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Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients?

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Abstract *Objective:* To investigate whether the respiratory changes in arterial pulse (ΔPP) and in systolic pressure (ΔSP) could predict fluid responsiveness in spontaneously breathing (SB) patients. Because changes in intrathoracic pressure during spontaneous breathing (SB) might be insufficient to modify loading conditions of the ventricles, performances of indicators were also assessed during a forced respiratory maneuver. *Design:* Prospective interventional study. *Setting:* A 34-bed university hospital medico-surgical ICU. *Patients and participants:* Thirty-two SB patients with clinical signs of hemodynamic instability. *Intervention:* A 500-ml volume expansion (VE). *Measurements and results:* Cardiac index, assessed using transthoracic echocardiography, increased by at least 15% after VE in 19 patients (responders). At baseline, only dynamic indicators were higher in responders than in nonresponders ($13 \pm 5\%$ vs. $7 \pm 3\%$, $p = 0.003$ for ΔPP and $10 \pm 4\%$ vs. $6 \pm 2\%$, $p = 0.002$ for ΔSP). Moreover, they significantly decreased after VE ($11 \pm 5\%$ to $6 \pm 4\%$, $p < 0.001$ for ΔPP and $8 \pm 4\%$ to $6 \pm 3\%$, $p < 0.001$ for ΔSP). ΔPP and ΔSP areas under the ROC curve were high (0.81 ± 0.08 and 0.82 ± 0.08; $p = 0.888$, respectively). A ΔPP $\geq$ 12% predicted fluid responsiveness with high specificity (92%) but poor sensitivity (63%). The forced respiratory maneuver reproducing a dyspneic state decreased the predictive power. *Conclusions:* Due to their lack of sensitivity and their dependence to respiratory status, ΔPP and ΔSP are clearly less reliable to predict fluid responsiveness during SB than in mechanically ventilated patients. However, when their baseline value is high without acute right ventricular dysfunction in a participating patient, a positive response to fluid is likely.

Keywords Fluid responsiveness · Volume expansion · Arterial pulse pressure · Arterial systolic pressure · Preload · Heart–lung interactions

Introduction

Volume expansion (VE) is frequently the first-line therapeutic measure used to improve the hemodynamic status. Unfortunately, only 40–70% of critically ill patients with acute circulatory failure significantly increase their cardiac output in response to VE [1]. This finding emphasizes the need for factors that predict fluid responsiveness in order to distinguish patients who might benefit from VE as well as to avoid ineffective VE. Numerous studies have focused on prediction of fluid responsiveness. These studies demonstrated that usual static hemodynamic measurements such as central venous pressure or pulmonary artery occluding pressure are of little value in predicting fluid responsiveness [2, 3]. However, these last years, numerous dynamic indicators of fluid responsiveness have been studied

using the arterial pressure waveform [2–4], transthoracic echocardiography [5–8] or esophageal Doppler [9, 10].

These indicators are dynamic because they reflect the respiratory changes in left-ventricular stroke volume (LVSV) due to heart–lung interactions induced by mechanical ventilation (MV) [11–18]. In any case, the currently validated data are about deeply sedated mechanically ventilated patients. Nevertheless, in spontaneously breathing (SB) patients, the need for predictive indicators of fluid responsiveness remains in order to select patients who might benefit from VE and to avoid potential deleterious VE. Thus, we hypothesized that dynamic indicators could be used in SB patients to predict response to fluid challenge.

The expected effect of spontaneous breathing (SB) on variations in LVSV may be inverted to the effect of MV, due to inverted cardiopulmonary interactions. Inspiration during SB decreases intrathoracic pressure, increasing preload of the right ventricle, resulting in an increase in right-ventricular stroke volume. This increase should result two or three heart beats later, because of the pulmonary transit time of blood, in an expiratory increase in LVSV [13, 19]. As reported during MV using low tidal volume, which could mask a biventricular preload dependence condition [20–22], respiratory changes in intrathoracic pressure during SB might be insufficient to modify loading conditions of ventricles to the extent that respiratory changes in LVSV would be measurable [23]. Consequently, a forced respiratory maneuver during SB might improve the predictive value of dynamic indicators.

We therefore conducted a prospective study to assess whether dynamic indicators calculated using the arterial pressure waveform [the respiratory changes in arterial pulse (ΔPP) and systolic pressure (ΔSP)], could predict fluid responsiveness in SB patients. Those indicators were assessed both during quiet SB and a forced respiratory maneuver.

