Respiratory Changes in Aortic Blood Velocity as an Indicator of Fluid Responsiveness in Ventilated Patients With Septic Shock*

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Study objective: **To investigate whether the respiratory changes in peak velocity (Vpeak) of aortic blood flow could be related to the effects of volume expansion on cardiac index.**
Design: **Prospective clinical study.**
Setting: **Medical ICUs of a university hospital (20 beds) and of a nonuniversity hospital (15 beds).**
Patients: **Nineteen sedated septic shock patients who were receiving mechanical ventilation and who had preserved left ventricular (LV) systolic function.**
Intervention: **Volume expansion.**
Measurements and results: **Analysis of aortic blood flow by transesophageal echocardiography allowed beat-to-beat measurement of Vpeak before and after volume expansion. Maximum values of Vpeak (Vpeakmax) and minimum values of Vpeak (Vpeakmin) were determined over one respiratory cycle. The respiratory changes in Vpeak (ΔVpeak) were calculated as the difference between Vpeakmax and Vpeakmin divided by the mean of the two values and were expressed as a percentage. The indexed LV end-diastolic area (EDAI) and cardiac index were obtained at the end of the expiratory period. The volume expansion-induced increase in cardiac index was ≥ 15% in 10 patients (responders) and < 15% in 9 patients (nonresponders). Before volume expansion, ΔVpeak was higher in responders than in nonresponders (20 ± 6% vs 10 ± 3%; $p < 0.01$), while EDAI was not significantly different between the two groups (9.7 ± 3.7 vs 9.7 ± 2.4 cm^2/m^2). Before volume expansion, a ΔVpeak threshold value of 12% allowed discrimination between responders and nonresponders with a sensitivity of 100% and a specificity of 89%. Volume expansion-induced changes in cardiac index closely correlated with the ΔVpeak before volume expansion ($r^2 = 0.83$; $p < 0.001$).**
Conclusion: **Analysis of respiratory changes in aortic blood velocity is an accurate method for predicting the hemodynamic effects of volume expansion in septic shock patients receiving mechanical ventilation who have preserved LV systolic function.**

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Key words: aortic blood velocity; cardiac output; fluid responsiveness; left ventricular end-diastolic area; mechanical ventilation; septic shock; transesophageal echocardiography; volume expansion

Abbreviations: EDAI = indexed left ventricular end-diastolic area; LV = left ventricle, ventricular; RV = right ventricle, ventricular; Vpeak = peak velocity; ΔVpeak = respiratory changes in peak velocity; Vpeakmax = maximum peak velocity; Vpeakmin = minimum peak velocity

Transesophageal echocardiography is now widely used in ICUs for the diagnosis and monitoring of acute circulatory failure. Indeed, it provides a reliable and noninvasive assessment of right ventricular (RV) and left ventricular (LV) functions,[1] and the innocuous nature of pulmonary artery catheterization is under question.[2] The echocardiographic measurement of the indexed LV end-diastolic area (EDAI) has been shown to reflect more accurately the LV preload when compared with pulmonary artery occlusion pressure[3] and to improve the ability to detect changes in LV function caused by acute blood loss.[4] However, the results of a study[5] performed in patients with sepsis-induced hypotension suggested that EDAI was a poor indicator of fluid responsiveness.

