Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock*

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Objective: **To characterize the time course of microcirculatory alterations and their relation to outcome in patients with septic shock.**

Design: **Prospective, observational study.**

Setting: **Thirty-one-bed, medico-surgical intensive care unit in a university hospital.**

Patients: **Forty-nine patients with septic shock.**

Interventions: **The sublingual microcirculation was investigated with an orthogonal polarization spectral imaging device on the day of onset of septic shock (baseline) and each day until resolution of shock.**

Measurements and Main Results: **Five sequences of 20 secs each were recorded and analyzed off-line by a semiquantitative method. Data were analyzed with nonparametric tests and presented as median (25th–75th percentiles). Three patients died after the resolution of shock from unrelated causes and were excluded. Of the other 46 patients, 26 survived and 20 died: 13 due to unresolving shock and seven due to persistent multiple organ failure after resolution of shock. At the onset of shock, survivors and nonsurvivors had similar vascular density (5.6 [4.7–7.0] vs. 6.2 [5.4–7.0]/mL; p = nonsignificant) and percentage of perfused small vessels (65.0 [53.1–68.9] vs. 58.4 [47.5–69.1]%; p = nonsignificant). Small vessel perfusion improved over time in survivors (analysis of variance, $p < .05$ between survivors and nonsurvivors) but not in nonsurvivors. Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients dying after the resolution of shock in multiple organ failure had a lower percentage of perfused small vessels than survivors (57.4 [46.6–64.9] vs. 79.3 [67.2–83.2]%; $p = .02$).**

Conclusions: **Microcirculatory alterations improve rapidly in septic shock survivors but not in patients dying with multiple organ failure, regardless of whether shock has resolved. (Crit Care Med 2004; 32:1825–1831)**

KEY WORDS: microcirculation; multiple organ failure; outcome; tissue oxygenation; orthogonal polarization spectral imaging

Despite major improvements in the management of patients with severe sepsis (1–3), many patients will develop multiple organ failure (MOF) and will subsequently die. Microvascular alterations are frequent in patients with sepsis (4) and may play a role in this evolution. Using nail fold capillaroscopy, Weinberg et al. (5) showed that capillary blood velocity decreased in febrile normotensive patients; however, this technique is limited by the need for large microscopes and the sensitivity of the nail fold area to changes in temperature. Studies using laser Doppler techniques (6–8) or plethysmography (8, 9) in patients with severe sepsis have reported an impaired microvascular blood flow and a blunted hyperemic response after transient ischemia obtained by cuff inflation. However, these techniques only provide a global measurement of microvascular blood flow and do not take into account heterogeneity of the microcirculation, a major feature reported in experimental data.

The recently developed, noninvasive, orthogonal polarization spectral (OPS) imaging technique can be applied to investigate the human microvasculature (10). Polarized light is emitted to illuminate the area of interest, is reflected by the background, and is absorbed by hemoglobin, producing high-contrast images of the microcirculation. The technique is particularly convenient for studying tissues protected by a thin epithelial layer, such as mucosal surfaces (11), and has been validated as an effective method of microvascular imaging in animals (10, 12, 13) and in humans (14).

With this technique, we recently observed major microvascular blood flow alterations in patients with severe sepsis (4). These alterations included a decreased vascular density, especially in the small vessels; a large number of nonperfused and intermittently perfused small vessels; and a marked heterogeneity between the areas. These alterations were more severe in nonsurvivors than in survivors but were not affected by the global hemodynamic state or vasopressor agents. These observations were obtained early in the course of disease, so that their time course has not been well characterized. Importantly, these alterations were totally reversible with the topical application of acetylcholine (4). As several interventions including dobutamine (15) and nitroglycerin (16) can improve the sublingual microcirculation, it is important to clarify the evolution of these microvascular alterations. The persistence of microcirculatory alterations in patients with a bad outcome would further emphasize the potential role of microcirculatory disturbances in the pathophysiology of sepsis-induced multiple organ failure. In addition, it may be interesting to identify some patients in whom further interventions may improve their microcirculation.

***See also p. 1963.**

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DOI: 10.1097/01.CCM.0000138558.16257.3F

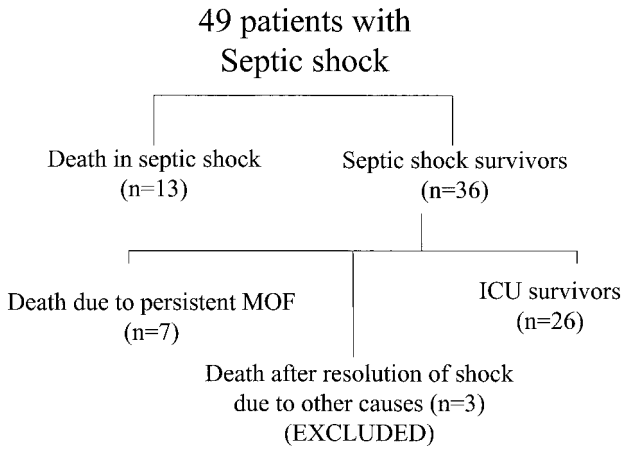

Figure 1. Schematic representation of the study group. *MOF*, multiple organ failure; *ICU*, intensive care unit.

