Acute left ventricular dilatation and shock-induced myocardial dysfunction*

Bélaïd Bouhemad, MD, PhD; Armelle Nicolas-Robin, MD; Charlotte Arbelot, MD; Martine Arthaud, PharmD; Frédéric Féger, PharmD, PhD; Jean-Jacques Rouby, MD, PhD

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the changes in left ventricular dimensions over time in septic shock patients.
2. Describe effects of septic shock on myocardial function.
3. Use this information in a clinical setting.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: **Whether cardiac ventricles can acutely dilate during septic myocardial dysfunction.**

Design: **A prospective echocardiographic study was performed to assess changes of left ventricular dimensions over time in patients with septic shock.**

Settings: **A 20-bed surgical intensive care unit of Pitié-Salpêtrière university hospital in Paris.**

Patients: **Forty-five patients were studied over the first 10 days of septic shock.**

Interventions: **None.**

Measurements and Main Results: **Left ventricular end-diastolic area (LVEDA), fractional area change (FAC), velocity time integral of the aortic flow, echocardiographic indices of left ventricular relaxation, and cardiac troponin I (cTnI) were measured at day 1, 2, 3, 4, 7, and 10. Three groups were defined: 29 patients without increased cTnI and cardiac impairment (group 1), eight patients with increased cTnI and left systolic ventricular dysfunction (group 2), and eight patients with increased cTnI and isolated impairment of left ventricular relaxation (group 3). At day 1, LVEDA was significantly higher in group 2 (13 ± 3 cm/m^2, $p < 0.05$) compared with groups 1 (10 ± 2 cm/m^2) and 3 (11 ± 2 cm/m^2). LVEDA did not change in groups 1 and 3. In group 2, LVEDA and FAC returned within 10 days to values observed in groups 1 and 2. A significant correlation was found between aortic velocity time integral and LVDEA ($r = .78$, $p = 0.022$) and FAC ($r = .89$, $p = 0.003$) only in group 2.**

Conclusions: **Acute and reversible left ventricular dilation accompanies septic shock-induced systolic left ventricular dysfunction. When septic myocardial abnormalities are limited to reversible impairment of left ventricular relaxation, left ventricular dimensions remain unchanged. (Crit Care Med 2009; 37:441–447)**

KEY WORDS: septic shock; myocardial dysfunction; echocardiography

Myocardial dysfunction during sepsis is detected by a sudden increase in cardiac troponin I (cTnI) without-electrocardiographic evidence of coronary ischemia (1). Echocardiographycally, it is characterized by a depression of left ventricular ejection fraction (2) or an isolated and reversible left diastolic dysfunction (3). Using serial radionuclide cineangiography, it was demonstrated that sepsis-induced reduction of ejection fraction was associated to ventricular dilation, so that cardiac output could be maintained. This pattern was character-

***See also p. 743.**

Hospital Practitioner (BB, ANR), Department of Anesthesiology, Réanimation Chirurgicale Pierre Viars, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, University Pierre et Marie Curie Paris-6, France; Associate Professor (CA), Department of Anesthesiology Réanimation Chirurgicale Pierre Viars, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, University Pierre et Marie Curie Paris-6, France; Hospital Practitioner (MA, FF), Laboratoire de Biologie des Urgences (MA, FF), Assistance Publique Hôpitaux de Paris, Hospital Pitié-Salpêtrière, University Pierre et Marie Curie Paris-6, France; Hospital Practitioner (FF), Faculté de Pharmacie, Paris, France; and Medical Director (JJR), Department of Anesthesiology, Réanimation Chirurgicale Pierre Viars, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, University Pierre et Marie Curie Paris-6, France.

For information regarding this article, E-mail: belaid.bouhemad@psl.aphp.fr

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istic of survivors and was reversible in 7–10 days after onset of sepsis (2, 4–7).

