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Profound but Reversible Myocardial Depression in Patients with Septic Shock

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To characterize the role of cardiac function in septic shock, serial radionuclide cineangiographic and hemodynamic evaluations were done on 20 patients with documented septic shock. Although all patients had a normal or elevated cardiac index, 10 patients had moderate to severe depression of their ejection fraction with values below 0.40. Thirteen of twenty patients survived their episode. Paradoxically, 10 of 13 survivors, but none of the 7 nonsurvivors, had an initial ejection fraction less than 0.40 (p < 0.005). The mean initial ejection fraction for the survivors was 0.32 ± 0.04, and their mean end systolic and end diastolic ventricular volumes were substantially increased with a normal stroke volume. The survivors’ serial scans showed a gradual return to normal ejection fraction and ventricular volume by 10 days after the onset of shock. Nonsurvivors had normal initial ejection fractions and ventricular volumes that did not change during serial studies.

SHOCK SECONDARY TO SEPSIS is a common and serious disorder with a high mortality. Efforts to define the cardiovascular abnormalities that characterize septic shock in humans have focused on both peripheral vascular and cardiac dysfunction (1-13). Myocardial depression, usually defined as a low cardiac index, has been described as a key factor in the pathogenesis of this syndrome. However, the hemodynamic pattern of septic shock in humans, as described in most large series of reported patients, is characterized by a high cardiac index and a low systemic vascular resistance index (2-8, 11, 12). The concept of a low cardiac output due to myocardial depression largely stems from animal models (4, 5) using endotoxin administration that results in a low cardiac output form of shock not at all analogous to that seen in humans. Further evidence for low cardiac output in septic shock stems from anecdotal cases of a falling cardiac output before the death of patients with septic shock (6). However, most patients with septic shock are “hyperdynamic” with high cardiac outputs, and the cases reported with a low cardiac index may represent the coexistence of septic shock and hypovolemia (3).

In evaluating the ventricular function of patients with coronary artery disease, the ejection fraction has been a more reliable indicator of overall ventricular performance and ultimate prognosis than the cardiac index (14). We have done serial hemodynamic studies and serial radionuclide cineangiographic studies on patients with septic shock. A previous recent study evaluated patients with sepsis but without shock using radionuclide cineangiography and found that the mean ejection fraction for this group was normal; however, one quarter of these patients had a reduced ejection fraction on a single study (13). We have evaluated a series of patients with moderate to severe septic shock using radionuclide cineangiography and hemodynamic evaluations. We report the presence of severe, reversible myocardial depression in a substantial proportion of these patients.

Methods

From April to December 1982, 20 patients with septic shock were studied in the medical intensive care unit of the National Institutes of Health. Seventeen patients had a temperature greater than 38°C, hypotension (mean arterial pressure less than 60 mm Hg), and positive blood cultures. Three patients had fever, hypotension, profound neutropenia (neutrophils less than 500/mm³), and a localized site of infection, but negative blood cultures that were attributed to concomitant broad spectrum antibiotic treatment.

Arterial pressure was monitored by an indwelling arterial catheter in the radial or femoral artery. A Swan-Ganz catheter was positioned with fluoroscopic guidance in the pulmonary artery of each patient. Serial measurements of central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output by the thermodilution technique were obtained. Measurements of pulmonary capillary wedge pressure were done from tracings on graph paper of the pulmonary capillary wedge pressure at end expiration. In patients on positive end expiratory pressure, measurements of pulmonary capillary wedge pressure were made at end expiration both on and after 10 seconds off positive end expiratory pressure. In the patients in this study, the pulmonary capillary wedge pressure on and off positive and expiratory pressure never differed by more than 2 mm Hg.

