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Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study

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Abstract *Objective:* The objective was to prospectively evaluate cardiac morphological and functional changes using transesophageal echocardiography (TEE) during early septic shock. *Design:* Prospective, observational study. *Setting:* Medical-surgical intensive care unit of a teaching hospital. *Patients and participants:* Ventilated patients with septic shock, sinus rhythm and no cardiac disease underwent TEE within 12 h of admission (Day 0), after stabilization of hemodynamics by fluid loading (median volume: 4.9 l [lower and upper quartiles: 3.7–9.6 l]) and vasopressor therapy, and after vasopressors were stopped (Day *n*). *Measurements and results:* Thirty-five patients were studied (median age: 60 years [range 44–68]; SAPS II: 53 [46–62]; SOFA score: 9 [8–11]) and 9 of them (26%) died while on vasopressors. None of the patients exhibited TEE findings of cardiac preload dependence. Between Day 0 and Day *n* (7 days [range 6–9]), mean left ventricular (LV) ejection fraction (EF) increased (47 ± 20 vs. $57 \pm 14\%$: $p < 0.05$), whereas mean LV end-diastolic volume decreased (97 ± 25 vs. 75 ± 20 ml: $p < 0.0001$). Out of 16 patients (46%) with LV systolic dysfunction on Day 0, 12 had normal LVEF on Day *n* and 4 patients fully recovered by Day 28. Only 4 women had LV dilatation (range, LV end-diastolic volume: 110–148 ml) on Day 0, but none on Day n. Doppler tissue imaging identified an LV diastolic dysfunction in 7 patients (20%) on Day 0 (3 with normal LVEF), which resolved on Day *n*. *Conclusions:* This study confirms that LV systolic and diastolic dysfunctions are frequent, but LV dilatation is uncommon in fluid-loaded septic patients on vasopressors. All abnormalities regressed in survivors, regardless of their severity. *Descriptors:* Shock: clinical studies (38), Cardiovascular monitoring (34).

Keywords Sepsis · Shock · Echocardiography · Doppler

Introduction

Circulatory failure associated with septic shock is characterized by marked hypovolemia (absolute, secondary to increased capillary permeability and relative, due to vasoplegia) and an intrinsic ventricular dysfunction partially masked by decreased vascular resistance [1–3]. Echocardiography Doppler, especially using the transesophageal route (TEE), is increasingly used in intensive care unit (ICU) settings for the assessment of patients presenting with circulatory failure [4]. By providing morphological as well as functional real-time information, TEE is ideally suited to promptly identifying the mechanisms of sepsis-induced hypotension in ventilated ICU patients [5].

Transient left ventricular (LV) systolic dysfunction has long been identified during the acute phase of septic shock using right heart catheterization [6] or echocardiography [7]. The presence of reversible

LV structural changes, suggesting preload adaptation, have also been described [3, 6], but remains controversial [8]. In addition, LV diastolic dysfunction has been reported during septic shock [9–11], but these descriptions relied on the use of conventional pulse wave Doppler parameters, which are sensitive to rapid changes in loading conditions, such as fluid therapy and vasopressor administration [12]. Finally, right ventricular (RV) dysfunction has been observed in up to 30% in one series of septic shock patients assessed using TEE [5], but has otherwise been scarcely reported.

The present study was aimed at prospectively evaluating both cardiac function and structure using TEE in ventilated patients with septic shock. Particular attention was directed toward the identification of LV diastolic dysfunction using preload-independent Doppler parameters and the assessment of potential ventricular structural changes (i. e., dilatation) during the early phase of septic shock.

