A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Introduction:

background & outline
Background

Septic shock can be pathophysiologically defined as a progressive circulatory dysfunction leading to hypoperfusion and bioenergetic failure, regardless of the presence of hypotension. Nevertheless, it has been difficult to translate this concept into clinical definitions, which need to be practical and simple in order to facilitate recognition. The 1991 ACCP-SCCM consensus included both volume-refractory hypotension and perfusion abnormalities as obligatory components of a septic shock definition [1]. Nevertheless, a simplified definition relying mainly on vasopressor requirements has been broadly used over the last decade (2001 Consensus Definition) [2]. In this later definition, perfusion abnormalities are not required for diagnosis. As a consequence, patients classified as septic shock because of the presence of septic-related volume-refractory hypotension, constitute a highly heterogeneous group in terms of tissue perfusion, explaining at least in part the extreme variability in mortality risk.

A fundamental challenge in septic shock resuscitation, independent of the diagnostic criteria employed, is to evaluate tissue perfusion. During the past decades, several parameters such as gastric tonometry [3,4], lactate [5,6], mixed (SvO₂) [7] or central venous oxygen saturations (ScvO₂) [6,8], peripheral perfusion [9,10], oxygen tissue saturation (StO₂) [11,12] and central venous-arterial pCO₂ gradient (P(cv-a)CO₂) [13,14] have been used to monitor perfusion status or as potential resuscitation goals in septic shock [3-14]. More recently, the pathophysiological relevance of septic-related microvascular dysfunction has been highlighted [15,16] and trials testing microcirculatory-oriented therapeutic strategies start to appear in the literature [17].

However, due to the extreme complexity of sepsis-related circulatory dysfunction, none of these markers has earned universal acceptance as the unique parameter to be considered as the hallmark to monitor tissue perfusion or guide septic shock resuscitation. Moreover, they have been tested in rather mutually exclusive protocols [6]. As a result, the lack of an integrative comprehensive approach is evident, with notable exceptions [3]. This trend contrasts with more holistic approaches in other settings, such as the multimodal monitorization proposed for neurocritical patients [18].

The case of central venous oxygen saturation (ScvO₂), a complex physiological parameter, is paradigmatic. It has been widely used as the resuscitation goal in critically ill patients [6,8], although several limitations may preclude a straightforward interpretation of its changes (10,14). The presence of a low ScvO₂ clearly indicates an imbalance in the DO₂/O₂ consumption (VO₂) relationship. This finding should prompt an aggressive DO₂ optimization strategy as was demonstrated by Rivers et al [8]. In contrast, the presence of normal ScvO₂ values, as frequently observed in ICU patients, should not be interpreted as evidence of global normal tissue perfusion because ScvO₂ is in strict terms a superior vena cava territory regional monitor. Thus, its correction does not assure the correction of global tissue hypoxia [14,19]. In addition, severe microcirculatory derangements could theoretically impair tissue oxygen extraction capabilities resulting in normal or supranormal ScvO₂ values despite the presence of tissue hypoxia [20].
The preceding example demonstrates that the idea of a single perfusion-related parameter representing the adequacy of the whole cardiovascular system in its essential role to provide oxygenated flow to tissues according to local demands, appears as over-simplistic and antiphysiologic under a critical view [21].

In effect, there are several conceptual problems with the “single representative parameter” paradigm:

1. The relative or comparative hierarchy is relatively unknown at least in terms of prognosis. Persistent hyperlactatemia appears as the strongest prognostic factor when analyzing literature, although its involved pathogenic mechanisms are complex, eventually representing an unbalanced physiological state rather than a simple manifestation of hypoxia [21]. On the contrary, patients able to maintain normal lactate levels under severe circulatory stress, are probably optimal physiological responders and exhibit an extremely low mortality [22]. Thus, besides its prognostic significance, development of hyperlactatemia is a powerful systemic biological signal. However, some guidelines recommend the indistinct use of lactate or ScvO₂ as resuscitation goals, a simplistic solution that does not resist a close scrutiny [23].

