 Persistent Preload Defect in Severe Sepsis Despite Fluid Loading*

A Longitudinal Echocardiographic Study in Patients With Septic Shock

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Study objective: To investigate the rate of recovery from septic shock in patients with suspected left ventricular (LV) preload deficiency and LV systolic dysfunction.

Design: A monitoring period was defined by the need for inotropic/vasopressor support, and LV function was assessed daily during this period by bedside two-dimensional echocardiography (2D-ECHO).

Setting: University hospital ICU.

Patients: During a 5-year period, 90 patients with an episode of septic shock (60% with gram-positive bacteria as the causative agent) were consecutively enrolled in the study (mean age, 55 ± 18 years). Standard volume resuscitation combined with inotropic/vasopressor support was used to maintain systolic arterial pressure > 90 mm Hg. All patients received mechanical ventilation because of associated respiratory failure. The average duration of hemodynamic support was 4.4 ± 1.6 days. Thirty-four patients were weaned from hemodynamic support during the monitoring period and ultimately recovered (group I). Twenty-eight patients died from refractory circulatory failure during the monitoring period, and 28 died later from ARDS or multiple organ dysfunction syndrome, leading to a 62% overall mortality rate (group II).

Methods: Daily bedside LV volumes and ejection fraction (LVEF) were recorded using 2D-ECHO. Data obtained at the start (day 1 and day 2) and end of the monitoring period (day n) were compared.

Results: LV end-diastolic volume was within the normal range of our laboratory values in all patients, but was initially smaller in group II than in group I, and remained so despite fluid loading. LVEF was significantly depressed in all patients, resulting in severe reduction in LV stroke volume (LVSV), which was initially more marked in group I. In group I patients, LVEF significantly improved during the monitoring period, resulting in an increase in LVSV.

Conclusion: 2D-ECHO changes during hemodynamic support in 90 septic patients confirmed defective LV preload with a propensity to worsen despite fluid loading in nonsurvivors (62% in the present study). Our results are also in agreement with previous studies reporting depressed LV systolic function at the initial phase of septic shock. Since LV dysfunction was more marked in patients who recovered, we suggest that the exact significance of this finding should be reevaluated.

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Key words: fluid loading; inotropic support; left ventricular dysfunction; sepsis; septic shock; two-dimensional echocardiography

Abbreviations: CVP = central venous pressure; 2D-ECHO = two-dimensional echocardiography; FiO2 = fraction of inspired oxygen; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular stroke volume; PAOP = pulmonary artery occlusion pressure; SAPS II = simplified acute physiology score II

In patients with an episode of septic shock, abnormal vascular tone was reported by Siegel et al1 in 1967 and has since been considered as the major hemodynamic consequence of sepsis.1,2 More recently, some depression of left ventricular (LV) systolic function was recognized,3–5 but its meaning and clinical importance remain controversial.6 Furthermore, in the most severe patients, LV myocardial depression is associated with preload impairment,3 and experts agree that fluid challenge plays an important part in hemodynamic support.7 The present study was devoted to a longitudinal description of the changes in echocardiographic LV function during resuscitation of septic patients, with particular attention to changes in LV systolic function, as reflected by the course of left ventricular...
ejection fraction (LVEF) and in preload preservation, derived from the course of left ventricular end-diastolic volume (LVEDV).

**Materials and Methods**

**Patients**

From January 1989 to December 1993, 90 of 144 adult patients admitted to our medical ICU for an episode of septic shock yielded high-quality echocardiographic visualization of the LV endocardium (transthoracic approach), thereby allowing reliable measurements of LV cavity dimensions at end-diastole (LVEDV) and end-systole (left ventricular end-systolic volume [LVESV]). These 90 patients (52 men and 38 women; mean age, 55 ± 18 years) were predominantly medical (77 medical vs 13 surgical patients) and were assigned to a longitudinal echocardiographic study. Prerequisites for entry of patients into this study were as follows: (1) hemodynamic support with a vasoactive agent for > 24 h; (2) absence of prior cardiopulmonary disease; and (3) identification of the causative bacterial agent. Positive blood cultures were obtained in 77 patients, and a bacterial species was isolated from a localized site of infection in 13 additional patients. In all patients, only the first episode of septic shock was considered, and measurements performed during a recurrent episode were not used in the study.

