A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Evolution of peripheral versus metabolic perfusion parameters during septic shock resuscitation: a clinical-physiologic study

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Abstract

Purpose
Perfusion assessment during septic shock resuscitation is difficult and usually complex determinations. Capillary refill time (CRT) and central-to-toe temperature difference (Tc-toe) have been proposed as objective reproducible parameters to evaluate peripheral perfusion. The comparative evolution of peripheral versus metabolic perfusion parameters in septic shock resuscitation has not been studied. We conducted a prospective observational clinical-physiological study to address this subject.

Methods
Patients with sepsis-related circulatory dysfunction were resuscitated according to a standard local algorithm. Perfusion assessment included serial determinations of metabolic (central venous O\textsubscript{2} saturation (ScvO\textsubscript{2}) and central venous to arterial pCO\textsubscript{2} gradient [P(cv-a) CO\textsubscript{2}]), and peripheral perfusion parameters (CRT, Tc-toe, among others). Successful resuscitation was defined as a normal plasma lactate at 24 h

Results
41 patients were included. The presence of normal values for both CRT and Tc-toe considered together at six hours was independently associated with a successful resuscitation (p 0.02), as compared to the behavior of metabolic parameters. CRT was the first parameter to be significantly normalized.

Conclusions
Early recovery of peripheral perfusion anticipates a successful resuscitation compared to traditional metabolic parameters in septic shock patients. Our findings support the inclusion of serial peripheral perfusion assessment in multimodal monitoring strategies for septic shock resuscitation.
Introduction

The ultimate goal of septic shock resuscitation is improvement of global hypoperfusion [1-4] and lactate normalization is an accepted standard for a successful resuscitation [2,3]. However, perfusion assessment might be a difficult task in critically ill patients. Relevant parameters such as lactate and central venous oxygen saturation (ScvO₂) could occasionally be misleading or non-interpretable [5-7]. On the other hand, occult hypoperfusion may be present despite normal macrohemodynamic parameters [8]. Therefore, a multimodal assessment of the adequacy of resuscitation has been proposed, including a renewed interest in peripheral perfusion [9].

Peripheral perfusion monitoring in the Intensive Care Unit (ICU) has been studied both in the acute and post-resuscitation stages of septic shock [10, 11, 12]. Capillary refill time (CRT) and central-to-toe temperature difference (Tc-toe), among others, have been proposed as objective, reproducible parameters to evaluate peripheral perfusion [12]. Moreover, peripheral perfusion can be severely compromised in this setting, which has been correlated to cardiac output, hyperlactatemia, and organ dysfunction [12].

However, no study has evaluated the temporal profile of changes in peripheral perfusion during severe sepsis and septic shock resuscitation, or has compared the dynamics of evolution of peripheral versus traditional metabolic perfusion parameters. This could provide valuable insights about perfusion monitoring in the critically ill and help to delineate the potential role and limitations of peripheral perfusion as a target for resuscitation.

We hypothesized that in patients with sepsis-related circulatory dysfunction, early recovery of peripheral perfusion parameters is associated with a successful resuscitation at 24 h, in contrast to metabolic perfusion parameters such as ScvO₂ and central venous to arterial pCO₂ gradient [P(cv-a)CO₂].

Our study was aimed at evaluating the evolution of peripheral and metabolic perfusion parameters in patients resuscitated for early sepsis-related circulatory dysfunction. An additional objective was to assess if early improvement in peripheral perfusion parameters could anticipate the presence of normal lactate levels at 24 hours.

Materials and methods

Setting

This prospective observational clinical-physiological study was conducted in the Intensive Care Units of two University Hospitals in Santiago, Chile, from October 2009 to October 2010. The Institutional Review Board of both centers approved this study and waived the requirement of informed consent, because the study design and intervention did not put critically ill patients at unnecessary risk of harm, or deviate from the best standard of care according to the state-of-the-art. According to our Institutional Review Board policy, clinical data can be used for research purposes without disclosing patients’ identities.
Patient selection

All consecutive adult patients admitted to the ICU within two hours of onset of sepsis-related circulatory dysfunction were considered eligible for this protocol.

For the purposes of this study, sepsis-related circulatory dysfunction was defined as the presence of any of the following conditions:
1. Septic shock according to the 2001 Consensus Definition [13].
2. Sepsis-induced hypoperfusion as represented by acute hyperlactatemia irrespective of blood pressure [2]. These patients could also be classified as septic shock according to a more recent consensus [3].

