

Microcirculatory Alterations in Patients With Severe Sepsis: Impact of Time of Assessment and Relationship With Outcome

Daniel De Backer MD, PhD; Katia Donadello MD; Yasser Sakr MD, PhD; Gustavo Ospina-Tascon MD; Diamantino Salgado MD; Sabino Scolletta MD; Jean-Louis Vincent MD, PhD, FCCM

Objectives: Sepsis induces microvascular alterations that may play an important role in the development of organ dysfunction. However, the relationship of these alterations to systemic variables and outcome is still not well defined. We investigated which factors may influence microcirculatory alterations in patients with severe sepsis and whether these are independently associated with mortality.

Design: Analysis of prospectively collected data from previously published studies by our group.

Setting: A 36-bed, medicosurgical university hospital Department of Intensive Care.

Patients: A total of 252 patients with severe sepsis in whom the sublingual microcirculation was visualized using orthogonal polarization spectral or sidestream darkfield imaging techniques.

Measurements and Main Results: Microcirculatory measurements were obtained either early, within 24 h of the onset of severe sepsis ($n = 204$), or later, after 48 h ($n = 48$). When multiple measurements were obtained, only the first was considered. Although global hemodynamic variables were relatively preserved (mean arterial pressure 70 [65–77] mm Hg, cardiac index 3.3 [2.7–4.0] L/min.m², and SvO_2 68.3 [62.8–74.7]%), microvascular variables were markedly altered (proportion of perfused small vessels 65

[50–74]%, microvascular flow index 2.15 [1.80–2.60], and heterogeneity of proportion of perfused small vessels 35 [20–50]%). Among microcirculatory variables, proportion of perfused small vessels was the strongest predictor of outcome (receiver operating characteristic curve area 0.818 [0.766–0.871], $p < 0.001$). Survival rates decreased markedly with severity of alterations in the proportion of perfused small vessels (70% and 75% in the two upper proportion of perfused small vessel quartiles compared with 3% and 44% in the two lower quartiles, $p < 0.0001$). Multivariable analysis identified proportion of perfused small vessels and sequential organ failure assessment score as independent predictors of outcome. Microcirculatory alterations were less severe in the later than in the earlier (proportion of perfused small vessels, 74 [57–82]% vs. 63 [48–71]%, $p = 0.004$) phase of sepsis. In multivariable analysis focused on the early period of sepsis, proportion of perfused small vessels and lactate were independent predictors of outcome.

Conclusions: Microcirculatory alterations are stronger predictors of outcome than global hemodynamic variables. (*Crit Care Med* 2013; 41:0–0)

Key Words: cardiac output; microcirculation; organ failure; outcome; tissue perfusion; vasopressor

Microvascular alterations are frequently observed in patients with sepsis (1–3). These alterations, which are characterized by decreased functional capillary density, increased perfusion heterogeneity, and increased proportion of stopped and intermittently perfused capillaries, contribute to the defect in oxygen extraction observed in sepsis (4, 5) and may be involved in the development of organ failure (3, 6). In rodents with sepsis, survival time is proportional to the density of perfused capillaries, functional capillary density, and a perfusion score (7). In humans, several small trials have shown that the severity of the alterations in microvascular perfusion is associated with a poor outcome (1, 8). Importantly, microvascular perfusion improves in survivors from septic shock but not in nonsurvivors (3, 9), even when shock resolves (3).

All authors: Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (<http://journals.lww.com/ccmjournal>).

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: ddebacke@ulb.ac.be

Copyright © 2013 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3182742e8b

A crucial question is whether these microcirculatory alterations just reflect the severity of the disease or contribute independently to morbidity and mortality. Although this issue can only be definitively addressed by interventional trials, evaluation of the relative contributions of microcirculatory and global alterations to outcome may provide a clue. Identifying which microcirculatory variables are most relevant for outcome could also help to define the best targets for these trials.

Importantly, resuscitation procedures, such as fluids or inotropic agents, may influence the microcirculation although this effect may be variable (10–12). Small-sized trials showed that microvascular alterations were relatively independent of arterial pressure, cardiac output, and vasopressor use, but these may have been underpowered to identify such a relationship (1, 11). Indeed, other small size trials reported that microcirculatory alterations were related to decreasing arterial pressure (8) and/or increasing doses of vasopressor agents (8, 13), individual factors may play an important role and it is thus important to perform a large scale trial to assess these factors. In addition, resuscitation procedures may influence the microcirculation though this effect may be variable. In one study, microcirculatory alterations improved in some patients already after 3 hrs of goal-directed therapy (6). In other studies, increasing arterial pressure improved microvascular perfusion in some patients but not in others (and may even worsen it (14–16)). Meeting all resuscitation goals, such as those included in the Surviving Sepsis Campaign (SSC) guidelines (17) may thus, at least theoretically, improve the microcirculation; however, patients may respond to one intervention but not to another. It would, therefore, be interesting to evaluate whether or not achievement of resuscitation goals can affect microcirculatory alterations.