**Circulatory Failure, Hemodynamic Monitoring, and Hemodynamic Support**

Septic shock was defined as hypotension (systolic arterial pressure < 90 mm Hg by invasive monitoring) despite apparently adequate fluid resuscitation, along with the presence of perfusion abnormalities including oliguria, lactic acidosis (blood lactate level > 2.5 mmol/L), and acute alteration of mental status. All patients also required mechanical ventilation because of associated respiratory failure (Paco2/Fraction of inspired oxygen [Fio2] of < 300) and/or severely depressed mental acuity. On the first day of hemodynamic support, a general severity index (simplified acute physiology score II [SAPS II]) was calculated as described by Le Gall et al.

The monitoring period corresponded to the duration of hemodynamic support, beginning on the first day of hemodynamic support (day 1) and ending on the last day of hemodynamic support (day n). During the study period, all patients underwent daily bedside two-dimensional echocardiography (2D-ECHO). Additionally, a final echocardiographic study was done before discharge from the ICU. Heart rate was obtained from an ECG lead. BP and central venous pressure (CVP) were monitored by discharge from the ICU. Heart rate was obtained from an ECG daily bedside two-dimensional echocardiography (2D-ECHO).

During the study period, all patients underwent 2D-ECHO studies by the same investigator and residents, or practitioners taking part in medical care in the ICU. For each patient, the same view was used during serial echocardiographic studies. Echocardiographic images were recorded on videotape for further quantitative analysis. Analysis was performed within a few hours by the same senior investigator (F. J.) who was, at this time, unaware of the final outcome. 2D-ECHO images were reviewed for single-frame stop-motion analysis. The end-diastolic frame was selected at the peak of the R wave on the simultaneous ECG recording, and the end-systolic frame was defined as the smallest ventricular dimension during the last half of the T wave. Using a microcomputer interfaced with the videotape player, stop-motion frames at end-diastole and end-systole were displayed on the microcomputer screen to digitize the endocardial outlines of the left ventricle. The LV end-diastolic and LV end-systolic areas were automatically processed. LV end-diastolic and LV end-systolic long axes were measured as the distance from the apex to the midpoint of the mitral valve ring, and LV volumes were calculated using the single-plane, area-length formula. Left ventricular stroke volume (LVS V) was calculated as LVEDV–LVESV. LVEF was calculated as LVS V/LVEDV.

**Control Group:** During the same period, 44 medical students, residents, or practitioners taking part in medical care in the ICU underwent 2D-ECHO studies by the same investigator and constituted the control group (30 men and 14 women; mean age, 33 ± 10 years).

**Statistical Analysis**

Statistical calculations were performed using a software package (SAS Version 5; SAS Institute; Cary, NC). Data are expressed as mean ± 1 SD. Echocardiographic measurements at day 1, day 2, day n, and recovery (group I) and at day 1, day 2, day n (group II) were compared by an analysis of variance for repeated measurements, followed by Fisher’s protected least significant difference test when significant changes were individualized. Unpaired t tests were used for comparisons between groups concerning initial echocardiographic measurements, changes in echocardiographic measurements between day 1 and day n, and the duration of the monitoring period. A Fisher’s Exact Test was performed to compare bacteriologic data and the distribution of severe LV hypokinesia. A p value < 0.05 was required to reject the null hypothesis.

**Results**

Due to 63% feasibility of transthoracic echocardiography, 90 of the 144 patients with severe sepsis hospitalized over a 5-year period were qualified for our study and underwent serial echocardiographic evaluation. Of these, only 34 recovered and were discharged from our ICU (group I). Fifty-six patients died, resulting in an overall mortality of 62% (group...
II). Among the 54 patients who were not included because of inadequate echocardiographic imaging, only 20 recovered, yielding a similar mortality rate (64%).

The average duration of the monitoring period was 4.4 ± 1.6 days, and was significantly shorter in group I than in group II (3.2 ± 0.6 days vs 5.1 ± 2.0 days, respectively). During this period, 28 patients of group II (50%) died from refractory circulatory failure associated with ARDS (1 patient) or multiple organ dysfunction syndrome (27 patients). The remaining patients of group II (50%) died later from ARDS (16 patients) or recurrent circulatory failure with multiple organ dysfunction syndrome (12 patients).

