A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
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Perfusion parameters exhibit markedly different recovery time courses throughout resuscitation in a cohort of septic shock survivors

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Abstract

Objectives
Several parameters have been used to monitor perfusion status or as potential resuscitation goals in septic shock under the assumption that they are flow-responsive. However, little is known about the specific recovery time course of individual parameters a fact that appears as relevant to select the most appropriate target at different time-points. We assessed the recovery time course for hemodynamic, peripheral, metabolic and microcirculatory parameters during early intensive care unit based resuscitation.

Design
A prospective observational clinical study.

Setting
A 16-bed mixed intensive care unit in a university hospital

Patients
Thirty-five septic shock patients with hyperlactatemia, mechanical ventilation and less than 2 h of evolution were originally included but final analysis was performed only in the 31 hospital-survivors.

Interventions
Patients were evaluated with a multimodal perfusion monitoring protocol.

Measurements and main results
Macrohemodynamic, metabolic, peripheral, and sublingual microcirculatory perfusion parameters were evaluated at baseline, 2, 6 and 24 after starting intensive care unit-based resuscitation. Some variables such as central venous oxygen saturation, central venous-arterial pCO$_2$ gradient, capillary refill time, thenar tissue oxygen saturation were already normal in more than 70% of survivors after 6 six hours of resuscitation. Lactate presented a much slower recovery trend, decreasing significantly at 6 h compared to baseline ([2.7 [2.2–3.9] vs. 4.0 [3.0–4.9] mmol/l p<0.01), but with only 48% of patients achieving normality at 24 h. Sublingual microcirculatory parameters exhibited the slowest recovery rate with persistent moderate derangements still present in almost 80% of patients at 24 h (proportion of perfused vessels 77% [68–84], and microvascular flow index 2.2 [2.0–2.5]).

Conclusions
Perfusion parameters exhibit markedly different recovery rates in response to early resuscitation in septic shock surviving patients. The recovery time course of microcirculatory abnormalities in survivors seems to be the slowest among all perfusion parameters.
Introduction

During the past decades, several parameters such as gastric tonometry [1,2], lactate [3,4], mixed (SvO₂) [5] or central venous oxygen saturations (ScvO₂) [4,6], peripheral perfusion [7,8], oxygen tissue saturation (StO₂) [9,10] and central venous-arterial pCO₂ gradient (P(cv-a)CO₂) [11,12] have been used to monitor perfusion status or as potential resuscitation goals in septic shock [1-12]. More recently, the pathophysiological relevance of septic-related microvascular dysfunction has been highlighted [13,14] and trials testing microcirculatory-oriented therapeutic strategies start to appear in the literature [15].

Currently recommended septic shock treatment strategies are based on the assumption that perfusion variables will improve after increasing oxygen transport (TO₂) mainly by cardiac output manipulation, a concept that can be defined as flow-responsiveness [4,6,16]. However, parameters traditionally considered as representing tissue perfusion can also be mechanistically determined by non-flow dependent or mixed mechanisms [17,18]. This may result in a wide variability in the recovery time courses of individual parameters after TO₂ optimization depending on the predominant pathogenic mechanism. This aspect has not been well addressed in experimental or clinical studies, although it seems to be important in order to determine the most appropriate target at different time-points. Parameters such as ScvO₂ [6] and P(cv-a)CO₂ [11] tend to improve rapidly after initial fluid resuscitation but others such as lactate may exhibit variable response curves depending on the relative preponderance of hypoxic versus non-hypoxic pathogenic mechanisms [17-19]. Furthermore, the dynamics of recovery of microcirculatory variables during septic shock resuscitation has only recently begun to be revealed [14].

In fact, pursuing complete normalization of a perfusion goal with repeated attempts to increase TO₂ without considering the above-mentioned aspects could also impose harm since it may induce fluid overload, pulmonary edema, intraabdominal hypertension, cardiac arrhythmias and myocardial ischemia, thus eventually increasing morbidity and mortality [20-22].

