

Early Preload Adaptation in Septic Shock?

A Transesophageal Echocardiographic Study

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Background: An accepted concept in septic shock is that preload adaptation by acute left ventricular dilatation, when occurring spontaneously or with the aid of volume loading, permits maintenance of an adequate cardiac output, leading to final recovery. From a physiologic point of view, this concept appears debatable because a normal pericardium exerts a restraining action on a normal heart.

Methods: During a 26-month period, the authors investigated, by transesophageal echocardiography, 40 patients hospitalized in their unit for an episode of septic shock. Transesophageal echocardiography was performed in the first hours after admission, proceeded by correction of any hypovolemia, and stabilization of arterial pressure by vasoactive agent infusion if necessary. Left ventricular dimensions were obtained in long- and short-axis views, permitting calculation of left ventricular ejection fraction (long axis) and fractional area contraction (short axis). Stroke index was simultaneously measured by the Doppler technique.

Results: Stroke index was strongly correlated with both echocardiographic left ventricle ejection fraction ($r = 0.75$; $P < 0.0001$) and left ventricle fractional area contraction ($r = 0.76$; $P < 0.0001$), whereas it was independent of echocardiographic left ventricle diastolic dimensions.

Conclusions: The transesophageal echocardiography study was unable to confirm the reality of the concept of early preload adaptation by left ventricular dilatation in septic shock. Conversely, because left ventricular volume always remained in a normal range after correcting hypovolemia, systolic function was the unique determinant of stroke index in septic shock.

THE concept of left ventricular (LV) preload adaptation in septic shock was introduced by Parrillo.¹ It was derived from a clinical study performed by his group that demonstrated that a severe reduction in LV ejection fraction initially observed in septic shock did not affect cardiac output in patients who recovered, because it was accompanied by an acute LV dilatation.²

The current study was performed to verify the reality of this concept, which may appear somewhat debatable, because the presence and the restraining action of the pericardium should theoretically limit LV preload reserve when an acute LV failure occurs in a previously normal heart. We used transesophageal echocardiogra-

phy (TEE) to evaluate early preload adaptation in a group of patients supported for an episode of septic shock.

Patients and Methods

Patients

From September 1997 through October 1999, 40 adult patients were admitted to our medical intensive care unit for an episode of septic shock. Septic shock was defined as hypotension (arterial systolic pressure less than 90 mmHg by invasive monitoring) occurring in septic context, despite adequate fluid resuscitation along with the presence of perfusion abnormalities including oliguria, lactic acidosis (blood lactate level > 2.5 mM), and acute alteration of mental status.³ All patients studied also required mechanical ventilation because of associated respiratory failure (arterial oxygen tension/fractional inspired oxygen tension < 300 mmHg), severely depressed mental acuity, or both. The causative bacterial agent was subsequently identified in all cases: positive blood cultures were obtained in 30 patients, and a bacterial species was isolated from a localized site of infection in 10 additional patients. This group had a general severity index (Simplified Acute Physiology Score version II) of 59 ± 19 , calculated on the first day of hemodynamic support.⁴

These 40 patients (33 men and 7 women; mean age 53 ± 18 yr), with no prior cardiopulmonary disease, were predominantly medical (35 vs. 5 surgical patients) and were assigned to a TEE and Doppler study within 6 hours of admission, after hemodynamic stabilization. Despite initial fluid resuscitation by a plasma expander (10 \pm 2 ml/kg of 6% hetastarch), hemodynamic support by a vasoactive agent was required in all cases to maintain invasive arterial systolic pressure between 90 and 110 mmHg. We also monitored in these patients the expiratory drop in arterial pulse during cyclic tidal ventilation. This drop was expressed as a percentage and was calculated as the maximal (inspiratory) value minus the minimal (expiratory) value divided by the average of the two values.

In our unit, where right heart catheterization is never used, TEE is routinely performed at regular intervals in mechanically ventilated patients to evaluate circulatory status. This protocol was thus considered as part of routine clinical practice, and no informed consent was required from the patients' next of kin, as confirmed by the Clinical Research Ethics Committee of the French Intensive Care Society, Paris, France.

