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Central venous pressure measurements improve the accuracy of leg raising-induced change in pulse pressure to predict fluid responsiveness

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Abstract *Purpose:* Passive leg raising (PLR) is a maneuver performed to test the cardiac Frank-Starling mechanism. We assessed the influence of PLR-induced changes in preload on the performance of PLR-induced change in pulse pressure ($\Delta_{PLR}PP$) and cardiac output ($\Delta_{PLR}CO$) for fluid responsiveness prediction. *Methods:* Sedated, non-arrhythmic patients with persistent shock were included in this prospective multicenter study. Cardiac output and pulse pressure were measured at baseline (patient supine), during PLR (lower limbs lifted to 45°) and after 500-ml volume expansion. Patients were classified as responders or not. *Results:* In the whole population ($n = 102$), the area under the receiver-operating characteristic curve (AUC) was 0.76 for $\Delta_{PLR}PP$ and was higher for $\Delta_{PLR}CO$ $(0.89)(p < 0.05)$, but likelihood ratios were close to 1. In patients with a PLR-induced increase in central venous pressure (CVP) of at least 2 mmHg ($n = 49$), $\Delta_{PLR}PP$ and $\Delta_{PLR}CO$ disclosed higher AUCs than in the rest of the population (0.91 vs. 0.66 and 0.98 vs. 0.83; $p < 0.05$); positive/negative likelihood ratios were 9.3/0.14 (8% cutoff level) and 30/0.07 (7% cutoff level), respectively. *Conclusions:* A PLR-induced change in CVP ≥ 2 mmHg was required to allow clinical usefulness of PLR-derived indices. In this situation, $\Delta_{PLR}PP$ performed well for predicting fluid responsiveness in deeply sedated patients.

Keywords Monitoring · Physiologic [MesH] · Hypovolemia [MesH] · Passive leg raising · Preload · Central venous pressure

Introduction

In case of persistent circulatory failure after initial resuscitation, intensivists often use additional volume expansion with the aim of increasing cardiac output (CO). However, nearly half of the patients in shock are not responsive to volume expansion [1–3] after the first hours of care, and an unnecessary volume load may be deleterious [4]. After the initial phase of resuscitation, clinical examination, cardiac volumes and filling pressures [central venous pressure (CVP); pulmonary artery occlusion pressure (PAOP)] are of little interest to predict the

response to volume expansion [5]. Therefore, new indices have been developed using passive leg raising (PLR) or heart-lung interactions [6].

Because of its simplicity and its safety due to the theoretical reversibility, PLR is an appealing test for predicting fluid responsiveness [7]. It mimics volume expansion by shifting blood from the capacitance veins of the legs towards the intrathoracic compartment [8], leading to an increase in right [9] and left [7] ventricular preload and then in left ventricular stroke volume (SV) and in CO, if the patient's ventricles work on the ascending portion of their Frank-Starling curve [2, 7]. As CO measurement may be cumbersome, PLR-induced changes in various SV surrogates have been evaluated for the prediction of volume responsiveness, with PLR-induced changes in pulse pressure (PP) being the easiest SV surrogate to record at the bedside ($\Delta_{PLR}PP$), but poor performance has been reported [2, 10]. We hypothesized that $\Delta_{PLR}PP$ performance may be downplayed mainly by the failure of the PLR maneuver to significantly increase cardiac preload. As a change in CVP reflects that the Frank-Starling mechanism of the heart has been tested [6, 11–14], $\Delta_{PLR}PP$ could be a reliable index among patients increasing their CVP during PLR.

The aim of this study was to assess the influence of PLR-induced changes in CVP on the performance of $\Delta_{PLR}PP$ and $\Delta_{PLR}CO$ for the prediction of fluid responsiveness.

Patients and methods

Patients

Participating centers were the Hôpital Bichat-Claude Bernard of Paris, the Centre Hospitalier Régional Universitaire of Tours and the Centre Hospitalier Régional of Orléans, France.

Patients

Adult patients undergoing volume-controlled mechanical ventilation without triggering the ventilator were included if they exhibited acute circulatory failure (systolic BP <90 mmHg, mean BP <65 mmHg, skin mottling, urine output <0.5 ml/kg/h, arterial lactate >2.5 mmol/l or vasopressor infusion), a Ramsay score >4 and no arrhythmia.

Patients were not included in case of diuretic treatment, uncontrolled hemorrhage, brain death, leg amputation, phlebitis, compression stockings, intra-aortic balloon pump support, severe hypoxemia (PaO_2/FiO_2 <70 mmHg), high risk of pulmonary edema [body weight indexed extravascular lung water (EVLWi) >22 ml/kg (PiCCO[TM] system: Pulsion Medical Systems AG[TM], Munich, Germany)] or

transmural PAOP >18 mmHg (PAOPtm, estimated via the measurement of respiratory changes in PAOP [15]; pulmonary artery catheter: Edwards Lifesciences[TM], Irvine, CA).

The study procedure was stopped in case of changes in respirator settings or vasoactive therapy, occurrence of arrhythmia or respiratory intolerance to volume expansion [EVLWi >22 ml/kg or PAOPtm >22 mmHg or 5% decrease in pulse oxymetry (SpO_2)].

