Research Square

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Do Changes in Pulse Pressure Variation and Inferior Vena Cava Distensibility During Passive Leg Raising and Tidal Volume Challenge Detect Preload Responsiveness in Case of Low Tidal Volume Ventilation?

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Abstract

Background

In patients ventilated with tidal volume (Vt) <8 mL/kg, pulse pressure variation (PPV) and, likely, the distensibility of the inferior vena cava diameter (IVCV) are unable to detect preload responsiveness. In this condition, passive leg raising (PLR) could be used but it requires a measurement of cardiac output. The tidal volume (Vt) challenge (PPV changes induced by a 1-min increase in Vt from 6 to 8 mL/kg) is another alternative, but it requires an arterial line. We tested whether, in case of Vt=6mL/kg, the effects of PLR could be assessed through changes in PPV or in IVCV rather than changes in cardiac output, and whether the effects of the Vt challenge could be assessed by changes in IVCV rather than changes in PPV.

Methods

In 30 critically ill patients without spontaneous breathing and cardiac arrhythmias, ventilated with Vt=6 mL/kg, we measured cardiac index (CI) (PiCCO2), IVCV and PPV before/during a PLR test and before/during a Vt challenge. A PLR-induced increase in CI ≥10% defined preload responsiveness.

Results

At baseline, IVCV was not different between preload responders (n=15) and non-responders. Compared to non-responders, PPV and IVCV decreased more during PLR (by -38±16% and -26±28%, respectively) and increased more during the Vt challenge (by 64±42% and 91±72%, respectively) in responders. ΔPPV_{PLR}, expressed either as absolute or percent relative changes, detected preload responsiveness (area under the receiver operating curve, AUROC: 0.98±0.02 for both). $\Delta IVCV_{PLR}$ detected preload responsiveness only when expressed in absolute changes (AUROC: 0.76±0.10), not in relative changes. ΔPPV_{Vt}, expressed as absolute or percent relative changes, detected preload responsiveness (AUROC: 0.98±0.02 and 0.94±0.04, respectively). This was also the case for $\Delta IVCV_{Vt}$ but, the diagnostic threshold (1 point or 4%) was below the least significant change of IVCV (9[3-18]%).

Conclusions

During mechanical ventilation with Vt=6 mL/kg, the effects of PLR can be assessed by changes in PPV. If IVCV is used, it should be expressed in percent and not in absolute changes. The effects of the Vt challenge can be assessed on PPV, but not on IVCV, since the diagnostic threshold is too small with regards to the reproducibility of this variable.

Trial registration

IDRCB: 2016-A00893-48

Introduction

The oldest and most investigated way to predict fluid responsiveness before fluid infusion during acute circulatory failure consists in measuring the respiratory variation in arterial pulse pressure (pulse pressure variation, PPV) and in stroke volume (stroke volume variations, SVV) during mechanical ventilation [1-2-3-4]. Nevertheless, PPV and SVV are limited because of the fact that many clinical conditions affect their reliability. In particular, if tidal volume (Vt) is ≤8 mL/kg, which is today a very common condition, many false negatives to these tests are to be deplored because the changes in cardiac loading conditions during ventilation are too small [3-5]. The respiratory variation of the diameter of the inferior vena cava (IVCV) is also often used. Nevertheless, for the same reason as PPV and SVV, it should suffer from some false negatives in case of low Vt, even though this has been suggested by one study only [6] (see Supplementary Table 1).

To overcome this limitation of PPV, some authors suggested to correct PPV by the respiratory changes in oesophageal pressure [7], which is however not commonly measured. Two easier and more applicable tests may be used for the same purpose. The first is passive leg raising (PLR). However, this test requires a direct measurement of cardiac output [8], which is not available in many conditions. Nevertheless, it is intuitively possible that a decrease in PPV or IVCV themselves during PLR, indicates the presence of preload responsiveness (Supplementary figure 1). This has not been investigated yet.

Another means to predict preload responsiveness in case of low Vt is to perform a “Vt challenge” [9]. It consists in transiently increasing Vt from 6 to 8 mL/kg of predicted body weight and observing the induced changes in PPV. A significant increase in PPV during a Vt challenge indicates the presence of preload responsiveness at a Vt of 6 mL/kg [10]. Nevertheless, assessing PPV requires an invasive catheter or a sophisticated and expansive non-invasive monitor [11]. An alternative for assessing the effects of the Vt challenge might be to look at the changes in IVCV, whose assessment only requires transthoracic echocardiography. This has not been investigated either.

Then, the primary goal of this study was to investigate if the effects of PLR on PPV (ΔPPV_{PLR}) and on IVCV ($\Delta IVCV_{PLR}$) accurately detect preload responsiveness when Vt is low. The secondary goals were (1) to test whether the effect of a Vt challenge on IVCV ($\Delta IVCV_{Vt}$) could detect preload responsiveness and (2) to confirm that IVCV does not do so in case of Vt at 6 mL/kg.

Patients And Methods

Patients

This prospective, observational, one-centre study was carried out in the 25-bed medical intensive care unit of a university hospital. It has been approved by our institutional review board (Comité pour la protection des personnes Ile-de-France VII). All patients or their relatives gave informed consent.