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Adequacy of Fluid Resuscitation

To ensure that fluid resuscitation was adequate, cyclic changes in arterial pulse during a controlled respiratory cycle and the end-expiratory value of central venous pressure (CVP) were checked just before the TEE study. If a patient had an expiratory drop in arterial pulse of more than 15% or a CVP of less than 12 mmHg, an additional volume expansion was performed to reduce the drop in arterial pulse to 10% and to obtain a CVP of 12 mmHg or more. This additional expansion (7 ml/kg of 6% hetastarch in 30 min) was only necessary in four patients.

Vasoactive Support

At the time of the study, four patients were given dopamine ($16.2 \pm 4.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) associated with dobutamine ($8.5 \pm 2.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), 30 were given epinephrine ($0.8 \pm 0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and the remaining six were given norepinephrine ($1.1 \pm 0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), combined in one case with epinephrine ($1.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Mechanical Ventilation

At the time of the study, mechanical ventilation was used in the controlled mode, with a tidal volume of 6–8 ml/kg (resulting in an average plateau pressure of $23 \pm 3 \text{ cm H}_2\text{O}$), a respiratory rate of 12–16 breaths/min, an end-inspiratory pause of 0.5 s, an inspiratory-to-expiratory time ratio of 1:2, and an average positive end expiratory pressure of $6 \pm 2 \text{ cm H}_2\text{O}$.

Transesophageal Echocardiographic Study

Two-dimensional real-time echocardiographic studies were performed with a wide-angle phased-array digital sector scanner and a transesophageal probe (Hewlett-Packard Sonos 500; Hewlett-Packard, Andover, MA; or Toshiba Corevision; Toshiba, Puteaux, France). We successively recorded a transesophageal, long-axis, four-chamber view, a transgastric, short-axis view of cardiac cavities, and a long-axis view of LV outflow tract to measure aortic diameter at the level of the aortic annulus. Doppler aortic flow, by pulsed or continuous wave if necessary, was obtained at the level of aortic annulus by a transgastric, long-axis approach. Measurements were directly performed during examination using the microprocessor software of the apparatus. Endocardial outlines in long- and short-axis views were manually traced and left ventricular end diastolic (LVED) and left ventricular end systolic (LVES) areas (A) were automatically processed. In the short-axis, the anterolateral and posteromedial papillary muscles were included within the ventricular area.⁵ The end-diastolic frame was selected at the peak of the R wave on the simultaneous electrocardiogram recording, and the end-systolic frame was defined as the smallest ventricular dimension during the last half of the T wave. LVED and LVES long axes

were measured as the distance from the apex to the midpoint of the mitral valve ring, and LV volumes (V) and ejection fraction (EF) were calculated using the single-plane, area-length formula from the long-axis, four-chamber view.⁶ Right ventricular end diastolic area (RVEDA) was also measured on the same long-axis view, and the RVEDA-to-left ventricular end diastolic area (LVEDA) ratio was calculated. In the short-axis view, LV fractional area contraction was calculated as $(\text{LVEDA} - \text{LVESA})/\text{LVEDA}$. By tracing the envelope of aortic flow, the velocity-time integral was automatically processed. Stroke index (SI) was obtained by multiplying the velocity-time integral by aortic area, which was calculated from the systolic aortic diameter.⁷ Cardiac output was calculated as SI times heart rate. All measurements were averaged during the whole respiratory cycle and indexed to body surface area.

Statistical Analysis

Statistical calculations were performed using the Statgraphics plus package (Manugistics, Rockville, MD). Data are expressed as mean \pm SD. Least square linear regression analysis was used to evidence significant determinants of SI. An analysis of variance followed by the Bonferroni multiple comparison procedure was used to compare data between subgroups. A *P* value < 0.05 was required to reject the null hypothesis.

Results

At the time of TEE study, 4 to 6 h after admission hemodynamic stabilization was obtained in all patients. Mean heart rate for the whole group was 102 ± 23 beats/min, mean systolic arterial pressure averaged during the whole respiratory cycle was 101 ± 7 mmHg and arterial pulse was 49 ± 3 and 52 ± 3 mmHg at end-expiration and end inspiration, respectively. End-expiratory CVP was 13 ± 1 mmHg.

Table 1. Normal Values for Echocardiographic Measurements Obtained by Transthoracic Echocardiography in a Group of 50 Young, Healthy Adults

	Average Value (mean \pm SD)	Range
LVEDV (cm^3/m^2)	71 ± 15	40–91
LVESV (cm^3/m^2)	22 ± 8	9–38
LVEF (%)	69 ± 7	55–83
LVEDA (cm^2/m^2)	13 ± 2	10–18
LVESA (cm^2/m^2)	5 ± 1	4–9
LVFAC (%)	60 ± 5	50–69

Mean BSA: 1.8 m².