By increasing pleural pressure and transpulmo-

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nary pressure (*ie*, alveolar pressure minus pleural pressure), mechanical insufflation may decrease RV filling[6] and impair RV ejection.[7,8] Therefore, RV stroke volume may decrease during the inspiratory period, leading to a reduction in LV preload during the expiratory period because of the long pulmonary transit time of blood.[9] These respiratory changes in LV preload may induce cyclic changes in LV stroke volume.[9,10] Interestingly, the cyclic changes in RV preload induced by mechanical ventilation should result in greater cyclic changes in RV stroke volume when the RV operates on the steep rather than on the flat portion of the Frank-Starling curve.[11,12] The cyclic changes in RV stroke volume, and hence in LV preload, also should result in greater cyclic changes in LV stroke volume when the LV operates on the ascending portion of the Frank-Starling curve.[11,12] Thus, the magnitude of the respiratory changes in LV stroke volume should be an indicator of biventricular preload dependence, and hence of fluid responsiveness. To this extent, several clinical studies[5,13,14] have demonstrated that the respiratory changes in arterial pressure (mainly related to the respiratory changes in LV stroke volume) accurately predict the hemodynamic effects of volume expansion in patients receiving mechanical ventilation. Transesophageal echocardiography allows a beat-to-beat measurement of aortic blood velocity. Because aortic blood flow is directly proportional to LV stroke volume, we postulated that an analysis of the respiratory changes in aortic blood velocity might provide an accurate estimation of the respiratory changes in LV stroke volume and, thus, might be used to assess biventricular preload dependence and, hence, fluid responsiveness.

Therefore, in septic shock patients receiving mechanical ventilation, we investigated whether EDAI and respiratory changes in aortic blood velocity could predict the hemodynamic effects of volume expansion.

Materials and Methods

The protocol was approved by the institutional review board for human subjects of our institutions, and written informed consent was obtained from each patient's next of kin.

Patients

We studied 19 patients receiving mechanical ventilation in whom septic shock had been diagnosed. This group comprised 11 men and 8 women who had an age range between 25 and 87 years (mean [± SD] age, 58 ± 16 years). Inclusion criteria were as follows: (1) septic shock defined by the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference[15]; and (2) hemodynamic stability, defined by a variation in heart rate and BP of < 10% over the 15-min period before starting the protocol. Patients were excluded if they had arrhythmias, severe hypoxemia (Pao_2/fraction of inspired oxygen ratio of < 100 mm Hg), any contraindication to transesophageal echocardiography, aortic valvulopathy, or LV systolic dysfunction (fractional area of contraction < 30%), and if Doppler LV output recordings using the transgastric view could not be obtained.

LV End-Diastolic Measurements

A transesophageal multiplane probe was positioned to obtain a transgastric, short-axis, cross-sectional view of the LV at the mid-papillary muscle level. Echocardiographic images were recorded together with the ECG. End-diastole was defined as the frame corresponding to the largest LV cross-sectional area immediately after the R-wave peak on the ECG. The LV short-axis, end-diastolic, cross-sectional area was measured by manual planimetry of the area circumscribed by the leading edge of the LV endocardial border. The anterolateral and posteromedial papillary muscles were included within the ventricular area. LV areas were divided by the surface body area of the patient to obtain EDAI. The mean of five measurements performed at the end of the expiratory period was used for statistical analysis.

Cardiac Output Measurements

By rotating the imaging array to approximately 120°, the LV outflow tract and ascending aorta were imaged when parallel to the ultrasound beam. Aortic blood flow then was measured by a pulsed-wave Doppler beam at the level of the aortic valve so that the click of the aortic closure was obtained. The aortic valve area was calculated from the diameter of the aortic orifice, measured at the insertion of the aortic cusp, as aortic valve area = $\pi \times$ (aortic diameter/2).^{2} The stroke volume was calculated as stroke volume = aortic valve area × the velocity time integral of aortic blood flow. The cardiac output was calculated as cardiac output = stroke volume × heart rate. Stroke volume and cardiac output were divided by the surface body area to obtain the stroke volume index and cardiac index. The mean of five measurements performed at the end of the expiratory period were used for statistical analysis.

Respiratory Changes in Aortic Blood Velocity

A simultaneous recording of the airway pressure curve and aortic blood flow allowed beat-to-beat measurement of peak velocity (Vpeak) and determination of maximum Vpeak values (Vpeakmax) and minimum Vpeak values (Vpeakmin) over a single respiratory cycle. The respiratory changes in Vpeak (ΔVpeak) were calculated using a formula similar to that recently proposed to assess the respiratory changes in pulse pressure in mechanically ventilated patients with acute lung injury[13] or acute circulatory failure related to sepsis[14]:

$$\Delta Vpeak\,(\%) = 100 \times (Vpeakmax - Vpeakmin)/[(Vpeakmax + Vpeakmin)/2].$$

An example taken from one subject of the data is shown in Figure 1. ΔVpeak was evaluated over each of five consecutive respiratory cycles. The mean value of the five determinations was used for statistical analysis.

