Right Ventricular Performance in Septic Shock: A Combined Radionuclide and Hemodynamic Study

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Twenty-five patients with septic shock underwent simultaneous radionuclide ventriculography and right heart catheterization to clarify the role of the right ventricle in this syndrome. A depressed right ventricular ejection fraction (<38%) was present in 13 patients and was found in patients with elevated cardiac output (4 of 6 patients) and with normal or low cardiac output (9 of 19 patients). Right ventricular dysfunction was seen with or without acute respiratory failure. In eight patients, a depressed right ventricular ejection fraction was seen in combination with an abnormal left ventricular ejection fraction (<48%), but in five patients, right ventricular ejection fraction impairment occurred with normal left ventricular ejection fraction. There was no significant correlation between abnormal right ventricular afterload and depressed right ventricular ejection fraction. No clinical or hemodynamic finding could be used to identify patients with diminished right ventricular ejection fraction. On follow-up study in 17 surviving patients, right ventricular ejection fraction improved in 6 and was unchanged in 11. Improvement in right ventricular ejection fraction occurred more frequently in patients without pulmonary hypertension or respiratory distress.

The results suggest that right ventricular dysfunction in septic shock may be more common than previously suspected. It may be caused by abnormalities in right ventricular afterload in some patients and depressed myocardial contractility in others. The findings are of therapeutic importance since interventions that diminish right ventricular afterload and increase right ventricular contractility would be appropriate in patients with septic shock and right ventricular dysfunction.

Septic shock presents a complex alteration of cardiovascular physiology that, despite significant advances in antimicrobial therapeutics, results in a high mortality rate (1,2). The cause of myocardial dysfunction in septic shock is unknown (3–6). Several mechanisms have been proposed, among them the presence of circulating myocardial depressant factors (7–10), myocardial ischemia (11–13), a variety of metabolic disorders (14,15) and an increase in left ventricular afterload (3,4,16,17).

Another proposed cause for low cardiac output in septic shock is right ventricular dysfunction associated with pulmonary hypertension (18–20). In the early stages of sepsis, pulmonary arterial pressure, pulmonary blood flow and pulmonary vascular resistance are usually normal. However, in those patients who develop the low output state, the pulmonary arterial pressures and pulmonary resistance can increase substantially (19,20). These changes are usually associated with a mortality rate of 80% (20). The increments in right ventricular afterload have been attributed to hypoxia, acidosis, acute respiratory failure, alpha-adrenergic stimulation and a number of humoral factors, including histamine, bradykinin, serotonin and prostaglandin F2 (21–24). Until recently, however, assessment of right ventricular performance in patients with septic shock was somewhat limited. Radionuclide ventriculography provides a noninvasive method for evaluation of right ventricular function. Measurements of right ventricular ejection fraction obtained by this technique are simple and reproducible (25,26). To clarify the role of the right ventricle in septic shock, we prospectively studied 25 such patients by catheterization of the right side of the heart and multiple-gated equilibrium radionuclide ventriculography.

Methods

Patient selection. The study group consisted of 25 patients with septic shock. Patients were eligible for inclusion...
if they met all of the following criteria: 1) a decrease in systolic blood pressure to less than 90 mm Hg; 2) fever or hypothermia; 3) potential source for sepsis; 4) symptoms and signs of hypoperfusion (that is, confusion or decreased urine output); 5) age between 18 and 85 years; 6) written informed consent; 7) requirement for catheterization of the right side of the heart and arterial line for clinical management; and 8) positive blood cultures drawn at onset of the shock syndrome. Women of childbearing potential were excluded.

Mean age (± SD) of the study group was 65 ± 18 years. Eleven patients had a history of heart disease, and five patients had a history of chronic obstructive lung disease; none had a history of pericardial disease. Twelve patients had acute respiratory failure, defined as requirement for mechanical ventilation and an FiO₂ greater than 50% to maintain arterial Po₂ 60 mm Hg or greater. Three of these twelve patients required the use of positive end-expiratory pressure breathing.

Data acquisition. Each patient was treated initially with intravenous fluids and vasoactive drugs, if indicated. Antibiotics were started after cultures of appropriate sites and blood were taken. Baseline hemodynamic measurements were recorded from a balloon flotation catheter and arterial line. Arterial, mean right atrial, pulmonary artery and pulmonary capillary wedge pressure were recorded. Cardiac output was obtained in triplicate using thermodilution technique and a cardiac output computer. The patients’ rhythm and heart rate were continuously monitored.