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction, all three values obtained by a long axis (apical four-chamber view); LVEDA = left ventricular end-diastolic area; LVESA = left ventricular end-systolic area; LVFAC = left ventricular fractional area contraction, all three values obtained by a short axis (parasternal approach at the level of papillary muscle).

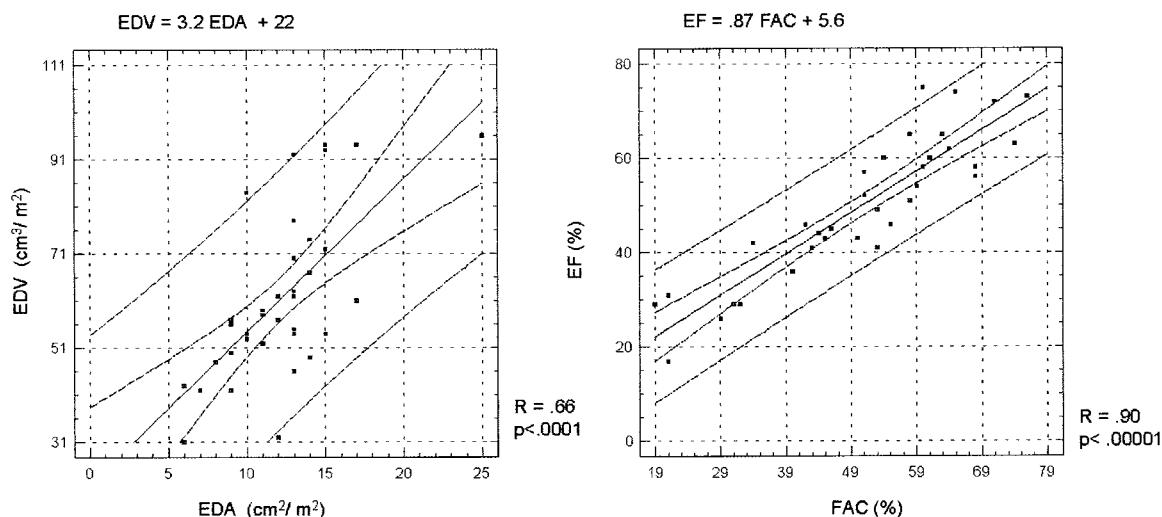


Fig. 1. Evaluation of left ventricular function in the long- and short-axis views by transesophageal echocardiography. In the left panel, individual values of end-diastolic area (EDA) by the short axis are plotted against simultaneous values of end-diastolic volume (EDV) by the long axis. In the right panel, individual values of fractional area contraction (FAC) by the short axis are plotted against simultaneous values of ejection fraction (EF) by the long axis.

For comparison with values observed in septic patients, normal values for echocardiographic measurements by a transthoracic echocardiography (TTE) approach used in our laboratory are given in table 1.

Evaluations of LV diastolic dimensions and systolic function by long- and short-axis views in septic patients are presented in figure 1. Average left ventricular end diastolic volume (LVEDV) in this group was $61 \pm 17 \text{ cm}^3/\text{m}^2$ (range, $31\text{--}96 \text{ cm}^3/\text{m}^2$), and average LVEDA in the short axis was $12 \pm 4 \text{ cm}^2/\text{m}^2$ (range, $6\text{--}25 \text{ cm}^2/\text{m}^2$). Average left ventricular ejection fraction (LVEF) in this group was $49 \pm 15\%$ (range, $17\text{--}75\%$), and average LV fractional area contraction in the short axis was $51 \pm 15\%$ (range, $19\text{--}76\%$). An

illustrative example of echocardiographic evaluation is shown in figure 2.

