



# The holistic view on perfusion monitoring in septic shock

Glenn Hernandez, Alejandro Bruhn, Ricardo Castro, and Tomas Regueira

## Purpose of review

To review recent evidence concerning the interactions between hemodynamic and perfusion parameters during septic shock resuscitation, and to propose some basic foundations for a more comprehensive perfusion assessment.

## Recent findings

Several recent studies have expanded our knowledge about the physiologic determinants and limitations of currently used perfusion parameters such as central venous oxygen saturation and lactate. Macrohemodynamic, metabolic, peripheral and microcirculatory parameters tend to change in parallel in response to fluid loading during initial resuscitation. In contrast, perfusion markers are poorly correlated in patients who evolve with a persistent circulatory dysfunction. Therefore, assessment of perfusion status based solely on a single parameter can lead to inaccurate or misleading conclusions.

## Summary

All individual perfusion parameters have extensive limitations to adequately reflect tissue perfusion during persistent sepsis-related circulatory dysfunction. A multimodal approach integrating macrohemodynamic, metabolic, peripheral and eventually microcirculatory perfusion parameters may overcome those limitations. This approach may also provide a thorough understanding on the predominant driving forces of hypoperfusion, and lead to physiologically oriented interventions.

## Keywords

central venous oxygen saturation, fluid challenge, lactate, microcirculation, tissue perfusion

## INTRODUCTION

A fundamental challenge in septic shock resuscitation is to evaluate tissue perfusion [1,2]. Macrohemodynamic [3], metabolic [4<sup>a</sup>,5,6,7<sup>ab</sup>], peripheral [8,9<sup>a</sup>], regional [10,11,12<sup>ab</sup>] and microcirculatory parameters [13–16] have been utilized to evaluate either perfusion status or resuscitation success. However, because of the extreme complexity of sepsis-related circulatory dysfunction, none of these markers have earned universal acceptance as the unique parameter to be considered as the hallmark to guide septic shock resuscitation [3,5,6,9<sup>a</sup>,17,18].

During the last decades several potential resuscitation targets have been explored. Among them, we can mention supernormal hemodynamic objectives [19], gastric tonometry [10,18], lactate [5,7<sup>ab</sup>], mixed (SvO<sub>2</sub>) or central venous oxygen saturations (ScvO<sub>2</sub>) [20,21], and more recently, sublingual microcirculatory flow [22], peripheral perfusion [9<sup>a</sup>] and venous-arterial pCO<sub>2</sub> gradient (p(cv-a)CO<sub>2</sub>) [6,23<sup>a</sup>]. Unfortunately, they have been tested in rather

mutually exclusive protocols [5,18]. As a result, the lack of an integrative comprehensive approach is evident, with notable exceptions [7<sup>ab</sup>,24]. This trend contrasts with more holistic approaches in other settings, such as the multimodal monitorization proposed for neurocritical patients [25].

In this article, we will review recent evidence concerning the relationship between hemodynamic and perfusion parameters during septic shock resuscitation, and propose some basic foundations for an integrative perfusion assessment.

Departamento de Medicina Intensiva, Pontificia Universidad Catolica de Chile, Santiago, Chile

Correspondence to Glenn Hernandez, MD, Departamento de Medicina Intensiva, Pontificia Universidad Catolica de Chile, Marcoleta 367, Santiago 8320000, Chile. Tel: +56 2 3543972; e-mail: glenn guru@gmail.com

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## KEY POINTS

- All individual perfusion parameters have extensive limitations to adequately reflect tissue perfusion during persistent sepsis-related circulatory dysfunction.
- Assessment of perfusion status based solely on a single parameter can lead to inaccurate or misleading conclusions.
- A multimodal approach integrating macrohemodynamic, metabolic, peripheral, and eventually microcirculatory perfusion parameters might overcome those limitations.

