The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects*

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Objective: **To evaluate the effects of dobutamine on microcirculatory blood flow alterations in patients with septic shock.**

Design: **Prospective, open-label study.**

Setting: **A 31-bed, medico-surgical intensive care unit of a university hospital.**

Patients: **Twenty-two patients with septic shock.**

Interventions: **Intravenous administration of dobutamine (5 μg/kg·min) for 2 hrs (n = 22) followed by the addition of 10^{-2} M acetylcholine (topically applied, n = 10).**

Measurements and Main Results: **Complete hemodynamic measurements were obtained before and after dobutamine administration. In addition, the sublingual microcirculation was investigated with an orthogonal polarization spectral imaging technique before and after dobutamine administration and after topical application of acetylcholine. Dobutamine significantly improved capillary perfusion (from 48 ± 15 to 67 ± 11%, $p = .001$), but with large individual variation, whereas capillary density remained stable. The addition of topical acetylcholine completely restored capillary perfusion (98 ± 1%, $p = .001$) and capillary density. The changes in capillary perfusion during dobutamine administration were not related to changes in cardiac index ($p = .45$) or arterial pressure ($p = .29$). Interestingly, the decrease in lactate levels was proportional to the improvement in capillary perfusion ($y = 0.07 - 0.02x$, $r^2 = .46$, $p = .005$) but not to changes in cardiac index ($p = .55$).**

Conclusions: **The administration of 5 μg/kg·min dobutamine can improve but not restore capillary perfusion in patients with septic shock. These changes are independent of changes in systemic hemodynamic variables. (Crit Care Med 2006; 34:403–408)**

Key Words: microcirculation; tissue perfusion; tissue oxygenation; inotropic agents; acetylcholine; lactate

Microvascular blood flow alterations are frequently observed in patients with severe sepsis (1, 2). These alterations include a decrease in the proportion of perfused vessels smaller than 20 μm, mostly capillaries, whereas the perfusion of larger vessels is preserved. As persistent microvascular alterations are related to the development of multiple organ failure and death (2), interventions able to improve the microcirculation are attractive. We recently reported that topical application of acetylcholine can completely restore a normal microcirculatory pattern in patients with septic shock (1), indicating that the microvascular endothelium is still responsive to vasodilatory agents and, more important, that these alterations can be manipulated. In experimental studies, several vasodilatory compounds have been shown to improve microvascular perfusion (3–7) and even improve outcome (5, 8). In a human study, Spronk et al. (9) observed that intravenous administration of nitroglycerin resulted in a marked improvement in capillary perfusion, but this intervention may induce severe arterial hypotension and also increase some nitric oxide-mediated cytotoxic effects (10, 11). Hence, other vasoactive compounds may be preferable.

Dobutamine is primarily a β-adrenergic agent, and experimental studies using videomicroscopy have demonstrated that β-adrenergic agents can improve microcirculatory blood flow (12–15). In endotoxemic rats, dobutamine maintained microvascular blood flow in intestinal villi (14) and in liver sinusoids (15). Data in critically ill patients are scarce. Christ et al. (16) reported that dobutamine increased skin microvascular blood assessed by plethysmography. Duranteau et al. (17) observed that dobutamine increased gastric mucosal blood flow, as assessed by a laser Doppler technique. However, these data were obtained with indirect techniques that do not directly visualize the microcirculation, so that heterogeneity in blood flow, a fundamental characteristic of the septic insult, was not taken into account. The orthogonal polarization spectral (OPS) imaging technique can directly visualize the microcirculation of tissues covered by a thin epithelial layer, such as the sublingual mucosa (18). Using this technique we were able to demonstrate at the bedside alterations in microvascular perfusion in patients with severe sepsis and septic shock (1, 2) and in patients with severe heart failure (19). This technique can easily be repeated to assess the evolution of these alterations over time (2) and thus can also be used to assess the effect of therapeutic interventions (9, 20).

Most agents that have been used to influence the microcirculation (9, 17) also have potent systemic effects, affecting cardiac output and/or blood pressure, so that it is difficult to differentiate the microcirculatory from the systemic effects of these agents. Most of the studies cited here measured only microvascular blood flow.

*See also p. 561.

