

# The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock\*

Shaman Jhanji, MRCP, FRCA; Sarah Stirling, MRCP, FRCA; Nakul Patel, MBBS; Charles J. Hinds, FRCP, FRCA; Rupert M. Pearce, FRCA, MD

**Objective:** To investigate the effect of escalating doses of norepinephrine, aimed at achieving incremental increases in mean arterial pressure (MAP), on microvascular flow and tissue oxygenation in patients with septic shock.

**Design:** Single-center interventional study.

**Setting:** University hospital intensive care unit.

**Patients:** Sixteen patients with established septic shock.

**Interventions:** The norepinephrine dose was escalated to achieve incremental increases in the MAP from 60 to 70, 80, and 90 mm Hg.

**Measurements and Main Results:** In addition to routine clinical measurements, cardiac output was determined using lithium dilution and arterial waveform analysis, cutaneous tissue  $P_{tO_2}$  was measured using a Clark electrode, cutaneous red blood cell flux was assessed using laser Doppler flowmetry, and sublingual microvascular flow was evaluated using sidestream darkfield imaging. The mean (SD) norepinephrine dose increased from 0.18 (0.18)  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  at 60 mm Hg to 0.41 (0.26)  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  at 90 mm Hg ( $p < 0.0001$ ). During this period, global oxygen

delivery increased from 487 (418–642) to 662 (498–829)  $\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$  ( $p < 0.01$ ), cutaneous  $P_{tO_2}$  increased from 44 (11) to 54 (13) mm Hg ( $p < 0.0001$ ) and cutaneous microvascular red blood cell flux increased from 26.1 (16.2–41.9) to 33.3 (20.3–46.7) perfusion units ( $p < 0.05$ ). No changes in sublingual microvascular flow index, vessel density, the proportion of perfused vessels, perfused vessel density, or heterogeneity index were identified by sidestream darkfield imaging.

**Conclusions:** In patients with septic shock, targeting higher MAP by increasing the dose of norepinephrine resulted in an increase in global oxygen delivery, cutaneous microvascular flow, and tissue oxygenation. There were no changes in preexisting abnormalities of sublingual microvascular flow. Further research is required to clarify the optimal end points for vasopressor therapy in patients with septic shock. (Crit Care Med 2009; 37: 1961–1966)

**KEY WORDS:** septic shock; norepinephrine; microcirculation; tissue oxygenation; global oxygen delivery

Sepsis is characterized by a complex combination of cardiovascular derangements, including vasodilatation, hypovolemia, myocardial depression, and altered microvascular flow (1–4). In severe cases, arterial hypotension may persist despite aggressive intravenous fluid resuscitation, a condition termed septic

shock (5). In health, constant organ blood flow is maintained by autoregulation over a range of mean arterial pressures (MAPs) between 60 and 100 mm Hg; when MAP falls below this range, organ blood flow also decreases in a linear fashion (6). Consequently, in septic shock, vasopressor therapy is recommended to maintain tissue perfusion and oxygenation (7), although sepsis-related changes in vascular reactivity may alter the normal autoregulatory range (8), and the optimal arterial pressure end point for vasopressor therapy remains uncertain (9). Indeed, the current recommendation to maintain MAP at  $>65$  mm Hg is supported by only limited evidence (10, 11), and some have advocated routine use of higher arterial pressure targets, or alternatively the restoration of MAP to pre-morbid values. Because the consequences of both inadequate and excessive vasopressor therapy can be serious (12), it is important to clarify the optimal end points to which these potent agents should be titrated and to investigate the effects of alternative vasopressor agents (13).

Sepsis results in a variety of deleterious microvascular changes that are associated with organ failure and death (14). These derangements include increased endothelial permeability, endothelial leukocyte adhesion (15), and a characteristic heterogeneity of blood flow that is associated with tissue hypoxia (4, 16, 17). The causes of heterogeneous microvascular flow are not fully understood but reduced vascular tone because of impaired endothelial signal transduction may be one explanation (18). It is possible, therefore, that vasopressors might correct the abnormalities of microvascular flow and the tissue oxygenation associated with septic shock.