The screening criteria were age ≥18 years, a transpulmonary thermodilution device in place (PiCCO2, Pulsion Medical Systems, Feldkirchen, Germany), mechanical ventilation in the volume assist control mode with a Vt of 6 mL/kg of predicted body weight, and the decision taken by the clinicians in charge to perform volume expansion.

Patients were excluded if the PLR manoeuvre was contra-indicated (intracranial hypertension) or possibly unreliable (venous compression stocking, intra-abdominal hypertension [12]). Other exclusion criteria were spontaneously triggered cycles on the airway pressure waveform, cardiac arrhythmias, impossibility to obtain haemodynamic stability (defined by no change in the norepinephrine dose and no change in systolic arterial pressure <10% within 5 minutes before the inclusion), poor echogenicity impeding the measurement of the IVC diameter and of the velocity time integral (VTI) in the left ventricular outflow tract.

Echocardiographic measurements

IVC sonography was performed by one 4-year experienced intensivist (TT), who holds a university degree in echocardiography. With the 3.5-MHz cardiovascular ultrasound probe of a Philips CX 50 device (Philips ultrasound system, Philips Healthcare, DA Best, The Netherlands), the IVC was examined in the subcostal window in longitudinal section. Its diameter was measured in M-mode coupled with two-dimensional mode and zoom; 2 cm upstream of the origin of the hepatic veins. Measurements were validated when the M-mode tracing was exactly perpendicular to the IVC.

The distensibility index of the IVC, which reflects the increase in its diameter on insufflation, was calculated as IVCV = (maximum diameter on inspiration - minimum diameter on expiration)/mean of maximum and minimum diameters [13].

The VTI was measured at end-expiration in the left ventricular outflow tract on the apical five-chamber window. On the apical four-chamber view, the left ventricular ejection fraction was calculated by the biplane method of disks summation (modified Simpson's rule). The average of three consecutive cardiac cycles was used for all ultrasound measurements in case of sinus rhythm and a representative cardiac cycle was chosen in case of atrial fibrillation [8]. Endocardial contours and VTI envelope were hand drawn. Measurements were analysed offline, blinded to the patient's response to the PLR test.

Haemodynamic measurements

All patients had a central venous catheter in the superior vena cava territory and a thermistor-tipped catheter inserted through the femoral artery, as required by the PICCO2 device. Transpulmonary thermodilution measurements were performed by the injection of 15-mL boluses of cold normal saline (<8°C) through the central venous catheter. The average result from three consecutive 15-mL injections was recorded at each time point [14] and was used to obtain CI, the global end-diastolic volume (marker of cardiac preload) and the cardiac function index (estimate of the left ventricular ejection fraction) [4]. Pulse contour analysis allowed the continuous and real-time calculation of CI after an initial calibration by thermodilution [15].

The intra-abdominal pressure was estimated from the bladder pressure, which was measured after the instillation of 25 mL of normal saline. The measurement was performed at end-expiration in the absence of abdominal muscle contractions. The transducer was zeroed and placed at the pubic symphysis [12].

Study design

At baseline, all patients were in the 45° semi recumbent position (Supplementary figure 2). A first set of thermodilution and echocardiographic measurements was performed, including CI (measured by thermodilution), PPV, SVV and IVCV. Then, we performed a PLR test as previously described [16]. Pulse contour analysis–derived CI, PPV, stroke volume variation (SVV) and IVCV were recorded at the maximal effect of PLR on CI, which occurs within one minute [14] (Figure 2). A third set of measurements (CI (pulse contour analysis), PPV, SVV and IVCV) was performed once patients were returned to the semi-recumbent position and a steady state was obtained again.

A "Vt challenge" was then performed by increasing Vt from 6 to 8 mL/kg of predicted body weight for one minute [17]. A fourth set of measurements (CI (pulse contour analysis), PPV, SVV and IVCV) was recorded once CI remained stable. Vt was then decreased back to 6 mL/kg of predicted body weight and another set of measurements was performed after a new stable state was reached, including CI (thermodilution), PPV, SVV and IVCV. Finally, in preload responsive patients, 500 mL of normal saline were infused over 10 minutes. In these patients, a last set of measurements was recorded after the end of fluid infusion (CI (thermodilution), PPV, SVV and IVCV).

Except Vt, ventilatory settings and treatments were unchanged during the study period. The intrabdominal pressure and the central venous pressure were measured at each study step. The CI measured by transpulmonary thermodilution and pulse contour analysis was continuously recorded by the PiCCO Win 4.0 software (Pulsion Medical Systems). The intravascular, intra-abdominal and airway pressure signals were continuously recorded by using a data acquisition software (HEM 4.2, Notocord, Croissy-sur-Seine, France).

Statistical analysis

Patients in whom PLR, performed at Vt = 6 mL/kg, induced an increase in CI (measured by pulse contour analysis) by more than 10%, were defined as preload responders. Variables were summarised as mean ± SD, median and interquartile range or counts and percentages. Variables before and after fluid administration were compared by a paired Student t-test or a Wilcoxon test. Variables between preload responders and non-responders were compared using a two-sample Student t-test, a Mann-Whitney U-test, a Chi-2 test or a Fisher exact test, as indicated.

