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Testing preload responsiveness by the tidal volume challenge assessed by the photoplethysmographic perfusion index

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Abstract

Background To detect preload responsiveness in patients ventilated with a tidal volume (Vt) at 6 mL/kg of predicted body weight (PBW), the Vt-challenge consists in increasing Vt from 6 to 8 mL/kg PBW and measuring the increase in pulse pressure variation (PPV). However, this requires an arterial catheter. The perfusion index (PI), which reflects the amplitude of the photoplethysmographic signal, may reflect stroke volume and its respiratory variation (pleth variability index, PVI) may estimate PPV. We assessed whether Vt-challenge-induced changes in PI or PVI could be as reliable as changes in PPV for detecting preload responsiveness defined by a PLR-induced increase in cardiac index (CI) ≥ 10%.

Methods In critically ill patients ventilated with Vt = 6 mL/kg PBW and no spontaneous breathing, haemodynamic ($PICCO_2$ system) and photoplethysmographic (Masimo-SET technique, sensor placed on the finger or the forehead) data were recorded during a Vt-challenge and a PLR test.

Results Among 63 screened patients, 21 (33%) were excluded because of an unstable PI signal and/or atrial fibrillation and 42 were included. During the Vt-challenge in the 16 preload responders, CI decreased by 4.8 ± 2.8% (percent change), PPV increased by 4.4 ± 1.9% (absolute change), PI_{finger} decreased by 14.5 ± 10.7% (percent change), PVI_{finger} increased by 1.9 ± 2.6% (absolute change), $PI_{forehead}$ decreased by 18.7 ± 10.9 (percent change) and $PVI_{forehead}$ increased by 1.0 ± 2.5 (absolute change). All these changes were larger than in preload non-responders. The area under the ROC curve (AUROC) for detecting preload responsiveness was 0.97 ± 0.02 for the Vt-challenge-induced changes in CI (percent change), 0.95 ± 0.04 for the Vt-challenge-induced changes in PPV (absolute change), 0.98 ± 0.02 for Vt-challenge-induced changes in $PI_{forehead}$ (percent change) and 0.85 ± 0.05 for Vt-challenge-induced changes in PI_{finger} (percent change) ($p = 0.04$ vs. $PI_{forehead}$). The AUROC for the Vt-challenge-induced changes in $PVI_{forehead}$ and PVI_{finger} was significantly larger than 0.50, but smaller than the AUROC for the Vt-challenge-induced changes in PPV.

Conclusions In patients under mechanical ventilation with no spontaneous breathing and/or atrial fibrillation, changes in PI detected during Vt-challenge reliably detected preload responsiveness. The reliability was better when PI was measured on the forehead than on the fingertip. Changes in PVI during the Vt-challenge also detected preload responsiveness, but with lower accuracy.

Keywords Fluids, Fluid accumulation, Catecholamine, Systemic venous return, Vasodilatation

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Introduction

In patients with acute circulatory failure, after initial fluid resuscitation, fluid infusion increases cardiac output in only half of them [1]. As undue fluid infusion may contribute to fluid accumulation, the deleterious effect of which is clearly demonstrated [2], it is recommended to assess preload responsiveness before deciding to perform volume expansion [3]. For this purpose, pulse pressure variation (PPV), i.e., the change in arterial pulse pressure amplitude during mechanical ventilation which reflects the simultaneous change in stroke volume, is very reliable, but can be used in few patients because of strict conditions of use [4, 5]. Among such conditions, tidal volume (Vt) must be ≥ 8 mL/kg of predicted body weight (PBW). Indeed, reducing Vt attenuates the amplitude of the heart–lung interactions that generate PPV, creating false negatives for PPV as a marker of preload responsiveness [6].

To overcome this limitation, the Vt challenge has been described in mechanically ventilated patients [7]. It consists in transiently increasing Vt from 6 to 8 mL/kg PBW, and looking for a significant increase in PPV, reflecting that the slope of the cardiac function curve is steep. However, the Vt challenge has two limitations. First, although it has been validated by several studies, the diagnostic threshold they reported is variable [8]. Second, it requires an arterial pressure waveform, which is usually obtained by using an arterial catheter.