The concept of early preload reserve with left ventricular dilation, however, was recently questioned by Vieillard-Baron et al (8), arguing that normal pericardium restraints acute left ventricular dilation. Another echocardiographic study reported normal values of end-diastolic left ventricular volume at the beginning of septic shock (9, 10). Several confounding factors may explain these contradicting results. In the presence of increased pulmonary microvascular permeability, early administration of catecholamine may be preferred to aggressive fluid therapy (11), a therapeutic option that potentially restricts the initial left ventricular dilation. The lack of follow-up of cardiac dimensions over time precludes any firm conclusion about left ventricular dilation in the absence of reference value. Furthermore, it has been recently reported that 50% of septic shock patients with increased cTnI have an isolated and reversible impairment of left ventricular relaxation, inconsistent with left ventricular dilation (3). Therefore, we hypothesized that left ventricular dilation observed during septic shock may be observed exclusively in patients with myocardial injury detected by an increased cTnI and may depend on the nature and degree of cardiac impairment. To verify the hypothesis, we performed a longitudinal prospective study combining transesophageal echocardiography and right ventricular catheterization to identify conditions during which left ventricular dilation is observed.

METHODS

This study is the second part of a larger investigation aimed at determining the incidence and nature of cardiac dysfunction resulting from septic shock and its evolution over time. In the first part of the investigation, we demonstrated that half of the patients with increased cTnI had isolated and reversible impairment of left ventricular relaxation and the other half left ventricular systolic dysfunction (3). The data concerning left ventricular dimensions that are reported in this study were obtained in the same series of patients.

Patients. Among 53 patients admitted to the Surgical Intensive Care Unit of la Pitié-Salpêtrière (Paris, France) for septic shock (12) and enrolled in a prospective study aimed at identifying echocardiographic abnormalities characterizing the early phase of septic shock (3), a subgroup of 45 patients who survived the first 10 days were analyzed to assess changes in left ventricular dimensions along time. The protocol was approved by our Institutional Review Board. All required norepinephrine, dobutamine, or epinephrine for hemodynamic support. During the study period, administration of vasoactive agents was decided by the clinician in charge of the patient. At the initial phase of septic shock, volume expansion was performed if respiratory changes in pulse pressure were >13% (13) and pulmonary artery occlusion pressure <15 mm Hg, if available. All patients were ventilated using controlled mechanical ventilation (Horus ventilator, Taema, France). Ventilator settings were adjusted by the clinician in charge of the patient to achieve $Paco_2$ values between 40 and 50 mm Hg and Sao_2 >90% at an Fio_2 <0.6, according to recent recommendations (14). Exclusion criteria were as follows: age <18 yrs, pregnancy, esophageal and gastric pathology, cervical spine instability, lack of sinus rhythm, right or left bundle branch block, and history of cardiac disease.

The patients were classified into three groups according to the results of the first part of the study (3). Group 1 included 29 patients with cTnI remaining <0.2 ng/mL and without septic shock-induced cardiac impairment. Group 2 included eight patients with a reversible increase in cTnI and acute and reversible left systolic ventricular dysfunction, defined as a left ventricular ejection fraction <50% returning to normal values at the recovery phase of septic shock. Group 3 included eight patients with a reversible increase in cTnI, left ventricular ejection fraction ≥50%, and transitory and reversible impairment of left ventricular relaxation.

Study Protocol and Echocardiographic Measurements. Patients were studied from the onset of septic shock to a maximum period of 10 days. cTnI and echocardiographic parameters were measured on days 1, 2, 3, 4, 7, and 10. All patients were anesthetized with a continuous intravenous infusion of fentanyl 5 μg kg^{-1} hr, midazolam 0.1 mg kg^{-1} hr, and cisatracurium 0.5 mg/kg. Transesophageal echocardiography was performed using an HP-SONOS 5500 (HewletPackard, Andover, MA) by an observer unaware of clinical and hemodynamic data. Images were stored digitally on magneto-optical disks (Hewlet Packard, Andover, MA) for later playback and analysis. Transesophageal echocardiographic data were obtained using standard views and techniques (15). Left ventricular end-diastolic area (LVEDA) and left ventricular end-systolic area (LVESA) were measured on the short axis