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Table 1. Study population (n = 22)

Age, yrs	67 ± 7
Gender, male/female, n	16/6
Source of sepsis, n	
Lung	10
Abdomen	7
Urinary tract	2
Other	3
Survival, n	10
APACHE II score	24 ± 5
SOFA score	9 ± 3
Dopamine, n (dose in μg/kg · min)	20; 15 ± 6
Norepinephrine, n (dose in μg/kg · min)	10; 0.4 ± 0.3
PEEP, cm H_2O	9 ± 3
F_{IO_2}	0.55 ± 0.15
Hemoglobin, g/dL	9.0 ± 0.9

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; PEEP, positive end-expiratory pressure.

Data are presented as mean ± SD, unless stated otherwise.

In this study we used the OPS imaging technique to investigate the sublingual microcirculation of patients in septic shock during dobutamine administration. We hypothesized that dobutamine may improve the sepsis-related alterations in microcirculatory perfusion, independent of its systemic effects.

PATIENTS AND METHODS

The study was approved by the ethical committee of Erasme University Hospital, and informed consent was obtained from the next of kin of each patient. The study included 22 patients with septic shock of <48 hrs duration. Septic shock was defined as hypotension (mean arterial pressure <65 mm Hg) requiring the administration of a pressor agent (dopamine >5 μg/kg·min or norepinephrine at any dose) in the presence of an infection (21). Pregnant women, patients younger than 18 yrs old, and patients with liver cirrhosis were not included.

All patients were already equipped with an arterial and pulmonary artery catheter with continuous cardiac output measurement (Vigilance CCO catheter; Edwards Lifesciences, Irvine, CA) and were receiving mechanical ventilation. Sedation was provided with midazolam (up to 5 mg/hr) and analgesia with morphine (up to 3 mg/hr).

Protocol. Before baseline measurements, hypovolemia was excluded by repeated volume challenges up to a point where stroke volume did not increase further, or when the pulmonary artery balloon-occluded pressure (PAOP) reached 18 mm Hg. In one patient, PAOP reached 18 mm Hg but the pulse pressure variation was >12% (22) so that fluid challenge was continued until the pulse pressure variation was <10%. After baseline measurements, dobutamine was administered intravenously in all patients at a dose of 5 μg/kg·min, and measurements were repeated after 120 mins. In the first ten patients, a gauze imbibed with acetylcholine at a concentration of 10^{-2} M was then applied topically to the sublingual area for 1 min while dobutamine administration was continued. After removal of the gauze, microvideoscopic measurements only were repeated.

Measurements. Temperature, heart rate, mean arterial pressure, pulmonary artery pressure, PAOP, and right atrial pressure were obtained. All pressures were measured at end expiration. Cardiac output was obtained as the average of the measurement displayed at the beginning and at the end of the hemodynamic measurement. After obtaining these measurements, arterial and mixed venous blood samples were withdrawn for the determination of blood gases, hemoglobin saturation, and arterial hemoglobin and arterial lactate concentrations (ABL700; Radiometer, Copenhagen, Denmark). Oxygen delivery, oxygen consumption ($\dot{V}O_2$), and oxygen extraction were calculated using standard formulas. The Acute Physiology and Chronic Health Evaluation II score (23) and the Sepsis-related Organ Failure Assessment score (24) were calculated.

Microvideoscopic Measurements and Analysis. The sublingual microvascular network was studied as previously described (1, 2) using the Cytoscan A/RII (Cytometrics, Philadelphia, PA) with a ×5 objective (×167 magnification). After removal of saliva and other secretions with a gauze, the device was applied without pressure on the lateral side of the tongue, in an area approximately 2–4 cm from the tip of the tongue. Sequences of 20 secs from five adjacent areas were recorded on disk using a personal computer and videocard (Miro Video; Pinnacle Systems, Mountain View, CA). These sequences were allocated a random number and were later analyzed using a semiquantitative method (1) by an investigator blinded to the patient's diagnosis and therapy. Briefly, three equidistant horizontal and three equidistant vertical lines were drawn. Vessel density (defined as the density of all vessels containing red blood cells, whatever the flow) was calculated as the number of vessels crossing the lines divided by the total length of the lines; the type of flow was defined as continuous, no flow, or intermittent during the 20-sec observation period. As OPS can only visualize vessels filled with red blood cells, this definition excludes empty vessels. The vessels were separated as large (>20 μm, mainly venules) and small (<20 μm, mainly capillaries). Vessel perfusion (total, large, and small) was defined as the proportion of perfused vessels, calculated as the number of vessels continuously perfused during the 20-sec observation period divided by the total number of vessels of the same type. In each patient and at each point, the data from the five areas were averaged. To assess the variability between the areas, we calculated the coefficient of variation of vessel perfusion as the SD of the five values of vessel perfusion divided by their mean value. The intra-observer and inter-observer variabilities have been previously determined (1). The coefficient of variability ranged from 2.5% to 4.7% (intra-observer) and from 3.0% to 6.2% (inter-observer) for the total number of vessels and from 0.9% to 4.5% (intra-observer) and from 4.1% to 10.0% (inter-observer) for the proportion of perfused vessels.