In this context, we used a large database of patients with severe sepsis, who had undergone evaluation of microvascular perfusion, to evaluate the relationship between microvascular variables and systemic hemodynamics and markers of disease severity. We also evaluated whether microcirculatory variables were independently associated with outcome and, if so, which had the strongest association. We hypothesized that microcirculatory alterations would be independently associated with a poor outcome and may persist despite achievement of global resuscitation goals.

PATIENTS AND METHODS

The patients included in this analysis had previously been included in trials approved by the local Ethical Committee and informed consent had been obtained from the patients or their relatives.

Patient Population

We reviewed data of all patients with severe sepsis included in nine published trials from our center related to the microcirculation (1, 3, 10, 11, 16, 18–21). Each patient was included only once. When multiple measurements were obtained, only the first was considered in this analysis. Severe sepsis was defined according to the International Sepsis Definitions Conference (22); its onset was defined as the time of hospital admission

for patients admitted through the Emergency Department and the time of identification of sepsis-related organ dysfunction for patients transferred from the hospital ward. Exclusion criteria were those from the original trials, including hematologic or advanced malignancies, liver cirrhosis, and, for practical reasons, oral mucosal lesions, patients with severe hypoxemia requiring administration of oxygen at an F_{IO_2} higher than 50% via a face mask, and agitation.

General Management

All patients were managed according to local guidelines. Each patient was equipped with an arterial and a central venous catheter; 208 patients were also monitored with a pulmonary artery flotation catheter (continuous cardiac output; Edwards, Irvine, CA). Treatment for septic shock was standardized, including vasopressors (dopamine and/or norepinephrine before 2009 and only norepinephrine thereafter, with epinephrine as rescue therapy) to maintain arterial pressure, in addition to repeated fluid challenges with crystalloids, natural albumin, and artificial colloids (gelatin or hydroxyethyl starch solutions) to optimize stroke volume and limit the doses of vasopressors. Hydrocortisone (50 mg every 6 hr) was added in severe patients (norepinephrine dose > 0.5–0.7 mcg/kg.min). During the initial phase of resuscitation, we attempted to maintain mixed venous (Sv_{O_2}) or central venous (Scv_{O_2}) oxygen saturation at 65% and 70%, respectively; thereafter, no specific oxygen saturation was targeted. If needed, mechanical ventilation was provided under light sedation (midazolam up to 4 mg/h) and analgesia (morphine up to 3 mg/h or remifentanyl up to 4 mcg/min). In mechanically ventilated patients treated with, tidal volume was limited to 6–8 mL/kg.

Measurements

Temperature, heart rate, arterial pressure, and central venous pressure (CVP) were measured in all patients. Pulmonary artery pressures, cardiac output, and Sv_{O_2} were also obtained in patients monitored with a pulmonary artery catheter. Arterial and mixed venous blood samples were withdrawn simultaneously, and blood gases, hemoglobin saturation, hemoglobin, and lactate concentrations were measured (ABL700, Radiometer, Copenhagen, Denmark). Oxygen delivery (D_{O_2}), oxygen consumption, and oxygen extraction ratio (O_2ER) were calculated using standard formulas. Acute Physiology and Chronic Health Evaluation II (APACHE II) (23) and Sequential Organ Failure Assessment (SOFA) (24) scores were computed at study inclusion. As different vasopressor agents were used, we computed an aggregate vasopressor dose based on large randomized studies (25, 26): (0.0095 dopamine) + norepinephrine + epinephrine; all doses being expressed in mcg/kg.min. Mortality was assessed at ICU discharge.

Microvideoscopic Measurements and Analysis

We evaluated the sublingual microcirculation with the orthogonal polarization spectral (OPS; Cytoscan ARII, Cytometrics; Philadelphia, PA) or sidestream darkfield (SDF; MicroVision Medical, Amsterdam, The Netherlands)

imaging techniques, both with a $\times 5$ objective. After removal of secretions with a gauze, we gently applied the device to the lateral side of the tongue, on an area 1.5–4 cm from the tip of the tongue. We recorded five sequences of 20 s each from adjacent areas and stored them under a random number. At the time of recording, we eliminated images with pressure artifacts, identified as containing a significant number of nonperfused large vessels (venules) (27). An investigator blinded to the origin of the sequence semiquantitatively analyzed (27) the sequences, drawing three equidistant horizontal and three vertical lines and computing vascular density as the number of vessels crossing these lines divided by the total length of the lines. We defined the type of flow as continuous, intermittent, or absent and separated the vessels according to their size into large and small using a cutoff value of 20 μm in diameter. We computed the proportion of perfused vessels (total, large, and small) as the number of vessels continuously perfused during the 20-s observation period divided by the total number of vessels of the same type. In each patient, the data from the five areas were averaged. Intraobserver and interobserver variabilities are around 5% in our department (1, 28). We also previously observed a 4 (1–8)% difference between two baseline measurements in 13 hemodynamically stabilized patients with septic shock, representing a coefficient of variability of 5% (21).

