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Pleth variability index is a weak predictor of fluid responsiveness in patients receiving norepinephrine

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Editor's key points

- Respiratory variations in the amplitude of plethysmography traces may correlate with fluid responsiveness in surgical patients.

- However, the effect of vasoconstrictor drugs on the quality and accuracy of plethysmography indices is unclear.

- This study of critically ill patients found that the plethysmography variability index did not reflect fluid responsiveness.

- Plethysmography variability was less useful than other indices of stroke volume.

Background. In patients receiving an infusion of norepinephrine, the relationship between the amplitude of the oximeter plethysmographic waveform and stroke volume may be variable and quality of the waveform might be reduced, compared with patients not receiving norepinephrine. We assessed the reliability of the pleth variability index (PVI), an automatic measurement of the respiratory variation of the plethysmographic waveform, for predicting fluid responsiveness in patients receiving norepinephrine infusions.

Methods. We measured the response of cardiac index (transpulmonary thermodilution) to i.v. fluid administration in 42 critically ill patients receiving norepinephrine. Patients with arrhythmias, spontaneous breathing, tidal volume <8 ml kg^{-1}, and respiratory system compliance <30 ml cm H$_2$O^{-1} were excluded. Before fluid administration, we recorded the arterial pulse pressure variation (PPV) and pulse contour analysis-derived stroke volume variation (SVV, PiCCO2) and PVI (Masimo Radical-7).

Results. In seven patients, the plethysmographic signal could not be obtained. Among the 35 remaining patients [mean SAPS II score$=77$ (SD$=17$)], i.v. fluid increased cardiac index $\geq 15\%$ in 15 'responders'. A baseline PVI $\geq 16\%$ predicted fluid responsiveness with a sensitivity of 47 (inter-quartile range$=21$–73)% and a specificity of 90 (68–99)%. The area under the receiver operating characteristic curve was significantly lower for PVI [0.68 (0.09)] than for PPV and SVV [0.93 (0.06) and 0.89 (0.07), respectively]. Considering all pairs of measurements, PVI was correlated with PPV ($r^2=0.27$). The fluid-induced changes in PVI and PPV were not significantly correlated.

Conclusions. PVI was less reliable than PPV and SVV for predicting fluid responsiveness in critically ill patients receiving norepinephrine. In addition, PVI could not be measured in a significant proportion of patients. This suggests that PVI is not useful in patients receiving norepinephrine.

Keywords: cardiorespiratory system, responses; cardiovascular system; equipment; fluid therapy; measurement techniques; pulse oximetry; responses

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Among the different indices that have been developed for predicting fluid responsiveness, the respiratory variation of stroke volume and surrogates has generated a large amount of evidence.[1] Schematically, insufflations during mechanical ventilation in the control mode induce cyclic regular decreases in the left ventricular preload. This can be used as a test for assessing the effects of preload changes on stroke volume and cardiac output, that is, for diagnosing preload dependence. At the bedside, the key question is to know on which surrogate of stroke volume one can rely for assessing the haemodynamic effects of mechanical ventilation and predicting fluid responsiveness. Initially, the arterial pulse pressure has been proposed for this purpose[2] and it is now well demonstrated that pulse

pressure variation (PPV) allows a reliable prediction of fluid responsiveness.[3] This is also the case for the respiratory variation of stroke volume estimated from pulse contour analysis (SVV).[1]

As a non-invasive alternative to arterial pulse pressure and pulse contour analysis-derived stroke volume, some authors proposed to use the amplitude of the oximeter plethysmographic signal as a surrogate of stroke volume. The respiratory variation of the 'pulse' of the plethysmographic signal was found to be correlated with PPV.[4] It was demonstrated to predict fluid responsiveness with reliability.[5–7] More recently, a commercial device has been developed for providing an automatic calculation of the respiratory variation of the plethysmographic signal through a 'pleth

variability index' (PVI).[8] This index was found to reliably predict fluid responsiveness.[8–11]