The photoplethysmography signal may be helpful in dispensing with the need for an arterial catheter. This signal is composed of a pulsatile portion and a non-pulsatile portion [9]. The ratio of the amplitude of the former to the latter, called the "perfusion index" (PI), has two determinants: the degree of vasoconstriction of the tissue in which the oxygen saturation of haemoglobin is measured, and stroke volume [9]. Thus, over short time periods, changes in PI may reflect changes in stroke volume, as shown during fluid loading [10, 11], passive leg raising (PLR) [10, 11], recruitment manoeuvres [12] and the end-expiratory occlusion test [11]. Also, the change in PI under mechanical ventilation, called "pleth variability index" (PVI), has been used as a surrogate of PPV [13]. PVI has been shown to detect preload responsiveness [14], while opposite results have been recorded in critically ill patients receiving norepinephrine [15]. To overcome this possible limitation of PVI due to vasoconstriction, it has been proposed to attach the photoplethysmography sensor to the forehead or the earlobe rather than to the finger [16]. It has not yet been tested whether the changes in PI or PVI could be used to assess the effects of the Vt challenge. If changes in PI and PVI actually reflect cardiac index and PPV changes, respectively, PI should decrease more and PVI should increase more during a Vt challenge in preload responders than in preload non-responders. This would allow one to perform the test without any arterial catheter.

Therefore, the primary goal of this study was to assess the ability of PI changes induced by a Vt challenge to diagnose preload responsiveness in critically ill adult patients. The secondary aims were (i) to test whether Vt-challenge-induced changes in PVI reliably diagnose preload responsiveness, (ii) to compare this diagnostic value of changes in PI and PVI according to the location of photoplethysmographic measurement (finger vs. forehead) and (iii) to compare the changes in PPV, PVI and PI during a PLR test and volume expansion.

Patients and methods

This prospective study was conducted in the 25-bed medical intensive care unit (ICU) of the Bicêtre hospital (Assistance publique-Hôpitaux de Paris). It was approved by the ethics committee of the French Intensive Care Society (SC016-18). All patients or their next of kin were informed about the study and agreed to participate. The study was registered on ClinicalTrials (NCT05428423). Note that the primary goal, which was to test whether Vt-challenge-induced changes in PVI reliably diagnose preload responsiveness has been changed for testing Vt-challenge-induced changes in PI.

Patients

Patients were included if they presented the following criteria: (i) age ≥ 18 y.o., (ii) hospitalization in the ICU, (iii) invasive mechanical ventilation in assist controlled mode with a Vt of 6 mL/kg PBW, (iv) monitoring already in place with a transpulmonary thermodilution $PICCO_2$ system (Pulsion Medical Systems, Getinge, Feldkirchen, Germany) and with a photoplethysmography Masimo SET device (Masimo Corporation, Irvine, CA) and (v) decision by the clinicians in charge to assess preload responsiveness through a Vt challenge and a PLR test.

Patients were excluded if (i) they presented spontaneous breathing activity, as assessed by visual observation of the airway pressure curve, (ii) they presented atrial fibrillation or frequent extrasystoles, because these conditions are responsible for an unstable PI signal (low signal-over-noise ratio) [10], (iii) the PI signal on the fingertip was unstable, as defined in the supplementary material, (iv) chest drainage was in place, and (v) they were pregnant. Patients were not included if they refused to participate in the study, and if the investigators were not available.

Measurements

All patients were equipped with an internal jugular venous catheter and a thermistor-tipped arterial catheter

introduced through the femoral artery. Cardiac output was measured by pulse contour analysis and transpulmonary thermodilution [17]. For the latter, three injections of cold saline boluses were averaged [18]. Intra-abdominal pressure was measured through bladder pressure [19]. Arterial, central venous and airway pressures were continuously recorded by HEM3.2 software (Notocord, Croissy-sur-Seine, France). Data from the $PICCO_2$ device, including cardiac index (CI), arterial and central venous pressures and PPV were continuously recorded by PICCOWin software (Pulsion Medical Systems, Getinge, Feldkirchen, Germany).

