A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock?

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Abstract

Purpose
The prognostic value of hyperlactatemia in septic shock is unquestionable. However, as current definitions do not include hyperlactatemia as a mandatory criterion, some hypotensive patients may be diagnosed as septic shock despite exhibiting normolactatemia. The significance of persistent sepsis-induced hypotension without hyperlactatemia is unclear. Is it really septic shock? Our aim was to determine differences in outcome between patients diagnosed as septic shock but exhibiting normal vs. elevated lactates during evolution. We also explored the potential implications of including hyperlactatemia as an obligatory diagnostic criterion.

Methods
Retrospective analyses on a cohort of 302 septic shock patients

Results
When we divided patients according to the presence of hyperlactatemia, 34% evolved without hyperlactatemia and exhibited a very low mortality risk (7.7% compared to 42.9% of those with hyperlactatemia). These patients also presented less severe organ dysfunctions, higher ScvO₂ values and required lower norepinephrine doses. The potential inclusion of hyperlactatemia in septic shock definition would reduce incidence in 34% but increase absolute mortality risk in 11%.

Conclusions
Persistent sepsis-induced hypotension without hyperlactatemia may not constitute a real septic shock. Our results support the need to review the current definition of septic shock. Hyperlactatemia could represent an objective parameter worth to be explored as a potential diagnostic criterion for septic shock.
Introduction

Septic shock exhibits a highly variable mortality in the range of 30 to 80% across epidemiologic and therapeutic studies [1]. This extreme variability has been attributed to an intrinsic heterogeneity of septic shock patients [1-2]. However, a complementary explanation could be the use of non-equivalent definitions [3-5].

Indeed, 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. Several definitions including new categories within the spectrum of septic circulatory dysfunction have been recently proposed (e.g. cryptic shock [6], occult hypoperfusion [7], non-sustained hypotension [8]), although none has been prospectively validated or gained universal acceptance [3-9].

The 1991 ACCP-SCCM consensus included both volume-refractory hypotension and perfusion abnormalities as obligatory components of a septic shock definition [3]. Lactic acidosis, acute mental changes or oliguria were mentioned as potential surrogates of perfusion abnormalities [3], suggesting a bioequivalence between these parameters, an assumption that subsequently has never been tested. Moreover, a simplified definition relying mainly on vasopressor requirements has been broadly used over the last decade (2001 consensus definition) [4]. In addition, the Surviving Sepsis Campaign (SSC) guidelines grouped septic shock, hyperlactatemia and oliguria as equally representing sepsis-induced tissue hypoperfusion [5]. Thus, not surprisingly highly variable diagnostic criteria have been used in recent major trials [10-16], a fact which may have important implications for clinical and epidemiologic research.

Recently, several clinical and experimental studies have addressed the physiological meaning of hyperlactatemia in shock and reinforced its prognostic value [17-20]. Therefore, current guidelines strongly recommend serial lactate monitoring [5]. However, some hypotensive septic patients never develop hyperlactatemia. The strong efforts to detect and understand hyperlactatemia are in sharp contrast with our poor understanding of what normal lactate levels represent in patients undergoing sepsis-induced hypotension. True septic shock may increase lactate levels by compromising several steps involved in lactate generation and metabolism. Therefore, the maintenance of normal lactate levels in vasopressor-requiring patients may represent a different physiologic stage in the setting of sepsis-related circulatory dysfunction.

We hypothesized that the outcome of patients with sepsis-induced hypotension but with normal lactate levels does not correspond to the severity expected for septic shock. Therefore, we designed a hypothesis-generating study to determine differences in outcome between patients with persistent sepsis-induced hypotension evolving without hyperlactatemia as compared to those presenting hyperlactatemia during evolution. In addition, we addressed the potential implications of including hyperlactatemia as an obligatory diagnostic criterion for septic shock.
**Material and methods**

We performed several retrospective analyses on a cohort of 302 septic shock patients treated during a 6 year-period from March 2002 through March 2008. For operative purposes, septic shock was defined as a state of severe sepsis developing persistent volume-refractory hypotension and thus requiring vasopressors (2001 consensus definition) [4]. According to our Institutional Review Board (IRB) policy, clinical data can be analyzed without disclosing patient’s identities.