We hypothesized that perfusion parameters exhibit markedly different recovery time courses resulting in varying degrees of normalization throughout the first 24 h of resuscitation. If potential resuscitation targets demonstrate a time-dependent recovery, this fact could be clinically relevant to determine the most appropriate goal at different time-points. Eventually the proper target can change over time depending on the degree of flow-responsiveness of individual parameters.

To address this subject, we designed a prospective observational study to assess the recovery time course for hemodynamic, peripheral, metabolic and microcirculatory parameters during early intensive care unit (ICU)-based resuscitation in a cohort of septic shock patients evaluated with a multimodal perfusion monitoring protocol. We were particularly interested a priori in describing the normalization of these parameters at different time-points in the subgroup of hospital survivors.
Materials and methods

Setting
We conducted an 18-month prospective observational study from April 2010 to September 2012 in a mixed 16-bed ICU at our University Hospital. The Institutional Review Board of our University approved this study and waived the need of an informed consent because of the observational nature of the study including no study-related invasive monitoring techniques, and considering that it did not deviate from the best standard of care.

Patient selection
All consecutive adult patients admitted to the ICU within two hours of onset of septic shock according to the 2001 Consensus Definition [23], with a basal arterial lactate >2 mmol/l, and requiring to be mechanically ventilated at or before admission, were considered eligible for the study. Mechanical ventilation was required as an inclusion criterion to facilitate sublingual microcirculatory assessment.

Patients were excluded if they had no commitment for full resuscitation, a do-not-resuscitate status or life expectancy less than 24; or if they presented conditions precluding a correct interpretation of measured parameters, such as uncontrolled hemorrhage or end-stage chronic liver failure.

Protocol and measurements
Patients were studied for the first 24 hours following start of ICU-based resuscitation. Outcome was followed until hospital discharge.

All patients were managed according to a local algorithm. Characteristics of this algorithm have been published previously [24] and include early aggressive source control and fluid loading, followed by norepinephrine (NE) as needed to maintain a mean arterial pressure (MAP) ≥ 65mmHg. Attending physicians decided about pulmonary artery catheter (PAC) placement and dobutamine use. Our protocol encourages a PAC insertion in patients who evolve with a persistent circulatory dysfunction and hyperlactatemia after an initial fluid challenge. Mechanical ventilation settings were adjusted according to currently recommended lung protective strategies [16]. Optimal fluid resuscitation was guided by pulse pressure variation analysis or by a Starling curve approach when the former was not feasible [16]. High-volume hemofiltration was indicated as a final salvage therapy in unresponsive patients [24]. Intra-abdominal pressure was monitored and treated according to recent recommendations [22, 25].

Clinical and demographic data, and all the variables of Acute Physiology and Chronic Health Evaluation II (APACHE II) [26] and Sequential Organ Failure Assessment (SOFA) [27] scores were collected for each patient at baseline.

The multimodal perfusion monitoring protocol included the following measurements obtained at baseline (immediately after starting ICU resuscitation= 0 h), 2, 6 and 24 h:
1. Macro-hemodynamic parameters: MAP, heart rate (HR), NE or vasoactive drug doses, central venous pressure (CVP), pulse pressure variation (%), and PAC-derived values (when in place). Fluid administration was also registered at each predefined time-point.
2. Metabolic-related perfusion parameters: ScvO₂ (normal values >70%, arterial lactate (normal values <2 mmol/L; Radiometer ABL 735, Copenhagen Denmark), and P(cv-a) CO₂ (normal values <6 mmHg).

3. Peripheral perfusion was assessed with the capillary refill time (CRT) [7], measured by applying firm pressure to the distal phalanx of the index finger for 10 seconds. A chronometer recorded the time for return of the normal color at the ventral surface (normal values <4.0 s).

