Impairments in microvascular reactivity are related to organ failure in human sepsis

Kevin C. Doerschug,1 Angela S. Delsing,1 Gregory A. Schmidt,1 and William G. Haynes1,2

1Department of Internal Medicine and 2General Clinical Research Center, University of Iowa Carver College of Medicine, Iowa City, Iowa

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Severe sepsis is an inflammatory response to infection that results in acute organ dysfunction. Vascular perfusion abnormalities are implicated in the pathology of organ failure, but studies of microvascular function in human sepsis are limited. We hypothesized that impaired microvascular responses to reactive hyperemia lead to impaired oxygen delivery relative to the needs of tissue and that these impairments would be associated with organ failure in sepsis. We studied 24 severe sepsis subjects 24 h after recognition of organ dysfunction; 15 healthy subjects served as controls. Near-infrared spectroscopy (NIRS) was used to measure tissue 1) microvascular hemoglobin signal strength and 2) oxygen saturation of microvascular hemoglobin (StO2). Both values were measured in thenar skeletal muscle before and after 5 min of forearm stagnant ischemia. At baseline, skeletal muscle microvascular hemoglobin was lower in septic than in control subjects. Microvascular hemoglobin increased during reactive hyperemia in both groups, but less so in sepsis. StO2 at baseline and throughout ischemia was similar between the two groups; however, the rate of tissue oxygen consumption was significantly slower in septic subjects than in controls. The rate of increase in StO2 during reactive hyperemia was significantly slower in septic subjects than in controls; this impairment was accentuated in those with more organ failure. We conclude that organ dysfunction in severe sepsis is associated with dysregulation of microvascular oxygen balance. NIRS measurements of skeletal muscle microvascular perfusion and reactivity may provide important information about sepsis and serve as endpoints in future therapeutic interventions aimed at improving the microcirculation.

METHODS

We studied 24 consecutive patients in our Medical Intensive Care Unit that fulfilled enrollment criteria, including 1) severe sepsis defined by consensus statement (5); 2) organ failure for no more than 24 h; and 3) signed informed consent, including from surrogate decision makers. Patients were excluded for the following reasons: 1) recent chemotherapy; 2) recent steroid or immunosuppressive agents; 3) severe peripheral vascular disease, dialysis fistulas, or mastectomies that would preclude safe forearm occlusion; and 4) “Do Not Resuscitate” order at time of enrollment. In addition to sepsis subjects, we studied 15 healthy volunteers. This study was approved by the University of Iowa Institutional Review Board.

Sepsis subjects were studied 24 h after the clinical recognition of organ dysfunction. All resuscitation goals were left to the intensive care unit team. Patient clinical data were collected prospectively. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system (41), and severe organ failure was defined as SOFA ≥10, a predictor of 50% mortality (18). Vasocostriclor use was defined as SOFA cardiovascular component ≥3.

NIRS measurements of perfusion and reactivity. We utilized NIRS as a noninvasive technique that detects differential absorption of oxy- and deoxyhemoglobin within arterioles, capillaries, and venules of skeletal muscle with little influence from blood flow to skin or other tissues (31). Because NIRS is limited to monitoring of only small vessels (according to Beer’s law; see Ref. 31), and because it monitors pre- and postcapillary vessels (i.e., before and after oxygen extraction), NIRS has previously been used to assess the oxygen balance in the microcirculation of skeletal muscles of septic individuals (21). In addition to microvascular oxy- and deoxyhemoglobin, NIRS detects

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Address for reprint requests and other correspondence: K. C. Doerschug, 200 Hawkins Dr., Iowa City, IA 52242 (e-mail: kevin-doerschug@uiowa.edu).

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oxy- and deoxymyoglobin in the muscle, although the latter chromophore has little influence on the total signal (6, 31). Nonetheless, nomenclature has evolved such that some literature and device manufacturers refer to tissue measurements, and we will use this nomenclature for the purpose of consistency.