## INITIAL CIRCULATORY DYSFUNCTION AND RESPONSE TO EARLY RESUSCITATION

Although many mechanisms are involved in the pathogenesis of sepsis-related circulatory dysfunction [26,27,28<sup>\*</sup>,29], hypovolemia is clearly the predominant factor in preresuscitated patients early on after hospital admission [30<sup>\*</sup>]. Depending on the severity and time course of hypovolemia, patients may exhibit an impaired peripheral perfusion, hyperlactatemia, low ScvO<sub>2</sub>, and altered microcirculatory flow, whether or not they are hypotensive.

A couple of studies have explored the relationship between hemodynamic and perfusion parameters in this preresuscitative phase. Trzeciak *et al.* [31] found an early significant correlation between macrohemodynamic parameters, lactate and microcirculatory flow alterations. Payen *et al.* [32] confirmed these findings in 43 septic shock patients undergoing initial resuscitation. They found that microvascular reactivity assessed by near-infrared spectroscopy (NIRS)-derived techniques was correlated to cardiac index and lactate levels.

The cornerstone of initial resuscitation is fluid loading. A series of dynamic studies evaluated the effects of a fluid challenge in this setting. Pottecher *et al.* [33<sup>\*\*</sup>] observed an improvement in sublingual microcirculatory perfusion after fluid administration in septic shock patients. Interestingly, improvement in microcirculatory flow correlated significantly to changes in global hemodynamics. In another septic shock study, early fluid loading improved mean arterial pressure, cardiac index, SvO<sub>2</sub> or ScvO<sub>2</sub> values, lactate levels, pulse pressure variation and microcirculatory flow in parallel [34].

Other studies explored the time course of changes in several perfusion parameters during early septic shock resuscitation confirming previous findings. Our group evaluated changes in metabolic and peripheral perfusion parameters at different time

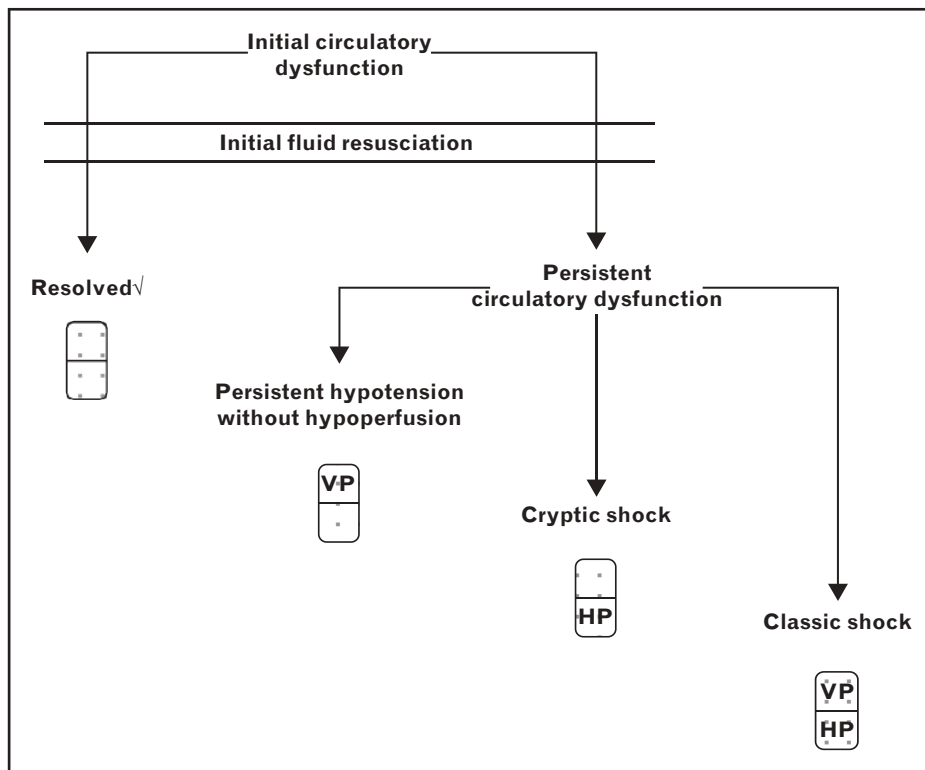
points during initial resuscitation in 41 patients with septic shock [9<sup>\*</sup>]. We found that capillary refill time, lactate and heart rate improved in parallel during 6 h of fluid-based resuscitation. In a previous landmark study, ScvO<sub>2</sub> and lactate exhibited a comparable recovery trend during early resuscitation [20]. A more recent study, by Ait-Oufella *et al.* [35<sup>\*\*</sup>], demonstrates that the opposite is also true. A worsening peripheral perfusion was associated to increasing hyperlactatemia in refractory septic shock patients.