Receiver operating characteristic (ROC) curves (with 95% confidence interval, CI) were generated for quantifying the ability of the following variables to detect preload responsiveness: 1) IVCV, PPV and SVV at baseline (Vt of 6 mL/Kg) 2) Changes in IVCV ($\Delta IVCV_{Vt}$), in PPV (ΔPPV_{Vt}) and in SVV (ΔSVV_{Vt}) induced by

the Vt challenge, expressed either as the change in absolute value (value during Vt challenge – value at baseline) or as the percent relative change from the baseline value ((value during Vt challenge – value at baseline)/ value at baseline x 100), 4) Changes in IVCV ($\Delta IVCV_{PLR}$), in PPV (ΔPPV_{PLR}) and in SVV (ΔSVV_{PLR}) induced by the PLR test, expressed either as the change in absolute value (value during PLR – value at baseline). The areas under ROC curves (AUROC) were compared by the Hanley-McNeil test. The best diagnostic threshold was determined as the one providing the best Youden index (sensitivity + specificity – 1).

The least significant change of IVCV was obtained from six successive measurements of IVCV performed during haemodynamic stability at Vt=6 mL/kg, by the same operator, removing the probe from the patient's skin for each measurement, as previously described [18].

In order to demonstrate a significant difference between groups of $\Delta IVCV_{Vt}$, assuming a variability of the IVC measurement of 12% [19-20] with an α risk of 5% and a β risk of 20%, we planned to include 15 preload responders and 15 preload non-responders. Statistical analysis was performed with MedCalc 11.6.0 software (MedCalc, Mariakerke, Belgium).

Results

Patients

Forty-two patients were screened (Supplementary figure 3). Five were not included because of haemodynamic instability, and seven due to a poor ultrasound window. No patient was excluded for other reasons. Thirty patients were finally included and analysed. The intra-observer variability of the measurement of IVCV at baseline was 9 [3-18]%.

Changes in CI over study steps. Characteristics of preload responders and non-responders

The PLR test (performed at Vt of 6 mL/kg) increased CI≥10% in 15 preload responders. Patients characteristics are detailed in Table 1. Increasing Vt from 6 to 8 mL/kg decreased CI and VTI in preload responders, but not in preload non-responders (Table 2). In preload responders, fluid infusion increased CI≥15% in all the patients.

Changes in IVCV over study steps, detection of preload responsiveness through IVC indices

At baseline at Vt = 6 mL/kg, the end-expiratory IVC diameter as well as IVCV were similar between preload responders and preload non-responders (Table 2). $\Delta IVCV_{PLR}$ was larger in preload responders than in preload non-responders (Table 2, Figure 1). $\Delta IVCV_{PLR}$ expressed in percent change from the baseline value reliably detected preload responsiveness, with a diagnostic threshold of -24% (Table 3). $\Delta IVCV_{PLR}$ was significantly correlated with the PLR-induced changes in CI. $\Delta IVCV_{PLR}$ expressed in absolute change did not detect preload responsiveness (AUROC not different from 0.5) and was not correlated with the PLR-induced changes in CI (Table 3, Figure 2).

$\Delta IVCV_{Vt}$ was larger in preload responders than in preload non-responders (Table 2, Figure and Figure 2). $\Delta IVCV_{Vt}$ expressed in percent change from the baseline value reliably detected preload responsiveness, with a diagnostic threshold of 4% (Table 3). This was also the case for $\Delta IVCV_{Vt}$ expressed in absolute change (Table 3, Figure 2). Both indices were correlated with the PLR-induced changes in CI (Table 3).

Changes in PPV and SVV over study steps, detection of preload responsiveness through PPV/SVV indices

At baseline at Vt = 6 mL/kg, PPV and SVV were similar between preload responders and preload non-responders (Table 2). ΔPPV_{PLR} was larger in preload responders than in preload non-responders (Table 2, Figure 1). The PLR-induced changes in PPV reliably detected preload responsiveness, either expressed in percent change from baseline (Table 3) or in absolute change (Table 3, Figure 2). Both indices were correlated with the PLR-induced changes in CI (Table 3). Similar results were observed for ΔSVV_{PLR} (Table 2 and 3).

ΔPPV_{Vt} was larger in preload responders than in preload non-responders (Table 2, Figure 1). The Vt challenge-induced changes in PPV reliably detected preload responsiveness, either expressed in percent change from baseline (Table 3) or in absolute change (Table 3, Figure 2). Both indices were correlated with the PLR-induced changes in CI (Table 3).

ΔSVV_{Vt} was larger in preload responders than in preload non-responders (Table 2, Figure 1). The Vt challenge-induced changes in SVV reliably detected preload responsiveness, either expressed in percent change from baseline (Table 3) or in absolute change (Table 3, Figure 2). However, both indices were not correlated with the PLR-induced changes in CI (Table 3).

Comparisons of ROC curves

The AUROC for $\Delta IVCV_{PLR}$ expressed in absolute value was significantly lower than the AUROC of any other index ($\Delta IVCV_{Vt}$, ΔPPV_{Vt}, ΔSVV_{Vt}, $\Delta IVCV_{PLR}$, ΔPPV_{PLR}, and ΔSVV_{PLR} expressed in percent change or in absolute value and $\Delta IVCV_{PLR}$ expressed in percent change). There was no significant difference of AUROC between all other indices.