However, the majority of studies validating the respiratory variation of the plethysmographic pulse or PVI as markers of fluid responsiveness were conducted in the perioperative setting in patients with a stable haemodynamic condition.[6–10] Altered sympathetic tone, induced either by circulatory failure or by vasoactive drugs, might alter the amplitude of the plethysmographic curve by modifying the distensibility of the small vessels where the plethysmographic curve is recorded and the proximal venous pressure. In such conditions, the plethysmographic pulse may not be related to stroke volume and its respiratory variation could fail to predict the haemodynamic response to fluid loading. In addition, vasoconstriction might alter the quality of the plethysmographic signal and impair the correct calculation of PVI. To date, available data are conflicting. Loupec and colleagues[11] found that PVI was a reliable predictor of fluid responsiveness in a population of patients receiving norepinephrine. In contrast, Biais and colleagues[12] found that the relationship between PVI and PPV was poorer in surgical patients receiving norepinephrine compared with patients who did not. However, since no volume challenge was performed, this study did not test whether the prediction of fluid responsiveness by PVI was impaired by norepinephrine administration. Thus, it is unclear whether PVI can predict fluid responsiveness in patients receiving norepinephrine.

The aims of this present study were to assess whether PVI can be recorded in patients with circulatory failure receiving norepinephrine and to test the ability of PVI to predict fluid responsiveness. We also aimed at comparing PVI with well-established indicators of fluid responsiveness, namely PPV and SVV.

Methods

Patients

After approval by the institutional review board of our institution (comité pour la protection des personnes Ile-de-France 7), patients' relatives were informed about the study at the time the patient was included and asked to provide assent. After assent and inclusion in the study, patients were informed as soon as their mental status enabled it and they were given the option to withdraw their participation to the study. Patients were prospectively included if they received norepinephrine and if they presented an acute circulatory failure for which the attending physician had decided to administer fluid. This decision was based on inadequate tissue perfusion defined by the presence of at least one of the following signs:[13–15] (i) systolic arterial pressure <90 mm Hg (or a decrease >50 mm Hg in previously hypertensive patients), (ii) urine output <0.5 ml kg^{-1} h^{-1} for at least 2 h, (iii) tachycardia >100 beats min^{-1}, (iv) skin mottling, or (v) blood lactate concentration >2 mmol litre^{-1}. Patients were excluded if they presented cardiac arrhythmias (atrial fibrillation and flutter, atrial and ventricular extrasystoles, and ventricular tachycardia), spontaneous triggering

of the ventilator, as assessed by visual observation of the pressure curve of the ventilator by investigators (L.G., A.B., M.J., F.J.). They were also excluded if their lungs were being ventilated with a tidal volume <8 ml kg^{-1} of predicted body weight[16] and if the compliance of respiratory system was ≤30 cm H$_2$O,[17] since these two conditions preclude using the respiratory variation of stroke volume to assess fluid responsiveness. Patients' lungs were ventilated with an Evita 4 (Dräger Medical Systems, Telford, PA, USA) in the volume-controlled mode. Tidal volume was not changed for the purpose of the study. All patients received sedation.

Assessment of the haemodynamic status

All patients had an internal jugular vein catheter and a thermistor-tipped arterial catheter (PV2024 Pulsion Medical Systems, Munich, Germany) in the femoral artery connected to the PiCCO$_2$ device (Pulsion Medical Systems). This device estimates global end-diastolic volume indexed for body surface and cardiac index by transpulmonary thermodilution. For this purpose, three cold boluses (15 ml saline at 6°C) were injected in the internal vein catheter. The average of three values was taken into account.[18] The PiCCO$_2$ device also measures PPV and SVV. Systemic vascular resistance index was calculated as the ratio of mean arterial pressure over cardiac index. A pulse oximeter probe (LNOPw Adt, Masimo Corp., Irvine, CA, USA) was placed on a finger of one hand and connected to a Masimo Radical-7 device (Masimo Corp.). This device measures a perfusion index, which is the ratio of the infrared pulsatile signal over the infrared non-pulsatile signal expressed as a percentage. PVI is calculated as the difference between maximal and minimal perfusion index over the maximal value.[8] The perfusion index is an indicator of the amplitude of the PVI signal. If the plethysmographic signal and PVI signal were not obtained from a finger, another finger was used until a signal could be obtained. If no signal could be obtained from any finger, efforts were made for rewarming the hand before all fingers were tested again. If the Masimo Radical-7 device did not eventually display any plethysmographic signal and PVI values, it was recorded that PVI 'was not obtainable'.

