Septic shock in humans is usually characterized by a high cardiac output, a low systemic vascular resistance, reversible depression of left ventricular ejection fraction, and transient left ventricular dilatation. The relationship of left ventricular to right ventricular function in septic shock is poorly understood. To evaluate right ventricular vs left ventricular performance and to evaluate the relation of biventricular performance to survival, we performed serial hemodynamic and radionuclide angiographic studies in 39 patients with septic shock. Right ventricular ejection fraction was calculated using the two regions of interest method. There were 22 survivors and 17 nonsurvivors. Comparing initial with final (after recovery for survivors; within 24 hours of death for nonsurvivors) studies, each survivor's cardiovascular performance returned toward normal, with significant increases in mean arterial pressure, left and right ventricular ejection fraction, and right ventricular stroke work index. Their profiles also demonstrated significant decreases in central venous pressure, pulmonary artery wedge pressure, pulmonary artery mean pressure, and left and right ventricular end-diastolic volume indices. From initial to final study in the nonsurvivors, there was a statistically significant increase in heart rate but no change in any other cardiovascular parameter, indicating a persistence of the initial cardiovascular dysfunction until death. Comparing serial studies, the pattern of change in right vs left ventricular function was very similar (same direction in 82 percent of patients). Thus, myocardial depression in human septic shock affects both ventricles simultaneously with a similar pattern of dysfunction.

(Chest 1990; 97:126-31)
METHODS

Patient Population

Thirty-nine patients with septic shock were studied in the Medical Intensive Care Unit at the Clinical Center of the National Institutes of Health, Bethesda, Md. All patients met our clinical definition of septic shock: fever (temperature >38°C), hypotension (mean arterial pressure <60 mm Hg), and positive blood cultures. The mean age of the patients was 45.2 years, with a range of 12 to 73 years. There were 23 male and 16 female patients. Twenty-two patients (56 percent) survived the acute septic shock episode; 17 did not. Underlying diseases included malignant neoplasms in 35 patients and one patient each with chronic hepatitis, Cushing’s syndrome, a-antitrypsin deficiency, and an immunodeficiency of undetermined cause. Sixteen patients had Gram-negative organisms in their blood, 12 had Gram-positive organisms, five had a fungus, and six had mixed infections with more than one organism cultured (two with a Gram-positive organism and fungus; one with a Gram-negative organism and a fungus; one with a Gram-positive and a Gram-negative organism; one with two different Gram-negative organisms; and one with a Gram-positive organism, a Gram-negative organism, and a fungus).

Eight of 17 nonsurvivors were mechanically ventilated at the time of the initial study, six of these with the use of positive end-expiratory pressure (mean 7.8 ± 1.6 cm H2O). An additional three nonsurvivors required mechanical ventilation at the time of the final study. Four of 22 survivors were mechanically ventilated at the time of the initial study with a mean of 7.0 ± 1.7 cm H2O of positive end-expiratory pressure.

Therapeutic Protocol

All patients were treated by one group of critical care physicians employing a standard sequential therapeutic protocol for the management of septic shock-associated hypotension. Initially, fluids were administered intravenously to maintain the pulmonary artery wedge pressure at 15 to 18 mm Hg. Patients remaining hypotensive (mean arterial pressure <60 mm Hg) were given dopamine hydrochloride titrated to a maximum dose of 20 μg/kg/min. If hypotension persisted, intravenous levaterenol was added and titrated to maintain a mean arterial pressure of at least 60 mm Hg, and dopamine hydrochloride was decreased to 2 μg/kg/min in an attempt to preserve renal perfusion.11

Nine of 22 survivors were receiving vasopressors on the initial study. None required vasopressor support at the time of the final study. Nine of 17 nonsurvivors required vasopressor support at the time of the initial study. Fifteen of 17 were receiving vasopressor support during the final study.

Hemodynamic Measurements

All patients were treated with an indwelling arterial catheter and a balloon-tipped pulmonary artery catheter. Serial hemodynamic measurements were performed at least daily, including heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and thermodilution cardiac output. Pulmonary artery wedge pressure was determined from paper tracings on a strip chart recorder at end expiration. Using 10 ml of 5 percent dextrose in water, three to five consecutive measurements of cardiac output using the thermodilution technique were performed. The cardiac output recorded was the mean of either the three cardiac output values that varied by less than 10 percent, or the mean of the three closest determinations (of five) after elimination of high and low values.

Radionuclide Ventriculography

Based on our previous studies of left ventricular function, four serial radionuclide scans (at shock onset, and at three, seven, and ten days following shock) were planned for each patient. In the present study, at least two radionuclide ventriculography studies were performed on each patient. The first scan was done as near to the onset of shock as technically feasible, always within the first 24 hours. The final study in survivors was done when they were hemodynamically stable and not receiving any vasopressors, usually 6 to 14 days after the onset of shock. The final study in nonsurvivors was done within 24 hours of death.

