Commentary

Blood flow, not hypoxia, determines intramucosal PCO_2

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See related research by Dubin *et al*. in this issue [http://ccforum.com/content/9/2/R66]

Abstract

Monitoring tissue hypoxia in critically ill patients is a challenging task. Tissue PCO_2 has long been proposed as a marker of tissue hypoxia, although there is considerable controversy on whether the rise in CO_2 with hypoxia is caused by anaerobic metabolism and excess CO_2 production or by the accumulation of aerobically produced CO_2 in the setting of blood flow stagnation. The prevention of increases in intestinal PCO_2 in aggressively resuscitated septic animals supports the notion that tissue CO_2 accumulation is a function of decreases in blood flow, not of tissue hypoxia.

Hypotension is strongly associated with poor patient outcome, and reversing this condition clearly should be a primary therapeutic goal when treating patients in the early stages of shock. Potent inotropic and vasoconstrictor agents are de rigueur in the treatment of shock. The therapeutic goal is to maintain the mean arterial pressure at levels above 60 mmHg, a value thought to be the minimal pressure head required for coronary and renal perfusion [1]. Our predicament is how best to determine the mean arterial pressure level that will result in optimal tissue perfusion in a given patient. In other words, is a mean arterial pressure of 60 mmHg sufficient to assure adequate perfusion to all organs? In some patients this accepted minimal mean arterial pressure may not suffice to insure adequate tissue perfusion. Should we aim for higher, or perhaps even lower, mean arterial pressure values? Catecholamines, while extremely useful in treating decreases in cardiac output, may produce an unwelcome increase in myocardial O_2 consumption in cardiogenic shock, or may impede blood flow to oxygen-starved tissues in hypovolemic shock [2]. In septic shock, the balance between the positive and the negative effects of vasopressor and inotropic agents are even more difficult to discern [3].

A reliable and practical method to detect the onset of tissue hypoxia in critically ill patients would be an invaluable tool in guiding the timing and aggressiveness of resuscitation efforts. Finding such a tool has bedeviled clinical investigators for many years. Given our present level of technology, our options in determining the adequacy of tissue oxygenation in the clinical setting remain limited. Direct measures of tissue oxygen concentration are not sufficient to characterize the complex interaction between cellular energy requirements and oxygen supply. More complex technology, such as magnetic resonance spectroscopy and near-infrared spectroscopy are either insensitive or impractical in the clinical setting.

A great deal of thinking has been devoted in the past to the relationship of systemic measures of O_2 delivery to O_2 consumption [4]. Enthusiastic acceptance of the 'supranormal' O_2 delivery concept, produced by the infusion of fluid volume, inotropic agents and blood products [5], has been tempered by studies finding no efficacy [6], or even increased mortality [7], with this approach. Other clinical studies, however, have shown improved survival in individuals when treated immediately upon their arrival at the emergency department with a protocol designed to increase O_2 delivery [8]. It appears that early efforts at resuscitation are critical to survival, whereas delays in restoring adequate O_2 delivery may result in an ischemia-reperfusion-type phenomenon and in greater mortality [9].

Measuring tissue PCO_2 with a gastric tonometer [10] or a sublingual tonometer [11,12] has been proposed as a physiologically sound method of detecting decreases in organ perfusion. Although numerous clinical and experimental studies show a strong correlation between increases in tissue PCO_2 and poor patient outcome, gastric tonometry or sublingual tonometry have encountered variable clinical acceptance. Technical difficulties certainly have dampened the initial enthusiasm for PCO_2 tonometry, but a more challenging obstacle to the widespread use of this technology has been an inadequate understanding of the mechanism(s) that result in tissue CO_2 accumulation. A crucial issue regarding the physiology of tissue CO_2 accumulation is whether the rise in tissue PCO_2 results from decreases in cellular O_2 delivery (or metabolism by mitochondria) or from decreases in blood flow and the

accumulation of 'aerobic' CO_2 generated in the tricarboxylic acid cycle [13].

Dubin and colleagues [14] explored this issue in the past by subjecting experimental animals to decreases in O_2 delivery produced by lowering flow (ischemic hypoxia) or by lowering arterial oxygen saturation (hypoxic hypoxia). There were increases in intestinal venous PCO_2 with ischemic hypoxia but not with hypoxic hypoxia. Given that both preparations presumably experienced similar degrees of tissue hypoxia, this finding suggests that blood flow, not dysoxia, is the primary determinant of increases in tissue PCO_2. This conclusion, moreover, was in consonance with the results obtained by Vallet and colleagues [15] in isolated dog skeletal muscle.

In the current issue of *Critical Care*, Dubin and colleagues [16] extend their findings by testing the hypothesis that increasing intestinal blood flow prevents a rise in tissue PCO_2 in septic animals. They subjected two groups of sheep to lipopolysaccharide infusion. One group received intravenous fluids at a rate that maintained baseline intestinal blood flow. The other group was aggressively fluid resuscitated, resulting in increases of 50% in intestinal blood flow over basal conditions. An additional group of animals served as a normal control. The intramucosal-to-arterial PCO_2 difference (ΔPCO_2) rose in the first group, whereas volume expansion prevented increases in ΔPCO_2 in the aggressively resuscitated group. Of interest, metabolic acidosis as evidenced by a widening of the anion gap was greater in the resuscitated group.

The avoidance of increases in tissue PCO_2 in this model of resuscitated sepsis supports the notion that hypoperfusion, not tissue hypoxia, is the mechanism responsible for the accumulation of CO_2 in tissues. This finding provides experimental validity to the concept developed in a mass transport model of tissue CO_2 exchange [17], in which increases in tissue and venous blood CO_2 concentration are shown to be markers of regional hypoperfusion and not of tissue hypoxia.

The mechanism responsible for the increased anion-gap acidosis due to unmeasured anions in the resuscitated animals cannot be ascertained from the measurements obtained in this study. It is conceivable that resuscitation with normal saline may have produced local tissue hypoxia, the result of O_2 radical species production. Measurements of intestinal lactate production would have been helpful in answering this question by establishing the degree of anerobiasis in the resuscitated animals.

The study of Dubin and colleagues is another milepost in our understanding of the mechanisms that govern increases in tissue PCO_2 during hypoxic and septic conditions. Since changes in tissue PCO_2 are likely to be determined by alterations in blood flow, this may explain why gastric mucosal PCO_2 improves with greater cardiac output but not with increases in O_2-carrying capacity produced by blood transfusions [18].

I believe that now is the time to renew our interest in clinical measures of tissue PCO_2, as we understand further the clinical importance of gastric and sublingual tonometry as markers of regional tissue perfusion.

Competing interests

The author(s) declare that they have no competing interests.

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