Study design

At baseline, we recorded heart rate, PPV, SVV, and PVI, and transpulmonary cardiac index was estimated by thermodilution. Immediately after, volume expansion was performed by infusing saline 500 ml over 30 min.[19] At the end of volume expansion, we again recorded heart rate, PPV, SVV, PVI, and transpulmonary thermodilution cardiac index.

Statistical analysis

Data normality was tested by the Kolmogorov–Smirnov test and are expressed as mean (SD) or as median (inter-quartile range), as appropriate. Data before and after fluid challenge were compared using a paired Student's *t*-test. The comparison of data between different groups of patients was performed using a two-sample Student's *t*-test or a

Mann–Whitney *U*-test, as appropriate. Correlations were analysed using the Spearman coefficient and compared.[20] Patients in whom volume expansion induced an increase in cardiac index ≥15% were prospectively defined as 'responders' to volume expansion. Receiver operating characteristics (ROC) curves were constructed to test the ability of PPV, SVV, and PVI to predict fluid responsiveness and were compared using the Hanley–McNeil test. The sensitivity, specificity, positive and negative predictive values, and likelihood ratios are expressed as mean (95% confidence interval). A *P*-value of <0.05 was considered statistically significant. Considering that the area under the ROC curve would be 0.95 for PPV[3] and 0.60 for PVI,[21] estimating that the correlation between PPV and PVI would be 0.20[12] and taking into account an α-risk of 5% and a β-risk of 20%, the minimal sample size was calculated to be 32 patients. From personal preliminary tests, we expected that the PVI signal could not be obtained in 25% of patients. Therefore, we planned to include 42 patients in the study. The statistical analysis was performed with MedCalc 8.1.0.0 software (Mariakerke, Belgium).

Results

Study population

All data were normally distributed except the dose of norepinephrine, mean arterial pressure, and cardiac index in patients in whom the plethysmographic signal could not be recorded. Among the 180 patients who presented with circulatory failure during the study period and who could potentially be investigated by the authors, 42 patients were included in the study (Fig. 1). The cause of acute circulatory failure was sepsis in most patients. In seven patients (16%), it was not possible to obtain a finger plethysmographic signal. Compared with the other patients, these patients were characterized by a higher dose of norepinephrine

[1.78 (inter-quartile range: 1.14–7.29) *vs* 0.56 (0.32–1.55) μg kg^{-1} min^{-1}, respectively, *P*=0.006], a lower cardiac index at baseline [2.3 (2.2–2.7) *vs* 2.9 (2.4–4.0) litre min^{-1} m^{-2}, respectively, *P*=0.006], and a lower mean arterial pressure at baseline [55 (48–59) *vs* 79 (65–86) mm Hg, respectively, *P*=0.003]. Three of these patients were volume responders and four volume non-responders. The characteristics of the 35 remaining patients in whom the PVI could be obtained are described in Table 1. Among these patients, 15 (43%) responded to volume expansion by an increase in cardiac index by more than 15% [35 (24)%] (Table 2). In volume non-responders, cardiac index increased by 7 (7)% (Table 2). No patient received dobutamine.

Pleth variability index, pulse pressure, and stroke volume variations

In the 35 patients in whom PVI could be obtained, PVI at baseline was 15 (9)% and decreased to 12 (7)% during volume expansion (*P*=0.01). Simultaneously, PPV decreased from 11 (7)% to 7 (4)% and SVV from 15 (5) to 13 (9)% (*P*=0.001 and 0.01, respectively).

Considering all the pairs of measurements performed during the study (35 before and 35 after volume expansion), the coefficient of determination between PVI and PPV was 0.27 (*P*<0.0001) (Fig. 2).