Table 1. Characteristics of the study group

	All Patients (n = 46)	Survivors (n = 26)	Nonsurvivors (n = 20)
Age	66 (51–78)	61 (48–78)	68 (56–78)
Male gender, %	32 (69.6)	18 (69.2)	14 (70)
APACHE II score	16 (13–19)	15.0 (12–17)	19 (15–23)[a]
SOFA score	10 (9–12)	9 (9–11)	11 (9–14)[a]
Source of infection, n (%)			
Lung	23 (50)	12 (46)	11 (55)
Abdomen	14 (30)	8 (31)	6 (30)
Urinary tract	6 (13)	4 (15)	2 (10)
Miscellaneous	3 (7)	2 (8)	1 (5)
Initial adrenergic dose			
Dopamine[b]	41, 15 (8–20)	22, 11.5 (5.8–20)	19, 18 (10–20)
Norepinephrine[b]	12, 0.2 (0.1–0.5)	6, 0.2 (0.1–0.5)	6, 0.3 (0.1–1.5)
Dobutamine[b]	18, 6 (5–20)	8, 5 (3.5–17.5)	10, 7 (5–20)
Analgo-sedation			
Midazolam[c]	36, 2 (1–2)	22, 2 (1–3)	14, 2 (2–2)
Morphine[c]	36, 1 (1–2)	22, 1 (1–2)	14, 1 (1–2)
Propofol[d]	2, 2 (2–2)	1, 2 (2–2)	1, 2 (2–2)
ICU length of stay, days	7 (3–14.3)	11.5 (4.8–18.8)	5.5 (2–12)[a]

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; ICU, intensive care unit.

[a]$p < .01$ compared with survivors; [b]values are n, dose in μg/kg·min; [c]values are n, dose in mg/hr; [d]values are n, individual doses are provided.

In this study, we used the OPS technique daily in patients with septic shock. We hypothesized that the time course of microvascular alterations is different according to disease severity. We also investigated whether the technique may help to identify patients at risk of death despite the apparent resolution of shock.

METHODS

After approval by the ethical committee of Erasme Hospital, informed consent was obtained from each patient's next of kin. Between May 1, 2001, and April 30, 2002, we studied 49 consecutive patients within 24 hrs of the development of septic shock, as defined by usual criteria of hypotension with a mean arterial pressure <65 mm Hg requiring the administration of pressor agents (dopamine at a dose >5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and/or norepinephrine at any dose, for >2 hrs) after the correction of hypovolemia. The diagnosis of infection was established using the Centers for Disease Control criteria (17). Exclusion criteria were liver cirrhosis, shock due to any other cause (cardiogenic, hemorrhagic, obstructive), oral injuries, and absence of invasive mechanical ventilation. Clinical, hemodynamic, and microvideoscopic assessments were carried out daily until the end of shock, until death, or for a maximum of 7 days.

General Management. All patients had an arterial and central venous catheter; 42 patients were also monitored with a pulmonary artery catheter (Edwards, Irvine, CA). Treatment for septic shock was standardized, including vasopressors (dopamine up to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and, if needed, addition of norepinephrine) to maintain a mean arterial pressure >65 mm Hg, in addition to repeated fluid challenges with crystalloids and artificial colloids (gelatin or hydroxyethyl starch) to optimize stroke volume and to allow the low-

Table 2. Hemodynamic variables on the first day of shock (start of follow-up)

	All Patients (n = 46)	Survivors (n = 26)	Nonsurvivors (n = 20)
Temperature, °C	37.1 (36.5–37.8)	37.3 (36.5–38.0)	36.9 (36.6–37.7)
Mean arterial pressure, mm Hg	70 (63–79)	72 (66–80)	67 (61–76)
Heart rate, beats/min	104 (96–118)	109 (94–121)	101 (98–117)
Central venous pressure, mm Hg	12 (8–16)	12 (8–15)	13 (9–17)
Mean pulmonary artery pressure,[a] mm Hg	29 (22–32)	27 (21–33)	29 (23–31)
Pulmonary artery occlusion pressure,[a] mm Hg	14 (11–18)	14 (11–18)	15 (11–19)
Cardiac index,[a] L/min·m^2	3.2 (2.8–4.2)	3.7 (2.8–4.5)	3 (2.8–3.5)
pH	7.37 (7.30–7.41)	7.39 (7.32–7.44)	7.36 (7.23–740)
$Paco_2$, mm Hg	37 (33–41)	38 (33–41)	37 (32–41)
Pao_2, mm Hg	91 (76–112)	85 (74–110)	93 (77–117)
Mixed venous oxygen saturation,[a] %	69 (62–74)	67 (63–72)	70 (60–76)
Hemoglobin concentration, g/dL	9.1 (8.0–10.9)	8.7 (7.8–10.8)	9.5 (8.1–11.1)
Arterial lactate, mEq/L	2.1 (1.2–3.4)	1.7 (1.2–2.4)	2.5 (1.5–4.0)[b]
Oxygen delivery,[a] mL/min·m^2	390 (318–484)	394 (317–481)	369 (318–494)
Oxygen consumption,[a] mL/min·m^2	113 (97–156)	114 (103–153)	104 (84–165)
Oxygen extraction ratio,[a] %	29.9 (22.5–35.5)	31.5 (26.5–33.3)	29.0 (20.4–37.5)

