EDITORIAL

Mystery of PCO_2 Gap in Sepsis

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Background

Exactly 2 years ago, an article was published in Indian Journal of Critical Care Medicine, which showed that high PCO_2 gap after 6 hours of resuscitation of septic shock patients was associated with high mortality.[1] The study by Arajuo et al, that is being published in this issue of Indian Journal of Critical Care Medicine fails to show any such correlation.[2]

The PCO_2 gap is difference between partial pressure of CO_2 in venous blood ($PvCO_2$) and arterial blood ($PaCO_2$). PCO_2 gap is considered to be a marker of relationship between cardiac output (CO) to global metabolic demand, i.e., a marker of adequacy of venous blood flow to eliminate CO_2 produced by peripheral tissues. Considering physiology, CO_2 is the end product of aerobic metabolism and therefore venous CO_2 content and thus, PCO_2 reflects the global tissue blood flow relative to metabolic demand. Under steady-state conditions, PCO_2 gap is determined by several factors: difference in veno-arterial CO_2 content, CO_2 dissociation curve (which expresses the relationship between CO_2 pressure and CO_2 content), CO and alveolar ventilation. It has been shown that out of all these factors, fall in CO has maximum influence on CO_2 gap.[3]

Is PCO_2 Gap a Good Marker of CO?

Many studies have shown that PCO_2 gap is inversely related to CO. A strong relationship between CO_2 gap and cardiac output was observed by Baker et al in 64 adult patients with septic shock. They also observed that the patients with increased CO_2 gap also had a higher $PaCO_2$ and a lower P/F ratio, showing that higher CO_2 gap is seen in patients with pulmonary impairment.[4] Similar relationship between CO_2 gap and CO was found by Cuschieri et al. in a mixed population of critically ill patients, in which about one-third of population were patients with circulatory and cardiogenic shock.[5] However, many studies involving septic shock patients failed to show any association between CO and CO_2 gap or showed a weak relationship suggesting that high CO_2 gap does not necessarily reflect low cardiac output in vasodialatory shock states.[6–8]

The increase in the venous-arterial pCO_2 gradient in shock states from baseline value of 2–5 mm Hg is generally due to inadequate washout of CO_2 from venous system. Under low-flow conditions due to slow transit time, CO_2 stagnation leads to increase in venous CO_2 content, $PvCO_2$ and PCO_2 gap. Sepsis is characterized by heterogeneity of microcirculation and decrease in functional capillary density with high cardiac output. This may contribute to inadequate washout of CO_2 and thus high CO_2 gap.

Does CO_2 Gap Predict Tissue Hypoxia?

One of the reasons for high morbidity and mortality in sepsis is tissue hypoxia. Vallet et al. showed in a canine model of isolated limb, that ischemic hypoxia (diminished DO_2 due to reduced blood flow) gave rise to increased CO_2 gap but hypoxic hypoxia (preserved blood flow with reduced arterial PO_2) resulted in normal CO_2 gap. This happened because the preserved blood flow was sufficient to clear the generated CO_2 in hypoxic hypoxia.[9] Similar findings were reported by Nevière et al.[10]

Wendon et al. prospectively studied 22 hypotensive patients with fulminant hepatic failure and found normal CO_2 gap with evident tissue hypoxia, suggesting that high flow states with tissue hypoxia can also have normal CO_2 gap. This was explained by low VO_2 with consequent low CO_2 production, which was removed by high CO.[11]

CO_2 produced at tissue level diffuses into vascular compartment due to pressure gradient and then removed by microcirculation. Microvascular alterations, present in sepsis and in other pathologic states involving the microcirculation, can impede the movement of CO_2 from the tissues into the vascular compartment. The end result of this is increased tissue CO_2 concentration without increase in vascular CO_2 content. Hence, increases in tissue CO_2 will go unnoticed by measurement of venous PCO_2 and CO_2 gap, although they may be detected by methods that measure tissue PCO_2, such as gastric tonometry or sublingual capnometry. Thus increases in venous PCO_2 and CO_2 gap are neither sensitive nor specific markers of tissue hypoxia.[12]

Another major limitation of CO_2 gap is that it reflects global status of circulation. A normal CO_2 gap does not rule out regional hypoperfusion. Studies have reported splanchnic hypoperfusion in sepsis with high cardiac output,[13,14] and gut mucosal ischemia can lead to translocation of bacteria and multiorgan dysfunction.

Probably these are the reasons why studies looking at CO_2 gap have been inconsistent in their findings. Bakker in their study found pH, lactate, and oxygen saturation as significant discriminators of survival. Adding CO_2 gap to these factors, however, did not increase the predictability of survival, indicating that CO_2 gap was a confounding variable.[4] Muller et al., in their prospective cohort study of 350 septic patients, found correlation between high PCO_2 gap and 28-day mortality in patients with cardiac dysfunction but not in patients without cardiac dysfunction.[15] Retrospective analysis conducted by Troskot et al. in 71 patients with septic shock found that High $P(v\text{-}a)CO_2$ was related to mortality in nonventilated patients but not in ventilated patients.[16] Guinot et al. failed to show any association between PCO_2 gap and postoperative complications and mortality in patients undergoing cardiac surgery.[17]

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In conclusion, CO_2 gap alone, is not the ideal biomarker that we are looking at, for guiding resuscitation in patients with septic shock, nor it can be used for prognosticating outcomes in this group of patients. It should be used along with other clinical and laboratory parameters to chart further course of action.

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