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Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity

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Abstract *Objective:* In hemodynamically unstable patients with spontaneous breathing activity, predicting volume responsiveness is a difficult challenge since the respiratory variation in arterial pressure cannot be used. Our objective was to test whether volume responsiveness can be predicted by the response of stroke volume measured with transthoracic echocardiography to passive leg raising in patients with spontaneous breathing activity. We also examined whether common echocardiographic indices of cardiac filling status are valuable to predict volume responsiveness in this category of patients. *Design and setting:* Prospective study in the medical intensive care unit of a university hospital. *Patients:* 24 patients with spontaneously breathing activity considered for volume expansion. *Measurements:* We measured the response of the echocardiographic stroke volume to passive leg raising and to saline infusion (500 ml over 15 min). The left ventricular end-

diastolic area and the ratio of mitral inflow E wave velocity to early diastolic mitral annulus velocity (E/Ea) were also measured before and after saline infusion. *Results:* A passive leg raising induced increase in stroke volume of 12.5% or more predicted an increase in stroke volume of 15% or more after volume expansion with a sensitivity of 77% and a specificity of 100%. Neither left ventricular end-diastolic area nor E/Ea predicted volume responsiveness. *Conclusions:* In our critically ill patients with spontaneous breathing activity the response of echocardiographic stroke volume to passive leg raising was a good predictor of volume responsiveness. On the other hand, the common echocardiographic markers of cardiac filling status were not valuable for this purpose.

Keywords Volume responsiveness · Passive leg raising · Stroke volume · Echocardiography · Cardiac preload · Spontaneous breathing

Introduction

In mechanically ventilated patients who do not trigger the ventilator the response to volume expansion can be predicted by the respiratory variation in stroke volume or arterial pressure [1–4]. However, such heart-lung interaction indices fail to predict fluid responsiveness in ventilated patients who experience inspiratory efforts [5–7]. The response of the descending aortic blood flow to passive

leg raising (PLR) has been proposed to predict volume responsiveness in mechanically ventilated patients with spontaneous breathing activity when monitored with an esophageal Doppler probe [5]. Transthoracic echocardiography (TTE) is increasingly used for noninvasive hemodynamic assessment of critically ill patients since high-quality images and Doppler signals are obtained with recent TTE equipment [8]. TTE provides clinicians with valuable information including stroke volume, left ventric-

ular preload, and filling. The stroke volume can be easily obtained using the left ventricular outflow track Doppler method [9]. The indexed left ventricular end-diastolic area (LVEDA_i) is considered a valuable indicator of left ventricular preload [10, 11]. The ratio of pulsed Doppler transmitral flow in early diastole to early diastolic mitral annulus velocity measured by tissue Doppler imaging (E/E_a) is considered the best estimate of left ventricular filling pressure [12, 13].

The aim of our study was to answer the question: can TTE be used as a tool for predicting volume responsiveness in critically ill patients who experience spontaneous respiratory movements whatever the presence of mechanical support? We first analyzed the predictive value of the TTE stroke volume response to PLR. We also analyzed the predictive value of the most commonly used static echocardiographic indicators of left ventricular filling, namely LVEDA_i and E/E_a. We expected that the response of TTE stroke volume to PLR was a better predictor of volume responsiveness than the preinfusion values of left ventricular filling indices.

Patients and methods

Patients

We studied patients with spontaneous breathing activity for whom the attending physician decided to perform a fluid challenge because of the presence of at least one of the following clinical signs of inadequate global perfusion: mean arterial pressure (MAP) below 60 mmHg, oliguria (urine output less than 0.5 ml/kg per hour for more than 2 h), delayed capillary refill, mottled skin, and tachycardia (heart rate higher than 100/min). Patients were excluded if they had aortic valvulopathy, mitral insufficiency greater than grade 2, or mitral stenosis, and if cardiac echogenicity was not satisfactory. This observational study was approved by the Ethics Committee of the Société de Réanimation de Langue Française. Patients were informed that they participated in this study.