THERAPEUTIC PROTOCOL

Each patient received the following treatment to maintain a mean arterial pressure greater than 60 mm Hg. Initially, all patients received intravenous fluids to maintain a pulmonary capillary wedge pressure of 12 to 15 mm Hg. Dopamine was then added if the patient remained hypotensive. If the patient required more than 20 µg/kg-min of dopamine, levartenol was added, and the dopamine was tapered to 2 to 5 µg/kg-min in an attempt to preserve renal perfusion. All patients received broad-spectrum antibiotic coverage, usually including an aminoglycoside, a cephalosporin, and a semisynthetic penicillin active against Pseudomonas aeruginosa. When blood culture results were obtained, the antibiotic agents were adjusted appropriately. Each patient was given two doses of methylprednisolone, 30 mg/kg body weight, one at the onset of shock, and the second 4 to 8 hours later. Respiratory support was given as needed to maintain a normal pH and an arterial partial pressure of oxygen (PaO₂) greater than 70 mm Hg; all studies were done when arterial PaO₂ and pH were normal. Fifteen patients required mechanical ventilation; the other 5 patients received supplemental oxygen. Metabolic parameters were checked on several occasions daily and abnormalities, especially of potassium, phosphate, and glucose, were corrected promptly.

RADIONUCLIDE CINEANGIOGRAPHY STUDIES

Serial radionuclide cineangiography studies were done on...
### Table 1. Clinical Characteristics of 20 Patients with Septic Shock

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Blood Culture</th>
<th>Outcome from Septic Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Glioblastoma, cryptococcal meningitis</td>
<td>Klebsiella pneumoniae</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>M</td>
<td>Diffuse poorly differentiated lymphoma</td>
<td>Clostridia septicum</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>F</td>
<td>Acute lymphocytic leukemia</td>
<td>Pseudomonas aeruginosa</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>Coronary artery disease mediastinitis</td>
<td>Escherichia coli, Serratia marcescans</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>F</td>
<td>Breast carcinoma</td>
<td>Alpha streptococcus</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>Diffuse poorly differentiated lymphoma</td>
<td>Escherichia coli</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>Coronary artery disease, acute myocardial infarction</td>
<td>Pseudomonas cepacia, Staphylococcus epidermidis</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>F</td>
<td>Non-obstructive hypertrophic cardiomyopathy</td>
<td>Pseudomonas cepacia, Staphylococcus epidermidis</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>M</td>
<td>Burkitt’s lymphoma</td>
<td>No growth</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>M</td>
<td>Hodgkin’s disease</td>
<td>No growth</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>M</td>
<td>Diffuse histiocytic lymphoma</td>
<td>Escherichia coli</td>
<td>Survived</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>F</td>
<td>Diffuse histiocytic lymphoma</td>
<td>Escherichia coli</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>M</td>
<td>Chronic granulomatous disease</td>
<td>Staphylococcus aureus</td>
<td>Survived</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>M</td>
<td>Burkitt’s lymphoma</td>
<td>Klebsiella pneumoniae</td>
<td>Died</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>M</td>
<td>Chronic lymphocytic leukemia</td>
<td>Pseudomonas aeruginosa</td>
<td>Died</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>M</td>
<td>Coronary artery disease, mediastinitis</td>
<td>Candida albicans</td>
<td>Died</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>M</td>
<td>Aplastic anemia</td>
<td>Pseudomonas aeruginosa</td>
<td>Died</td>
</tr>
<tr>
<td>18</td>
<td>54</td>
<td>M</td>
<td>Mycosis fungoides</td>
<td>No growth</td>
<td>Died</td>
</tr>
<tr>
<td>19</td>
<td>54</td>
<td>F</td>
<td>Ovarian carcinoma</td>
<td>Candida albicans</td>
<td>Died</td>
</tr>
<tr>
<td>20</td>
<td>31</td>
<td>F</td>
<td>Acute lymphocytic leukemia</td>
<td>Klebsiella pneumoniae</td>
<td>Died</td>
</tr>
</tbody>
</table>

### STATISTICAL CALCULATIONS

Comparisons were made between initial time points in the survivors and nonsurvivors using the Student’s t-test. To compare the serial hemodynamics obtained from survivors and non-survivors, the serial values obtained from each patient were averaged; the mean of the patient averages was obtained and a Student’s t-test was used to compare the differences. The analysis of variance was not used because the serial hemodynamic values obtained in these patients were not judged to be completely independent of one another. Independence of serial values is one of the necessary statistical requirements for use of variance analysis. A p value < 0.05 was considered statistically significant.