We measured the microvascular flow index (MFI) for small vessels (29). Each image was divided into four quadrants, and the predominant type of flow (0 = absent, 1 = intermittent, 2 = sluggish, and 3 = normal) was evaluated in each quadrant. The MFI reports the mean value of the score in the four quadrants. Using this score, several studies have reported excellent inter- and intrarater agreement, with Kappa scores of 0.78 for intrarater variability (29) and 0.77 (8), 0.81 (30), 0.85 (29), and 0.87 (6) for interrater variability.

Finally, we calculated a heterogeneity index (27), defined as the difference between maximal and minimal proportions of perfused small vessels (PPVs) evaluated at each point in the five areas divided by the mean value of the five areas.

Exploratory Subgroup Analyses

We first evaluated whether achieving the resuscitation goals of mean arterial pressure (MAP, ≥ 65 mm Hg), CVP (≥ 8 mm Hg), and ScvO_2 ($\geq 70\%$) proposed by the SSC (17) influenced the severity of microcirculatory alterations.

We then separated patients according to the time elapsed between the defined onset of severe sepsis and the time at which the microvascular evaluation was performed. We considered as “early phase,” patients in whom measurements were made less than 24 hrs after onset of severe sepsis as defined above and as “later phase” those in whom measurements were made more than 48 hrs after sepsis onset. Because of the inclusion criteria in the various clinical trials, no patient was evaluated between 24 and 48 hrs.

We also separated patients into ICU survivors and nonsurvivors and into those who received vasopressor agents and those who did not. Finally, we separated patients into quartiles of PPV.

Statistical Analysis

Data were analyzed using SPSS 18 for Windows (SPSS Inc, Chicago, IL). We computed descriptive statistics for all study variables. We used a Kolmogorov-Smirnov test and stratified distribution plots to verify the normality of distribution of continuous variables. As most hemodynamic and microcirculatory variables were not normally distributed, we present data as median [25th–75th percentiles]. Categorical variables are presented as number (%). We assessed differences between subgroups using chi-square test, Fisher’s exact test, and Mann-Whitney U test as appropriate, with Bonferroni correction for multiple comparisons. We used a generalized linear models procedure to evaluate the difference between quartiles of microvascular perfusion. We evaluated relationships between microcirculatory variables and hemodynamic variables or vasopressor doses using Spearman’s correlation.

To evaluate relationship with outcome, we constructed receiver operating characteristic (ROC) curves, computing their area and Youden’s index to identify the best cutoff value. We also performed a multivariable analysis (backward selection) to identify factors independently associated with outcome. We included all factors associated with ICU outcome with a p value ≤ 0.20 in univariable analysis. If variables were correlated (i.e., cardiac index, hemoglobin, and D_{O_2}), we entered the variable that had the highest area under the ROC curve (AUROC) for predicting outcome.

For all analyses, a p value < 0.05 was considered to be significant.

RESULTS

The main characteristics of the 252 patients are presented in **Table 1**. Almost 90% of the patients were being treated with mechanical ventilation and almost 60% with vasopressor agents (median vasopressor dose 0.19 [0.11–0.39] mcg/kg.min) at the time of their microvascular assessment.

Global hemodynamic variables were within satisfactory ranges, with an MAP of 70 [65–77] mm Hg, CVP 12 [9–15] mm Hg, cardiac index 3.3 [2.7–4.0] L/min.m², SvO_2 68.3 [62.8–74.7] %, and lactate 2.1 [1.3–3.3] mEq/L (**Table 2**).

Microvascular variables were markedly altered (PPV 65 [50–74]%, MFI 2.15 [1.80–2.60], and heterogeneity of PPV 35 [20–50]%), except for large vessels, which had normal perfusion (**Table 2**). PPV was normal ($\geq 90\%$) in only 9 (4%) patients and moderately altered (between 80% and 90%) in 35 (15%) patients.

There was a weak correlation between PPV and D_{O_2} , SvO_2 and pH (Spearman’s Rho 0.188, $p = 0.007$; 0.238, $p < 0.001$; and 0.192, $p = 0.002$, respectively) and an inverse correlation with the degree of vasopressor support and O_2ER (Spearman’s Rho -0.171 , $p = 0.006$ and -0.211 , $p = 0.001$, respectively). There was no significant correlation between PPV and MAP, cardiac output, CVP, hemoglobin levels, or lactate (**Supplemental Table 1** and **Supplemental Figs. 1–6**, Supplemental Digital Content 1, <http://links.lww.com/CCM/A564>).