Material and methods

This prospective study was conducted over a 6-month period (November 2003 to April 2004) in the medical intensive care unit of the Calmette Hospital (Lille University Hospital). The institutional review board for human subjects of our institution (Comité Consultatif de Protection des Personnes dans la Recherche Médicale, Lille II University Hospital), considered our protocol to be a part of routine clinical practice and approved the present study.

Patients

Inclusion criteria were as follows: (a) spontaneous breathing; (b) instrumentation with a radial or femoral arterial catheter inserted before the study in view of the patient's condition; (c) presence of at least one of the following criteria of hemodynamic instability: low blood pressure defined by a systolic blood pressure (SAP) < 90 mmHg and/or mean arterial pressure (MAP) < 75 mmHg and/or a decrease in SAP of more than 40 mmHg from baseline values; oliguria defined by a urine output less than 0.5 ml/kg/h during the last 3 h preceding inclusion; tachycardia defined by a heart rate (HR) > 100/min; mottled skin.

Patients were excluded if they had arrhythmia, absence of cooperation, or a lack of transthoracic echogenicity.

Methods

General characteristics

Age, sex, weight, indication(s) for ICU admission, underlying diseases, use of vasoactive drugs, saline or colloid infusion during the 24 h before inclusion, urine output during the 24 h preceding inclusion and criteria of hemodynamic instability were recorded at inclusion.

Hemodynamic measurements

All the hemodynamic parameters were collected by the same physician using the Cardiology Medical System (CMS) M11-67 monitor (Philips Medical). Patients were all studied while supine. Zero pressure (measured at the midaxillary line), functionality and the correct position of the catheter were checked out before each measurement. Heart rate (HR) and systemic arterial pressure were measured both at baseline and after VE using a radial or femoral artery catheter. Three measurements were averaged. Respiratory rate was also recorded at baseline and after VE.

Respiratory changes in arterial pressure

All measurements were collected both at baseline and after VE. Pulse pressure (PP) and systolic pressure (SP) were recorded after freezing the arterial pressure curve on an optimal scale, using a numerical cursor. Maximal and minimal values for systolic (SPmax and SPmin, respectively) and pulse pressure (PPmax and PPmin, respectively) were determined over three respiratory cycles. ΔPP and ΔSP were calculated as previously described [2] in two different conditions: during quiet SB during which the patient breathed with his own pattern (ΔPP and ΔSP, respectively) and during a forced respiratory maneuver consisting of forced inspiratory effort followed by a forced expiratory effort (ΔPPf and ΔSPf, respectively). In

both conditions, three consecutive measurements were averaged.

Cardiac index measurements

Commercially available equipment (Image Point M2410, Hewlett-Packard) with a 2-MHz transthoracic transducer was used for all measurements. Patients were all studied while supine. All measurements were performed by the same operator at baseline and after VE. Cardiac index (CI) was calculated as follows: CI = (SV × HR)/body surface area, where SV is the stroke volume. SV was calculated according to a validated pulsed Doppler subaortic method in the transthoracic long-axis view [24, 25]. SV was determined as follows: SV (l/m^2) = ($\pi \times D^2$)/4 × VTIao, where D (cm) is the diameter of aortic annulus and VTIao, the velocity–time integral from the subaortic pulsed Doppler flow above the aortic valve. D was measured in the parasternal long-axis view at the insertion of the aortic cusp. To reduce the variability of SV measurements, the same determination of D was used both before and after VE. Pulsed Doppler aortic flow was recorded at the level of the aortic annulus in the apical five-chamber view as previously described [24]. Because the VTIao included in the calculation of SV may itself vary over respiratory cycles [5], the mean values of all measurements realized during a complete respiration cycle were calculated. The VTIao was then averaged over three complete respiratory cycles. Finally, the left-ventricular ejection fraction (LVEF) was also calculated before VE.

Study protocol

All hemodynamic and echocardiographic measurements were performed at baseline and immediately after a 20-min VE using 500 ml of 6% hydroxyethylstarch.

Statistical analysis

Results were expressed as mean ± SD.

First, patients were divided into two groups according to the percent increase in CI in response to VE. Assuming that a 15% change in CI was required for clinical significance, patients with a VE-induced increase in CI of ≥15% and < 15% were classified as responders and nonresponders, respectively.

Second, the effects of VE on hemodynamic parameters were assessed using a nonparametric Wilcoxon rank sum test. The comparison of clinical and hemodynamic parameters before and after VE between responders and nonresponders was performed using a nonparametric Mann–Whitney U test for continuous variables and a chi-square test for categorical variables.

Finally, for each indicator, a receiver operating characteristic (ROC) curve was generated, allowing the determination of the optimal threshold value and the corresponding sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The ability for each indicator to discriminate between responders and nonresponders was determined by the area under the ROC curve (AUC). The AUCs were then compared as previously described [26]. Additionally, linear correlations between indicators' baseline values and CI increase after VE were determined using the Spearman correlation rank method. A p-value < 0.05 was considered statistically significant.