Table 1. Clinical characteristics of the patients

		Patients with Increased Cardiac Troponin I (n = 16)	
	Patients without Increased Cardiac Troponin I (n = 29) Group 1	Fractional Area Change <50% (n = 8) Group 2	Fractional Area Change ≥50 (n = 8) Group 3
Age (yrs)	55 ± 17	60 ± 13	61 ± 21
Male/Female	21/8	5/3	6/2
Severity Acute Physiological Score II	42 ± 15	55 ± 15[a]	55 ± 18[a]
Acute lung injury (n)/Acute respiratory distress syndrome (n)	15/7	3/2	3/3
Positive end-expiratory pressure (cm H_2O)	9 ± 3	9 ± 3	9 ± 3
Type of surgery			
Abdominal surgery	2	2	1
Urology	4	2	1
Gynecology	1	0	0
Neurosurgery	3	1	0
Vascular surgery	11	2	4
Other	0	1	0
Medical	0	0	1
Multiple trauma	8	0	1
Causes of sepsis			
Postoperative bronchopneumonia	21/29	2/8[b]	2/8[b]
Medical bronchopneumonia	0	0	1
Abdominal sepsis	5	3	3
Urosepsis	1	2	1
Cellulitis	1	1	0
Mediastinitis	0	0	1
Prosthetic vascular grafts infection	1	0	0
Norepinephrine	29 (100%)	8 (100%)	8 (100%)
Epinephrine and/or dobutamine	0	2	0

Data are presented as mean ± SD or number.

[a]Statistically significant differences between group 1 and groups 2 and 3 (nonpaired *t* test, $p < 0.05$); [b]statistically significant difference between group 1 and groups 2 and 3 (Fisher's exact test, $p < 0.05$).

Table 2. Hemodynamic and echocardiographic characteristics of the patients at day 1

	Patients without Increased Cardiac Troponin I (n = 29) Group 1	Patients with Increased Cardiac Troponin I (n = 16)	
		Fractional Area Change <50% (n = 8) Group 2	Fractional Area Change ≥50 (n = 8) Group 3
Left ventricular end-diastolic area (cm^2/m^2)	10 ± 2	13 ± 2[a]	11 ± 2
Fractional area change (%)	61 ± 11	34 ± 11[a]	64 ± 14
Aortic velocity time integral (cm)	17 ± 5	13 ± 4[b]	15 ± 3
Right ventricular end-diastolic area/left ventricular end-diastolic area (%)	67 ± 12	61 ± 20	67 ± 9
Mean arterial pressure (mm Hg)	82 ± 12	80 ± 17	74 ± 14
Heart rate (b/min)	101 ± 23	111 ± 25	99 ± 21
Cardiac index (l min/m)	4.1 ± 1.2	3.4 ± 0.7	3.8 ± 0.8
Mean pulmonary arterial pressure (mm Hg)	25 ± 7	25 ± 4	24 ± 5
Right atrial pressure (mm Hg)	9 ± 3	13 ± 4	9 ± 2
Pulmonary capillary wedge pressure (mm Hg)	10 ± 4	11 ± 5	9 ± 2

Using a one-way analysis of variance following by a Bonferroni's test, comparisons were made between patients of group 1 and patients of groups 2 and 3. [a]Statistical difference ($p < 0.0001$) between group 2 and groups 1 and 3; a pulmonary artery catheter was present in 19 of 29 (66%) patients in group 1 and in 13 of 16 (80%) patients in groups 2 and 3; [b]statistical difference ($p < 0.01$) between group 2 and group 1.