Spearman coefficients of rank correlation were calculated to evaluate whether the dose of pressor agents correlated positively or negatively with certain hemodynamic parameters.

Radionuclide cineangiography was done according to a protocol approved by the Clinical Research Committee of the National Institutes of Health and with the informed consent of the patient or guardian.

### Results

The clinical characteristics of the patients are shown in Table 1. The mean age was 43.6 years, with a range of 9 to 64 years. Of the 20 patients, 14 had an underlying malignancy, 4 had heart disease, 1 had aplastic anemia, and 1 had chronic granulomatous disease of childhood. Thirteen of the twenty patients survived the episode of septic shock. The other 7 patients died of refractory hypotension. There were 10 patients with gram-negative bacteremia, 3 with gram-positive bacteremia, 2 with mixed bacteremia, 2 with candidiasis, and 3 with negative blood cultures. Six patients’ hypotension responded to fluids alone; the other patients required vasopressors to maintain a mean arterial pressure greater than 60 mm Hg. Fifteen patients required mechanical ventilation, of whom 8 survived and 7 did not. The amount of positive end expiratory pressure required in these patients is ana-
lyzed below.

Autopsies were done on six of the seven nonsurvivors; five patients had no coronary artery disease, and one patient had an adequately bypassed coronary stenosis. Two of the survivors later died of causes unrelated to septic shock; neither had significant coronary artery disease seen at autopsy.

HEMODYNAMIC STUDIES

The cardiac index plotted against time is shown in Figure 1. In both the survivors and nonsurvivors the initial mean cardiac index is elevated and remains elevated throughout the course of this study. The nonsurvivors tend to have a higher initial cardiac index (5.4 ± 0.7 L/min · m²) than the survivors (4.1 ± 0.4 L/min · m²) but the difference is not statistically significant (0.05 < p < 0.1). When the serial values of cardiac index for each patient are averaged over the first 4 days of the study and compared, there is a higher mean cardiac index in the nonsurvivors (5.3 ± 0.8 L/min · m²) than the survivors (3.9 ± 0.4 L/min · m²) but again, this difference lacks statistical significance (0.05 < p < 0.1).

The stroke volume index is shown in Figure 2A. Both the survivors (40 ± 4 mL/beat · m²) and the nonsurvivors (43.4 ± 4.1 mL/beat · m²) have normal mean stroke volume indices that remained normal throughout this study. Again, the difference between the survivors and the nonsurvivors is not significant (p > 0.1).

The systemic vascular resistance index plotted versus time can be seen in Figure 2B. The mean systemic vascular resistance index remains low or low normal in both survivors and nonsurvivors. The nonsurvivors (1127 ± 159 dyne · s · cm⁻²/m²) have a lower initial systemic vascular resistance index than the survivors, (1559 ± 168 dyne · s · cm⁻²/m²), but this difference lacks statistical significance (p > 0.05). When the serial values of systemic vascular resistance index for each patient are averaged over the first 4 days of the study and compared, there is a statistically significantly lower mean systemic vascular resistance index (p < 0.05) in the nonsurvivors (1109 ± 147 dyne · s · cm⁻²/m²) than the survivors (1611 ± 133 dyne · s · cm⁻²/m²).

The ejection fraction as determined by radionuclide cineangiography is shown in Figure 3. The group as a whole (left panel of Figure 3) has an initially low mean ejection fraction of 0.40 ± 0.04 (normal ejection fraction, 0.45 to 0.55), which gradually rises over 7 to 10 days to 0.55 ± 0.05. The 13 survivors have an initial ejection fraction of 0.32 ± 0.04, which remains low for up to 4 days and then returns to normal (0.55 ± 0.05). The final ejection fraction obtained in the survivors is significantly higher than the initial ejection fraction (p < 0.005).

The nonsurvivors have an initially normal mean ejection fraction (0.55 ± 0.03) that remains above or in the normal range on serial scans to within 24 hours of death. The survivors have a significantly lower initial ejection fraction than the nonsurvivors (p < 0.005). When serial values of the ejection fraction for each patient are averaged over the first 4 days and compared, there is a significantly lower mean ejection fraction (p < 0.001) in the survivors (0.33 ± 0.04) than the nonsurvivors (0.55 ± 0.03).