TABLE 1. Patient Characteristics

	All (n = 252)	Early (n = 204)	Late (n = 48)	p
Age (yr)	69 [55–76]	69 [56–76]	68 [52–76]	0.43
Acute Physiology and Chronic Health Evaluation II score	22 [17–27]	21 [17–27]	24 [21–29]	0.019
Sequential organ failure assessment score	10 [8–13]	10 [8–12]	12 [9–14]	0.001
Source of sepsis				(0.07)
Lungs, n (%)	94 (37)	71 (35)	23 (48)	
Abdomen, n (%)	75 (30)	59 (29)	16 (33)	
Urine, n (%)	11 (4)	8 (4)	3 (6)	
Skin, n (%)	23 (9)	17 (8)	6 (13)	
Other, n (%)	49 (20)	49 (24)	0 (0)	
Vasopressor use, n (%)	147 (58)	130 (64)	17 (35)	0.001
Vasopressor dose ^{ab} (mcg/kg.min)	0.19 [0.11–0.39]	0.19 [0.11–0.36]	0.36 [0.16–0.90]	0.006
Dobutamine use, ^b n (%)	83 (33)	63 (31)	20 (42)	0.007
Dobutamine dose ^b (mcg/kg.min)	6 [5–5]	8 [5–20]	5 [5–12]	0.40
Mechanical ventilation, ^b n (%)	225 (89)	180 (88)	45 (94)	0.48
Renal support, ^b n (%)	38 (15)	15 (7)	18 (38)	0.001
ICU survival, n (%)	122 (48)	105 (51)	17 (35)	0.06

Data are presented as n (%) or median [25th–75th percentiles].

^aThe aggregate vasopressor dose was computed as the sum of dopamine, norepinephrine, and epinephrine doses (see text for details).

^bAt time of microcirculatory assessment.

Relationship With Mortality

There were differences between survivors and nonsurvivors in most systemic hemodynamic variables and microcirculatory variables (Table 3). In univariable analysis, numerous factors were associated with mortality, including arterial pressure, cardiac index, pH, lactate, APACHE II, SOFA score, and all microcirculatory variables. PPV was the microcirculatory variable associated with the largest AUROC (Fig. 1 and Supplemental Table 2, Supplemental Digital Content, <http://links.lww.com/CCM/A564>) and was thus the only microvascular variable retained for further analysis. In multivariable analysis, only the SOFA score and PPV remained associated with mortality (Table 4).

Survival rates were significantly lower in patients in the lower PPV quartiles (Fig. 2).

The severity of PPV alterations was similar in patients who achieved the MAP, CVP, and ScvO₂ resuscitation goals proposed by the SSC and in patients who did not (Fig. 3).

Early vs. Later Periods

The time from defined onset of severe sepsis to evaluation was 16 [14–19] hrs (range 6–24) in the early and 69 [48–86] hrs (range 48–169) in the later subgroup. There were no differences in systemic hemodynamic variables between the two subgroups. In contrast, total vascular density, the density of perfused small vessels, and PPV were higher in the later than in the early subgroup (Table 2). As a consequence, the propor-

tion of patients with normal PPV increased over time from 3% to 8%, and with moderately altered PPV from 9% to 33% ($p = 0.07$ and $p < 0.0001$). In both subgroups, PPV was lower in nonsurvivors than in survivors: 48 [37–61]% vs. 69 [64–77]% ($p < 0.0001$) in the early subgroup and 68 [47–77]% vs. 80 [75–85]% ($p = 0.001$) in the later subgroup. The AUROC was similar in early (0.877 [0.829–0.924]) and later (0.744 [0.602–0.885]) subgroups (Supplemental Fig. 7, Supplemental Digital Content, <http://links.lww.com/CCM/A564>), but the cutoff value was lower in the early (PPV 56%) than in the later (PPV 75%) subgroup.

Most observations made in the population as a whole also applied to the patients in the early subgroup (Supplemental Figs. 8 and 9, Supplemental Digital Content, <http://links.lww.com/CCM/A564>). However, multivariable analysis in this subgroup identified lactate and PPV as independently associated with mortality (Table 4). These analyses were not performed in the later subgroup because of insufficient sample size.

Influence of Vasopressor Agents

Patients receiving vasopressor agents ($n = 147$) had a lower MAP and higher lactate levels but otherwise similar global hemodynamic variables compared with the other patients (Table 5). Total vessel density, density of perfused small vessels, and PPV were lower in patients receiving vasopressor agents compared with the other patients. ICU survival was reduced in patients treated with vasopressor agents (42% vs. 57%, $p = 0.016$).

TABLE 2. Main Hemodynamic and Microcirculatory Variables at Early (≤ 24 h) or Late (≥ 48 h) Stages of Sepsis