Materials and methods

Patients

For 12 months, adult patients presenting to our medical-surgical ICU with septic shock were eligible to participate in this descriptive study if they fulfilled all the following criteria:

1. Mechanical ventilation
2. Evidence of a source of infection for < 6 days
3. At least 2 of the 4 SIRS criteria, as previously defined [13]
4. Two or more signs of tissue hypoperfusion of organ dysfunction out of the following: $PaO_2/F_IO_2 < 300$, urinary output < 0.5 ml/kg/h for at least 2 h, arterial lactate ≥ 3 mmol/l, platelet count $< 100,000/mm^3$ per cubic millimeter [14]
5. For less than 24 h, sustained hypotension (systolic blood pressure < 90 mmHg) lasting at least 30 min that required ≥ 1 l of blood volume expansion and the administration of vasopressor therapy (norepinephrine or epinephrine)
6. Stable hemodynamics after fluid loading and initiation of vasopressor therapy

Patients were excluded in the presence of at least one of the following criteria:

1. Other cause of shock
2. Previous cardiac disease
3. Absence of sinus rhythm
4. Contra-indication for performing a TEE
5. Polynuclear neutrophil count $< 500/mm^3$

6. Moribund status or decision to withhold aggressive therapy

Hypovolemia was considered corrected in the presence of a respiratory variation of invasive pulse arterial pressure $< 13\%$ [15]. Associated treatment (e. g., corticosteroids, recombinant activated protein C) was left to the discretion of the attending intensivists [16]. We have long used TEE for the routine hemodynamic assessment of critically ill patients sustaining circulatory failure in our medical-surgical ICU [17]. Since we routinely monitor septic shock patients using TEE, iterative examinations are performed including at the time of vasopressor weaning. As such, the protocol was approved by the Ethics Committee of the Société de Réanimation de Langue Française that waived the need for signed informed consent.

TEE studies

In each patient, TEE was performed by experienced intensivists with a level III competence in echocardiography [18] within 12 h of admission (Day 0) in hemodynamically stable patients, and when vasopressors were stopped (Day n). In the presence of persistent abnormalities on Day n, transthoracic echocardiography (spontaneously breathing patients) was performed on Day 28 in survivors. TEE was performed as previously described [17], using a Sonos 5500 upper-end platform (Philips, France) connected to a multiplane 5-MHz TEE probe. Patients received midazolam (0.15 mg/kg) and pancuronium bromide (0.1 mg/kg) prior to esophageal probe insertion. Therapeutic changes based on real-time TEE results interpretation were recorded while digital loops and still-frames were stored on optical disks for off-line measurement and further analysis. In each patient, the following TEE parameters were measured off-line (mean of three end-expiratory measurements): LV end-diastolic and LV end-systolic volumes using the modified Simpson's rule and four-chamber area-length methods, LV stroke volume using pulse wave Doppler at the level of the LV outflow tract [19], LV and RV end-diastolic areas, and early diastolic Doppler tissue imaging (DTI) velocities (Ea) of the lateral aspect of the mitral ring in the transesophageal long axis view [12]. The LV ejection fraction (EF) was conventionally calculated and the RV/LV end-diastolic area ratio was computed. In addition, the superior vena cava collapsibility index and respiratory variation of aortic Doppler velocities were determined, as previously described [20, 21]. LV systolic dysfunction was classified as mild ($40\% <$ LVEF $< 50\%$), moderate ($20\% <$ LVEF $< 40\%$), or severe (LVEF $< 20\%$). LV diastolic dysfunction was defined by a decreased Ea < 8.5 cm/s [22] and LV filling pressures were deemed elevated when E/Ea > 7.0 [23]. LV dilatation corre-

sponded to a LV end-diastolic volume of > 170 ml for men and > 101 ml for women using the modified Simpson's rule method, and > 193 ml for men and > 136 ml for women using the four-chamber area-length method [24]. RV was considered dilated when the RV/LV end-diastolic area ratio exceeded 0.6 [25]. We have previously shown that our inter- and intra-observer variability in the measurement of echocardiographic parameters is globally $< 11\%$ [12, 26].

Statistics

All values are expressed as medians with lower and upper quartiles. On Day 0, clinical and TEE variables were compared between patients who subsequently died in the ICU and survivors using the Mann–Whitney test or Fisher's exact test, as appropriate. In each patient who has been discharged from the ICU, the parameters studied were compared at Day 0 and at Day n using the Wilcoxon matched-pairs signed-rank test. A p value < 0.05 was considered statistically significant.