The dose-related effects of vasopressor therapy on microvascular flow and tissue oxygenation in sepsis have not been previously fully investigated. The aim of this investigation was to evaluate, in more detail, the effects of increasing doses of norepinephrine, targeted to achieve successively greater MAPs, on microvascular flow and tissue oxygenation in patients with septic shock.

## \*See also p. 2120.

From the Barts and The London School of Medicine and Dentistry, Queen Mary's University of London, London, United Kingdom.

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For information regarding this article, E-mail: [rupert.pearce@bartsandthelondon.nhs.uk](mailto:rupert.pearce@bartsandthelondon.nhs.uk)

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## PATIENTS AND METHODS

This single-center, interventional study was approved by the local Research Ethics Committee and the Medical and Healthcare products Regulatory Agency (UK). Adult patients admitted to intensive care with a diagnosis of septic shock, who were deemed to require vasopressor therapy despite adequate fluid resuscitation, were eligible for recruitment. Written informed consent was sought from the patient when possible. Where patients lacked capacity to give consent because they were unconscious, the consent of a relative was sought. Patients who survived were subsequently asked for written permission to use their data, once capacity had been regained. Exclusion criteria were refusal of consent by the patient or relative, concurrent lithium therapy, acute myocardial ischemia, acute arrhythmias, pregnancy, patients receiving palliative treatment only, and weight <40 kg.

**Clinical Management and Study Interventions.** The clinical management of each patient was determined by clinical staff in accordance with care bundles based on the Surviving Sepsis Guidelines that were current at the time of the study (19). This included compliance with the guidelines for fluid resuscitation, low-dose steroid therapy, tight glycaemic control, administration of drotrecogin alfa activated, red cell transfusion, and invasive ventilation. Adherence to these care bundles is regularly audited in our intensive care unit. The norepinephrine infusion was initially titrated by the research team to achieve an MAP of 60 mm Hg. After a 45-minute period of observation to ensure that the blood pressure and hemodynamics had stabilized, initial measurements were taken. The norepinephrine infusion was then increased to achieve an MAP of 70 mm Hg, followed by another 45-minute stabilization period before the next set of measurements. This process was repeated with the norepinephrine infusion rate being increased to achieve an MAP of 80 mm Hg and finally 90 mm Hg. Patients were monitored throughout the 4-hour intervention period for adverse events, in particular, tachycardia, arrhythmias, myocardial ischemia, hypertension, or other signs of excessive vasoconstriction. The physician in charge was free to request dose adjustment or cessation of the study at any time.

**Measurements.** In addition to routine clinical measurements, cardiac output and oxygen delivery index were determined using transpulmonary lithium indicator dilution analysis software (LiDCoplus, LiDCO, Cambridge, UK). In brief, 0.3 mmol (2 mL) of lithium chloride is injected via a central venous catheter. The arterial lithium ion concentration is then measured using an external electrode attached to a radial arterial catheter. A concentration–time curve is constructed,

allowing calculation of cardiac output using a modified Stewart-Hamilton equation. These data are then used to calibrate arterial waveform analysis software that determines changes in stroke volume with each cardiac cycle. This technology has been well validated against other methods of cardiac output monitoring and is described in detail elsewhere (20). Arterial and central venous blood samples were taken from indwelling cannulae after stabilization at each time point for analysis of blood gas tensions, lactate and hemoglobin concentration (ABL 600 and OSM3, Radiometer, Copenhagen, Denmark). Cutaneous tissue oxygen pressure ( $P_{tO_2}$ ) was measured at the same time point at two sites overlying the deltoid muscle using a Clark electrode (TCM400, Radiometer). The electrode is heated to 44°C to reduce artifact due to local vasoconstriction and to increase the permeability of the skin to oxygen. Oxygen molecules diffuse through a thin membrane covering the electrode where it is reduced at the cathode to produce a current proportional to the  $P_{O_2}$ . Laser Doppler flowmetry (Moorlab, Moor Instruments, Axminster, UK) was used to measure red blood cell flux at two sites overlying the deltoid muscle. This technique is based on the reflection of a beam of laser light that undergoes a change in wavelength (Doppler shift) when moving blood cells are encountered. The magnitude and frequency distribution of these changes are related to the number and velocity of red cells. The quantitative value derived from these measurements (red blood cell flux) is expressed in arbitrary perfusion units. To account for changes in blood pressure, cutaneous vascular conductance was also calculated by dividing red blood cell flux by MAP (perfusion units/mm Hg) (21). Sublingual microvascular flow was evaluated using sidestream darkfield (SDF) imaging with a  $\times 5$  objective lens (Microscan, Microvision Medical, Amsterdam, Netherlands) (22, 23). Image acquisition and subsequent analysis were performed according to published consensus criteria (24). In brief, SDF images were obtained from at least three sublingual areas at each time point. Microvascular flow index (MFI) was calculated after divid-