Results

Thirty-two SB patients (19 responders and 13 nonresponders) were prospectively included in the study. The main characteristics of the patients are summarized in Table 1. Eight patients (25%) received a saline or colloid infusion during the 24 h before inclusion, and only three patients required vasopressor support (dopamine) at inclusion. All the included patients had a LVEF > 45% and none of them exhibited an acute right-ventricular dilatation. The respiratory change in VTIao was 8 ± 3%. Before VE, only the dynamic indicators were significantly higher in responders than in nonresponders (Table 1). The individual patients' ΔPP baseline values, comparing responders and nonresponders, are presented in Fig. 1.

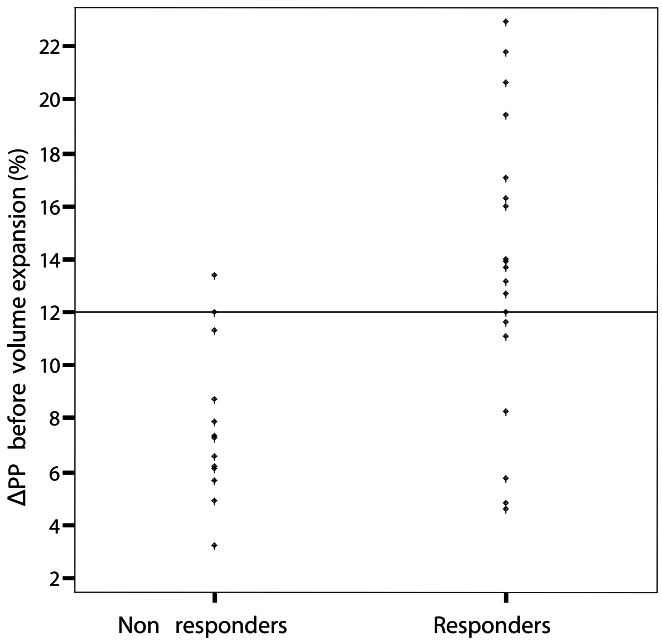

Fig. 1 Individual patients' ΔPP baseline values comparing responders and nonresponders to volume expansion

Table 1 General characteristics and hemodynamic parameters at baseline*

	Overall population ($n=32$)	Responders ($n=19$)	Nonresponders ($n=13$)	p
Age (years)	61 ± 13	58 ± 14	64 ± 10	0.14
Sex (F/M)	9/23	6/13	3/10	0.60
Indication for ICU admission				
Severe sepsis or septic shock	4 (12.5%)	3 (15.8%)	1 (7.7%)	0.50
Pneumonia	24 (75%)	14 (73.7%)	10 (76.9%)	0.60
Hematological disease	1 (3.1%)	0 (0%)	1 (7.7%)	0.40
Traumatologic surgery	2 (6.3%)	2 (10.5%)	0 (0%)	0.78
Abdominal surgery	1 (3.1%)	0 (0%)	1 (7.7%)	0.22
Hemodynamic criteria for VE				
Arterial hypotension	6 (18.8%)	5 (26.3%)	1 (7.7%)	0.19
Oliguria	20 (75%)	14 (73.7%)	6 (46.2%)	0.11
Tachycardia	24 (75%)	13 (68.4%)	11 (84.6%)	0.30
Mottled skin	12 (37.5%)	7 (36.8%)	5 (38.5%)	0.93
Hemodynamic parameters				
CVP (mmHg)	8 ± 3	8 ± 2	9 ± 4	0.16
HR (beats/min)	103 ± 16	103 ± 17	101 ± 16	0.78
MAP (mmHg)	89 ± 14	86 ± 15	93 ± 11	0.23
ΔPP (%)	11 ± 5	13 ± 5	8 ± 3	0.003
ΔSP (%)	8 ± 4	10 ± 4	6 ± 2	0.002
ΔPPf (%)	25 ± 18	31 ± 21	18 ± 10	0.035
ΔSPf (%)	22 ± 13	26 ± 14	17 ± 10	0.074
Respiratory rate (cycles/min)	22 ± 5	22 ± 3	22 ± 4	0.802
Urine output (ml/24 h)	1298 ± 560	1313 ± 554	1273 ± 591	0.863
Stroke volume (ml)	65 ± 7	63 ± 7	69 ± 13	0.165
Cardiac index (ml/min/m^2)	3.6 ± 0.8	3.5 ± 0.7	3.9 ± 0.9	0.186

