Review Article

Usefulness of venous-to-arterial partial pressure of CO_2 difference to assess oxygen supply to demand adequacy: effects of dobutamine

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Abstract: The central venous O_2 saturation value and lactic acid levels are part of the diagnostic and therapeutic work up of patients in shock. These usual indicators of tissue hypoxia don't fully describe the adequacy of tissue perfusion. There is ample evidence that supplementing this data with the venous-to-arterial partial pressure of CO_2 (PCO_2) difference (ΔPCO_2) complements the clinician's tools when treating patients with shock. Based on a modified Fick equation as it applies to CO_2, in patients in a steady state, the ΔPCO_2 reflects the cardiac output (CO). This observation has been shown to be of clinical value in resuscitating patients in shock. Moreover, the ΔPCO_2 can be used to titrate inotropes, and differentiate the hemodynamic from the metabolic effect of dobutamine.

Keywords: Pressure of CO_2 (PCO_2) gap; tissue hypoperfusion; venous oxygen saturation (SVO_2); oxygen consumption; oxygen delivery (DO_2); dobutamine

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Introduction

Shock is defined as an imbalance between oxygen delivery (DO_2) and O_2 demand. O_2 derived parameters have been historically used as reflections of the state of organ perfusion and as targets for resuscitation (1). While such parameters, including the mixed venous oxygen saturation (SVO_2) and lactic acid levels, have great clinical information, studies have shown that they fail to fully describe the clinical picture and can be deficient when assisting the clinician in deciding on the next therapeutic step (2-6). In the following review, we will address the clinical utility of integrating venous-to-arterial partial pressure of CO_2 (PCO_2) difference (ΔPCO_2) in patients in septic shock receiving dobutamine.

Why O_2 based parameters draw an incomplete picture during shock

For patients in shock, a reduced SVO_2 often reflects an exaggerated O_2 extraction, secondary to low DO_2. When DO_2 drops below a critical threshold, anaerobic metabolism is triggered and lactic acidosis ensues. While a reduced SVO_2 reflects low O_2 availability to the tissues, a normal SVO_2 does not exclude persistent tissue hypoperfusion. This observation is explained by a heterogeneous microcirculation, capillary shunting or mitochondrial dysfunction, where SVO_2 is normal or even elevated, despite hypoxia at the cellular level, and as is often seen in patients with sepsis (7). Similarly, lactic acid, while increased when

tissues are under perfused and anaerobic metabolism sets in, can also be increased in other conditions, such as liver dysfunction or inflammatory induced aerobic glycolysis (8).

Our current emphasis to monitor tissue perfusion by focusing on systemic blood flow, and the usual indicators of global tissue hypoxia (such as SVO_2 and blood lactate levels) can be misleading, especially when used alone. The ΔPCO_2 can assist the clinician in making adequate diagnostic and therapeutic decisions.

The Fick principle as it applies to CO_2

Historically, investigators described a rise in partial pressure of venous CO_2 in patients in cardiac arrest or in various types of shock. This has triggered an interest in studying the ΔPCO_2 in these clinical scenarios.

The Fick principle allows the determination of the cardiac output (CO) based on arterial and mixed venous O_2 contents and O_2 metabolism, in patients in a steady state. According to the classical equation, CO equals O_2 uptake (VO_2) divided by the arteriovenous O_2 content difference.

$$CO = VO_2/(CaO_2 - CvO_2) \quad [1]$$

Where CaO_2, arterial oxygen content; CvO_2, venous oxygen content.

This same principle of conservation of mass applies to CO_2. CO_2 is transported in the blood mostly as bicarbonate with a small percentage dissolved in plasma and another fraction bound to hemoglobin (Hb). PCO_2 can substitute for the CO_2 content over the physiologic range of PCO_2, given the quasi linear relation over that range (9). This relationship can be affected by oxygenation of Hb (Haldane effect); low O_2 saturation favors CO_2 binding to Hb, increasing CO_2 content for the same PCO_2 level. Similarly, the acid base status affects carbaminohemoglobin so that metabolic acidosis increases PCO_2 for the same level of CO_2 content (10).

While the Fick equation relies on mixed venous values obtained from a pulmonary artery catheter (and reflecting total venous blood returning to the heart), central venous values obtained from a central venous catheter correlate with the mixed venous and are more readily available at the bedside (11,12). Based on these studied assumptions, we can reach the following equation:

$$CO = K \times VCO_2/(PcvCO_2 - PaCO_2) \quad [2]$$

Where $(PcvCO_2 - PaCO_2) = \Delta PCO_2$ with $PcvCO_2$ being the central venous PCO_2, $PaCO_2$ being the arterial PCO_2, VCO_2 the CO_2 production by the cells, K is the pseudo-linear coefficient supposed to be constant in physiological states.