Radionuclide cineangiographic scans were also done in the intensive care unit on 32 patients at the onset of an acute illness (21 with respiratory failure, 2 with hemorrhage, 2 with pericardial tamponade, and 1 each with renal failure, arrhythmias, pulmonary emboli, drug overdose, acute abdomen, tumor lysis, and volume depletion) but who were not in shock and had negative blood cultures. These control patients had uniformly normal ejection fractions with a mean ejection fraction ± SE of 0.54 ± 0.01. None of the patients in this group had an ejection fraction below 0.40. The 22 patients with a malignancy had a similar mean ejection fraction of 0.54 ± 0.02. The 10 patients without a malignancy also had a similar mean ejection fraction of 0.55 ± 0.03. The 20 septic shock patients had statistically significantly lower initial mean ejection fractions when compared with this control group (p < 0.001).

The individual ejection fraction obtained are shown in Figure 4. Ten of thirteen surviving patients have an initial ejection fraction during shock less than 0.40. In contrast, none of the seven nonsurvivors has an initial ejection fraction less than 0.40. One nonsurvivor has an initial ejection fraction less than 0.45. As shown in Table 2, by chi-squared analysis, this difference between surviving and nonsurviving patients is statistically significant (p<0.005). Thus, somewhat paradoxically, a low initial ejection fraction is associated with survival.
It is of interest that three surviving patients had radionuclide cineangiographic studies done before the onset of septic shock. Two of these patients had previously known heart disease. All three patients had an acute fall in ejection fraction from their baseline values, with full recovery over 7 to 10 days. All of the survivors show a rise in their ejection fraction over the 7 to 10 day period, whereas the nonsurvivors show no consistent change in ejection fraction.

End diastolic and end systolic volume indices were calculated and are plotted against time in Figure 5. Ejection fraction curves are plotted for comparison. The survivors have an acutely dilated left ventricle with a large end diastolic volume index (159 ± 29 mL/m²; normal range, 50 to 90 mL/m²). In these survivors both the end diastolic and end systolic volume indices (normal range, 20 to 40 mL/m²) fall to normal values (72 ± 12 and 33 ± 8 mL/m², respectively) over 7 to 10 days as the patients recover (p < 0.05 comparing initial end diastolic or end systolic volume indices with final value in survivors). The end diastolic and end systolic volume indices decrease in parallel fashion as the stroke volume remains normal. The nonsurvivors have normal initial mean left ventricular volume (end diastolic volume index, 81 ± 9 mL/m²; end systolic volume index, 38 ± 6 mL/m²) that do not change with time (p not significant comparing initial end diastolic or end systolic volume indices with final value in nonsurvivors).

**ANALYSIS OF FACTORS THAT CAN INFLUENCE EJECTION FRACTION**

Although ejection fraction has been used as a measure of cardiac contractility, it can be altered by acute changes in preload, afterload, and heart rate (15). Therefore, it is important to analyze these variables in the survivor and nonsurvivor groups.

Pulmonary capillary wedge pressure was used as a measure of left ventricular preload. The initial pressure of the survivors (13.7 ± 1.6 mm Hg) is not different than that of the nonsurvivors (10.6 ± 1.5 mm Hg, p > 0.1). When the pressure of each patient is averaged over the first 4 days of the study and compared, the survivors (14.1 ± 1.7 mm Hg) and nonsurvivors (12.3 ± 2.0 mm Hg) have similar (and not statistically different) values. In patients who are on positive end expiratory pressure, the pulmonary capillary wedge pressure cited above was obtained after 10 seconds off positive end expiratory pres-
Figure 4. The individual ejection fractions plotted versus time. The hatched area shows the normal range. Three of the survivors had baseline studies done before the onset of shock. With the onset of shock, all three had an acute fall in ejection fraction. All survivors show an ejection fraction that recovers to baseline over 10 days.

sure. If pulmonary capillary wedge pressure on positive end expiratory pressure is used in comparing survivors and nonsurvivors, again no statistical difference is seen between survivors and nonsurvivors in initial or serial (days 1 to 4) pulmonary capillary wedge pressure.