Discussion

In this study performed on critically ill patients , we (i) demonstrate the PLR-induced decrease in PPV detects preload responsiveness (ii) show that the PLR-induced decrease in IVCV has a reliable diagnostic value but only expressed in percent change, (iii) show that the increase in IVCV during a Vt challenge may

detect preload responsiveness, but with a diagnostic threshold far lower than the least significant change of IVCV,(iv) confirm that the increase in PPV during a Vt challenge detects preload responsiveness and (v) confirm that the variations in IVC diameter with mechanical ventilation are poor markers of preload responsiveness in case of Vt = 6 mL/kg.

Several tests are today available for detecting preload responsiveness and predicting the response of cardiac output to fluid infusion [3]. Nevertheless, they differ regarding their conditions of use and the monitoring devices that are required to assess their effects. PPV and SVV are reliable but only in the absence of spontaneous breathing, cardiac arrythmias and Vt <8 mL/kg [21]. The PLR test has a similar reliability [22-23], but its main drawback is that its effects cannot be assessed simply on systolic or pulse arterial pressure [8]. The goal of the present study was basically to describe means to overcome these respective limitations.

First, our findings confirm the results of the single study [24] (Supplementary table 1) showing the IVCV was not a reliable indicator of preload responsiveness in case of Vt = 6 mL/kg. The changes in IVC dimensions under mechanical ventilation are due to the cyclic changes in its transmural pressure created by the changes in CVP and likely in intra-abdominal pressure. Then it is not surprising that a low Vt, inducing lower changes in intrathoracic and transmural pressures, is responsible for a lower diagnostic ability compared to Vt ≥8 mL/kg. Nevertheless, it is important to emphasize that the reliability of IVCV for detecting preload responsiveness has been found to be poor or moderate by many studies and meta-analyses, even in studies including patients with Vt ≥8 mL/kg [25]. Along with these studies, the present one shows that IVCV is likely the dynamic index of fluid responsiveness with the poorest diagnostic value.

Second, we found that the PLR-induced decrease in PPV reliably detected preload responsiveness, whatever the way it was calculated. This was the case when expressed either in absolute or relative change, and ΔPPV_{PLR} was the index with the highest correlation with the degree of preload responsiveness, as assessed by the PLR-induced changes in CI. ΔSVV_{PLR} provided similar results, though the correlation with preload responsiveness intensity was a bit lower. This result might be of clinical importance. Indeed, PLR, the main alternative to PPV and SVV in case of Vt <8 mL/kg requires a direct measurement of cardiac output [26] and many studies attempted to find cardiac output surrogates that may be used for this purpose. Provided that the patient is equipped with an arterial catheter, PPV is readily available and assessing the effects of PLR on it might be very easy. In this regard, this result should be compared to the assessment of the PLR test through the perfusion index of plethysmography [27] or its respiratory variation [15].

Third, the PLR-induced decrease in IVCV detected preload responsiveness but only when expressed in percent change. Even in this way, the predictive ability was not excellent: the AUROC was 0.76±0.10, tending to be lower than for the PLR-induced changes in PPV. The correlation with the PLR-induced changes in CI was only -0.50. When IVCV changes were expressed in absolute value, it changes during PLR were no more able to detect preload responsiveness. For explaining these results poorer than those obtained with PPV, a possibility might be that since IVCV is itself a poorer index of preload responsiveness than PPV, its relative changes during preload manipulations must be poorer than the changes in PPV. Also, moving the patient to the PLR position undoubtedly introduces a difficulty in the measurement of IVCV, which can only contribute to hamper its diagnostic value.

Fourth, we confirm that the Vt challenge is a reliable means to get around the limitation of PPV in case of low Vt. The increase in PPV when increasing Vt from 6 to 8 mL/kg, demonstrating an increase in preload dependency, well discriminated preload responders from preload non-responders. The diagnostic threshold expressed in absolute value (1%) was lower than the one observed by Myatra et al. (3.5%) [10], and like the one reported by Messina et al. [28]. This point is very important, because a 1-point change is very low regarding the mean of PPV value. This may induce diagnostic mistakes, especially in patients in whom PPV is unstable. Note that the correlation with PLR-induced changes in CI tended to be looser when ΔPPV_{Vt} was expressed in percent changes than in absolute value. The effects of the Vt challenge on SVV were also able to detect preload responsiveness, but the AUROC tended to be lower than obtained with PPV. Also, the correlation between the PLR-induced changes in CI and ΔSVV_{Vt}, expressed either in absolute or relative value, was not significant. This suggests that PPV rather than SVV, which is inferred from PPV by pulse contour analysis [29], should be preferred when performing a Vt challenge.

Fifth, the results regarding the changes in IVCV during a Vt challenge were disappointing. The AUROC was significantly different from 0.5, for absolute as for relative changes, but the diagnostic threshold was much lower than the least significant change of IVCV we calculated. Also, the correlation between $\Delta IVCV_{Vt}$ and the PLR-induced changes in CI was weak. This is a disappointing result, because it means that the Vt challenge can be performed only if an arterial line is present.

The first limitation of the study is that we assessed preload responsiveness through the effects of a PLR test and not through a fluid challenge. This is explained by ethical reasons, as it would be today unacceptable to plan fluid infusion in preload unresponsive patients only for research purposes. Nevertheless, one must admit that the reliability of the PLR test has been well established by a number of previous studies [22-23]. Also, we did not investigate the superior vena cava collapsibility, which is an equivalent of IVCV [30]. However, its assessment requires a transoesophageal echocardiography, which would have made the study much more complex. We did not assess the “grey zone” of the tests we investigated, which may avoid binary decisions when using such tests [31]. Finally, we did not include in our analysis some other interesting tests predicting fluid responsiveness, like for instance the recruitment manoeuvres [32].