ing each image into four equal quadrants. Quantification of flow was determined using an ordinal scale (0, no flow; 1, intermittent flow; 2, sluggish flow; 3, normal flow) for small (<20  $\mu$ m) and large (>20  $\mu$ m) vessels. MFI is the average score of all quadrants for a given category of vessel size at a given time point. Images were recorded at three sites at each time point giving a total of 12 quadrants for analysis. To determine heterogeneity of flow across sublingual sites, a heterogeneity index was calculated as the highest MFI minus the lowest MFI divided by the mean MFI across all sublingual sites at that time point (25). Vessel density was calculated by inserting a grid of three equidistant horizontal and three equidistant vertical lines over the image. Vessel density is equal to the number of vessels crossing these lines divided by their total length. Flow was then categorized as present, intermittent, or absent, allowing calculation of the proportion of perfused vessels and perfused vessel density (4). Analysis of the videos was performed by two observers (S.J. and S.S.) blinded to each others observations and the clinical data.

**Statistical Analysis.** The primary outcome measure was the difference in sublingual MFI at different MAPs. Assuming a type I error rate of 5% and a type II error rate of 20%, we calculated that 16 patients would be required to detect a difference of 0.5 perfused vessels  $\text{mm}^{-2}$  (SD of difference between measurements:  $\pm 0.7$  vessels  $\text{mm}^{-2}$ ) between an MAP of 60 and 90 mm Hg. This calculation was based on data from a previous study of heterogeneity of microvascular flow in patients with severe sepsis (4). For continuous data, differences over time were tested using a repeated-measures analysis of variance with Dunnett's *post hoc* test for comparison against baseline. Non-normally distributed data were tested with the Friedman test. Analysis was performed using GraphPad Prism version 4.0 (GraphPad Software, San Diego, CA). Significance was set at  $p < 0.05$ . Data are presented as mean (SD) where normally distributed, and median (interquartile range) where not normally distributed.

Table 1. Baseline patient characteristics

Patient characteristics	
Age (yrs)	67 (55–72)
Gender	9 males (56%)
Body weight (kg)	75 (60–80)
APACHE II score	23 (17–30)
Duration of intensive care stay (d)	8 (5–14)
Mortality	10 deaths (62.5%)
Source of sepsis	
Respiratory infection (%)	7 (44%)
Abdominal infection (%)	6 (38%)
Urological infection (%)	2 (12%)
Soft tissue (%)	1 (6%)

APACHE, Acute Physiology and Chronic Health Evaluation.

Data presented as median (interquartile range) or absolute values (%).

Table 2. Clinical management at or between measurement time points

	60 mm Hg	70 mm Hg	80 mm Hg	90 mm Hg	<i>p</i>
Norepinephrine ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	0.18 (0.18)	0.25 (0.22)	0.35 (0.27)	0.41 (0.26)	<0.0001
Propofol ( $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ )	1.4 (1.3–2.3)	1.4 (1.3–2.3)	1.4 (1.3–2.3)	1.4 (1.3–2.3)	>0.99
Fentanyl ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ )	1.6 (1.4–2.0)	1.7 (1.4–2.1)	1.7 (1.4–2.1)	1.7 (1.4–2.1)	0.39
Midazolam ( $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ )	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	>0.99
Intravenous crystalloid (mL)	109 (89–160)	118 (74–142)	89 (67–134)	96 (48–143)	0.68

Data presented as infusion rate at each time point or, in the case of intravenous crystalloid, the volume administered during the stabilization period between time points. Data presented as mean (SD) or median (interquartile range). Significance testing with repeated-measures analysis of variance and Friedman test.

