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Article

2007

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How to cite

FEISSEL, Marc et al. Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. In: Intensive care medicine, 2007, vol. 33, n° 6, p. 993–999. doi: 10.1007/s00134-007-0602-6

This publication URL: <https://archive-ouverte.unige.ch/unige:26446>

Publication DOI: [10.1007/s00134-007-0602-6](https://doi.org/10.1007/s00134-007-0602-6)

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Received: 16 May 2006
Accepted: 27 February 2007
Published online: 29 March 2007
© Springer-Verlag 2007

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-007-0602-6) contains supplementary material, which is available to authorized users.

Funding: No external funding

This work was performed in the Medical Intensive Care Unit, Centre Hospitalier, Belfort, France.

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Abstract Objectives: In septic patients, reliable non-invasive predictors of fluid responsiveness are needed. We hypothesised that the respiratory changes in the amplitude of the plethysmographic pulse wave (ΔP_{PLET}) would allow the prediction of changes in cardiac index following volume administration in mechanically ventilated septic patients.

Design: Prospective clinical investigation. **Setting:** An 11-bed hospital medical intensive care unit. **Patients:** Twenty-three deeply sedated septic patients mechanically ventilated with tidal volume ≥ 8 ml/kg and equipped with an arterial catheter and a pulse oximetry plethysmographic sensor. **Interventions:** Respiratory changes in pulse pressure (ΔPP), ΔP_{PLET} and cardiac index (transthoracic Doppler echocardiography) were determined before and after volume infusion of colloids (8 ml/kg). **Measurements and main results:** Twenty-eight volume challenges were performed in 23 patients. Before volume expansion, ΔPP correlated with ΔP_{PLET} ($r^2 = 0.71$, $p < 0.001$). Changes in

cardiac index after volume expansion significantly ($p < 0.001$) correlated with baseline ΔPP ($r^2 = 0.76$) and ΔP_{PLET} ($r^2 = 0.50$). The patients were defined as responders to fluid challenge when cardiac index increased by at least 15% after the fluid challenge. Such an event occurred 18 times. Before volume challenge, a ΔPP value of 12% and a ΔP_{PLET} value of 14% allowed discrimination between responders and non-responders with sensitivity of 100% and 94% respectively and specificity of 70% and 80% respectively. Comparison of areas under the receiver operator characteristic curves showed that ΔPP and ΔP_{PLET} predicted similarly fluid responsiveness. **Conclusion:** The present study found ΔP_{PLET} to be as accurate as ΔPP for predicting fluid responsiveness in mechanically ventilated septic patients.

Keywords Fluid resuscitation · Heart–lung interactions · Volume responsiveness · Monitoring

Introduction

There are now a great number of clinical studies supporting the usefulness of dynamic indices based on heart–lung interaction for guiding volume resuscitation in patients receiving mechanical ventilation [1, 2]. Accordingly, the respiratory variations of arterial pulse pressure, of “pulse con-

tour” stroke volume, and of Doppler aortic blood velocity have been shown to predict volume responsiveness far better than static markers of preload such as cardiac filling pressures or dimensions [3–5]. The pulse oximeter could be an attractive device for detecting volume responsiveness since it is non-invasive and easy to use and also since the pulse oximetry plethysmographic signal resembles the pe-

ripheral arterial pressure waveform [6]. In this regard, respiratory variation of pulse oximeter waveforms has been correlated with that of systolic arterial pressure [6–8] and pulse pressure [9].

The plethysmographic “pulse” wave (nadir–peak) displayed on the monitor is assumed to reflect the pulsatile changes in absorption of the infrared light between the light source and the photo detector of the pulse oximeter [10]. Consequently, the beat-to-beat changes in the amplitude of the plethysmographic pulse wave are assumed to be the result of the beat-to-beat changes in stroke volume transmitted to the arterial blood [11]. In this respect, the degree of respiratory changes in the amplitude of the plethysmographic pulse (ΔP_{PLET}) wave should be a potential marker of respiratory stroke volume variation and hence a marker of volume responsiveness [12, 13]. In this regard, ΔP_{PLET} was demonstrated to be influenced by changes in preload [14]. In a clinical study, it was recently shown that each time ΔP_{PLET} was greater than the threshold value of 15%, fluid challenge resulted in an increased of cardiac output by more than 15% [15]. On the other hand, ΔP_{PLET} values lower than 15% poorly predicted volume responsiveness, maybe because half of the patients were ventilated with tidal volumes lower than 8 ml/kg [15], a condition where dynamic indices like pulse pressure variation fail to predict accurately volume responsiveness [16].