[a]Measured in 42 patients only; 23 survivors and 19 nonsurvivors; [b]$p < .01$ between survivors and nonsurvivors.

est dose of vasopressors. Several indicators were used to trigger fluid challenge, including pulse pressure variations, decrease in stroke volume, and/or pulmonary artery occlusion pressure from a point at which stroke volume had been maximized. If needed, dobutamine was added (up to a dose of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$). All patients were initially mechanically ventilated. Light sedation (with midazolam up to 4 mg/hr) and analgesia (with morphine up to 3 mg/hr) was provided according to individual needs.

Measurements. Measurements, obtained at study inclusion and repeated at 24-hr intervals during the period of shock, included temperature, heart rate, arterial pressure, and central venous pressure in all patients, in addition to complete hemodynamic measurements in patients monitored with a pulmonary artery catheter. Arterial and mixed venous blood samples were withdrawn simultaneously, and blood gases, hemoglobin saturation, and hemoglobin and lactate concentrations were measured (ABL700, Radiometer, Copenhagen, Denmark). Oxygen delivery, oxygen consumption, and oxygen extraction ratio were calculated using standard formulas. The Acute Physiology and Chronic Health Evaluation II score (18) was obtained on admission, and the Sepsis-related Organ Failure Assessment score (19) was calculated daily during the shock period.

Microvideoscopic Measurements and Analysis. We used the Cytoscan ARII (Cytometrics, Philadelphia, PA) to study the sublingual microvascular network, with a ×5 objective providing a ×167 magnification. After the removal of saliva and other secretions using gauze, the device was gently applied (without any pressure) on the lateral side of the tongue, in an area approximately 1.5–4 cm from the tip of the tongue. Five sequences of 20 secs each from different adjacent areas were recorded using a computer and a videocard (MiroVideo, Pinnacle Systems, Mountain Views, CA) and stored under a random number for later analysis. Every effort was made to avoid movement artifacts. An investigator, blinded to the patients' clinical course and the order of the sequences, analyzed the sequences semiquantitatively (4). Briefly, three equidistant horizontal and three vertical lines were drawn. The vascular density was calculated as the number of vessels crossing these lines divided by the total length of the lines. The type of flow was defined as continuous, intermittent, or absent. The vessels were separated into large and small vessels using a cutoff value of 20 μm in diameter. In each patient, the data from the five areas were averaged.

Statistical Analysis. Data were analyzed using SPSS 11.0 for Windows (SPSS, Chicago, IL). Descriptive statistics were computed for all study variables. A Kolmogorov-Smirnov test was used, and stratified distribution plots were examined to verify the normality of distribution of continuous variables. Nonparametric measures of comparison were used as all variables evaluated were not normally distributed. Differences between groups were assessed using a chi-square, Fisher's exact test, and Mann-Whitney U test as appropriate, with Bonferroni correction for multiple comparisons. A Friedman test was done to assess the evolution of microvascular perfusion in each group followed by a Wilcoxon test with Bonferroni correction to evaluate intragroup evolution. As nonparametric tests do not allow the assessment of group vs. time comparisons, analysis of variance was used to evaluate the difference in the evolution of microvascular perfusion between groups. The predictive value on outcome of changes in small vessel perfusion and changes in other hemodynamic variables within the first 24 hrs of resuscitation was calculated using a receiver operator characteristic (ROC) curve, and the area under the curve was computed. We considered $p < .05$ to be significant. Data are presented as median (25th–75th percentiles).

RESULTS

Of the 49 patients fulfilling the inclusion and exclusion criteria, 36 survived the episode of septic shock and were weaned from vasopressors; seven of these died later from persistent MOF. Three patients were excluded as they died from causes other than MOF and sepsis (two patients due to massive intracranial hemorrhage and one patient due to severe gastrointestinal hemorrhage). Twenty-six patients were thus discharged alive from the intensive care unit (ICU, Fig. 1). The characteristics of the 46 patients included in the study are presented in Table 1. As expected, survivors had lower Acute Physiology and Chronic Health Evalua-

Table 3. Physiologic variables on the first and last day of shock in survivors and patients dying after resolution of shock in multiple-organ failure (death MOF) and patients dying in acute circulatory failure (death in shock)