Positive end expiratory pressure can potentially affect preload and afterload and potentially alter ejection fraction. Initial positive end expiratory pressure values in survivors (6.4 ± 1.8 cm H₂O) and nonsurvivors (7.9 ± 2.4 cm H₂O) are not statistically different (p > 0.1), and an average of individual patient values during the first 4 days in survivors (4.2 ± 1.5 cm H₂O) and nonsurvivors (8.4 ± 2.3 cm H₂O) are not significantly different (p > 0.1).

Regarding afterload, the systemic vascular resistance index has been analyzed above and in Figure 2B. Although the initial systemic vascular resistance index between the survivors and nonsurvivors is not statistically different, when individual patient resistance indices are averaged for the first 4 days and compared, the indices of the nonsurvivors are significantly lower than those of the survivors.

Heart rate was analyzed in the survivors and nonsurvivors. The initial mean heart rate in the nonsurvivors (119 ± 5.8 beats/min) is somewhat higher than in the survivors (103 ± 6.3 beats/min) but this difference lacks statistical significance (p > 0.1). When the heart rate of each patient is averaged over the first 4 days of the study, the mean value found, and compared, the nonsurvivors (118 ± 5.6 beats/min) and survivors (103 ± 6.8 beats/min) show similar heart rates that are not significantly different (p > 0.1).

Because the vasopressors dopamine and levarterenol can affect cardiac contractility and afterload, the doses of dopamine and levarterenol were examined in the survivors and the nonsurvivors. At the time of the initial study the dopamine dose in the survivors was 2.8 ± 0.7 µg/kg · min (range, 0 to 9 µg/kg · min) and in the nonsurvivors was 10 ± 6 (range, 0 to 45 µg/kg · min). These initial dopamine dosages are not significantly different from one another. When the dopamine dosage for each patient over the first 4 days is averaged and the survivors (2.6 ± 0.7 µg/kg · min) compared to nonsurvivors (6.1 ± 3.0 µg/kg · min), again no statistically significant difference is found (p > 0.1).

Initial levarterenol dosages in the survivors (3.6 ± 2.2 µg/min) and nonsurvivors (16 ± 8.5 µg/min) were significantly different (p < 0.05). When doses of individual patients are averaged over the initial 4 days of the study, the mean levarterenol dosage is higher in nonsurvivors (34.0 ± 13.0 µg/min) than survivors (1.6 ± 1.0 µg/min, p < 0.01). The physiologic effect of levarterenol includes moderate beta-stimulation of the heart and a peripheral increase in systemic resistance that is profound. High levels of levarterenol would be expected to severely increase the systemic vascular resistance index in nonsurvivors. In fact, this index is lower in nonsurvivors than survivors despite high doses of levarterenol. Presumably this decreased value represents a peripheral vascular ef-

<table>
<thead>
<tr>
<th>Ejection Fraction</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 0.4</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Greater than 0.4</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

* Comparison of survivors to nonsurvivors with a chi-squared analysis (2-tailed test), p < 0.005.
The mean (± SE) end diastolic and end systolic volume indices plotted against time, with mean (± SE) ejection fraction curves shown for comparison. The mean end diastolic and end systolic volume indices are initially increased in the survivors and decrease in parallel, as the mean stroke volume index remains normal. The mean end diastolic and end systolic volume index of the nonsurvivors remains normal throughout.

Effect of the microorganism that has precipitated the shock syndrome. In the nonsurvivors the systemic vascular resistance index is lower showing a more severe peripheral vascular abnormality.

To further evaluate a relationship between vasopressors and hemodynamic parameters, Spearman rank correlation coefficients were calculated between the cardiac index, systemic vascular resistance index, and ejection fraction, and the doses of dopamine and levaterenol in the survivors and nonsurvivors. Neither the dose of dopamine nor the dose of levaterenol correlated with the ejection fraction, cardiac index, or systemic vascular resistance index in the survivors or nonsurvivors.

The hemodynamic and ejection fraction responses of all survivors and nonsurvivors were the same regardless of the type of organism (gram-positive versus gram-negative versus fungi) recovered from blood cultures.