Patients were excluded for ethical reasons or if they presented conditions precluding a correct interpretation of measured parameters. These conditions included any of the following conditions: Do-Not-Resuscitate (DNR) status; life expectancy less than 24 h; pre-existing conditions precluding peripheral perfusion assessment, such as hypothermia, Raynaud disease, severe peripheral vascular disease, among others; severe arrhythmias; pregnancy; uncontrolled hemorrhage; failure of arterial or central venous catheterization; surgery or dialytic procedure anticipated during the study period; and liver failure.

Protocol and measurements

The study period corresponded to the first 24 hours of ICU resuscitation. Patients were considered as successfully resuscitated if they had normal lactate levels (< 2 mmol/l) in addition to stable macrohemodynamics at the end of this period.

All patients were managed according to a local algorithm and entered in a prospective data set. Characteristics of this algorithm have been published elsewhere [14-17]. The protocol was aimed at normalizing perfusion parameters. It included early aggressive source control and fluid loading, followed by norepinephrine (NE) as needed to maintain a mean arterial pressure (MAP) > 65mmHg. Basic monitoring included central venous, arterial and bladder catheters. The attending physicians decided respiratory support and pulmonary artery catheter placement. Fluid loading was guided according to pulse pressure variation in ventilated patients or a classic Starling curve approach in patients with a pulmonary artery catheter in place.

Protocol-related measurements were obtained at baseline (immediately after central venous catheter placement= 0 h), 2, 6 and 24 h. These included:
1. Peripheral perfusion parameters: CRT, Tc-toe, forearm-to-fingertip skin temperature gradient (Tskin-diff), and subjective assessment.
3. Arterial lactate as the standard of successful resuscitation.

Two months before patient enrollment, a group of investigators were trained in a standardized method to assess peripheral perfusion according to previously published studies [11, 12]. Group training sessions included a review of theoretical background, a written checklist, video recording, and supervised patient assessment.
Demographic characteristics and all the variables of Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) were collected for each patient at baseline. Fluid administration, macrohemodynamic parameters (i.e., mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), diuresis), vasopressor requirements and pulmonary artery catheter-derived parameters when applicable, were registered at the pre-established time-points. Changes in SOFA score at 24 hours (dSOFA) and mortality at 28 days were also recorded.

Peripheral perfusion assessment was performed only by the trained investigators as follows:

1. Capillary refill time was measured by applying firm pressure to the distal phalanx of the index finger for 15 seconds. A chronometer recorded the time for return of the normal color at the ventral surface, and 4.0 seconds was defined as the upper normal limit [11, 12].
2. Central-to-toe temperature difference: central temperature was measured by pulmonary arterial catheter or a rectal probe. Great toe temperature was measured on the ventral face with a skin probe. A difference up to 7°C was considered as normal [12].
3. Forearm-to-fingertip skin temperature gradient: obtained from two skin probes attached to the index finger and on the radial side of the forearm, mid-way between the elbow and the wrist. The presence of any temperature gradient was considered as abnormal [12].
4. Subjective assessment: the examiners hands were applied to the anterior surface of the thorax and to the dorsal surface of the foot of the patient. The presence of a perceived temperature gradient (Tthorax-limb) was recorded as 1= absent, 2= mild or 3= marked. The presence of livedo reticularis was recorded as 1= absent, 2= mild or 3= marked. Patients were maintained in closed individual rooms with an active ambient temperature control at 22°C.

**Statistical analysis**

Categorical data were analyzed with Fisher's exact test, and repeated measures with Friedman test. Differences between repeated measures were explored with post-hoc Dunn test. All data are presented as median and interquartile range. All reported p values are two-sided, with a significant alpha level of <0.05. Finally we performed a logistic regression to determine perfusion variables independently associated with a lactate < 2.0 mmol/l at 24 hours. SPSS (SPSS for Windows Release 17.0.0; SPSS Inc, Chicago, IL) package was used for statistical analysis.

**Results**

Forty-one patients fulfilling inclusion criteria were enrolled, of whom 39 survived the 24 h study period and 34 were alive at 28 days. Baseline demographic and physiologic data, as well as severity scores are shown in Table 1. Twenty-seven patients requiring NE were
### Table 7.1 General characteristics of the study population.