The main clinical findings (SAPS II, blood lactate level, PaO2/FiO2, causative bacterial agents, amount of fluid used for resuscitation) are presented in Table 1. General severity, as assessed by SAPS II, was more marked in group II. There was a prevalence of Gram-positive (60%) vs Gram-negative bacteria (40%). There was no significant difference between groups in this distribution. The total amount of fluid used for resuscitation did not differ significantly between the groups, but the proportion of colloids required was three times greater in group II.

Echocardiographic measurement in the control group established a normal value for LVEDV of 68.5 ± 14.7 mL/m² and for LVEF of 69.1 ± 6.1%, resulting in an LVSV of 47.0 ± 9.9 mL/m², with a mean heart rate of 71 ± 9 beats/min. The main echocardiographic data in septic patients are presented in Table 2. The mean heart rate was significantly elevated in both groups when compared with the value in the control group or in group I at recovery, and tachycardia persisted during the monitoring period. At day 1, LVEDV was 75.3 ± 20.1 mL/m² and 64.9 ± 25.0 mL/m² in groups I and II, respectively, remaining within the normal range. However, LVEDV was significantly smaller in group II than in group I. At day n, LVEDV was 75.4 ± 21.8 mL/m² and 60.2 ± 21.6 mL/m² in groups I and II, respectively, still within the normal range. However, LVEDV in group II tended to decrease and remained significantly smaller than in group I. At day 1, LVEF was 43.9 ± 16.4% and 52 ± 14% in groups I and II, respectively, and significantly lower than in the control group. Moreover, LVEF was significantly more reduced in group I than in group II. In group I at day 1, nine patients (27%) had severe hypokinesia with LVEF < 30%, whereas the same finding was only noted in five patients (8%) in group II (p < 0.05). At day n, LVEF was 53.2 ± 11.7% and 51 ± 16.8% in groups I and II, respectively, and no significant between-group difference persisted. During the monitoring period, although LVEF significantly increased in group I, it remained significantly lower than in the control group and returned to normal (60.2 ± 16.4%) at discharge. At day 1, LVSV was significantly smaller in both groups I and II (32.6 ± 13.8 mL/m² and 32.7 ± 15.1 mL/m², respectively) than in the control group. During the monitoring period, LVSV significantly increased in group I but remained unchanged in group II.

Echocardiographic data recorded for gram-positive and gram-negative sepsis did not differ significantly.

### Table 1—Characteristics of Treatment Groups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 34)</th>
<th>Group II (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>55 ± 14</td>
<td>55 ± 19</td>
</tr>
<tr>
<td>SAPS II</td>
<td>51.7 ± 18.8</td>
<td>68.1 ± 21†</td>
</tr>
<tr>
<td>Blood lactate level, mmol/L</td>
<td>8 ± 3.5</td>
<td>6.1 ± 2.7</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>135.5 ± 64.4</td>
<td>149.5 ± 126.9</td>
</tr>
<tr>
<td>Fluid total, L/d</td>
<td>4.1 ± 0.9</td>
<td>5.2 ± 1.6</td>
</tr>
<tr>
<td>Colloids total, L/d</td>
<td>0.5 ± 0.3</td>
<td>1.5 ± 0.4†</td>
</tr>
<tr>
<td>Gram-positive agents†</td>
<td>19</td>
<td>35</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No.
†Identified Gram-positive agents: Staphylococcus aureus (20 cases), Streptococcus pneumoniae (19 cases), Streptococcus pyogenes (11 cases), enterococcus (3 cases), and Clostridium perfringens (1 case).
Identified Gram-negative agents: Escherichia coli (16 cases), Pseudomonas aeruginosa (8 cases), Proteus mirabilis (2 cases), Enterobacter cloacae (2 cases), Yersina enterocolitica (1 case), Klebsiella pneumoniae (1 case), Serratia marcescens (1 case), Acinetobacter calcoaceticus (1 case), and Neisseria meningitidis (2 cases).