A commercially available, clinical spectrometer (InSpectra Tissue Spectrometer model 325; Hutchinson Technology) was applied to the thenar eminence throughout the study. This monitor uses 15-mm spacing between emission and detection points and provides tissue attenuation measurements at four discreet wavelengths (680, 720, 760, and 800 nm). Details of this wide-gap second derivative spectroscopic method have been described previously (34). The monitor provides the total hemoglobin signal strength (TH) in the volume of tissue sensed by the probe, as well as fractions of oxy- and deoxymyoglobin through a tissue depth approximating the probe length (34). Values were recorded directly to computer every 3.5 s. The positioning of the probe on the thenar eminence was chosen because of relatively low adiposity, consistency with other studies, and because of its amenability to forearm manipulation.

A vascular cuff (Hokanson) was inflated to 250 mmHg on the forearm to achieve stagnant ischemia for 5 min and then rapidly deflated. For each subject, we assessed the following: 1) total hemoglobin signal, an indicator of blood volume in the region of microvasculature sensed by the probe (referred to as TH by the manufacturer) expressed in arbitrary units (AU). TH was measured at baseline and recorded as the average of five values immediately before ischemia; 2) microvascular hemoglobin during reactive hyperemia (TH-RH), defined as the average of five TH values obtained during the interval 18–32 s following the release of occlusion. This prospectively defined interval depicts a plateau that follows a rapid increase during the initial 14 s of flow and precedes a decline toward baseline values; 3) change in TH (%ΔTH), defined as the difference of TH-RH – TH, and percent change in TH (%ΔTH) defined as %ΔTH × 100/TH; 4) oxygen saturation of hemoglobin in the microvasculature, referred to as tissue oxygen saturation (StO2) by the device manufacturer, expressed as percent; 5) oxygen consumption of skeletal muscle tissue through a tissue depth approximating the probe length (34). Values were recorded directly to computer every 3.5 s. The positioning of the probe on the thenar eminence was chosen because of relatively low adiposity, consistency with other studies, and because of its amenability to forearm manipulation.

Table 1. Clinical data of severe sepsis subjects

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>55</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72</td>
<td>121</td>
<td>93</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>94</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>7.9</td>
<td>14.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Blood lactate*</td>
<td>1.1</td>
<td>10.3</td>
<td>4</td>
</tr>
<tr>
<td>SOFA score</td>
<td>2</td>
<td>18</td>
<td>9.6</td>
</tr>
</tbody>
</table>

SpO2, oxygen saturation of microvascular hemoglobin; SOFA, sequential organ failure assessment; n, no. of subjects. *n = 11 subjects. ‡Severe organ failure defined as SOFA ≥10. †Vasoconstrictor use defined as SOFACardiovascular component ≥3.

with only modest dysfunction; however, it was lower in those subjects receiving vasoconstrictor infusions than in those who did not receive these medications [13.4 AU(SD3.5) vs. 18.4 AU(SD5.7), P = 0.01]. Among subjects with severe sepsis, there was no relationship between TH and age (linear regression r² = 0.005, P = 0.74). TH-RH. During and after the period of stagnant ischemia, there were no observed changes in systemic pulse rate or blood pressure. Following the release of the forearm vascular cuff and the subsequent return of blood flow, TH increased rapidly (within 30 s) to baseline levels or higher and remained elevated for ∼2 min in both severe sepsis and control subjects. TH-RH was significantly lower in septic subjects with both extensive and modest organ dysfunction compared with control subjects (P = 0.0002, see Table 2), but there was no significant difference between the two septic subgroups. When we examined the incremental change in TH from baseline to reactive hyperemia (%ΔTH), subjects with severe sepsis culminating in extensive organ dysfunction tended to have less increase in TH compared with either those with modest organ failure or control subjects. Because TH was lower in severe sepsis subjects, however, when %ΔTH was expressed as a percent of baseline (%ΔTH), the values were similar in all three groups.

We examined the effect of vasoconstrictor infusions on TH-RH and found this measure to be somewhat lower in subjects receiving these medications [16.8 AU(SD6.0)] compared with those who did not receive these medications [22.3 AU(SD6.5); Student’s t-test, P = 0.05]. However, we found virtually no effect of vasoconstrictor use on %ΔTH (P = 0.7) and %ΔΔTH (P = 0.91).