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>41</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64 [53-75]</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48.9%</td>
</tr>
<tr>
<td>SOFA at admission</td>
<td>9 [5-11]</td>
</tr>
<tr>
<td>APACHE II</td>
<td>20 [14-24]</td>
</tr>
<tr>
<td>Second day SOFA</td>
<td>7 [5-10]</td>
</tr>
<tr>
<td>PAC</td>
<td>9/41 (22%)</td>
</tr>
<tr>
<td>MV</td>
<td>26/41 (63%)</td>
</tr>
<tr>
<td>Basal lactate level (mmol/l)</td>
<td>3.3 [1.6-4.5]</td>
</tr>
<tr>
<td>Basal MAP (mmHg.)</td>
<td>71.5 [65.7-81.2]</td>
</tr>
<tr>
<td>Basal NE requirements (μg/kg/min)</td>
<td>0.05 [0-0.013]</td>
</tr>
<tr>
<td>First day mortality</td>
<td>2/41 (5%)</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>7/41 (17%)</td>
</tr>
</tbody>
</table>

Values are expressed as median and interquartile range. PAC, pulmonary artery catheter; MV, mechanical ventilation; MAP, mean arterial pressure; NE, norepinephrine.

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**Figure 7.1** Percentage of patients with normal perfusion parameters at each time point.
classified as septic shock, and fourteen presented a sepsis-related hyperlactatemia. The most frequent septic sources were pulmonary and abdominal. On average, patients received 5900cc [4200-7100] of fluids (isotonic crystalloids and colloids) during the study period.

The evolution of peripheral and metabolic perfusion parameters over time is shown in Table 2. Lactate and CRT exhibited a significant decrease at six hours which was maintained at 24 hours, while change in P(cv-a)CO₂ was significant only at the end of the study period. A significantly higher proportion of patients exhibited normal CRT values at two and six hours, as compared to other peripheral and metabolic perfusion parameters as shown in Figure 1.

Thirty patients normalized lactate at 24 hours and 11 did not. When analyzed individually, none of the studied parameters was associated with lactate normalization at 24 h. Nevertheless, 85% of patients who exhibited normal values for both CRT and Tc-toe together at six hours achieved a successful resuscitation at the end of the study period, compared to only 50% of those who did not (p= 0.015). In contrast, normalization of metabolic parameters (ScvO₂, and P(cv-a)CO₂ or both) was not significantly associated with a successful resuscitation (p= 0.48).

After multivariate analysis the presence of normal values of both CRT and Tc-toe (peripheral perfusion) at six hours was independently associated with a successful resuscitation (p= 0.02). In contrast, the normalization of ScvO₂ and P(cv-a)CO₂ at six hours, considered separately or together, did not show a significant association with lactate <2.0 mmol/l at 24 h. Subjective assessment and Tskin-diff exhibited no correlation with the other studied parameters at different time points, when analyzed individually or in different combinations (data not shown). SOFA improvement at 24 h was not associated with changes in any perfusion parameter in this study. The only single parameter significantly associated with 28-day mortality was persistent hyperlactatemia at 24 h.

### Table 7.2 Evolution of perfusion parameters and heart rate over the study period.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 h</th>
<th>6 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate level (mmol/l)</td>
<td>3.3 [1.6-4.5]</td>
<td>2.5 [1.2 - 4.2]</td>
<td>2.4 [1-3.1] *</td>
<td>1.4 [1-2.2] *</td>
</tr>
<tr>
<td>P(cv-a)CO₂ (mmHg)</td>
<td>6 [4.1-8]</td>
<td>5 [4-7.2]</td>
<td>4 [3-7]</td>
<td>3.7 [2.5-5.7] *</td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>75 [64-81]</td>
<td>75 [65-78]</td>
<td>74 [69-82]</td>
<td>77 [72-80]</td>
</tr>
<tr>
<td>Tc-toe (°C)</td>
<td>6.7 [4.7-9.8]</td>
<td>6.9 [3.7-9.7]</td>
<td>6 [4-9]</td>
<td>4.7 [2.3-7.2]</td>
</tr>
</tbody>
</table>

*: p<0.05 for comparison with values at 0 hr. Values are expressed as median [inter-quartile range]. P(cv-a)CO₂, central venous to arterial pCO₂ gradient; ScvO₂, central venous oxygen saturation; CRT, capillary refill time; Tc-toe, Central-to-toe temperature difference.
Discussion

The main finding of our study was that early recovery of peripheral perfusion might predict successful resuscitation at 24 h in patients with sepsis-related circulatory dysfunction. Among all the studied perfusion parameters, capillary refill time exhibited the earliest normalization. Thus, serial peripheral perfusion monitoring appears as a simple but powerful tool to assess global resuscitation status.