Mechanical ventilation, vasoactive therapy, sedation and paralysis were set by the attending physician and not modified.

Our regional ethics review board approved the study protocol. Patients were included either after written informed consent from a relative or after emergency enrollment followed by delayed consent [16].

Study protocol

The study was divided into five phases: baseline 1; 45° PLR (the lower limbs were lifted in a straight manner to 45°, with the trunk and the bed being kept horizontal [7]); return to baseline position (baseline 2); 300 ml over 18 min (to assess the respiratory tolerance) and an additional 200-ml volume expansion (modified fluid gelatin) over 12 min (Fig. 1) [7].

Measurements

One minute after the beginning of each study phase, we started to measure invasive BP, heart rate (HR), SpO_2, CVP, PAOP (end-expiratory value, measured on frozen waveform), total positive end-expiratory pressure (PEEPt) and CO.

CO was measured through end-expiratory injection of 10 ml or 15 ml (transcardiac and transpulmonary thermodilution, respectively) of an iced dextrose solution [using a closed injection system with in-line temperature measurement: CO-set+[TM] system (Edwards Lifesciences, Irvine, CA) or included in the PiCCO[TM] system]. Three consecutive measurements within 10% (if not, seven measurements) were averaged.

The correct placement of the pulmonary artery catheter was ascertained by visualization of concordant waveforms and calculation of the respiratory changes in PAOP-to-respiratory changes in the PAP ratio [17].

CVP, PAOP and BP were measured with a disposable transducer (TruWave[TM], Baxter[TM] Division Edwards, Maurepas, France), zeroed at the level of the mid-axillary line. Four recordings of BP, 60-s apart, were performed by "at a glance" direct readings of the value displayed by the monitor, regardless of the respiratory cycle. We calculated change in PP (average of four measurements) and CO induced by PLR ($\Delta_{PLR}PP$ and $\Delta_{PLR}CO$):

Fig. 1 Diagram of the study protocol
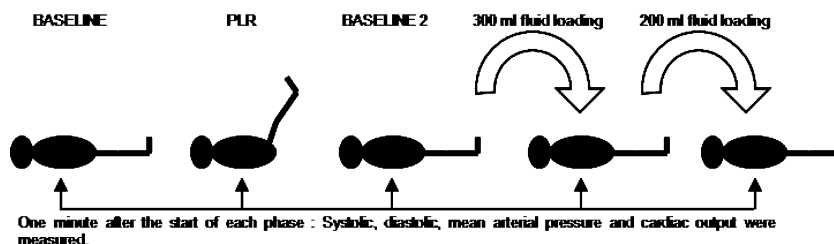
$$\Delta_{PLR}PP = (PP \text{ during } PLR - PP \text{ at baseline})/$$
$$PP \text{ at baseline } (\%)$$

$$\Delta_{PLR}CO = (CO \text{ during } PLR - CO \text{ at baseline})/$$
$$CO \text{ at baseline } (\%)$$

Using off-line, high-resolution paper tracings, including airway and BP waveforms, and after their numerical enlargement, "expiratory $\Delta_{PLR}PP$" was also calculated, based on end-expiratory measurements of PP, in order to avoid any influence of respiratory changes in BP. The absence of any spontaneous respiratory motion and of any triggering of the respirator was verified in each patient by (1) clinical observation, (2) similar settled and measured respiratory rates, and (3) no negative accident on airway pressure recording.

An echocardiography was performed within 6 h of measurements in order to quantify valvular regurgitations or intracardiac shunts.

Statistical analysis

After volume expansion, patients were classified as responders if CO increased by more than 10% and as nonresponders otherwise. This cutoff value was chosen because a measured 9% change in CO (which we rounded to 10%) reliably reflects that a real change has taken place [18]. To validate this choice in our patients (assessment of inter-measurement variability within each set of measurements), we calculated the least significant change for each set of CO measurements in each patient at each phase [$(1.96\sqrt{2})Cv/\sqrt{}$number of measurements within one set] with Cv = coefficient of variation (SD/mean). This allowed us to ascertain that each individual patient classified as a responder had a CO increase above his/her individual least significant change [19]. We also made all the calculations using a 15% cutoff value to define fluid responsiveness [2].

For each index, we calculated the area under the receiver-operating characteristic curve (AUC), and determined the best cutoff value (Youden method) [20] and its corresponding positive and negative likelihood ratio (LR+ and LR−) [21]. As proposed, the values of 5 and 10 for the LR+ (or 0.2 and 0.1 for the LR−) helped to divide the continuous scale of LR+ and LR− into three categories: weak, good and strong evidence of discriminative power [21]. AUC comparisons were made between the different indices [22] and between different subgroups [23]. The objective was to compute the AUC, LR+ and LR− of $\Delta_{PLR}PP$ and $\Delta_{PLR}CO$ in the whole population and in the predefined subgroups of patients with a CVP increase ≥2 and <2 mmHg during PLR [6]. The cutoff value of 2 mmHg was chosen because a change of this magnitude (1) can be identified with confidence on most monitors and recording devices, and (2) ascertains that the Frank-Starling mechanism has been tested [6, 11, 12]. Variables [expressed as mean ± SD or n (%)] were compared using Student's t test and Fisher's exact test (between responders and nonresponders), paired Student's t test (within each patient), analysis of variance and Scheffé test (between subgroups of patients) and analysis of variance or the chi-square test (between centers).