Considering all the 35 pairs of measurements performed during the study, the correlation between the fluid-induced changes in PVI and PPV was not significant (*P*=0.11).

Prediction of fluid responsiveness

PPV, SVV, and PVI were significantly higher in volume responders than in volume non-responders (Table 2). PPV and SVV predicted fluid responsiveness with similar reliability and both were better than PVI (Table 3, Fig. 3). There was a significant inverse correlation between the perfusion index
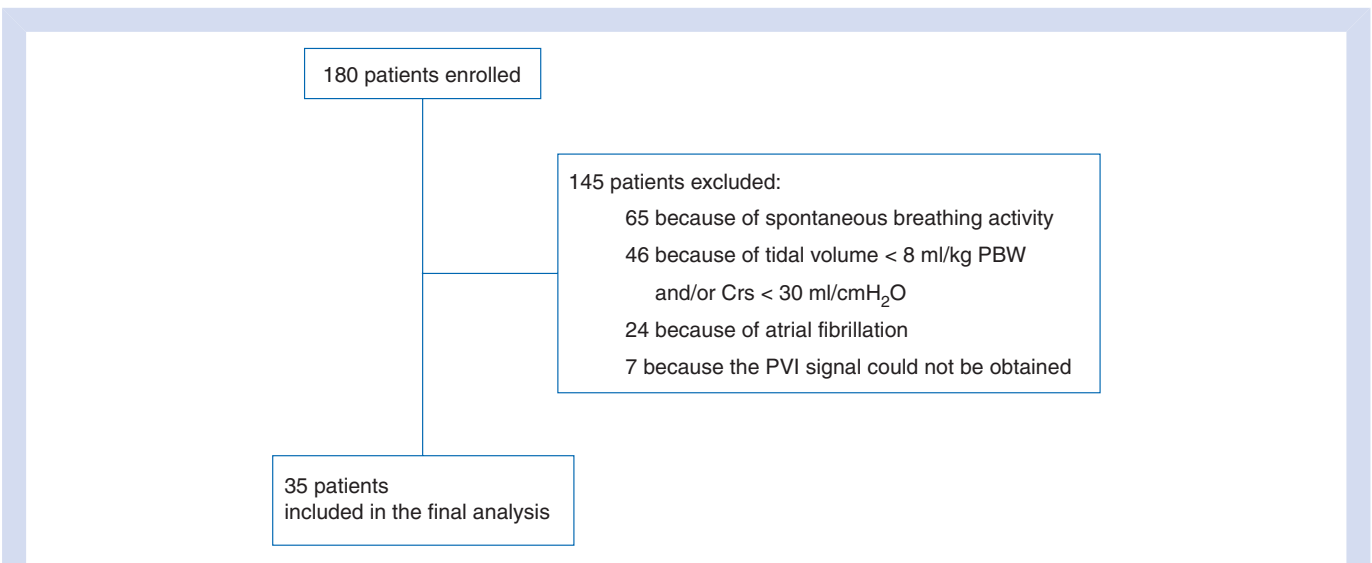
Fig 1 Flow diagram of patients screened and entered into the study. PBW, predicted body weight; PVI, pleth variability index; Crs, compliance of the respiratory system.

before fluid infusion and the dose of norepinephrine ($r^2=0.34$, $P=0.0003$). The ROC curve describing the diagnostic ability of PPV and SVV in the whole population, including the seven patients in whom PVI was not obtainable, is presented in Figure 4.

Discussion

We found that the calculation of the plethysmographic respiratory variation by PVI predicted fluid responsiveness with less accuracy than PPV and SVV in critically ill patients. The absolute values of PVI were weakly correlated with PPV and the fluid-induced changes in PVI were not correlated with the simultaneous changes in PPV. PVI could not be recorded in 16% of the patients.