Study Protocol

All patients received mechanical ventilation in a volume-controlled mode with a tidal volume of 8 to 10 mL/kg and an inspiratory/expiratory ratio of one half to one third. All but two patients received ventilation with a positive end-expiratory pressure (6 ± 3 cm H_2O). All patients were sedated, and seven

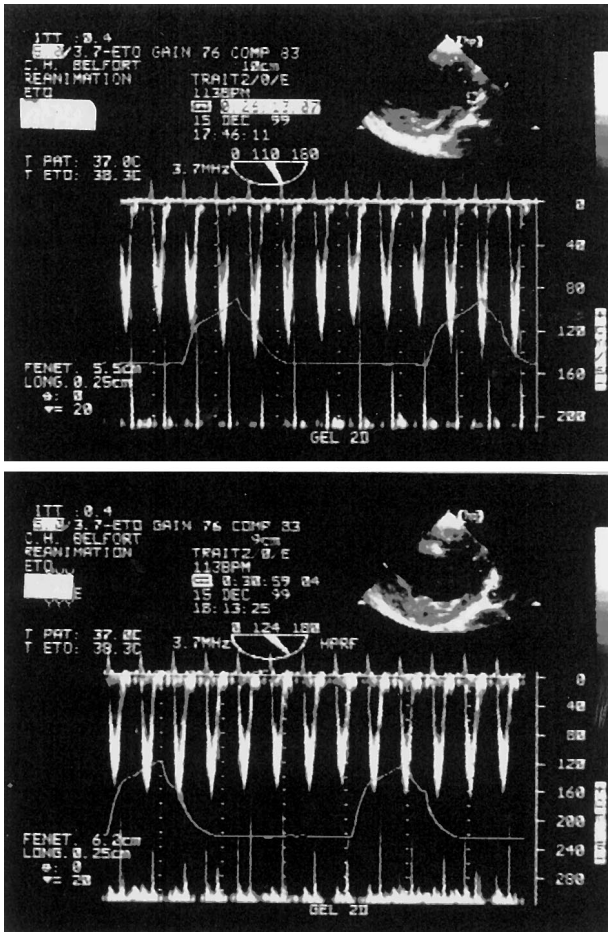

FIGURE 1. Simultaneous recording of aortic blood flow and airway pressure curve in one illustrative patient. Beat-to-beat measurement of aortic blood Vpeak allowed the determination of Vpeakmax and Vpeakmin over a single respiratory cycle. The ΔVpeak was calculated as the difference between Vpeakmax and Vpeakmin divided by the mean of the two values and was expressed as a percentage. In this patient, volume expansion induced a decrease in the ΔVpeak from 23% (*top*: Vpeakmax, 144 cm/s; Vpeakmin, 114 cm/s) to 9% (*bottom*: Vpeakmax, 169 cm/s; Vpeakmin, 155 cm/s) and an increase in cardiac index from 2.8 to 3.6 L/min/m^2.

patients were therapeutically paralyzed by decision of the attending physician. In 2 of the 12 remaining patients, a significant inspiratory effort was detected by visual inspection of the airway pressure curve. To ensure that the respiratory changes in aortic blood flow reflected only the effects of positive-pressure ventilation, these two patients were temporarily paralyzed. Measurements were performed in duplicate, first prior to volume expansion and then immediately after volume expansion using 8 mL/kg 6% hydroxyethylstarch (Hesteril; Fresenius Kabi; Sèvres, France) over 30 min. Ventilatory settings as well as dosages of inotropic and vasopressive drugs were held constant. All echocardiographic measurements were made offline from the videotape recording. Intraobserver and interobserver variabilities were determined by repeating measurements in 10 randomized patients. Variability, expressed as the mean percent error (*ie*, the difference between two observers divided by the mean of the two observed values) for measurements of EDAI and cardiac output were 6 ± 3% and 8 ± 4% by the same observer and 7 ± 4% and 9 ± 5% between two different observers.