	All (n = 252)	Early (n = 204)	Late (n = 48)	p
Temperature ($^{\circ}$ C)	37.4 [36.6–38.0]	37.3 [36.5–38.0]	37.6 [36.8–38.3]	0.34
Heart rate (bpm)	105 [91–117]	103 [91–115]	109 [94–127]	0.46
Mean arterial pressure (mm Hg)	70 [65–77]	70 [65–77]	68 [64–77]	0.43
Mean pulmonary arterial pressure (mm Hg)	29 [25–34]	29 [25–35]	30 [25–34]	0.92
Pulmonary artery occlusion pressure (mm Hg)	15 [12–18]	15 [12–18]	14 [12–18]	0.28
Central venous pressure (mm Hg)	12 [9–15]	12 [9–15]	12 [9–15]	0.74
Cardiac index (L/min.m ²)	3.3 [2.7–4.0]	3.3 [2.7–3.9]	3.2 [2.7–4.1]	0.47
pH	7.36 [7.30–7.41]	7.36 [7.29–7.41]	7.38 [7.32–7.45]	0.23
PaCO ₂	37 [32–41]	37 [32–41]	36 [31–41]	0.36
PaO ₂	92 [75–109]	92 [76–109]	93 [74–121]	0.71
SaO ₂	97.0 [95.0–98.7]	97.0 [95.0–98.6]	97.5 [95.3–98.7]	0.23
Svo ₂ (%)	68.3 [62.8–74.7]	68.0 [62.0–74.0]	69.9 [64.4–75.5]	0.44
Hemoglobin (g/dL)	9.0 [8.0–10.5]	9.2 [8.2–10.8]	8.4 [7.7–9.5]	0.01
Lactate (mEq/L)	2.1 [1.3–3.3]	2.1 [1.3–3.4]	2.0 [1.4–3.3]	0.46
Do ₂ (mL/min.m ²)	401 [317–513]	404 [327–515]	359 [300–500]	0.30
Vo ₂ (mL/min.m ²)	118 [94–147]	120 [97–151]	116 [83–136]	0.47
O ₂ ER (%)	30 [23–35]	30 [24–35]	29 [23–33]	0.76
Total vessel density (n/mm)	7.1 [5.5–8.7]	7.0 [5.4–8.3]	8.7 [5.9–9.9]	0.025
Density of perfused small vessels (n/mm)	2.8 [1.9–4.0]	2.7 [1.8–3.7]	4.2 [2.3–5.5]	0.004
Perf all (%)	80 [73–86]	78 [72–86]	84 [78–89]	0.10
Perf large (%)	100 [100–100]	100 [100–100]	100 [100–100]	0.99
Proportion of perfused small vessels (PPV, %)	65 [50–74]	63 [48–71]	74 [57–82]	0.004
Microvascular flow index	2.15 [1.80–2.60]	2.00 [1.80–2.45]	2.50 [1.95–2.75]	0.031
Heterogeneity PPV (%)	35 [20–50]	36 [21–58]	26 [19–46]	0.76

Svo₂ = mixed venous or central venous O₂ saturation; Do₂ = oxygen delivery; Vo₂ = oxygen consumption; O₂ER = oxygen extraction ratio. Data are presented as median [25th–75th percentiles].

A pulmonary artery catheter was used in 179 patients (88%) in the early group and 29 patients (60%) in the late group.

Trends Over Time

The study span lasted 10 yrs, with 76 patients (30%) being included after 2006. There was a slight but significant increase in PPV over time (**Supplemental Fig. 10**, Supplemental Digital Content, <http://links.lww.com/CCM/A564>). However, including the year of study in the multivariable analysis did not alter the results (data not shown).

DISCUSSION

This analysis of a large collection of data underlines again that microcirculatory alterations are common in patients with severe sepsis and are independently associated with ICU mortality. These alterations are weakly associated with some systemic hemodynamic variables. Furthermore, achievement of systemic resuscitation goals did not always prevent development of microcirculatory alterations.

An important observation of this study is the association of microvascular alterations with outcome. This effect has been reported previously (1, 3, 8, 9), but the large size of this database allowed us to conduct more detailed analyses. First, we identified that PPV was the strongest predictor of outcome. This was not an on/off phenomenon: Mortality progressively increased with decreasing quartiles of PPV, indicating that the more altered the microvascular perfusion is, the lower the chances of survival. Second, the large number of patients allowed us to conduct a multivariable analysis, which identified PPV as an independent prognostic factor.

Another important observation is that the severity of the microvascular alterations differed over time, with more severe alterations at early stages and less severe alterations in persistent sepsis, especially in survivors. This observation is in line with previous trials following patients over time and

TABLE 3. Main Hemodynamic and Microcirculatory Variables in ICU Survivors and Nonsurvivors

	ICU Survivor (n = 122)	ICU Nonsurvivor (n = 130)	p
Heart rate (bpm)	102 [88–117]	105 [94–116]	0.54
Mean arterial pressure (mm Hg)	71 [66–78]	69 [64–75]	0.11
Cardiac index (L/min.m ²)	3.5 [2.8–4.3]	3.2 [2.6–3.8]	0.036
Central venous pressure (mm Hg)	12 [9–14]	13 [10–16]	0.013
Svo ₂ (%)	70.0 [64.4–76.7]	67.0 [62.0–72.0]	0.005
Lactate (mEq/L)	1.9 [1.2–2.8]	2.4 [1.4–4.0]	0.004
pH	7.37 [7.32–7.44]	7.35 [7.27–7.40]	0.19
Total vessel density (n/mm)	7.5 [6.2–8.9]	6.8 [5.1–8.3]	0.08
Density of perfused small vessels (n/mm)	3.4 [2.7–4.6]	2.2 [1.6–3.2]	0.001
Proportion of perfused small vessels (PPV, %)	71 [65–78]	50 [40–66]	0.001
Microvascular flow index	2.35 [1.90–2.52]	1.95 [1.65–2.60]	0.036
Heterogeneity PPV (%)	27 [17–47]	41 [23–60]	0.08
Acute Physiology and Chronic Health Evaluation II score	20 [17–27]	23 [18–28]	0.07
Sequential organ failure assessment score	10 [8–11]	11 [9–14]	0.002
Vasopressor use, n (%)	61 (50)	86 (66)	0.016
Vasopressor dose ^a (mcg/kg.min)	0.20 [0.11–0.40]	0.19 [0.11–0.39]	0.18