Statistical Analysis. Normal distribution of the data was confirmed by a Kolgomorov-Smirnov test; data were analyzed using parametric tests. Evolution over time was assessed by analysis of variance followed by a Student's *t*-test with Bonferroni correction for multiple comparisons. Relationships between changes at the systemic and microcirculatory level were assessed linear regression. Data are presented as mean ± SD. We considered $p < .05$ as significant.

RESULTS

The clinical data of the 22 patients are presented in Table 1. All patients were treated with dopamine, and ten were also treated with norepinephrine. The hemodynamic effects of dobutamine are reported in Table 2. Dobutamine administration significantly increased cardiac index (21 ± 10%, $p = .001$) and oxygen delivery (21 ± 10%, $p = .001$) without affecting mean arterial pressure (3 ± 9%, $p = .15$). The changes in $\dot{V}O_2$ (3 ± 17%) were not significant ($p = .82$). Blood lactate concentrations decreased slightly but significantly (−11 ± 11%, $p = .001$).

Dobutamine significantly increased both total vascular density and capillary perfusion (Table 3). Accordingly, the density of perfused capillaries increased by 52 ± 46% ($p = .001$). However, the changes in capillary perfusion were quite variable (Fig. 1), and these were larger when mi-

Table 2. Hemodynamic effects of dobutamine (n = 22)

	Baseline	Dobutamine	*p* Value
Temperature, °C	37.3 ± 1.0	37.2 ± 1.1	.033
Heart rate, beats/min	89 ± 13	95 ± 13	.020
Mean arterial pressure, mm Hg	69 ± 5	71 ± 6	.145
Mean pulmonary artery pressure, mm Hg	31 ± 9	30 ± 8	.339
Pulmonary artery occluded pressure, mm Hg	14 ± 4	14 ± 4	.66
Right atrial pressure, mm Hg	11 ± 3	11 ± 3	.89
Cardiac index, L/min · M^2	3.63 ± 0.90	4.36 ± 1.07	.001
pH	7.30 ± 0.07	7.30 ± 0.07	.847
$Paco_2$, mm Hg	38 ± 6	38 ± 6	.278
Pao_2, mm Hg	89 ± 17	91 ± 22	.546
Sao_2, %	97 ± 2	97 ± 2	.525
Svo_2, %	69 ± 5	73 ± 6	.001
$\dot{D}o_2$, mL/min · M^2	452 ± 132	544 ± 157	.001
$\dot{V}o_2$, mL/min · M^2	129 ± 29	130 ± 25	.817
O_2ER, %	29 ± 5	25 ± 6	.001
Lactate, mEq/L	2.3 ± 0.7	2.1 ± 0.7	.001

Sao_2, arterial oxygen saturation; Svo_2, venous oxygen saturation; $\dot{D}o_2$, oxygen delivery; $\dot{V}o_2$, oxygen consumption; O_2ER, oxygen extraction.

Data are presented as mean ± SD.

Table 3. Effects of dobutamine on microcirculatory perfusion in the entire population (n = 22)

	Baseline	Dobutamine	*p* Value
Total vascular density, n/mm^2	6.5 ± 1.1	7.4 ± 1.1	.001
Proportion perfused venules, %	99 ± 1	100 ± 0	.50
Proportion perfused capillaries, %	48 ± 16	67 ± 11	.001
Density of perfused capillaries, n/mm^2	5.2 ± 1.3	6.3 ± 1.1	.001
Proportion of nonperfused capillaries, %	19 ± 14	10 ± 8	.004
Proportion of intermittently perfused capillaries	31 ± 8	15 ± 7	.002
Coefficient of variation perfused vessels, %	15 ± 8	12 ± 7	.16

Data are presented as mean ± SD.