The aim of our study was to test the hypothesis that ΔP_{PLET} could be as valuable to predict volume responsiveness as respiratory changes in arterial pulse pressure in septic patients receiving mechanical ventilation with a tidal volume > 8 ml/kg and exhibiting neither inspiratory efforts nor arrhythmias.

Materials and methods

The institutional review board for human subjects approved the protocol, considering it as a part of routine clinical practice, and patients were informed that they were participating in this study. We included only mechanically ventilated patients with septic shock, as defined by the International Sepsis Definitions Conference [17], who were equipped with a systemic arterial catheter and for whom the decision to give fluid was taken by their attending physician in the context of standard treatment. We excluded those patients with moderate to severe valve disease and those who experienced inspiratory efforts or cardiac arrhythmias.

Patient management

Sedation and analgesia were provided by continuous infusion of midazolam and remifentanyl titrated for a Ramsay score of 6 [18]. Patients were therapeutically paralysed

(with cisatracurium) if the attending physician deemed this appropriate. All patients were ventilated with positive pressure ventilation (tidal volume, 8–10 ml/kg of body weight). The respiratory rate was set to obtain a PaCO_2 of 35–45 mmHg. The inspired fraction of oxygen was adjusted in order to obtain an arterial oxygen saturation > 92%. Inspiratory to expiratory ratio was approximately 0.5:1 in all patients.

Haemodynamic monitoring

All pressure transducers were referenced to mid-chest. All patients were monitored using a pulse oximetry sensor with plethysmography ($\text{SpO}_2/\text{Pleth}$, M3150A technology, Philips Medical Systems, Andover, MA) attached to the patient's finger (phalanx) with a clip.

Cardiac output measurements

All patients had a colour-Doppler echocardiography investigation shortly before and after volume infusion. Complete two-dimensional echocardiography and colour-Doppler ultrasound examinations were performed using a commercially available echocardiographic system (Sonos 5500, Philips Medical Systems, Eindhoven, Netherlands) in a semi-recumbent position with head at 45°. All tracings were recorded by one investigator, and each value represented the average of five tracings. Echocardiography–Doppler traces were analysed off line. The cardiac output was measured at the level of the aortic annulus. Aortic annulus diameter (D_{Ao}) was measured at mid-systole, (T wave on ECG) and during the expiratory phase of the respiratory cycle, from a zoomed two-dimensional image in the parasternal long axis view. From an apical five-chamber view, aortic flow (at the annulus level) was recorded using pulsed Doppler. Velocity–time integral for aortic flow (VTIAo) was measured at the end of the expiratory period. With the use of these measurements, stroke volume could be calculated using the following formula: $(D_{\text{Ao}})^2 \times 3.14 \times \text{VTIAo} / 4$. To obtain cardiac output, stroke volume was multiplied by heart rate. The cardiac output was divided by the body surface area (in m^2) to obtain the cardiac index. We did not recalculate the area of the aortic orifice over time since it is assumed to be unchanged because of the fibrotic nature of the annulus.