Table 1 Patients characteristics at baseline in volume responders ($n=15$) and non-responders ($n=20$). Unless indicated otherwise, data are expressed as mean (SD). PEEP, positive end-expiratory pressure. No significant difference was observed between responders and non-responders

	Responders	Non-responders
Age (range, yr)	(23–82)	(35–81)
Origin of shock (no. of patients)		
Septic	15	14
Hypovolaemic	2	3
Tidal volume (ml kg^{-1} of predicted body weight)	9.0 (0.7)	9.1 (0.8)
Total PEEP (cm H$_2$O)	6 (3)	7 (3)
Compliance of the respiratory system (ml cm H$_2$O^{-1})	41 (12)	40 (11)
Left ventricular ejection fraction (%)	51 (17)	56 (10)
Time from onset of shock (h)	2.1 (1.8)	2.8 (2.0)
Lactate (mmol litre^{-1})	2.3 (1.3)	2.2 (1.2)
Dose of norepinephrine (inter-quartile range, μg kg^{-1} min^{-1})	1.00 (0.62–3.4)	0.68 (0.18–3.2)

The plethysmographic waveform is generated by changes in blood volume in the vessels of the tissue volume that is illuminated by the red and infrared light. Hypothesizing that the amplitude of this signal is directly related to stroke volume, some authors proposed to assess the respiratory variation of stroke volume by measuring the respiratory variation of the plethysmographic 'pulse'. This plethysmographic respiratory variation was shown to correlate with PPV.[4] Several studies demonstrated that the respiratory variation of the plethysmographic curve predicts changes in cardiac output resulting from different preload manipulations, induced either by fluid loading,[5–7] passive leg raising,[22] or fluid removal.[23] These studies were mainly conducted in the perioperative setting.[6 7] More recently, PVI has been proposed as an automatic calculation of the respiratory variation of the plethysmographic signal.[8] In validation studies, PVI reliably predicted fluid responsiveness[8–10] and changes in cardiac output induced by the elevation of PEEP[24] or passive leg raising.[25] Nevertheless, most of these studies were conducted after induction of anaesthesia and before surgical intervention[8–10 24] or in healthy subjects,[25] that is, in subjects without shock and vasopressors. This different setting of investigation could explain the discrepancy between these and the present data.

Stroke volume is not the only determinant of the amplitude of the plethysmographic waveform.[26] It is also influenced by the arterial and venous distensibility[27] and by the venous pressure forward to the sample site.[28] Consequently, the respiratory variation of the plethysmographic curve might not only result from preload dependence but also from features of the local skin microcirculation. Also, the respiratory variation of plethysmographic pulse depends not only on changes in arterial blood volume but also on the slower ventilatory changes in local venous blood volume resulting from changes in venous return.[29] All these factors might be confounding when estimating stroke volume from the plethysmographic signal. Vasopressors may even worsen the relationship between stroke volume and the plethysmographic pulse, since they impact the compliance of the arterial and venous vessels at the level of measurement and the peripheral venous pressure.

Table 2 Haemodynamic variables before and after volume expansion in volume responders ($n=15$) and non-responders ($n=20$). Data are expressed as mean (SD). PVI, pleth variability index; PPV, pulse pressure variation; SVV, stroke volume variation. *$P<0.05$ *vs* responders; #$P<0.05$ *vs* before volume expansion

	Before volume expansion		After volume expansion	
	Responders	Non-responders	Responders	Non-responders
Heart rate (beats min^{-1})	99 (17)	90 (19)	96 (18)#	88 (19)
Cardiac index (litre min^{-1} m^{-2})	2.8 (0.9)	3.7 (1.3)*	3.6 (1.0)#	3.9 (1.6)#
Mean arterial pressure (mm Hg)	73 (10)	80 (14)	82 (13)#	87 (16)#
Systemic vascular resistance index (dyn s cm^{-5} m^2)	2329 (796)	1940 (737)	2053 (659)#	2007 (764)
Perfusion index (%)	1.9 (2.3)	2.5 (2.5)	2.4 (2.9)#	2.3 (2.6)
PVI (%)	18 (10)	12 (7.0)*	12 (6)#	11 (7.0)*
PPV (%)	16 (6)	6 (3.0)*	9 (4)#	6 (4.0)*
SVV (%)	17 (7)	10 (5.0)*	11 (6)#	9 (3)

In this respect, Landsverk and colleagues[30] demonstrated that the plethysmographic respiratory variation was influenced by the sympathetic activity, while PPV was not.