4. Thenar muscle oxygen saturation (StO₂) was measured by a tissue spectrometer (InSpectra Model 650, Hutchinson Technology, Mn, USA). A value >75% was considered as normal for this protocol [28]. The near-infrared spectroscopy (NIRS) probe was placed on the skin of the thenar eminence free of arterial line, and a sphygmomanometer cuff was wrapped around the arm over the brachial artery. After a 5 min period to stabilize the NIRS signal, a vascular occlusion test (VOT) was performed [10]. Inflating the cuff up to 50 mmHg above the systolic arterial pressure stopped arterial inflow. After 3 min of ischemia, cuff pressure was released, and StO₂ recorded continuously for another 3 min (reperfusion period). Baseline StO₂ (mean value of a 5 min period) before VOT was registered. During the reperfusion phase, the recovery slope of the StO₂ signal was registered and calculated with a software provided by the manufacturer (InSpectra V3-03, Hutchinson Technology, Mn, USA), and expressed in percent per second (values >3.5 %/s were considered as normal for this study) [10].

5. Microcirculatory-derived parameters: Sublingual microcirculation was assessed with sidestream dark field (SDF) videomicroscopy imaging obtained with a 5x lens (Microscan® for NTSC, Microvision Medical, Amsterdm, NL). At each assessment, at least five 10-20 sec video images were recorded. Image acquisition and analysis were performed following recent recommendations of a consensus conference [29]. A trained independent investigator performed image analysis in all cases and these data were not disclosed to attending physicians. Parameters considered for this study were proportion of perfused vessels (PPV; values >90% were considered as normal for this study); perfused vessel density (PVD; values >14 n/mm were considered as normal for this study); and microcirculatory flow index (MFI; values >2.5 were considered as normal for this study).

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**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 Bonferroni test. All data are presented as median and interquartile range (25th-75th percentile). All reported p values are two-sided, with a significant alpha level of <0.05. SPSS (SPSS for Windows Release 17.0.0; SPSS Inc, Chicago, IL) package was used for statistical analysis.
Results

Thirty-five septic shock patients were originally included in the study, of whom 31 were discharged alive from the hospital. Basal demographic, clinical and physiological data, and severity scores for the whole group and for survivors/non-survivors are shown in table 1. The four non-survivors exhibited median lactate and PPV values of 2.7 mmol/L [1.9–12.3] and 69% [61–77], respectively at 24 h, and died in the ICU at a median of 16 days [5-25] after admission. Due to the very low observed mortality and because it was beyond the scope of our study, no formal statistical comparison between survivors and non-survivors was performed.

All the following data and analyses are for the 31 hospital survivors. Three patients had a previous chronic atrial fibrillation, and eight a past medical history of coronary artery disease. The main septic sources were abdominal (n=15), pulmonary (n=6), urinary tract (n=5), and others (n=5). Eight patients were admitted directly from the operating room.

Patients received 1560 [570-2150] ml of crystalloids in the pre-ICU setting after developing septic shock criteria. The rate of fluid administration tended to decrease over time. A total of 815 [360–1540] ml of crystalloids were administered during the first two hours, 500 [238–1050] ml from two to six hours, and 810 [150-2400] ml from 6 to 24 hours of ICU-based resuscitation. A PAC was placed in twenty-one patients. The maximal cardiac index was registered at 2 h, and the highest CVP and PAOP values were observed at 6 h. The evolution of different hemodynamic parameters is shown in table 2. Dobutamine was used in three patients (2 mcg/kg/min fixed doses) as decided by attending physicians. Basal and 24 h intraabdominal pressures were 11 [9-14] and 12 [8-14] mmHg, respectively.