Table 3. Physiologic data at different measurement points with increasing mean arterial pressure

	60 mm Hg	70 mm Hg	80 mm Hg	90 mm Hg
Heart rate (bpm)	87 (17)	84 (18)	86 (18)	87 (17)
Cardiac index ( $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ) <sup>b</sup>	3.86 (1.22)	4.24 (1.26)	4.43 (1.43) <sup>f</sup>	4.79 (1.61) <sup>e</sup>
Oxygen delivery index ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ) <sup>c</sup>	487 (418–642)	536 (446–720)	550 (474–800)	662 (498–829)
Systemic vascular resistance index ( $\text{dynes}\cdot\text{sec}^{-1}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$ ) <sup>b</sup>	1195 (448)	1260 (392)	1402 (467) <sup>e</sup>	1451 (571) <sup>e</sup>
ScvO <sub>2</sub> (%) <sup>d</sup>	71 (6.4)	72 (6.7)	73 (7.1)	74 (6.7) <sup>e</sup>
Serum lactate (mmol L <sup>-1</sup> )	2.2 (1.4)	2.3 (1.3)	2.1 (1.2)	2.2 (1.2)
Serum base excess (mmol L <sup>-1</sup> ) <sup>d</sup>	−2.3 (0.2 to −4.2)	−1.6 (0.1 to −4.7)	−1.5 (1.3 to −3.7)	−1.9 (1.3 to −3.9)
Urine output (mL hr <sup>-1</sup> )	53 (38)	63 (41)	61 (39)	55 (38)
Pao <sub>2</sub> (mm Hg)	85 (17)	89 (17)	86 (18)	81 (17)
Cutaneous Pto <sub>2</sub> (mm Hg) <sup>a</sup>	44 (11)	51 (16) <sup>f</sup>	54 (13) <sup>e</sup>	54 (13) <sup>e</sup>
Pto <sub>2</sub> :Pao <sub>2</sub> ratio <sup>a</sup>	0.53 (0.19)	0.57 (0.21)	0.62 (0.17) <sup>e</sup>	0.67 (0.19) <sup>e</sup>

Pto<sub>2</sub>, tissue oxygen pressure; ScvO<sub>2</sub>, central venous oxygen saturation.

<sup>a</sup>*p* < 0.0001; <sup>b</sup>*p* < 0.001; <sup>c</sup>*p* < 0.01 and <sup>d</sup>*p* < 0.05 over time (repeated measures analysis of variance and Friedman test); <sup>e</sup>*p* < 0.01 and <sup>f</sup>*p* < 0.05 compared to baseline of mean arterial pressure 60 mm Hg (*post hoc* Dunnett's test). Data presented as mean (SD) or median (interquartile range).

## RESULTS

Sixteen patients were recruited a median of 1 day (0.5–3.5) after the onset of septic shock. Baseline characteristics are presented in Table 1. All patients had indwelling intra-arterial and central venous catheters. Increasing doses of norepinephrine were required to increase the MAP from 60 to 90 mm Hg (*p* < 0.0001). There were no changes in sedation or crystalloid infusion during the study period (Table 2). Three patients each received a single 250-mL bolus of colloid solution: one while the MAP was 60 mm Hg, one at 70 mm Hg, and one at 80 mm Hg. One patient was receiving an infusion of dobutamine and one an infusion of vasopressin, the doses of which remained constant throughout the study period ( $2.63 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and  $0.04 \text{ U}\cdot\text{min}^{-1}$ , respectively). A third patient received an infusion of drotrecogin alfa activated. All patients received low-dose steroids (hydrocortisone 50 mg every 6 hours) (19). Four patients were receiving continuous venovenous hemodiafiltration during the course of the study and passed no measurable volume of urine. In four patients, the attending physician requested that we not increase the MAP to 90 mm Hg because of theoretical concerns regarding the pos-