We included all consecutive septic shock patients with confirmed infectious foci requiring vasopressors for at least 4 hours during ICU-based resuscitation. All patients committed to full resuscitation were managed according to a local algorithm and entered in a prospective dataset, with the aim of building a framework to assess compliance, perform quality control, and evaluate the potential impact of novel therapies added over time. The IRB approved this management protocol and relatives or surrogates signed an informed consent to be treated in the ICU according to standard care including this algorithm.

The protocol was aimed at normalizing perfusion parameters. It included early aggressive source control and fluid loading, followed by norepinephrine (NE) to maintain a mean arterial pressure (MAP) > 65 mmHg. Septic patients presenting a circulatory dysfunction in the emergency department (ED) or the pre-ICU service were subjected to vigorous fluid resuscitation followed by central venous catheter insertion, and basal measurements of lactate (Radiometer ABL 735, Copenhagen Denmark) and central venous O₂ saturation (ScvO₂). If developing persistent hypotension or hyperlactatemia, patients were transferred to the ICU, where perfusion parameters were measured at least every 4 hours during the first ICU day and then every six hours during the first 72 hours. Additional volume was guided by a Starling-curve approach in the early period but more recently was indicated according to dynamic predictors or bedside echocardiographic assessments. Complementary therapies were implemented over time according to specific indications. Mechanical ventilation (MV) and sedation were managed according to current protective strategies. Different aspects and results of our management algorithm have been published elsewhere [21-24]. In summary, every patient had an initial pre-ICU lactate assessment and then at 0, 4, 8, 12, 16, 20, 24 hrs during the first ICU day, and every 6 hrs thereafter, until normalization or death. A normal range of 0.1-2.4 mmol/l is accepted according to our laboratory standards. Therefore, a lactate of ≥ 2.5 mmol/l is considered as elevated, a cut-off recently revalidated by Shapiro et al. [25]

Three- hundred and two patients fulfilled our inclusion criteria. We divided this cohort according to the presence or not of hyperlactatemia during the whole evolution and compared the resulting subgroups for differences in mortality and other clinical relevant variables. Additionally, we applied two different definitions of septic shock to the same cohort, one including hyperlactatemia as an obligatory qualifier and the other not, and observed for potential changes in 28-day mortality, incidence and other clinical variables.
Statistical analysis

Continuous variables were compared between subgroups using t-test and categorical values using chi-square test. Results are expressed as mean ± SD and a probability value < 0.05 was considered as statistically significant. SPSS 17.0 (Chicago IL, USA) statistical software was used.

In addition, we used fractional polynomials analyses in order to examine continuous predictors, because of their sensitivity to non-straight relationships between continuous variables. This more complex statistical analysis was performed using Stata 11 (StataCorp, College Station, TX. USA) statistical package.

Results

The 302 patients (mean age 61.0 ± 17.5 yrs; basal APACHE II score 19.7 ± 7.2; peak SOFA score 9.6 ± 3.9; MV 84.1%) presented more frequently abdominal (44.7%) and respiratory septic sources (26.8%), with an ICU length of stay (LOS) of 9.6 ± 9.5 days and a 28-day mortality of 30.8% (93 patients). As a whole they used NE for 62 ± 12 hrs without differences between subsequent compared subgroups.

When we categorized patients according to the presence of hyperlactatemia, 198 patients presented at least one lactate value ≥ 2.5 mmol/l during evolution (66%) and 104 did not (34%). Although no differences in basal comorbidities or sources of infection between these subgroups were found, they exhibited highly significant statistical differences in severity scores, outcome and other biochemical parameters (Table 1 and Figure 1).