Conclusion

The present study proves that IVCV is not a reliable indicator of preload responsiveness in patients with Vt at 6 mL/kg. It describes how the changes in IVCV, like the changes in PPV, induced by a PLR test and by a transient increase in Vt from 6 to 8 mL/kg detects preload responsiveness assessed at 6 mL/kg.

Declarations

Ethics approval and consent to participate

- Information and consent obtained for each patient

- Name of the ethics committee that approved the study and the committee's reference number: Comité pour la Protection des Personnes, Ile-de-France VII. Trial registration ID RCB: 2016-A00893-48. Registered 26 July 2016. The patients were included prospectively.

Consent for publication

All patients of the manuscript or their relatives have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript. The data were used anonymously.

Availability of data and material

Individual, de-identified participant data are available from the corresponding author on reasonable request.

Competing Interests

J-L Teboul and X Monnet are members of the Medical Advisory Board of Pulsion Medical Systems. J-L Teboul and X Monnet have given lectures for Cheetah Medical. The other authors have no conflict of interest to declare. No financial support

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Authors' contribution

TT collected data, analysed and interpreted the data and drafted the manuscript.

FG collected data, analysed and contributed to interpret the data and to draft the manuscript.

JLT designed the study, contributed to interpreting the data and drafting the manuscript.

RS contributed to data analysis.

XM designed the study, supervised it, interpreted the data and drafted the manuscript.

All authors approved the final version of the manuscript.

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Tables

Table 1. Patient characteristics at baseline.

	Preload responders (n=15)	Preload non-responders (n=15)	p value
Age (years)	63 ± 18	70 ± 10	ns
Male gender (%)	80	73	ns
SAPS2	52 ±15	56 ± 14	ns
Mortality (%)	45	40	ns
Septic shock (%)	70	80	ns
Cardiogenic shock (%)	17	13	ns
Hypovolemic shock (%)	7	7	ns
Vasoplegic shock (non septic) (%)	6	0	ns
CRRT (%)	18	27	ns
ARDS (%)	39	33	ns
Lactate (mmol/L)	1.8 ± 0.6	1.3 ± 0.6	ns
PaO_2/FiO_2	228 ± 105	276 ± 105	ns
PEEP (cmH_2O)	10.7 ± 3.6	10.4 ± 3.0	ns
C_{rs} (mL/cmH_2O)	31 ± 12	32 ± 13	ns
Acute cor pulmonale (%)	0	0	ns
LVEF (%)	45 ± 9	49 ± 11	ns
Patients receiving norepinephrine (%)	100	100	ns
Dose of norepinephrine (µg/kg/min)	1.2 ± 0.6	0.6 ± 0.4	0.02

ARDS: acute respiratory distress syndrome, **CRRT**: continuous renal replacement therapy, **C_{rs}**: compliance of the respiratory system, **LVEF**: left ventricular ejection fraction, **PaO_2/FiO_2**: ratio of the arterial oxygen partial pressure over the oxygen inspired fraction, **PEEP**: positive end-expiratory pressure, **SAPS**: simplified acute physiologic score.