Statistical Analysis

Results were expressed as mean ± SD. The effects of volume expansion on hemodynamic parameters were assessed using a nonparametric Wilcoxon rank sum test. Patients were divided into two groups according to the percent increase in cardiac index in response to volume expansion. Assuming that a 15% change in cardiac index was needed for clinical significance, patients with a volume expansion-induced increase in cardiac index of ≥ 15% and < 15% were classified as responders and nonresponders, respectively. The comparison of hemodynamic parameters prior to volume expansion in responder and nonresponder patients was performed using a nonparametric Mann-Whitney test. Linear correlations were tested using the Spearman rank method. A p value < 0.05 was considered to be statistically significant.

RESULTS

The 19 patients studied had clear evidence of sepsis (abdominal sepsis, 10 patients; bacterial pneumonia, 9 patients). All patients received inotropic and vasopressor drugs. Thirteen patients received epinephrine (0.3 to 2.5 μg/kg/min; mean dose, 1.4 ± 0.6 μg/kg/min), 6 patients received dopamine (12 to 20 μg/kg/min; mean dose, 16 ± 4 μg/kg/min), and 11 patients received dobutamine (5 μg/kg/min). Transesophageal echocardiography was performed between 12 and 72 h after the diagnosis of septic shock. Before echocardiographic measurements, all patients had already received colloids (3 ± 2 L) and/or crystalloids (1 ± 1 L). Eight patients survived (42%).

Hemodynamic parameters before and after volume expansion are given in Table 1. Ten patients were responders (cardiac index increase, ≥ 15%) and 9 patients were nonresponders

Before volume expansion, the ΔVpeak was higher in responder patients than in nonresponder patients (20 ± 6% vs 10 ± 3%; $p < 0.001$), while EDAI was not significantly different between the two groups (9.7 ± 3.7 vs 9.7 ± 2.4 cm^2/m^2). Before volume expansion, all responders had a ΔVpeak > 12%, while eight of the nine nonresponders had a ΔVpeak

Table 1—*Hemodynamic Parameters Recorded at Baseline and After Volume Expansion

Parameters	Baseline	Volume Expansion
HR, beats/min	118 ± 24	110 ± 21†
MAP, mm Hg	68 ± 12	79 ± 12†
EDAI, cm^2/m^2	9.7 ± 3.1	11.8 ± 3.9†
Cardiac index, L/min/m^2	3.6 ± 1.0	4.1 ± 1.0‡
SVI, mL/m^2	32 ± 11	39 ± 11‡
ΔV peak, %	15 ± 7	8 ± 4‡

*Values are expressed as mean ± SD. HR = heart rate; MAP = mean arterial pressure; SVI = stroke volume index.
†$p < 0.01$.
‡$p < 0.001$.

≤ 12% (Fig 2). Therefore, the threshold ΔVpeak value of 12% allowed for discrimination between responder and nonresponder patients with a sensitivity of 100% and a specificity of 89%.

A positive, tight linear correlation was found between the ΔVpeak before volume expansion and volume expansion-induced changes in cardiac index ($r^2 = 0.83$; $p < 0.001$) such that the higher the ΔVpeak before volume expansion, the greater the increase in cardiac index in response to fluid infusion (Fig 3). In contrast, baseline EDAI did not correlate significantly with the volume expansion-induced changes in cardiac index ($r^2 = 0.11$; $p = 0.17$) [Fig 3].

Volume expansion induced a significant decrease in ΔVpeak and a significant increase in EDAI (Table 1). The decrease in ΔVpeak was significantly correlated with the volume expansion-induced increase in cardiac index ($r^2 = 0.45$; $p < 0.01$), such that the greater the decrease in ΔVpeak, the higher the increase in cardiac index. The increase in EDAI was also significantly correlated with the percent increase in cardiac index ($r^2 = 0.49$; $p < 0.01$), such that the greater the increase in EDAI, the higher the increase in cardiac index in response to volume expansion.