Early cardiac output Doppler evaluation in this group gave an average value of $3.2 \pm 1.1 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (range, $1.3\text{--}6 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$). A hypokinetic state (cardiac index $< 2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) was present in seven patients, cardiac index was in the normal range (between 2 and $4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) in 27 patients, and a hyperkinetic state (cardiac index $> 4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) was seen in six patients. Heart rate ($126 \pm 25 \text{ beats/min}$) and LVEF ($67 \pm 7\%$) in this latter subgroup were significantly higher than in the other subgroups (heart rate, 90 ± 13 and 101 ± 21 ; and LVEF, $39 \pm 10\%$ and $49 \pm 13\%$; in the hypokinetic and normal

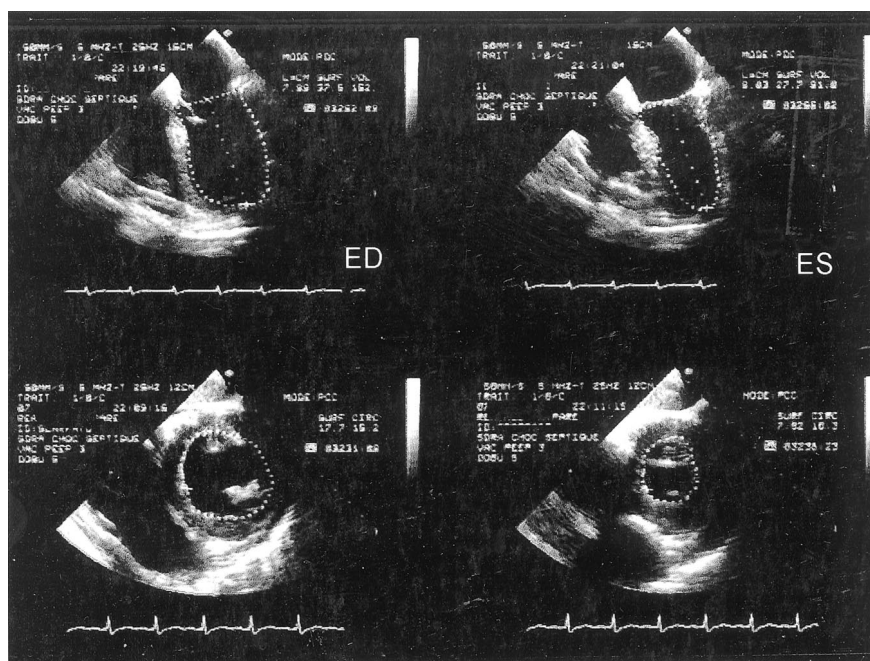


Fig. 2. An example of transesophageal echocardiography left ventricular measurements by long-axis (top) and short-axis (bottom) views. ED = end diastole; ES = end systole.

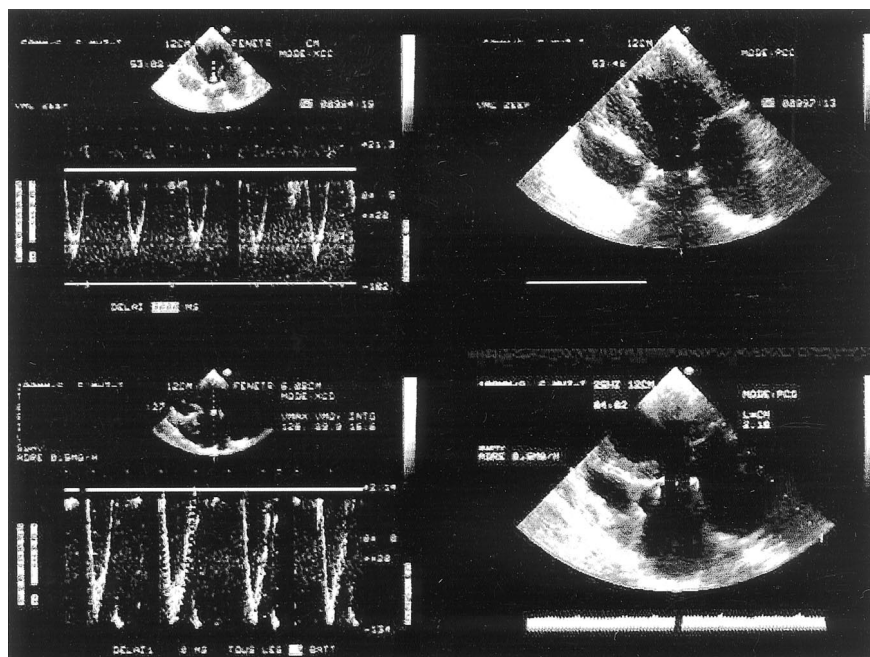


Fig. 3. Two examples of Doppler measurement of aortic flow (left) and aortic diameter (right) by transesophageal echocardiography.

output states, respectively). The mortality rate among patients in a hyperkinetic state at presentation (100%) was significantly higher than in the other subgroups (43% and 24% in hypokinetic and normal output states, respectively). Illustrative examples of Doppler stroke index measurement are given in figure 3.