Although forty years ago Weil et al. reported the prognostic value of an increased central-to-toe temperature difference in critically ill patients [10], the subject of peripheral perfusion assessment during septic shock resuscitation has been only recently re-addressed. Kaplan et al. retrospectively demonstrated a good correlation between subjective skin temperature, hemodynamic and metabolic parameters in a heterogeneous group of surgical ICU patients [11]. Subsequently, Lima et al. proposed a standardized quantitative clinical assessment of peripheral perfusion [12]. An abnormal peripheral perfusion as demonstrated by this approach was associated with hyperlactatemia and predicted a worsening SOFA score at 48 hours. More recently, Boerma et al. found no relation between Tc-toe and microcirculatory dysfunction in septic patients [18], although more studies exploring the relationship between microcirculation and peripheral perfusion are clearly needed [19]. We believe that the main difference between this and previous studies is the focus on dynamic changes in peripheral perfusion along the course of severe sepsis resuscitation.

To our knowledge, this is the first study to address the dynamic association between metabolic and clinical perfusion parameters in sepsis-related circulatory dysfunction. We found that most of the evaluated parameters changed in parallel and improved significantly at 24 hours as expected after ICU resuscitation. However, CRT was normalized at two and six hours in a significant proportion of patients, notably earlier than any other parameter during the study period. Of special note was that the presence of normal values for both CRT and Tc-toe at six hours was significantly associated with successful resuscitation, while ScvO₂ and P(cv-a)CO₂ were not, as confirmed by multivariate analysis. The behavior of

<table>
<thead>
<tr>
<th>Hour</th>
<th>Lactate &gt;2 mmol/l</th>
<th>P(cv-a)CO₂ &gt;6 mmHg</th>
<th>CRT &gt;4s</th>
<th>Tc-toe &gt;6°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65% (15/23)</td>
<td>26% (6/23)</td>
<td>48% (11/23)</td>
<td>57% (13/23)</td>
</tr>
<tr>
<td>2</td>
<td>63% (15/24)</td>
<td>29% (7/24)</td>
<td>29% (7/24)</td>
<td>63% (15/24)</td>
</tr>
<tr>
<td>6</td>
<td>70% (16/23)</td>
<td>39% (9/23)</td>
<td>17% (19/23)</td>
<td>48% (11/23)</td>
</tr>
<tr>
<td>24</td>
<td>29% (9/31)</td>
<td>23% (7/31)</td>
<td>13% (4/31)</td>
<td>39% (12/31)</td>
</tr>
</tbody>
</table>

Values are expressed as percentage of patients exhibiting an abnormal perfusion parameter at different time points in a subgroup of patients with already normal ScvO₂ values.

P(cv-a)CO₂, central venous to arterial pCO₂ gradient; ScvO₂, central venous oxygen saturation; CRT, capillary refill time; Tc-toe, Central-to-toe temperature difference.
Tc-toe is interesting since although it did not per se show statistically significant changes during the first hours, when added and interpreted together with a normal CRT, it may add valuable information about resuscitation status. Thus, according to our results, non-invasive clinical evaluation integrating skin temperature gradients and CRT may be used as surrogates of more invasive and complex monitors, at least during initial resuscitation. This could be an important contribution to pre-hospital and emergency department (ED) management.

Another interesting finding was that heart rate decreased almost in parallel with the other perfusion parameters along the study period. Although it is beyond the scope of this study to address a potential mechanistic relationship between these phenomena, it makes physiological sense. In fact, both tachycardia and peripheral vasoconstriction are consequences of the adrenergic stress response. Moreover, a role of epinephrine as a trigger of aerobic glycolysis and massive lactate production during circulatory stress has been nicely demonstrated by Levy et al. [20]. Therefore, as resuscitation goes on, an improvement in peripheral perfusion, lactate and tachycardia, may reflect a flow-driven decrease in adrenergic tone. Future studies should evaluate the potential role of heart rate as a surrogate of adrenergic tone in the setting of multimodal perfusion monitoring.

Despite this sound body of evidence, surprisingly, clinical assessment of perfusion has not attained a definite role in current septic shock resuscitation guidelines [2]. Several concerns about peripheral perfusion evaluation have been raised, including inter-observer variability, dispersion of normal values, influence of ambient temperature, the need for central temperature determinations, and feasibility in certain settings [21, 22]. We acknowledge these limitations and the fact that this kind of evaluation cannot be universally implemented. Nevertheless, we confirmed that peripheral perfusion assessment using a standard protocol by trained personnel is feasible in the clinical ICU setting.