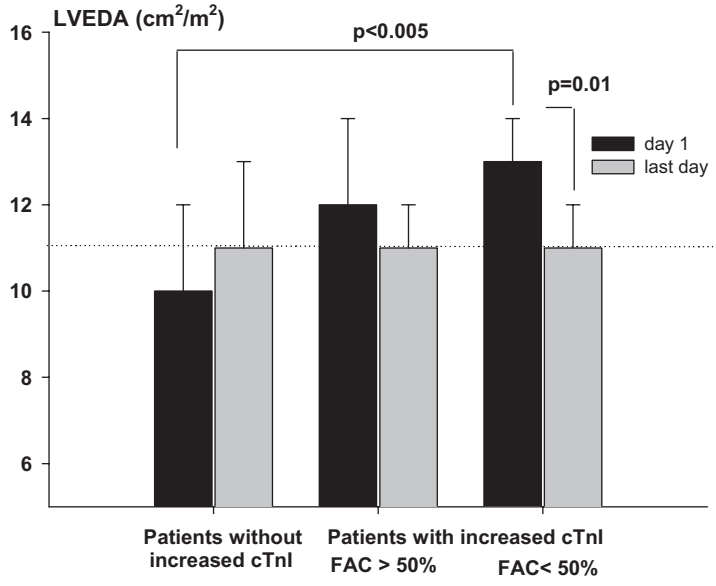

Figure 1. Variations of left end-diastolic area (*LVEDA*) in patients with and without increased cardiac troponin I (*cTnI*) during septic shock. Significant differences were found among the three groups of patients. *FAC,* fractional area change.

transgastric view at the mid-papillary muscle level. The aortic flow was recorded by pulsed Doppler with the sample volume placed at the left ventricular outflow tract using a long-axis transgastric approach. The ultrasound beam was placed as parallel as possible to aortic flow. Pulsed Doppler was recorded at horizontal sweep speed of 100 mm/s, and aortic velocity time integral (AoVTI) was measured. RVEDA/LVEDA ratio was measured from the four chamber view (16). All measurements were made at end expiration and averaged over five consecutive cardiac cycles. Left ventricular systolic function was assessed by calculating the fractional area change defined as (LVEDA − LVESA)/LVEDA.

Cardiac Troponin I Measurements. cTnI was measured on blood samples collected through the arterial catheter, in 4-mL vacutainers containing lithium-heparin (Becton Dickinson, Plymouth, UK), using a sandwich-immunoassay test performed on the Opus Plus analyzer (Dade Behring, Newark, DE). The sensitivity of the assay was 0.1 ng/mL, the liner range 50 ng/mL, and the limit of normal 0.2 ng/mL.

Statistical Analysis. All data are expressed as mean ± SD. Normality of the data's distribution was assessed by a Kolmogorov-Smirnov test. At day 1, echocardiographic parameters were compared using a one-way analysis of variance. In the presence of statistical significance, a Bonferroni test was performed to identify differences between groups. Other comparisons were made using a chi-squared test for data showing a normal distribution or a Mann-Withney *U* test or a Fisher's exact test for data without normal distribution. Evolution of echocardiographic parameters over time was compared among the three groups using a two-way analysis of variance for 1 within factor (change between day 1 and day 10) and one grouping factor. Correlations between LVEDA, fractional area change, and AoVTI were made using linear regression analysis (r) or coefficient correlation of spearman (rho) when needed in each group. Statistical analysis was performed using Statview 5.0 software (SAS institute, Carry, NC), and statistical significance level was fixed at 0.05.

RESULTS

Initial clinical characteristics of the three groups of patients are summarized in Table 1. At day 1 (Table 2), patients of group 2 had a higher LVEDA, a lower AoVTI, and fractional area change than patients of groups 1 and 3 ($p < 0.01$). In patients of group 1, echocardiographic parameters remained unchanged throughout the study. In patients of group 2, LVDEA (Fig. 1), AoVTI, and fractional area change returned to similar values as those observed in patients of group 1 at day 10 (Fig. 2). It has to be pointed out that systolic arterial pressure remained unchanged throughout the study period, attesting of unchanged afterload conditions required for interpreting changes in LVDEA and AoVTI (17). As shown in Figure 3, at day 1, AoVTI was significantly correlated to LVEDA only in patients of group 2.