These data taken together suggest an intricate relationship between macrohemodynamics, perfusion parameters and microcirculatory flow indices. All these elements are affected by hypovolemia and tend to improve in parallel in fluid-responsive patients. Their relative changes, though, are not well correlated. The beneficial effects of fluids may be explained by an increase in cardiac output, a decrease in the neurohumoral response to hypovolemia, and by direct effects at the microcirculatory level [26]. The clinical expression of these effects is variable according to several preexisting factors such as preload responsiveness, the magnitude of adrenergic induced redistributive vasoconstriction, or local microvascular dysfunction.

The fundamental challenge in this phase is rapid and complete reversal of the low-flow state secondary to hypovolemia. Simple, readily available and validated monitoring tools such as subjective peripheral perfusion and lactate can be used to guide this process. Normalization of these parameters indicates a successful reversal of initial circulatory dysfunction. Such an approach was recently demonstrated to be as effective as ScvO<sub>2</sub>-guided resuscitation, but appears as more practical for the pre-ICU setting [5]. However, a significant proportion of patients may develop a persistent circulatory dysfunction characterized by variable degrees of volume-refractory hypotension and/or perfusion abnormalities.

## PERSISTENT CIRCULATORY DYSFUNCTION AFTER INITIAL RESUSCITATION

Persistent circulatory dysfunction after fluid resuscitation can be expressed through diverse clinical profiles. In our opinion, at least three distinct hemodynamic patterns can be recognized at this stage: overt or classic septic shock (vasopressor requirements and hypoperfusion) [36], cryptic shock (persistent hypoperfusion without hypotension) [37<sup>\*</sup>], and a state of persistent sepsis-related hypotension without hypoperfusion [38<sup>\*</sup>] (Fig. 1).



**FIGURE 1.** Clinical patterns which can be recognized in patients with persistent sepsis-related circulatory dysfunction. HP, hypoperfusion; VP, vasopressors.

In contrast to the preresuscitative phase, more complex mechanisms may lead the pathogenesis of persistent circulatory dysfunction [27,39]. Vascular dysfunction induces vasoplegia, capillary leak and distributive abnormalities [29]. Myocardial depression is frequently manifested by a decreased left ventricle ejection fraction [28<sup>¶</sup>]. The role of micro-circulatory derangements has been highlighted in recent years and these abnormalities may hasten the development of tissue hypoxia and/or multiple organ dysfunction [30<sup>¶</sup>]. It is likely that evolution into different expressions of persistent sepsis-related circulatory dysfunction is influenced by the relative preponderance of any of these mechanisms at the individual level. To add more complexity, other factors such as hyperadrenergia [40], hypermetabolism [41], hyperinflammation [42], organ dysfunctions [43] or the effect of concurrent therapies may further complicate the interpretation of each perfusion marker.

Several recent studies support the heterogeneity of hemodynamic and perfusion profiles in persistent sepsis-related circulatory dysfunction. Boerma *et al.* [44] found no correlation between peripheral perfusion, microvascular flow index and systemic hemodynamics in 35 septic patients after fluid resuscitation. In the same line, Lima *et al.* [45] found no

correlation between systemic hemodynamics and thenar basal StO<sub>2</sub> or its recovery slope after a vascular occlusion test assessed by NIRS. Other experiences have found no association between ScvO<sub>2</sub> and lactate clearance [5] or peripheral perfusion changes [9<sup>¶</sup>]. Moreover, discrepancies between ScvO<sub>2</sub> and *p*(cv-a)CO<sub>2</sub> values after initial resuscitation have been also described [6].