The study included 24 patients, 14 of whom were mechanically ventilated but experienced spontaneous breathing. Patients' characteristics are presented in Table 1. Three were ventilated with pressure support (inspiratory pressure level 18 ± 3 cmH₂O, end-expiratory pressure 5 ± 0 cmH₂O), and 11 were ventilated in the assist controlled-mode (tidal volume 464 ± 56 ml) with a significant inspiratory effort which was detected by the inspection of the airway pressure curve and the monitoring of the spontaneous respiratory rate. Ten patients were breathing spontaneously without any mechanical support. Twelve received vasoactive drugs (11 norepinephrine, 1 dobutamine). Six patients presented with atrial fibrillation but did not exhibit abrupt or marked changes in the

Table 1 Characteristics of the study population ($n = 24$)

Age (years)	65 ± 15
Gender: M/F	13 (54%)/11 (46%)
Body surface area (m ²)	1.75 ± 0.20
Reason for ICU admission	
Acute respiratory failure	9 (38%)
Septic shock	9 (38%)
Nonseptic hypovolemia	4 (17%)
Coma	2 (7%)
Origin of hemodynamic disturbance	
Severe sepsis and septic shock	18 (75%)
Non septic hypovolemia	6 (25%)
Supportive treatment	
Mechanical ventilation with ventilator triggering	14 (58%)
Nasal oxygen administration	10 (42%)
Norepinephrine use	11 (48%)
Dobutamine use	1 (4%)
Blood lactate level (mmol/l; range)	2.2 ± 1.3 (0.7–6.4)

ventricular rate. No patient was excluded because of poor quality TTE images.

Echocardiographic measurements

The echocardiographic examination was performed by the same operator (B.L.) using a transthoracic ultrasound device (EnVisor, Philips), equipped with the tissue Doppler imaging program and a phased array transducer of 2.5 MHz. Conventional echocardiography including M-mode, two-dimensional, and Doppler measurements was performed. Echocardiographic images were recorded together with the electrocardiogram. All measurements were recorded on paper at a speed of 100 mm/s and were stored digitally in the hardware for later playback and analysis. All measurements were evaluated by two physicians (B.L. and A.O.) and the average values were considered for the analyses.

Stroke volume

The stroke volume was calculated as the product of the velocity time integral of aortic blood flow (VTIA_o) by the aortic valve area. Using the apical five-chamber view the VTIA_o was computed from the area under the envelope of the pulsed-wave Doppler signal obtained at the level of the aortic annulus. The VTIA_o value was averaged over five to ten consecutive measurements in sinus rhythm patients and over ten measurements in patients with atrial fibrillation. Using the parasternal long axis view the diameter of the aortic orifice was measured at the insertion of the aortic cusp and the aortic valve area was calculated ($\pi \text{ diameter}^2/4$). As the diameter of the aortic orifice is assumed to remain constant in a given patient, the diameter was measured once at baseline. The stroke volume index

(SVi) was calculated as the ratio of stroke volume over body surface area. The cardiac output was calculated as the product of stroke volume by the heart rate.

Left ventricular end diastolic area

Using the short-axis, cross-sectional view the left ventricular end-diastolic area was measured by manual planimetry of the area circumscribed by the leading edge of the left ventricular endocardial border. The mean value of at least five consecutive measurements was calculated. The LVEDAi was calculated as the ratio of the averaged left ventricular end-diastolic area over body surface area.

Ratio of the transmitral flow in early diastole to the early diastolic mitral annulus velocity

Using the apical four-chamber view the early (E) peak diastolic velocity was measured by the pulsed-wave Doppler. The early (Ea) velocity of the lateral mitral annulus was measured by tissue Doppler imaging. The E/Ea ratio for the lateral mitral annulus was then calculated. The mean value of at least five consecutive measurements was considered for the analysis.

Left ventricular ejection fraction

We measured left ventricular ejection fraction (LVEF) using the biplane Simpson's method from the apical-two and four-chamber views.

Blood pressure measurements

Systolic arterial pressure (SAP) and MAP were measured either using an oscillometric cuff system at the brachial artery level or using an artery catheter when available.