A photoplethysmography sensor (Masimo Corporation, Irvine, CA) was placed on the index finger of either hand and another one on the forehead and connected to the Masimo SET device to measure pulse oxygen saturation, PI and PVI. The forehead sensor was sticked to the forehead and held by a compressive band provided with the device. Data were extracted a posteriori through a USB stick and analysed on an Excel spreadsheet (Microsoft, Richmond, CA). PI values were averaged over a 25-s moving period. Among ventilatory data, we collected Vt, respiratory rate, and plateau and positive end-expiratory pressures.

Study design

Once the patient was included in the study, demographic and ventilatory data were collected, the $PICCO_2$ device was calibrated and a first set of haemodynamic and photoplethysmography data was recorded. A Vt challenge was then performed. Vt was increased from 6 to 8 mL/kg PBW for one minute [7]. At the end of the challenge, haemodynamic data (including pulse contour analysis-derived CI) and photoplethysmography data were recorded. Vt was then lowered to 6 mL/kg PBW.

After the Vt challenge, once CI had returned to its baseline value, a PLR test was performed as previously described [20]. Briefly, while the patient was initially in a semi-recumbent position at 30–45°, the bed was brought to a position in which the trunk was horizontal and the lower limbs elevated at 30–45°, thanks to the automatic movement of the bed. When pulse contour analysis-derived CI was stable, i.e., within one minute, haemodynamic data (including pulse contour analysis-derived CI) and photoplethysmography data were collected. The bed was then returned to its baseline semi-recumbent position at 30–45°. Transpulmonary thermodilution was performed again, and haemodynamic and photoplethysmography data were recorded. Finally, if the clinicians in charge decided to perform volume expansion, haemodynamic and photoplethysmography data were recorded, and immediately after, a 500 mL bolus of 0.9% saline was infused over 15 min. Immediately after volume expansion, a final transpulmonary thermodilution measurement was performed, and all haemodynamic data (including thermodilution-derived CI) and photoplethysmography data were recorded.

Statistical analysis

Data distribution was assessed visually. Discrete numerical data were presented as numbers, continuous numerical data as median and interquartile range or mean ± SD, while categorical numbers were presented as number and percentage.

The comparison between different study times was performed with a paired Student's t test or a Wilcoxon test. Comparisons between patient groups were performed by an unpaired Student's t test or a Mann–Whitney U test. We assessed association between selected variables using repeated measures correlation techniques. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of changes in PI, PPV, and CI induced by a Vt challenge to detect preload responsiveness, defined by a $\geq 10\%$ increase in CI during PLR. The diagnostic threshold was selected as the threshold providing the best Youden index. Comparison of the areas under the ROC curves for multiple measurements (AUROCs) was carried out with the Hanley-McNeil test. Grey zones were calculated using the method defining three levels of response: positive, uncertain, and negative. Uncertain responses were defined using a two-step procedure. We first calculated the 95% CI of the Youden's index resulting from a 1000 population bootstrap [21]. Then, we determined cut-off values for a sensitivity < 90% or a specificity < 90% (diagnosis tolerance of 10%). The largest interval from these two steps was used to determine the grey zone [21].

By estimating that the difference in PVI changes induced by the Vt challenge between preload responders and non-responders would be 4% [15], that the standard deviation of PVI changes would be 5% in responders and 2% in non-responders [15], considering an α risk of 5% and a β risk of 10%, we estimated that 42 patients should be included in the study. All tests were bilateral. A p value < 0.05 was considered significant. Statistical analysis was performed with MedCalc 20.218 software (MedCalc software Ltd., Mariakerke, Belgium).

Results

Sixty-three patients were screened between September 2022 and June 2023, of whom 14 were excluded because of an unstable PI signal on the fingertip and 7 because of atrial fibrillation. Their characteristics are shown in Supplemental Table 1. The baseline characteristics of the 42 included patients are summarized in Table 1 and Supplemental Table 2.