Therefore, in contrast to the preresuscitative phase wherein all perfusion markers tend to improve in parallel, during persistent circulatory dysfunction individual perfusion markers may change in unpredictable or even opposite directions. Consequently, the assessment of perfusion status based solely on one marker can lead to incomplete, inaccurate or misleading conclusions. This highlights the necessity of a multimodal approach for this phase.

### INTERPRETATION OF PERFUSION MARKERS: TOWARD A MULTIMODAL APPROACH

Hypoperfusion is not a simple and unique condition. Several mechanisms are potentially involved and are distinctively reflected on perfusion parameters leading to a wide array of clinical

profiles. An integrative approach including at least macrohemodynamic, metabolic-related and peripheral perfusion parameters may aid to identify the predominant pathophysiological determinant in each individual case, and to guide physiologically based therapies.

Although hypoperfusion is the most common cause of hyperlactatemia [7<sup>■</sup>], increasing evidence for nonhypoxic-related mechanisms has recently expanded our understanding of the physiological meaning of lactate in sepsis. Sustained hyperadrenergia [40,46<sup>■</sup>,47], hypermetabolism [41], hyperinflammation [42], liver dysfunction [43], among others, may contribute to hyperlactatemia. Thus, interpretation of this parameter is particularly difficult in some cases. The distinction between these two scenarios (hypoxic versus nonhypoxic hyperlactatemia) may strongly impact the therapeutic approach. As an example, treatment of a nonhypoxic-related hyperlactatemia with sustained efforts aimed at increasing oxygen delivery ( $DO_2$ ) could lead to detrimental effects of excessive fluids or inotropes.

On the contrary, the ability of some patients to maintain normal lactate levels even under severe circulatory stress provides additional valuable information. It suggests an adequate physiologic reserve, a relative indemnity of multiple underlying mechanisms involved in lactate genesis or metabolism, and is associated to a better prognosis [38<sup>■</sup>]. Our recent study involving 302 septic shock patients supports this notion since patients with sepsis-related hypotension without hyperlactatemia exhibited a very low mortality of less than 8% [38<sup>■</sup>]. In contrast, the presence of hyperlactatemia even without hypotension (cryptic shock) is associated to a very high mortality risk as was recently shown by Puskarich *et al.* [37<sup>■</sup>].

From our point of view the real challenge in overt (classic) or cryptic shock is to determine the source of persistent hyperlactatemia. Therefore, lactate assessment should be the starting point for a multimodal perfusion monitoring approach. A practical integrative algorithm to interpret hyperlactatemia is shown in Fig. 2.