While using the Fick equation as it applies to CO_2, ΔPCO_2 depends on CO_2 production (aerobic and anaerobic metabolism) and the CO (13).

As CO_2 is produced in the peripheral tissues during metabolism, the venous CO_2 content and venous PCO_2 are higher than their arterial values. Under normal physiological conditions, ΔPCO_2 ranges between 2 and 6 mmHg (14).

CO_2 metabolism and physiology

The relationship between metabolism and ΔPCO_2 is complex. When patients develop shock and a low CO state, DO_2 drops. Initially aerobic metabolism is maintained, VO_2 remains constant as O_2 extraction increases in a compensatory fashion. This is reflected by a drop in SVO_2. Interestingly, ΔPCO_2 is found to widen in this clinical scenario of hypoperfusion, and not because of metabolic changes. This is rather due to the low flow state causing CO_2 stagnation (i.e., reduction in CO_2 washout) (10). Vallet *et al.* nicely demonstrated that it is the blood flow, rather than partial pressure of oxygen (PaO_2) which affects the ΔPCO_2 (by comparing ischemic hypoxia, where blood flow is reduced below a critical DO_2 threshold *vs.* hypoxic hypoxia where PaO_2 was reduced) (15). When DO_2, drops below a critical level and anaerobic metabolism is triggered, anaerobic CO_2 production is initiated, causing ΔPCO_2 to widen further. Despite the contributions from aerobic and anaerobic metabolism, the impact of CO is much larger on ΔPCO_2, given the curvilinear relationship between ΔPCO_2 and CO.

Clinical evidence

Multiple studies observed the clinical value of ΔPCO_2 in patients in septic shock. As previously described through the Fick equation, ΔPCO_2, in the right clinical context of a steady state, reflects the CO and its adequacy to wash out CO_2 relative to the patient's metabolic state (16). This correlates with observational studies showing how ΔPCO_2 reflects tissue perfusion parameters. Patients with high ΔPCO_2 on admission have high lactate levels (17). Lactate clearance is much improved in patients whose ΔPCO_2 normalized (it was reduced to <6 mmHg), reflecting improved organ perfusion (18). An elevated ΔPCO_2 (above 6 mmHg) identifies patients who are inadequately resuscitated, despite central venous oxygen saturation ($ScvO_2$) >70% (19). Reflecting the state of

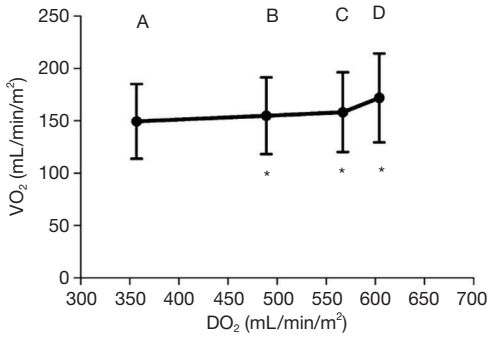

Figure 1 Time course of oxygen consumption and oxygen delivery during dobutamine infusion. Data are presented as mean ± SD. *, P<0.001 *vs.* baseline (17). A, baseline; B, dobutamine 5 µg/kg/min; C, dobutamine 10 µg/kg/min; D, dobutamine 15 µg/kg/min (22).

organ perfusion, an exaggerated ΔPCO_2 also carries a prognostic weight and signals an increased mortality (13,17). Patients with a high ΔPCO_2 at the time of presentation have worse outcomes, perhaps because of low organ perfusion. Similarly, patients whose gap is not reduced at 6 h have a higher risk of progressing to multiorgan failure.

The role of ΔPCO_2 in titrating inotropes

The observation that the venous-to-arterial difference in PCO_2 can be used clinically to reflect changes in CO has been evaluated in treating patients with septic and cardiogenic shock.

Mecher *et al.* studied 37 patients with severe sepsis, before and after fluid resuscitation (16). They found that an initial high ΔPCO_2 reflected a low CO. Upon completion of fluid resuscitation, ΔPCO_2 was reduced to <6 mmHg, as the CO was found to have increased. This opens the door for ΔPCO_2 to be used as a resuscitation target.