Table 1 Patient characteristics in preload responsive and non-responsive patients

	All patients (n = 42)	Preload responders (n = 16)	Preload non-responders (n = 26)	*p* value
Age (years)	62 ± 10	67 ± 10	59 ± 10	0.02
Sex (M/F)	32(76%)/10(23%)	10(63%)/6(37%)	22(85%)/4(15%)	0.11
SAPS II	55 ± 16	60 ± 15	51 ± 17	0.08
SOFA	15 ± 2	15 ± 2	14 ± 2	0.61
Lactate (mmol/L)	2.8 [1.7–3.6]	3.3 [2.3–4.5]	2.7 [1.8–3.7]	0.33
Richmond agitation sedation scale	− 3.9 ± 0.6	− 3.8 ± 0.6	− 4.0 ± 0.5	
Echocardiographic LV ejection fraction (%)	40 ± 8	38 ± 7	41 ± 8	0.51
Origin of shock				
Septic	38 (90.5%)	16 (100%)	22 (84.6%)	0.11
Hypovolaemic	1 (2.4%)	0	1 (3.8%)	0.42
Cardiogenic	1 (2.4%)	0	1 (3.8%)	0.42
Vasoplegic non-septic	2 (4.8%)	0	2 (7.7%)	0.29
Norepinephrine infusion	42 (100%)	16 (100%)	26 (100%)	
Dose of norepinephrine (µg/kg/min)	0.59 [0.29–1.09]	0.67 [0.30–1.09]	0.46 [0.24–0.82]	0.32
Vasopressin infusion	3 (7%)	2 (13%)	1 (4%)	0.29
ARDS	27 (64%)	9 (56%)	18 (69%)	0.40
Vt (mL/kg PBW)	5.0 ± 0.5	4.7 ± 0.4	5.1 ± 0.5	0.01
Respiratory rate (breaths/min)	25 ± 4	24 ± 4	26 ± 3	0.14
Plateau pressure (cmH_2O)	20 ± 4	19 ± 4	21 ± 4	0.11
PEEP (cmH_2O)	10 ± 2	10 ± 2	10 ± 2	0.52
PaO_2/FiO_2 (mmHg)	205 ± 105	189 ± 98	214 ± 110	0.44
GEDVI (mL/m^2)	732 ± 168	716 ± 135	743 ± 188	0.62
EVLWI (mL/kg PBW)	11 ± 4	10 ± 3	12 ± 4	0.09
PVPI	2.0 ± 0.8	1.9 ± 0.6	2.3 ± 0.8	0.10

Values are expressed as n (%), mean ± SD or median [interquartile range]

ARDS acute respiratory distress syndrome, *EVLWI* extravascular lung water indexed for body weight, *GEDVI* global end-diastolic volume indexed for body surface, *ICU* intensive care unit, *LV* left ventricular, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, PaO_2/FiO_2 oxygen arterial partial pressure over inspired fraction of oxygen, *PVPI* pulmonary vascular permeability index, *SAPS* simplified acute physiologic score, *SOFA* sequential organ failure assessment, *Vt* tidal volume

Effects of PLR and volume expansion

Changes in haemodynamic variables are shown in Table 2. In the 16 preload responders (38%), PLR increased CI by 16.9 ± 6.5%, while it did not change significantly during PLR in the 26 preload non-responders. During PLR in preload responders, PPV decreased in absolute value (PPV during the PLR test—PPV before the PLR test) by 3.5 ± 2.3%. During PLR in preload responders, PI measured on the finger increased by 0.09 ± 0.04 (absolute change) and by 25.8 ± 21.6% (percent change), PVI measured on the finger decreased by 0.3 ± 1.4% (absolute change). All these changes except changes in PVI were larger than those observed during the PLR test in preload non-responders. Results from measurements performed on the forehead during PLR are shown in Table 2.

Volume expansion was performed in four of the preload responsive patients. It increased CI by 21 ± 5%. In all these patients, the PLR test had increased CI changes by ≥ 10%. The changes in other haemodynamic variables during volume expansion are shown in Table 2.