*Data presented as mean ± SD; *CVP*, central venous pressure; *HR*, heart rate; *MAP*, mean arterial pressure; Δ*PP*, respiratory change in arterial pulse pressure; Δ*SP*, respiratory change in arterial systolic pressure; Δ*PPf*, respiratory change in arterial pulse pressure during the forced respiratory cycle; Δ*SPf*, respiratory change in arterial systolic pressure during the forced respiratory cycle; *RR*, respiratory rate

Dynamic indicators predicted fluid responsiveness with high specificity, excellent positive predictive value, high likelihood ratio but low sensitivity (Table 2). Indeed, a threshold ΔPP value of 12% allowed discrimination between responders and nonresponders with a specificity of 92% and a sensitivity of 63%. ΔPP and ΔSP areas under the ROC curve were high without any difference between them ($p=0.888$) (Fig. 2). The forced respiratory

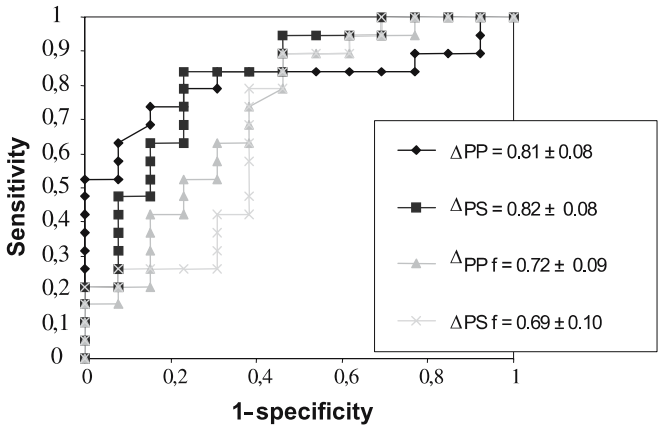

Fig. 2 ROC curves comparing the ability of ΔPP, ΔSP, ΔPPf, and ΔSPf to discriminate responders and nonresponders patients to volume expansion. The areas under the ROC curve for ΔPP and ΔSP were not statistically different ($p=0.888$)

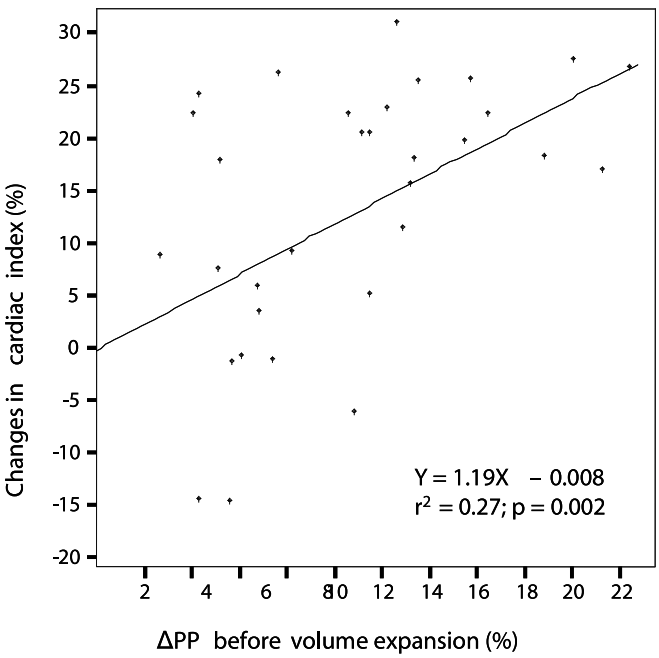

Fig. 3 Relationship between ΔPP before VE and the VE-induced changes in cardiac index. Δ*PP* = respiratory changes in arterial pulse pressure; *CI* = cardiac index

Table 2 Threshold values and performances of the indicators to predict the increase in cardiac index during volume expansion

	Threshold value	Sensitivity	Specificity	PPV	NPV	PLR	NLR
ΔPP	12%	63%	92%	92%	63%	8.20	0.39
ΔSP	9%	47%	92%	90%	54%	6.15	0.57
ΔPPf	33%	21%	92%	80%	44%	3.01	0.85
ΔSPf	30%	26%	92%	83%	46%	3.75	0.80

PPV, positive predictive value; *NPV*, negative predictive value; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio