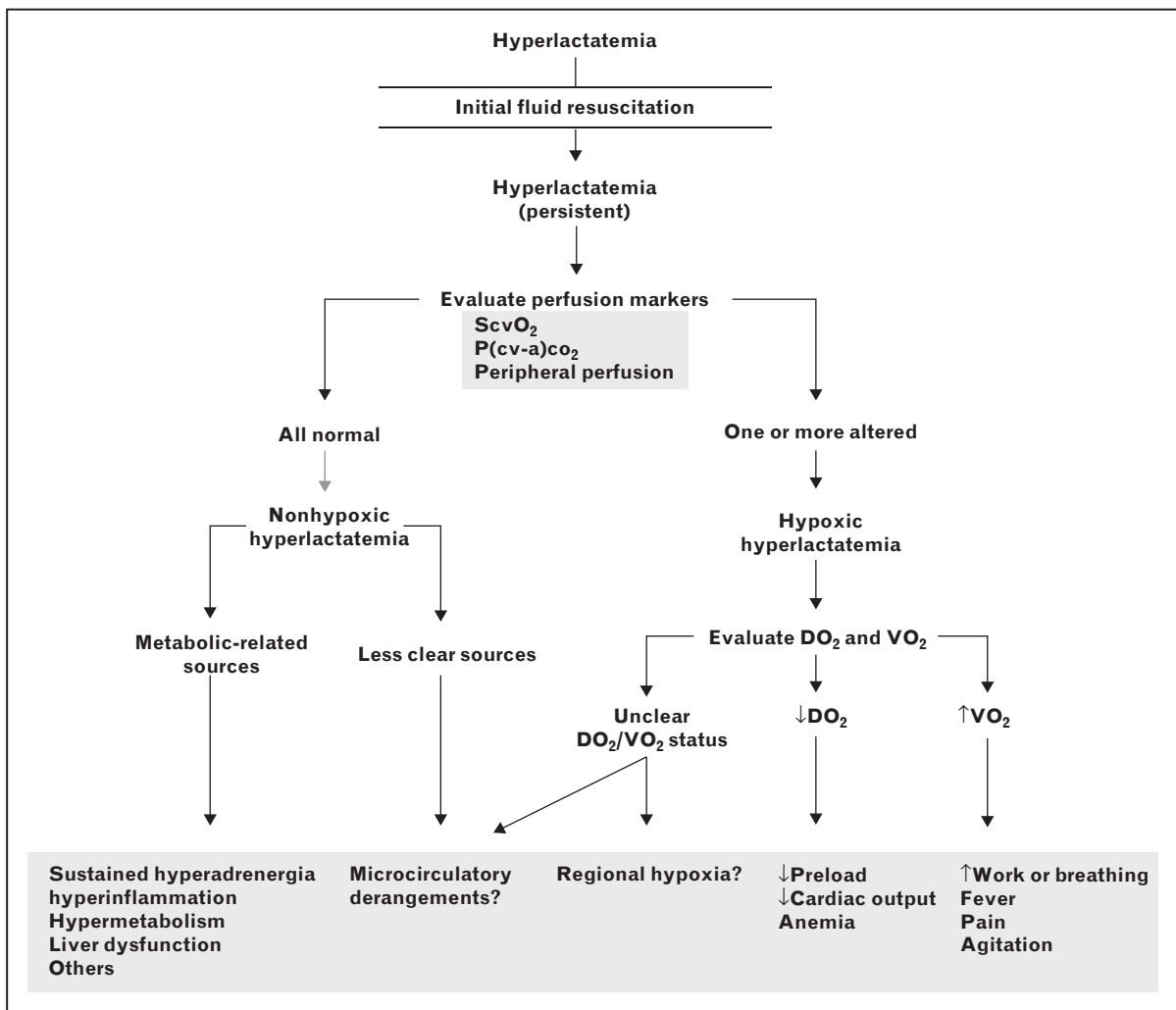
In a septic patient, the foremost priority is to rule out a hypoxic cause for hyperlactatemia. Analysis of  $ScvO_2$ ,  $P(cv-a)CO_2$  and peripheral perfusion may be helpful. The presence of a low  $ScvO_2$  clearly indicates an imbalance in the  $DO_2/VO_2$  oxygen consumption ( $VO_2$ ) relationship. This finding should prompt an aggressive  $DO_2/VO_2$  optimization strategy as was demonstrated by Rivers *et al.* [20]. In contrast, the presence of normal or even supernormal  $ScvO_2$  values, as frequently observed in ICU patients, should not be interpreted as evidence of