Ability of PI changes to reflect CI changes, and of PVI to reflect PPV absolute values

Taking all the changes measured between different study times (n = 88), the coefficient of correlation between changes in CI and in PI was 0.83 (0.67; 0.91) ($p < 0.001$) when measured on the forehead and 0.76 (0.57; 0.87) ($p < 0.001$) when measured on the finger (Supplementary Figs. 1 and 2). Taking all the measurements performed at different study times (n = 214), the coefficient of correlation between PVI measured on the forehead and PPV absolute values was 0.35 (0.16; 0.51) ($p < 0.001$) (Supplementary Fig. 3).

Effects of the Vt challenge

The value of CI at Baseline 2 was not different from Baseline 1, in preload responders ($p = 0.77$) as in

Table 2 Haemodynamic and photoplethysmography variables at different study times in preload responsive and non-responsive patients

	Baseline 1	Vt challenge	Baseline 2	PLR	Baseline 3	After volume expansion[a]
Heart rate (beats/min)						
Preload responders (n = 16)	93 ± 15	93 ± 16	95 ± 17	93 ± 18*	87 ± 17	81 ± 16
Preload non-responders (n = 26)	86 ± 16	85 ± 16	84 ± 16*	82 ± 16		
Systolic arterial pressure (mmHg)						
Preload responders (n = 16)	118 ± 22	117 ± 23	112 ± 16	124 ± 20*	118 ± 36	127 ± 37
Preload non-responders (n = 26)	126 ± 22	125 ± 24	130 ± 26#	134 ± 28*		
Mean arterial pressure (mmHg)						
Preload responders (n = 16)	77 ± 13	76 ± 14	71 ± 7	81 ± 9*	74 ± 22	84 ± 25*
Preload non-responders (n = 26)	81 ± 20#	82 ± 21	85 ± 22#	83 ± 28*		
Diastolic arterial pressure (mmHg)						
Preload responders (n = 16)	57 ± 11	57 ± 11	55 ± 7	62 ± 10*	56 ± 14	62 ± 1*
Preload non-responders (n = 26)	63 ± 11	63 ± 12	64 ± 10#	67 ± 10		
Central venous pressure (mmHg)						
Preload responders (n = 16)	8 ± 5	9 ± 5	9 ± 5	12 ± 5*	7 ± 2	11 ± 6
Preload non-responders (n = 26)	11 ± 4	12 ± 4*	11 ± 3.62	13 ± 4.33*		
PPV (%)						
Preload responders (n = 16)	9 ± 7	13 ± 8*	12 ± 6	10 ± 8*	13 ± 9	10 ± 10*
Preload non-responders (n = 26)	9 ± 7	10 ± 8*	6 ± 5#	6 ± 5		
Cardiac index (L/min/m^2)						
Preload responders (n = 16)	2.54 ± 0.71	2.42 ± 0.70*	2.38 ± 0.75	2.77 ± 0.82*	2.12 ± 0.44	2.57 ± 0.54*
Preload non-responders (n = 26)	2.98 ± 0.89	2.91 ± 0.89 *	3.08 ± 0.99#	3.14 ± 1.10		
PI (%)						
Preload responders (n = 16)	0.44 ± 0.25	0.38 ± 0.23*	0.41 ± 0.21	0.49 ± 0.23*	0.47 ± 0.32	0.59 ± 0.41
Preload non-responders (n = 26)	1.47 ± 1.83#	1.45 ± 1.78#	1.84 ± 1.93#	1.81 ± 2.02*#		
PVI (%)						
Preload responders (n = 16)	16 ± 8	17 ± 8	20 ± 8	17 ± 6	18 ± 2	11 ± 5
Preload non-responders (n = 26)	15 ± 13	15 ± 12	16 ± 12	16 ± 11		

Values are expressed as mean ± SD

PI perfusion index, *PPV* pulse pressure variation, *PVI* pleth variability index