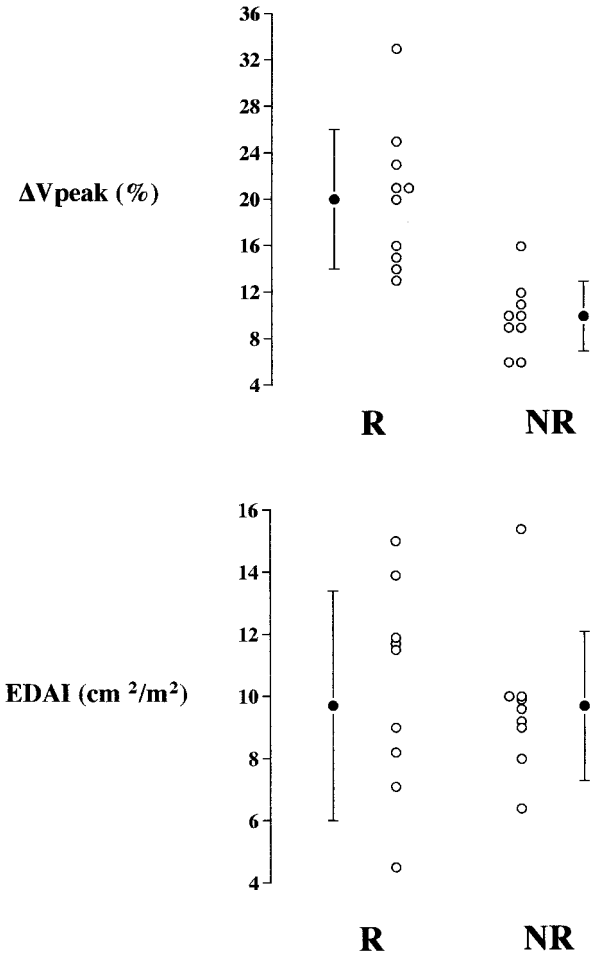

FIGURE 2. Individual values (open circles) and mean ± SD values (closed circles) of the ΔVpeak of aortic blood flow (top) and EDAI (bottom) before volume expansion in responder (R) [*ie*, volume expansion-induced increase in cardiac index, ≥ 15%] and nonresponder (NR) patients.