Figure 3.1 Kaplan-Meier survival curves of septic shock patients classified according to the presence or not of hyperlactatemia.

Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock?
<table>
<thead>
<tr>
<th></th>
<th>Lactate-depending definition (n=198)</th>
<th>2001 consensus definition (n=302)</th>
<th>p</th>
<th>Lactate &lt;2.5 mmol/l (n=104)</th>
<th>Lactate ≥2.5 mmol/l (n=198)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.5 ± 17.4</td>
<td>61.0 ± 17.4</td>
<td>0.7</td>
<td>61.9 ± 17.5</td>
<td>60.5 ± 17.4</td>
<td>0.5</td>
</tr>
<tr>
<td>APACHE II</td>
<td>21.1 ± 7.1</td>
<td>19.7 ± 7.2</td>
<td>0.001 *</td>
<td>17.0 ± 6.6</td>
<td>21.1 ± 7.1</td>
<td>0.0001 *</td>
</tr>
<tr>
<td>Peak SOFA</td>
<td>10.6 ± 3.9</td>
<td>9.6 ± 3.9</td>
<td>0.1</td>
<td>7.8 ± 3.2</td>
<td>10.6 ± 3.9</td>
<td>0.0001 *</td>
</tr>
<tr>
<td>Mortality n (%)</td>
<td>85 (42.9)</td>
<td>93 (30.8)</td>
<td>0.005 † *</td>
<td>8 (7.7)</td>
<td>85 (42.9)</td>
<td>0.0001 † *</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>9.8 ± 10.0</td>
<td>9.6 ± 9.6</td>
<td>0.2</td>
<td>9.3 ± 8.6</td>
<td>9.7 ± 10.0</td>
<td>0.7</td>
</tr>
<tr>
<td>MV (days)</td>
<td>6.2 ± 7.5</td>
<td>6.1 ± 7.9</td>
<td>0.4</td>
<td>5.7 ± 8.7</td>
<td>6.2 ± 7.5</td>
<td>0.6</td>
</tr>
<tr>
<td>MV n (%)</td>
<td>148 (86)</td>
<td>217 (84)</td>
<td>0.3</td>
<td>69 (79.3)</td>
<td>148 (86.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>NE max (µg/K/min)</td>
<td>0.59 ± 1.1</td>
<td>0.45 ± 0.9</td>
<td>0.1</td>
<td>0.17 ± 0.14</td>
<td>0.59 ± 1.1</td>
<td>0.0001 *</td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>63.6 ± 9.7</td>
<td>64.6 ± 9.4</td>
<td>0.3</td>
<td>66.7 ± 8.6</td>
<td>63.6 ± 9.7</td>
<td>0.04 *</td>
</tr>
<tr>
<td>Peak lactate (mmol/L)</td>
<td>6.2 ± 3.6</td>
<td>4.7 ± 3.6</td>
<td>0.001 *</td>
<td>1.6 ± 0.4</td>
<td>6.2 ± 3.6</td>
<td>0.0001 *</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>188 ± 93</td>
<td>197 ± 98</td>
<td>0.2</td>
<td>215 ± 106</td>
<td>189 ± 93</td>
<td>0.04 *</td>
</tr>
<tr>
<td>Platelets (1.000/mL)</td>
<td>82 ± 70</td>
<td>111 ± 110</td>
<td>0.0001 *</td>
<td>170 ± 147</td>
<td>82 ± 70</td>
<td>0.0001 *</td>
</tr>
<tr>
<td>Creatinine (md/dl)</td>
<td>3.2 ± 3.8</td>
<td>2.9 ± 3.5</td>
<td>0.1</td>
<td>2.3 ± 2.6</td>
<td>3.1 ± 3.8</td>
<td>0.06</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>25 ± 11</td>
<td>26 ± 11</td>
<td>0.1</td>
<td>27 ± 12</td>
<td>25 ± 11</td>
<td>0.1</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>4.5 ± 7.0</td>
<td>3.7 ± 6.3</td>
<td>0.09</td>
<td>1.9 ± 3.9</td>
<td>4.4 ± 7.0</td>
<td>0.008 *</td>
</tr>
</tbody>
</table>