### Table 2—Echocardiographic Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day n</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>Gr I: 111 ± 24†</td>
<td>113 ± 22†</td>
<td>103 ± 14†</td>
<td>82 ± 9</td>
</tr>
<tr>
<td></td>
<td>Gr II: 115 ± 25</td>
<td>117 ± 23</td>
<td>110 ± 24</td>
<td></td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>Gr I: 75.3 ± 20.1†</td>
<td>80.3 ± 20.9†</td>
<td>75.4 ± 21.8†</td>
<td>70.5 ± 14.7</td>
</tr>
<tr>
<td></td>
<td>Gr II: 64.9 ± 25.0</td>
<td>62.2 ± 15.2</td>
<td>60.2 ± 21.6</td>
<td></td>
</tr>
<tr>
<td>LVESV, mL/m²</td>
<td>Gr I: 42.4 ± 17.9†</td>
<td>43.6 ± 15.0†</td>
<td>35.7 ± 14.9†</td>
<td>27.6 ± 10.2</td>
</tr>
<tr>
<td></td>
<td>Gr II: 32.2 ± 17.7</td>
<td>34.8 ± 16.6</td>
<td>30.2 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>LVSV, mL/m²</td>
<td>Gr I: 32.6 ± 13.8†</td>
<td>36.7 ± 12.1†</td>
<td>39.7 ± 12.0†</td>
<td>42.9 ± 11.3</td>
</tr>
<tr>
<td></td>
<td>Gr II: 32.7 ± 17.7</td>
<td>27.4 ± 13.9</td>
<td>30.0 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>Gr I: 43.9 ± 16.4†</td>
<td>41.6 ± 10.6†</td>
<td>53.2 ± 11.7†</td>
<td>60.2 ± 16.4</td>
</tr>
<tr>
<td></td>
<td>Gr II: 52.0 ± 14.0</td>
<td>45.7 ± 15.7</td>
<td>51.0 ± 16.8</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD; HR = heart rate; LVESV = LV end-systolic volume; Gr = Group.
†p < 0.05 group I vs group II.
‡Identified Gram-positive agents: Staphylococcus aureus (20 cases), Streptococcus pneumoniae (19 cases), Streptococcus pyogenes (11 cases), enterococcus (3 cases), and Clostridium perfringens (1 case).
Identified Gram-negative agents: Escherichia coli (16 cases), Pseudomonas aeruginosa (8 cases), Proteus mirabilis (2 cases), Enterobacter cloacae (2 cases), Yersina enterocolitica (1 case), Klebsiella pneumoniae (1 case), Serratia marcescens (1 case), Acinetobacter calcoaceticus (1 case), and Neisseria meningitidis (2 cases).
DISCUSSION

Septic shock is considered as a “hyperdynamic” or “hyperkinetic” state. This concept, which was derived from experimental data using animal models acutely infected by gram-negative agents,2.13 might differ somewhat from human septic shock. The hyperkinetic concept has been corroborated in the past by clinical studies reporting that cardiac output was either normal or increased.13,14 But most of these studies were performed in patients submitted to aggressive fluid loading. Our echocardiographic data suggest that the term “hyperkinetic” is not appropriate to describe a setting in which the left ventricle was always hypokinetic, sometimes so severely that it looked as if it was “stunned.”5

LV hypokinesia in septic shock was first established by Parker et al,3 working in the Parillo group. These authors also proposed an original concept to explain the recovery of patients with septic shock. They suggested that survival mainly depends on the ability of the left ventricle to dilate owing to volume loading. In their survivors, despite a severely depressed LVEF, adequate LV stroke output could be maintained through this acute LV dilatation,15 a compensatory mechanism similar to that operating in chronic congestive cardiac failure.16 Although our echocardiographic data showed a similar trend in the time-course of LV diastolic dimensions, the extent of LV enlargement in survivors was much smaller than that reported in the study by Parker et al.3 In our patients who survived, LVEDV increased by approximately 14%, whereas Parker et al3 reported a 100% increase. In our patients, LV dilatation was therefore limited in response to volume loading, and the progressive increase in stroke output in survivors mainly resulted from a progressive improvement in LVEF. Methodological differences should be considered to explain this discrepancy. Contrast ventriculography, the “gold standard” for LV volume measurements, is not available at the bedside, and other methods suffer from some inaccuracies. Transthoracic echocardiography has been validated for LV volume measurements,12 but generally underestimates LV volumes in comparison with contrast ventriculography,12 particularly with the single-plane apical four-chamber area-length algorithm used in the present study.12 Moreover, image quality in patients receiving mechanical ventilation patients is often poor, and 54 of the 114 patients in this cohort were not included because of inadequate endocardial visualization. But this potential limitation will be circumvented in the future by using transesophageal echocardiography, which permits a perfect visualization of endocardial borders in patients receiving mechanical ventilation. Radionuclide angiography provides precise measurements of LVEF that correlate well with values from contrast ventriculography.17 However, this method does not permit direct measurement of LV volumes; combining cardiac output measurement by thermodilution and LVEF by radionuclide angiography, the LV volume calculation performed by Parker et al,3 may well produce serious inaccuracies.18 Using the same methodology, Schneider et al19 found only a 17% LVEDV increase in septic patient responders to volume loading, an LV dilatation far removed from the 100% increase described by Parker et al.3 Moreover, the minor LV dilatation observed in the present study was expected because pericardial stiffness usually precludes acute LV dilatation despite the amount of fluid used for resuscitation, and a normally filled LV did not have preload reserve because it operates on the steep portion of its pressure-volume relation beyond its optimal filling pressure.20 In a recent study using transesophageal echocardiography, Poelaert et al21 did not find any LV dilatation in persistently vasopressor-dependent patients with septic shock.