Study design

SAP, MAP, heart rate, LVEF, VTIAo, and aortic valve area were measured at baseline while the patient was in the semirecumbent position (45°). From this position an automatic bed elevation allowed to lift the lower limbs of the patient to a 45° angle while the patient's trunk was lowered from semirecumbent to supine position. The position of the Doppler probe was adjusted so as to obtain the best aortic flow signal. A second set of SAP, MAP, heart rate, and VTIAo measurements was collected during PLR at the moment when VTIAo plateaued at its highest value. The patient was then returned to his/her initial semirecumbent position. Measurements of SAP,

MAP, heart rate, and VTIAo were performed once again. Measurements of LVEDAi and E/Ea were also obtained. Finally, measurements of SAP, MAP, heart rate, VTIAo, LVEDAi, and E/Ea were obtained after volume expansion, which was performed for 15 min with 500 ml saline. Since the aortic area was measured only at baseline, the value of SVi at each period was calculated as the product of the baseline aortic area by the VTIAo measured at each period. The ventilator settings and drugs were maintained at constant levels throughout the study period. All volume challenges were performed at the discretion of the attending physician according to the presence of one or more of the following criteria: MAP 60 mmHg or higher ($n = 9$), oliguria ($n = 6$), mottled skin ($n = 7$), and tachycardia ($n = 10$).

An increase in SVi of 15% or more after volume expansion defined a responder patient. According to this definition of fluid responsiveness, 13 patients were responders. These included seven who were intubated and three who had atrial fibrillation. The 11 nonresponders included seven who were intubated and three who had atrial fibrillation. baseline LVEF was similar in responders ($50 \pm 12\%$) and nonresponders ($52 \pm 13\%$). Before PLR the heart rate, SAP, MAP, VTIAo, and SVi did not differ between responders and nonresponders, and in neither responders nor nonresponders was there a difference between values before PLR or before volume expansion in any of the hemodynamic variables that were measured at both times (Table 2).

Statistical analysis

Results are expressed as mean \pm SD. Hemodynamic variables were compared between responders and nonresponders before PLR and volume expansion using the nonparametric Mann-Whitney test. For the overall population and for each subgroup (responders and nonresponders) the nonparametric Wilcoxon rank sum test was used to assess the statistical significance of changes in hemodynamic parameters induced by PLR or by volume expansion and to compare the pre-PLR and preinfusion values of the variables measured at these two baseline periods (heart rate, SAP, MAP, SVi, VTIAo). The area under the receiver operating characteristic (ROC) curves (\pm SE) for PLR-induced changes in SVi (or in VTIAo), baseline (before volume expansion) LVEDAi and E/Ea were compared in all patients using the Hanley-McNeil test. Interobserver variability was assessed in ten randomly selected sets of measurements of VTIAo; LVEDAi and E/Ea and was calculated as the ratio (expressed as a percentage) of the difference between the values obtained by each observer (expressed as absolute value) divided by the mean of the two values. Each value (obtained by each observer) was the average of five to ten consecutive measurements. Intraobserver variability was calculated by

Table 2 Effects of passive leg raising and volume expansion on hemodynamic variables in responders and nonresponders (*HR* heart rate, *MAP* mean arterial pressure, *PLR* passive leg raising, *SAP* systolic arterial pressure, *SVi* stroke volume index, *VE* volume expansion, *VTIAo* velocity-time integral of aortic blood flow, *CO* cardiac output)

	Before PLR	During PLR	Before VE	After VE
HR (beats/min)				
Responders	95 ± 22	92 ± 25	96 ± 22	93 ± 23
Nonresponders	96 ± 30	94 ± 31	97 ± 32	92 ± 28**
SAP (mmHg)				
Responders	100 ± 20	113 ± 20*	105 ± 22	115 ± 24**
Nonresponders	102 ± 10	112 ± 11*	100 ± 10	113 ± 13**
MAP (mmHg)				
Responders	67 ± 9	76 ± 12*	70 ± 14	76 ± 11**
Nonresponders	68 ± 9	73 ± 10*	70 ± 10	76 ± 8**
SVi (ml/m ²)				
Responders	35 ± 11	44 ± 15*	37 ± 11	47 ± 13**
Nonresponders	40 ± 14	42 ± 14*	41 ± 15	43 ± 16**
VTIAo (cm)				
Responders	20 ± 6	25 ± 7*	20 ± 6	26 ± 7**
Nonresponders	21 ± 6	22 ± 6*	21 ± 6	22 ± 7**
CO (l/min)				
Responders	5.7 ± 1.2	6.8 ± 1.4*	6.0 ± 1.3	7.5 ± 1.4**
Nonresponders	6.3 ± 2.2	6.4 ± 2.1	6.5 ± 2.5	6.3 ± 2.3