Results

During the study period, 132 of the 1,026 patients (13%) admitted to our ICU with suspected sepsis were screened for eligibility. Of 42 eligible patients with septic shock, 7 were excluded because of arrhythmia ($n = 4$), known cardiopathy ($n = 2$), or Boerhaave syndrome ($n = 1$). Finally, 35 patients were studied (19 men; median age: 60 years [lower and upper quartiles: 44–68]; Simplified Acute Physiologic Score [SAPS] II: 53 [46–62]; Sepsis-related Organ Failure Assessment [SOFA]: 9 [8–11]).

Median duration of sepsis before TEE assessment of hemodynamics on Day 0 was 48 h (36–96 h). At the time of initial TEE examination, patients had received a median fluid volume of 4.9 l (3.7–9.6 l). The vasoactive drugs administered were norepinephrine ($n = 32$), epinephrine ($n = 12$), or both ($n = 9$), but none of the patients received dobutamine. Nine patients (26%) died while on vasopressors (no TEE on Day n), whereas vasoactive drugs were stopped after a median of 7 days (range 6–9 days) in the remaining 26 patients who were all discharged from the ICU. Twenty-five patients presented with a community-acquired infection whereas the 10 remaining patients had a nosocomial infection. Sites of infection were: intra-abdominal (37%), pneumonia (29%), urinary tract (11%), skin (9%), and miscellaneous (14%). The source of sepsis was documented in 25 patients (71%) and 14 patients (40%) had bacteremia. Twelve patients died during their hospital stay (34%).

Patients had frequent comorbidities, including chronic alcoholism ($n = 12$), cancer or hemopathy ($n = 9$), diabetes ($n = 5$), chronic renal failure ($n = 3$), and hypertension ($n = 13$). Five patients were receiving long-term treatment by beta-blockers and 7 patients by angiotensin conversion enzyme inhibitors. At the time of inclusion, patients who subsequently died during their ICU stay required higher doses of vasopressor, had greater blood lactate levels and exhibited more organ dysfunctions, as reflected by a higher SOFA score, compared with survivors (Table 1).

Transesophageal echocardiography findings recorded on Day 0 and Day n are summarized in Table 2. None of the patients exhibited TEE findings of cardiac preload dependence at the time of the examinations, since both the collapsibility index of the superior vena cava and the respiratory variations of aortic Doppler velocities were consistently within the lower range (Table 2). On Day 0,

Table 1 Patients' characteristics during the early phase (within 12 h) of septic shock after fluid loading and initiation of vasopressor therapy (Day 0) and after the interruption of vasoactive drugs (Day n)

Parameters	Day 0 ($n = 35$)		Day n ($n = 26$)
	ICU death ($n = 9$)	ICU discharge ($n = 26$)	
Age (years)	68 (56–78)	54 (43–67)	–
Male	5	14	–
Heart rate (bpm)	124 (114–142)	114 (101–133)	95 (81–100)**
Systolic blood pressure (mmHg)	112 (103–126)	120 (114–126)	121 (115–128)
Mean blood pressure (mmHg)	82 (79–86)	84 (80–91)	86 (82–92)
Fluid resuscitation (l)	5.0 (4.0–7.0)	5.0 (3.5–8.0)	–
Vasopressors (µg/kg/min)			
Norepinephrine	0.41 (0.30–0.51)	0.21 (0.09–0.33)*	–
Epinephrine	0.41 (0.19–0.52)	0.21 (0.11–0.37)	–
Tidal volume (ml/kg)	7.1 (6.3–9.4)	7.7 (7.2–8.4)	8.0 (7.0–9.0)
PaO$_2$/F$_I$O$_2$	172 (94–257)	233 (160–252)	267 (233–292)**
Arterial lactates (mmol/l)	10.4 (8.7–16.9)	6.0 (3.8–7.7)*	1.7 (1.2–2.2)**
SOFA	12 (11–13)	9 (7–10)*	3 (2–5)**

Data are expressed as medians and numbers in parentheses are lower and upper quartiles
* $p < 0.05$ compared with deceased patients
** $p < 0.05$ compared with survivors on Day 0

Table 2 Transesophageal echocardiography (TEE) parameters measured within 12 h of septic shock after fluid loading and initiation of vasopressor therapy (Day 0) and after the interruption of vasoactive drugs (Day *n*)