Svo₂ = mixed venous or central venous O₂ saturation.

Data are presented as median [25th–75th percentiles] unless stated otherwise.

^aThe aggregate vasopressor dose was computed as the sum of dopamine, norepinephrine, and epinephrine doses (see text for details).

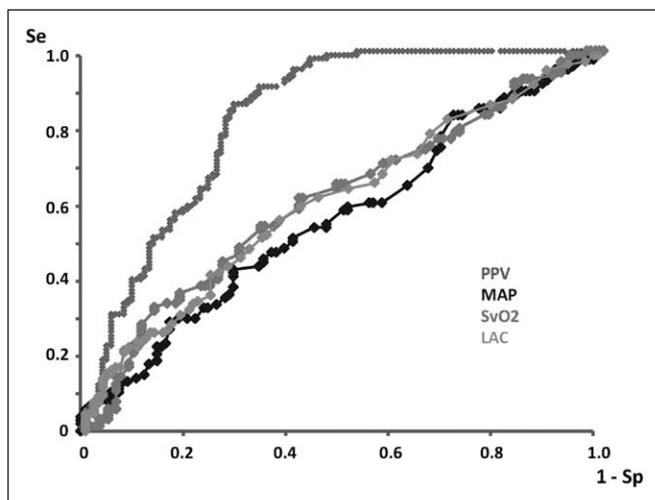


Figure 1. Receiver operating characteristic (ROC) curve for prediction of ICU outcome. The ROC curve areas were 0.818 [0.766–0.871] for proportion of perfused small vessels (PPV), 0.576 [0.505–0.647] for mean arterial pressure (MAP), 0.616 [0.543–0.689] for Svo₂, and 0.612 [0.542–0.681] for lactate (LAC). Svo₂ or Scvo₂ = mixed or central venous oxygen saturation.

showing that microvascular perfusion improves rapidly in survivors (3, 9). However, it allows two important additional observations. First, microcirculatory alterations remain an important prognostic factor in persistent sepsis, even if values

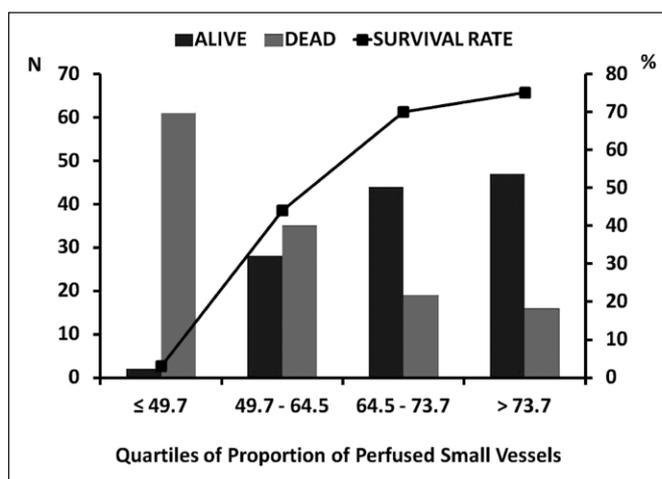


Figure 2. ICU outcome according to quartiles of proportion of perfused small vessels. Each quartile counts 63 patients. The left axis is used to report the numbers of ICU survivors (black rectangles) and nonsurvivors (gray rectangles). The right axis is used to report ICU survival rate. Chi-square $p < 0.001$.

are less altered. Second, the value discriminating survivors from nonsurvivors also evolves over time. These data support the use of microcirculatory variables to guide resuscitation.