**Lactate-depending definition:** septic volume-refractory hypotension plus hyperlactatemia as an obligatory qualifier; **2001 consensus definition:** septic volume-refractory hypotension regardless of lactate levels; **APACHE II** Acute Physiology and Chronic Health Evaluation score II on ICU admission; **SOFA** Sequential Organ Failure Assessment score; **Mortality** 28-day mortality; **LOS** length of stay; **MV** mechanical ventilation; **NE max** peak norepinephrine dose; **ScvO₂** central venous O₂ saturation lowest value; **CRP** C-reactive protein; **Platelets, creatinine and bilirubin** worst values.

† Statistics computed using Chi-square test.

Values expressed as mean ± SD, p<0.05 considered as significant (*).

* p <0.05
After adjusting for APACHE II and SOFA scores, hyperlactatemia remained as a powerful predictor of death in the logistic regression model. Preexistent chronic liver disease, a condition potentially confounding lactate interpretation, was not related to outcome \((p=0.98)\). Multivariate analysis adjusting for demographics, vasopressor requirements, ScvO\(_2\), mechanical ventilation and comorbidities (including liver disease) showed that only age and hyperlactatemia were significantly associated with mortality \((p<0.002)\).

To better address the relationship between lactate levels and survival probability, we performed fractional polynomials analyses where the statistical significance of lactate as a predictor of survival remains \((p<0.001)\). Survival clearly decreases as lactate levels increase, in a practically lineal relationship (Figure 2).

When analyzing for quartiles of lactate \((0.2 \text{ to } 16 \text{ mmol/l})\), mortality exhibited stepwise increments for each quartile \((from 15.64 \text{ up to } 87.5\% \ (p=0.0001))\).

One hundred and sixteen patients \((59\%)\) presented an early (admission) peak lactate value, and 82 \((41\%)\) exhibited a delayed peak value \((20\pm12 \text{ hrs})\) within the hyperlactatemia group. Although both subgroups exhibited higher mortality than patients without hyperlactatemia, the former registered a better prognosis \((37 \text{ vs. } 61\% \text{ 28-day mortality; } p<0.0015)\). Interestingly, 19 patients presenting a delayed peak lactate exhibited a normal value at admission. These patients were indistinguishable within the hyperlactatemia subgroup in several baseline characteristics such as age, comorbidities, source, severity and perfusion parameters. Taken together with the 104 patients who never increased lactate, 19 of 123 patients \((15\%)\) presenting normolactatemia at admission, increased lactate later during ICU evolution.

When we applied two different definitions of septic shock to the same cohort, one including hyperlactatemia as an obligatory qualifier (lactate-depending definition) and the

\[\text{Figure 3.2 Fractional Polynomial analysis (Lactate vs. 28-day survival).}\]
other not (2001 consensus definition), we also found important differences in incidence and clinical outcomes. One-hundred and ninety-eight patients would have been classified as septic shock during the 6-years period if using the lactate-depending definition, contrasting to the whole cohort of 302 patients when using the 2001 consensus definition (a 34% lower incidence with the former). Twenty-eight day mortalities for both definitions were 42.9% and 30.8%, respectively (p<0.01) (Table 1 and Figure 3).