DISCUSSION

Myocardial injury resulting from severe sepsis is characterized by a transi-

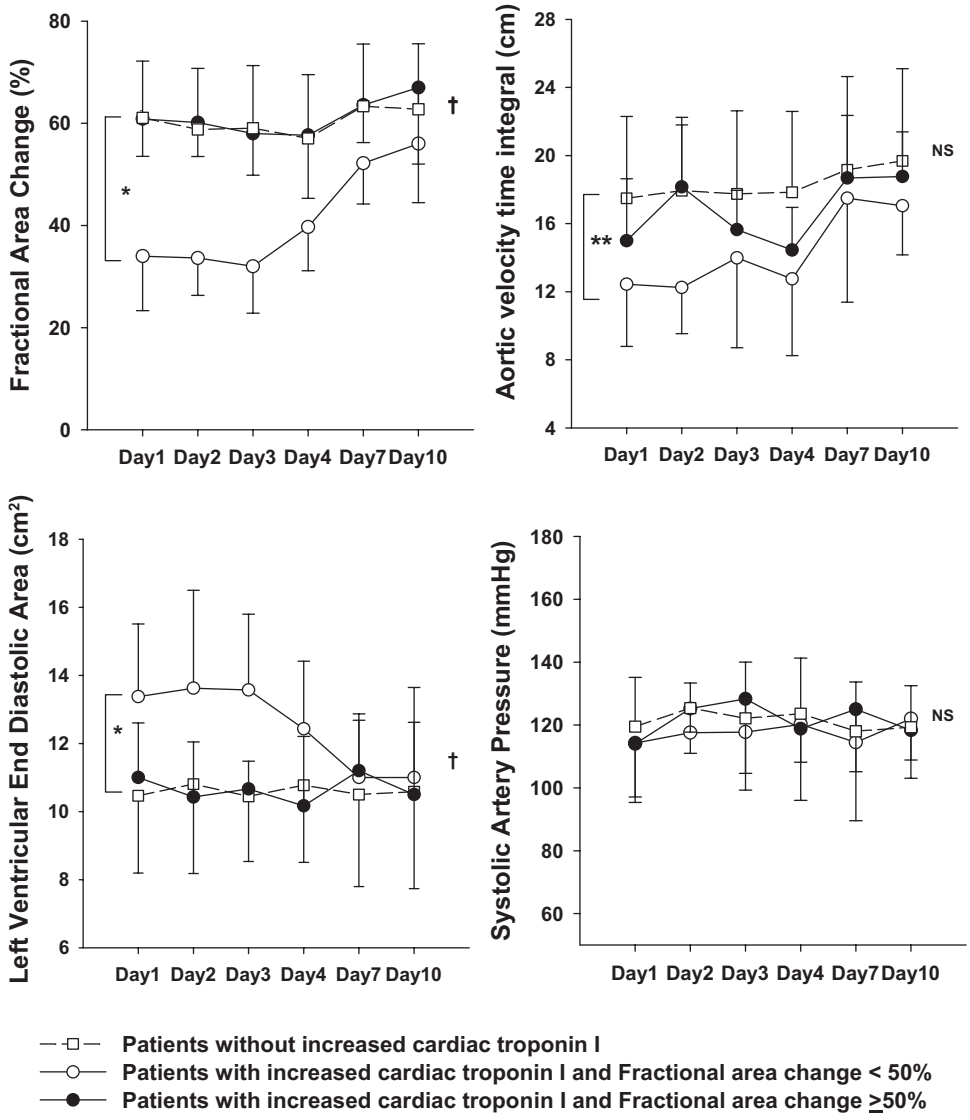

Figure 2. Comparative changes of left ventricle end diastolic area, fractional area change, and aortic velocity time integral from the onset of septic shock to recovery in the three groups of patients. Evolution of parameters over time was compared between the three groups using a two-way analysis of variance for 1 within factor (change between day 1 and day 10) and one grouping factor. "†" indicates a significant interaction between changes over time in the different groups ($p < 0.05$). *, ** and brackets indicate a statistical difference between groups with a $p < 0.0001$ and $p < 0.01$, respectively. *NS*, not significant.