Interestingly, indexes of microcirculatory function have improved over the years. PPV increased significantly from

TABLE 4. Multivariable Analysis of Factors Associated With ICU Survival

	Beta Coefficient	Odds Ratio [95% Confidence Interval]	<i>p</i>
All patients (<i>n</i> = 252)			
Proportion of perfused small vessels (PPV)	0.101 ± 0.016	1.107 [1.072–1.143]	< 0.001
Sequential organ failure assessment score	−0.159 ± 0.061	0.853 [0.756–0.962]	0.010
Constant	−4.885 ± 1.124	0.008	< 0.001
Early group (<i>n</i> = 204)			
PPV	−0.279 ± 0.105	1.163 [1.107–1.223]	< 0.001
Lactate	0.151 ± 0.026	0.757 [0.615–0.930]	0.008
Constant	−8.585 ± 1.554	0.000	< 0.001

TABLE 5. Main Hemodynamic and Microcirculatory Variables in Patients According to Whether or Not They Were Treated With Vasopressor Agents

	No Vasopressor Support (<i>n</i> = 105)	Vasopressor Support (<i>n</i> = 147)	<i>p</i>
Heart rate (bpm)	103 [91–117]	106 [91–117]	0.44
Mean arterial pressure (mm Hg)	73 [66–78]	68 [65–75]	0.007
Cardiac index (L/min.m ²)	3.3 [2.5–3.7]	3.3 [2.7–4.2]	0.59
Central venous pressure (mm Hg)	12 [9–14]	13 [9–15]	0.024
Sv _o ₂ (%)	69.6 [63.7–76.0]	68.0 [62.0–73.9]	0.19
Lactate (mEq/L)	1.8 [1.2–2.7]	2.3 [1.5–3.8]	0.006
pH	7.38 [7.32–7.43]	7.35 [7.28–7.40]	0.06
Total vessel density (n/mm)	8.1 [7.1–9.0]	6.3 [4.8–7.9]	0.001
Density of perfused small vessels (n/mm)	3.5 [2.7–4.4]	2.3 [1.6–3.2]	0.001
Proportion of perfused small vessels (PPV, %)	68 [58–77]	59.9 [46.5–70.6]	0.006
Microvascular flow index	2.00 [1.70–2.50]	2.45 [2.00–2.85]	0.09
Heterogeneity PPV (%)	39 [21–59]	27 [17–49]	0.42
Acute Physiology and Chronic Health Evaluation II score	23 [18–28]	21 [17–27]	0.53
Sequential organ failure assessment score	9 [7–12]	11 [9–14]	0.09

Sv_o₂ = mixed venous or central venous O₂ saturation.
Data are presented as median [25th–75th percentiles].

55%–60% in studies before 2007 to 65%–75% in those during and after 2007. The reasons for these differences are difficult to determine. Resuscitation strategies may have improved, although we did not notice any differences in systemic hemodynamics. Changes in case-mix may also have occurred, but survival rates did not increase significantly over the years (data not shown). Technologic improvements may play a role. We changed from OPS to SDF imaging in 2006. As SDF provides better contrast images than OPS (31), some perfused capillaries may have been better recognized in the more recent period. Interestingly, PPV was similarly associated with outcome before and after 2006 (data not shown), so that

our observations remain valid regardless of these technologic aspects.

Finally, a weak relationship was found with flow or oxygen-derived variables (cardiac output, Do₂, Sv_o₂, and O₂ER) but not with forward (MAP) or backward (CVP) pressure. We also found some relationship with the intensity of vasopressor support. These observations are in agreement with data from smaller cohorts (8, 13). However, these correlations, although significant, were weak and it is difficult to identify cutoff values associated with good microcirculatory perfusion. Hence, achieving resuscitative goals cannot be considered reassuring in terms of microcirculatory improvement.

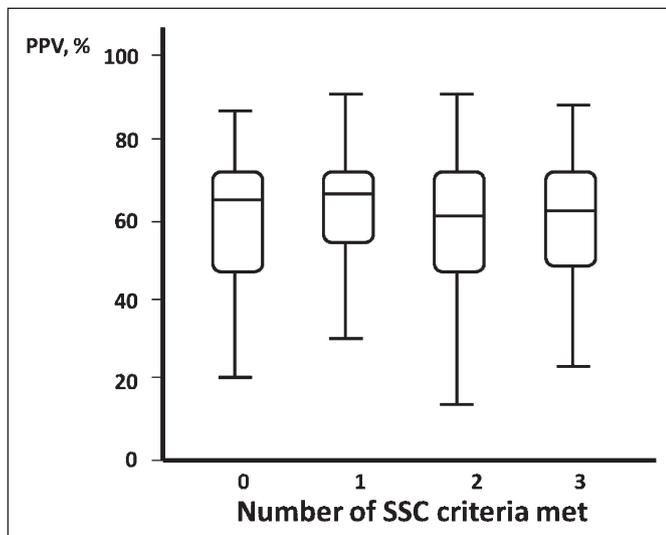


Figure 3. Proportion of perfused small vessels (PPV) according to achievement of resuscitative goals. Patients were characterized as achieving Surviving Sepsis Campaign (SSC) guidelines for resuscitation (mean arterial pressure > 65 mm Hg, SvO_2 or $ScvO_2$ above 65 or 70%, and CVP between 8 and 12 mm Hg) (17) or not. $p = 0.81$.