**Discussion**

We studied a cohort of 302 patients fitting the 2001 consensus definition [2]. When categorized by the presence of hyperlactatemia, two subgroups with major differences in severity and outcome could be identified, remarkably exhibiting a 35% absolute difference in mortality. At least one-third of these patients evolved with a persistent circulatory dysfunction without hyperlactatemia and although requiring intensive treatment (e.g. 79% MV and > 48 hrs of NE), exhibited a very low mortality rate and may not qualify for a true septic shock diagnosis. Adding hyperlactatemia as an obligatory diagnostic criterion to septic shock definition may reduce the incidence of disease in 34% but increase absolute mortality risk in 11%.

Our results reveal the complexities involving septic shock definitions. In fact, the pragmatic 2001 consensus definition with major or minor adaptations has been used in many septic shock studies [10,13-16]. Only two trials considered hyperlactatemia as a specific hypoperfusion-related inclusion criterion in concordance with the 1991 ACCP-SCCM consensus suggestions. In the EGDT study, septic patients presenting volume-refractory hypotension or

![Figure 3.3 Kaplan-Meier survival curves of septic shock patients classified according to two definitions: one involving hyperlactatemia as an obligatory qualifier (lactate-depending definition) and the other not (2001 consensus definition).](image-url)
hyperlactatemia > 4 mmol/l were recruited [11]. The French steroid multicentric trial included hyperlactatemia among obligatory entry criteria, although this status was changed to optional by a later amendment [12]. The control arms of these 2 trials exhibited basal lactates of 6.9 ±4.5 and 4.3±4.3 mmol/l, respectively and presented very high mortalities (49-61%). In contrast, other important studies using an adapted 2001-consensus definition, exhibited both lower basal lactates (range 2.5-3.5 mmol/l) and mortalities (range 29-39%) in their control arms [13,14,16]. Thus, as expected, definitions including lactate may lead to selection of patients with higher risk of death. In this sense our results are obvious, but what is rather surprising is that very important research trials have used the broad 2001 consensus definition [10,13-16], therefore inevitably mixing up patients with and without hyperlactatemia, and thus with a dramatic heterogeneity in risk of death. As a matter of fact, some controversial therapies may only show efficacy in more severely ill patients (e.g. the PROWESS trial [10]) and this potential effect could be neglected by using a less stringent definition. The fact that mortality steadily increased in an almost linear relationship with lactate, may justify a reappraisal of current definitions.

Our results confirm that even a single elevated lactate level confers a higher mortality risk, although in concordance with other studies [26], patients who cleared admission hyperlactatemia over time did better than those presenting a progressive increment. The strong and independent prognostic value of hyperlactatemia was confirmed by univariate and multivariate analyses. On the other hand, the fact that 15% of vasopressor-requiring septic patients increased lactate during resuscitation should not preclude the potential inclusion of hyperlactatemia as a necessary diagnostic criterion for septic shock. Indeed, the transition of patients into different stages of severity during ICU stay is very frequent. As examples, patients with sepsis can evolve into severe sepsis or septic shock; or patients admitted with acute lung injury (ALI) can evolve into full ARDS. Unfortunately, no single basal parameter could positively identify patients who later increased lactate in our study. This fact reinforces the necessity of serial monitoring and awareness of such possible transition for an early recognition and additional resuscitation [5].

It was beyond our scope to explore the physiologic meaning of our findings. Moreover, the true physiologic significance of lactate has been recently matter of debate and research [17-20]. Serum lactate levels represent the balance between massive production and consumption during circulatory dysfunction. Thus, the maintenance of normal serum levels may represent a state of physiologic compensation eventually implying an adequate peripheral perfusion and mitochondrial function, a preserved hepatosplanchnic perfusion or clearance, and a physiologic adrenergic tone [17-20]. In contrast, progressive hyperlactatemia may reflect a failure of any or all of these aspects, thus representing the collapse of the compensatory response and a real progressive shock state. This speculation may contribute to explain the lactate paradox: a physiologic protective molecule contrasting with the very poor prognosis associated with progressive hyperlactatemia.