Other studies looked at the impact of inotropic agents, specifically dobutamine. Inotropes play an integral role in resuscitating patients with shock. While most patients with cardiogenic shock are likely to benefit from inotropic support, patients with vasodilatory shock will behave differently. In septic shock every effort is made to improve DO_2. This includes optimizing the stroke volume by increasing the intravascular volume, improving O_2 content and delivery by transfusing blood, adjusting the mean arterial pressure (MAP) to enhance the perfusion pressure. Patients who continue to exhibit signs of hypoperfusion despite adequate MAP and hemoglobin concentration could suffer from reduced cardiac function and benefit from increasing cardiac contractility and organ perfusion through the use of inotropes (20).

These investigators looked at patients with no evidence for anaerobic metabolism or global tissue hypoxia. They explicitly included patients who had signs of hypoperfusion (based on oliguria, mottled skin and $ScvO_2$ <70%), but whose MAP was >65 mmHg, Hb was >8 g/dL, who were no longer fluid responsive and whose lactate levels were normal. These were patients who exhibited signs of low perfusion, despite optimal intravascular volume, blood O_2 carrying capacity and MAP, and would potentially benefit from inotropy at this clinical stage. Two such studies have been conducted: Mallat *et al.* studied 22 patients in septic shock while Teboul *et al.* studied 10 patients with congestive heart failure (21,22). These studies investigated the impact of an incremental increase of dobutamine by 5, from 0 to 15 µg/kg/min.

Both investigators found that increasing the rate of dobutamine infusion was accompanied by an increase in cardiac index (CI) and DO_2, as anticipated. A dichotomous response was found for dobutamine doses between 0 and 10 and 10–15 µg/kg/min.

Between 0 and 10 µg/kg/min, dobutamine increased the CI and DO_2, in a dose dependent fashion (CI increased from 3 to 4.6 L/min/m^2). VCO_2 increased, but to a much lesser extent compared to CI (*Figure 1*). This explains the commensurate decrease in ΔPCO_2, from 8±2 to 4.2±1.6 mmHg (*Figure 2*), attributed to increased blood flow and improved CO_2 wash out. As anticipated, SVO_2, $ScvO_2$, and O_2 extraction improved as DO_2 increased to organs who were still in need for O_2. At these lower doses, dobutamine's main impact is on the patient's hemodynamics, improved organ perfusion and CO_2 clearance.

On the other hand, while increasing dobutamine from 10 to 15 µg/kg/min CI increased from 4.6 to 5.2 L/min/m^2, and VCO_2 was found to increase to similar levels. As such, ΔPCO_2 remained constant (*Figure 2*). The increase in CO_2 production is explained by the β adrenergic simulation effect of dobutamine. It has a direct cellular metabolic effect, increasing O_2 consumption and CO_2 production. This thermogenic effect is only seen at these higher doses of dobutamine (10–15 g/kg/min).

Conclusions

Tissue hypoperfusion during circulatory failure is associated with stagnation of CO_2 in the tissues and

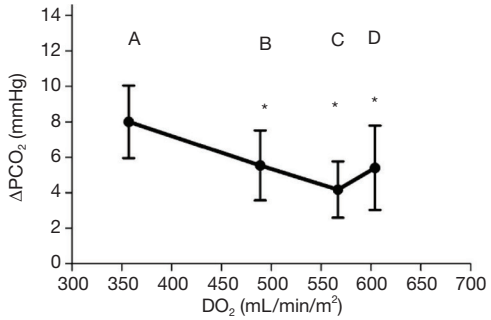

Figure 2 Evolution of ΔPCO_2 and oxygen delivery during dobutamine infusion. *, P< 0.001 *vs.* baseline (17). A, baseline; B, dobutamine 5 µg/kg/min; C, dobutamine 10 µg/kg/min; D, dobutamine 15 µg/kg/min. Data are presented as mean ± SD (22).

increased tissues venous PCO_2. The ΔPCO_2 could be considered as a marker of adequacy of venous blood flow to remove the CO_2 produced by the peripheral tissues, based on the Fick equation. This requires the patient to be in a steady state, and assumes the mixed venous values are close to the central venous values, which is the case in most patients.

In patients in cardiogenic or vasodilatory shock, without signs of global hypoxia or anaerobic metabolism, ΔPCO_2 can be used to reflect the CO. This inverse correlation is a marker of the adequacy of the venous blood efflux to remove the total CO_2 produced by the peripheral tissues. ΔPCO_2 can be used to distinguish the hemodynamic from the metabolic effect of dobutamine when this inotropic agent is selected.

ΔPCO_2 is easily obtained at the bedside and when included with other markers for tissue perfusion, can provide ample information to the clinician. This makes it an attractive marker in the ICU setting.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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