Tissue oxygenation before, during, and after stagnant ischemia. Baseline, or resting, StO2 in control subjects was 84% (SD 10), consistent with a vascular bed that includes pre- and postcapillary vessels, and with previous reports (34). Resting StO2 was similar in severe sepsis subjects [82% (SD13), see Fig. 2]. In parallel, resting StO2 measured 24 h after the onset of organ dysfunction was not associated with organ failure or survival at 7, 14, or 30 days.

During stagnant ischemia, StO2 decreased in both control and severe sepsis subjects. StO2 was similar in both groups at 30
and 60 s of ischemia, as well as at the end of ischemia (Fig. 2). Neither the absolute StO₂ nadir nor change in StO₂ during ischemia was associated with the degree of organ failure in septic subjects. However, V˙O₂tis was significantly lower in severe sepsis [233 AU(SD 156)] compared with control subjects [382 AU(SD 120); P < 0.003].

With the return of blood flow, StO₂ increased rapidly and remained elevated above baseline values for ~2 min in both severe sepsis subjects and normal controls. Representative StO₂ curves of two individual subjects during RH are shown in Fig. 3. In severe sepsis subjects with only modest organ dysfunction, RR tended to be slower [3.6%/s (SD 1.2)] than in normal controls [4.7%/s (SD 1.1)]. Severe sepsis subjects with severe organ failure (SOFA ≥ 10) had significant and pronounced impairments in RR [2.3%/s (SD 1.5)] when compared with septic subjects with less organ dysfunction as well as normal controls (see Fig. 4). RR tended to be slower in those that did not survive hospitalization [2.5%/s (SD 1.5)] than in those who survived [3.3%/s (SD 1.4)], although this fell short of statistical significance (P = 0.20). RR was not associated with mean arterial pressure (r² = 0.01; P = 0.62) nor serum glucose concentration. Because exogenous norepinephrine and other vasoconstrictors may affect vasodilation and RH, we compared RR values in severe sepsis subjects receiving vasoconstrictors [2.5%/s (SD 1.7)] with sepsis subjects not receiving vasoconstrictors [3.7%/s (SD 1.3)] and found no significant differences (Student’s t-test, P = 0.11). There was no relation-

Table 2. Total tissue hemoglobin index in reactive hyperemia

<table>
<thead>
<tr>
<th>Subject group</th>
<th>TH</th>
<th>TH-RH</th>
<th>ΔTH</th>
<th>%ΔTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>22.7 ± 2.4</td>
<td>27.7 ± 5.1</td>
<td>5 ± 4.2</td>
<td>21.7 ± 17.6</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modest organ failure</td>
<td>15.8 ± 5.5*</td>
<td>19.7 ± 6.5†</td>
<td>4.5 ± 3.8</td>
<td>30.2 ± 28.4</td>
</tr>
<tr>
<td>Severe organ failure</td>
<td>15.2 ± 4.9*</td>
<td>16.9 ± 6.9*</td>
<td>2.4 ± 3.6</td>
<td>16.7 ± 23.9</td>
</tr>
</tbody>
</table>

All values are means ± standard deviation. Definition of abbreviations: TH, total tissue hemoglobin index, at baseline, expressed in arbitrary units; TH-RH, TH during reactive hyperemia; ΔTH, change in TH from baseline to reactive hyperemia; %ΔTH, the ratio ΔTH × 100/TH. *P < 0.001 vs. control. †P < 0.01 vs. control.
ship between RR and age in septic subjects as investigated by linear regression ($r^2$ = 0.001; $P$ = 0.85).

To further investigate the microvascular milieu resulting in impaired tissue oxygen balance during RH in septic subjects, we analyzed the relationships of RR with both tissue hemoglobin and tissue oxygen consumption. In septic subjects, RR correlated significantly with TH-RH ($r^2$ = 0.47, $P$ = 0.0006; see Fig. 5) such that those with pronounced impairments in RR also had less total microvascular hemoglobin during RH. Interestingly, we also found a linear relationship between $\dot{V}O_2tis$ and RR in severe sepsis subjects ($r^2$ = 0.38; $P$ = 0.002; see Fig. 6).