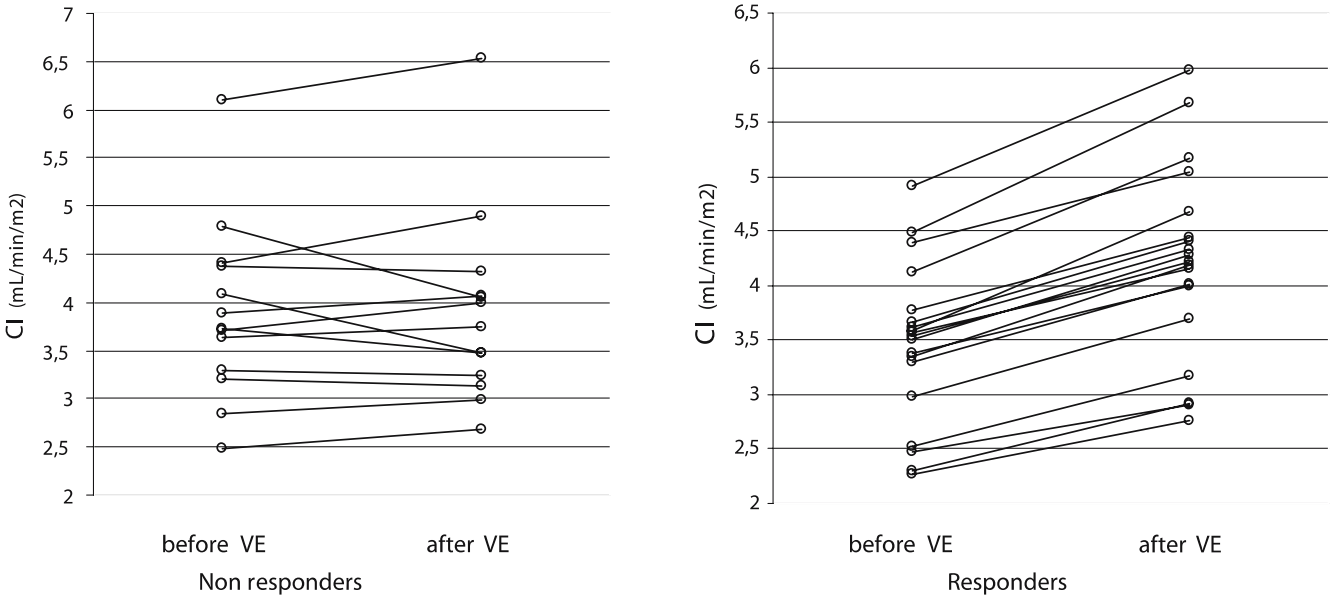

Fig. 4 Individual changes in CI during VE in responder and in responders

cycle decreased the prediction of fluid responsiveness. Indeed, the areas under the ROC curves for ΔPPf and ΔSPf were significantly lower than for ΔPP and ΔSP ($p = 0.002$ for ΔPP and $p = 0.001$ for ΔSP) (Fig. 2).

A positive linear correlation ($r^2 = 0.27$; $p = 0.002$) was found between ΔPP before VE and VE-induced changes in CI (Fig. 3). By contrast, the baseline values of the other indicators (ΔSP, ΔPPf and ΔSPf) were not correlated with the VE-induced changes in CI. Only dynamic indicators significantly decreased after VE. Indeed, ΔPP decreased from $11 \pm 5\%$ at baseline to $6 \pm 4\%$ after VE ($p < 0.001$), ΔSP from $8 \pm 4\%$ to $6 \pm 3\%$ ($p < 0.001$), ΔPPf from $25 \pm 18\%$ to $15 \pm 14\%$ ($p < 0.001$) and ΔSPf from $22 \pm 13\%$ to $16 \pm 12\%$ ($p < 0.001$). Nevertheless, the VE-induced changes in the value of the indicator (value after VE minus value before VE) were not correlated with VE-induced changes in CI ($r^2 = 0.04$; $p = 0.125$ and $r^2 = 0.03$; $p = 0.205$ for ΔPP and ΔSP, respectively). The individual changes in CI after VE are presented in Fig. 4.

About a third of the patients ($n = 11$) had a chronic obstructive pulmonary disease (COPD) but none of them exhibited an acute right-ventricular dysfunction. The ability of ΔPP to discriminate responders and nonresponders patients to VE was not statistically different between COPD patients and non-COPD patients in terms of sensitivity (56% for COPD vs. 54% for non-COPD), specificity (90% vs. 88%) or area under the ROC curve (0.81 ± 0.08 vs. 0.77 ± 0.07; $p = 0.104$).

Discussion

The main results of our study are the following: first, the search for predictive factors of fluid responsiveness in SB patients was justified since, at baseline, as reported in MV patients [2, 3], none of the general characteristics and standard hemodynamic parameters were statistically different between responders and nonresponders. Moreover, as evidence of the poor quality of classic indicators, fluid responsiveness occurred in only 60% of the patients. Second, during SB, dynamic indicators predicted response to fluid with globally the same specificity, positive predictive value and area under the ROC curve as reported in MV patients [2, 3]. By contrast, the sensitivity of the indicators during SB was lower than in MV patients [2, 3, 27].