* $p < 0.05$ during PLR vs. before PLR, ** $p < 0.05$ after VE vs. before VE

a similar approach. Differences with a p value less than 0.05 were considered statistically significant. Statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Berkeley Calif., USA) and Medcalc 8.1.0.0 software (Mariakerke, Belgium).

Results

Changes in VTIAo and SVi induced by PLR and by volume expansion

In all patients the highest plateau value of VTIAo recorded during PLR was obtained within the first 90 s following leg elevation. The proportional changes in VTIAo induced by PLR were correlated with the proportional changes in VTIAo induced by volume expansion ($r = 0.83$, $p < 0.0001$). The proportional changes in cardiac output induced by PLR were also correlated with the proportional changes in cardiac output induced by volume expansion ($r = 0.79$, $p < 0.0001$; Fig. 1). The PLR-induced changes in VTIAo or in SVi of 12.5% or more predicted fluid responsiveness with a sensitivity of 77% and a specificity of 100% (Fig. 2). Intubated and nonintubated patients did not differ. Among the three patients with false-negative findings (volume responders with a PLR-induced increase in VTIAo less than 12.5%) one was intubated and two nonintubated.

LVEDAi, E/Ea, and the effects of volume expansion

Before volume expansion LVEDAi and E/Ea did not differ between responders and nonresponders (Table 3, Fig. 2). The area under the ROC curve for PLR-induced changes in

VTIAo (0.96 ± 0.04) was significantly greater than that for LVEDAi before volume expansion (0.58 ± 0.12) and that for E/Ea before volume expansion (0.65 ± 0.11) (Fig. 3). For VTIAo measurements interobserver variability was $3.2 \pm 2.5\%$ and intraobserver variability $2.8 \pm 2.2\%$. For LVEDAi measurements the interobserver variability was $6.5 \pm 4.2\%$ and intraobserver variability $5.8 \pm 3.1\%$. For E/Ea measurements interobserver variability was $7.2 \pm 5.3\%$ and intraobserver variability $4.9 \pm 4.5\%$. Finally, a fluid-induced increase in SVi of more than 10% (in 16 patients) was predicted by a PLR-induced increase in VTIAo greater than 8% with a sensitivity of 100% and a specificity of 100%.

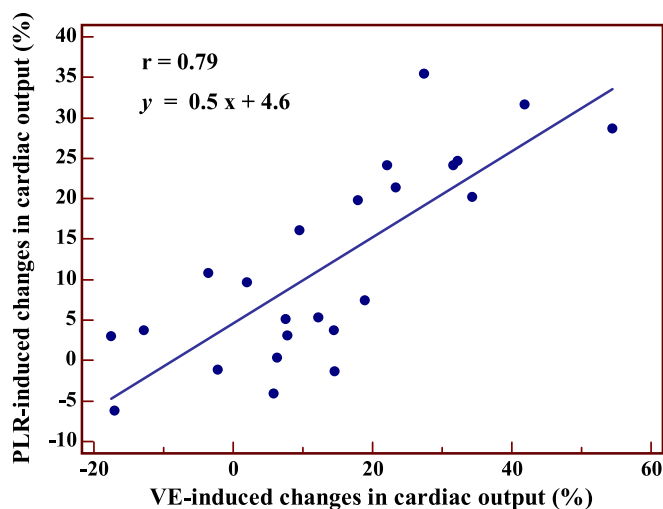


Fig. 1 Relationship between proportional changes in cardiac output induced by volume expansion (VE) and proportional changes in cardiac output induced by passive leg raising (PLR)

