

Hypercapnic acidosis principally affects the innate immune response by inhibiting the nuclear factor-κB (NF-κB), with its main effect being anti-inflammatory.[25] It appears that the inhibition of NF-κB is independent of acidosis,[26] with hypercapnia per se noted to be an inhibitor of NF-κB activation. This may inhibit neutrophil adherence to pulmonary endothelial cells and inhibit pulmonary epithelial wound healing.[25,27] Hypercapnic acidosis may also cause inhibition of cytokine and chemokine production.[11] Acidosis is known to impair the function of immune cells by inhibiting chemotaxis, respiratory activity, bactericidal capacity in polymorphonuclear leukocytes and cytotoxicity and proliferation of lymphocytes.[28] Thus, it appears that hypercapnia may modulate immunity and host defence through pH-independent and/or pH-dependent mechanisms.

Hypercapnic acidosis can impair neutrophil function. It impairs binding of neutrophil to endothelium and migration of neutrophils out of the vascular system by inhibiting the expression of selectins, chemokines and intercellular adhesion molecules.[9,11,25] Hypercapnia has been noted to reduce the concentrations of the pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α), interleukin (IL)-1-β and the anti-inflammatory cytokine IL-10.[29] The phagocytic function of neutrophils is inhibited by hypercapnic acidosis.[13] In a murine model of *Pseudomonas aeruginosa* pneumonia, hypercapnia reduced phagocytosis of neutrophils, reduced early chemokine response (reduction of secretion of IL-6 and TNF-α and increased mortality.[30] These harmful effects of hypercapnia appear to be reversible if hypercapnia is corrected.[30] The bactericidal effects of neutrophils after phagocytosis are mediated by free radicals, such as hydrogen peroxide, superoxide and hypochlorous acid. This free radical production is reduced by acidic pH.[31] In a study by Norozian and colleagues,[32] when endotoxemic rats were treated with therapeutic hypercapnia, they noted worsening of endotoxin-induced lung injury.

Beneficial effects

While hypercapnia and acidosis appear to have detrimental effects on immune function, they have also been shown to be beneficial in early acute severe lung injury induced by endotoxin and bacterial pneumonia, possibly due to prevention of tissue injury by excessive inflammatory

response.[33-35] In an *Escherichia coli*-induced septic lung injury in rats, hypercapnic acidosis protected against worsening lung injury, attenuated the increase in airway pressure, and the impairment of lung compliance and arterial Pa_{O_2} (arterial partial pressure of oxygen).[35] Hypercapnic acidosis was also known to reduce the magnitude of lung injury in an experimental established pneumonia model of *E. coli*-induced septic lung injury.[12] Enhancement of the protective effects of hypercapnic acidosis in septic lung injury has been noted in the presence of antibiotics.[12] Buffering of hypercapnic acidosis in acute lung injury induced by *E. coli* or endotoxin has been associated with worsening of arterial oxygenation, pulmonary compliance and structural lung damage.[10,36] The effects of hypercapnia and acidosis have been investigated further in peritoneal sepsis with a rodent model of peritoneal sepsis induced by caecal ligation puncture. Hypercapnic acidosis prevented the development or reduced severity of hypotension and lactate accumulation as compared with normocapnia.[34] There was also no increased bacterial load noted in lungs, peritoneum or blood with hypercapnic acidosis.[34]

The effects of hypercapnia appear to vary with its duration. In an animal model of experimental *E. coli* pneumonia that was studied over a 6-hour period, hypercapnia attenuated disease progression and preserved lung function.[12] In the same animal model of *E. coli* pneumonia, sustained hypercapnia over a 48-hour period worsened the lung injury.[13] The effects of hypercapnic acidosis in bacterial sepsis also appear to vary with the duration of sepsis.[11] In early sepsis, hypercapnic acidosis appears to reduce the inflammatory response and decrease bacterial toxin-mediated injury to tissues, thereby reducing the overall lung injury.[11] In contrast, prolonged or late bacterial sepsis hypercapnic acidosis appears to decrease host response to infection, which might result in unopposed bacterial proliferation with worsening lung injury.[11] These deleterious effects of hypercapnic acidosis appear to be offset by antibiotic therapy.[13] The implications of these varying effects of hypercapnia in experimental sepsis models on patients with sepsis are not known.