The results obtained during quiet SB demonstrated that the respiratory changes in arterial pressure are influenced by the volemic status of the patients. Indeed, ΔPP and ΔSP are significantly higher before VE in responders than in nonresponders, they both statistically significantly decreased after VE and the correlation between ΔPP before VE and the VE-induced changes in CI, even if not so good, was significant. Furthermore, due to their high specificity, a baseline ΔPP $\geq$ 12% and/or a baseline ΔSP $\geq$ 9% predicted with high probability a favorable response to fluid. By contrast, two recently published studies focusing in particular on SB patients highlighted a lower specificity of ΔPP than in our series [28, 29]. However, in those studies, the patients were not strictly SB but they had spontaneous movements during MV. In that case, the indicators' baseline values may be less effective to predict fluid responsiveness than during completely spontaneous breathing. Indeed, two different levels of intrathoracic pressures occur during the inspiratory phases, and thus, the results may depend both on the magnitude of the inspiratory effort and on the magnitude of the inspiratory pressure support. This phenomenon may explain the lack of specificity of dynamic indicators in those studies compared with ours. Nevertheless, it must be underlined that in SB patients, high baseline values of indicators may raise questions. First, we performed all the hemodynamic measurements in participating patients. Second, a high indicator baseline value may reflect either a preload dependence condition or an acute right-ventricular dysfunction. Indeed, in the case of acute right-ventricular dilatation, there is an inspiratory decrease in left-ventricular diastolic compliance, resulting in an exaggeration of the normal inspiratory decrease in arterial systolic pressure which is called pulsus paradoxus [30–32]. In this situation, VE might be deleterious. This mechanism may not account for all high ΔPP and ΔSP baseline values of our population (none of the studied patients suffered from acute asthma or cardiac tamponade, none of them exhibited echographic sign of acute right-ventricular dysfunction, and the analyses distinguishing COPD and non-COPD patients proved that the exclusion of COPD patients did not enhance the prediction of fluid responsiveness). However, the observation of respiratory changes in arterial pressure during SB must be integrated into the clinical context, is only valid in a quiet and participating patient, and the absence of acute ventricular dysfunction must be confirmed before carrying out a fluid therapy.

In MV patients, ΔPP and ΔSP predicted fluid responsiveness with a sensitivity of 94% and 100%, respectively [2], whereas in our series, sensitivity was only 63% and 47%, respectively. Two hypotheses may explain this lack of sensitivity during SB. First, the respiratory changes in pleural pressure may be of insufficient magnitude to modify loading conditions of ventricles to the extent that respiratory variations in hemodynamic variables would become measurable [23, 33, 34]. This phenomenon has already been reported in MV, during which the use of small tidal volumes masks a biventricular preload dependency status and reduces the predictive value of ΔPP [20, 21, 35]. Therefore, when interpreting values from SB patients, a low ΔPP and/or ΔSP baseline value may reflect either a biventricular preload independence condition, or a preload dependence condition masked by insufficient changes in pleural pressure. Second, in the case of profound hypovolemia, collapse of the inferior vena cava at its point of entry into the thorax may occur during inspiration, decreasing right-ventricular preload, thus decreasing the magnitude of ΔPP and ΔSP values. Thus, during SB, a low ΔPP and/or ΔSP baseline value does not allow prediction of the response to VE. In addition, due to their lack of sensitivity, in SB patients ΔPP and ΔSP are predictors of a positive response to VE rather than predictors of a negative response to fluid therapy. However, the risk of a deleterious VE must be particularly taken in consideration in SB patients, and the clinician would also need markers of nonresponse to fluid. In that case, as recently described by Monnet and coworkers, passive leg raising could be one of the investigations used to improve the prediction of fluid responsiveness in SB patients [28].

We had designed the forced respiratory maneuver in order to enhance the sensitivity of the indicators. Nevertheless, their performances during this maneuver were significantly lower than during quiet respiration. The main explanation of this result is that the magnitude of the respiratory changes in arterial pressure during SB is probably influenced by the respiratory status of the patients. Indeed, the forced respiratory maneuver reproducing a dyspneic state highlighted that the greater the patient's dyspnea, the lower was the predictive power. Consequently, ΔPP and ΔSP may be useful only in quiet and participating SB patients which was the status of our patients. Another hypothesis for the poor performances of indicators during the forced respiratory maneuver is that this maneuver (a forced inspiratory effort followed by a forced expiratory effort) may not increase the phenomenon of respiratory changes in LVSV. Indeed, the forced expiratory effort, by increasing left-ventricular afterload (increase in abdominal pressure), may limit the increase in LVSV induced by the decrease in pleural pressure during the forced inspiratory effort. This hypothesis could be tested in further studies analyzing the effects of an active inspiratory effort followed by a passive expiration.