This report has several limitations. First, it was an observational study, and the possibility remains that microvascular alterations are simply a marker of severity. Nevertheless, multivariable analysis, used to limit the impact of confounding factors, retained PPV alterations as an independent prognostic factor. Second, selection bias may have occurred with inclusion of larger numbers of severely ill patients. Third, we evaluated ICU mortality and not longer term outcomes, but the latter may be influenced by other factors, more related to the underlying disease and comorbidities. Finally, we only evaluated the sublingual microcirculation. Anatomical and local factors, such as increased abdominal pressure, may induce more severe lesions in specific areas. In septic pigs, the time course and severity of sublingual and gut mucosal microvascular lesions were similar (32). Nevertheless, disparity between sublingual and gut microcirculations was observed in some (but not all) patients in a series with peritonitis (33).

In conclusion, microcirculatory alterations are frequently observed in severe sepsis and have profound implications on outcome. Microcirculatory alterations are less pronounced at later stages of sepsis, but seldom normalize, even in survivors. PPV is probably the best variable to characterize the microcirculation, as it is the strongest predictor of mortality.

REFERENCES

- De Backer D, Creteur J, Preiser JC, et al: Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; 166:98–104
- Spronk PE, Ince C, Gardien MJ, et al: Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002; 360:1395–1396
- Sakr Y, Dubois MJ, De Backer D, et al: Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004; 32:1825–1831
- Farquhar I, Martin CM, Lam C, et al: Decreased capillary density *in vivo* in bowel mucosa of rats with normotensive sepsis. *J Surg Res* 1996; 61:190–196
- Ellis CG, Bateman RM, Sharpe MD, et al: Effect of a maldistribution of microvascular blood flow on capillary O_2 extraction in sepsis. *Am J Physiol Heart Circ Physiol* 2002; 282:H156–H164
- Trzeciak S, McCoy JV, Phillip Dellinger R, et al: Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive Care Med* 2008; 34:2210–2217
- Santos AO, Furtado ES, Villela NR, et al: Microcirculatory effects of fluid therapy and dopamine, associated or not to fluid therapy, in endotoxemic hamsters. *Clin Hemorheol Microcirc* 2011; 47:1–13
- Trzeciak S, Dellinger RP, Parrillo JE, et al: Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 2007; 49:88–98, 98.e1
- Top AP, Ince C, de Meij N, et al: Persistent low microcirculatory vessel density in nonsurvivors of sepsis in pediatric intensive care. *Crit Care Med* 2011; 39:8–13
- Ospina-Tascon G, Neves AP, Occhipinti G, et al: Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med* 2010; 36:949–955
- De Backer D, Creteur J, Dubois MJ, et al: The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–408
- Dubin A, Pozo MO, Casabella CA, et al: Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. *J Crit Care* 2010; 25:659.e1–659.e8
- Edul VS, Enrico C, Laviolle B, et al: Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. *Crit Care Med* 2012; 40:1443–1448
- Jhanji S, Stirling S, Patel N, et al: The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. *Crit Care Med* 2009; 37:1961–1966
- Dubin A, Pozo MO, Casabella CA, et al: Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: A prospective study. *Crit Care* 2009; 13:R92
- Thooft A, Favory R, Salgado DR, et al: Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 2011; 15:R222
- Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
- Sakr Y, Chierego M, Piagnerelli M, et al: Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007; 35:1639–1644
- Creteur J, De Backer D, Sakr Y, et al: Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 2006; 32:516–523
- De Backer D, Verdant C, Chierego M, et al: Effects of drotrecogin alfa activated on microcirculatory alterations in patients with severe sepsis. *Crit Care Med* 2006; 34:1918–1924
- Büchele GL, Silva E, Ospina-Tascón GA, et al: Effects of hydrocortisone on microcirculatory alterations in patients with septic shock. *Crit Care Med* 2009; 37:1341–1347
- Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256
- Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
- Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
- De Backer D, Biston P, Devriendt J, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779–789

26. Myburgh JA, Higgins A, Jovanovska A, et al: A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34:2226–2234
27. De Backer D, Hollenberg S, Boerma C, et al: How to evaluate the microcirculation: Report of a round table conference. *Crit Care* 2007; 11:R101
28. Bracht H, Krejci V, Hildebrand L, et al: Orthogonal polarization spectroscopy to detect mesenteric hypoperfusion. *Intensive Care Med* 2008; 34:1883–1890
29. Boerma EC, Mathura KR, van der Voort PH, et al: Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: A prospective validation study. *Crit Care* 2005; 9:R601–R606
30. Jhanji S, Lee C, Watson D, et al: Microvascular flow and tissue oxygenation after major abdominal surgery: Association with post-operative complications. *Intensive Care Med* 2009; 35:671–677
31. Goedhart PT, Khalilzada M, Bezemer R, et al: Sidestream Dark Field (SDF) imaging: A novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. *Opt Express* 2007; 15:15101–15114
32. Verdant CL, De Backer D, Bruhn A, et al: Evaluation of sublingual and gut mucosal microcirculation in sepsis: A quantitative analysis. *Crit Care Med* 2009; 37:2875–2881
33. Boerma EC, van der Voort PH, Spronk PE, et al: Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis. *Crit Care Med* 2007; 35:1055–1060