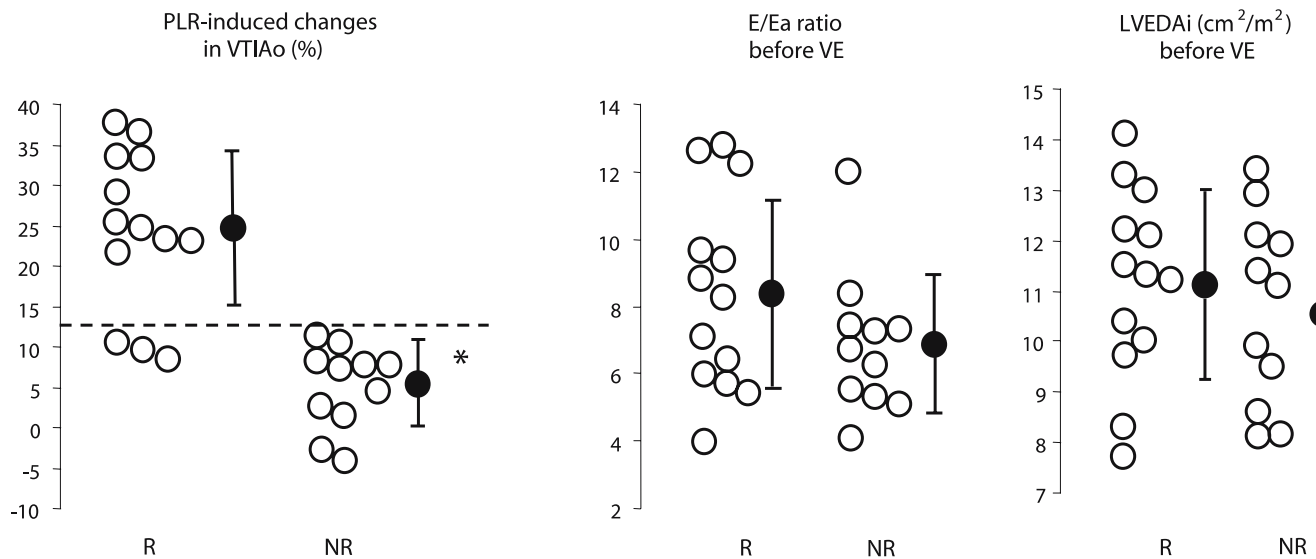


Fig. 2 Individual values (*open circles*) and mean \pm SD values (*closed circles*) of the passive leg raising (PLR) induced changes in VTIAo (velocity time integral of aortic blood flow), E/Ea [ratio of pulsed Doppler transmitral flow in early diastole (E) to the early diastolic mitral annulus velocity (Ea) measured by tissue Doppler imaging] before volume expansion (VE), and indexed left

ventricular end-diastolic area (LVEDAi) before VE in responders (R, patients experiencing VE-induced increase in stroke volume $\geq 15\%$) and nonresponders (NR). Dotted line Best threshold value (+12.5%) of PLR-induced change in VTIAo that discriminates responders from nonresponders to VE

Table 3 Effects of volume expansion on static echocardiographic indexes of left ventricular filling in responders and nonresponders (E/Ea ratio of pulsed Doppler transmitral flow in early diastole to the early diastolic mitral annulus velocity, LVEDAi indexed left ventricular end-diastolic area, VE volume expansion)

Parameters	Before VE	After VE
LVEDAi (cm ² /m ²)		
Responders	11.1 \pm 1.9	12.0 \pm 1.5*
Nonresponders	10.6 \pm 1.9	11.2 \pm 2.4
E/Ea		
Responders	8.3 \pm 2.9	7.9 \pm 2.2
Nonresponders	6.8 \pm 2.1	7.4 \pm 2.0

* $p < 0.05$ after VE vs. before VE

Discussion

The main results of our study performed in patients with spontaneous breathing activity are as follows: (a) a PLR-induced increase in VTIAo or in SVi of 12.5% or more predicted an increase in SVi of 15% or more after volume expansion with a sensitivity of 77% and a specificity of 100%, (b) the echocardiographic markers of filling status as LVEDAi and E/Ea did not accurately predict volume responsiveness.

