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EDITORIAL

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# Venous-to-arterial carbon dioxide difference: an experimental model or a bedside clinical tool?

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In the present issue of *Intensive Care Medicine*, Ospina-Tascón et al. present an intriguing observational study in which they assessed the association between venous-to-arterial carbon dioxide difference (Pv-a$CO_2$) and microvascular perfusion in patients with early septic shock [1]. A total of 75 adult patients with septic shock from a 60-bed mixed ICU in Columbia were included in the study. Potentially eligible patients with septic shock in the ICU were screened, and those eligible had a pulmonary artery catheter (PAC) inserted and were included in the study. Arterial and mixed venous blood samples were collected at the insertion of the PAC (T0) and at 6 h (T6), and Pv-a$CO_2$ was defined as the difference between mixed-venous and arterial $CO_2$ partial pressures. A side-stream dark-field imaging device was used to evaluate the microcirculation of the tongue at T0 and T6, and the association between Pv-a$CO_2$ and the microcirculation of the tongue was assessed. Furthermore, the association between Pv-a$CO_2$ and global haemodynamic variables was evaluated. The authors conclude that Pv-a$CO_2$ was closely related to microcirculatory blood flow parameters during the early phase of septic shock, whereas Pv-a$CO_2$ was poorly related to systemic haemodynamic variables [1].

Septic shock is a serious and frequent condition in the ICU, and early recognition and adequate treatment of tissue hypoperfusion is crucial [2, 3]. Oxygen-derived parameters such as central venous oxygen saturation ($ScVO_2$) have failed to demonstrate clinical benefit as resuscitation targets in recent large randomised controlled trials and systematic reviews [4–6]. Mean baseline $ScVO_2$ was above 70 % in all the trials, which may be explained by early recognition and aggressive treatment of shock. Nevertheless, while a low $ScVO_2$ can prompt further resuscitation [3], in the context of normal or high $ScVO_2$ its role is more questionable. Indeed, one of the limitations of using $ScVO_2$ as a marker of hypoperfusion is that normal to high values cannot discriminate whether oxygen delivery is adequate or in excess of demand. High $ScVO_2$ in the context of high lactate has for instance been shown to be associated with poor survival rates [7]. In this situation other tissue perfusion variables such as Pv-a$CO_2$ have been proposed [8, 9]. In normal circumstances the difference between the arterial and the venous carbon dioxide is less than 6 mmHg. However, in states of low perfusion this difference can increase. In areas of the microcirculation that are poorly perfused there is an increased local production of $CO_2$. Despite poor perfusion, since $CO_2$ is about 20 times more soluble than $O_2$, the likelihood of $CO_2$ diffusing out of ischemic tissues and into the venous effluent is high, making it a very sensitive marker of hypoperfusion. Vallée et al. demonstrated that in septic patients with normalized $ScVO_2$, high central venous-to-arterial $CO_2$ difference (Pcv-a$CO_2$) was associated with worse outcomes in terms of lower lactate clearance, lower cardiac index, and higher sepsis-related organ failure assessment (SOFA) score [8]. Ospina-Tascón et al.'s study adds to the evidence that