The preceding concepts may give theoretical support for including lactate into septic shock definitions. Indeed, one of the most interesting aspects of our results was the very low mortality of the subgroup of patients that maintained normal lactate levels even while...
requiring vasopressor support (7.7% compared to 42.9% in those with hyperlactatemia). These patients also exhibited less severe organ dysfunctions, higher ScvO₂ values and required lower doses of NE, probably representing a minor expression of sepsis-related circulatory dysfunction and not real septic shock. In fact, their evolution and outcome are almost incompatible with a physiological definition of shock. This low mortality risk although surprising is consistent with the reports of Howell et al. involving hypotensive septic patients without hyperlactatemia [7], and Marchick et al. addressing non-sustained hypotension [8].

The potential inclusion of lactate as an obligatory diagnostic criterion in future septic shock definitions could also have relevance in clinical and epidemiological research. For instance, research power calculations are based on estimates of mortality risk. If the use of the 2001-consensus definition vs. a lactate-depending definition leads to more than a 10% difference in the probability of death, this fact could induce an inappropriate sample size calculation and therefore, may distort results in unpredictable ways.

Our message should not be interpreted under any circumstance as a signal to reserve aggressive resuscitation and source control only for patients with hyperlactatemia. As stated above, all patients with clinical manifestations of sepsis-related circulatory dysfunction, including early hyperadrenergia, sustained or non-sustained hypotension, should receive adequate treatment (e.g. early goal directed therapy), monitoring, and triage irrespective of lactate levels. In our opinion, this stage of early sepsis-related circulatory dysfunction can evolve into a persistent septic-induced hypotension after initial resuscitation, a stage that should be classified as septic shock if developing hyperlactatemia at least for research, epidemiological and clinical purposes. As a clinical consequence, patients with progressive hyperlactatemia should be subjected to additional evaluation (e.g. inadequate resuscitation, microcirculatory dysfunction, hepatosplanchnic hypoperfusion, pathologic adrenergic response, etc.) and treatment. Patients without hyperlactatemia, although representing a minor expression of sepsis-related circulatory dysfunction and probably a compensated physiologic state, should nonetheless be carefully monitored and treated until complete resolution.

A potential objection for the inclusion of lactate in a septic shock definition is the lack of specificity of hyperlactatemia as a marker of tissue hypoperfusion, a problem unfortunately shared by most of other potential markers such as peripheral vasconstriction, oliguria, mental changes and even hypotension. In the case of hyperlactatemia several conditions not necessarily related to global hypoperfusion may be involved. Among them we could mention necrotic foci, liver failure, unresolved infection or hyperinflammation [8]. However, the present and previous studies confirm the strong and independent prognostic value of hyperlactatemia in the setting of sepsis-related circulatory dysfunction [11,12,25-27], but more importantly hyperlactatemia may constitute a signal of physiologic descompensation. Therefore, it mandates not only a resuscitative approach specially during the first 24 hrs, but also parallel efforts to pursue definitive source control (radiologic images, cultures) and biochemical/hematological analyses that may help to rule out a non-hypoxic related hyperlactatemia. We acknowledge that it may be difficult to isolate lactate as “the variable” to define a septic shock condition but doubtless it is a critical parameter.
Our study has several other limitations including the retrospective analysis; the inclusion of patients from a single center; the complexity of comparing two populations that are not independent cohorts (performed here as an exercise for the 2 potential definitions); the controversial cut-off value for a “normal” lactate [27]; the possibility of having missed some high lactate values between sampling; and the lack of long-term outcome data (e.g. 90 days mortality). Nevertheless, we believe that our results are valuable and may contribute for a reappraisal of current definitions.

Conclusions

According to our results, hyperlactatemia appears as an objective parameter worthy to being prospectively explored and validated as a potential obligatory diagnostic criterion for septic shock. Addressing this subject may be relevant for research and epidemiologic arenas and also for clinical management. The clinical and physiologic significance of maintaining normal lactate levels during circulatory stress should also be explored.

References