TEE parameters	Day 0 (*n* = 35)		Day *n* (*n* = 26)
	ICU death (*n* = 9)	ICU discharge (*n* = 26)	
SVC collapsibility index (%)	13 (6–16)	14 (9–22)	14 (9–19)
Respiratory variations of aortic Doppler velocity (%)	3 (2–4)	4 (2–6)	4 (3–6)
LVEF, modified Simpson's rule (%)	51 (18–57)	50 (34–62)	58 (54–64)
LVEF, four-chamber area-length (%)	52 (20–59)	51 (33–63)	58 (54–65)
LV stroke volume (ml)	41 (34–55)	53 (47–69)	64 (56–74)*
LV end-diastolic volume, modified Simpson's rule (ml)	104 (80–113)	95 (76–110)	76 (65–94)*
LV end-diastolic volume, four-chamber area-length (ml)	102 (83–117)	99 (79–114)	80 (66–96)*
Ea lateral mitral ring (cm/s)	12.0 (11.1–13.4)	11.4 (9.1–16.0)	11.1 (10.2–12.5)

Data are expressed as medians and numbers in parentheses are 95% confidence intervals

TEE, transesophageal echocardiography; *SVC*, superior vena cava; *LV*, left ventricle; *EF*, ejection fraction; *Vp*, early diastolic blood flow propagation velocity; *Ea*, early diastolic tissue Doppler imaging velocity of the lateral mitral ring
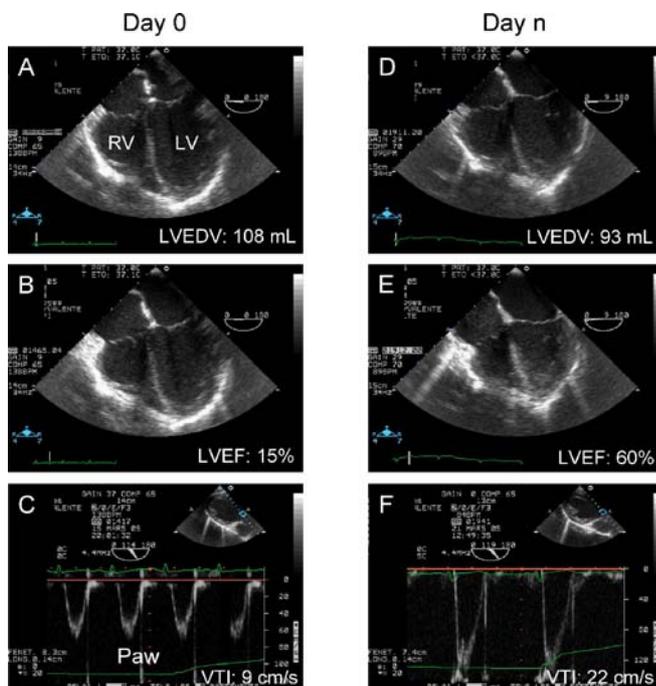
* $p < 0.05$ compared with survivors on Day 0

Fig. 1 Example of reversible left ventricular (LV) systolic dysfunction during the early phase of septic shock. In this patient, who received 4 l of blood volume expansion on Day 0, transesophageal echocardiography (TEE) disclosed **a** a normal LV end-diastolic volume and **b** a severe global LV systolic dysfunction reflected by a low ejection fraction and **c** reduced stroke volume. When vasopressors were stopped 6 days later (Day *n*), TEE depicted **d** a smaller LV cavity size and **e** total recovery of LV systolic performance as reflected by a normal ejection fraction and **f** stroke volume. *LV*, left ventricle; *RV*, right ventricle; *LVEDV*, LV end-diastolic volume; *LVEF*, LV ejection fraction; *Paw*, airway pressure; *VTI*, velocity time integral