**DISCUSSION**

We have shown that microvascular function is abnormal in septic subjects studied within 24 h of organ dysfunction. First we found that the skeletal muscle tissue hemoglobin signal is reduced in sepsis. Most blood volume and thus hemoglobin is likely to be contained within postcapillary venules in skeletal muscle, and therefore these data imply impaired venous vessel capacitance. However, this is in contrast to common descriptions of increased venous capacitance in the macrovasculature during septic shock (13). Catecholamine infusions decrease venous capacitance (9) and hence could explain some of the differences in tissue hemoglobin found in our septic subjects. However, septic subjects not receiving these medications also had impaired tissue hemoglobin compared with controls. Several characteristics of sepsis, such as anemia, and abnormal microvascular perfusion due to vessel constriction, decreased microvascular density, or venular leukostasis could also account for this reduced signal. Because we could show no correlation between TH and blood hemoglobin concentration, we suspect that microvascular perfusion abnormalities underlie this finding.

In addition to deficits in tissue hemoglobin during sepsis, we demonstrated abnormal tissue oxygen balance during and after stagnant ischemia. Baseline $StO_2$ was normal in resuscitated sepsis, a finding that parallels findings of normal or high central venous oxygen saturations after resuscitation (37). Despite normal resting $StO_2$, $\dot{V}O_2tis$ was significantly reduced during ischemia in septic subjects. Measurements of oxygen consumption in the absence of flow should be interpreted carefully, since flow-induced vasomotion may increase oxygen expenditures (8). However, our finding is in line with several studies showing that oxygen extraction and consumption are indeed low (24, 25), in contrast to the teaching of a decade ago.

Our most provocative finding is that the rate of tissue reoxygenation is markedly impaired in sepsis and that RR is related to the degree of organ dysfunction. Although our method does not measure blood flow, per se, an acute rise in $StO_2$ can only reasonably be explained by an influx of oxygen-rich arterial blood. The NIRS method does not detect hemoglobin in a single vessel but rather the bulk of hemoglobin...
within the entire microvascular bed within the probed region. It stands to reason that impaired RR may represent either reduced (bulk) arterial influx to the tissue or rapid desaturation of hemoglobin within the capillaries; both explanations describe an imbalance of O₂ delivery relative to the needs of the tissue. Furthermore, our findings of similar rates of StO₂ decrease during ischemia in sepsis, as well as the relationship between RR and TH-RH, argue against an increase in deoxyhemoglobin as a cause for impaired RR.

These data suggest that the thenar microvascularature is unable to respond appropriately to ischemia by augmenting blood flow, especially in the sickest subjects. Microvascular perturbation resulting from abnormal vasoconstriction in sepsis is evident in studies describing improved microvascular flow after administration of vasodilators (10, 39). Sepsis is associated with increased nitric oxide (NO) synthesis via inducible nitric oxide synthase in many cells and tissues, which down-regulates endothelial NOS (17, 30), leading to impaired reactivity (2).

Catecholamines will counteract NO and impair RH. It is interesting that microvascular reoxygenation rates of subjects receiving vasoconstrictor infusions were somewhat lower than of those subjects not receiving these medications, but this difference did not exceed that which may occur through statistical chance. Similarly, the total microvascular hemoglobin during RH was statistically lower in subjects on vasoconstrictors compared with the same measure in their counterparts. Yet neither the absolute change nor relative change in microvascular hemoglobin was affected by vasoconstrictors, suggesting this difference may reflect differences in baseline microvascular hemoglobin (including both pre- and postcapillary vessels) more than the hyperemic response. We suspect that the following three factors contribute to a lack of evidence of catecholamine effects on the microvascular hyperemic response in severe sepsis: 1) adrenergic receptors have decreased binding affinity for norepinephrine (20) and are downregulated in sepsis (7), thus diminishing the response to norepinephrine and other catecholamines; 2) endogenous vasoconstrictors are prevalent in the septic bloodstream (43), and thus the relative contribution of exogenous catecholamines to arteriolar constriction may be small; and 3) additional patient factors beyond catecholamines likely contribute to impaired microvascular blood flow.