[a] performed in 4 preload responders

* $p < 0.05$ vs. Baseline

# $p < 0.05$ vs. Preload responders

preload non-responders ($p = 0.22$). During the Vt challenge, CI decreased by 4.8 ± 2.8% in preload responders and by 2.3 ± 2.6% in preload non-responders ($p < 0.001$) (Table 2). Simultaneously, in preload responders, PPV increased by 4.4 ± 1.9% (absolute change), PI measured on the finger decreased by 0.07 ± 0.04 (absolute change) and 14.5 ± 10.7% (percent change), PVI measured on the finger increased by 1.9 ± 2.6% (absolute change), PI measured on the forehead decreased by 18.7 ± 10.9 (percent change) and PVI measured on the forehead increased by 1.0 ± 2.5 (absolute change). All these changes were significantly larger than in preload non-responders. The changes in other variables are shown in Table 2.

Detection of preload responsiveness

The ability of the changes in the variables investigated during PLR and the Vt challenge to detect preload responsiveness defined by a PLR-induced increase in CI ≥ 10% is described in Table 3 and Fig. 1. The AUROCs generated by the Vt-challenge-induced changes in PI measured on the forehead were significantly larger than the Vt-challenge-induced changes in PI measured on the finger. Compared to the AUROCs generated by the Vt-challenge-induced changes in PPV and in PI measured

Table 3 Ability of tidal volume challenge-induced and passive leg raising-induced changes in haemodynamic variables to detect preload responsiveness

	AUROC	*p* value vs. 0.5	Diagnostic threshold	Se	Sp	PPV	NPV	+LR	−LR
PLR-induced changes in $PI_{(finger)}$ (% change)	0.84 ± 0.08	**0.001**	> 18%	54.55	100.00	100.00	78.30	–	0.45
PLR-induced changes in $PI_{(forehead)}$ (% change)	0.95 ± 0.05	**< 0.001**	> 12%	90.00	94.12	90.00	94.10	15.30	0.11
PLR-induced changes in PPV (abs. change)	0.98 ± 0.02	**< 0.001**	≤ − 2 points	90.91	100.00	100.00	95.20	–	0.09
PLR-induced changes in $PVI_{(finger)}$ (abs. change)	0.60 ± 0.12	0.41	< − 2 points	0.00	100.00	–	66.70	–	1.00
PLR-induced changes in $PVI_{(forehead)}$ (abs. change)	0.53 ± 0.15	0.86	≤ − 2 points	28.57	94.44	66.70	77.30	5.14	0.76
Vt-challenge-induced changes in CI (% change)	0.97 ± 0.02	**< 0.001**	≤ − 3%	86.00	100.00	100.00	92.60	–	0.13
Vt-challenge-induced changes in $PI_{(finger)}$ (% change)	0.86 ± 0.06	**< 0.001**	≤ − 7%	75.00	88.00	80.00	84.60	6.25	0.28
Vt-challenge-induced changes in $PI_{(forehead)}$ (% change)	0.98 ± 0.02	**< 0.001**	≤ − 9%	86.67	95.83	92.90	92.00	20.80	0.14
Vt-challenge-induced changes in PPV (abs. change)	0.95 ± 0.04	**< 0.001**	> 2 points	87.50	96.15	93.30	92.60	22.75	0.13
Vt-challenge -induced changes in $PVI_{(finger)}$ (abs. change)	0.74 ± 0.08	**0.007**	> 1 point	53.33	91.67	80.00	75.90	6.40	0.51
Vt-challenge -induced changes in $PVI_{(forehead)}$ (abs. change)	0.62 ± 0.12	0.32	> 1 point	40.00	95.65	80.00	78.60	9.20	0.63

AUROC values are presented as value ± SE (standard error)

P values < 0.05 are indicated in bold

+*LR* positive likelihood ratio, −*LR* negative likelihood ratio, *AUROC* area under the receiver operating characteristic curve, *CI* cardiac index, *NPV* negative predictive value, *PLR* passive leg raising, *PPV* positive predictive value, *PI* perfusion index, *PVI* pleth variability index, *Se* sensitivity, *Sp* specificity, *Vt* tidal volume