2. If the hallmark of shock is tissue hypoperfusion or hypoxia, then abnormalities in the proposed parameters should be always and unequivocally related to the presence of hypoperfusion. However, this is not the case for several parameters. Hyperlactatemia or a prolonged capillary refill time may be simply related to adrenergic-induced aerobic lactate production or vasoconstriction [21]. Oliguria is frequently multifactorial. Thus, some relevant parameters may be influenced by non-hypoxic conditions and therefore are non-specific and occasionally unreliable as perfusion markers.

3. Currently recommended septic shock treatment strategies are based on the assumption that perfusion-related variables will improve after increasing oxygen delivery mainly by cardiac output manipulation, a concept that can be defined as flow-responsiveness [6-8,23]. However, parameters traditionally considered as representing tissue perfusion can also be mechanistically determined by non-flow dependent or mixed mechanisms. Thus, to propose intense DO₂ increasing maneuvers to normalize any single abnormal parameter without considering specific involved pathogenic mechanisms appears as non-rational and may eventually lead to severe adverse events such as fluid overload and arrhythmias, among others.

4. In strict relation to the preceding point, the dynamics of recovery for individual parameters has not been well addressed in experimental or clinical studies. A predominant hypoxic versus a non-hypoxic pathogenic mechanism may result in a wide variability in the recovery time courses of individual parameters after DO₂ optimization [21]. This fact should be taken into account when selecting a resuscitation strategy in order to determine the most appropriate target at different time-points, to avoid over- or under-resuscitation.

5. The relationship of macrohemodynamics with metabolic, peripheral, regional or microcirculatory perfusion parameters is controversial, and may change throughout the resuscitation process [21].
6. The normalization of one parameter does not necessarily assure the normalization of others non-measured parameters. Even more, in the case of ScvO₂, a normalization trend to supranormal values may occasionally reflect a worsening microvascular dysfunction rather than a systemic flow improvement [20].

7. The normal values for some parameters are unknown: e.g., microcirculatory perfused vessel density, or thenar muscle tissue saturation, among others.

When analyzing potentially useful perfusion-related parameters under the above described considerations, it is clear that all individual parameters have extensive limitations to adequately reflect tissue perfusion during persistent sepsis-related circulatory dysfunction. Therefore, the only rational approach to perfusion monitoring is a multimodal one, integrating macrohemodynamic, metabolic, peripheral, regional, and eventually microcirculatory perfusion parameters to overcome those limitations. This approach may also provide a thorough understanding on the predominant driving forces of hypoperfusion, and lead to physiologically-oriented interventions. As an example, it is far more easy to understand the underlying mechanism of an increasing lactate level, if a low flow state is first ruled-out by simultaneous assessment of systemic hemodynamics, ScvO₂, P(cv-a)CO₂ and peripheral perfusion [21].

A comprehensive assessment of several determinants or markers of tissue perfusion is now possible through minimally or non-invasive techniques. Cardiac output, tissue oxygen saturation, sublingual microcirculatory flow, ear lobe cutaneous or intragastric pCO₂, transcutaneous indocyanine green plasma disappearance rate as an indicator of liver blood flow, among others, can be assessed at the bedside almost simultaneously.

In this thesis, we will review the basic foundations for the development of a comprehensive and holistic model for perfusion assessment in septic shock, and outline its application to evaluate the impact of resuscitation strategies on tissue perfusion.