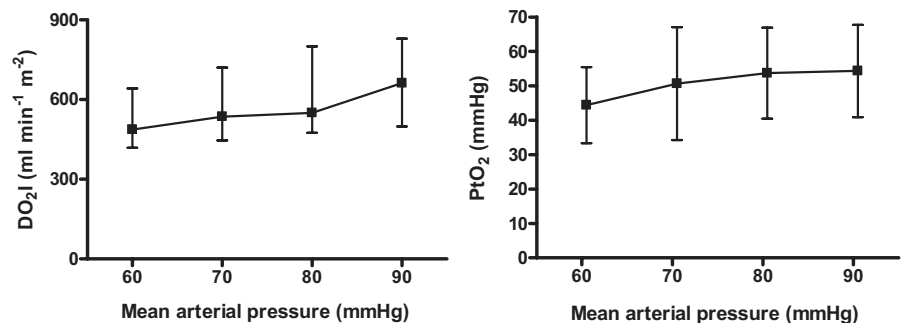


Figure 1. Increases in global oxygen delivery index (DO<sub>2</sub>I) (*p* < 0.01, Friedman test) and cutaneous tissue oxygen pressure (Pto<sub>2</sub>) (*p* < 0.0001, repeated-measures analysis of variance) associated with the increasing dose of norepinephrine required to achieve an increasing target mean arterial pressure. Pto<sub>2</sub> data presented as mean (SD), DO<sub>2</sub>I data presented as median (interquartile range).

sibility of impaired splanchnic perfusion. None of the patients developed tachycardia, arrhythmias, myocardial ischemia, signs of excessive vasoconstriction, or any other adverse effects that could be attributed to the intervention. In one patient, it was not possible to collect reliable SDF images because of patient movement.

There was a significant increase in global oxygen delivery (*p* < 0.01), cutaneous Pto<sub>2</sub> (*p* < 0.0001), and Pto<sub>2</sub>:Pao<sub>2</sub> ratio (*p* < 0.0001) as the MAP increased from 60 to 90 mm Hg (Table 3 and Fig. 1). Cardiac index and central venous oxygen saturation (ScvO<sub>2</sub>) also increased

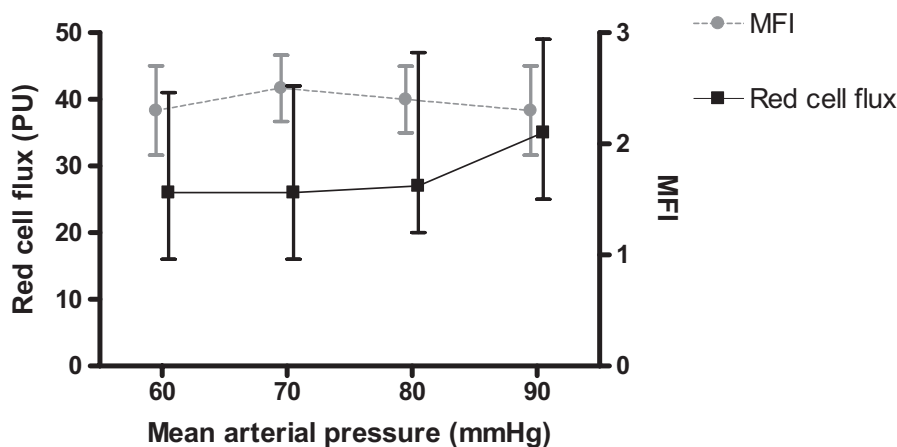
while base deficit improved. There were no changes in serum lactate or urine output (Table 3). There was an improvement in cutaneous red blood cell flux and a decrease in cutaneous vascular conductance as assessed by laser Doppler flowmetry (Table 4). There were no changes in small (<20  $\mu\text{m}$ ) or large (>20  $\mu\text{m}$ ) vessel MFI, vessel density, the proportion of perfused vessels, perfused vessel density, or heterogeneity index as assessed by SDF imaging (Table 4; Fig. 2 and Supplementary Table [see Table, Supplemental Digital Content 1, <http://links.lww.com/A866>]). The kappa coefficient with linear weighting