a normal tissue perfusion because of several reasons: First, Vallee *et al.* [6] found persistent abnormal  $P(cv-a)CO_2$  values in 50% of septic shock patients who had already achieved normal  $ScvO_2$  values after initial resuscitation. Second,  $ScvO_2$  is in strict terms a regional monitor. We demonstrated that the maneuver of sedation and connection to mechanical ventilation rapidly normalizes this parameter in septic patients subjected to emergency intubation by decreasing regional oxygen extraction, but this does not assure the correction of global tissue hypoxia [48]. Third, as severe microcirculatory derangements could theoretically impair tissue oxygen extraction capacities, a normal  $DO_2/VO_2$  relationship may coexist with profound tissue hypoxia [29]. Moreover, abnormally high  $ScvO_2$  values have been recently shown to be associated to bad prognosis [49<sup>■</sup>]. Therefore, an isolated normal  $DO_2/VO_2$  relationship is not sufficiently sensitive to rule out tissue hypoperfusion in patients with persistent sepsis-related circulatory dysfunction.

The assessment of peripheral perfusion in the context of hyperlactatemia may provide additional physiological information. An abnormal peripheral perfusion may be caused by a low cardiac output and thus a complementary evaluation of cardiac function through invasive or noninvasive techniques is obligatory. It should also prompt a reassessment of preload status, as triggering of adrenergic response by ongoing hypovolemia could induce peripheral vasoconstriction.

More sophisticated techniques assessing microcirculatory oxygenation, flow or reactivity have been helpful as research tools. NIRS can be used to evaluate tissue oxygenation at the thenar muscle, and complementarily can give relevant information about microvascular reactivity [13]. These parameters exhibit a significant correlation with other markers of peripheral perfusion [45]. In addition, videomicroscopic techniques have allowed to directly visualize microvascular flow, especially at the sublingual mucosa [15]. Microcirculatory flow or density abnormalities have been described and linked to bad outcome [15,16]. Microcirculatory dysfunction with microvascular shunting could contribute to the genesis of hyperlactatemia in selected patients. We recently demonstrated a significant correlation between hyperlactatemia and microcirculatory derangements in a large series of septic shock patients. A very high proportion of patients with hyperlactatemia more than 4 mmol/l presented severe microcirculatory dysfunction [50].

As microcirculatory derangements can be present even in patients with normal peripheral perfusion and  $ScvO_2$  values, a microcirculatory



**FIGURE 2.** Assessment of hyperlactatemia in patients with persistent sepsis-related circulatory dysfunction. Status of perfusion markers can aid on differentiating between nonhypoxic and hypoxic causes of persistent hyperlactatemia. DO<sub>2</sub>, oxygen delivery; P(cv-a)CO<sub>2</sub>, central venous-to-arterial carbon dioxide difference; ScvO<sub>2</sub>, central venous oxygen saturation; VO<sub>2</sub>, oxygen consumption.

assessment through different technologies might provide valuable data for a better interpretation of microperfusion [29]. Eventually, these techniques could be incorporated in a multimodal monitoring algorithm for a more comprehensive understanding of persistent tissue hypoperfusion, especially in the context of discrepant signals from other classic parameters.

Although the assessment of hepatosplanchnic perfusion has a strong physiological rationale, unfortunately technical limitations have precluded further development of valuable tools such as gastric tonometry [18]. Rather novel techniques such as transcutaneous assessment of indocyanine green plasma disappearance rate have become available [11]. We believe that these techniques could be

useful in the context of multimodal perfusion monitoring but their precise role should be addressed by future research.

### CONCLUSION

Sepsis-related circulatory dysfunction is usually manifested as an early hypovolemic state that can be completely reversed with initial fluid resuscitation, or eventually progresses into a persistent circulatory dysfunction. In contrast to a quite predictable course during the initial phase, persistent circulatory dysfunction can be expressed in complex and heterogeneous patterns. All individual perfusion parameters have extensive limitations to adequately reflect tissue perfusion status in this

phase. However, a multimodal approach integrating macrohemodynamic, metabolic, peripheral and eventually microcirculatory perfusion parameters can overcome their individual limitations. This proposal may provide a holistic understanding of the predominant underlying mechanisms of hypoperfusion, and lead to individualized and physiologically oriented therapeutic strategies.

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## Conflicts of interest

There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 293).

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