Using a portable gamma camera, radionuclide ventriculography was done at each patient’s bedside in the Intensive Care Unit after in vivo labeling of the patient’s erythrocytes with stannous pyrophosphate followed by 20 mCi of technetium-99m. The camera was positioned in a 35° left anterior oblique orientation with a 15° caudal tilt to isolate the left ventricle. Left ventricular and background regions of interest were labeled, and background-corrected left ventricular time-activity curves were generated from the image sequence. The left ventricular ejection fraction was calculated as left ventricular end-diastolic counts minus left ventricular end-systolic counts divided by left ventricular end-diastolic counts, all corrected for background.

Right ventricular ejection fraction was calculated from an equilibrium scan using the two regions of interest method of Maddahi et al.12 In our laboratory, the two regions of interest method produced good interobserver and intraobserver reproducibility for measuring right ventricular ejection fraction. Each study was analyzed independently by two observers (M.M.P. and K.E.M.), who determined right ventricular ejection fractions to be within 10 percent of each other on 89 percent of the studies. These observers also found changes in the same direction in all patients. Right ventricular end-diastolic and end-systolic regions of interest and a paraventricular background region of interest were drawn. The right ventricular ejection fraction was calculated from the same equation used for the left ventricle, substituting right ventricular for left ventricular counts.

Hemodynamic Calculations

Calculations of hemodynamic parameters included the following:

\[ SVI (mL/m^2) = \frac{CI}{HR} \]

\[ SVRI (dyne·s·cm^{-5}·m^2) = \frac{(MAP - CVP)}{CI} \times 80 \]

\[ PVRI (dyne·s·cm^{-5}·m^2) = \frac{(PAM - PAWP)}{CI} \times 80 \]

\[ LVSWI (gm/m^2) = \frac{SVI \times (MAP - CVP) \times 0.0136}{CI} \]

\[ RVSWI (gm/m^2) = \frac{SVI \times (PAM - CVP) \times 0.0136}{CI} \]

\[ EDVI (mL/m^2) = \frac{SVI}{EF} \]

\[ SVI = \text{stroke volume index}, \ CI = \text{cardiac index}, \ HR = \text{heart rate}, \ SVRI = \text{systemic vascular resistance index}, \ MAP = \text{mean arterial pressure}, \ CVP = \text{central venous pressure}, \ PVRI = \text{pulmonary vascular resistance index}, \ PAM = \text{pulmonary artery mean pressure}, \ PAWP = \text{pulmonary artery wedge pressure}, \ LVSWI = \text{left ventricular stroke work index}, \ RVSWI = \text{right ventricular stroke work index}, \ \text{and EDVI = end diastolic volume index}. \]

Statistical Methods

Results are reported as the mean ± SEM. A paired sample t test was used to compare initial with final values. Spearman coefficients of rank correlation were used to assess the relation between right ventricular ejection fraction or end-diastolic volume index and pulmonary artery mean pressure or pulmonary vascular resistance index. A p value of less than 0.05 was considered statistically significant.
Table 1—Initial to Final Hemodynamic Changes in Survivors and Nonsurvivors of Septic Shock

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survivors (n = 22)</th>
<th></th>
<th>Nonsurvivors (n = 17)</th>
<th></th>
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<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>p*</td>
<td>Initial</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td>95</td>
<td>NS†</td>
<td>111</td>
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<td>Mean arterial pressure, mm Hg</td>
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<td>85</td>
<td>.017</td>
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<td>Pulmonary artery wedge pressure, mm Hg</td>
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<td>Cardiac index, L/min/m²</td>
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<td>150</td>
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<tr>
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</table>

*Paired sample t test.
†NS indicates not statistically significant.

Results

Catheter-Derived Hemodynamic Studies

Table 1 shows the hemodynamic changes from initial to final study in the 22 survivors and 17 nonsurvivors of septic shock.

The changes from initial hemodynamic measurements to final studies in the survivors generally showed a return toward the normal range of the hemodynamic profile. The mean heart rate decreased from 105 to 95 beats/min, not a statistically significant difference. Mean arterial pressure increased significantly from 77 to 85 mm Hg (p = 0.017). Central venous pressure and pulmonary artery wedge pressure decreased significantly from 9.5 to 4.4 mm Hg (p = 0.016) and 13.7 to 9.6 mm Hg (p = 0.047), respectively. There were no significant changes in cardiac index, stroke volume index, and systemic vascular resistance index. Pulmonary artery mean pressure fell from 22 to 17 mm Hg (p = 0.036), and right ventricular stroke work index increased from 5.4 to 7.3 g/m² (p = 0.03). Pulmonary vascular resistance index and left ventricular stroke work index did not change significantly.