In contrast to PPV and SVV, PVI allowed only a weak prediction of fluid responsiveness in this specific population of patients receiving vasopressor drugs. This result is in accordance with the fact that studies reporting the worst results with pleth variability were conducted in such patients receiving vasoactive drugs[31] or undergoing major hepatic surgery.[32] Our findings are also in line with a recent study reporting that the relationship between PVI and PPV was poor in patients receiving vasopressors.[12] In contrast, our results are in discrepancy with the study by Loupec and colleagues[11] showing that PVI adequately predicted fluid responsiveness in critically ill patients receiving norepinephrine. This might be explained by the fact that the proportion of septic shock patients was lower in the latter study (55%)[11] than in ours (86%).

Independently from any failure of the plethysmographic signal to estimate stroke volume, estimation of its variation might be impaired by a poor quality of the plethysmographic signal. Again, this is more likely to occur in patients with shock, due to vasoconstriction or to peripheral oedema. Accordingly, the perfusion index was much lower in the present study than in previous ones showing a good reliability of PVI.[8 10] The plethysmographic signal was not obtainable in a significant proportion of patients. Not surprisingly, these patients received the highest dose of norepinephrine. Interestingly, vasoconstriction should lead to a dampening of the plethysmographic curve and to an underestimation of PPV by PVI while we observed some overestimations. In fact, vasopressors may not only dampen the plethysmographic signal but could also modify some determinants of PVI like ventilatory changes in local venous blood.[29] Since vasopressors can alter arterial and venous beds in a complex way, this could explain why the respiratory variation of the signal could be larger than that of PPV under norepinephrine.
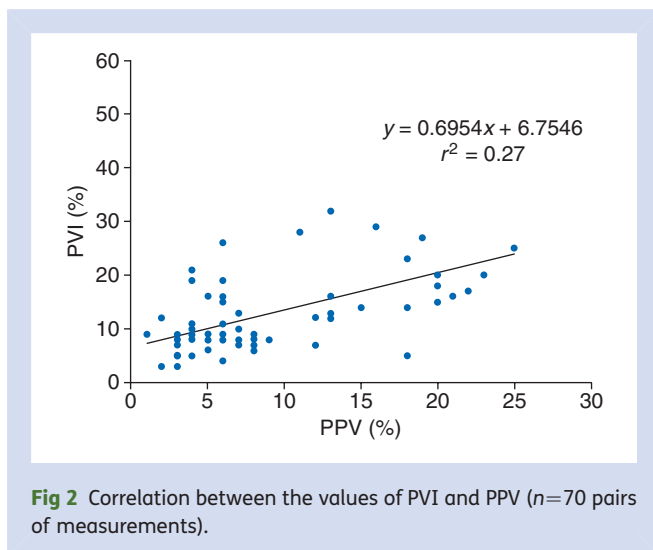

$$y = 0.6954x + 6.7546$$
$$r^2 = 0.27$$

Fig 2 Correlation between the values of PVI and PPV ($n=70$ pairs of measurements).

Table 3 Diagnostic ability of the different indices of fluid responsiveness. AUC, area under the ROC curve; PPV, respiratory variation of arterial pulse pressure; SVV, respiratory variation of stroke volume. $n=35$, mean (SD) or mean (95% confidence interval). *Not significantly different from 0.50