Discussion

Significant myocardial depression, shown by decreased ejection fraction and ventricular dilatation, frequently can occur early in septic shock, even in the presence of a normal or elevated cardiac index. Furthermore, if the patient survives, this myocardial depression is reversible over a period of 7 to 10 days after the episode of septic shock (Figure 6).

We have extensively evaluated a number of factors that are known to effect ejection fraction—preload, afterload, heart rate (15), and positive end expiratory pressure—and found that they cannot account for the changes in ejection fraction. The levels of pulmonary capillary wedge pressure, positive end expiratory pressure, and heart rate were the same in both the survivors and nonsurvivors. Afterload, as measured by systemic vascular resistance index, was not significantly different on initial studies; however, when the first 4 days of the study were evaluated, the systemic vascular resistance index in the nonsurvivors was significantly lower than in the survivors (P < 0.05). This difference raises the following postulate: all patients with septic shock may develop myocardial depression; however, nonsurvivors have a lower systemic vascular resistance index (Figure 2B) than survivors. This lower afterload may result in a normal ejection fraction in the nonsurvivors despite a reduced myocardial contractility. Further study will be necessary to evaluate the validity of this postulated mechanism. Although lower systemic vascular resistance index in nonsurvivors may account for the differences in ejection fraction seen between survivors and nonsurvivors, this postulated mechanism does not invalidate the major finding of this study, that myocardial depression with a reduced ejection fraction is common in patients with septic shock.

Previous studies have reported a small proportion of patients with septic shock who have myocardial depression as shown by a low initial cardiac index (9, 12), serial progression to low cardiac index (8), or an abnormal response to fluid loading (6). Animal studies have uniformly produced a picture of myocardial depression, with falling cardiac index and reduced left ventricular performance (16-18). There is also evidence for a humoral factor producing depression of ventricular performance in animals (16-18). In our series, as with most large series in humans (2, 6, 11, 19), it was unusual to see a hypodynamic pattern with low cardiac index. Only one of the 20 patients (a survivor) had a cardiac index less than 2.5 L/min · m², whereas most patients had a cardiac index greater than 3.5 L/min · m². Even in the studies done within 24 hours of death, the cardiac index was always elevated. Thus, cardiac index and stroke volume index were maintained despite a marked decrease in myo-

**Figure 5.** The mean (± SE) end diastolic and end systolic volume indices plotted against time, with mean (± SE) ejection fraction curves shown for comparison.

**Figure 6.** A schematic representation of the reversible myocardial depression seen in the survivors of septic shock.
cardial performance as shown by a low ejection fraction and ventricular dilatation.

In our judgment, the use of dopamine and levaterenol did not explain the low ejection fractions seen in the survivors or the lack of evidence of myocardial depression in the nonsurvivors. Dopamine would be expected to increase myocardial contractility, thus increasing the ejection fraction. In low doses (1 to 5 µg/kg · min) used in this study, dopamine may also decrease the systemic vascular resistance index, tending to increase the ejection fraction. Eight of the 13 survivors during their initial study were on doses of dopamine that would be expected to increase the ejection fraction; however, 6 of 8 had a profound reduction in the ejection fraction to less than 0.4 and the ejection fraction recovered toward normal values in all surviving patients by 10 days after septic shock. Importantly, five of the 13 survivors were not on dopamine (or any vasopressor) during their initial study, and 4 of 5 had ejection fractions less than 0.4 and all 5 had substantial reductions below their recovery values at 7 to 10 days after shock. The doses of dopamine in the survivors were not significantly different from those of the nonsurvivors and did not correlate with ejection fraction or systemic vascular resistance index. Thus, dopamine does not account for the myocardial depression seen in the survivors.

Two of the seven nonsurvivors during the initial study were not on dopamine (or any pressors) and four others were on less than 10 µg/kg-min of dopamine (a dose comparable to the eight survivors on dopamine), yet these six nonsurvivors all had ejection fractions greater than 0.4 that did not significantly change to within 24 hours of their death. The dopamine dosage in the survivors and nonsurvivors was not significantly different. We conclude that dopamine administration does not account for the normal ejection fractions seen in the nonsurvivors.