Simultaneous radionuclide and hemodynamic studies were then obtained an average of 15 ± 9 hours (range 2.5 to 31 from onset of hypotension). All patients received intravenously 25 mCi of technetium-99m in vitro labeled autologous red blood cells (27). Standard imaging equipment was used, including a portable scintillation camera (Ohio-Nuclear 410), an all purpose parallel-hole collimator and a mobile minicomputer (MDS mugacart). Gated imaging was performed in three positions (anterior, left anterior oblique 45° and left anterior oblique 70°), taking 4 to 7 minutes per view. For each view, an average of 200,000 counts/min in each of 16 frames/cycle were obtained. Hemodynamic measurements were recorded simultaneously with the scintigraphic imaging. Weight and height of the patients were recorded to calculate body surface area. The protocol was repeated 1 to 3 days after the initial study in 15 of the 25 patients and 8 days after initial study in 2 patients. The other eight patients died before a repeat study could be obtained.

Data analysis. We measured right ventricular ejection fraction from scintigraphic imaging (26). Right and left ventricular ejection fractions were determined in the left anterior oblique 45° view by light-pen assignment of right and left ventricular end-diastolic and end-systolic regions of interest and light-pen assignment of a left paraventricular background region of interest. Ejection fraction was calculated as end-diastolic counts minus end-systolic counts divided by background corrected end-diastolic counts.

The following values were derived from hemodynamic and radionuclide data:

\[
\text{Cardiac index} \, \, \text{liters/min per m}^2 = \frac{\text{Cardiac output}}{\text{Body surface area}}
\]

(Normal range: 2.5 to 4.0 liters/min per m²).

\[
\text{Stroke volume index} \, \, \text{ml/m}^2 = \frac{\text{Cardiac index}}{\text{Heart rate}} \times 1,000
\]

(Normal range: 30 to 65 ml/m²).

\[
\text{Pulmonary vascular resistance index} \, \, \text{dynes} \cdot \text{s} \cdot \text{cm}^{-5} \, \, \text{per m}^2 = \frac{80 \times (\text{Mean pulmonary artery pressure} - \text{Mean pulmonary capillary wedge pressure})}{\text{Cardiac index}}
\]

(Normal range: 69 to 177 dynes·s·cm⁻⁵ per m²).

\[
\text{Right ventricular end-diastolic volume index} \, \, \text{ml/m}^2 = \frac{\text{Stroke volume index}}{\text{Right ventricular ejection fraction}} \times 100
\]

(Normal range: 56 to 82 ml/m²).

The stroke volume index was obtained from hemodynamic measurements, and the right ventricular ejection fraction by simultaneous radionuclide study.

Statistical analysis. Results in this study were reported as the mean value ± 1 standard deviation. The statistical significance of differences between group means was assessed by Student’s t test. A probability value of less than 0.05 was considered significant. The relation between right ventricular ejection fraction and mean pulmonary arterial pressure, pulmonary vascular resistance index and right ventricular end-diastolic volume index were examined by linear regression analysis. Sequential changes in right ventricular ejection fraction in patients with and without pulmonary hypertension were compared by chi-square analysis.

Results

Incidence of initial right ventricular ejection fraction impairment (Table 1). Impaired initial right ventricular ejection fraction (<38%) was commonly seen both in the high output state (4 of 6 patients) and in the normal or low output state (9 of 19 patients). Thus, 13 patients (52% of our study group) demonstrated a depressed right ventricular ejection fraction. Eight of these patients had biventricular impairment of ejection fraction (left ventricular ejection fraction <48% and right ventricular ejection fraction <38%), whereas five had isolated impairment of right ventricular ejection fraction (left ventricular ejection fraction ≥ 48%).

None of the patients with selective impairment of right ventricular ejection fraction had a history of heart disease, and only one patient had a history of chronic obstructive pulmonary disease. In two of these five cases (Patients 16 and 24), although left ventricular ejection fraction was in...
Table 1. Radionuclide and Physiologic Data in 25 Patients at Initial and Repeat Evaluation

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Relation of right ventricular ejection fraction to right ventricular afterload (Table 1). Relation to mean pulmonary arterial pressure. Linear regression failed to reveal a significant relation between right ventricular ejection fraction and mean pulmonary arterial pressure at initial study. In addition, there was no statistically significant difference (p>0.05) in right ventricular ejection fraction between patients with pulmonary arterial hypertension (mean right ventricular ejection fraction = 36 ± 12%) and those with normal pulmonary arterial pressure (mean right ventricular ejection fraction = 39 ± 8%). In fact, nine patients with a normal right ventricular ejection fraction had pulmonary hypertension and three patients with depressed right ventricular ejection fraction had a normal mean pulmonary arterial pressure (<19 mm Hg). One of these three patients with impairment of right ventricular ejection fraction and normal right ventricular afterload (Patient 6) probably sustained acute subendocardial myocardial infarction. The second and third subjects (Patients 3 and 24) had associated segmental left ventricular dysfunction with normal left ventricular ejection fraction.