Myocardial depression in sepsis in humans has been shown to result from circulatory myocardial depressant mediators.22–25 Participation of cardiac ischemia has been excluded by studies assessing coronary circulation during sepsis.26,27 The prognostic value of myocardial depression in sepsis appears controversial. Whereas a previous report6 related the risk of a fatal outcome from septic shock due to the intensity of myocardial depression, the present study found that LVEF did not predict outcome in individual patients. On the contrary, LVEF was initially lower in patients who recovered, as previously observed by others.3 A first explanation of this apparently paradoxical finding is that LVEF might not be a reliable index of LV systolic function in septic shock since the left ventricle is unloaded by the fall in systemic vascular resistance. Therefore, the finding of a normal or near-normal LVEF might just indicate depressed LV systolic function associated with an abnormally low resistive arterial compartment, with the potential risk of marked LVEF reduction when using vasopressor agents.

Associated with a less-depressed LV systolic function, we found a significantly smaller LVEDV in nonsurvivors than in survivors, as already reported by others.3 Moreover, despite fluid resuscitation, LV size continued to decrease during the monitoring period. In our opinion, this finding is suggestive of persistent fluid leak outside the vascular bed in the most severe cases, as has been suggested in septic patients.28,29 A recent study30 demonstrated that
microvascular permeability was increased during sepsis. Thus, one can suggest a second explanation for the paradoxical relation between the intensity of LV systolic function impairment and the likelihood of recovery: reduced LVEF might represent an initially lifesaving process that limits cardiac output and related fluid leak across the vascular compartment. Other factors may also have contributed to preload reduction: reduced LV diastolic compliance resulting in filling impairment\(^2\)\(^1\),\(^3\)\(^3\)\(^3\) and also tachycardia, because LVEDV decreases linearly with increasing heart rate.\(^3\)\(^2\)

Some may object that the lack of pulmonary artery occlusion pressure (PAOP) monitoring in our study might have led to inadequate fluid resuscitation, thereby letting hypovolemia persist in our patients. In fact, most authors use PAOP as a target for fluid resuscitation.\(^3\)\(^3\)\(^3\)\(^4\) In recent years, however, repeated echocardiographic studies have established that PAOP measurement did not allow assessment of LV preload\(^3\)\(^4\)–\(^3\)\(^6\); at variance with others, we preferred CVP monitoring during fluid resuscitation. CVP provides a measure of the filling pressure for the whole heart.\(^3\)\(^7\) A target CVP value of 12 mm Hg was achieved in the present study by fluid resuscitation. Beyond this level, because the right heart is on the flat part of its function curve between 6 and 12 mm Hg,\(^3\)\(^7\) supplemental fluid therapy to reach a target PAOP unavoidably results in an excess fluid intake.

Be that as it may, prognosis of septic shock has not improved during the past 20 years despite a rational therapeutic approach, taking into consideration hemodynamic assessment by bedside right heart catheterization or echocardiography. The overall mortality (62%) in this study was quite similar to that reported in recent studies.\(^3\)\(^8\)\(^3\)\(^9\) Such poor results should prompt the search for a novel approach to the treatment of severe sepsis complicated by circulatory failure.

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