Tissue oxygen transport is exceedingly complex in sepsis since tissue perfusion (37), oxygen diffusion, and mitochondrial function (19) are disturbed and interdependent. Mathematical models from experimental sepsis predict that vessel density, flow heterogeneity, and oxygen consumption all play a role in tissue hypoxia in skeletal muscle (22, 23). Specifically, the regulation of capillary density in response to changes in oxygen delivery is impaired in septic animals (15) and may contribute to impaired oxygen extraction. Meanwhile, if oxygen consumption is limited as we found in our subjects, RH may be impaired, since flow-mediated dilation has tremendous oxygen costs (8). Our data provide further insight into the myriad microvascular perturbations in severe sepsis.

Previous studies have evaluated vascular reactivity in sepsis. Two studies have evaluated forearm blood flow before and after stagnant ischemia using venous plethysmography (1, 27). These studies noted that the ratio of flow during RH to that at baseline was lower in septic subjects than in controls. Unfortunately, this ratio may be biased by the baseline high flow in the forearms of septic patients. Additionally, these studies addressed regional forearm blood flow rather than specifically addressing the skeletal muscle microcirculation. Other studies utilized laser-Doppler (35) or NIRS (12) measurements of the skeletal muscle microcirculation and found impaired microvascular perfusion and RH, but there was no assessment of associated organ dysfunction. Several previous studies excluded patients receiving vasopressors, thereby not representing the population seen commonly in practice. Ours is the largest study to date to use NIRS to specifically measure microvascular reactivity in patients at high risk of death and the first to identify a relationship between the degree of impaired reactivity with the degree of organ failure.

NIRS monitors vary greatly in terms of wavelength selection, number of wavelengths, optode spacing, and algorithms

Fig. 5. RR is related to microvascular hemoglobin during reactive hyperemia. The tissue hemoglobin index (TH-RH; arbitrary units) and the rate of increase of tissue oxygen saturation (reoxygenation rate, RR; %/s) were measured in the thenar muscles of severe sepsis subjects during reactive hyperemia. RR correlated with TH-RH (\( r^2 = 0.47, P = 0.0006 \)), demonstrating that low RR is associated with reduced influx of hemoglobin to the tissue bed.

Fig. 6. RR is related to tissue oxygen consumption. \( V_{O2m} \) was calculated by the rate of decrease of oxygen content during 5 min of ischemia in thenar skeletal muscles. Following ischemia, the rate of increase of tissue oxygen saturation during the first 14 s of reactive hyperemia (RR) was measured in the thenar skeletal muscles of septic subjects. RR had a significant linear relationship with \( V_{O2m} \) (\( r^2 = 0.38, P = 0.002 \)).
used to calculate data from the absorption data (6). Accord-
ingly, great care should be used when comparing reports
generated from different spectrometers.

NIRS does not measure individual vessels, which may limit
its use in mechanistic studies of individual vessel responses
during sepsis. However, blood flow is variable between tissues
(32) as well as within the tissues of septic humans (4). Indi-
vidual vessels therefore very likely have different impairments
in reactivity as hemostatic activation (33), impaired red blood
cell deformation (36), leuko-adherence (26), and perturbations
of endothelial vasomotor function all potentially affect micro-
vascular perfusion and contribute to heterogeneous blood flow.

The importance of this heterogeneous flow is demonstrated in
studies that show that the ratio of fast-flow to slow-flow
capillaries relates to tissue oxygenation in animal models of
sepsis (16). To this end, NIRS may be better suited to measure
bulk microvascular regulation in a heterogeneous tissue bed
than instruments that look at individual or select groups of
vessels.

Our study is limited by the lack of systemic, macrovascular,
and hemodynamic data other than blood pressure, reflecting the
global trend away from the use of invasive cardiac output
monitoring (14). It is noteworthy that mean arterial pressure
was not associated with RR just as mean arterial pressure >65
has not been shown to affect organ perfusion or oxygen
kinetics in other studies (29). Low cardiac output does occur in
septic patients, and this would certainly lead to decreased
perfusion and RH. However, because the incidence of low-
output states in resuscitated sepsis is low (13, 37), decreased
systemic flow seems an unlikely explanation of our observa-

tions.