Relation to pulmonary vascular resistance index. Linear regression also failed to show a significant relation between right ventricular ejection fraction and pulmonary vascular resistance index. The mean value of right ventricular ejection fraction for patients with increased pulmonary vascular resistance index (mean right ventricular ejection fraction = 38 ± 58%). ∆RVEF = change in right ventricular ejection fraction (absolute %).
36 ± 11%) was similar to the mean value for patients with normal pulmonary vascular index (mean right ventricular ejection fraction 37 ± 12%).

Relation of right ventricular ejection fraction to respiratory status (Table 1, Fig. 1). At initial study, 12 patients had acute respiratory failure. Six (50%) of these patients with acute respiratory failure had impairment of right ventricular ejection fraction. Of the 13 patients without acute respiratory failure, seven (54%) had impaired right ventricular ejection fraction. There was no significant difference in mean right ventricular ejection fraction for patients with acute respiratory failure (35 ± 11%) and for patients without acute respiratory failure (38 ± 12%). A history of chronic obstructive pulmonary disease was not associated with a depressed right ventricular ejection fraction.

Relation between right ventricular ejection fraction and right ventricular preload (Fig. 2). There was no apparent correlation between the initial mean right atrial pressure and the initial right ventricular end-diastolic volume index. Six patients with an increased right atrial pressure (mean >8 mm Hg) had a normal right ventricular end-diastolic volume index, whereas three patients with a normal right atrial pressure had an increased right ventricular end-diastolic volume index. Linear regression showed a significant inverse relation between right ventricular ejection fraction and right ventricular end-diastolic volume index (r = −0.65, p = 0.001) for the patients with pulmonary hypertension. However, no such relation was found for patients with normal pulmonary arterial pressures.

**Figure 1.** Relation of respiratory status to initial right ventricular ejection fraction (RVEF). The left panel depicts 12 patients with acute respiratory failure and the right panel 13 without acute respiratory failure. The broken lines represent the lower limit of normal right ventricular ejection fraction (38%). There was no significant difference in mean right ventricular ejection fraction for patients with acute respiratory failure (mean 35 ± 11%) and for patients without acute respiratory failure (mean 38 ± 12%).

**Figure 2.** Relation between initial mean right atrial pressure (RAP) and initial right ventricular end-diastolic volume index (RVEDVI) in 25 patients. The shaded area represents the normal ranges. There was no apparent correlation between these two variables. Six patients with an increased right atrial pressure (right atrial pressure >8 mm Hg) had a normal right ventricular end-diastolic volume index, while three with a normal right atrial pressure had an increased right ventricular end-diastolic volume index.

Sequential changes in right ventricular ejection fraction (Table 1). Of 13 patients with initial right ventricular ejection fraction impairment, 3 had normal pulmonary arterial pressure and 10 had pulmonary hypertension. All three patients without pulmonary arterial hypertension had a normal right ventricular ejection fraction on repeat study. In contrast, only 3 of the 10 patients with pulmonary hypertension had improvement in right ventricular ejection fraction. This observation suggests it is more common that patients without pulmonary hypertension improve their right ventricular ejection fraction than those with increased pulmonary arterial pressure, but the analysis is limited by small sample size (chi-square analysis, p = 0.07).

Changes in right ventricular ejection fraction were often correlated with the respiratory status of patients with acute respiratory failure. Of the six patients with right ventricular ejection fraction impairment associated with respiratory failure, two died before a repeat study could be obtained, two had no significant improvement in their respiratory status or right ventricular ejection fraction and two had increases in their right ventricular ejection fraction as their respiratory status improved. In seven patients, initial impairment of right ventricular ejection fraction occurred in the absence of respiratory failure. In four of these seven patients, right ventricular ejection fraction normalized on repeat study.

Isolated right ventricular ejection fraction impairment: repeat radionuclide study (Table 1). Five patients demonstrated initial impairment of right ventricular ejection fraction (mean 32 ± 2%) in the absence of left ventricular ejection fraction impairment (mean 55 ± 6%). In three patients, impairment of right ventricular ejection fraction...
was associated with pulmonary hypertension (mean 40 ± 9 mm Hg) and increased pulmonary vascular resistance index (mean 501 ± 313 dynes·s·cm⁻⁵ per m²). Two other patients, (Patients 3 and 24) had normal right ventricular afterload. On repeat study, done an average of 48 hours after initial evaluation, two of the three patients with pulmonary hypertension who survived showed no improvement in right ventricular ejection fraction, whereas in the two patients with normal right ventricular afterload the right ventricular ejection fraction returned to normal.