Determinants of SI (LV systolic function and LV diastolic dimensions) are depicted in figure 4. Whereas SI appeared strongly correlated with both LVEF obtained

by the long axis and LV fractional area contraction obtained by the short axis (in the upper panel of fig. 4), no significant correlation was observed either with LVEDV in the long axis or with LVEDA in the short axis (lower panel of fig. 4).

Minor RV dilatation was present in 13 patients (RVEDA-to-LVEDA ratio, 0.81 ± 0.11), whereas RV size was normal in 27 patients (RVEDA-to-LVEDA ratio, 0.48 ± 0.10). Evaluation of pulmonary artery systolic pressure by the Dopp

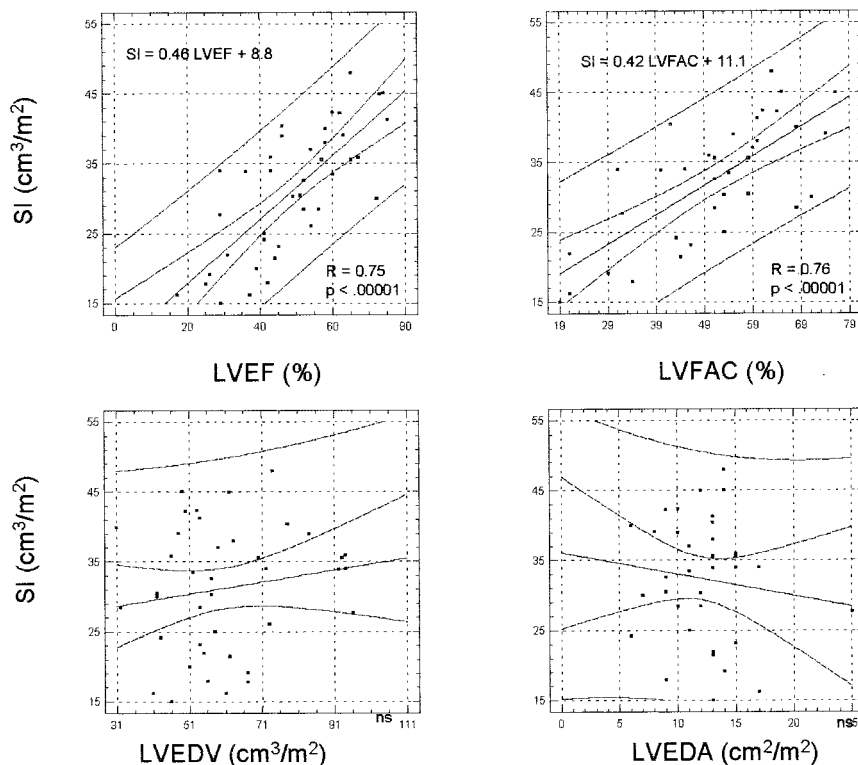


Fig. 4. In the upper panel, individual values of Doppler stroke index (SI) are plotted against simultaneous measurements of left ventricular ejection fraction in the long axis (LVEF; top left) or left ventricular area contraction in the short axis (LVFAC; top right). In the lower panel, the same values of Doppler SI are plotted against simultaneous measurements of left ventricular end-diastolic volume in the long axis (LVEDV; bottom left) or left ventricular end-diastolic area in the short axis (LVEDA; bottom right).

ler technique could be adequately performed in nine of these 13 patients with RV dilatation, giving an average value of 41 ± 5 mmHg. In this subgroup of 13 patients, average LVEF was $47 \pm 17\%$, not significantly different from the average value for the 27 patients without RV dilatation ($50 \pm 14\%$).

Discussion

Our study demonstrated that, during septic shock, SI was essentially determined by the quality of LV systolic function. Conversely, SI was little influenced by the LV diastolic dimension, when any hypovolemia was corrected. Thus, the early preload adaptation described by Parrillo's group was never detected by TEE in our patients who were in septic shock. This finding did not surprise us, because the restraining action of the pericardium theoretically precludes any acute LV dilatation. LV diastolic dimensions observed in the current study were thus in the normal range despite septic shock.

