Elevation of Cardiac Output and Oxygen Delivery Improves Outcome in Septic Shock*

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Septic shock is characterized by hypoperfusion and tissue energy defects. We prospectively evaluated the therapeutic benefit of augmenting cardiac output and therefore oxygen delivery (DO₂) on mortality in patients with septic shock. Twenty-five patients were randomized to a normal treatment (NT) group and 26 patients were randomized to an optimal treatment (OT) group. All patients had a clinically evident site of infection, sepsis as defined by a systemic response to the infection, and shock indicated by systemic hypoperfusion. Patients were treated during the initial 72 h by an algorithm differing only in the end point of resuscitation. The cardiac index (CI) was increased to 3.0 L/min/m² in the NT group and to 6 L/min/m² in the OT group. There were no significant differences in cardiorespiratory parameters in the NT and OT groups on entrance into the study. During treatment, CI averaged 3.6±0.2 L/min/m² and DO₂ averaged 8.6±0.8 ml/min/kg in the NT group and CI averaged 5.1±0.2 L/min/m² and DO₂ averaged 12.2±0.7 ml/min/kg in the OT group (p<0.01). A significant correlation between DO₂ and survival was observed. Seventy-two percent of the OT patients died vs 50 percent of the NT patients (p=0.14). Surviving NT patients stayed 13.7±3 days in the ICU vs 7.4±0.6 days (p<0.05) for the OT patients. Since some of the NT patients were spontaneously hyperdynamic and some of the OT patients did not achieve their desired end point, patients were arbitrarily subsetted using a midpoint CI of 4.5 L/min/m². The NT <4.5 group had a CI of 3.1±0.2 L/min/m² and DO₂ of 10.9±1.0 ml/min/kg while the OT group >4.5 L/min/m² had a CI of 5.7±0.2 L/min/m² and a DO₂ of 13.5±0.7 ml/min/kg (p<0.01). Mortality in the NT <4.5 group was 74 percent as compared with 40 percent in the OT >4.5 group (p<0.05). (Chest 1992; 102:216-20)

S eptic shock is characterized by an imbalance between systemic oxygen demand and oxygen supply. The marked lactic acidosis observed during septic shock is indicative of a severe tissue energy deficit.1-3 Primary metabolic failure, shifts in the oxygen dissociation curve, and circulatory flow abnormalities have all been postulated to contribute to impaired oxygen utilization during sepsis.4 Experimental studies have demonstrated a relationship between tissue energy deficits and effective organ perfusion.5-6 Clinical observations of regional hypoperfusion and altered microvascular response to reactive hyperemia are consistent with circulatory maldistribution.7,8 These studies suggest the potential for reversing tissue energy deficits by increasing oxygen delivery during septic shock. The optimal levels of oxygen delivery appear to be significantly higher than under normal physiologic conditions both because of increased metabolic demands and decreased oxygen extraction.9,10 Recently, Shoemaker et al10 and Edwards et al11 reported improved survival in critically ill patients, some of whom were septic, when therapy was titrated to increased indices of flow and oxygen metabolism.

The purpose of this study was to prospectively evaluate the therapeutic effect of augmenting cardiac output and therefore oxygen delivery on mortality in patients with septic shock. Our data suggest that mortality may be reduced by increasing cardiac output and oxygen delivery.