	Survivors (n = 26)		Death MOF (n = 7)		Death in Shock (n = 13)	
	Baseline	Last	Baseline	Last	Baseline	Last
Temperature, °C	37.3 (36.5–38.0)	37.2 (36.8–37.6)	37.2 (36.6–38.8)	37.0 (36.7–37.9)	36.7 (36.3–37.9)	37.2 (36.7–37.5)
Mean arterial pressure, mm Hg	72 (66–80)	78 (71–94)[a]	78 (70–82)	76 (66–80)	66 (61–71)	63 (56–83)
Heart rate, beats/min	109 (94–121)	95 (81–116)[a]	100 (99–128)	101 (93–117)	101 (99–119)	99 (83–128)
Central venous pressure, mm Hg	12 (8–15)	12 (11–14)	16 (10–19)	16 (12–19)	11 (8–16)	16 (13–21)
Mean pulmonary artery pressure,[b] mm Hg	27 (21–33)	30 (24–40)	29 (23–33)	30 (29–36)	28 (21–31)	29 (26–32)
Pulmonary artery occlusion pressure,[b] mm Hg	14 (11–18)	16 (13–19)	18 (14–24)	17 (13–22)	15 (10–18)	20 (14–26)
Cardiac index,[b] L/min·m^2	3.7 (2.8–4.5)	3.3 (2.7–4.1)	4.0 (3.6–4.5)	3.6 (2.9–4.3)	3.0 (2.4–3.3)	2.9 (2.2–4.1)
pH	7.39 (7.32–7.44)	7.39 (7.35–7.42)	7.37 (7.29–7.40)	7.36 (7.22–7.36)	7.39 (7.25–7.42)	7.37 (7.20–7.41)
$Paco_2$, mm Hg	38 (33–41)	37 (34–45)	37 (35–39)	39 (37–41)	36 (31–41)	41 (29–44)
Pao_2, mm Hg	85 (74–110)	91 (77–122)	114 (101–134)	93 (91–111)	91 (71–120)	73 (68–108)
Mixed venous oxygen saturation,[b] %	67 (63–72)	70 (67–74)	73 (69–74)	70 (55–76)	70 (61–77)	70 (69–76)
Hemoglobin concentration, g/dL	8.7 (7.8–10.8)	8.8 (8.0–10.0)	8.8 (8.0–9.1)	9.0 (7.5–10.9)	9.8 (8.1–11.3)	8.7 (7.6–10.0)
Arterial lactate, mEq/L	1.7 (1.2–2.4)	1.0 (1.0–1.9)[a]	1.7 (1.3–4.0)	2.1 (1.1–4.0)	2.9 (2.3–3.9)	2.2 (1.8–4.1)
Oxygen delivery,[b] mL/min·m^2	394 (317–481)	397 (292–485)	482 (424–520)	402 (369–639)	336 (308–467)	402 (227–448)
Oxygen consumption,[b] mL/min·m^2	114 (103–153)	116 (93–140)	125 (113–150)	165 (101–169)	99 (75–140)	80 (62–126)
Oxygen extraction ratio,[b] %	31.5 (26.5–33.3)	28.1 (24.7–31.6)	26.0 (25.4–30.4)	29.4 (21.8–42.5)	29 (20–37)	26 (23–28)
Initial adrenergic dose						
Dopamine[c]	22,11.5 (5.8–20)	20, 5 (4–11)[a]	6,16.5 (8.8–20)	5, 7 (4–20)[a]	13,20 (12–20)	7,20 (17–20)
Norepinephrine[c]	6, 0.2 (0.1–0.5)	6, 0.05 (0.04–0.05)[a]	3, 0.1 (0.1–0.3)	1, 0.05	6, 0.3 (0.2–0.6)	6, 0.5 (0.4–0.9)
Dobutamine[c]	8, 5 (3.5–17.5)	9, 8 (3.5–20)	3, 5 (5–10)	3,10 (10–14)[a]	7, 8 (6–20)	6,10 (5–20)

[a] $p < .05$ compared with baseline; [b] measured in 42 patients only, 23 survivors and 19 nonsurvivors; [c] values are n, dose in $\mu g/kg \cdot min$.

tion II and Sepsis-related Organ Failure Assessment scores and lower serum lactate concentration than nonsurvivors ($p < .01$). We found no difference in the type or the dose of initial vasopressor/inotropic agents or the analgo-sedation between survivors and nonsurvivors, who had similar hemodynamic and oxygenation variables at the onset of shock (Table 2). The evolution of hemodynamic variables was similar in survivors and in patients dying with persistent MOF (Table 3).

Time Course of Sublingual Microvascular Perfusion. At the onset of shock, vascular density (5.6 [4.7–7.0] vs. 6.2 [5.4–7.0]/mL; p = nonsignificant) and the percentage of perfused small vessels (65.0 [53.1–68.9] vs. 58.4 [47.5–69.1] %; p = nonsignificant) were similar in survivors and nonsurvivors. Large vessels were completely perfused (100%) over the entire period of follow-up in all patients. The evolution of small vessel perfusion differed between survivors and nonsurvivors (analysis of variance, $p < .05$): it improved over time in the survivors (to 79.3 [67.2–79.3]; $p < .01$) but not in the nonsurvivors (to 58.4 [43.1–65.7]; p = nonsignificant, Fig. 2).