In contrast, the nonsurvivors had no statistically significant change in any hemodynamic parameter from initial to final values except for an increase in heart rate from 111 to 129 beats/min (p = 0.006). Thus, the hemodynamic abnormalities in nonsurvivors of septic shock either worsened or were persistent throughout their courses.

Comparing the change from initial to final for the survivors with that of the nonsurvivors, the changes in heart rate, central venous pressure, pulmonary artery mean pressure, and pulmonary vascular resistance index were statistically significant. In each case the change in the survivors was toward normal, while in the nonsurvivors each parameter became more abnormal.

Radionuclide Determined Ejection Fractions and Ventricular Volumes

Table 2 shows the initial and final right and left ventricular ejection fractions and the right and left ventricular end-diastolic volume indices for the survivors and nonsurvivors of septic shock. Survivors had a substantial depression of initial left ventricular ejection fraction at 0.31 and a depressed initial right ventricular ejection fraction of 0.35. With recovery these values increased significantly to 0.47 (p < 0.001) and 0.51 (p < 0.001), respectively. The initial left and right ventricular end-diastolic volume indices were substantially increased (145 ml/m² and 124 ml/m², respectively) and decreased toward normal with recovery (to 106 ml/m², p = 0.012; and to 88 ml/m², p = 0.03, respectively). Thus, survivors showed a pattern of transient biventricular depression of ejection fraction associated with transient biventricular dilatation.

In contrast, the nonsurvivors had an initial left ventricular ejection fraction of 0.40 and right ventric-
ular ejection fraction of 0.41; these did not change significantly from initial to final studies. The initial left and right ventricular end-diastolic volume indices were 124 ml/m² and 120 ml/m², respectively; these also did not change significantly from initial to final studies.

Comparing the change in survivors from initial to final with that of the nonsurvivors, the changes in both right and left ventricular ejection fraction were statistically significant. The changes in the end-diastolic volume index were not statistically significant comparing the two groups; the nonsurvivors had small decreases in both the right and left ventricular end-diastolic volume index while the survivors had statistically significant decreases in these parameters.

An examination of serial studies showed that changes in right ventricular ejection fraction followed the same direction as changes in left ventricular ejection fraction in 31 of 38 (82 percent) patients. Changes in right ventricular end-diastolic volume index followed the same direction as changes in left ventricular end-diastolic volume index in 25 of 37 (76 percent) patients. Pulmonary artery pressure did not consistently change in direction with either the ejection fraction or the end-diastolic volume index, nor did the pulmonary artery pressures consistently change in direction with right ventricular, as opposed to left ventricular, size or function. By Spearman rank correlation the change in right ventricular ejection fraction correlated strongly with the change in left ventricular ejection fraction (r = 0.5, p < 0.001). Thus, myocardial dysfunction in septic shock is usually a biventricular phenomenon. Characteristically, the left and right ventricle demonstrate similar qualitative as well as temporal relationships in a variety of ventricular performance measurements.

**Pulmonary Vascular Changes and Right Ventricular Dysfunction**

To evaluate a possible relationship between right ventricular performance and pulmonary vascular abnormalities, pulmonary artery mean pressure and pulmonary vascular resistance index were correlated with right ventricular performance or size. The Spearman rank correlation was used to evaluate the initial values in each individual patient. Pulmonary artery mean pressure did not correlate with either right ventricular ejection fraction or right ventricular end-diastolic volume index. Pulmonary vascular resistance index did not correlate with right ventricular ejection fraction. However, pulmonary vascular resistance index did correlate negatively with right ventricular end-diastolic volume index in the survivors (r = 0.50, p = 0.02), but it did not correlate in the nonsurvivors (r = 0.30, p = 0.21).

**DISCUSSION**

In this study, 39 patients with blood culture-positive septic shock and a characteristic hyperdynamic hemodynamic profile were found to have biventricular cardiac dysfunction. This was characterized by depression of both the right and left ventricular ejection fractions with simultaneous dilatation of both ventricles. In the survivors, these abnormalities were severe at shock onset, but returned toward normal (for both ventricles) as the patients recovered. The septic shock–induced serial changes for the right ventricle usually paralleled those of the left ventricle, demonstrating that the myocardial depression and ventricular dilatation seen in humans with septic shock is a biventricular phenomenon. It is not clear why a small number of patients had changes in right ventricular size or function in a direction that was opposite the changes in left ventricular size or function. All of these patients were critically ill, and it is possible that a number of different factors acted together to produce different responses of the ventricles in individual patients.

In the nonsurvivors, the initial right and left ventricular ejection fractions were minimally depressed (not statistically significantly different from the survivors); there was no significant change in ventricular function or size in the nonsurvivors during their course, in contrast to the survivors.