Table 2. Haemodynamic variables at different study steps

		Baseline 1 (Vt = 6 mL/kg)	PLR (Vt = 6 mL/kg)	Baseline 2 (Vt = 8 mL/kg)	Vt Challenge (Vt = 8 mL/kg)	Baseline 3 (Vt = 6 mL/kg)	After VE (Vt = 6 mL/kg)
HR (beats/min)	*Preload responders*	85 ± 18	77 ± 11	85 ± 17	88 ± 19	84 ± 17	90 ± 15
	Preload non-responders	74 ± 18	74 ± 19	74 ± 18	75 ± 22		
SAP (mmHg)	*Preload responders*	118 ± 17	124 ± 21	119 ± 17	116 ± 19	120 ± 17	129 ± 13
	Preload non-responders	128 ± 16#	126 ± 19	128 ± 16	130 ± 16		
MAP (mmHg)	*Preload responders*	75± 12	79 ± 14	76 ± 12	75 ± 14	79 ± 13	83 ± 10
	Preload non-responders	87 ± 12#	86 ± 12	87 ± 12	85 ± 8#		
DAP (mmHg)	*Preload responders*	57 ± 10	59 ± 12	57 ± 11	59 ± 15	56 ± 11	58 ± 9
	Preload non-responders	61 ± 10	60 ± 8	62 ± 9	69 ± 10		
CVP (mmHg)	*Preload responders*	9 ± 5	14 ± 6*	9 ± 5	10 ± 5	11 ± 3	12 ± 6***
	Preload non-responders	12 ± 4	12 ± 3	12 ± 4	11 ± 4		
IAP (mmHg)	*Preload responders*	8 ± 3	7 ± 4*	8 ± 3	8 ± 3	6 ± 2	6 ± 2
	Preload non-responders	7 ± 4	6 ± 3	7 ± 3	7 ± 3		
CI ($L/min/m^2$)	*Preload responders*	3.0 ± 0.9	3.5 ± 1.3*	3.0 ± 1.3	2.7 ± 1.1*	2.8 ± 0.9	3.4 ± 1.2***
	Preload non-responders	3.0 ± 1.1	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 0.8		
PPV (%)	*Preload responders*	8 ± 3	5 ± 2*	8 ± 3	13 ± 4**	8 ± 2	4 ± 2***
	Preload non-responders	6 ± 3	6 ± 3	7 ± 3	6 ± 3#		
SVV (%)	*Preload responders*	8 ± 2	6 ± 2*	8 ± 2	12 ± 3**	8 ± 2	5 ± 2***
	Preload non-responders	6 ± 3	6 ± 3	6 ± 3	5 ± 2#		
IVCV (%)	*Preload responders*	9 ± 3	7 ± 2*	10 ± 2	15 ± 3**	8 ± 2	6 ± 3***
	Preload non-responders	7 ± 3	6 ± 2	7 ± 3	6 ± 3#		
IVC max diam (cm)	*Preload responders*	2.0 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	2.1 ± 0.3***
	Preload non-responders	2.0 ± 0.4	2.1 ± 0.4*	2.3 ± 0.3	2.3 ± 0.3		
VTI (cm)	*Preload responders*	20 ± 4	24 ± 6*	21 ± 5	18 ± 6**	20 ± 4	25 ± 5***
	Preload non-responders	21 ± 4	21 ± 4	21 ± 4	21 ± 4		
EVLW (mL/Kg)	*Preload responders*	14 ± 7		14 ± 7		14 ± 6	13 ± 5
	Preload non-responders	13 ± 4		13 ± 4			
PVPI	*Preload responders*	2.6 ± 1.0		2.7 ± 1.0		2.7 ± 1.2	2.6 ± 1.0
	Preload non-responders	2.5 ± 1.0		2.6 ± 1.0			
GEDV (mL/m^2)	*Preload responders*	725 ± 142		645 ± 100		695 ± 124	794 ± 135***
	Preload non-responders	821 ± 125		820 ± 178#			
CFI ($^{-1}$)	*Preload responders*	4.1 ± 1.5		4.2 ± 1.7		4.2 ± 1.6	4.2 ± 1.6
	Preload non-responders	4.5 ±2.1		4.2 ± 1.6			
ΔCI (% change)	*Preload responders*		18 ± 6		-9 ± 8		25 ± 9
	Preload non-responders		4 ± 4#		2 ± 6 #		
ΔVTI (% change)	*Preload responders*		16 ± 3		-10 ± 7		+16 ± 8
	Preload non-responders		1 ± 1#		1 ± 7 #		
ΔPPV (% change)	*Preload responders*		-38 ± 16		64 ± 42		-50 ± 12
	Preload non-responders		- 4 ± 8#		1 ± 28 #		
ΔPPV (absolute change)	*Preload responders*		-3 ± 1		5 ± 2		-4 ± 2
	Preload non-responders		0 ± 1#		0 ± 1#		
ΔSVV	*Preload responders*		-24 ± 20		44 ± 22		-40 ± 17

(% change)	*Preload non-responders*	1 ± 15[#]	-1 ± 3[#]	
ΔSVV	*Preload responders*	-2 ± 2	3 ± 2	-4 ± 2
(absolute change)	*Preload non-responders*	0 ± 1[#]	-1 ± 3[#]	
ΔIVCV	*Preload responders*	-26 ± 28	91 ± 72	-25 ± 15
(% change)	*Preload non-responders*	-3 ± 20[#]	-10 ± 52[#]	
ΔIVCV	*Preload responders*	-2 ± 3	6 ± 4	-2 ± 4
(absolute change)	*Preload non-responders*	-1 ± 2[#]	-1 ± 4[#]	

CI: Cardiac index, **CFI**: Cardiac function index, **CVP**: Central venous pressure, **ΔCI:** percent changes in cardiac index, **ΔIVCV:** percent changes in the inferior vena cava diameter variation, **ΔPPV:** percent changes in pulse pressure variation, **ΔSVV:** percent changes in stroke volume variation, **ΔVTI:** percent changes in velocity time integral, **DAP**: Diastolic arterial pressure, **EVLW**: extravascular vascular lung water indexed for body weight, **GEDV:** global end-diastolic volume indexed for body surface, **HR**: Heart rate, **IAP**: Intra-abdominal pressure, **IVC**: Inferior vena cava, **IVCV**: Inferior vena cava variation, **MAP**: Mean arterial pressure, **PLR**: Passive leg raising, **PPV**: Pulse pressure variation, **PVPI**: Pulmonary vascular permeability index, **SAP** : Systolic arterial pressure, **SVV**: Stroke volume variation, **VE**: Volume expansion, **Vt:** Tidal volume, **VTI:** Velocity time integral.

* p<0.05 *vs.* Baseline 1, ** p<0.05 *vs.* Baseline 2, *** p<0.05 *vs.* Baseline 3.

[#] p<0.05 *vs.* preload responders.