Effects of hypercapnia and hypercapnic acidosis on cardiac output and tissue oxygenation

The effects of hypercapnic acidosis on cardiac output and tissue oxygenation were well studied in various clinically relevant models of animal sepsis and septic shock. Stubbs and colleagues[37] studied the effects of hypercapnic acidosis and buffered hypercapnia (with normal pH) in microcirculatory oxygenation of the colon in a rodent model of peritonitis. In this experimental model, the splanchnic microcirculation was preserved, and oxygenation improved similarly under both hypercapnic acidosis and buffered hypercapnia.[37] In a rat model of lung injury induced by systemic sepsis, Higgins and colleagues[10] investigated the effects of hypercapnic acidosis and compensated hypercapnia. They found that the hypotension induced by systemic sepsis was attenuated by both hypercapnic acidosis and compensated hypercapnia. However, the severity of sepsis-induced lung injury was only reduced by hypercapnic acidosis. Wang and colleagues[19] investigated the effects of acute hypercapnic acidosis in a sheep model of faecal peritonitis and septic shock. Hypercapnic acidosis was shown to increase heart rate, cardiac output, systemic oxygen delivery and lactate clearance. Furthermore, the shunt fraction and alveolar arterial gradient reduced with hypercapnic acidosis.[19] However, there was no difference in survival times in the animals that were treated with hypercapnic acidosis as compared with those managed with normocapnia.[19]

Most of the animal experiments investigating hypercapnic acidosis targeted surrogate and short term outcome measures[12,20,30,34] and perhaps are not particularly relevant to clinical practice or understanding the effects of improved tissue oxygenation or management of hypercapnia in sepsis in clinical practice.

Hypercapnia and cerebral vascular reactivity in sepsis

Hypercapnia causes cerebral vasodilation, with a linear increase in cerebral blood volume and cerebral blood flow in rhesus monkeys.[38,39] In animal models of sepsis, this vasodilatory response to hypercapnia may be impaired. In a canine model of gram-negative endotoxic shock, cerebrovascular reactivity to hypercarnia was impaired with increased cerebral vascular resistance and reduced cerebral blood flow despite hypercapnia.[23] In a swine model of sepsis, a 4-hour infusion of group B streptococci not only affected cardiac output but also showed impaired cerebrovascular reactivity to hypercarnia, as compared with a non-septic group of piglets, despite similar reduction in cardiac output.[24]

To summarise, animal experiments on hypercapnic acidosis in sepsis have, to some extent, helped to expand our understanding, but much remains unknown, especially, the differentiating effects of compensated hypercapnia and hypercapnic acidosis.

Clinical studies on hypercapnia and hypercapnic acidosis in sepsis

Permissive hypercapnia was shown to be associated with a reduction in mortality in patients with acute respiratory distress syndrome who are mechanically ventilated.[40]

Subsequent literature, including randomised controlled trials and large observational studies, showed varying results.[41-45] Targeted hypercapnia was also shown to minimise cerebral injury in the setting of out-of-hospital cardiac arrest.[46] Studies investigating the effects of hypercapnia in clinical sepsis, especially in critically ill patients, are very limited.

The effects of hypercapnia are well studied in physiological and various pathophysiological conditions and in vitro studies including human blood. Under physiological conditions, in healthy volunteers or patients undergoing elective surgery, hypercapnia was reported to increase cardiac output[47,48] and, therefore, perfusion and oxygenation of splanchnic, myocardial and subcutaneous tissues.[21,49-51] These effects were also noted in patients with morbid obesity.[50] The effects of hypercapnia on cerebrovascular reactivity and autoregulation were investigated in a few studies.[52-56] Some studies reported hypercapnia to impair cerebrovascular reactivity and autoregulation in most but not all patients with sepsis and septic shock,[55,56] with no such impairment noted in other studies.[52,53] The clinical implications of these findings and reasons for the lack of consistent effect on cerebrovascular reactivity and autoregulation observed in different studies are not clear at this stage. Further clinical studies are required to establish the effects of hypercapnia on cerebral perfusion in patients with sepsis and septic shock.