tory and reversible increase in cTnI. This study demonstrates that acute left ventricular dilation is observed only when septic myocardial injury results in acute systolic left ventricular dysfunction, defined by reduced ejection fraction, reduced stroke volume, or by both. When the increase in cTnI is not associated with significant systolic dysfunction, left ventricular dimensions do not increase. This study also provides evidence that acute left ventricle dilation, although an essential determinant of AoVTI at the early phase of sepsis-induced systolic left ventricular dysfunction (Fig. 3), is not sufficient to maintain stroke volume. These results are in accordance with initial experimental and clinical findings of Parrillo and co-workers and clarify some aspects of the ongoing controversy on acute left ventricular dilation in septic shock.

Short- and long-term adaptive mechanisms to a primary disturbance in myocardial contractility are different (18). In the presence of acute moderately severe systolic heart failure, cardiac output is maintained because the end-diastolic fiber length and the ventricular end-diastolic volume are elevated through the operation of the Franck-Starling mechanism. Very likely, such a mechanism explains the transitory and reversible increase in left ventricular end-diastolic volume observed in critically ill patients at the early phase of septic shock and associated to transitory and reversible left ventricular systolic dysfunction. If the increased diastolic wall stress persists over weeks and months, ventricular remodeling results from replication of sarcomeres in series and elongation of myocytes and leads to nonreversible cardiac chamber dilation and increases myocardial mass (18). Such a mechanism cannot be involved in the acute left ventricular dilation reported in this study.

We found that more than 38% of patients who survived to septic shock had an increase in cTnI. In previous studies, such an increase was correlated to left ventricular systolic dysfunction, mortal-