METHODS

Patients

All patients admitted over a 24-month period to the Critical Care Service at Los Angeles County/University of Southern California Medical Center, Los Angeles, with a suspected diagnosis of septic shock had their conditions evaluated. The study was approved by the Institutional Review Board. Infection was confirmed in patients with bacteremia or an identifiable site of infection. Sites of infection were identified by positive bacterial cultures with evidence of inflammatory cells on Gram stain of exudates. Sepsis was defined as a systemic response to infection as characterized by four of the following clinical signs: (1) fever (temperature >38.3°C) or hypothermia (temperature <35.5°C); (2) tachycardia (heart rate >90 beats/min); (3) tachypnea (>20 breaths/min); (4) leukocytosis (WBC >11,000/µl mm³); or (5) delirium. Shock was identified by any one of the following signs: (1) systolic intra-arterial pressure <90 mm Hg on two measurements, 1 h apart; (2) intravenous (IV) infusion of dopamine for greater than 1 h to maintain intra-arterial systolic pressure ≥90 mm Hg; or (3) arterial lactate ≥3.0 mmol/L. All patients were entered within 4 h of diagnosing shock and enrolled with a suspected site of infection, evidence of sepsis, and criteria for shock. Patients without an identified site of infection at 48 h were removed from the study. Once entered, the patients were assigned to the normal treatment (NT) group or optimal treatment.
(OT) group by dynamic randomization.

**Patient Management**

After obtaining appropriate blood and site cultures, all patients received gentamicin 2 mg/kg IV followed by 1.7 mg/kg IV every 8 h (monitored with serum levels) and clindamycin 900 mg IV every 8 h. Additional antibiotics were added depending on the presumed site of infection and suspected bacteriology. Once an organism was isolated, the antibiotic regimen was tailored appropriately. Every effort was made to identify and drain infected sites.

Resuscitation from shock was standardized by the use of a printed algorithm, which also served as a notification of group assignment. The algorithms for the NT and OT groups were identical except with respect to the end point of resuscitation. The NT resuscitative efforts were considered to be complete when a cardiac index (CI) \(\geq 3.0 \text{ L/min/m}^2\) and a systolic arterial pressure (SAP) of \(\geq 90\) mm Hg were achieved. A CI \(\geq 6.0 \text{ L/min/m}^2\) and a SAP \(\geq 90\) mm Hg defined resuscitative end points for the OT patients. The algorithm consisted of first determining whether patients satisfied the resuscitation goals. If they did not, 5 percent albumin was administered by aliquots to achieve a pulmonary artery occlusion pressure (PAOP) \(\geq 15\) mm Hg. In hypotensive patients with a PAOP \(\geq 15\) mm Hg, a dopamine infusion was titrated to maintain a SAP \(\geq 90\) mm Hg. When the PAOP was \(\geq 15\) mm Hg, the SAP was \(\geq 90\) mm Hg, and the CI was below the desired goal, dobutamine was infused and titrated to maintain the CI. Patients receiving dopamine with a PAOP \(< 15\) mm Hg, who otherwise met the assigned goals, were fluid challenged with 5 percent albumin in an effort to withdraw vasopressor support.

The resuscitative goals were maintained for 72 h. Patients were transfused to maintain a hemoglobin of at least 10 g/dl. All patients were intubated and mechanically ventilated. Supplemental oxygen and PEEP were adjusted to maintain the arterial oxygen saturation \(\geq 90\) percent, with the least possible 

**Hemodynamic Measurements**

Intravascular pressures were measured with strain gauge transducers (Baxter Edwards Laboratories, Irvine, Calif), zeroed to atmospheric pressure at the midaxillary line, and calibrated against a mercury manometer. Cardiac output (CO) values were obtained in triplicate by thermodilution using iced saline solution cooled to \(< 1\)°C. Hemoglobin saturation was measured with a CoOximeter (282, Instrumentation Laboratories, Lexington, Mass). Hemodynamic variables, arterial and mixed venous blood gases, and arterial lactate were obtained simultaneously, at least every 6 h. Oxygen delivery (DO\(_2\)) was calculated as DO\(_2\) = CI \(\times\) Hgb \(\times\) SaO\(_2\) and oxygen consumption (VO\(_2\)) as VO\(_2\) = CI \(\times\) (Hgb - CvO\(_2\)). Oxygen content was calculated as follows: CaO\(_2\) = 1.39 \(\times\) (Hgb) \(\times\) SaO\(_2\) and CvO\(_2\) = 1.39 \(\times\) (Hgb) \(\times\) SvO\(_2\), where SaO\(_2\) and SvO\(_2\) are the arterial and mixed venous oxygen saturations, respectively.