The medians values for individual perfusion parameters at different time-points are shown in table 3. Median lactate values had significantly decreased 6 h following inclusion (2.7 [2.2–3.9] vs. 4.0 [3.0–4.9] mmol/l, p<0.01; Table 3), When analyzing the percentage of patients that normalized their parameters over time, a high proportion of patients started ICU-based resuscitation with already normal values for some variables: 64% for CRT and P(cv-a) CO2, and 72% for baseline StO2. This proportion increased to >70% at 6 h, and >80% at 24 h for these parameters. Ninety-two percent of the patients had already a normal ScvO2 at baseline without significant changes in this proportion during the study. By definition, all patients had an abnormal lactate level at baseline. Lactate levels had normalized in 48% of the patients at 24 h (Figure 1). During follow-up of the 16 patients with persistent hyperlactatemia at 24 h, nine normalized lactate at 48 h, four at 72 h, and the remainder three patients between the fifth and seventh days. In contrast, microcirculatory parameters remained abnormal in the majority of the patients. PPV had only normalized in 10% of the cases at 24 hours whereas MFI only in 24% of cases (Figure 1). Similarly persistent abnormalities in StO2 recovery slope were still detected at 24 h (Table 3) in 81% of patients. Finally, the normalization trend for some individual perfusion parameters in these 31 hospital survivors is shown in figure 2.
### Table 10.1 General characteristics of the study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68 [56–78]</td>
<td>67 [56–76]</td>
<td>73 [37–82]</td>
</tr>
<tr>
<td>Male / Female (%)</td>
<td>37/ 63</td>
<td>39/ 61</td>
<td>25/75</td>
</tr>
<tr>
<td>Basal NE requirements (mcg/kg/min)</td>
<td>0.16 [0.05–0.3]</td>
<td>0.16 [0.03– 0.3]</td>
<td>0.18 [0.07– 0.52]</td>
</tr>
<tr>
<td>Basal Lactate (mmol/L)</td>
<td>4 [2.8–4.9]</td>
<td>4 [3.0 – 4.9]</td>
<td>3.0 [2.4–15.1]</td>
</tr>
</tbody>
</table>

Values are expressed as median [interquartile range] or percentage. APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; MV, mechanical ventilation; NE, norepinephrine.

### Table 10.2 Evolution of different hemodynamic parameters in a cohort of 21 septic shock patients monitored with a pulmonary artery catheter.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>2 hours</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (L/min/m²)</td>
<td>2.3 [1.9–3.8]</td>
<td>2.9 [2.3–3.3]</td>
<td>2.8 [2.2–3.6]</td>
<td>2.7 [2.4–3.3]</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>75 [67–82]</td>
<td>73 [68–77]</td>
<td>70 [68–74]</td>
<td>72 [69–77]</td>
</tr>
<tr>
<td>NE dose (mcg/kg/min)</td>
<td>0.16 [0.05–0.3]</td>
<td>0.18 [0.06–0.31]</td>
<td>0.17 [0.06–0.34]</td>
<td>0.04 [0–0.24]*</td>
</tr>
</tbody>
</table>

Values expressed as median [interquartile range]. *p<0.01 for comparison with values at baseline. ** p<0.01 for comparison with 2 hour values. Friedman test – Bonferroni posthoc correction. CI, cardiac index; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine.

Perfusion parameters exhibit markedly different recovery time courses...
Table 10.3 Evolution of different perfusion parameters in a cohort of hospital survivors during the first 24 h of septic shock resuscitation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>2 hours</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/L)</td>
<td>4.0 [2.8–4.9]</td>
<td>3.3 [2.4–4.1]</td>
<td>2.7 [2.2–4.0]*</td>
<td>2.2 [1.6–2.8]*</td>
</tr>
<tr>
<td>P(cv-a)CO₂ (mHg)</td>
<td>5.6 [2.2–7.0]</td>
<td>3.7 [2.5–6.0]</td>
<td>3.8 [2.0–5.5]</td>
<td>2.8 [1.2–4.6]*</td>
</tr>
<tr>
<td>MFI (score)</td>
<td>1.9 [1.5–2.2]</td>
<td>2.1 [1.7–2.3]</td>
<td>2.1 [1.8–2.3]</td>
<td>2.2 [2.0–2.5]</td>
</tr>
<tr>
<td>PVD (n/mm)</td>
<td>8.6 [8.2–9.9]</td>
<td>9.1 [8.0–10.7]</td>
<td>9.0 [8.3–9.7]</td>
<td>10.6 [8.7–11.6]*</td>
</tr>
<tr>
<td>StO₂ (%)</td>
<td>78 [73–84]</td>
<td>81 [74–85]</td>
<td>82 [77–88]</td>
<td>80 [77–87]</td>
</tr>
<tr>
<td>StO₂ recovery slope (%)/s</td>
<td>1.8 [1.0–2.9]</td>
<td>2.4 [1.1–3.2]</td>
<td>2.4 [1.3–3.3]</td>
<td>2.4 [1.7–3.3]</td>
</tr>
</tbody>
</table>