Table 3. Ability of different variables to detect preload responsiveness.

	r vs. PLR-induced changes in CI	p vs. 0.5	AUROC	sd	p *vs.* 0.50	Cut-off	Se	95% CI	Sp	95% CI	+ PV	95% CI	- PV	95% CI	+ LR	95% CI	- LR
GEDV (mL/m^2)			0.59	0.10	0.47												
CVP (mmHg)			0.56	0.11	0.57												
IVC max diameter (mm)			0.58	0.11	0.49												
PPV (%)			0.66	0.10	0.10												
SVV (%)			0.61	0.10	0.10												
IVCV (%)			0.64	0.11	0.20												
ΔPPV_{PLR} (% change)	-0.77	< 0.01	0.98	0.02	< 0.01	≤-20%	100	78-100	93	61-100	94	69-99	100		15.0	2.3-99.6	0.0
ΔPPV_{PLR} (abs. change)	-0.70	< 0.01	0.98	0.02	< 0.01	≤-2 points	93	68-100	93	68-100	94	69-99	94	69-99	14.0	2.1-93.4	0.1
ΔPPV_{Vt} (% change)	0.53	< 0.01	0.94	0.04	< 0.01	>20%	93	68-100	87	59-98	87	66-96	94	69-99	7.0	1.9-25.6	0.1
ΔPPV_{Vt} (abs. change)	0.71	< 0.01	0.98	0.02	< 0.01	>1 point	93	68-100	100	78-100	100		94	69-99			0.1
ΔSVV_{PLR} (% change)	-0.66	< 0.01	0.90	0.07	< 0.01	≤-19%	80	52-96	100	78-100	100		83	65-93	5.5	1.5-20.7	0.3
ΔSVV_{PLR} (abs. change)	-0.73	< 0.01	0.88	0.07	< 0.01	≤-2 points	73	45-92	100	78-100	100		79	62-90			0.3
ΔSVV_{Vt} (% change)	0.07	0.69	0.82	0.08	< 0.01	>20%	100	78-100	67	38-88	70	55-81	75	60-86	3.0	1.5-6.1	0.0
ΔSVV_{Vt} (abs. change)	0.21	0.26	0.94	0.04	< 0.01	>1 point	93	68-100	73	45-92	78	60-89	100		3.5	1.5-8.2	0.1
$\Delta IVCV_{PLR}$ (% change)	-0.50	< 0.01	0.76	0.10	< 0.01	≤-24%	73	45-92	87	85	83	59-95	77	58-89	5.5	1.5-20.7	0.3
$\Delta IVCV_{PLR}$ (abs. change)	-0.30	0.09	0.56	0.11	0.60												
$\Delta IVCV_{Vt}$ (% change)	0.52	< 0.01	0.88	0.06	< 0.01	>4%	100	78-100	67	38-88	75	60-86	100		3	1.5-6.1	0.0
$\Delta IVCV_{Vt}$ (abs. change)	0.57	< 0.01	0.92	0.05	< 0.01	>1 point	100	78-100	60	32-84	71	57-83	100		2.5	1.3-4.6	0.0

AUROC: area under the receiver operating characteristic curve, **CI**: confidence interval, **GEDV**: global end-diastolic volume indexed for body surface, **IVC** = inferior vena cava, **IVCV** = respiratory variation of the diameter of the inferior vena cava, **PPV** = pulse pressure variation, **Se**: sensitivity, **sd**: standard deviation, **Sp**: specificity, **SVV** = Stroke Volume Variation, **+ PV**: positive predictive value, **- PV**: negative predictive value, **+ LR**: positive likelihood ratio, **- LR**: negative likelihood ratio, **ΔPPV_{PLR}**: changes in pulse pressure variation induced by passive leg raising, **ΔSVV_{PLR}**: changes in stroke volume variation induced by passive leg raising, **$\Delta IVCV_{PLR}$**: changes in the respiratory variation of the diameter of the inferior vena cava induced by a tidal volume challenge, **ΔPPV_{Vt}**: changes in pulse pressure variation induced by a tidal volume challenge, **ΔSVV_{Vt}**: changes in stroke volume variation induced by a tidal volume challenge, **$\Delta IVCV_{Vt}$**: changes in the respiratory variation of the diameter of the inferior vena cava induced by a tidal volume challenge.