We have shown that microvascular perfusion and reactivity
to ischemia are impaired in humans with severe sepsis. Impor-
tantly, impaired microvascular reactivity is related to tissue
dysxiax as well as organ dysfunction. NIRS is an effective tool
to study these impairments, providing important information
in physiological studies, and could measure relevant endpoints
in therapeutic interventions aimed at improving the microcircu-
latory function in severe sepsis.

REFERENCES

1. Astiz ME, DeGent GE, Lin RY, Rackow EC. Microvascular function and
2. Avontuur JA, Bruining HA, Ince C. Nitric oxide causes dysfunction of
   coronary autoregulation in endotoxemic rats. Cardiovasc Res 35: 368–
   376, 1997.
3. Bateman RM, Walley KR. Microvascular resuscitation as a therapeutic
   Quantifying bedside-derived imaging of microcirculatory abnormalities
   2005.
5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA,
   Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and
   guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM
   Consensus Conference Committee American College of Chest Physicians/
   alpha1-adrenergic receptor expression during endotoxia. Crit Care Med
8. Cabrera P, Tsai AG, Johnson PC, Intaglietta M. Oxygen release from
   arterioles with normal flow and no-flow conditions. J Appl Physiol 100:
9. Coffman JD. Alpha-adrenergic and serotonin receptors and forearm
10. De Backer D, Creteur J, Dubois MJ, Sakr Y, Koch M, Verdant C,
    Vincent JL. The effects of dobutamine on microcirculatory alterations
    in patients with septic shock are independent of its systemic effects.
11. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Micro-
    vascular blood flow is altered in patients with sepsis. Ann J Respir Crit
    S, Pinto G. Microvascular dysfunction and skeletal muscle oxygenation
    assessed by phase-modulation near-infrared spectroscopy in patients
14. Dellinger RP, Karat JM, Masur H, Gerlach H, Calandra T, Cohen J,
    Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G,
    Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign
    guidelines for management of severe sepsis and septic shock. Crit Care
    PT. Regulation of perfused capillary density in canine intestinal mucosa
16. Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R. Effect of a
    maldistribution of microvascular blood flow on capillary O(2) extraction
17. Ermert M, Ruppert C, Gunther A, Duncker HR, Seeger W, Ermert L.
    Cell-specific nitric oxide synthase-isoenzyme expression and regulation
18. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation
    of the SOFA score to predict outcome in critically ill patients. JAMA 286:
19. Fink MP. Bench-to-bedside review: Cytopathic hypoxia. Crit Care
    perfusion and oxygen consumption by near-infrared spectroscopy in sep-
    tic-shock and non-septic-shock patients. Intensive Care Med 29: 1173–1176,
    2003.
22. Goldman D, Bateman RM, Ellis CG. Effect of decreased oxygen supply
    on skeletal muscle oxygenation and oxygen consumption during sepsis:
    role of heterogeneous capillary spacing and blood flow. Am J Physiol
23. Goldman D, Bateman RM, Ellis CG. Effect of sepsis on skeletal muscle
    oxygen consumption and tissue oxygenation: interpreting capillary oxygen
    transport data using a mathematical model. Am J Physiol Heart Circ
    Myocardial oxygen extraction ratio is decreased during endotoxemia in
25. Jakob SM, Ruokonen E, Takala J. Effects of dopamine on systemic and
    regional blood flow and metabolism in septic and cardiac surgery patients.
    circulating E-selectin, intercellular adhesion molecule 1, and von Wille-
    brand factor in patients with severe infection. Am J Respir Crit Care
27. Kirschbaum LA, Astiz ME, Rackow EC, Saha DC, Lin R. Micro-
28. Lam C, Tyml K, Martin C, Sibbald W. Microvascular perfusion is
29. LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion
    pressure on tissue perfusion in septic shock. Crit Care Med 28: 2729–