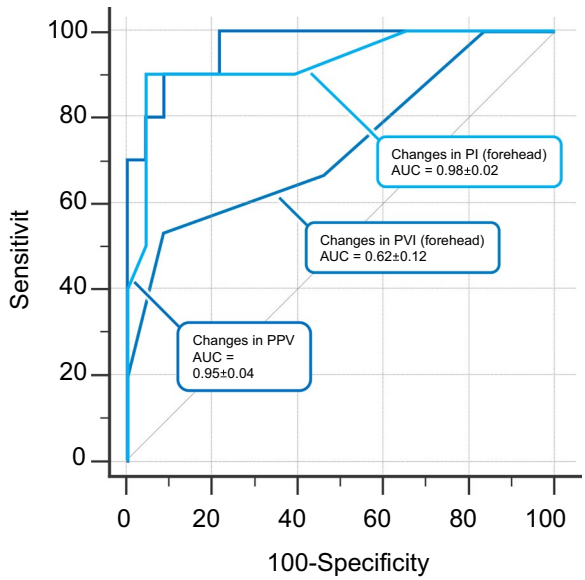

Fig. 1 Receiver operating characteristics curves describing the ability to detect preload responsiveness of the tidal-volume-challenge-induced changes in pulse pressure variation (PPV, change in absolute value), in the pleth variability index measured on the forehead (PVI, change in absolute value) and in the perfusion index measured on the forehead (PI, change in percent)

on the forehead, the AUROCs generated by the PLR-induced changes in PVI (finger and forehead) were significantly smaller, while the other AUROCs were similar (Table 3). The grey zone for the Vt-challenge-induced changes in PI on the forehead to detect preload responsiveness ranged between − 3% and − 4%, in which 2 (5%) patients were situated (Supplementary Fig. 4).

Discussion

This study conducted in critically ill adult patients showed that the Vt challenge can detect preload responsiveness, as assessed by the PLR test, when performed by assessing the changes in PI. It is less reliable when assessing the changes in PVI. The study also confirms that preload responsiveness can be diagnosed by measuring the effects of PLR on PPV and PI. Conversely, the PLR-induced changes in PVI do not distinguish preload responsive from preload unresponsive patients. Placing the photoplethysmography sensor on the forehead improved the diagnostic ability of PI changes compared to placing the sensor placed on a finger.

The Vt challenge has been described as a test that overcomes the limitation of PPV in patients ventilated with a Vt value at 6 mL/kg PBW, which generates false negatives for PPV as a marker of preload responsiveness [6, 22, 23]. A significant increase in PPV while Vt is transiently increased to 8 mL/kg reflects that the slope of the cardiac function curve is steep, predicting preload responsiveness. An advantage of the test is that it requires only a PPV measurement, i.e., it can be performed even if no direct cardiac output measurement is available. However, PPV requires an arterial catheter or a specific device

providing the arterial curve non-invasively ("volume clamp" method).

As the ratio of the pulsatile and non-pulsatile portions of the photoplethysmography signal, PI has stroke volume as a determinant, among others. It has been shown to assess changes in CI induced by fluid loading [24, 25] and various tests of preload responsiveness [10–12]. The present study shows that this is also the case for the Vt challenge. Vt-challenge-induced changes in PI detected preload responsiveness, defined by a positive PLR test, with a large AUROC and a narrow grey zone. This result was not obvious before the study, as the changes in CI induced by the Vt challenge are small, and the PI signal may have been unable to detect such small variations. This raises the possibility of performing the Vt challenge without any arterial pressure curve, for instance, before an arterial line is in place, in the operating setting in which no arterial catheter will be inserted, or in low-resource settings. Our study also shows that the Vt-challenge-induced decrease in CI measured by pulse contour analysis was excellent for detecting preload responsiveness. The diagnostic threshold was small, but it was larger than the least significant change of the measurement of CI by pulse contour analysis [10, 26].