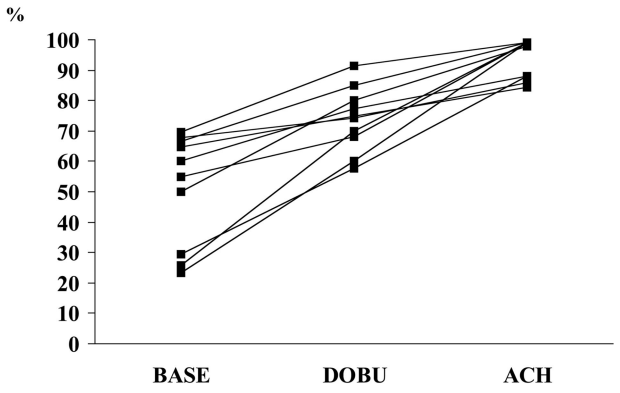

Figure 1. Individual changes in capillary perfusion in the subset of ten patients also investigated with acetylcholine. *BASE*, baseline; *DOBU*, dobutamine; *ACH*, acetylcholine.

crovascular perfusion was more severely altered at baseline. The increase in perfused capillaries was due to a similar decrease in nonperfused (−53 ± 21%, p = .004) and intermittently perfused (−49 ± 24%, p = .002) capillaries. However, the variability between the five areas, assessed by the coefficient of variation, was not significantly affected (−8 ± 32%, p = .16). All venules were already perfused at baseline and this was not affected by dobutamine administration. The topical application of acetylcholine, in addition to dobutamine, increased total vascular density (21 ± 11%, p = .009) as shown in Table 4. The proportion of perfused capillaries further increased and was then close to 100%.

Capillary perfusion was not related to cardiac index or mean arterial pressure, at baseline or after dobutamine administration (data not shown). The increase in capillary perfusion was not related to the changes in cardiac index (Fig. 2, *upper panel*), in arterial pressure (Fig. 2, *lower panel*), or in systemic vascular resistance (data not shown). Interestingly, the changes in arterial lactate levels were inversely related to the increase in capillary perfusion ($y = -0.15x + 0.07$, $r^2 = .45$, p = .005, Fig. 3, *upper panel*) but not to changes in cardiac index (Fig. 3, *lower panel*). Finally, changes in capillary perfusion and lactate levels were not related to changes in $\dot{V}o_2$ (data not shown).

DISCUSSION

The present study demonstrates that dobutamine improves microvascular perfusion in the early phase of septic shock and that these changes are independent of its global hemodynamic effects. However, dobutamine did not fully recruit the microcirculation, as the addition of topically applied acetylcholine further increased vascular density and capillary perfusion.

The improvement in microvascular perfusion is in accordance with several experimental studies. In rodents, β-adrenergic agents improved the liver or gut microcirculatory alterations that were observed after induction of fecal peritonitis or endotoxin administration (12, 13, 15). The dose of dobutamine may of course be challenged. By using a fixed dose of dobutamine, we may have underestimated some of the effects of dobutamine and cannot be sure that a higher dose may not have further improved the microcirculation. However, increasing the dose of dobutamine from 5 to 10 μg/kg·min did not further improve liver or gut mucosal blood flow in experimental endotoxic shock (25, 26) and Pco_2 gap in patients with septic shock (27). In these studies also, dobutamine failed to normalize the alterations. An important question is whether the increase in microvascular perfusion was large enough, as it could be further improved with acetylcholine. This cannot be determined on our data set and can only be determined in experimental conditions with simultaneous measurements of microvascular blood flow and local metabolism.

Another key issue is whether the changes in microcirculatory perfusion were related to changes in systemic hemodynamic variables. Experimental (28, 29) and clinical (1, 2) observations sug-

Table 4. Evolution of microcirculatory perfusion in the subset of ten patients also investigated with acetylcholine

	Baseline	Dobutamine	Acetylcholine
Total vascular density, n/mm^2	6.4 (5.2–7.1)	6.4 (6.0–7.1)	7.3 (7.1–7.8)[a,b]
Proportion perfused venules, %	100 (100–100)	100 (100–100)	100 (100–100)
Proportion perfused capillaries, %	58 (29–66)	75 (68–80)[a]	98 (88–99)[a,c]
Density of perfused capillaries, n/mm^2	2.1 (0.8–3.5)	3.5 (3.0–4.0)[a]	4.9 (4.3–5.7)[a,c]
Proportion of nonperfused capillaries, %	11 (9–29)	6 (3–20)[a]	2 (1–2)[a,b]
Proportion of intermittently perfused capillaries	30 (23–36)	16 (10–20)[a]	2 (1–10)[a,c]
Coefficient of variation perfused vessels, %	13 (10–18)	11 (8–13)	9 (6–16)

As these data were not normally distributed, evolution over time was assessed by a Friedman test followed by a Wilcoxon's signed rank test with Bonferroni correction for multiple comparisons. Data are presented as median (percentiles 25–75).