The major strength of our study was to bring evidence that the response to volume expansion can be noninvasively predicted by a simple tool (PLR) in pa-

tients experiencing spontaneous respiratory movements. In such patients volume responsiveness is difficult to predict [1, 14] since heart-lung interaction indices such as stroke volume and arterial pulse pressure variations are not reliable for this purpose [5–7]. Importantly, this subgroup of patients represents the great majority of critically ill patients considered for volume expansion [3] including patients breathing spontaneously without any mechanical support and patients triggering their ventilator.

The PLR is able to induce a reversible increase in venous return from the legs to the thorax and then a reversible increase in preload of the right [15] and left ventricle [16]. Thus the PLR can be considered as a reversible self fluid challenge [17]. However, the effects of PLR on cardiac output are variable [5, 16, 18–20] depending upon the degree of leg elevation and the presence of cardiac preload reserve. Using pulmonary artery thermodilution Boulain et al. [19] found that the increase in stroke volume induced by PLR occurs only in patients who increase their stroke volume after a subsequent volume loading. Consequently PLR has been proposed to detect fluid responsiveness in critically ill patients [3, 17]. Recently we reported that PLR-induced changes in the descending aorta blood flow accurately predict volume responsiveness in patients monitored with an esophageal Doppler probe [5]. In our previous study a PLR increase in aortic blood flow of 10% or more predicted fluid responsiveness with a sensitivity of 97% and a specificity of 94% [5]. One of the major

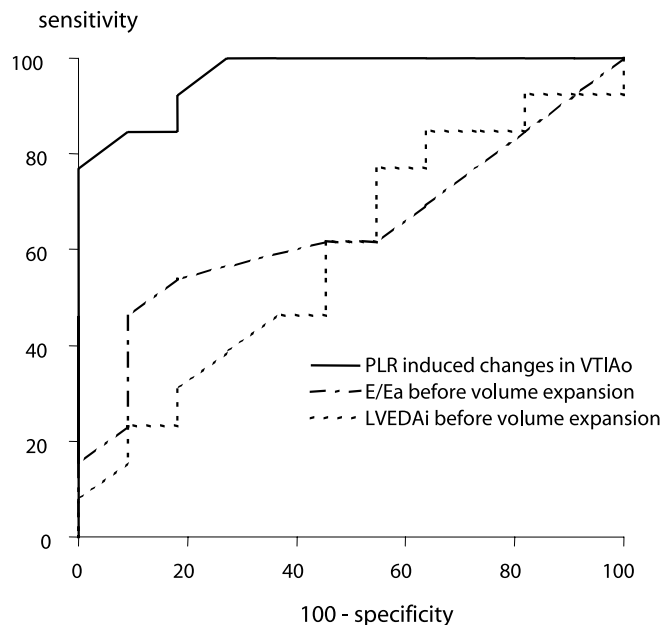


Fig. 3 Receiver operating characteristics curves comparing the ability of passive leg raising (PLR) induced changes in VTIAo (velocity time integral of aortic blood flow), E/Ea [ratio of pulsed Doppler transmitral flow in early diastole (*E*) to the early diastolic mitral annulus velocity (*Ea*) measured by tissue Doppler imaging] before volume expansion (VE), and indexed left ventricular end-diastolic area (LVEDAi) before VE to discriminate responders and nonresponders in the overall population. The area under the curve for PLR-induced changes in VTIAo was significantly greater than that for E/Ea before VE (difference 0.301, 95% confidence interval 0.077–0.524, $p=0.008$) and for LVEDAi before VE (difference 0.374, 95% confidence interval 0.175–0.573, $p=0.0001$). There was no difference between the area under the curve values for E/Ea before VE or for LVEDAi before VE

strengths of the present study was to find fairly consistent results by using a totally noninvasive device.

