

## Commentary

# Searching for non-invasive markers of tissue hypoxia

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### Abstract

Tissue hypoxia is a common end product of circulatory shock and a primary target for resuscitation efforts. In this issue Podbregar and Mozina show that thenar tissue O<sub>2</sub> saturation (StO<sub>2</sub>) and mixed venous O<sub>2</sub> saturation (SvO<sub>2</sub>) co-vary in patients in left ventricular failure, but in patients with sepsis StO<sub>2</sub> was higher than SvO<sub>2</sub>. Although StO<sub>2</sub> may co-vary with SvO<sub>2</sub> they have different determinants such that after shock StO<sub>2</sub> may increase well before SvO<sub>2</sub> as a result of increased O<sub>2</sub> demands to repay O<sub>2</sub> debt incurred during hypoperfusion. Thus, the use of StO<sub>2</sub> alone to define the endpoint of resuscitation may be misleading.

In this issue of the journal Podbregar and Mozina propose the use of tissue oxygen saturation (StO<sub>2</sub>), monitored non-invasively with near-infrared spectroscopy of the thenar muscle, as a surrogate measurement of tissue perfusion [1]. They measured StO<sub>2</sub> in patients with left ventricular (LV) failure and with or without sepsis. They reasoned that StO<sub>2</sub> would discriminate between patients with low cardiac output and preserved or unimpaired O<sub>2</sub> extraction ratio (not present in septic patients) from those septic patients with poor ventricular function and low O<sub>2</sub> extraction ratio as assessed by SvO<sub>2</sub> [1]. Not unexpectedly, they found the lowest StO<sub>2</sub> values in patients with LV failure without sepsis. Interestingly, StO<sub>2</sub> was significantly higher in patients with both LV failure and sepsis than in normal volunteers. Unfortunately, the authors did not address the fundamental differences between peripheral StO<sub>2</sub> and SvO<sub>2</sub> even though they suggest that StO<sub>2</sub> may replace SvO<sub>2</sub> in the absence of sepsis. These issues deserve comment.

Severe shock is characterized by inadequate O<sub>2</sub> delivery relative to metabolic demands [2]. Unfortunately, present monitoring techniques for the assessment of O<sub>2</sub> delivery and O<sub>2</sub> utilization are invasive, impracticable, give an incomplete picture of the circulation, and may not be useful in guiding

effective resuscitation, as documented by the poorer outcomes for SvO<sub>2</sub>-guided therapy in patients with established shock [3,4]. Recently, however, early goal-directed therapy in patients with sepsis presenting to an emergency department improves outcome when central venous O<sub>2</sub> saturation is used as one of the endpoints of resuscitation [5]. Still, neither SvO<sub>2</sub> nor central venous O<sub>2</sub> provide any insight on the state of oxygen utilization in tissues.

The relationship between StO<sub>2</sub> and SvO<sub>2</sub> is not always predictable. Although StO<sub>2</sub> should decrease when tissues are starved of O<sub>2</sub> relative to their needs, the physiological events dictating changes in StO<sub>2</sub> and SvO<sub>2</sub> are different. Ischemic tissues initially sustain metabolism by anaerobic respiration, leading to an 'O<sub>2</sub> debt' shown by a transient increase in O<sub>2</sub> consumption during reoxygenation. Similarly, StO<sub>2</sub> must increase before SvO<sub>2</sub> increases because its increase is the cause of the increase in SvO<sub>2</sub>. SvO<sub>2</sub> may therefore remain low for a while despite normalization of StO<sub>2</sub>. Thus, with decreases in O<sub>2</sub> delivery one would expect both SvO<sub>2</sub> and StO<sub>2</sub> to decrease in parallel, but with resuscitation StO<sub>2</sub> should increase before SvO<sub>2</sub>.

Shock is a complex process with neurovascular, metabolic and inflammatory responses occurring simultaneously. Changes in StO<sub>2</sub> capture the vasoconstriction associated with reduced cardiac output during progressive hypovolemia. In fact, StO<sub>2</sub> is as good a predictor of multiple organ dysfunction syndrome in trauma patients as base deficit, with the advantage that StO<sub>2</sub> is continuous and noninvasive [6]. Initially, the O<sub>2</sub> extraction ratio in hemorrhagic shock is high, and cellular metabolism is not compromised. However, as flow decreases, extremity flow usually decreases first; therefore decreases in thenar StO<sub>2</sub> should occur before significant visceral ischemia develops, and when thenar StO<sub>2</sub>

LV = left ventricular; StO<sub>2</sub> = thenar tissue O<sub>2</sub> saturation; SvO<sub>2</sub> = mixed venous O<sub>2</sub> saturation.

has recovered after resuscitation most other organs should also show resolution of ischemia. Unfortunately, when shock progresses to generalized mitochondrial dysfunction, tissue wellness will not be captured by StO<sub>2</sub> values alone. Therefore an ideal noninvasive monitoring platform for shock should indicate not only that O<sub>2</sub> delivery is impaired but also the extent to which this has affected cell metabolism. Such parameters may include tissue pH, partial pressure of CO<sub>2</sub>, and ideally the levels of a mitochondrial function product such as NADH. Furthermore, many of these changes are dynamic and multidirectional depending on the integrity of the patient's compensatory response and the timeliness and effectiveness of the resuscitation.

It is necessary to understand the hysteresis of the StO<sub>2</sub> response throughout the continuum of shock and resuscitation. Such information is lacking in the report by Podbregar and Mozina. However, a physiologic perturbation such as inducing a brief episode of forearm ischemia as a circulatory stress test, to note the rapidity of re-oxygenation upon release, may be more revealing about the physiologic reserve of the patient and the metabolic activity of the muscle. We have used this approach in a fashion similar to that of De Blasi and colleagues [7]. Our preliminary study [8] supports previously published findings that resting StO<sub>2</sub> levels in both normal volunteers and patients with sustained circulatory shock are not dissimilar and thus cannot be used for early monitoring of tissue hypoperfusion [9]. However, by inducing an occlusion stress, emergent parameters can be defined that allow one to assess local metabolic demand and reperfusion reserve. Potentially, this approach might prove useful in clinical decision making. We are still searching for measures of circulatory adequacy, and non-invasive measures of StO<sub>2</sub> reflect one exciting avenue of exploration. Let us use it to define the adequacy of resuscitation therapy in those in circulatory shock. Whether its value may or may not track SvO<sub>2</sub> is less of an issue than its potential to define circulatory sufficiency.

## Competing interests

The authors declare that they have no competing interests.

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