Respiratory change in the amplitude of the plethysmographic pulse wave

Arterial blood pressure–time, pulse plethysmography–time, ECG–time and airway pressure–time curves were

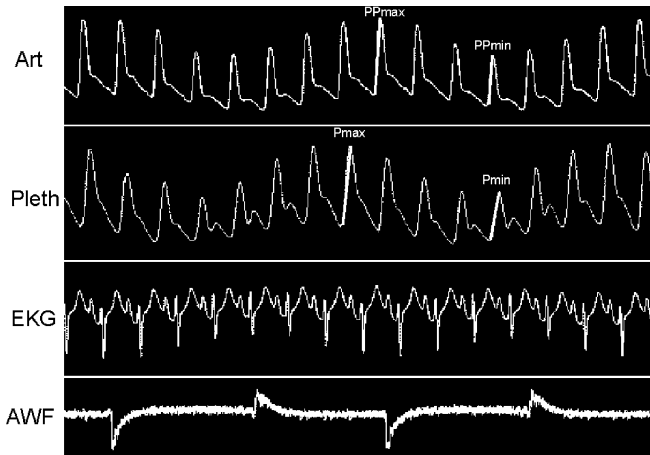


Fig. 1 Simultaneous recording of systemic arterial pressure (*Art*), plethysmographic “pulse” (*Pleth*), EKG and airway flow (*AWF*) curves in one patient with large ΔPP and ΔP_{PLET} . (AcqKnowledge software, Biopac Systems, Santa Barbara, CA, USA)

digitised at 500 Hz and sampled using an analogue/numeric system (Biopac Systems, Goleta, CA, USA). Recording was assessed using an MP100wsw Starter system for PC/Windows (AcqKnowledge software, Biopac Systems, Santa Barbara, CA, USA). The data acquired online were stored on a laptop computer for subsequent analysis of the respiratory changes in arterial pulse pressure (ΔPP) and ΔP_{PLET} (Fig. 1). The inter-observer variability of ΔPP and ΔP_{PLET} measurements was determined in a “blinded” fashion, with a second observer (M. F., J. B.). All measurements were made before the analysis of ΔPP so as not to be influenced by the results. The ΔPP and ΔP_{PLET} were calculated as previously described [4] and expressed in percentage. Pulse pressure was calculated on a beat-to-beat basis as the difference between systolic and diastolic arterial pressure. Maximal pulse pressure (PPmax) and minimal pulse pressure (PPmin) values were determined over a single respiratory cycle. To assess the respiratory changes in pulse pressure, the percent change in pulse pressure was calculated as: $\Delta PP = 100 \times \{ (PP_{max} - PP_{min}) / [(PP_{max} + PP_{min}) / 2] \}$.

Study protocol

All studies were performed in patients in a semi-recumbent position with head at 45° position. Measurements were performed in duplicate, first before volume expansion and then 30 min after volume expansion using 8 ml/kg 6% hydroxyethyl starch (Voluven; Fresenius Kabi, Sèvres, France). The ventilatory settings and the rate of administration of vasoactive drugs were not changed throughout the study. Regarding the echocardiographic measurement of cardiac output, the area of the aortic orifice has been measured only before fluid infusion as it is assumed to be

unchanged because of the fibrotic nature of the annulus. Therefore, VTIAo was the only variable measured before and after fluid challenge.

Statistical analysis

For the statistical analysis, Stata Statistical Software, Release 8.0® (Stata Corporation, College Station, TX, USA) was used. Data were compared using paired *t*-test for continuous variables. Ordinal data or non-normally distributed continuous data were compared using the Mann–Whitney *U*-test or the non-parametric Wilcoxon rank sum test for paired observations. Correlations were determined using linear regression analysis. We also randomly selected a single paired observation for each of the $n = 23$ patients and performed all analyses that had already been conducted.

For the set of measurements obtained before fluid challenge, the intraobserver and interobserver variability of VTIAo measurements was determined in all patients and expressed as the mean percent error (i.e. the difference between two observations, divided by the mean of the two observed values).

Patients were divided into two groups according to the percent increase in cardiac index in response to volume expansion. In accordance with previous studies [1, 2, 15, 16, 19], we took the benchmark of 15% for differentiating responders from non-responders [20]. We compared haemodynamic parameters before and after volume expansion in responder and non-responder patients using a paired *t*-test for continuous variables. Receiver operating characteristic (ROC) curves for responders–non-responders were generated for ΔPP and ΔP_{PLET} , varying the discriminating threshold of each parameter. The areas under the ROC curves (\pm SE) were calculated for each parameter and compared [21]. A method of comparing the areas under ROC curves derived from the same cases. All tests were two-tailed, and a *p*-value less than 0.05 was considered statistically significant.

