CRITICAL CARE

COMMENTARY

Hypercapnia and ventilator-induced diaphragmatic dysfunction

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See related research by Jung et al., http://ccforum.com/content/17/1/R15

Abstract

In the previous issue of *Critical Care*, Jung and colleagues report on the preventive effects of hypercapnia on ventilator-induced diaphragmatic dysfunction (VIDD) under controlled ventilation. Possibly, a combination of controlled hypercapnia and allowed spontaneous breathing efforts may provide complementary protection for diaphragm and respiratory functionality during mechanical ventilation. However, further safety and efficacy studies need to be performed in various different animal models and patients before a universal application of hypercapnia in the critical care setting for the prevention of VIDD can be considered.

In the previous issue of *Critical Care*, Jung and colleagues [1] report on the effects of moderate hypercapnia on diaphragmatic function in mechanically ventilated piglets, in the absence of muscle relaxants. Ventilator-induced diaphragmatic dysfunction (VIDD) is a recently recognized complication of prolonged controlled ventilation, which may progress to diaphragmatic muscle atrophy and result in long-term dependence on mechanical ventilation [2]. Diaphragmatic muscle weakening is partially explained by proteolysis, apoptosis and oxidative stress [3], and appears to be directly proportional to duration of mechanical ventilation [4]; anti-oxidant and anti-inflammatory agents such as steroids may attenuate the process [5,6].

Hypercapnia and hypercapnic acidosis at mild to moderate levels have protective effects in many experimental models of organ injury. Hypercapnia increases cardiac output, and this effect appears to be due to inotropy rather than chronotropy, when tested using an arterial carbon dioxide pressure ($PaCO_2$) of up to 60 mmHg [7]. Hypercapnia also improves tissue oxygenation and perfusion [7-10]. Possibly, effects on oxygenation and perfusion are guided by elevating cardiac output and partially by peripheral vasodilatation effects as well as the rightward shifting of the oxyhemoglobin dissociation curve. In addition, hypercapnia has important effects on inflammatory responses. Its effects on altering the pro-inflammatory response, preserving organ function during mechanical, mechano-chemical, and ischemia-reperfusion injury are a few examples of its potential benefits in the prevention of organ failure [11]. Laffey and colleagues showed prophylactic and therapeutic roles of hypercapnia on oxygenation, inflammation, and immunological outcomes [12]. They concluded that hypercapnic acidosis was beneficial in lipopolysaccharide-induced lung injury both prophylactically and therapeutically. Hypercapnic acidosis provided better alveolar-arterial oxygen gradients, better static compliance, histological outcomes, and diminished neutrophil counts in the bronchoalveolar lavage fluid as shown in this landmark work.

Jung and colleagues reported that after 72 hours of controlled mechanical ventilation, diaphragm contractions to maximal stimulus were preserved in hypercapnic animals compared to a 25% decrease in the normocapnic ventilated animals. These important findings strengthen the potential role of hypercapnia in injury prevention. Although the authors did not design the study to assess potential mechanistic explanations for their promising results, diaphragmatic function was likely preserved due to improved tissue perfusion and decreased pro-inflammatory responses. Controlling lung injury, preventing diaphragmatic dysfunction, and altering exaggerated pro-inflammatory responses may suggest an important potential role for mild to moderate hypercapnia and hypercapnic acidosis in acutely developing systemic inflammatory processes.

However, there are various hurdles to overcome before therapeutic utilization of hypercapnia can be considered. First, it should be noted that most of the organ-specific benefits have been shown in animal studies. Therefore,

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most of these therapeutic effects need to be tested in relevant clinical settings under controlled environments and during critical illness. Second, the effects on inflammatory responses need to be further detailed before giving consideration to its use in acute disease processes. While hypercapnic acidosis is protective against lung injury, there are major concerns about its potential side effects in the setting of pulmonary sepsis. Some of these are due to its effects in altering pro-inflammatory responses during acute infection [13,14]. Hypercapnic acidosis appears to inhibit pulmonary epithelial wound healing by reducing cell migration via an NF-κB-dependent mechanism. This mechanism may involve alterations in matrix metalloproteinase activity. Beneficial effects of hypercapnia are mediated partially by inhibition of the host immune response, particularly the cytokine pathway, phagocyte function, and the adaptive immune response. These immunosuppressive properties may prevent host defense systems from responding to pathogenic microorganisms sufficiently [15].

In summary, we applaud Jung and colleagues for their promising work of using hypercapnia to prevent initiation of VIDD. Possibly, a combination of controlled hypercapnia and allowed spontaneous breathing efforts may provide complementary protection for diaphragm and respiratory functionality during mechanical ventilation. However, further safety, duration of therapy, and dose-finding studies need to be performed in various different animal models and patients before a universal application of hypercapnia in the critical care setting for the prevention of VIDD can be considered.

Abbreviations
NF, nuclear factor; VIDD, ventilator-induced diaphragmatic dysfunction.

Competing interests
The authors declare that they have no competing interests.

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