Time Course of Sublingual Microvascular Perfusion in Patients Dying of MOF After Resolution of Shock. Despite similar hemodynamic and oxygenation profiles (Table 3), an improvement in microcirculatory variables was observed in the 26 ICU survivors but not in the 13 patients dying in shock or in the seven patients who died later of persistent MOF (Fig. 3, analysis of variance group vs. time effect <.01). Similar findings were observed when we looked at the changes in microvascular perfusion between the first and last measurement (Fig. 4). Although small vessel perfusion at the end of shock was still lower in all groups than in normal individuals, it was higher in the ICU survivors (79.3 [67.2–79.3]%) than in patients dying in shock (64.4 [32.6–66.7]%; $p < .01$ vs. survivors) or in those who died in MOF after resolution of shock (57.3 [46.6–64.9]%; $p < .05$ vs. survivors). Actually, the microcirculatory alterations were similar in those who died in MOF after the resolution of shock and those who died in shock. There was an inverse relationship between the perfusion of small vessels at the end of shock in survivors and patients dying in MOF and the degree of organ failure in these patients evaluated the same day by the Sepsis-related Organ Failure Assessment

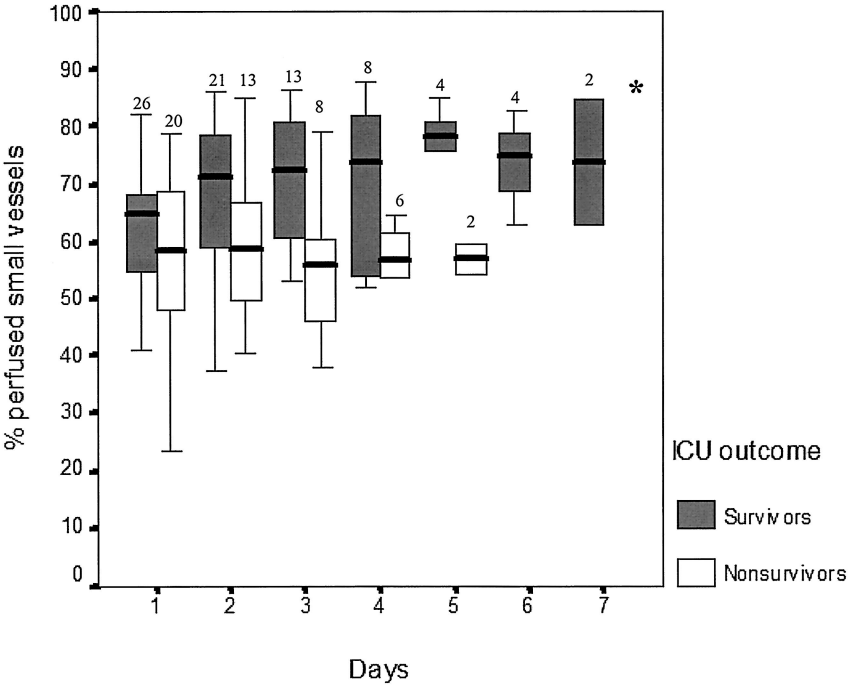

Figure 2. Box plot demonstrating the time course of small vessel perfusion in survivors and nonsurvivors. The numbers above the boxes show the numbers of patients at each time point and, of course, decrease during the study period. The evolution was significantly different between survivors and nonsurvivors (*analysis of variance, $p < .05$). There was a significant increase in small vessel perfusion in survivors ($p < .05$) and not in nonsurvivors. *ICU*, intensive care unit.