**Statistical Analysis**

We compared continuous variable data using the Student’s t test and compared mortality data using \(x^2\) analysis. The CI and other variables were averaged over the 72-h period following the initial resuscitative efforts (>6 h after entry) to obtain the postresuscitation values.

Some patients assigned to the NT group exceeded their treatment goal on admission to the study, and some patients randomized to the OT group failed to achieve a CI \(\geq 6.0 \text{ L/min/m}^2\). We therefore subsetted patients into two groups with a midpoint CI value of 4.5 \(\text{L/min/m}^2\) and compared the NT group with a postresuscitation CI <4.5 \(\text{L/min/m}^2\) to the OT group with a CI >4.5 \(\text{L/min/m}^2\). These groups were then compared using the same statistical methods.

Results are reported as mean \(\pm\) SEM. Statistical significance is reported at a p<0.05.

**RESULTS**

Seventy patients were enrolled during the course of the study. Nineteen of these were not included in the analysis for the following reasons: in nine patients, blood and site cultures were negative; six patients died prior to treatment; three patients did not meet shock criteria. Fifty-one subjects were analyzed, 25 patients in the NT group and 26 patients in the OT group. The most common infections were pneumonia in 53 percent, urosepsis in 10 percent, and peritonitis in 8 percent. Fifty-seven percent of the patients had positive blood cultures. Sixty-five percent of the patients had Gram-negative infections and 35 percent had Gram-positive infections.

**Normal vs Optimal Treatment**

The clinical and hemodynamic profiles of the patients on entry into the study are shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n = 25)</th>
<th>OT (n = 26)</th>
<th>NT (n = 25)</th>
<th>OT (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>53±4</td>
<td>49±3</td>
<td>37.3±0.11</td>
<td>37±0.06</td>
</tr>
<tr>
<td>Apache II</td>
<td>21±1</td>
<td>22±1</td>
<td>22±3</td>
<td>22±1</td>
</tr>
<tr>
<td>Temp, °C</td>
<td>37.7±0.17</td>
<td>37.8±0.11</td>
<td>37.3±0.11</td>
<td>37±0.06</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>24±2</td>
<td>26±1</td>
<td>24±2</td>
<td>26±1</td>
</tr>
<tr>
<td>Pulse, beats/min</td>
<td>124±4</td>
<td>112±4</td>
<td>124±3</td>
<td>110±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>74±3</td>
<td>74±3</td>
<td>73±2</td>
<td>75±2</td>
</tr>
<tr>
<td>MPA, mm Hg</td>
<td>27±2</td>
<td>26±1</td>
<td>30±1</td>
<td>27±1</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>13±1</td>
<td>15±1</td>
<td>16±1</td>
<td>16±1</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.9±0.3</td>
<td>4.0±0.3</td>
<td>3.6±0.2</td>
<td>5.1±2*</td>
</tr>
<tr>
<td>Hgb, g/dl</td>
<td>11.0±0.5</td>
<td>11.0±0.4</td>
<td>10.3±0.4</td>
<td>10.2±0.3</td>
</tr>
<tr>
<td>DO₂, ml/min/kg</td>
<td>14.9±1.5</td>
<td>16.1±1.2</td>
<td>14.0±0.3</td>
<td>18.8±0.4*</td>
</tr>
<tr>
<td>VO₂, ml/min/kg</td>
<td>3.5±0.2</td>
<td>3.6±0.3</td>
<td>3.7±0.6</td>
<td>3.7±0.1</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>5.1±0.6</td>
<td>4.7±0.1</td>
<td>4.5±0.8</td>
<td>3.8±0.6</td>
</tr>
</tbody>
</table>