A major question concerning this study is to be sure that hypovolemia was corrected in our patients. Adequate fluid resuscitation in critically ill patients, neither too much nor too little, remains a difficult challenge. Pulmonary artery occlusion pressure monitoring has repeatedly been evidenced as inaccurate in assessing LV preload.^{5,8} Central venous pressure monitoring has recently been rehabilitated.⁹ With a central venous pressure between 6 and 12 mmHg, the RV is thought to act on the flat part of its function curve,⁹ and we systematically adjust fluid resuscitation in mechanically ventilated patients to obtain a CVP of 12 mmHg or more. When available, other studies have reported lower values for CVP in septic patients considered to be well fluid resuscitated: 11 mmHg in the second study of Parker *et al.*¹⁰ (CVP was not given in the first study²), 11 mmHg in the study of Schneider *et al.*,¹¹ 12 mmHg in the study of Vincent *et al.*,¹² and 9 mmHg in the study of Dhainaut *et al.*¹³ Unlike others, we do not use fluid challenge to maximize cardiac output.¹⁴ In our opinion, this strategy induces a serious risk of overperfusion, because a hyperkinetic LV may well continue to increase its output during incremental fluid challenge, long after adequate fluid resuscitation has been achieved. In septic patients, with abnormal capillary permeability, this strategy may be harmful, particularly by promoting pulmonary edema. Recently, Michard *et al.*¹⁵ demonstrated that monitoring of cyclic changes in arterial pulse during respiratory support permitted detection of hypovolemia in septic patients. These authors found that when a patient exhibited an expiratory drop in arterial pulse of more than 13%, an efficient increase in cardiac output was obtained by rapid fluid administration and minimized the expiratory drop in arterial pulse. We have long studied cyclic changes in arterial pulse,¹⁶ and we also

routinely monitor this parameter to detect potential hypovolemia. The threshold of 15% used in the current study is very close to that of 13% advocated by Michard *et al.*¹⁵ With these two precautions, that is, a central venous pressure higher than 12 mmHg and a drop in arterial pulse during expiration of less than 10%, we do not think that any patients of the current study remained hypovolemic. Another strong argument against persisting hypovolemia was that LVED in both the long- and short-axis views was in a normal range.¹⁷ Finally, if some patients did remain hypovolemic, this should have resulted in some correlation between SI and LVEDV, and this was not the case.

Measurements of LV diastolic volume in septic shock have given conflicting results. Measured by the "gold standard" biplane contrast ventriculography, normal LV volume is approximately $70\text{--}80$ cm³/m² at end diastole.¹⁸ Because contrast ventriculography is not available at the bedside, authors interested in this problem have used different methods to evaluate LV dimensions. A first technique was to measure cardiac output by thermodilution and to combine this with LVEF measurement by radionuclide angiography. Using this technique, Parker *et al.*² noted marked LV dilatation in septic patients, with an average LVEDV of 159 cm³/m², whereas other authors using the same technique have reported mild dilations, with LVEDV between 80 and 110 cm³/m².^{11,19} A second method for LV measurements is TTE, a technique that usually underestimates LV volumes in comparison with contrast ventriculography.⁵ Normal values in a large population were reported as 70 ± 26 cm³/m² by Triulzi *et al.*,⁵ and the normal value of our laboratory is 71 ± 15 cm³/m² (see table 1). We have in the past used TTE to measure LVEDV in septic patients and found an average value of 73 ± 20 cm³/m² in a first study of 20 patients,²⁰ 66 ± 18 cm³/m² in a second study of 32 patients,⁸ and 69 ± 24 cm³/m² in a third study of 90 patients.²¹ In the current study, we used TEE, which, in our experience, underestimates LVEDV evaluation in the long axis by approximately 12% when compared with TTE, whereas short-axis evaluation by TEE gives results identical to those of TTE. Thus, an LVEDV of 61 ± 17 cm³/m² in the current study was perfectly consistent with our previous studies. In the current study, we also evaluated LV diastolic dimensions in the short axis at the level of papillary muscle and found an average LVEDA of 12 ± 4 cm²/m². Normal values in a large population were reported as 12 ± 2 cm²/m² by Weyman²² using TTE by a parasternal approach at the same level of papillary muscle (after indexing the Weyman value for a mean body surface area of 1.8 m²). The normal value of our laboratory by the same approach is 13 ± 2 cm²/m² (see table 1). Recently, Polaert *et al.*²³ and Tavernier *et al.*²⁴ also reported that, in septic patients, LV diastolic dimensions determined by TEE in the short axis were not increased. The reason for the major discrepancy between combining thermodilution and radionuclide

angiography on the one hand, and echocardiography on the other hand, seems to lie in methodologic problems.