Importantly, a significant proportion of patients were excluded from analysis because of an unstable PI signal despite a 25 s averaging period. This limitation was observed in previous studies performed in the ICU [11]. In contrast, it was absent in a study that tested PI changes to reflect changes in stroke volume during lung recruitment manoeuvres in the operating room setting, where the baseline value of PI was higher because of a lower degree of vasoconstriction [12]. Indeed, in the present study, the PI value of patients in whom PI was unstable was low, likely explaining a high noise-to-signal ratio. Also, we excluded patients with cardiac arrythmias, which are also responsible for PI instability because of high noise-over-signal ratio [11]. Technical improvements may fix these instability problems, which limit the clinical applicability of our results in ICU patients. In the included patients, the PI changes were relatively small, but they were larger than the least significant change of PI and the grey zone of the Vt challenge-induced changes in PI was low. In our patients, in whom the dose of norepinephrine was fairly high, the diagnostic ability of the Vt-challenge-induced changes in PI was better when measured on the forehead than on the fingertip. Indeed, it has already been suspected that the influence of vasoconstriction is less when the photoplethysmography sensor is placed on the forehead than on the finger. The finger walls of the cutaneous vessels are richly innervated by alpha-adrenoceptors, and more sensitive to vasoconstriction than other areas of the body [27].

In the initial study describing the test, the haemodynamic effects of the Vt challenge were assessed not on stroke volume, but on PPV. This was based on the principle that if the 2 mL/kg-increase in Vt increases the degree of preload responsiveness, both ventricles are likely working in the steep part of the cardiac function curve. Based on the same principle, the decrease in PPV induced by a PLR test [28–30] or a PEEP test [30] also detects preload responsiveness. However, in the present study, changes in PVI induced by the Vt challenge or by PLR were unreliable in detecting preload responsiveness. This inability of PVI to correctly estimate PPV has been previously described, especially in studies conducted in critically ill patients [15]. This could, again, be linked to the instability of the PI signal. We do not know the method used by the manufacturer to calculate PVI from PI. It is possible that this method does not solve the problem of PI instability, as we did by averaging the latter variable over 25 s. This could explain why preload responsiveness is detected correctly by the Vt challenge-induced changes in PI but not by those in PVI, which at first glance might seem surprising.

Our study has some limitations. First, we defined preload responsiveness using the effects on CI of PLR and not of fluid administration. We thought it was unethical to administer a fluid bolus even in the presence of preload responsiveness in critically ill patients—including some with ARDS—in whom an increased fluid balance is an independent risk factor of mortality [31]. Nevertheless, PLR has proven to be very reliable in predicting fluid responsiveness [32] and was used in previous studies to define preload responsiveness [11, 28, 30, 33]. Accordingly, among the patients with a positive PLR test and who received fluid, all were fluid responsive. Second, our study included critically ill patients which, as stated above, may have decreased the ability of PVI to estimate PPV [15]. Third, we could not analyse the PVI signal, which was extracted directly from the Radical7 device, so that we cannot explain its poor reliability in estimating PPV.

Conclusions

We found that in mechanically ventilated patients without spontaneous breathing and/or atrial fibrillation, changes in PI but not changes in PVI during a Vt challenge accurately detected preload responsiveness. PI changes were more reliable when PI was measured on the forehead rather than on the finger.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05085-w.

Additional file1 (DOCX 283 KB)

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None.

Author contributions
C.B., C.L. and X.M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: C.B. and X.M., with advice from all authors. Acquisition of data: C.B., R.S, D.R., G.F. and J.H. Analysis or interpretation of data: C.B., K.D., T.P. and X.M. Drafting of the manuscript: C.B. and X.M. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: C.B., T.P. and X.M. Administrative, technical, or material support: C.B., and X.M. Supervision: X.M.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
ClinicalTrial.gov (NCT05428423). The trial protocol was approved by the ethics committee of the French Intensive Care Society (SC016-18) and registered on ClinicalTrials (NCT05428423). Informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. Alternatively, deferred informed consent was obtained from patients. The current study was performed in accordance with French law and the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
X.M. is a member of the Medical Advisory Board of Pulsion Medical Systems (Getinge) and received honoraria for lectures from Pulsion Medical Systems (Getinge), Baxter and AOP health. J-L.T. is a member of the Medical Advisory Board of Pulsion Medical Systems (Getinge). The other authors have no conflict of interest to disclose.

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