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EDITORIAL

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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 (CO_2) differences ($mvaCO_2gap$ and $cvaCO_2gap$, respectively) and the relation between the $cvaCO_2gap$ ("pCO_2gap" or the "gap"), cardiac index (CI), and outcome. The authors observed a strong agreement between pCO_2 measured from either mixed venous or central venous sites with relatively small limits of agreement. The authors claim that combining $ScvO_2$ values, as easily obtained from a central venous catheter, as a surrogate for global tissue hypoxia, and pCO_2gap 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 "$ScvO_2$-$cvaCO_2gap$-guided protocol" (Fig. 1). Cuschieri et al. [2] previously demonstrated in a mixed population of critically ill patients that the relationships between the $mvaCO_2gap$ or the $cvaCO_2gap$ 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 $cvaCO_2gap$, as an easily available clinical monitoring tool, is attractive. At ICU admission, 24 patients in the van Beest et al. study had a pCO_2gap greater than 0.8 kPa (or 6 mmHg). Persistence of such a large pCO_2gap 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 $ScvO_2$ 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 $ScvO_2$ displayed a large $cvaCO_2gap$ (greater than 6 mmHg). CO_2 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 CO_2 is about 20 times more soluble than O_2 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 O_2 diffusion barrier exists (resulting from non-functional and obliterated capillaries), "masking" poor O_2 extraction (O_2ER) and increased tissue O_2 debt, CO_2 still diffuses to the venous effluent, "unmasking" the low perfusion state for the clinician when venous-to-arterial CO_2 difference is evaluated. Consistently Vallée et al. [3] evidenced that patients with high $cvaCO_2gap$ 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 $cvaCO_2gap$. Thus, the $cvaCO_2gap$

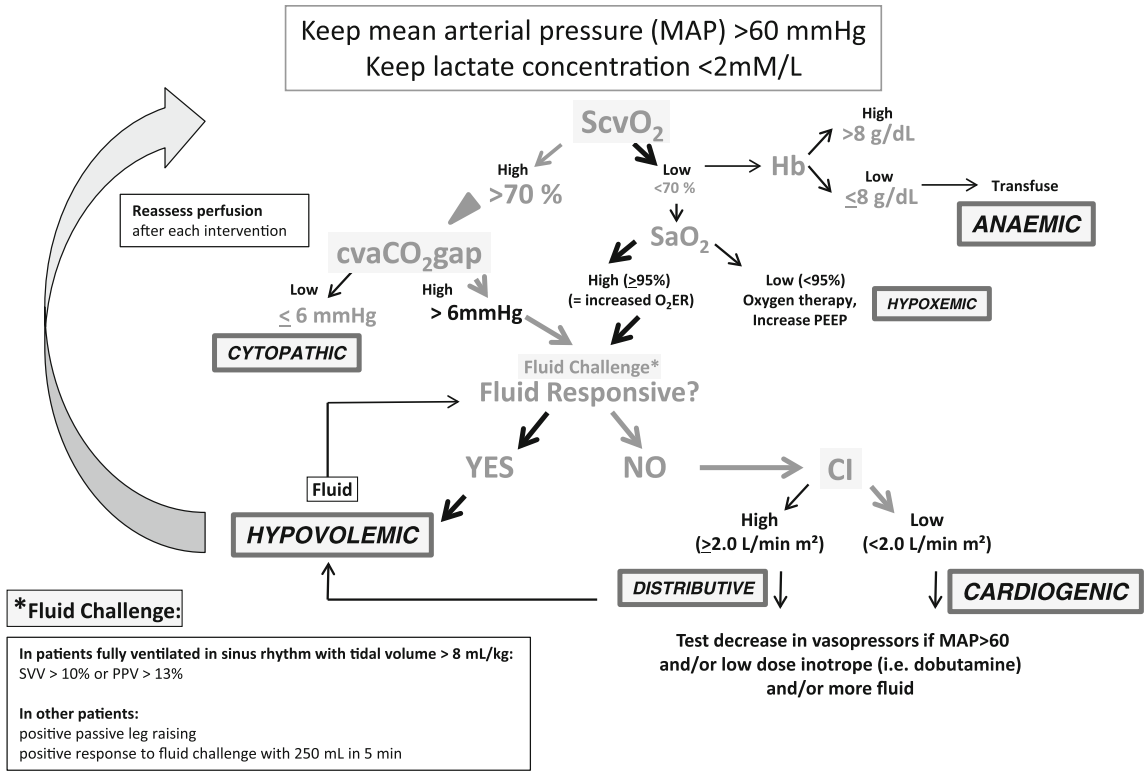

Fig. 1 The $ScvO_2$-$cvaCO_2gap$-guided protocol. *$ScvO_2$* venous central O_2 saturation, *$cvCO_2gap$* central venous-to-arterial pCO_2 difference, *SaO_2* arterial O_2 saturation, *CI* cardiac index, *SVV* stroke volume variability, *PPV* pulse pressure variability

represents a useful complementary tool to identify patients who remain inadequately resuscitated when the 70 % $ScvO_2$ threshold value has been reached.

The obvious limitation of $ScvO_2$ is therefore that normal/high values cannot discriminate whether delivery is adequate or in excess to demand. High $ScvO_2$ profiles have even been shown to be related to elevated blood lactate concentration and poor survival rates [5]. Although $ScvO_2$ may thus not miss any global oxygen delivery (DO_2) disorder, it may remain "blind" to local perfusion disorders, which abound in sepsis because of impaired microcirculation. Under conditions where O_2 uptake (VO_2) does not meet O_2 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 pCO_2 gap depends in principle on the flow state or anaerobic CO_2 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 DO_2 was reduced beyond its critical threshold in IH (dysoxia), this was associated with an increased limb venous-to-arterial pCO_2gap [6]. Conversely, in HH, pCO_2gap did not increase in spite of a marked VO_2 and VCO_2 reduction, clearly evidencing the gap as a marker of adequacy of venous blood flow to remove CO_2 produced rather than a marker of tissue hypoxia or dysoxia.

Table 1 Lactate-$ScvO_2$-$cvaCO_2gap$ as shock diagnostic tools

Shock type	Lactate	O_2ER	$ScvO_2$	$cvaCO_2gap$
Cardiogenic hypovolemic	HI	HI	LO	HI
Anemic hypoxemic	HI	HI	LO	LO
Distributive	HI	LO	HI	HI
Cytopathic	HI	LO	HI	LO

$ScvO_2$ venous central O_2 saturation, *$cvCO_2gap$* central venous-to-arterial pCO_2 difference, *O_2ER* O_2 extraction ratio, *HI* high, *LO* low

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 $ScvO_2$ 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 DO_2 to VCO_2, 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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