Values expressed as Median [interquartile range]. * p < 0.01 for comparison with values at baseline. Friedman Test – Bonferroni post-hoc correction

ScvO₂, central venous oxygen saturation; P(cv-a)CO₂, central venous-arterial pCO₂ gradient; CRT, capillary refill time; PPV, proportion of perfused vessels; MFI, microcirculatory flow index; PVD, perfused vessel density; StO₂, tissue oxygen saturation.

Figure 10.1 Percentage of abnormal perfusion parameters in septic shock survivors at different time-points during the first 24 hours of intensive care unit-based resuscitation. ScvO₂, central venous oxygen saturation; P(cv-a)CO₂, central venous-arterial pCO₂ gradient; CRT, capillary refill time; StO₂, tissue oxygen saturation; PPV, proportion of perfused vessels; MFI, microvascular flow index.
Discussion

This study showed that perfusion parameters exhibited markedly different recovery time courses in response to resuscitation in a cohort of surviving septic shock patients. Some variables such as ScvO₂, P(cv-a) CO₂, CRT and StO₂ were already normal in more than 70% of patients six hours after starting ICU-based resuscitation. Lactate presented a biphasic recovery trend, where a large part of the survivors cleared their lactate at 6h, while it took much longer for the remaining. Indeed, although lactate had decreased significantly at six hours, only 48% of the patients achieved normal values at 24 hours. Sublingual microcirculatory parameters exhibited the slowest recovery rate with persistent moderate derangements still present in almost 80% of patients at 24 h. To our knowledge, this is the first study in survivors showing the recovery dynamics of several perfusion parameters during septic shock resuscitation.

Central venous oxygen saturation, P(cv-a) CO₂, CRT and StO₂ values were already normal in the majority of patients at ICU admission. This finding might be explained by the fact that these variables appear to be particularly responsive to maneuvers that increase cardiac output and thus TO₂ [6,9,11,30]. In a previous landmark study, admission ScvO₂...
values increased from 49 to 77% in septic shock patients subjected to 6 h of aggressive TO$_2$ optimization [6]. The sensitivity of ScvO$_2$ to pre-ICU fluid loading probably explains the almost negligible incidence of low ScvO$_2$ values in the ICU setting [8,17]. In the present study, ScvO$_2$ was already normal in 92% of patients after having received a median of only 1560 ml of crystalloids as fluid bolus immediately before admission. In the case of capillary refill time, this variable is also controlled by vasoconstrictive sympathetic activity. However, since TO$_2$ optimization can decrease adrenergic tone, it may also improve rapidly after fluid resuscitation [8]. There are less data for StO$_2$ but 45% of critically ill patients enrolled in a recent study exhibited normal values at ICU admission while others normalized this variable after early resuscitation [31]. In our study ScvO$_2$, P(cv-a) CO$_2$, CRT and StO$_2$ were already normal in at least 70% of patients at 6 h. Changes thereafter appear to be slower eventually representing the delayed influence of non-flow dependent mechanisms [17]. Interestingly, none of the hospital survivors had 100% normal parameters at 6 or at 24 h. In our opinion, the validity of pursuing complete normalization of the preceding parameters after the initial 6 h of resuscitation with TO$_2$ increasing maneuvers should be challenged by further research.