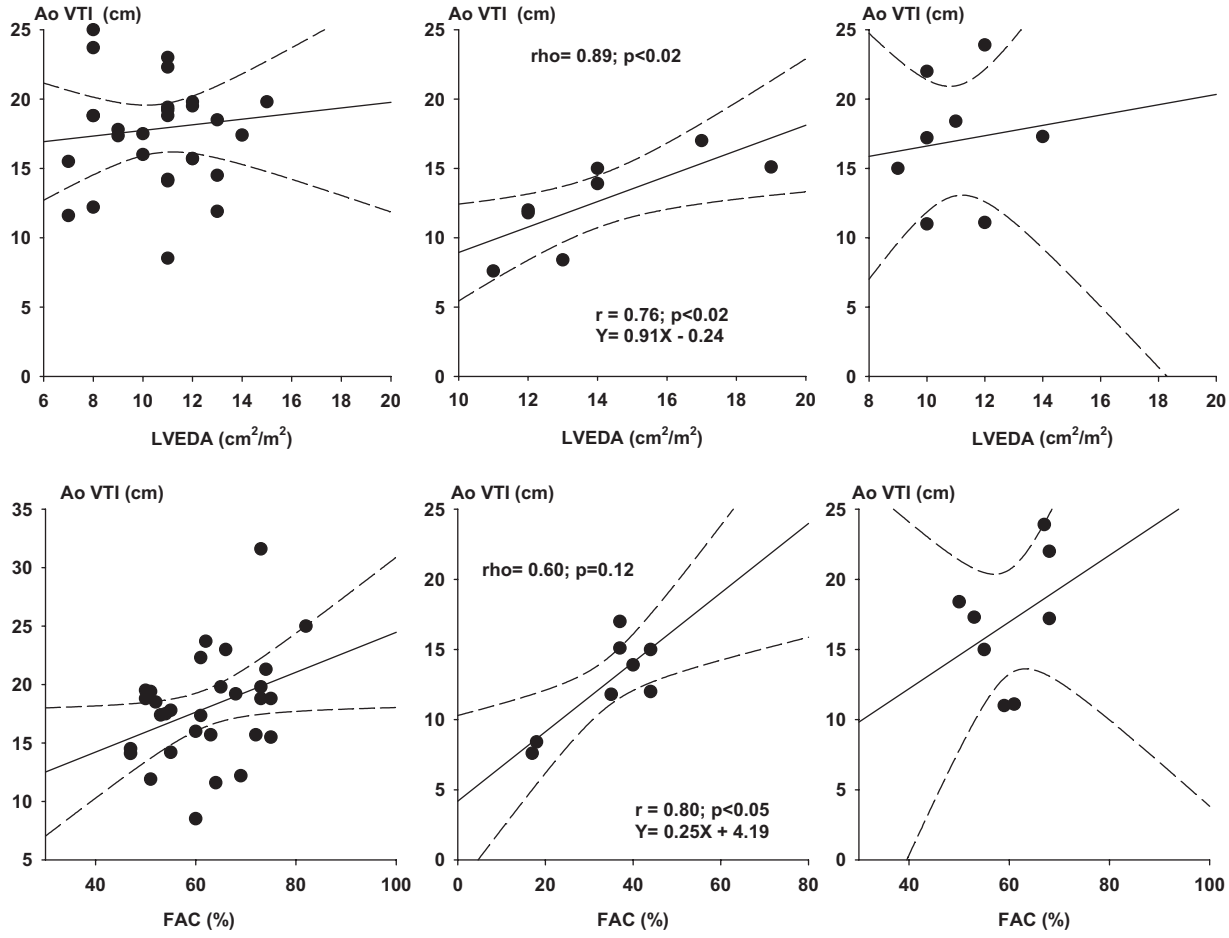

Figure 3. Correlations existing at day 1, between aortic velocity time integral (*AoVTI*) and left end-diastolic area (*LVEDA*) and Fractional Area Change (FAC) in patients without increased in cardiac troponin I (cTnI) (*left*), in patients with increased cTnI and FAC <50% (*middle*), and in patients with increase cTnI and FAC >50% (*right*). Significant correlations were found between AoVTI and FAC and between AoVTI and LVEDA only in patients with increased cTnI and FAC <50% (continuous line indicates the linear regression line and dashed line the 95% confidence interval).

ity, and need for inotropes (1, 19–22). Even if septic cardiac dysfunction is characterized by global akinesia, wall motion abnormalities have been reported in 45% of patients with septic shock (23). An ischemic origin can be ruled out because coronary flow and oxygen delivery are preserved during septic shock by coronary vasodilatation and increased oxygen availability (24, 25), as attested by normal electrocardiogram, coronarography, and histologic examination (1, 20, 26). During septic shock, increase in cTnI may be the consequence of transient increase in myocyte membrane permeability caused by the release of proinflammatory cytokines (27).

Initially, Parrillo and co-workers described myocardial dysfunction during severe sepsis as a biventricular dilation associated with a depressed left ventricular ejection fraction (2, 4). This pattern was characteristic of survivors and was reversible in 7–10 days after onset of sepsis (2, 4–7). Other groups reported the occurrence of left ventricular dilation associated to left ventricular systolic impairment in animals (28–31) and humans with septic shock (32, 33). Two subsequent echocardiographic studies, however, failed to find such an acute left ventricular dilation in critically ill patients with septic shock (10, 34). In a series of 60 patients with septic shock, Vieillard-Baron et al (8) showed that LVEDA was not an important determinant of stroke index, thereby questioning the validity of the concept of early preload adaptation by left ventricular dilation in septic shock. In addition, autopsy studies have shown interstitial myocarditis with polymorphonuclear cells infiltrate within myocardial fibers (35) that should be responsible of reduced compliance and lack of ventricular dilation in septic shock.