none of the TEE parameters allowed us to distinguish patients who would die during their ICU stay from survivors. LVEF was decreased in 16 patients (46%), reflecting a LV systolic dysfunction classified as mild in 3 patients (LVEF range: 41–49%), moderate in 7 patients (LVEF range: 24–38%), and severe in the remaining 6 patients (LVEF range: 7–18%). From Day 0 to Day *n*, LVEF tended to increase while LV stroke volume reached significantly greater values (Table 2). Out of the 16 patients with a depressed LV systolic function on Day 0, 12 patients had normal LV systolic performance on Day *n* (LVEF range: 54–82%), and the remaining 4 patients fully recovered by Day 28 (LVEF range: 57–62%). Median LV end-diastolic volume significantly decreased between the two TEE examinations (Table 2). Only 4 women had a true LV dilatation using the modified Simpson's rule (LV end-diastolic volume range: 110–148 ml) and 1 woman using the four-chamber area-length method (LV end-diastolic volume: 152 ml) on Day 0, but none on Day *n* (Fig. 1). All of them were alive on Day 28. Median values of Ea were similar between Day 0 and Day *n* (Table 2). On Day 0, DTI identified an LV diastolic dysfunction in 7 patients (20%). In this subset of patients, median Ea maximal velocity was significantly slower than that recorded in the remaining patients (7.7 cm/s [range 7.4–8.1] vs. 13.9 cm/s [range 9.1–25.7]: $p < 0.0001$). Isolated LV diastolic dysfunction (LVEF > 50%) was identified in 3 patients (9%) using DTI. On Day *n*, Ea significantly increased to reach normal values in all of those patients (14.2 cm/s [range: 9.6–32.7]: $p = 0.03$). Finally, 4 patients (11%) with acute respiratory distress syndrome exhibited mild RV dilatation, as reflected by an

increased RV/LV end-diastolic area ratio (range 0.7–1.0). In all cases, RV dilatation regressed with the pulmonary recovery.

No blood volume expansion was performed based on initial TEE study. In the presence of a moderate-to-severe LV systolic dysfunction ($n = 13$), inotropic support was either introduced or increased. LV diastolic dysfunction identified on the basis of reduced DTI mitral ring velocities led to fluid restriction and diuretic therapy only when associated with increased LV filling pressures in patients with acute lung injury or acute respiratory distress syndrome ($n = 3$). The identification of LV dilatation had a therapeutic impact only when associated with LV systolic dysfunction ($n = 2$). Finally, RV dilatation led to the initiation/increase in vasopressor support in conjunction with the maintenance of airway plateau pressure < 28 cm H_2O ($n = 4$).

Discussion

This study confirms echocardiographic findings previously reported by Jardin et al. [5, 8, 27] and suggests the presence of a transient LV diastolic dysfunction using relatively preload-independent Doppler parameters. Entry criteria for participating in the present study selected the most severe patients admitted to our medical-surgical ICU for septic shock, as reflected by elevated blood lactate level and by both the number and severity of organ dysfunctions. Surprisingly, hospital mortality was fairly low in these high-risk patients, presumably due to the high proportion of intra-abdominal and urinary sepsis (48%).

Nearly half of our patients exhibited a LV systolic dysfunction during the early phase of septic shock. Importantly, TEE was initially performed after stabilization of hemodynamics obtained by substantial volume loading (median: 4.9 l [3.7–9.6]) and the administration of vasopressors. Accordingly, LV systolic dysfunction could not be ascribed to persistent hypovolemia, as reflected by the absence of TEE findings consistent with cardiac preload dependence [20, 21]. Although vasopressors may have unmasked underlying decreased myocardial contractility by increasing LV afterload [1], 34% of our patients were receiving epinephrine at the time of the initial TEE examination for clinically suspected LV systolic dysfunction. In contrast with the fairly high proportion of our patients (37%) with moderate-to-severe LV systolic dysfunction, Rivers et al. [28] previously reported a 14% incidence of LV failure in the group of patients with $SCvO_2$ monitoring during the early course of severe sepsis and septic shock. This apparent discrepancy may be related to different population characteristics, earlier hemodynamic assessment, and mainly indirect and blind evaluation of LV performance. Our results based on direct TEE quantitative evaluation of LV systolic function corroborate previous echocardiographic studies obtained

in similar clinical settings [5]. Specifically, cardiac index measured using pulsed wave Doppler at the level of the LV outflow tract [19] was < 3 l/min/m^2 in 15 of our 35 patients (43%) on Day 0, similar to a proportion of 35% reported elsewhere [5]. In the majority of our surviving patients, a significant improvement in LV systolic function was observed at the time of interruption of vasopressor therapy (Day n). In all remaining patients, LV systolic performance fully recovered by Day 28, as previously reported [6, 27].