**Table 4.** Indices of heterogeneity of sublingual microvascular flow for small vessels (<20  $\mu\text{m}$ ), cutaneous red blood cell flux, and cutaneous vascular conductance with increasing mean arterial pressure

	60 mm Hg	70 mm Hg	80 mm Hg	90 mm Hg	<i>p</i>
Microvascular flow index	2.3 (0.4)	2.5 (0.3)	2.4 (0.3)	2.3 (0.4)	0.45
Vessel density ( $\text{mm}^{-1}$ )	6.9 (1.5)	7.1 (1.5)	7.1 (1.3)	6.9 (0.9)	0.96
Proportion of perfused vessels (%)	75 (66–87)	84 (74–90)	85 (71–93)	77 (72–84)	0.57
Perfused vessel density ( $\text{mm}^{-1}$ )	5.3 (1.9)	5.9 (1.8)	5.8 (1.5)	5.3 (1.3)	0.75
Heterogeneity index	0.41 (0.28)	0.37 (0.25)	0.32 (0.12)	0.33 (0.22)	0.84
Cutaneous red blood cell flux (PU)	26 (16–42)	27 (18–44)	27 (20–47)	33 (20–47)	0.04
Cutaneous vascular conductance (PU/mm Hg)	0.44 (0.27–0.70)	0.39 (0.25–0.63)	0.34 (0.24–0.59)	0.37 (0.23–0.52)	0.003

PU, perfusion units.  
Data presented as mean (SD) or median (interquartile range). Significance testing with repeated-measures analysis of variance and Friedman test.



**Figure 2.** Significant changes in cutaneous red blood cell flux ( $p < 0.05$ , Friedman test) but not sublingual microvascular flow index (*MFI*) ( $p = 0.45$ , repeated-measures analysis of variance) associated with the increasing dose of norepinephrine required to achieve an increasing target mean arterial pressure. MFI data presented as mean (SD), red blood cell flux data presented as median (interquartile range). PU, perfusion units.

for interobserver reliability for calculation of MFI was 0.82 (95% confidence interval 0.78–0.86).

## DISCUSSION

The principal finding of this study is that the use of incremental doses of norepinephrine to achieve increasing targets for MAP was associated with increases in global oxygen delivery, cutaneous  $\text{Pto}_2$ , and cutaneous red blood cell flux. Deranged indices of sublingual microvascular flow remained unchanged. We also identified an increase in  $\text{ScvO}_2$  and a decrease in base deficit as the dose of norepinephrine increased. However, in both cases, these changes were small and of limited clinical significance. There were no changes in serum lactate or urine output.

Although a number of pharmacologic interventions have been shown to improve microvascular flow in patients with septic shock (26–28), there are only limited data from clinical studies describing

the microvascular effects of different doses of norepinephrine in such patients. LeDoux et al reported that, despite an increase in global oxygen delivery, gastric mucosal  $\text{Pco}_2$  and cutaneous microvascular flow were unchanged when MAP was increased from 65 to 85 mm Hg using escalating doses of norepinephrine (10). In a subsequent study, patients were randomized to MAP targets for vasopressor therapy of 65 or 85 mm Hg (11). Global oxygen delivery and mixed venous oxygen saturation were greater in the 85 mm Hg group, although there were no differences in renal function (11). However, in a recent clinical investigation, urine output improved as MAP increased in response to noradrenaline (29), contrasting with our findings and those of others (11). None of these investigations included a visual assessment of the microcirculation, although improvements in sublingual microvascular flow have been described with the use of both dobutamine and vasodilator therapy in septic

shock (26, 27). Laboratory investigations of the effects of norepinephrine on global hemodynamics, tissue oxygenation, and the microvasculature in sepsis have also proved inconsistent. In a rodent endotoxemia model, treatment with norepinephrine improved tissue oxygenation (30), whereas in a more detailed investigation in a rodent fecal peritonitis model, norepinephrine was not associated with any changes in microvascular flow or tissue  $\text{Po}_2$  (31). In porcine models of sepsis, the increased dose of norepinephrine required to achieve higher MAP targets was associated with improved global hemodynamics (32, 33). In the first of these studies, this hemodynamic improvement was associated with an increase in regional and microvascular flow to the viscera (32), whereas in the subsequent studies, both regional and microvascular visceral flow were decreased (33). In another study in nonseptic pigs, no changes were identified in gut microvascular flow or oxygenation during norepinephrine infusion (34).