Results

Twenty-three patients (mean age 62 ± 17 years) were included. Fourteen patients survived. Mean tidal volume was 9.0 ± 0.9 ml/kg and plateau pressure less than 30 cmH₂O in all patients. A total of 28 fluid challenges were analysed. All patients received catecholamines: dobutamine (5 µg/kg/min) in association with norepinephrine ($n = 4$), norepinephrine alone ($n = 15$) and dopamine (5 µg/kg/min) alone ($n = 4$). Mean norepinephrine dose was 0.42 ± 0.24 µg/kg/min. No patient experienced hypothermia at the time of the study. Haemodynamic variables before and after volume infusion are shown in Table 1. Volume infusion produced an increase in cardiac index from 2.5 ± 0.7 to 3.0 ± 0.9 l/min/m² ($p < 0.0001$).

Table 1 Effects of volume infusion on patients' haemodynamic parameters (28 fluid challenges in 23 patients)

	Before VE	After VE	<i>p</i> ^a
HR (beats/min)	111 ± 25	101 ± 24	<0.001
MAP (mmHg)	74 ± 16	87 ± 19	<0.01
ΔPP (%)	18 ± 11	5 ± 3	<0.001
ΔP _{PLET} (%)	23 ± 15	7 ± 5	<0.001
CI (l/min/m ²)	2.5 ± 0.7	3.0 ± 0.9	<0.001

HR, heart rate; MAP, mean arterial pressure; ΔPP, respiratory changes in arterial pulse pressure; ΔP_{PLET}, respiratory changes in the amplitude of the plethysmographic pulse wave (with pulse oximeter); CI, cardiac index; VE, volume expansion; ^a Before VE/after VE (paired *t*-test)

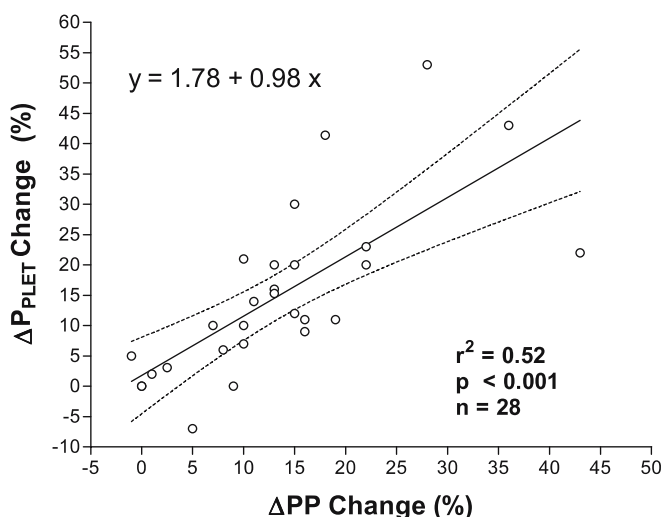


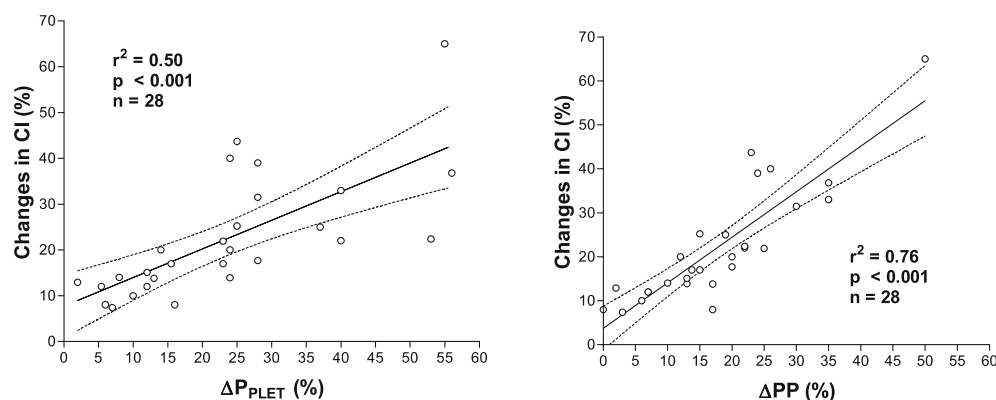
Fig. 2 Linear regression analysis of the relationship between change in ΔPP and change in ΔP_{PLET} following volume infusions (28 fluid challenges in 23 patients). ΔPP, respiratory changes in arterial pulse pressure; ΔP_{PLET}, respiratory changes in the amplitude of the plethysmographic pulse wave (with pulse oximeter)