The administration of levaterenol would be expected to produce a severe increase in systemic vascular resistance index resulting from alpha-agonist-induced peripheral vasoconstriction and also a modest increase in cardiac contractility from B1-adrenergic stimulation. The increase in afterload would reduce the ejection fraction. Nine of the thirteen survivors were not on levaterenol at any point in their course, but 7 of these 9 had decreased ejection fractions less than 0.4. All 13 survivors were off levaterenol by 24 hours after septic shock, yet the depressed ejection fraction in the survivors persisted for 4 days (Figure 3). Thus, levaterenol cannot account for the reduced ejection fraction in the survivors.

In the seven nonsurvivors, the mean dosage of levaterenol was higher than in the survivors; however, the nonsurvivors had lower systemic vascular resistance indices and high ejection fractions. This finding is the opposite of the effect that would have been predicted if levaterenol were accounting for the changes in ejection fraction. One could postulate that the peripheral effects of levaterenol are ineffective in severe septic shock (due perhaps to circulating mediators), and levaterenol-induced increases in cardiac contractility account for the normal ejection fractions of nonsurvivors; that is, all septic shock patients would show initially reduced ejection fraction but the high levaterenol dosage increases the ejection fraction to normal in nonsurvivors. This postulate appears unlikely, however, because three of the seven nonsurvivors were not on levaterenol during their initial study, but all three patients had ejection fractions greater than 0.45. We conclude that levaterenol administration cannot account for the normal ejection fractions in nonsurvivors.

Three patients who ultimately survived had baseline radionuclide cineangiographic studies done within 1 week before the onset of septic shock (Figure 4). At the onset of shock these three patients had an acute fall in ejection fraction, with a gradual recovery to their baseline level of ventricular function. It is of interest that one of these patients had hypertrophic cardiomyopathy with a resting ejection fraction of 0.83. With the onset of septic shock, the ejection fraction fell to 0.63 ("depressed") with recovery to 0.87 at 10 days after shock. It is likely, therefore, that most of the patients in this study had normal ventricular function before developing septic shock, and that the survivors developed an acute myocardial depression that was reversible. The available autopsy data from this study gives no evidence for unsuspected coronary artery disease or other pathologic findings in patients believed to have normal hearts.

The survivors had acute dilatation of the heart, enabling them to maintain a normal stroke volume and cardiac index, despite a profound loss of myocardial contractility. This finding is shown schematically in Figure 5. The nonsurvivors did not have this left ventricular dilatation and decrease in ejection fraction, although they also maintained a normal stroke volume and cardiac index. The reason for this seemingly paradoxical result is not known; however, the nonsurvivors had a more severe peripheral vascular defect leading to a somewhat lower systemic vascular resistance index. This action could well result in a more profound capillary leak with increasing edema and multi-organ failure. It is possible that severe myocardial capillary leak and myocardial edema resulted in a loss of myocardial compliance and caused an inability of the left ventricle to dilate. Animal studies have suggested a possible role for myocardial edema in septic shock (20). The ability of the left ventricle to dilate may be an adaptive response important to the patient with septic shock. The survivors may have less myocardial edema, permitting ventricular dilatation in response to the unknown stimulus causing myocardial depression, and thus maintain cardiac output and survive septic shock.

The patients in our study had similar hemodynamic responses to septic shock produced by different organisms, although the number of patients with gram-positive and fungal sepsis was small. In general, this finding is in agreement with other groups that found that the response to sepsis is similar regardless of the organism (2, 21). Some authors have argued that gram-negative sepsis produces a different hemodynamic pattern from gram-positive sepsis (10).

The mechanism of myocardial depression in septic shock has been debated but remains poorly understood.
Although there is some evidence for a humoral myocardial depressant factor in animals (16-18), such a substance has never been clearly identified in man. In animal models changes in coronary perfusion have been suggested as a possible cause of myocardial depression in sepsis (22). Factors such as complement, endorphins, and histamine (23) have also been proposed as possible agents in producing myocardial depression in septic shock. Further studies are needed to elucidate both the mechanisms by which myocardial depression occurs in septic shock and the methods for preventing or reversing this depression.

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