| Variable	AUC	Best cut-off value (%)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value (%)	Negative predictive value (%)	Youden index
PPV	0.93 (0.06)	11	93 (68–100)	95 (74–100)	17.7 (14.9–21.1)	0.1 (0.0–1.0)	93 (68–100)	95 (73–100)	0.88
SVV	0.89 (0.07)	10	93 (68–100)	90 (68–100)	9.3 (7.6–11.4)	0.1 (0.0–0.7)	88 (61–99)	95 (74–100)	0.83
PVI	0.68 (0.09)*	16	47 (21–73)	90 (68–99)	1.9 (1.2–3.0)	0.3 (0.1–1.0)	61 (38–80)	80 (52–96)	0.37
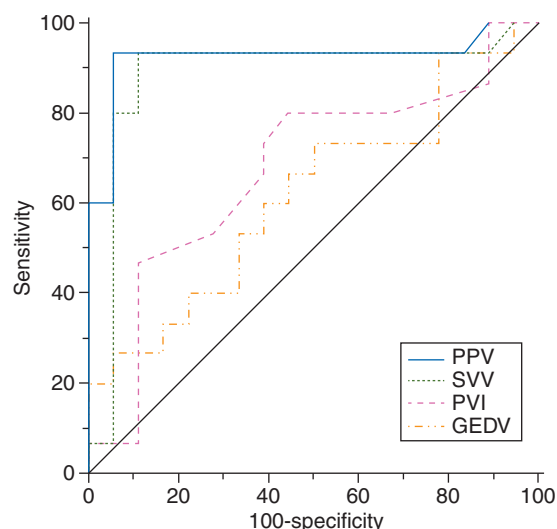
Fig 3 ROC curves describing the ability of the PPV, of the respiratory variation of pulse contour analysis-derived stroke volume (SVV), global end-diastolic volume (GEDV) and of PVI to predict an increase in cardiac index ≥15% induced by the fluid challenge (*n*=35).
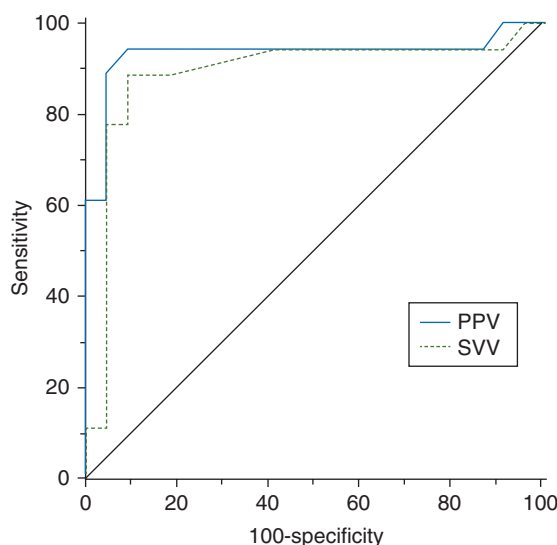

Fig 4 ROC curves describing the ability of the PPV and of the respiratory variation of pulse contour analysis-derived stroke volume (SVV) to predict an increase in cardiac index ≥15% induced by the fluid challenge when considering all patients included in the study (*n*=42).

Our results suggest that PVI is not suitable for use in critically ill patients. Also, a majority of such patients are equipped with an arterial catheter, so that fluid responsiveness can be easily predicted through PPV, SVV, and, provided that cardiac output is monitored, by passive leg raising[15] and the end-expiratory occlusion test.[13] [17] In addition, the

respiratory variation of stroke volume cannot be used in a large proportion of critically ill patients, due to spontaneous breathing activity, low tidal volume and/or respiratory system compliance, or cardiac arrhythmias.[1] These conditions apply in a large proportion of critically ill patients and hence a large proportion of patients screened for inclusion into the study were excluded. Taken together, these limitations suggest that PVI is more suitable for the operating theatre than for the intensive care unit setting. Nevertheless, even in the perioperative field, anaesthetists should be aware of the limitations of PVI in patients receiving vasopressors.

Our study has some limitations. First, since we did not analyse the plethysmography signal, we could not test whether the poor reliability of PVI was related to the failure of the PVI algorithm to calculate the true plethysmographic respiratory variation. Secondly, the severity of the patients we included in the study was very high, what may limit to generalize our results. Finally and in the same line, we included only septic patients which may limit the generalizability of our results.

In conclusion, we found that the prediction of fluid responsiveness by PVI was less reliable than PPV or SVV in patients with acute circulatory failure receiving norepinephrine. In addition, the plethysmographic signal could not be obtained in a non-negligible proportion of patients. This suggests that PVI is not useful in patients receiving vasopressors.

Declaration of interest

J.-L.T. and X.M. are members of the Medical Advisory Board of Pulsion Medical Systems.

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