In vitro studies investigating the effects of hypercapnia and hypercapnic acidosis on immune function in endotoxin-stimulated whole human blood suggest that hypercapnia can modulate cytokine levels in whole blood cell cultures and have a potential role in therapeutic modulation of the inflammatory cascade in sepsis.[29] Hypercapnia was shown to inhibit TNF-α and IL-6 expression in macrophages that were stimulated with lipopolysaccharide.[57] This inhibition was shown to be rapid, concentration-dependent and reversible at levels of $Paco_2$ (arterial partial pressure of carbon dioxide) that may be seen in patients with acute and chronic lung diseases. The inhibition of IL-6 is independent of acidosis.[57]

Hypercapnia and hypercapnic acidosis was investigated in clinical studies aimed at the prevention of sepsis and the association of hypercapnia with adverse clinical outcomes.

Prevention of wound infections

Mild hypercapnia was investigated as an intervention to prevent wound infection in patients undergoing elective colorectal surgery.[22] In a large randomised controlled trial that included over 1200 patients, each participant was allocated to either mild hypercapnia or normocapnia during the intra-operative period. In this study, patients who had mild hypercapnia did not have a significant reduction in wound infections. However, the authors indicated that this lack of reduction in wound infections was possibly due to inadequate sample size.[22]

Association of hypercapnia on clinical outcomes in established sepsis

The association of hypercapnia with adverse clinical outcomes was studied in patients with pulmonary sepsis due to community-acquired pneumonia. Patients presenting to emergency departments with hypercapnia were found to have an increased risk of ICU admission[58] and association with increased mortality.[58,59] Hypercapnia was shown to be independently associated with an increased risk of mortality after hospitalisation due to an acute exacerbation of chronic obstructive pulmonary disease.[60,61] Furthermore, hypercapnia was also known to be associated with increased mortality in children with lower respiratory tract infections caused by adenovirus.[62] There are no studies investigating the effects of hypercapnia in sepsis other than pulmonary sepsis.

While the data from some animal experimental models suggest benefit with hypercapnia in positively modulating the immune system and tissue oxygenation, the small number of clinical studies in non-critical care settings suggests that hypercapnia is associated with increased mortality. Hypercapnia was initially thought to be associated with improved clinical outcomes in patients who are mechanically ventilated,[40,63] but more recent studies suggest hypercapnia and hypercapnic acidosis to be independently associated with increased hospital mortality in patients who are mechanically ventilated.[44,45]

Furthermore, extracorporeal clearance of hypercapnia associated with ultraprotective lung ventilation is currently investigated in two randomised controlled trials (ClinicalTrials.gov NCT02654327, NCT02282657). Targeted hypercapnia is also currently being investigated as an intervention to minimise cerebral injury in patients (NCT03114033). Given this changing paradigm, further studies are required, particularly in critically ill patients, to define the impact of hypercapnia and hypercapnic acidosis in sepsis.

Conclusion

The effects of hypercapnic acidosis have been extensively studied in various in vivo animal models of sepsis and ex-vivo studies with varying results. Hypercapnia and hypercapnic acidosis may be beneficial in some organs sepsis and harmful in others. The effects may also vary at different time points during the course of sepsis.

Clinical data, specifically pertaining to critically ill patients, are required to further our understanding of the impact of hypercapnia and hypercapnic acidosis in sepsis, particularly given the imminent increase in modulation of carbon dioxide in these patients. Unfortunately, data of this nature are very limited.

Competing interests

None declared.

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