Several reasons explain why acute left ventricular dilation was missed in the study by Vieillard-Baron and co-workers (8). From a cardiovascular standpoint, patients with septic shock cannot be considered as a single homogeneous population. Half of them only exhibit an increase in cTnI attesting of sepsis-induced myocardial injury. Among them, half have isolated and reversible impairment of left ventricular relaxation (3) whereas the other half suffers from systolic left ventricular impairment. Acute left ventricular dilation can be evidenced exclusively in this category. In other words, the concept of preload recruitment only applies to the subgroup of patients with systolic left ventricular dysfunction. Now, in the study by Jardin and co-workers, patients with septic shock were globally analyzed without any specific attention paid to patients with sepsis-induced cardiac injury. Troponin I was not measured precluding the possibility of iden-

tifying sepsis-induced myocardial injury. In addition, a single echocardiographic measurement was performed at the early phase of septic shock, and LVEDA could not be compared with control values measured at the resolution of septic shock. Interestingly, at day 1 of septic shock, individual values of LVEDA are comparable in the study by Vieillard-Baron and co-workers and in this study: seven of 40 patients had LVEDA $\geq$15 cm^2/m^2 in the study by Vieillard-Baron and co-workers (8) and 5 of 45 in our study. Our data, however, demonstrate that the highest values of LVEDA are observed in patients with sepsis-induced alterations of left ventricular ejection fraction and significantly decrease to values around 10 cm^2/m^2 at the resolution of septic shock. These data confirm the difficulty of defining normal value of LVEDA or volume in patients with septic shock. Indeed, the reported values for left ventricular area are ranging between 5.5 and 15 cm^2/m^2 in a large and nonselected population (36), and it is, therefore, difficult to define a specific cutoff value for diagnosing left ventricular dilation.

Two other confounding factors may have also contributed to contradictory findings in previous investigations. Echocardiography underestimates true left ventricular volume (37), and excessive fluid loading may contribute to left ventricular dilation. In this study, however, fluid loading was stopped when respiratory changes in pulse pressure were <13%. Therefore, volume expansion was less in group 2 patients than in groups 1 and 3 patients, and it is unlikely that left ventricular dilation could have been caused by fluid overloading. Finally, comparative changes over time between different groups appear as a better evaluation of sepsis-induced changes of left ventricular dimensions than assessing absolute values during a single measurement.

In our study, left ventricular dilation at the acute phase of septic shock reached 30%. We did not find the 100% increase in left ventricle end-diastolic volume initially described by Parker et al (4). Echocardiography likely facilitates hemodynamic care of patients with septic shock (38) by diagnosing decreased preload, a characteristic of septic shock (39). In the setting of increased microvascular permeability, aggressive fluid challenge can lead to elevated cardiac filling pressures and can worsen pulmonary edema. In patients with septic shock, vasoactive agents are very often required to obtain an adequate tissue perfusion pressure (11). This explains why our group, as many teams, prefers the early administration of vasoconstrictors to aggresive fluid therapy at the early stage of septic shock (11). Such a therapeutic option may limit the hyperkinetic state and sepsis-induced left ventricular dilation. It is most likely that if an aggressive fluid therapy had been adopted, left ventricular dilation would have been even greater. This may explain why the greater left ventricular dilation initially described by Parrillo and co-workers (4) was not observed in this study.

Sepsis-induced acute left ventricular dilation is generally considered as allowing maintenance of cardiac output in response to the impairment of systolic left ventricular ejection. This hypothesis is supported by the correlation that was documented at onset of septic shock between LVEDA and AoVTI in patients with increased cTnI and impaired left ventricular ejection fraction. When considering all patients together, no correlation was found between AoVTI and LVEDA confirming that preload adaptation is not a universal finding in septic shock (8).

CONCLUSION

Our study demonstrates that the early described acute left ventricular dilation during septic shock is effectively observed in patients with sepsis-induced systolic left ventricular dysfunction. Further studies are required to elucidate mechanisms by which a previously healthy left ventricle can acutely dilate in response to systolic ejection impairment.

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