A first theoretical problem is that calculation of LVEDV by an indirect method, combining cardiac output measurements by thermodilution and LVEF by radionuclide angiography, leads to a result that adds the inaccuracies of the two methods. However, probably more important are the limitations of the thermodilution method in measuring cardiac output in critically ill patients. In such patients, there are several reasons for abnormal thermal loss, which potentially affects the accuracy of the thermodilution method and causes cardiac output overestimation. In mechanically ventilated patients, we have previously shown that cyclic increase in thoracic pressure produced cyclic backward flow of the thermal indicator from the right atria toward the inferior vena cava.²⁵ Additionally, in low-flow states, thermal loss leads to overestimation of cardiac output.^{26,27} Thus, the marked LV enlargement reported by Parker *et al.*² may well be explained by an overestimated cardiac output and SI. As we have observed in our previous studies^{8,20,21} and confirmed by the current study, a low LVEF in septic shock was associated with a low cardiac output. Thus, in patients with a low EF, overestimation of cardiac output by thermodilution is highly likely to be the result of the presence of a low-flow state. The end result is an overestimated cardiac size when evaluated by combining radionuclide EF.

We also assessed RV size by TEE in the current study. Measured by the gold standard biplane contrast ventriculography, the normal RV has an end-diastolic volume identical to that of the LV.²⁸⁻³⁰ But, unlike the LV, the RV may well dilate acutely. This original property results from a sudden flattening or even reversal of interventricular septum curvature, producing an enlargement in the RV cavity through a change in shape of this cavity.³¹ In a clinical setting, where this acute RV dilatation was observed by TTE, it was always accompanied by an acute reduction in LV diastolic dimensions, resulting in a constant cardiac size.³² Combination of thermodilution cardiac output measurement and radionuclide angiographic determination of ejection fraction has been used to determine RV dimensions in septic shock. Using this technique, Parker *et al.*¹⁰ described a major RV dilatation in septic patients that was associated with LV enlargement, suggesting an acute reduction in pericardial elastance by the septic process. This acute RV dilatation in septic shock was confirmed by Schneider *et al.*¹¹ and by Kimchi *et al.*³³ using the same technique. But, as we have previously mentioned, this technique may be influenced by a serious artifact produced by the thermal loss that occurs in low-flow states.^{26,27} Another attempt to measure RV dimension in septic patients was performed by Vincent *et al.*¹² using a fast-response thermodilution catheter, permitting simultaneous measurement of cardiac output and RV EF. With this technique, these au-

thors found some RV enlargement in septic shock. In another study, Dhainaut *et al.*,¹³ using the same thermodilution technique, found an average value for RVEDV in the normal baseline range in a group of 18 patients with severe sepsis. Additionally, RVEDV was increased by 14% on average after a loading challenge produced by medical antishock trousers.¹³ In the current study, we assessed RV dimensions by calculation of the RVEDA-to-LVEDA ratio in the long axis. We have previously defined normal RV echocardiographic size in the long axis as an RVEDA-to-LVEDA ratio of 0.6 or less, moderate RV dilatation as an RVEDA-to-LVEDA ratio between 0.6 and 1, and severe RV dilatation as an RVEDA-to-LVEDA ratio or more than 1.³⁴ Using these definitions we found in the current study a normal RV size in most patients. However, moderate RV dilatation was present in approximately 30%, with an elevated pulmonary artery systolic pressure, when it could be measured noninvasively.

The other results of the current study are in accordance with accepted notions and do not require specific comments. The data confirm that a hyperdynamic state is not the general rule in septic shock.²¹ However, when present, it resulted from marked tachycardia and from an elevated LVEF suggesting a severe fall in systemic arterial resistance. A hyperdynamic state was associated with 100% mortality rate in the current study, and this severity has previously been underscored.³⁵

In conclusion, in contrast to a well-accepted notion we did not observe any preload adaptation in this group of patients with septic shock, and we demonstrated that the quality of LV systolic function was the major determinant of cardiac output in this setting. We also observed that the RV, whose mechanical properties are somewhat different from those of the LV, was moderately dilated in 30% of patients studied.

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