Discussion
Measurement of right ventricular ejection fraction. Although a number of studies have evaluated myocardial failure in septic shock, few have specifically examined right ventricular performance in this disease (28). We measured right ventricular ejection fraction in patients with septic shock by equilibrium radionuclide ventriculography in the left anterior oblique 45° view (26). Measurements of right ventricular ejection fraction by this method have been shown to be reproducible and have been validated by comparison with first-pass scintigraphy in the anterior view (26). Right ventricular ejection fraction is not an independent measure of right ventricular myocardial contractility, but rather reflects global ventricular performance. In addition to myocardial contractility, right ventricular ejection fraction depends on afterload conditions and, to a lesser extent, on preload (29,30). To determine its implications in septic shock, right ventricular ejection fraction measurements have been interpreted in light of changes of right ventricular preload and afterload. We derived right ventricular end-diastolic volume index by simultaneous measurements of right ventricular ejection fraction and stroke volume index. Although each of these techniques has been validated independently, we are unaware of any studies that have compared calculated values of right ventricular end-diastolic volume index with those measured by invasive techniques.

Occurrence of right ventricular dysfunction in septic shock. We found that right ventricular dysfunction was common in our patient group. This abnormality occurred as an isolated finding or in conjunction with left ventricular dysfunction and was not associated with a specific hemodynamic state. In addition, none of our patients had a low right ventricular preload. Finally, right ventricular dysfunction was not correlated with a history of cardiopulmonary disease, the presence of acute respiratory failure or with any measure of right ventricular afterload. These observations suggest that although most patients develop right ventricular failure as the result of an abnormally high right ventricular afterload, others can develop right ventricular dysfunction as a result of myocardial depression.

Potential mechanisms of right ventricular dysfunction. From our data we were unable to determine the mechanism of right ventricular dysfunction. The variable association with pulmonary hypertension and left ventricular dysfunction suggests that several different mechanisms may be operative. In one subset of patients, a short-term increase in right ventricular afterload may result in right ventricular dilation and dysfunction. In dogs, the right ventricle may demonstrate dilation and deterioration of function with progressive pulmonary arterial occlusion (31). This is most pronounced when coronary blood flow is reduced by diminished systemic arterial pressure and, therefore, coronary perfusion (32). The observed increases in right ventricular end-diastolic volume index may increase wall stress (through the Laplace relation) and, thus, increase myocardial oxygen demand in some patients, resulting in right ventricular ischemia. In other patients, a primary reduction in coronary flow or the action of myocardial depressant factors may be pathogenetic. Finally, with an intact pericardium, right ventricular dilation may cause leftward interventricular septal displacement diminishing left ventricular compliance, volume and performance (33–35).

Unfortunately, we were unable to predict the presence of right ventricular dysfunction on the basis of clinical or hemodynamic data alone. Moreover, right atrial pressures were very poorly correlated with right ventricular end-diastolic volumes, a more accurate measure of right ventricular preload (36,37). These observations suggest that clinical and hemodynamic data are inadequate in guiding parenteral fluid therapy and that radionuclide studies of ventricular volume may be important during fluid challenges.

Sequential changes in right ventricular performance. Our data suggest that patients who have impairment of right ventricular ejection fraction without pulmonary hypertension when first studied are likely to have normalization of function at follow-up. This was not true in patients with a depressed right ventricular ejection fraction associated with persistent pulmonary hypertension. Thus, right ventricular dysfunction due to depressed myocardial contractility may improve more rapidly than that associated with pulmonary hypertension. In addition, it is not surprising that improvement in respiratory status and pulmonary vascular status is associated with improvement in right ventricular ejection fraction.

Potential limitations of study design. Our study group was not representative of all patients with septic shock because only one-half of our patients required the insertion of a balloon flotation catheter for clinical management. Furthermore, we found that only two-thirds of our patients with presumed septic shock had positive blood cultures and were eligible for this study. Therefore, our patients were selected for a more severe degree of illness. In addition, our patient group was relatively elderly with an average age of 65 years.
and heterogeneous with respect to underlying diseases predisposing to sepsis, complicating cardiac and pulmonary dysfunction and the type of organism causing the sepsis. Finally, not all patients were initially studied at the same time after the onset of their shock syndrome. Therefore, differences in the apparent pathogenesis of right ventricular dysfunction may be accounted for by time of observation in a given patient and not distinct differences between patients. Nevertheless, we found a spectrum of hemodynamic abnormalities similar to those reported by other investigators (17,38,39).

Conclusions. This study suggests that right ventricular dysfunction is responsible for myocardial decompensation in a significant number of patients with septic shock. Evaluation by hemodynamic variables alone does not accurately predict right ventricular function or ventricular mechanisms. Radionuclide ventriculography, however, greatly enhances the ability to assess global right ventricular performance. Depression of right ventricular ejection fraction is not seen in all patients and appears to be secondary to abnormalities in right ventricular afterload in one group and depression of myocardial contractility in a second group. Much greater attention should be given to therapy that decreases right ventricular afterload and improves right ventricular myocardial contractility in these patients.

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