Outline of the thesis

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 where all perfusion parameters tend to improve in parallel, persistent circulatory dysfunction can be expressed in complex and heterogeneous patterns. Several recent studies support the heterogeneity of hemodynamic and perfusion profiles in persistent sepsis-related circulatory dysfunction. A conceptual framework for understanding the relationship between macrohemodynamics, and metabolic, peripheral and microcirculatory perfusion parameters in this setting is provided in Chapter 1. The superior hierarchy of lactate as a fundamental physiologic signal is highlighted, a subject extensively addressed later in Chapters 3 to 5. An algorithm to interpret a persistent hyperlactatemia with a holistic approach is finally suggested and should be tested in further research.
Microcirculatory dysfunction has been recently recognized as a key pathophysiologic process in the evolution of sepsis. Clinical interest in this field has been strongly growing during the last decade after the introduction of bedside videomicroscopic techniques, demonstrating that these microcirculatory disturbances can not only be observed in septic shock patients but have also a strong prognostic significance. Fundamental aspects of microcirculatory abnormalities during septic shock that are highly relevant for the development of this thesis are discussed in Chapter 2. Particularly, studies focused on the clinical relevance and correlates of individual microcirculatory indices, and the dynamic relationship between systemic hemodynamics, global perfusion parameters and microcirculatory abnormalities are reviewed. These aspects are later explored in depth in Chapters 4 and 5.

Both adrenergic-driven aerobic and hypoxia-related anaerobic lactate production may increase during septic shock. However, our understanding of lactate has changed dramatically during the last decade, shifting from a bad to a good lactate conception. Lactate appears to exert fundamental metabolic and signaling effects. Thus, patients able to maintain normal lactate levels despite a massive aerobic release from muscles in this setting, probably represent a physiological compensated state eventually associated to a high survival rate. We address this subject in Chapter 3. Three hundred and two patients diagnosed as septic shock according to the 2001 Consensus Conference were treated with a common perfusion-oriented management algorithm and registered in a prospective dataset. In a retrospective analysis, we found that one third of patients never elevated lactate and exhibited a very low mortality risk (<8%), less organ dysfunctions and norepinephrine requirements. Interestingly, patients with at least one elevated lactate value exhibited a mortality of 43%, which was much higher (61%) in patients with a delayed peak value as compared with those in whom peak lactate levels were registered at admission. Although all patients fulfilled the 2001 Consensus Definition and required vasopressors, patients without hyperlactatemia exhibit a physiologic pattern and clinical evolution incompatible with a true shock state. Therefore, these results clearly challenge current definitions, a subject extensively discussed in this Chapter.

In Chapter 4 we prospectively explored the clinical, hemodynamic, perfusion and microcirculatory profiles associated to the absence of hyperlactatemia during septic shock resuscitation in 124 patients. Thirty percent evolved without hyperlactatemia presenting less severe microcirculatory abnormalities and higher platelet counts. Systemic flow parameters were not related to the presence or absence of hyperlactatemia. Our data suggest a relationship between coagulation, microcirculatory derangements and lactate levels, and tend to support the notion that patients with persistent sepsis-induced hypotension without hyperlactatemia exhibit a distinctive clinical and physiological profile within the spectrum of septic shock.

In Chapter 5, we examine the relationship between systemic hemodynamics, global perfusion parameters and microcirculatory derangements. Perfused vessel density (PVD) is significantly related to organ dysfunctions and mortality in a multicentric cohort of septic shock patients, but patients exhibiting more severe microcirculatory abnormalities
as represented by the lowest quartile of distribution for PVD largely explain this effect. The probability of finding a PVD value in the lowest quartile (< 9.4 mmHg) is particularly high in patients with more severe septic shock as represented by norepinephrine requirements > 0.2 mcg/kg/min and/or hyperlactatemia > 4 mmol/l. In contrast, it is highly unlikely to find a severely abnormal microcirculation in patients with normal lactate levels, supporting the findings described in Chapter 4.

The dynamics of recovery of systemic and microcirculatory perfusion parameters throughout septic shock resuscitation is explored in Chapters 6 to 10. In Chapter 6 we demonstrate the extreme vulnerability of ScvO₂ to maneuvers that decrease superior vena cava oxygen consumption. ScvO₂ increases significantly fifteen minutes after sedation and emergency intubation in critically ill septic and non-septic patients. In almost thirty percent of patients this sole maneuver increased ScvO₂ over 70%, a level considered as a resuscitation goal by current guidelines, although it is not clear if this truly represents an improvement in global dysoxia. The fact that the majority of critically ill patients are mechanically ventilated may explain the uncommon finding of low ScvO₂ values in ICU patients.