*NS vs OT, p<0.01.
OT patients required 775 ± 25 ml of 5 percent albumin for volume repletion compared with 938 ± 33 ml for the NT group. Twenty-one of 26 OT patients received dobutamine at an average dose of 30 ± 1 µg/kg/min, whereas 12 of 25 NT patients received dobutamine at 12 ± 1 µg/kg/min (p<0.01). CI increased by 4 ± 2 percent with therapy in the NT group and by 30 ± 2 percent in the OT group (p<0.01). After resuscitation, OT patients had a significantly higher CI and Do2 throughout their course (Table 1, Fig 1 and 2). Mortality was strongly correlated ($r^2 = 0.94$, p = 0.016) with the postresuscitation level of oxygen delivery (Fig 3). In the NT patients, mortality rate was 72 percent and 50 percent in the OT patients (p = 0.14) (Fig 4). Of the patients who died during the study, the OT patients survived 6.1 ± 0.3 days and the NT patients survived 4.3 ± 0.3 days (p<0.001).

We also examined the length of ICU stay for patients in the NT and OT groups. NT patients received ICU care for 8.9 ± 0.6 days compared with 5.3 ± 0.2 days for patients in the OT group (p<0.05). When only survivors were considered, NT survivors stayed in the ICU 13.7 ± 3 days in contrast to 7.4 ± 0.6 days for OT survivors (p<0.05).

**Subset Analysis**

There were 19 patients in the NT group with a postresuscitation CI <4.5 L/min/m² and 19 patients in the OT group with a postresuscitation CI >4.5 L/min/m². There were no significant differences in these groups preresuscitation. Postresuscitation Do2 averaged 13.8 ± 0.7 ml/min/kg and Vo2 averaged 4.3 ± 0.3 ml/min/kg in the OT >4.5 patients and Do2 averaged 7.2 ± 0.7 ml/min/kg and the Vo2 averaged 3.5 ± 0.3 ml/min/kg in the NT <4.5 patients (p<0.05). Lactate levels averaged 2.5 ± 0.3 mmol/L in the OT >4.5 group and 4.8 ± 0.1 mmol/L in the NT <4.5 group (p<0.05). CI increased by 1 ± 2 percent in the NT patients with therapy and by 40 ± 2 percent in the OT patients (p<0.05). Mortality was 74 percent in the NT <4.5 group and 40 percent in the OT >4.5 group (p<0.05) (Fig 5).

**Discussion**

The development of septic shock is associated with systemic hypoperfusion and a tissue energy deficit. Tissue hypoperfusion appears to be a major factor.
Figure 5. Survival rate for the normal treatment (NT) group with a cardiac index (CI) <4.5 L/min/m² (dashed line) and optimal treatment (OT) group with a CI >4.5 L/min/m² (solid line) over 14 days.

...contributing to impaired oxidative metabolism during septic shock. Mitochondrial oxidative function appears to be maintained during septic shock. Alterations in systemic and microvascular flow have been reported in both experimental and clinical studies that may compromise effective organ perfusion. Clearance of lactic acid levels following resuscitation is associated with survival emphasizing the importance in increasing systemic oxygen delivery in restoring tissue perfusion and enhancing outcome during septic shock. The concept of titrating hemodynamic therapy to supranormal levels has been advanced recently. Sepsis and septic shock are hypermetabolic syndromes with increased tissue oxygen requirements. Increased levels of systemic oxygen delivery and consumption have been associated with improved outcome from severe sepsis. The increased levels of oxygen consumption require increased systemic blood flow and oxygen delivery both because of increased metabolic rate and because of circulatory abnormalities that impair the ability of tissues to maximally extract oxygen. Recently, Shoemaker et al reported that titration of therapy to supranormal values of CI and oxygen metabolism in critically ill surgical patients was associated with a marked reduction in mortality rate from 33 percent to 4 percent. Using the same end points, Edwards et al noted a reduction in mortality from septic shock when compared with historic controls.