Importantly, the findings of the present study also demonstrate that the usual echocardiographic measures of cardiac filling, namely LVEDAi and E/Ea, are not reliable in predicting the response to volume expansion. The LVEDAi is considered a more valuable indicator of left ventricular preload than the pulmonary artery occlusion pressure (PAOP) [10], and LVEDAi has been shown to decrease during acute blood losses [21]. However, in mechanically ventilated patients LVEDAi appears to be of little value in predicting volume responsiveness [2, 22–24]. Pulsed Doppler analysis and tissue Doppler imaging are other approaches to assess cardiac filling. The E/Ea ratio is now considered as one of the best Doppler estimates of left ventricular filling pressure [12, 13, 25]. Its advantage is that *Ea* is assumed to be preload independent, thus allowing the effect of left ventricular relaxation on the *E* velocity to be corrected [25]. In addition, E/Ea is still reliable in patients with atrial fibrillation [26]. In critically ill patients the agreement between E/Ea and PAOP is only

fair [27, 28]. In the present study the E/Ea value before volume expansion did not reliably predict volume responsiveness, and this finding was in accordance with the poor value of PAOP to predict volume responsiveness [1, 14]. In addition, in healthy volunteers E/Ea has been shown to be poorly correlated with PAOP during changes in preload [29], and it has been recently hypothesized that *Ea* varies with preload under conditions where left ventricular relaxation is normal [30, 31]. This may partly account for the absence of change in E/Ea with volume expansion in our patients.

There are at least three reasons for explaining the poor value of echocardiography indices of left ventricular filling to predict volume responsiveness. First, these parameters do not reflect the preload of the right ventricle, which is important to take into account when volume responsiveness is considered [3]. Second, none of these markers are accurate measures of left ventricular preload, which is conceptually considered as the left ventricular end-diastolic stress [32]. Third, a given value of ventricular preload can be associated with various degrees of ventricular preload reserve since the slope of the Frank–Starling curve (ventricular preload vs. stroke volume) highly depends on systolic cardiac function [32].

The limitations of our study must be discussed. We have learned from previous studies performed by our group [5, 19] and by others [33] that PLR results in transient hemodynamic effects. Thus we anticipated that we would not have enough time to perform a complete echocardiographic examination during PLR. Consequently we chose to focus on the responses of VTIAo to PLR, and this was both relevant with respect to our hypothesis and feasible within approx. 1 min. We measured stroke volume using the classical left ventricular outflow track Doppler method, which has been previously validated against the thermodilution technique [9] and is commonly used in critically ill patients [34], especially for predicting volume responsiveness [24, 35]. We defined the positive response to volume expansion as an increase in SVi of 15% or more with volume expansion. This cutoff value seems clinically relevant, and it was chosen by reference to previous studies [1, 2, 23–25, 36]. Six of our patients had atrial fibrillation with no abrupt, marked changes in ventricular rhythm. The distribution among responders ($n=3$) and nonresponders ($n=3$) was similar to that in the subgroup of patients with sinus rhythm. However, our findings cannot be extrapolated to patients experiencing abrupt and marked changes in the ventricular rate. It is known that the aortic area measured at the level of aortic annulus is unchanged during acute hemodynamic changes. Consequently, evaluating the response of VTIAo to PLR makes simpler the TTE detection of volume responsiveness and thus would enhance its clinical applicability. We obtained good quality imaging with transthoracic approach in all patients. This is now the general case in the intensive care units utilizing the new generations of TTE

imaging equipments [8], although there are still particular patients with poor echogenicity in whom this technique cannot be reliably used.

Conclusion

Our study shows that the response of TTE stroke volume to PLR is a good predictor of volume responsiveness in patients with spontaneous breathing activity. Conversely, TTE static measures of cardiac preload were not found

to be valuable for this purpose. Because predicting the response to volume expansion is a difficult challenge in patients with spontaneous breathing activity, we suggest that performing TTE during a simple test such as PLR may be useful. The response of VTIAo to PLR can predict the hemodynamic efficacy of fluid therapy, although it seems rather a marker of a positive response than a marker of a nonindication to fluid administration. Such findings should encourage clinicians to extend further the use of echocardiography as a first-line hemodynamic approach in patients with hemodynamic instability [37–39].

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