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Resuscitation of patients with septic shock: please "mind the gap"!

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Van Beest et al. [1] performed a post hoc analysis of 53 patients with severe sepsis or septic shock to investigate the interchangeability of mixed and central venous-to-arterial carbon dioxide (CO₂) differences (mvaCO₂gap and cvaCO₂gap, respectively) and the relation between the cvaCO₂gap ("pCO₂gap" or the "gap"), cardiac index (CI), and outcome. The authors observed a strong agreement between pCO₂ measured from either mixed venous or central venous sites with relatively small limits of agreement. The authors claim that combining ScvO₂ values, as easily obtained from a central venous catheter, as a surrogate for global tissue hypoxia, and pCO₂gap as a surrogate for CI, obtained from the same central venous catheter, may be useful in assessing cardiovascular state during resuscitation in critically ill patients. We cannot

agree more and propose thereafter a tentative "ScvO₂-cvaCO₂gap-guided protocol" (Fig. 1). Cuschieri et al. [2] previously demonstrated in a mixed population of critically ill patients that the relationships between the mvaCO₂gap or the cvaCO₂gap and the CI were equivalent. Since central venous blood is readily available from a central venous catheter, whereas mixed venous blood requires a pulmonary artery catheter, the cvaCO₂gap, as an easily available clinical monitoring tool, is attractive. At ICU admission, 24 patients in the van Beest et al. study had a pCO₂gap greater than 0.8 kPa (or 6 mmHg). Persistence of such a large pCO₂gap after 24 h of treatment was predictive of higher mortality.

These data are in line with results of Vallée et al. [3] who prospectively tested this hypothesis in 56 septic shock patients resuscitated to an ScvO₂ greater than 70 % (according to the Rivers' study results [4]). They found that patients who still had altered tissue perfusion (assessed by serum lactate levels greater than 2 mmol L⁻ 1) in spite of a normalized ScvO₂ displayed a large cvaCO₂gap (greater than 6 mmHg). CO₂ is the end product of aerobic metabolism and its concentration in the venous blood reflects the global tissue blood flow relative to metabolic demand. Since CO₂ is about 20 times more soluble than O2 the likelihood of it diffusing out of ischemic tissues and into the venous effluent is great, making it a very sensitive marker of hypoperfusion. Thus, in situations where an O₂ diffusion barrier exists (resulting from non-functional and obliterated capillaries), "masking" poor O₂ extraction (O₂ER) and increased tissue O₂ debt, CO₂ still diffuses to the venous effluent, "unmasking" the low perfusion state for the clinician when venous-to-arterial CO₂ difference is evaluated. Consistently Vallée et al. [3] evidenced that patients with high cvaCO₂gap values had lower lactate clearance and CI values, and presented a significant lower decrease in Sepsis-related Organ Failure Assessment score than patients with a low cvaCO₂gap. Thus, the cvaCO₂gap

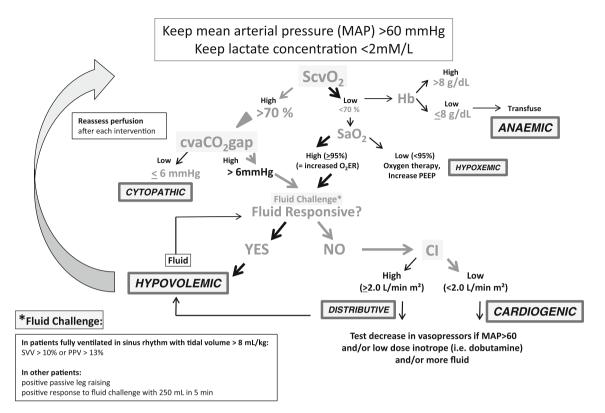


Fig. 1 The ScvO₂-cvaCO₂gap-guided protocol. ScvO₂ venous central O₂ saturation, cvCO₂gap central venous-to-arterial pCO₂ difference, SaO₂ arterial O₂ saturation, CI cardiac index, SVV stroke volume variability, PPV pulse pressure variability

represents a useful complementary tool to identify Table 1 Lactate-SevO₂-cvaCO₂gap as shock diagnostic tools patients who remain inadequately resuscitated when the 70 % ScvO₂ threshold value has been reached.

The obvious limitation of ScvO₂ is therefore that normal/high values cannot discriminate whether delivery is adequate or in excess to demand. High ScvO₂ profiles have even been shown to be related to elevated blood lactate concentration and poor survival rates [5]. Although ScvO₂ may thus not miss any global oxygen delivery (DO₂) disorder, it may remain "blind" to local perfusion disorders, which abound in sepsis because of impaired microcirculation. Under conditions where O₂ uptake (VO₂) does not meet O₂ demand, tissue dysoxia occurs, leading to organ failure and death. The crucial point here is that these tissues might remain however accessible to conventional therapeutic hemodynamic management (inotropes and fluid infusion).

Whether the resultant effect on pCO₂ gap depends in principle on the flow state or anaerobic CO₂ production was tested by Vallet et al. [6] in an experimental model of isolated limb in which ischemic hypoxia (IH) and hypoxic hypoxia (HH) were compared. The authors demonstrated that when DO₂ was reduced beyond its critical threshold in IH (dysoxia), this was associated with an increased limb venous-to-arterial pCO₂gap [6]. Conversely, in HH, pCO₂gap did not increase in spite of a marked VO₂

Shock type	Lactate	O ₂ ER	ScvO ₂	cvaCO ₂ gap
Cardiogenic hypovolemic	HI	HI	LO	HI
Anemic hypoxemic	HI	HI	LO	LO
Distributive	HI	LO	HI	HI
Cytopathic	HI	LO	HI	LO

ScvO₂ venous central O₂ saturation, cvCO₂gap central venous-toarterial pCO₂ difference, O₂ER O₂ extraction ratio, HI high, LO low

and VCO₂ reduction, clearly evidencing the gap as a marker of adequacy of venous blood flow to remove CO₂ produced rather than a marker of tissue hypoxia or dysoxia.

In conclusion, determining the gap during resuscitation of critically ill patients is useful when deciding when to stop resuscitation despite persistent evidence of organ ischemia and an ScvO₂ of greater than 70 % (see Fig. 1, Table 1). All forms of circulatory stress are potentially associated with hyperlactatemia, but hyperlactatemia is not a discriminatory factor in defining the cause of that stress. A goal of a gap lower than 6 could be a useful complementary tool to evaluate the adequacy of blood flow to global metabolic demand. In this regard it can help to titrate inotropes in order to adapt DO₂ to VCO₂, or to choose between hemoglobin correction or fluid/inotrope

infusion. Whatever way you use it or like it, from mixed or central venous, in patients with septic shock, please "mind the gap"!

Conflicts of interest None.

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