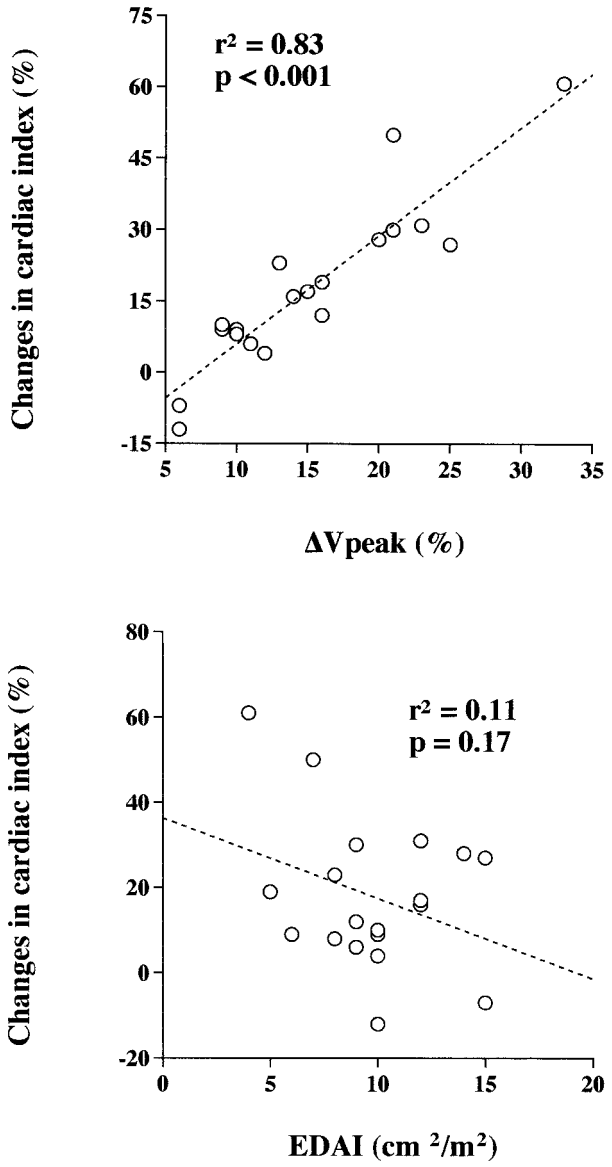

FIGURE 3. *Top*: relationship between the ΔVpeak of aortic blood flow before volume expansion (*ie*, baseline ΔVpeak) and the volume expansion-induced changes in cardiac index. *Bottom*: relationship between the EDAI before volume expansion (*ie*, baseline EDAI) and the volume expansion-induced changes in cardiac index.

DISCUSSION

In patients with septic shock who are receiving mechanical ventilation, our results demonstrate a strong relationship between ΔVpeak and the effects

of volume expansion on cardiac output. They strongly suggest that ΔVpeak before volume expansion is an accurate indicator of fluid responsiveness while EDAI is of little value in predicting the effects of volume expansion on cardiac output.

Volume expansion is proposed as a first-line therapy for septic shock in order to improve hemodynamics.[16] Both the increase in microvascular permeability and venous pooling reduce cardiac preload to such an extent that a large amount of fluid is usually needed during the early phase of resuscitation.[16] However, as previously demonstrated[5,14,17] and confirmed by the present study, volume expansion does not improve hemodynamics in all patients and, in some patients, may lead to interstitial fluid accumulation, which may worsen gas exchange, decrease myocardial compliance, and limit oxygen diffusion to the tissues.[18] Therefore, in patients with septic shock, reliable predictors of a positive response to fluid administration are needed at the bedside. Unfortunately, the prediction of fluid response remains particularly difficult in clinical practice. Indeed, in patients with septic shock who require ventilation, invasive measurements of cardiac filling pressures poorly reflect cardiac preload[19] and have been shown to be of little value in predicting volume expansion efficacy.[5,14] Transesophageal echocardiography allows a measurement of EDAI, which has been shown to reflect more accurately LV preload when compared with pulmonary artery occlusion pressure.[3] In nine anesthetized mongrel dogs, Swenson et al[20] reported a significant relationship between baseline EDAI and changes in cardiac index induced by IV fluid therapy, suggesting that EDAI may be an indicator of fluid responsiveness. However, a 1998 study[5] performed in 15 patients with sepsis-induced hypotension demonstrated that EDAI was of little value in predicting volume expansion efficacy. Our results are quite consistent with this study since (1) baseline EDAI was not significantly different between responder and nonresponder patients and (2) baseline EDAI was not significantly correlated with the volume expansion-induced increase in cardiac index. These findings could be explained as follows. If the RV operates on the flat portion of the Frank-Starling curve, a beneficial hemodynamic effect of volume expansion cannot be expected, even in the case of low LV preload.[21,22] This phenomenon is more likely to occur in patients with septic shock[17,23,24] and/or in patients whose lungs are being mechanically ventilated.[8] In three patients, we observed a significant RV dilation. These three patients were nonresponders, and in two of them EDAI slightly decreased in response to volume expansion. These findings suggest that RV dysfunction may have limited the effect of volume expansion on cardiac index and emphasize the fact that LV preload measurement is not a useful tool to assess fluid responsiveness in this setting. In patients undergoing repair of abdominal aortic aneurysms, a close relationship was reported between EDAI and LV end-diastolic volume.[25] In contrast, in patients following coronary artery bypass grafting, Urbanowicz et al[26] found a significant but weak relationship between EDAI and LV end-diastolic volume, demonstrating that EDAI does not provide a reasonable estimate of LV end-diastolic volume in all clinical situations. To our knowledge, the relationship between EDAI and LV end-diastolic volume has not been investigated in patients with septic shock. Since LV end-diastolic volumes were not measured in our patients, the relationship between EDAI and LV end-diastolic volume was not analyzed. Therefore, we cannot definitely exclude that EDAI was a poor indicator of LV end-diastolic volume and, hence, of LV preload in our patients, which may also explain why EDAI was found to be a poor indicator of fluid response in the present study.