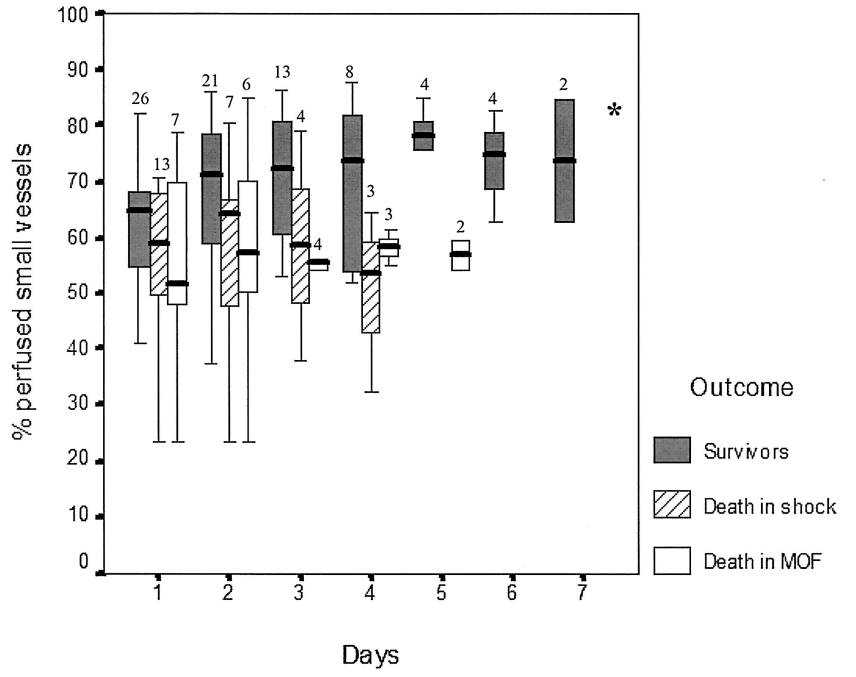

Figure 3. Box plot demonstrating the time course of small vessel perfusion in survivors, patients dying in shock, and patients dying after resolution of shock due to persistent multiple organ failure (*MOF*). The numbers above the boxes show the numbers of patients at each time point and, of course, decrease during the study period. The evolution was significantly different between survivors and patients dying in shock or dying after the resolution of shock due to persistent MOF (*analysis of variance, $p < .05$). Small vessel perfusion increased only in survivors ($p < .05$).

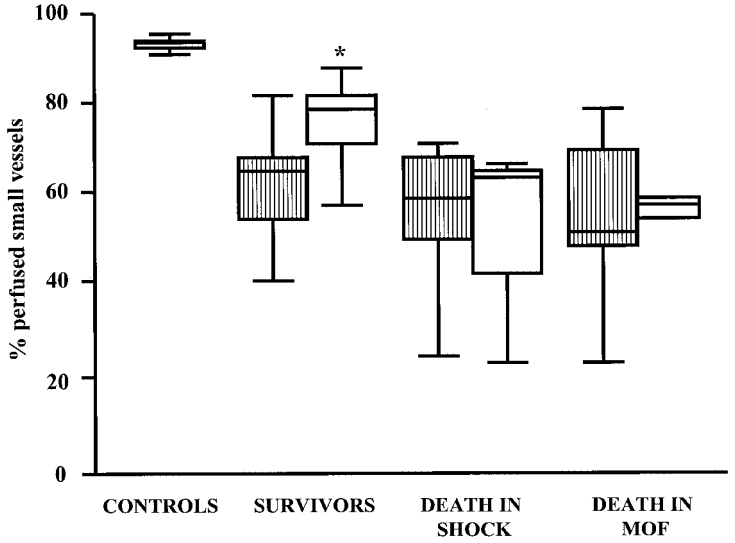

Figure 4. Evolution of small vessel perfusion between first (*hatched*) and last (*white*) measurement. For comparison, values for healthy volunteers (n = 4) are shown. Small vessel perfusion increased only in survivors (*$p < .01$ last vs. first).

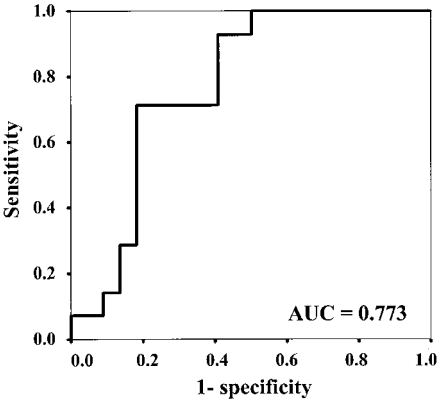

Figure 5. Receiver operator characteristic curve for the change in small vessel perfusion within the first 24 hrs of the onset of shock. The best cutoff is 7.8%. *AUC*, area under the curve.

score ($y = 16.2 - 0.1x$; $R^2 = .34$, data not shown).

Prognostic Value of Early Microvascular Changes. A ROC curve (Fig. 5) showed that the change in small vessel perfusion after 24 hrs was a good predictor of ICU death (area under the curve = 0.773). An improvement in small vessel perfusion of 7.8%, the best cutoff, had a sensitivity of 71% and a specificity of 82%. The ICU mortality rate was 71%, if the change in small vessel perfusion was <7.8%, and only 19% if the perfusion increased above 7.8%. Interestingly, these two groups had similar baseline characteristics, Acute Physiology and Chronic Health Evaluation scores, and hemodynamic and oxygenation profiles at the onset of shock (Table 4). The areas under the curve of the ROC curves for changes in small vessel perfusion between the first and second day of shock as well as between the first and last day of shock were higher than for changes in any of the other hemodynamic and biological variables (Table 5).