It is unclear why cutaneous microvascular flow and tissue oxygenation improved as the noradrenaline dose increased while sublingual microvascular flow remained unchanged. Previous reports suggest that microvascular flow and tissue oxygenation may differ between organs in sepsis (35–37). It is also possible that local responses to norepinephrine differ between vascular beds because of differences in metabolic demand between organs, heterogeneity in receptor distribution (38), or differential expression of inducible nitric oxide synthase (39). It should also be emphasized that while SDF imaging allows direct visualization of the microcirculation, laser Doppler flowmetry measures overall microvascular flow in the underlying tissues. Furthermore, in our patients, the abnormalities in sublingual microvascular flow

were less severe than those identified in previous reports, perhaps because of differences in the severity of illness or vasoactive drug therapy (4, 27). It is also possible that subtle changes in sublingual microvascular flow would have been identified if a much larger population of patients had been studied. In health, autoregulation would be expected to maintain constant tissue blood flow within this range of arterial pressures. Consequently, one would expect a decrease in vascular conductance with increasing arterial pressure and hence constant tissue blood flow. Interestingly, despite a decrease in cutaneous vascular conductance, there was still an increase in cutaneous red blood cell flux. This finding suggests disruption of autoregulatory mechanisms, either because of sepsis (8) or because of the administration of exogenous norepinephrine (40).

We used a variety of methods to obtain a more comprehensive assessment of alterations in microvascular flow. SDF imaging is a valuable technique that has been used successfully to evaluate the intact microcirculation in the clinical environment (23, 41). However, this technique remains semiquantitative and accuracy may be affected by interobserver bias and pressure artifact from the SDF camera. We specifically evaluated these potential sources of error and excluded any significant bias (see "Patients and Methods" section and Supplementary Table [see Table, Supplemental Digital Content 1, <http://links.lww.com/A866>]). Although a recent study has shown that sedative drugs can affect sublingual microvascular flow (42), doses of sedation remained unchanged throughout the current study. SDF imaging was complemented by laser Doppler flowmetry, a technique that provides an objective measure of overall microvascular flow but does not allow discrimination between flow in larger and smaller vessels. In addition, we evaluated cutaneous  $P_{tO_2}$  using a Clark electrode. With this method, the skin underneath the probe is warmed slightly to minimize artifact due to vasoconstriction; this active warming may, therefore, have counteracted the local vasoconstrictive effects of norepinephrine. However, the degree of warming remained constant throughout the experiment and, therefore, cannot explain the progressive increase in  $P_{tO_2}$ .

Although all patients were in established septic shock and had been adequately fluid resuscitated, variation in the delay between the diagnosis of septic

shock and study enrollment is a potential limitation of this study. This and the other differences between the patients, such as the use of other vasoactive agents, hemofiltration, and drotrecogin alfa activated, may have influenced microvascular function and hence the response to norepinephrine. Nevertheless, we were able to identify consistent and significant changes in microvascular flow and tissue oxygenation. Finally, it is important to emphasize that we explored only the short-term effects of norepinephrine on global hemodynamics, tissue microvascular flow, and oxygenation in the current study. Our understanding of the long-term effects of escalating vasopressor doses on these variables remains incomplete.

In summary, the use of norepinephrine to achieve incremental targets for MAP was associated with increases in global oxygen delivery, cutaneous microvascular flow, and tissue oxygenation in patients with established septic shock. However, there were no associated changes in the preexisting abnormalities of sublingual microvascular flow. These findings suggest that in patients with septic shock significant improvements in global hemodynamics and tissue oxygen delivery can be achieved using escalating doses of norepinephrine to achieve higher values for MAP, without exacerbating microcirculatory flow abnormalities. Further research is required to confirm our findings and to explore in more detail the long-term effects of higher arterial pressure targets for the administration of vasopressors.

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