[a] $p < .01$ vs. baseline; [b] $p < .05$ and [c] $p < .01$ acetylcholine vs. dobutamine.

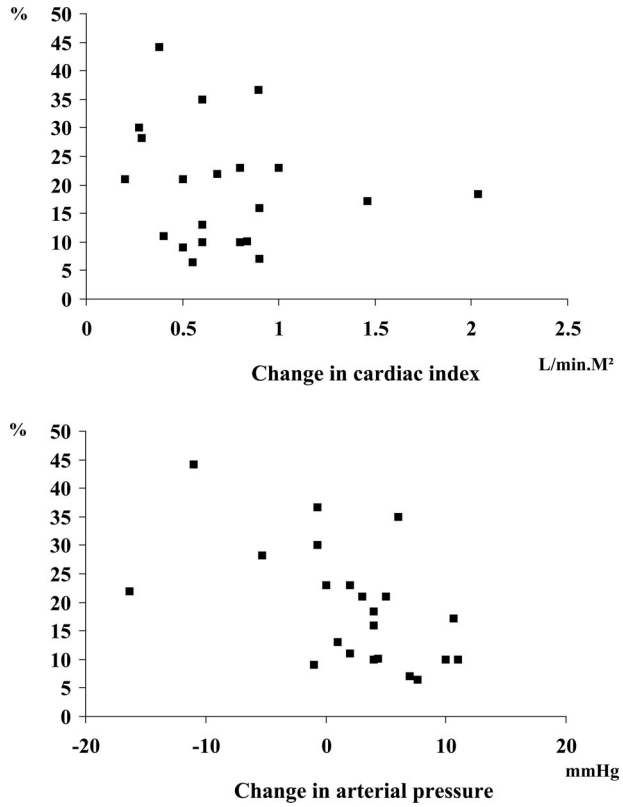

Figure 2. Relationship between changes in capillary perfusion and changes in cardiac output (*upper panel*) or changes in mean arterial pressure (*lower panel*). Absolute changes in capillary perfusion, cardiac index, and mean arterial pressure are reported for the entire population (n = 22). These changes were not corrected for baseline value. Neither the relationship between capillary perfusion and cardiac index nor that between capillary perfusion and arterial pressure was significant ($r^2 = .03$, $p = .45$, and $r^2 = .11$, $p = 0.29$, respectively)

gest that sepsis-related microcirculatory alterations are independent of systemic variables. Najakima et al. (28) reported that endotoxin induced microvascular blood flow alterations independent of changes in blood pressure. In our previous clinical observations, we reported that capillary perfusion was not related to arterial pressure or cardiac index (1, 2). In our study, the microcirculatory effects of dobutamine were clearly independent from its effects on blood pressure and cardiac index. We cannot exclude that dobutamine selectively increased facial and tongue blood flows, but we do not see why this would be the case. In addition, dobutamine had similar effects on bowel and liver microcirculation in septic conditions (14, 15, 17). This suggests that dobutamine specifically affected the microcirculation. As capillaries are deprived of β-adrenergic receptors, it is likely that these effects were mediated by effects on larger arterioles, which could not be visualized by OPS imaging.

An important finding is that the improvement in microcirculatory alterations was related to arterial lactate levels. The interpretation of blood lactate concentrations in septic shock is notoriously complex (30) and may involve circulatory as well as metabolic components. Our study was probably too short for the decrease in blood lactate to be explained only by an increased lactate clearance due to an improved liver blood flow (15). The decrease in lactate levels was not related to changes in $\dot{V}O_2$ in these patients, but whole body $\dot{V}O_2$ measurements may not be sensitive enough to detect changes in tissue metabolism. Whole body $\dot{V}O_2$ is affected not only by microvascular blood flow but also by blood flow distribution and cellular metabolism. Dobutamine can also have some metabolic effects. Reinelt et al. (31) reported that dobutamine increased splanchnic blood flow but did not increase splanchnic $\dot{V}O_2$, at least in part because it also decreased some energy-requiring metabolic pathways such as glucose production. Even though changes in $\dot{V}O_2$ may be dissociated from changes in lactate levels (32), this does not imply that the increase in perfusion was not beneficial. Although indirect, the proportional decrease in blood lactate levels provides a strong index that the increase in microvascular perfusion was associated with an improved metabolism. In a rat model of endotoxic shock, van Lambalgen et al. (33) observed that dobutamine increased tissue adenosine triphosphate and phosphocreatine levels. Similarly, the addition of dobutamine to norepinephrine in a sheep model of septic shock decreased lactate levels and Pco_2 gap and prolonged survival time when compared with norepinephrine alone (34).