The fact that septic shock produces both biventricular depression of function and biventricular dilatation has several potential clinical implications. Both right and left heart filling pressures and/or end-diastolic volume may be important in determining how much volume resuscitation a patient requires to optimize cardiac function. In some patients, the biventricular depression may progress, leading ultimately to an inadequate cardiac output and a cardiogenic shock-like state. Understanding the biventricular nature of myocardial depression in septic shock may help in formulating decisions regarding the use of vasopressors and/or inotropic agents. For example, in volume unresponsive patients with a persistently low systemic vascular resistance, vasopressors with potent vasoconstricting activity may be an appropriate choice, while patients with a falling cardiac output due to persistent myocardial depression may do better with administration of inotropic agents.

The pulmonary artery mean pressure and pulmonary vascular resistance index did not correlate with the right ventricular ejection fraction in this study. This suggests that the depression of right ventricular ejection fraction in these patients is most likely related to septic shock and not to changes in pulmonary afterload on the right ventricle. However, the pulmonary vascular resistance index did correlate negatively
with the right ventricular end-diastolic volume index in the survivors, but not in the nonsurvivors. The reason for this finding is not clear. In fact, pathophysiological one would expect the opposite correlation (a higher resistance producing a more dilated ventricle). Pulmonary hypertension has been reported to be common in experimental endotoxemia and also in the presence of sepsis and the adult respiratory distress syndrome. In the present series of patients, pulmonary hypertension was uncommon. In fact, there was no difference in any hemodynamic parameter, right ventricular size, or right ventricular function between those patients with respiratory failure (due to pneumonia or the adult respiratory distress syndrome) and those without significant pulmonary disease. In another recent study, pulmonary hypertension was not seen in a population of normal volunteers who received small doses of intravenous endotoxin. Animal models of endotoxin-induced shock or respiratory failure have clearly demonstrated a marked species variability in sensitivity to endotoxin. In humans, pulmonary hypertension has primarily been reported in association with severe respiratory failure. Reports of septic shock in humans without severe respiratory failure do not emphasize the presence of pulmonary hypertension. Pulmonary hypertension does not seem to be an essential part of the pathophysiology of septic shock in humans. It is likely, then, that the pulmonary pressures and pulmonary vascular resistance were not the major causal determinants of right ventricular size and function in this series of patients with septic shock.

Many of the patients in this series required vasopressor therapy during the course of septic shock. It could be argued that the hemodynamic and myocardial changes found are related in part to the use of vasoressors. There are no differences in the data and subsequent conclusions, however, in the mean initial hemodynamic findings, the right ventricular or left ventricular ejection fractions, or the right ventricular or left ventricular volumes if one analyzes only the subset of patients not receiving vasopressor therapy (n = 22). Therefore, the entire patient group studied is presented herein.

More of the nonsurvivors than the survivors required mechanical ventilation and positive end-expiratory pressure, especially on the final study. It would be expected that the effects of increased positive end-expiratory pressure would be to increase pulmonary artery pressures and thereby increase right ventricular end-diastolic volume and decrease right ventricular ejection fraction. Initially, however, the survivors tended to have a lower right ventricular ejection fraction than the nonsurvivors, and the nonsurvivors did not have a significant change in either right ventricular ejection fraction or end-diastolic volume index from initial to final studies. Thus, it is unlikely that the changes in mechanical ventilation account for the differences in right ventricular function between survivors and nonsurvivors.

The mechanism by which myocardial depression is produced in humans with septic shock has been the subject of intense investigation. Studies of coronary sinus blood flow have demonstrated that myocardial perfusion is not significantly compromised in patients with septic shock. The presence of a circulating humoral factor is believed by many to be the major cause of myocardial depression in septic shock. In vitro studies have provided convincing evidence that this is the case. In this model, a spontaneously beating rat heart cell culture was used as an in vitro assay of myocardial performance to evaluate patients' serum samples for the presence of a circulating substance that depressed myocardial cell extent and velocity of shortening. Serum samples from patients in the acute phase of septic shock produced a significant decrease in the extent and velocity of myocardial cell contractility. Serum samples from control groups or from patients who had recovered from septic shock did not produce significant changes in extent or velocity of contraction. The degree of depression produced in vitro correlated with the depression of left ventricular ejection fraction found in vivo. The global, biventricular dysfunction seen in the group of patients with septic shock in this study is consistent with the theory that a circulating myocardial depressant substance affects the performance of both the right and left ventricles.

Myocardial dysfunction in septic shock remains a common and important clinical problem. It is hoped that a better understanding of the effects of septic shock on the myocardium will lead to more effective treatment of patients with this highly lethal syndrome.

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