Finally, our study has some limitations. First, as described during MV, arrhythmias lead to misinterpretation of respiratory changes in arterial pressure. Patients with arrhythmias, therefore, were excluded from the study. Second, CI was not measured by the reference thermodilution technique and the intraobserver variability of CI measurements was not calculated. However, all the transthoracic echocardiography examinations were performed by the same operator using a method which was

previously validated against thermodilution in critically ill patients [36]. Third, fluid responsiveness was defined by an increase in CI $\geq$ 15% after VE. Nevertheless, this cut-off value was the same as the one used in previous studies assessing fluid responsiveness in MV patients [2–8].

In conclusion, our findings confirm the poor value of clinical signs and/or standard hemodynamic parameters to predict the effects of fluid expansion in SB patients. Moreover, the results suggest that ΔPP and ΔSP are less effective in predicting fluid responsiveness during SB than in MV patients. Indeed, they only help the decision to fluid expansion when their baseline value is high without evidence of acute right-ventricular dysfunction in a quiet and participating patient. In that case, a positive response to fluid is likely. In other cases, due to their lack of sensitivity, ΔPP and ΔSP are in clinical practice unreliable for prediction of fluid responsiveness during spontaneous breathing.

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EDITORIAL

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Can one predict fluid responsiveness in spontaneously breathing patients?

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Prediction of fluid responsiveness has become a topic of intense interest. Although measurements of preload, by whatever technique, are still commonly used to guide fluid therapy [1, 2], these fail to estimate the response to fluids in one-half of the patients [3]. Accordingly, many patients may be subjected to the hazards of fluids [4], without benefiting from hemodynamic improvement.

In patients receiving mechanical ventilatory support predictable heart lung interactions can be used to accurately identify fluid responsiveness by noting the arterial pulse pressure or aortic stroke volume variation over three or more breaths [5]. This is because positive-pressure inspiration induces cyclic increases in right atrial pressure causing in turn inverse changes in venous return, right ventricular filling and ejection and ultimately left ventricular preload. In preload-dependent patients these cyclical changes in ventricular filling induce cyclic changes in stroke volume and arterial pulse pressure, provided that both the right and left ventricles are preload responsive. These cyclic changes in pressure and flow are referred to as pulse pressure variation (Δ PP) and stroke volume variation (Δ SV), respectively. In spontaneously breathing patients the situation is more complex. Spontaneous inspiration induces negative cyclic changes in intrathoracic pressure causing right atrial pressure to also decrease increasing the pressure gradient for venous blood flow. In calves with total artificial hearts spontaneous ventilation induced opposite changes in left ventricular stroke volume than mechanical ventilation [6]. However, unlike artificial hearts whose right and left side filling is independent of each other, in patients with normal hearts Δ PP failed to predict preload response during under either pressure support [7, 8] or spontaneously breathing [8]. Various factors may explain this lack of reliability. Both pressure support ventilation and spontaneous breathing are associated with variability in tidal volume, and both Δ PP and Δ SV are dependent on tidal volume [9, 10]. Similarly, spontaneous inspiratory efforts may increase intra-abdominal pressure because of active compression of abdominal muscles, exaggerating the preload response. Finally, sudden increases in right ventricular end-diastolic volume decrease left ventricular diastolic compliance by the process of ventricular interdependence, which may decrease left ventricular filling and stroke volume independent of preload-responsiveness, because even failing hearts need some end-diastolic volume to generate stroke volume. Soubrier et al. [11] in their contribution to *Intensive Care Medicine* now reason that forced expiratory maneuvers (Valsalva maneuver) may identify preload responsiveness in spontaneously breathing patients when normal spontaneous ventilation do not. Using standardized amplitude of respiratory movements they compared the effects of both a Valsalva maneuver and spontaneous

breathing on Δ PP to predict preload responsiveness in 32 critically ill patients. During regular spontaneous breathing activity Δ PP was higher in responders to fluid challenge than in nonresponders, but the test performed poorly with a sensitivity of Δ PP greater than 12% of only 63% although specificity was good (92%). The forced maneuver failed to improve the performance of the test, with a decrease in sensitivity to 21% but a maintained specificity (92%). Importantly, the cutoff value of Δ PP increased to 33% during the forced expiratory maneuver, indicating that during this large swing in pleural pressure moderate fluctuations in arterial pressure may not indicate fluid responsiveness. This may be due to several factors. First, applying larger tidal volumes and more negative pleural pressure may transiently shift the patient to preload dependency, which disappears when the patient breaths normally. Second, the Valsalva maneuver may also affect right and left ventricular afterload, which may contribute to respiratory variations in stroke volume [12]. Thus, regrettably, Δ PP and other derived indices cannot be used in spontaneously breathing patients, as slight and sometimes undetected changes in breathing pattern may affect these variables.