Nevertheless, it is quite obvious that dobutamine improved but failed to normalize microcirculatory perfusion in these septic patients. Moreover, our short-term data do not provide evidence that long-term administration of dobut-

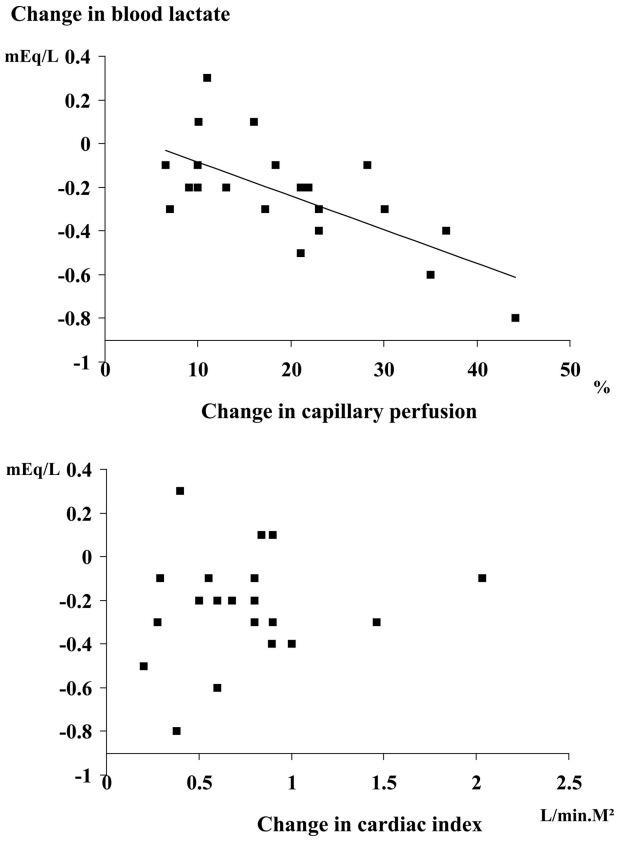

Figure 3. Relationship between changes in capillary perfusion (*upper panel*) or cardiac index (*lower panel*) and changes in arterial lactate concentrations. In this graph, absolute changes in capillary perfusion, cardiac index, and lactate levels are reported for the entire population (n = 22). These changes were not corrected for baseline value. The relationship between changes in capillary perfusion and in lactate levels was statistically significant ($y = -0.15x + 0.07$, $r^2 = .45$, $p = .005$) but not the relationship between changes in cardiac index and lactate levels ($r^2 = .04$, $p = .55$).

amine is beneficial. These data nevertheless highlight that dobutamine, one of the components of the Rivers approach (35), can have beneficial effects on microcirculatory alterations in the early stages of sepsis. Of note, acetylcholine fully normalized the microcirculation in these patients. This suggests that vasodilatory compounds may be more effective than dobutamine for improving microcirculatory blood flow, a concept supported by Ince and collaborators (4, 9).

A limitation of this study is that blood flow in venules and capillaries was not measured. However, measurement of red blood cell velocity in the microvascular network is very difficult. This is due in part to the movement of the background, and it is often difficult to separate movement of red blood cells within a vessel from movement of the vessel itself. In addition, the sublingual microvascular network is quite tortuous, and all vessels are not in the same plane, but the OPS images provide only a two-dimensional projection of these vessels. Unfortunately, other techniques do not perform better, as laser Doppler measures the average velocity of all vessels included in the sampling volume and is, of course, mostly affected by high flow vessels. Of note, the sampling volume of the most recent laser Doppler is 1 mm^3, which represents the total surface investigated by our ×5 OPS probe over a depth of 20 μm.

CONCLUSIONS

The administration of 5 μg/kg·min dobutamine improved but failed to restore capillary perfusion in patients with septic shock. The changes in microcirculatory perfusion were independent of changes in systemic hemodynamic variables and thus cannot be predicted by global hemodynamic measurements. The concomitant decrease in blood lactate levels suggests that changes in microvascular perfusion were associated with improved cellular metabolism.

The administration of 5 μg/kg·min dobutamine improved but failed to restore capillary perfusion in patients with septic shock.

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