Before volume expansion, ΔPP correlated with ΔP_{PLET} ($r^2 = 0.71$, $p < 0.001$). Changes in ΔPP correlated with changes in ΔP_{PLET} following volume expansion, ($p < 0.01$; Fig. 2). Changes in cardiac index

after volume expansion significantly ($p < 0.001$) correlated with baseline ΔPP ($r^2 = 0.76$) and ΔP_{PLET} ($r^2 = 0.50$) (Fig. 3). The fluid-induced decreases in ΔPP and ΔP_{PLET} were significantly correlated with the fluid infusion-induced increases in cardiac index ($r^2 = 0.64$ and $r^2 = 0.38$; $p < 0.01$, respectively). In 18 cases patients were classified as responders (cardiac index increase $\geq 15\%$), and in 10 cases patients were classified as non-responders. Before volume expansion, mean ΔPP and ΔP_{PLET} were significantly higher in responders than in non-responders ($p < 0.01$; Fig. 4). Before volume challenge, a ΔPP value of 12% and a ΔP_{PLET} value of 14% allowed discrimination between responders and non-responders with sensitivity of 100% and 94% respectively and specificity of 70% and 80% respectively. Comparison of areas under the ROC curves showed that ΔPP and ΔP_{PLET} predicted fluid responsiveness similarly (Fig. 5). The combination of the two measurements (ΔPP and ΔP_{PLET}) did not improve the power of prediction.

When a single paired observation for each of the 23 patients was selected (after removing five pairs of values using a random selection) the results were statistically unchanged (see ESM). For 23 pairs of measurements, the areas under the ROC curves were 0.99 (0.98–1.0) and 0.96 (0.85–1.0) for ΔPP (optimal cut-off value of 13%) and ΔP_{PLET} (optimal cut-off value of 12%) respectively.

Fig. 3 Linear regression analysis of the relationship between ΔPP and ΔP_{PLET} measured before volume expansion and changes in cardiac index (CI) following volume expansion (28 fluid challenges in 23 patients). $p < 0.05$ was considered significant