Another way to predict fluid responsiveness is to perform an endogenous fluid challenge using passive leg raising. This approach has been used by cardiologists in the cardiac catheterization laboratory for over 50 years. In critically ill patients under mechanical ventilation, with or without spontaneous respiratory movements, an increase in mean aortic flow of more than 10% during passive leg raising reliably predicts the response to fluid challenge [7, 13, 14]. Until now this test has been difficult to apply in conscious and spontaneously breathing patients. Passive leg raising requires the use of a fast response measurement of cardiac output as the increase in cardiac output is transient and may not be maintained when legs are raised for more than a few minutes. Hence esophageal Doppler measures of descending aortic blood flow was used in the three reported studies [7, 13, 14]. Unfortunately, using an esophageal flow probe may be quite uncomfortable in conscious patients. To address this issue both Lamia et al. [15] and Maizel et al. [16] in their contributions to *Intensive Care Medicine* demonstrate that transthoracic echocardiography can be used to measure mean cardiac output during leg raising. They report that an increased change in aortic flow, measured as velocity time interval at the aortic valve (VTIao) by 10–13%, was associated with a positive response to fluid challenge. In both cases the performance of the tests was very good (receiver operating characteristic curve area of 0.96 [15] and 0.90 [16]) with sensitivity and specificity above 80%. Importantly, one-half of the patients in the study by Lamia et al. [15] and all patients in the study by Maizel et al. [16] were spontaneously breathing without any mechanical support.

These studies provide several lessons. First, changes in mean arterial pressure during passive leg raising failed to predict the response to fluid. Similarly, changes in arterial pressure during fluid challenge were only loosely related to changes in cardiac output, again demonstrating that the only way to assess a positive response to fluid in a spontaneously breathing subject is to measure the changes in cardiac output by whatever the technique. Second, changes in left ventricular area or mitral Doppler, reflecting left ventricular preload, were not useful for predicting the response to fluids, indicating again that preload-responsiveness is not the same as preload.

Several limitations of these last two studies should be acknowledged. First, VTIao rather than stroke volume or cardiac output was measured in order to limit errors in calculation. Both studies considered that aortic diameter did not change during passive leg raising and fluid challenge, and thus VTIao reflected stroke volume. However, if passive leg raising induced increased flow and also increased arterial pressure, aortic diameter may also increase, reducing the accuracy of the VTIao to track flow changes [17]. This limitation may not apply to the aortic outflow tract where VTIao is obtained with echocardiography, as this area is somewhat protected by the aortic annulus. Also, although tachycardia is common in hypovolemia, many studies have reported that there is no major change in heart rate during fluid challenge, even in responders, and therefore stroke volume can be used to assess cardiac output changes, which define fluid responsiveness. Second, some patients experienced a significant decrease in cardiac output both during passive leg raising and fluid challenge. This may reflect a stress-induced change in metabolic requirements or reflect vasoconstriction occurring between baseline and subsequent passive leg raising measurements. This underscores the axiom that hemodynamic evaluation should always be performed carefully in conscious patients and that external factors may interfere with the hemodynamic response to an intervention. Finally, although reliable in experts hands (the inter- and intraobserver variability of VTIao were lower than 5% in both studies), investigators less experienced with echocardiographic techniques may not reach this level of accuracy. In particular, small changes in the angle of the echo beam may induce errors in measurements that may be misinterpreted (a 15° angle inducing a 5% error in measurement). More importantly, echocardiography is not always available at any time of the day and cannot be used for continuous monitoring needed for trend analysis. It is likely that other cardiac output measurement techniques, such as pulse contour determinations, would provide similar results and may supplant echocardiography in bedside monitoring of dynamic changes in cardiac output.

Hence the prediction of fluid responsiveness is now feasible in spontaneously breathing patients, but this requires the performance of a passive leg raising test and the dynamic measure of changing cardiac output using fast response measurements techniques. In the hands of

the unskilled, much caution needs to be placed on the interpretation of these parameters, but when the data are accurately collected, it represents a new and powerful tool in the critical care diagnostic armamentarium.

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