The comparative evolution of peripheral versus metabolic perfusion parameters during early septic shock resuscitation is studied in Chapter 7. Capillary refill time (CRT) exhibits the earliest normalization among all evaluated parameters with significant changes after only 2 hours. More importantly, normalization of CRT and central-to-peripheral temperature difference is associated with a successful resuscitation at 24 hours, as evaluated by lactate normalization, whilst other metabolic parameters do not. Thus, serial peripheral perfusion monitoring appears as a simple but powerful tool to assess global resuscitation status.

High volume hemofiltration (HVHF) is a potential rescue therapy in severe septic shock patients, and some experimental and clinical studies suggest that HVHF can improve systemic hemodynamics and decrease lactate levels, although its impact in other perfusion parameters has not been previously evaluated. In Chapter 8, we demonstrate that a 12 hours HVHF session is associated with an improvement in microcirculatory derangements in a cohort of severe hyperdynamic septic shock patients, particularly in those with more severe baseline abnormalities. Lactate levels improve in parallel with microcirculatory alterations, while other systemic parameters such as cardiac index and SvO₂ show no significant change after the procedure.

In Chapter 9, we develop and apply a multimodal perfusion-monitoring protocol to determine potential parameters associated to 6 h lactate clearance in a cohort of hyperdynamic septic shock patients with persistent hyperlactatemia. Patients with a 6 h lactate clearance ≥ 10% versus those with less than 10% were compared in several macrohemodynamic, metabolic, peripheral, hepatosplanchnic and microcirculatory parameters assessed immediately after preload optimization and 6 h thereafter. We demonstrated that impaired 6 h lactate clearance is associated to hepatosplanchnic hypoperfusion in some hyperdynamic septic shock patients subjected to aggressive early resuscitation. An improvement in systemic, metabolic and peripheral perfusion parameters does not rule out the persistence of hepatosplanchnic hypoperfusion.
A fundamental problem in septic shock resuscitation is addressed in Chapter 10. Currently recommended septic shock treatment strategies are based on the assumption that perfusion variables will improve after increasing $\text{DO}_2$, a concept that can be defined as flow-responsiveness. However, parameters traditionally considered as representing tissue perfusion can also be mechanistically determined by non-flow dependent or mixed mechanisms. This may result in a wide variability in the recovery time courses of individual parameters after $\text{DO}_2$ optimization depending on the predominant pathogenic mechanism.

In this study we assess the recovery time course for hemodynamic, peripheral, metabolic and microcirculatory parameters during early ICU-based resuscitation in a cohort of septic shock patients evaluated with a multimodal perfusion-monitoring protocol. A decision was made a priori to include only ultimately surviving patients in the final analysis in order to gain a better perspective on the relative importance of detected patterns. Our main finding is that perfusion parameters exhibit markedly different recovery time courses in response to resuscitation. Some variables such as $\text{ScvO}_2$, $\text{P(cv-a) CO}_2$, CRT and $\text{StO}_2$ are already normal in more than 70% of patients six hours after starting ICU-based resuscitation.

Lactate presents a biphasic recovery trend with a rapid significant decrease at 6 h, but a much slower recovery rate thereafter. Sublingual microcirculatory parameters exhibit the slowest recovery rate with persistent moderate derangements still present in almost 80% of patients at 24 h. These markedly different recovery time courses should be taken into account when composing a resuscitation protocol to avoid potentially harmful and inappropriate therapies.

Finally, we apply our multimodal perfusion-monitoring protocol to explore the systemic and microcirculatory effects of dobutamine in hyperdynamic septic shock patients with persistent hypoperfusion in a randomized placebo-controlled double-blind crossover study (Chapter 11). Dobutamine fails to improve sublingual microcirculatory, hepatosplanchnic, peripheral perfusion parameters or lactate levels, despite inducing a significant increase in systemic hemodynamic variables. Our results challenge current septic shock guidelines recommending dobutamine to improve tissue hypoperfusion after initial resuscitation.

References

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