DISCUSSION

Our study demonstrates that different patterns of microvascular alterations in septic shock can characterize outcome. Although microcirculatory alterations were initially similar within the first 24 hrs of shock, capillary perfusion increased over time in survivors but not in nonsurvivors, whether they died during the septic shock episode or later due to persistent MOF. At the end of shock, only microvascular perfusion discriminated ICU survivors and patients dying of MOF after shock had resolved, as global hemodynamic measurements did not differ at the end of shock. Capillary perfusion at the end of the septic shock episode was related to the severity of MOF, as assessed by the Sepsis-related Organ Failure Assessment score. The early change in small vessel perfusion was a good predictor of ICU mortality.

Previous studies reported that microcirculatory alterations can be observed in patients with septic shock (4, 9, 16, 20). These studies noted that these alterations were more severe in nonsurvivors than in survivors, but the time factor was not taken into account. In our study, microcirculatory alterations were similar during the initial 24 hrs of shock, but the persistence of these alterations was associated with the development of MOF and ultimate death. An important finding was that microcirculatory alterations, but not the global hemodynamic or oxygenation variables, were related to the occurrence and the severity of MOF. Global hemodynamic and oxygenation variables were similar on the last day of shock despite the significantly altered perfusion in nonsurvivors. These may, of course, have been partly influenced by the therapeutic interventions we applied, which were guided by global hemodynamic measurements. The microcirculation is thus highlighted as an important player in the pathophysiology of shock and MOF.

Interestingly, the microvascular alterations improved but failed to normalize, as the microvascular perfusion was still lower in survivors than in healthy subjects or ICU controls (4, 21). This is in accordance with the fact that the septic insult was not fully resolved at that time, as the patients were still in their last day of shock. Markers of the activation of coagulation in sepsis, such as D-dimers, are also usually persistently increased during severe sepsis, even when other signs of inflammation have normalized (2). This may suggest that the endothelial alteration is still ongoing.

The crucial role of the interaction between endothelial and circulating cells in sepsis is further emphasized by the beneficial effects of therapeutic interventions acting at this level, both in animals (22) and in patients (2). Hence, microvascular recruitment can be a possible target for resuscitation in patients with septic shock (23). We (4) previously reported that local application of acetylcholine reversed the sublingual microcirculatory alterations in 11 patients with septic shock treated with high doses of vasoactive agents, even in nonsurvivors. Recently, Spronk et al. (16) reported that nitroglycerin administration can increase sublingual microcirculatory flow in patients with septic shock. Unfortunately, nitroglycerin can also have strong hemodynamic effects, and excessive nitric oxide may also have direct cellular toxicity (24). Further studies are necessary to define potentially beneficial interventions, and OPS studies may be helpful in evaluating their effects on the microcirculation.

Table 4. Comparison of variables in the first 24 hrs of septic shock according to the 7.8% cutoff point of change in capillary perfusion

	<7.8%		>7.8%		*p* Value
Age, yrs	72	(66–80)	58	(42–77)	.06
APACHE II score	15	(15–19)	15	(13–19)	.67
SOFA score	10.5	(8–12.3)	10	(9–12)	.84
Temperature, °C	36.7	(36.6–37.5)	37.5	(36.7–38.2)	.13
Mean arterial pressure, mm Hg	67	(64–73)	73	(63–80)	.20
Heart rate, beats/min	101	(98–112)	106	(93–122)	.55
Mean pulmonary artery pressure, mm Hg	31	(29–35)	27	(21–33)	.07
Pulmonary artery occlusion pressure, mm Hg	17	(13–23)	13	(9–17)	.06
Central venous pressure, mm Hg	14	(10–18)	12	(10–15)	.31
Cardiac index, L/min·m^2	3.1	(2.8–3.7)	3.3	(2.8–4.0)	.69
pH	7.37	(7.2–7.41)	7.38	(7.34–7.42)	.43
$Paco_2$, mm Hg	38	(29–41)	39	(34–40)	.87
Pao_2, mm Hg	93	(77–123)	91	(76–118)	.71
$S\bar{v}o_2$, %	70	(64–74)	68	(62–74)	.85
Sao_2, %	98	(96–99)	97	(95–99)	.88
Hemoglobin concentration, g/dL	9.4	(7.9–11.2)	9.5	(8.4–10.9)	.78
Arterial lactate concentration, mEq/L	2.5	(1–4)	1.9	(1.3–2.8)	.44
Oxygen delivery, mL/min·m^2	369	(327–422)	416	(322–518)	.42
Oxygen consumption, mL/min·m^2	100	(92–165)	128	(105–154)	.25
Oxygen extraction ratio, %	29	(23–35)	31	(27–34)	.65
Capillary density, n/mm^3	5.2	(4–6.6)	6.5	(5.3–7)	.10
% all vessel perfusion	79	(70–87)	77.6	(69.6–84.7)	.61
% capillary perfusion	61	(45–68)	61.8	(50.1–68)	.71

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; $S\bar{v}o_2$, mixed venous oxygen saturation; Sao_2, arterial oxygen saturation.