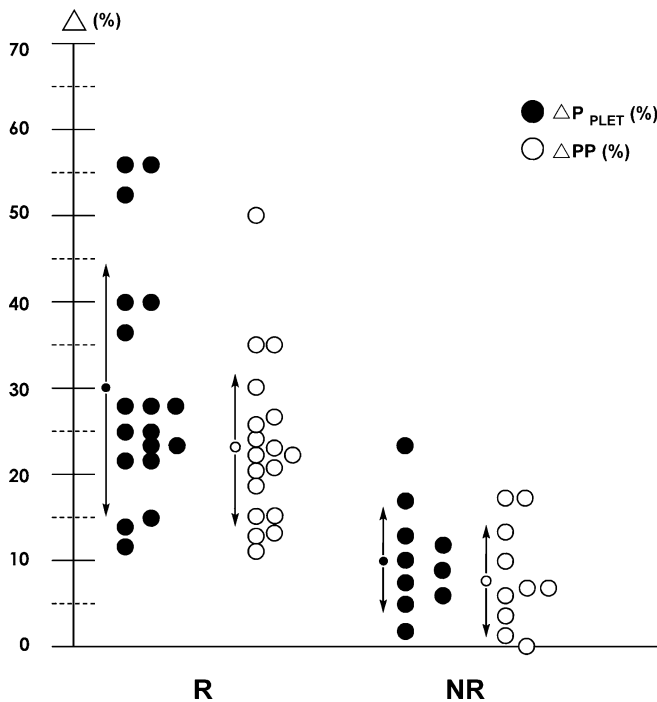


Fig. 4 Distribution of all the individual results (28 fluid challenges in 23 patients) of ΔPP and ΔP_{PLET} (measured before volume expansion in %). *R*, Responders (cardiac index increase $\geq 15\%$ after volume challenge); *NR*, non-responders (cardiac index increase $< 15\%$ after volume challenge). Points and arrows indicate mean and SD respectively

The intraobserver variability of VTIAo measurements was $0.5 \pm 0.7\%$ and the interobserver (M. F., J. B.) variability of VTIAo measurements was $2.2 \pm 0.8\%$.

Discussion

The present study shows that ΔP_{PLET} is as valuable as ΔPP for predicting volume responsiveness in mechanically ventilated septic patients. Similar threshold values were found for ΔP_{PLET} (14%) and for ΔPP (12%).

Previous studies demonstrated that pulse pressure variation was more reliable than static parameters of preload to predict volume responsiveness in critically ill patients receiving mechanical ventilation [1, 4, 16, 19]. The rationale for guiding fluid therapy on ΔPP or on other heart–lung interaction indices [1–3, 21] is that influence of positive pressure ventilation on haemodynamics is greater when central blood volume is low than when it is normal or high.

The finger pulse oximetry plethysmographic signal resembles the peripheral arterial pressure waveform [12]. Analysis of the respiratory variation in pulse oximeter waveforms has been proposed for a long time as a technique with which to assess blood volume status in mechanically ventilated patients [13]. In a recent study,

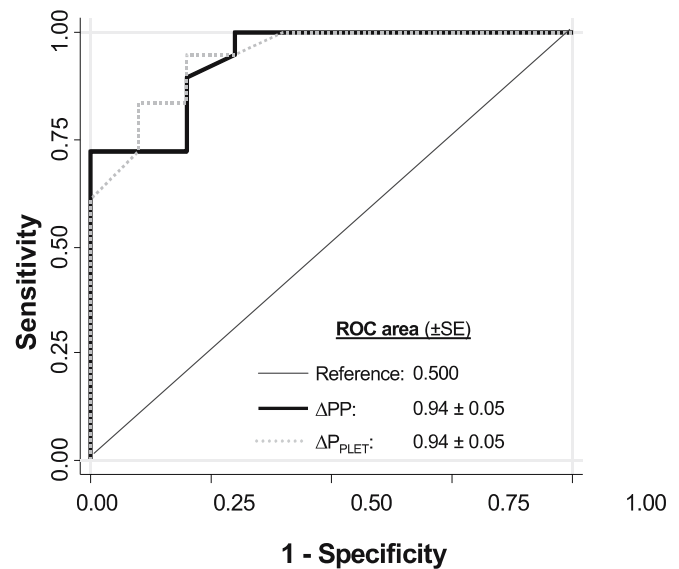


Fig. 5 Receiver operating characteristic (ROC) curves comparing the ability of ΔPP and ΔP_{PLET} to discriminate responders (cardiac index increase $\geq 15\%$) and non-responders to volume expansion ($n=28$). The areas under the ROC curve were not significantly different ($p=NS$)