The case of hyperlactatemia is paradigmatic. Although tissue hypoperfusion has been traditionally considered the most common cause of hyperlactatemia, there is increasing evidence for concomitant non-hypoxic and thus, non-flow dependent mechanisms such as epinephrine-driven aerobic muscle lactate production and liver dysfunction, among others [17-19]. These mechanisms may influence the time course of lactate recovery rate. The distinction between these two scenarios (flow-responsive versus non-flow dependent hyperlactatemia) may strongly impact the therapeutic approach. As an example, treatment of the latter with sustained efforts aimed at increasing TO$_2$ could lead to detrimental effects of excessive fluids or inotropes. Abnormalities in ScvO$_2$, P(cv-a)CO$_2$ or peripheral perfusion may be helpful to determine if a persistent hyperlactatemia is still flow-responsive [3,6,8,12], and prompt an aggressive TO$_2$ optimization strategy [3]. In our study, lactate exhibited a fast and significant decrease of almost 50% of basal median values during the first 6 hours of resuscitation associated with a rapid normalization of other metabolic and peripheral perfusion parameters (Figure 2). More interestingly, further decrease in lactate values was very slow since 52% of patients normalized lactate beyond the first ICU day. Thus, it appears that lactate decrease can be characterized by a biphasic evolution: an early rapid response followed by a later slower recovery trend potentially explained by non-flow dependent mechanisms. Indeed, a recently published therapeutic algorithm focused lactate-driven resuscitation exclusively in the first eight hours of ICU management with a significant favorable impact on outcome [3].

The time-course of microcirculatory recovery during septic shock resuscitation may also follow a biphasic pattern with an early apparently flow-responsive phase as was demonstrated by several other clinical studies targeting the microcirculation during early fluid resuscitation [32-34]. However, further improvements appear to be very slow with a full recovery that may take several days even in survivors [14,34,35]. In the
present study, sublingual microcirculatory parameters and thenar muscle microvascular dysfunction exhibited the slowest recovery rate with persistent moderate derangements still present in more than 75% of these ultimately surviving patients at 24 h (Figure 2). Moreover, since concomitant clinical and metabolic perfusion parameters were already normal in the great majority of our patients, it appears as highly unlikely that persistent microcirculatory abnormalities may respond to additional fluids or TO$_2$ optimization maneuvers after 24 h of resuscitation. This speculation is supported by the study of Ospina-Tascon et al. demonstrating that fluid loading after 48 h of severe sepsis fails to improve microcirculatory derangements [34]. More recently, De Backer et al. reported that microcirculatory abnormalities still persisted in a large number of surviving patients after 48 h of ICU treatment despite achievement of adequate systemic resuscitation goals [14]. Thus, our and previous data suggest that persistent microcirculatory abnormalities after 24 hours of resuscitation may represent different pathogenic mechanisms not responsive to TO$_2$ increasing maneuvers [36]. Whether additional non-hemodynamic interventions that have been shown to improve microcirculatory parameters may improve morbidity or mortality should be the focus of studies that recognize the different time-courses found in this report [37].

We acknowledge several limitations of our study. We included a small and highly selected subgroup of patients. Thus we do not know if our findings can be universally extrapolated but at the very least they can be considered as hypothesis generating. Second, the study period may be considered not long enough and the selected time points are arbitrary. Third, the intensity of TO$_2$ optimization maneuvers could be criticized since no significant changes in several hemodynamic parameters could be observed within the study period. However, fluid administration rates, cardiac index and central filling pressures reached maximal values within the first 6 h of resuscitation together with normal pulse pressure variation values, reflecting a clear impact of therapy in central hemodynamics.

In conclusion, perfusion parameters exhibit markedly different recovery rates in response to resuscitation in septic shock patients. Parameters such as ScvO$_2$, CRT, P(cv-a) CO$_2$ and StO$_2$ show a rapid response expressed as high percentages of normalization during the first six hours of resuscitation. Lactate exhibits a biphasic response with an initial fast normalization in a large proportion of surviving patients, followed by a much slower trend thereafter in which more than 50% of the patients normalize the parameter only beyond 24 h. The recovery time course of microcirculatory abnormalities seems to be the slowest among all perfusion parameters. These markedly different recovery time courses should be taken into account when composing a resuscitation protocol to avoid potentially harmful and inappropriate therapies.
References


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