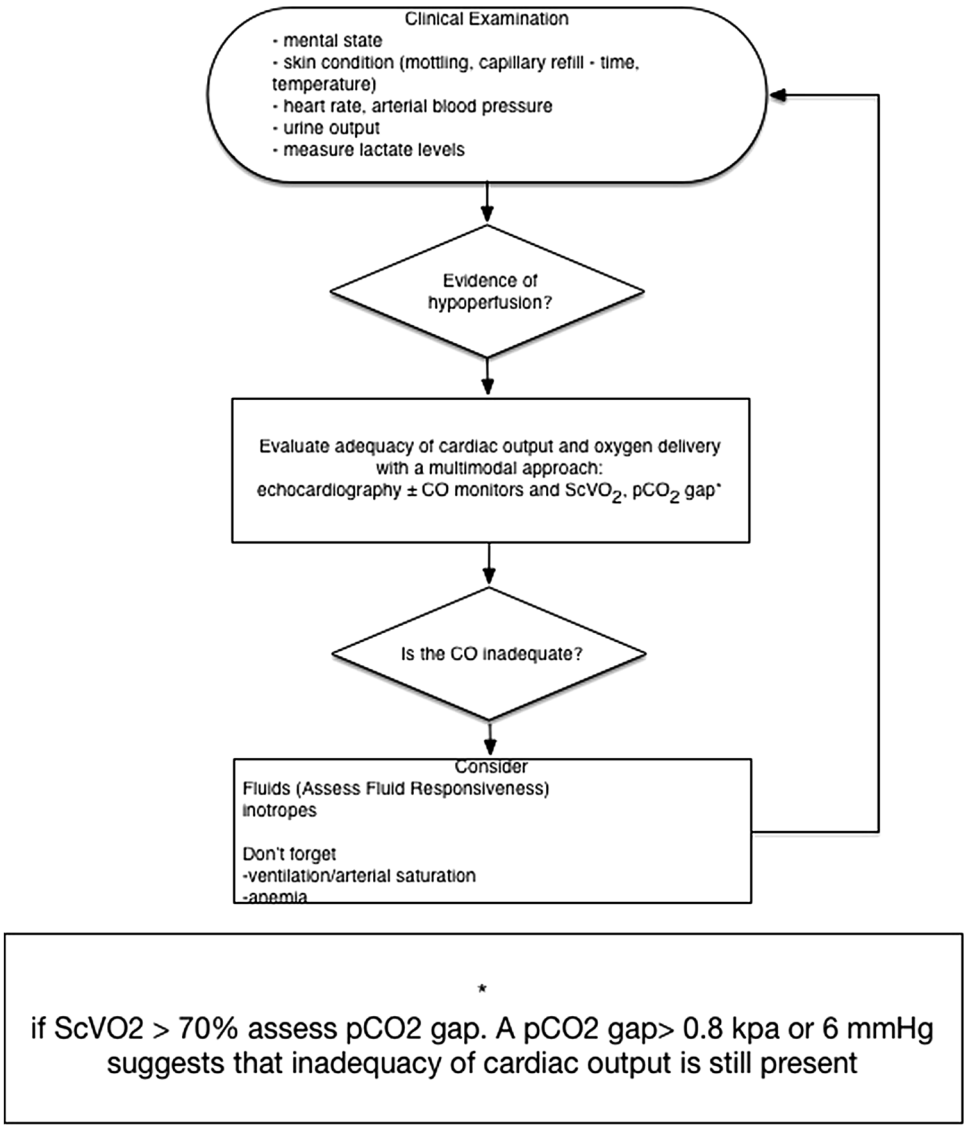


**Fig. 1** Algorithm for the assessment of patients with shock

P(c)v-a$CO_2$ may be a useful tool to identify patients who remain inadequately resuscitated when an $ScVO_2$ of 70 % has been reached [10]. Consequently, Pv-a$CO_2$ may prove useful in the assessment of patients with shock (Fig. 1).

While there seems to be convincing evidence that P(c)v-a$CO_2$ is a marker of (microcirculatory) hypoperfusion, a number of unanswered questions and limitations regarding routine clinical bedside use of Pv-a$CO_2$ exist. First, use of Pv-a$CO_2$ has not been tested in (randomised) clinical trials. Consequently, there is a risk of falsely inflated estimates [11], and the balance between benefits and harms are unknown. Second, there is a lack of Pv-a$CO_2$ studies assessing patient-important outcome measures with adequate follow-up [12]. Trials using non-patient-important outcome measures (surrogate outcomes) overestimate the intervention effect by 40–50 % [13]. Third, existing studies have mainly been conducted in small single-centre institutions, which increases the risk of reporting falsely inflated estimates [14, 15]. Finally, the unblinded assessment of the association between Pv-a$CO_2$ and the microcirculation increases the risk of selection bias [15].

In conclusion, Pv-a$CO_2$ is an interesting and potentially important new tool for evaluation of the microcirculation in critically ill patients with shock; however, additional clinical evaluation, including adequate assessment of benefits and harms in high-quality randomised clinical trials, is needed prior to routine clinical use at the bedside.

**Compliance with ethical standards**

**Conflicts of interest** None.

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