we demonstrated that a derived plethysmographic index—the respiratory change in pre-ejection period—was as accurate as ΔPP to assess preload responsiveness in septic mechanically ventilated patients [22]. In the present study, we used ΔP_{PLET} since we postulated that this index might reflect the respiratory changes in left ventricular stroke volume. Indeed, by reflecting the pulsatile changes in absorption of infrared light between the light source and the photo detector of the pulse oximeter, the ‘pulse’ wave is assumed to be the result of the beat-to-beat changes in stroke volume transmitted to arterial blood, which was reported to correlate with ΔPP in mechanically ventilated patients [9]. In this respect, ΔP_{PLET} is potentially a marker of respiratory stroke volume variation and thus of volume responsiveness [14, 15]. Interestingly, we found threshold values of 12% and 14% that allowed discrimination between responder and non-responder patients for ΔPP and ΔP_{PLET} respectively. These values were very close to the threshold values (13%, 11.8%, 17%, 12%) found in previous studies examining the significance of ΔPP to predict fluid responsiveness in septic patients [4, 16, 22, 23]. It has to be noted that the prediction of fluid responsiveness was not improved by the combination of the two measurements (ΔPP and ΔP_{PLET}). This may suggest that these indices give similar information in terms of prediction of fluid responsiveness. However, as indicated by the data displayed in Fig. 3, the proportionality between ΔPP and cardiac index changes following volume expansion was closer to the identity line than was the proportionality between ΔP_{PLET} and cardiac index

changes. These results emphasise the clinical usefulness of ΔPP not only for predicting volume responsiveness but also for quantifying the haemodynamic response to fluid challenge, thus confirming the findings of a previous study [4]. On the other hand, the advantages of ΔP_{PLET} are its acquisition with a non-invasive technique (pulse plethysmography) and its immediate availability, which allows accurate assessment of volume responsiveness in mechanically ventilated patients before insertion of any arterial catheter.

Some limitations of this work should be acknowledged. First, we studied sedated patients such that our results cannot be extrapolated to patients experiencing spontaneous breathing activity, a condition that is frequently encountered in the intensive care unit (ICU). Second, our patients had regular cardiac rhythm, a mandatory condition for the use of heart-lung interaction indices [1]. Third, we used a tidal volume > 8 ml/kg in our patients and thus we cannot extrapolate our results to patients ventilated with lower tidal volume. Indeed, in such conditions of low cyclic changes in intrathoracic and transpulmonary pressures, volume responsiveness may coexist with low values of ΔPP [16] and presumably in ΔP_{PLET} . In this regard, in a series of 22 hypotensive patients ventilated with tidal volumes ranging from 6 to 10 ml/kg (median value of 8 ml/kg), Natalini et al. showed that ΔP_{PLET} values lower than the threshold value of 15% poorly predicted volume responsiveness, while all ΔP_{PLET} values above 15% were associated with a positive response to fluid challenge [15]. Fourth, we defined the positive response to volume challenge as an increase in cardiac index by more than 15% after fluid administration. We chose 15% because this benchmark was employed in

numerous previous studies which addressed the issue of fluid responsiveness [4, 15, 16, 22]. Since the diameter of the aortic annulus is assumed to remain constant during short-term haemodynamic interventions, we only measured the response of VTIAo to volume challenge. In this respect, the benchmark of 15% increase was far above the low intraobserver variability of the VTIAo ($0.5 \pm 0.7\%$) that we calculated. Fifth, we did not measure abdominal pressure since there was no clinical suspicion of increased abdominal pressure in this series of medical ICU patients suffering from septic shock. Our results cannot be extrapolated to patients with significant increase in abdominal pressure, since an animal study recently showed that increasing intra-abdominal pressure may result in increase in ΔPP [24]. Finally, in our study, we recorded correct pulse oximetry signals in all patients who were not hypothermic and in whom peripheral vasoconstriction was unlikely. Indeed, in this context of septic shock, vasomotor tone was expected to be reduced and catecholamines were given in the attempt to restore organ perfusion pressure. However, the pulse oximetry signal might be of poor quality in the presence of hypothermia or arterial vasoconstriction, although the quality of the displayed signal has been improved with the current generation of pulse oximetry devices.

In conclusion, the present study shows that ΔP_{PLET} may be as valuable as ΔPP for predicting volume responsiveness in septic patients ventilated with a tidal volume greater than 8 ml/kg. Since ΔP_{PLET} is obtained from pulse oximetry, a totally non-invasive monitoring technique, it may represent an attractive method to detect fluid responsiveness in mechanically ventilated patients in whom arterial catheters have not yet been inserted.

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