Left ventricular cavity dilatation was not observed in a large proportion of our patients, since only 4 women (11%) had an increased LV end-diastolic volume measured using the modified Simpson's rule on Day 0, and 1 woman when using the four-chamber area-length method. These results are in keeping with those reported by others in the same clinical setting [8, 11, 20, 29] and fail to corroborate the hypothesis of true LV dilatation during the early phase of septic shock in survivors [6]. Although echocardiography tends to underestimate true LV volumes compared with angiography, LV adaptation to preload is limited since its cavity cannot acutely dilate [8]. Therefore, pioneer studies that reported acute LV dilatation during the early phase of septic shock presumably overestimated actual volumes due to inherent cumulative errors relative to the combined techniques used for cavity measurements (i. e., thermodilution and radionuclide ventriculography) [3, 6, 30]. In the present study, the significant decrease in LV end-diastolic volumes between Day 0 and Day n presumably reflects the reduction in preload secondary to decreased fluid loading after the acute phase of septic shock, hence the existing yet limited LV adaptation to preload.

Left ventricular diastolic dysfunction was identified during the acute phase of septic shock in 20% of our patients. Prolonged relaxation has been documented in animal models of septic shock using invasive measurement of the time constant of LV pressure fall [31]. In septic shock patients, LV diastolic dysfunction has been previously documented using conventional pulsed wave Doppler parameters [9–11]. Unfortunately, these parameters have been shown to be markedly influenced by abrupt variations in LV preload [12], and are therefore of little value in the setting of resuscitated septic shock. In contrast, DTI velocity applied to the lateral aspect of the mitral ring appears independent of loading conditions [12]. In all our patients, DTI velocities reached normal values on Day n. Accordingly, the current data support the presence of a transient LV diastolic dysfunction, frequently associated with depressed LV systolic function, during the early phase of septic shock. The potential role of increased LV end-diastolic volume secondary to augmented preload and elevated heart rate in the development of LV diastolic dysfunction observed on Day 0 and its clinical relevance remain unclear. In the present study, the identification of LV diastolic dysfunction led to fluid restriction and diuretic therapy in 3 of the 7 patients who exhibited

associated increased filling pressure with concomitant respiratory compromise.

We observed mild RV dilatation in only 4 of our septic shock patients (11%). In this setting, acute RV dysfunction may be secondary to either an intrinsic depression in RV contractility [1] or to acute cor pulmonale [5, 32]. In our patients, RV dilatation was secondary to an acute cor pulmonale, which accompanied an acute respiratory distress syndrome. Although the incidence of RV dysfunction has been reported to be as high as 32% in septic shock patients [5], we observed a lower frequency in the present study, as did others [33]. This discrepancy may be attributed to different study populations. In this specific setting, TEE is particularly valuable in guiding ventilator settings that should be protective, not only for the lungs, but also for the RV [34], as in 4 of our patients.

The present descriptive study is limited by the relatively small sample size, which precludes any definite conclusion from the comparison between deceased and surviving patients. In addition, we did not evaluate the efficacy of therapeutic changes that directly resulted from the initial TEE examination. Finally, the precise delay in total recovery of LV systolic and diastolic function could not be precisely determined since TEE was not serially performed on a daily basis, but rather when vasoactive drugs could definitely be stopped.

Conclusions

This study confirms that LV systolic dysfunction is frequent, but initial true LV dilatation is uncommon during the acute phase of septic shock in fluid-loaded patients on vasopressors. In addition, the present study suggests that LV diastolic dysfunction assessed using a preload-independent Doppler parameter is commonly observed during the early phase of septic shock. RV dysfunction was less frequently observed and associated with acute respiratory distress syndrome. Importantly, all these changes regressed in survivors, regardless of their severity. Further studies are needed to determine whether certain echocardiographic findings could be associated with a poor prognosis in septic shock patients.

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