In contrast, our results demonstrate that ΔVpeak accurately predicts fluid response in patients with septic shock who are receiving mechanical ventilation. Indeed, a patient with a ΔVpeak value of $> 12\%$ was very likely to respond to volume expansion by increasing cardiac index by $\geq 15\%$ (positive predictive value, 91%). Conversely, if ΔVpeak was $\leq 12\%$, the patient was unlikely to respond to a fluid challenge (negative predictive value, 100%). Moreover, the ΔVpeak before volume expansion closely correlated with the volume expansion-induced increase in cardiac index, such that the higher the ΔVpeak before fluid infusion, the greater the increase in cardiac index in response to volume expansion (Fig 3). These findings are in excellent agreement with recent clinical studies demonstrating that the respiratory changes in arterial pressure (mainly related to the respiratory changes in LV stroke volume) accurately predict the hemodynamic effects of volume expansion in patients receiving ventilation who have acute lung injury[13] or acute circulatory failure related to sepsis.[5,14] They suggest that an analysis of the ΔVpeak could be of particular help in the decision-making process concerning volume expansion in such patients.

Volume expansion induced a significant decrease in the ΔVpeak in our patients. This decrease could be explained as follows. First, volume expansion is assumed to increase RV preload such that the operating point of the RV moves rightward (*ie*, toward the flatter portion of the Frank-Starling curve).[11,12] Each inspiratory decrease in RV preload would, therefore, have a less marked effect on RV stroke volume after volume expansion than before.[11,12] Second, volume

expansion may induce a recruitment of pulmonary capillaries, leading to a decrease in West's zone 2[27,28] and, hence, to a potential decrease in RV afterload during insufflation. Through these two mechanisms, volume expansion should attenuate the inspiratory decrease in RV stroke volume and, hence, the subsequent expiratory decrease in LV preload. This latter phenomenon, in combination with a volume expansion-induced rightward shift of the LV operating point, should result in attenuated changes in LV stroke volume and aortic blood flow over the respiratory cycle. However, because our study was not designed to elucidate why the ΔVpeak decreased with volume expansion, we cannot determine which mechanism was the most important. Interestingly, the volume expansion-induced decrease in ΔVpeak was significantly correlated with the volume expansion-induced increase in cardiac index. This finding emphasizes the fact that the ΔVpeak is strongly related to cardiac preload.

It must be emphasized that arrhythmias lead to misinterpretation of respiratory changes in aortic blood flow. Patients with arrhythmias, therefore, were excluded from the present study. For standardization of the protocol and to ensure the best conditions for measurements, only sedated patients were studied by transesophageal echocardiography. Therefore, further studies are required in which a transthoracic approach is used and in which nonsedated patients are included in order to extend the clinical utility of the ΔVpeak as an indicator of fluid responsiveness. Moreover, since we studied patients with a fractional area of contraction of $> 30\%$, our results cannot be extrapolated to patients with an LV systolic dysfunction. Finally, cardiac output was not measured by the reference thermodilution technique. However, transesophageal echocardiographic measurement of ascending aortic flow velocity has been improved by the use of a multiplane probe,[29] and cardiac output was measured using a methodology previously validated against the thermodilution technique in critically ill patients.[30]

To summarize, our findings suggest that, in contrast with EDAI, ΔVpeak is an accurate indicator of fluid responsiveness in sedated septic shock patients who are receiving mechanical ventilation and who have preserved LV systolic function. Therefore, an analysis of the ΔVpeak could facilitate the hemodynamic management of such patients. Whether the ΔVpeak could predict the hemodynamic effects of volume expansion in other clinical situations remains to be determined.

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