Since our study was designed as an acute clinical-physiological study, it was beyond our scope to analyze the prognostic significance of a persistent abnormal peripheral perfusion, a subject elegantly addressed by Lima et al. in a recent study [12]. Nevertheless, the finding that improvement in peripheral perfusion is associated with an 85% probability of a normal lactate level at 24 h, appears to be relevant since in concordance with other studies [23,24], persistent hyperlactatemia was associated to a higher probability of 28-day mortality. One could argue that there are some patients (15%) who despite having normalized peripheral perfusion parameters do not clear lactate at 24 h but this concern could be also applicable to other traditional parameters such as ScvO\textsubscript{2} or $P(\text{cv-a})\text{CO}_2$, which exhibited a worse behavior. As a matter of fact, a recent study by Vallee et al. found a persistent elevated $P(\text{cv-a})\text{CO}_2$ in 50% of resuscitated septic patients with already normal ScvO\textsubscript{2} values [6]. Therefore, our data reinforce the need for a multimodal monitoring approach and in this sense peripheral perfusion may add valuable complementary information concerning resuscitation trend.

Our results should not be interpreted under any circumstance as a signal to stop resuscitation when peripheral perfusion has been normalized. Improvement in peripheral perfusion simply implies that resuscitation is moving in the right direction and should...
be continued until the background resuscitation goal, such as lactate clearance, has been achieved. On the contrary, a failure to improve peripheral perfusion should alert physicians about a possible inadequate source control or resuscitation strategy.

Our study has several limitations. The reduced number of patients is an important issue and our findings should be confirmed in a larger multicenter study before being translated into regular clinical practice. Second, the study period may be considered not long enough to evaluate other relevant clinical outcomes and the selected time points are arbitrary. Third, we included heterogeneous patients with potential underlying subgroups presenting different patterns of recovery. Fourth, the study was conducted by a reduced number of trained evaluators, thus eventually introducing bias and limiting extrapolation of results. Fifth, the evaluated hemodynamic parameters could be considered insufficient. On the other hand, some of the drawbacks mentioned could be considered as assets, in terms that a reduced number of patients makes significant findings more difficult to attain, so our results are truly relevant; a reduced but diverse number of operators may reduce interobserver bias since peripheral perfusion assessment was performed under more similar conditions and training, although we did not evaluate it formally; lastly, the heterogeneity of the study population makes our findings more generalizable to a general ICU context.

There is another potential limitation that deserves some special considerations, the lack of sample size calculation. Before launching this study, an extensive review of current literature provided no background data over which we could build up a sample size calculation. Indeed, previous studies addressing the subject of peripheral perfusion [11,12,18], exhibit a completely different design since they performed single, static, nonserial assessments of peripheral perfusion. In contrast, our study was aimed at comparing the dynamics of evolution of peripheral vs. metabolic parameters over time, assessing both mean values at baseline, 2, 6 and 24 hrs, and also the specific proportion of patients with normal values at each time point (Figure 1). Since no serial assessment was performed in the studies cited above, we had no previous data concerning the dynamics of recovery for each parameter. Nevertheless, we did include a number of patients similar to those admitted in some previous published reports, i.e. 35 to 50 (12,18). Additionally, and more importantly, we found statistically significant differences, and therefore the probability of type 1 error is fairly low independently of the additional number of patients that could have been included. For non-significant findings, our study may be used for future sample size calculations.

Our results open up several potential research pathways. Additional modalities of perfusion assessment could be explored to contrast their evolution with the proposed clinical evaluation. Of particular physiological interest could be the assessment of parallel changes in microcirculatory flow and microvascular reactivity in this setting [25, 26]. Eventually, this may lead to a better understanding of the complex dynamic interrelationship between clinical, hemodynamic, metabolic, regional, and microcirculatory parameters during septic shock resuscitation [27].
Conclusions

Early recovery of peripheral perfusion assessed by non-invasive, simple techniques at bedside was associated with normal lactate levels at 24 h during sepsis resuscitation. In contrast, the evolution of perfusion-related metabolic parameters was not clearly associated to a successful resuscitation. Our findings support a role for serial peripheral perfusion assessment and suggest that it should be incorporated into future multimodal monitoring strategies for septic shock resuscitation.

References