Our study suggests that increased levels of CO and systemic oxygen delivery are important in improving outcome from septic shock. A 28 percent reduction in hospital mortality was observed when CI was titrated to 6 L/min/m². The importance of oxygen delivery in determining outcome is further emphasized by the relationship of increases in systemic oxygen delivery to decreases in mortality. In the OT patients who died of septic shock, survival time was significantly increased allowing for the potential impact of other therapeutic interventions to take their clinical effect. ICU stay was also significantly reduced in the OT group suggesting decreased morbidities and more rapid clinical improvement in the survivors. Presumably this was related to enhanced recovery and a decrease in patient morbidity. This decrement in ICU stay should translate into a significant cost savings. Indeed, Shoemaker et al reported that hospital costs were significantly decreased in the group of patients where therapy was titrated to optimal hemodynamic end points. The substantial increase in CI following therapy in the OT group as compared with the NT group suggests that these benefits were related to the therapeutic interventions.

The lack of statistical significance in the overall mortality rates probably reflects the spontaneously higher CIs of some of the patients in the NT group, as well as the inability to achieve the desired end point in a portion of patients in the OT group. In order to assess this hypothesis, we arbitrarily subsetted the patients on the basis of achieved CIs at a midpoint value between the two treatment end points. The 50 percent reduction in mortality observed in the OT patients with a CI >4.5 L/min/m² when compared with the NT patients with a CI <4.5 L/min/m² adds further substance to the interpretation that an improvement in outcome was achieved in the OT group. The 40 percent increase in CI observed in the OT patients following randomization supports this thesis. The associated increases in DO₂ and VO₂ with enhanced lactate clearance suggest that the benefit observed in the OT patients was related to enhanced tissue perfusion and oxidative metabolism. An alternative method of subsetting the data by excluding outliers in either group would have yielded the same results. Because of the significance of the reduction in mortality observed in the subset of OT patients with a CI of >4.5 L/min/m², the study was discontinued.

The optimal level of CO and oxygen delivery in patients with septic shock needs to be delineated. We utilized a higher CI (6.0 L/min/m²) in the treatment group, which resulted in a higher DO₂ of 726±16 ml/min/m² than end points reported by Shoemaker et al (CI≥4.5 L/min/m², DO₂≥600 ml/min/m²). Approximately one fourth of our patients were not able to achieve this desired end point. Achieving these end points required the use of significantly greater amounts of catecholamines in the OT group reflecting both the significantly increased level of CI desired and the degree of myocardial depression resulting from the septic process. In an older group of patients with less cardiovascular reserve, an even greater percentage of patients might not achieve the desired end points. In addition, patients with septic shock have widely varying metabolic requirements. Age, fever, nutritional status, degree of sedation, and du-

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ration of illness affect metabolic needs. An alternative approach might be to titrate therapy to index of perfusion that reflects the oxygen demand/supply relationship, such as clearance of lactic acid.

Our observations are consistent with studies that have demonstrated improved outcome in the patients who were able to achieve higher CIs. They contrast with recent reports in which higher CIs were not associated with improved survival. The reason for these differences is not entirely clear but may reflect differences in patient populations and treatment protocols.

A considerable controversy has arisen as to the risks and benefits of pulmonary artery catheterization. A potentially adverse effect on outcome in patients with acute myocardial infarction has been suggested by the retrospective study of Gore et al. In contrast, our prospective study and the prospective study of Shoemaker et al indicate that when hemodynamic monitoring is employed to titrate therapy to specific end points, significant benefits in survival can be accrued. Both studies emphasize the fact that it is not the hemodynamic monitoring itself, but the therapeutic end points utilized that determine outcome. The clinical impact of hemodynamic monitoring should be examined with special reference to the way in which hemodynamic data are interpreted and utilized. This is particularly important given the recent report of Iberti et al demonstrating the widespread deficiencies in the interpretation of hemodynamic measurements.

In summary, outcome in patients with septic shock appears to be related to the level of systemic oxygen delivery. Titration of therapy to increased levels of CI and therefore oxygen delivery may be associated with improved survival from septic shock.

REFERENCES