Figures

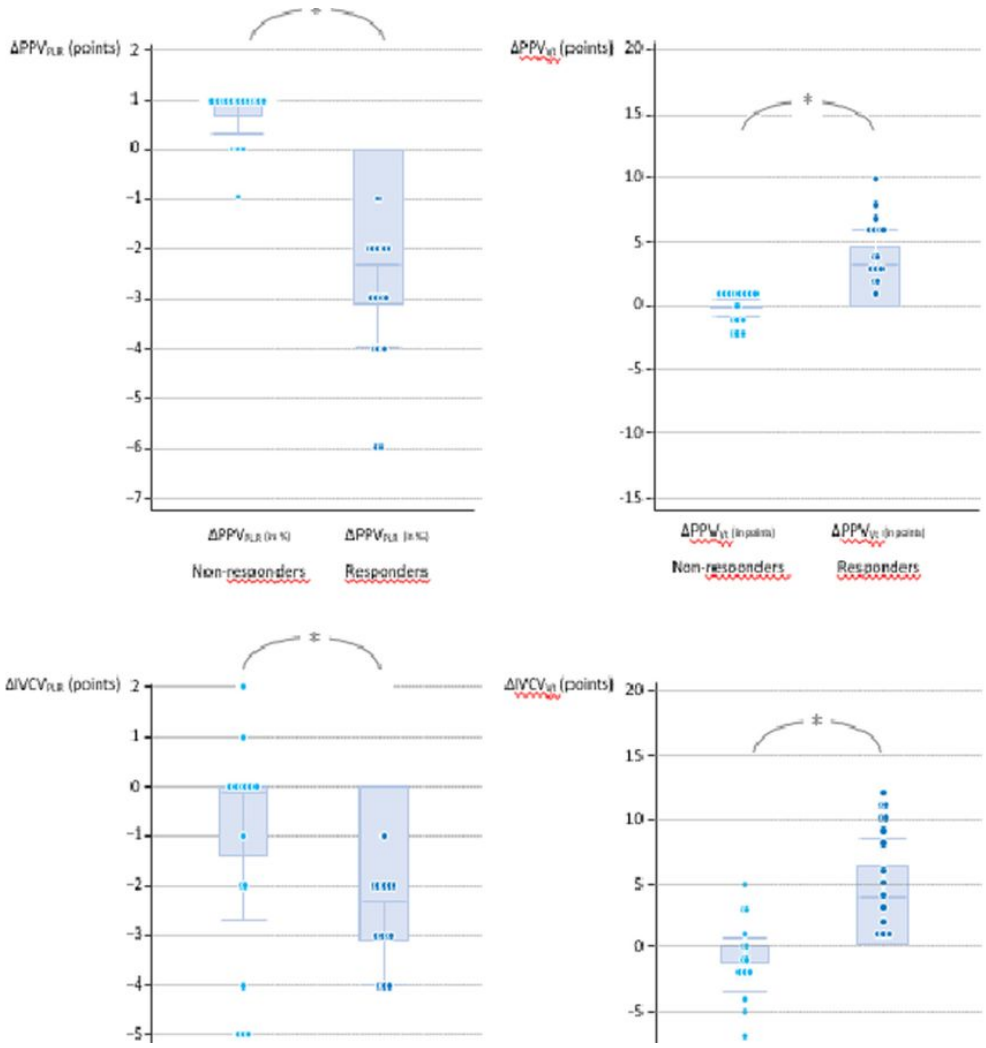

Figure 1

Upper panel: PLR-induced percent changes in pulse pressure variation during a passive leg raising test (ΔPPVPLR) (expressed in percent changes relative to baseline) and a tidal volume challenge (ΔPPVVt) (expressed in absolute changes) in preload responders and non-responders. Bottom panel: PLR-induced percent changes in inferior vena cava variation during a passive leg raising test (ΔIVCVPLR) (expressed in percent changes relative to baseline) and a tidal volume challenge (ΔIVCVVt) (expressed in absolute changes) in preload responders and non-responders. * p<0.05 preload responders vs. preload non-responders.

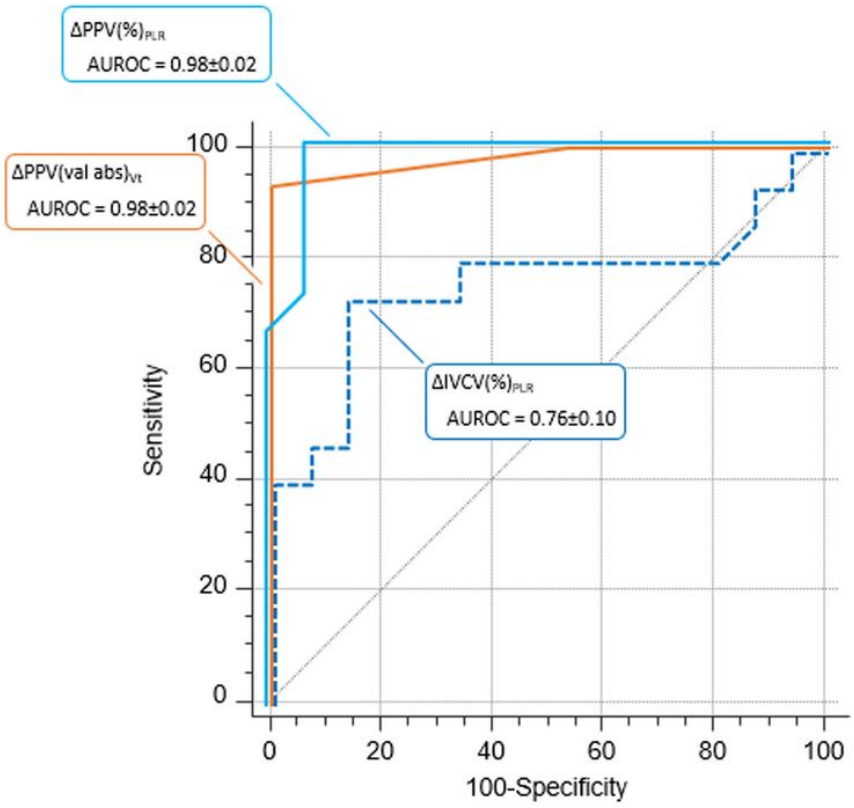

Figure 2

Figure 2

Receiver operating characteristic curves describing the ability to diagnose preload responsiveness of the changes in passive leg raising-induced changes of pulse pressure variation in percent (ΔPPV(%)PLR), passive leg raising-induced changes and of inferior vena cava variation in percent (ΔIVCV(%)PLR), and of the tidal volume challenge-induced changes of pulse pressure variation in absolute value (ΔPPV(valabs)Vt). AUROC: area under the receiver operating characteristic curve (expressed as mean ± standard deviation).

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