Table 5. Area under the curve (AUC) of the receiver operating characteristics curves of changes over time (between first and second day of shock and first and last day of shock) in the main hemodynamic and biologic variables

	AUC Second-First	AUC Last-First
Heart rate	0.57	0.66
Mean arterial blood pressure	0.53	0.64
Central venous pressure	0.51	0.51
Pulmonary artery occlusion pressure	0.64	0.52
Cardiac index	0.51	0.57
$S\bar{v}o_2$	0.52	0.53
$\dot{D}o_2$	0.52	0.56
$\dot{V}o_2$	0.50	0.55
Lactate	0.63	0.82
Microvascular perfusion	0.77	0.83
SOFA score	0.61	0.74

$S\bar{v}o_2$, mixed venous oxygen saturation; $\dot{D}o_2$, oxygen delivery; $\dot{V}o_2$, oxygen consumption; SOFA, Sepsis-related Organ Failure Assessment. For comparison, AUC for Acute Physiology and Chronic Health Evaluation II - 0.74, age - 0.55, and admission lactate = 0.68.

Microcirculatory alterations improve rapidly in septic shock survivors but not in patients dying with multiple organ failure, regardless of whether shock has resolved.

One may argue that microvascular alterations may be the consequence rather than the cause of death, as alterations in oxidative metabolism have also been reported in septic patients (25). Although this facet may only be fully addressed in trials targeting therapeutic interventions on microvascular perfusion, several indexes suggest that microvascular blood flow alterations are likely to be involved in the pathophysiology of shock. First, alterations in microvascular perfusion are an independent predictor of outcome (26). Second, the area under the curve of changes in microcirculatory perfusion was higher than that of changes in any other variable, both between the first and second day of shock and between the first and last day of shock, suggesting that changes in microvascular perfusion were the most powerful outcome predictors. Finally, microvascular blood flow alterations are related to sublingual Pco_2 (27), which would not be expected if microvascular blood flow just matched patchy zones of altered metabolism, as tissue Co_2 increases only when flow is insufficient in relation to Co_2 production. Microvascular perfusion alterations thus may be involved in the processes leading to multiple organ failure and death.

Other indexes of impaired tissue perfusion also improved more rapidly in survivors than in nonsurvivors. Arterial lactate concentrations were, as expected, higher in nonsurvivors and decreased more slowly than in survivors. Several factors may explain these differences, including, of course, the more severe microcirculatory alterations. As mentioned previously, the ROC curve area was higher for changes in microcirculatory perfusion than for any other variable, indicating the predominant role of microcirculatory alterations.

There were some limitations to our study. First, our observations are limited by the semiquantitative analysis of the data. Direct quantitative measurement of blood flow in each vessel is limited by the multiple projection of vessels in the area of interest and the movement artifacts. However, we previously reported with this semiquantitative analysis that the interobserver variability is around 5% (4). In addition, data analysis was blind to the clinical condition and the sequence of images. Second, the sublingual mucosa, which shares a similar embryonic origin with the digestive mucosa, may not reflect other microcirculatory beds. Nevertheless, Weil and coworkers (28, 29) reported that the sublingual capnometry similarly reflected the severity of shock states and outcome. Sublingual capnometry and gastric tonometry revealed parallel alterations, suggesting that both areas can be similarly and simultaneously affected. Recently, we studied the evolution of sublingual Pco_2 during resuscitation of patients with septic shock (30) and compared it with the evolution of gastric

mucosal P_{CO_2} and sublingual microcirculation assessed by OPS imaging. The decrease in sublingual P_{CO_2} with various therapeutic interventions was accompanied by an improvement in the sublingual microvascular perfusion and later decrease in gastric mucosal P_{CO_2}. The sublingual region has the advantage of being more readily accessible but still as useful as the splanchnic area for monitoring. Third, the microcirculation may be influenced by vasopressors and hypotension. However, experimental (31) and clinical (4) data do not support these findings. Animal studies suggest that the microcirculatory alterations are independent of arterial hypotension. The perfusion of diaphragmatic capillaries (31) and of gut villi (32) was markedly decreased in septic rodents compared with hypovolemic controls with a similar degree of hypotension. In patients with septic shock, Ledoux et al. (33) reported that increasing mean arterial pressure from 65 to 85 mm Hg with norepinephrine was associated with an increase in cardiac index, whereas skin microvascular blood flow and gastric mucosal P_{CO_2} remained unchanged. We (4) also previously reported in patients with severe sepsis that microcirculatory alterations were not correlated with blood pressure, cardiac index, and other global hemodynamic variables. Hence, the OPS technique may be more helpful than global monitoring variables to guide therapy.

CONCLUSION

Microcirculatory alterations improved rapidly in septic shock survivors but not in nonsurvivors. Persistent microcirculatory alterations were associated with MOF and death, even though global hemodynamic and oxygenation variables were similar. Improvement in microvascular perfusion, as early as 24 hrs after the onset of shock, can be a good predictor of ICU mortality. OPS imaging can be useful to identify patients in septic shock with persistent microcirculatory alterations in whom microvascular recruitment may be an important therapeutic target.

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