A value of $p < 0.05$ was considered significant. All statistical tests were two-tailed, performed using MedCalc® (Mariakerke, Belgium) and Statview® (SAS Institute, Cary, NC).

Results

One hundred two patients were included (Table 1).

The mean least significant change of CO measurements was 6.4 and 6.1% at baseline and after volume expansion, respectively.

Forty-three (42%) patients were responders after 500 ml volume expansion. They all exhibited individual CO changes from baseline to volume expansion greater than their individual least significant change.

Volume expansion was interrupted in two patients after 300 ml intolerance; data after 300 ml volume expansion were used for analysis.

In the whole population, HR and MAP were similar between baselines 1 and 2.

Hemodynamic parameters at baseline and their evolution after volume expansion are detailed in Table 2.

No difference between centers was noted concerning the proportion of responders, the Simplified Acute Physiology Score II, baseline MAP, HR, CO, $\Delta_{PLR}PP$ and $\Delta_{PLR}CO$ (all $p > 0.05$).

Table 1 Main characteristics of the patients at inclusion

Age (years)	59 ± 16
Gender male/female	72/30
SAPS II	57 ± 18
Main diagnosis at admission	
Septic shock	52
Cardiogenic shock	17
Acute respiratory failure	12
Other	21
Delay between admission and inclusion	
<24 h	61 (60%)
24–48 h	18 (18%)
>48 h	23 (23%)
Center	
Paris	50 (49%)
Orléans	28 (28%)
Tours	24 (23%)
Mean dosage of continuous iv midazolam ($n = 97$) (mg/h)	6.6 ± 3.2
Mean dosage of continuous iv fentanyl ($n = 102$) (µg/h)	178 ± 139
Ramsay score = 5 or 6	21 (21%)/81 (79%)
Neuromuscular blocking agent use	35 (34%)
Arterial lactate concentration (mmol/l) ($n = 90$)	3.6 ± 4
Arterial lactate concentration >2.5 mmol/l	42 (41%)
Urine output during the last hour (ml/kg)	0.8 ± 0.8
Urine output during the last hour <0.5 ml/kg	37 (36%)
Skin mottling	32 (31%)
Catecholamine infusion	94 (92%)
Norepinephrine (µg/kg/min) ($n = 78$)	0.67 ± 0.8
Epinephrine (µg/kg/min) ($n = 18$)	0.46 ± 0.4
Dobutamine (µg/kg/min) ($n = 24$)	10.6 ± 9.9
Cardiac output measured by PiCCO^{TM}/pulmonary artery catheter	52 (51%)/50 (49%)
Arterial catheter site: femoral/radial	83 (81%)/19 (19%)
PEEPt (cmH$_2$O)	8 ± 3
Plateau pressure (cmH$_2$O)	20 ± 5
ARDS	65 (64%)

SAPS Simplified Acute Physiology Score, *PEEPt* total positive end-expiratory pressure, *ARDS* acute respiratory distress syndrome

Quantitative values are expressed as mean $\pm$ standard deviation, with qualitative values in *n* (%)

Table 2 Hemodynamic parameters of the whole population at baseline 1 and after 500 ml volume expansion

	Before volume expansion	After volume expansion	*p*
Heart rate (bpm)	97 ± 23	93 ± 22	<0.0001
Mean arterial pressure (mmHg)	71 ± 13	80 ± 16	<0.0001
Arterial pulse pressure (mmHg)	53 ± 15	62 ± 18	<0.0001
Central venous pressure (mmHg)	11 ± 4	15 ± 5	<0.0001
PAOP (mmHg) ($n = 50$)	12 ± 4	17 ± 4	<0.0001
Transmural PAOP (mmHg) ($n = 50$)	9 ± 4	13 ± 5	<0.0001
Mean pulmonary arterial pressure (mmHg) ($n = 50$)	27 ± 6	32 ± 8	<0.0001
Cardiac output (l/min)	6.0 ± 2.3	6.6 ± 2.6	<0.0001
Cardiac index (l/min/m^2)	3.4 ± 1.4	3.8 ± 1.6	<0.0001

PAOP pulmonary artery occlusion pressure

Values are expressed as mean $\pm$ standard deviation

In the whole population, the AUC of $\Delta_{PLR}CO$ for predicting fluid responsiveness was significantly higher than the AUC of $\Delta_{PLR}PP$ [0.89 (0.81–0.94) and 0.76 (0.67–0.84), respectively, $p = 0.007$]. The best cutoff values were 7 and 9% for $\Delta_{PLR}CO$ and $\Delta_{PLR}PP$, respectively (LR+ of 7.8 and 3.3 and LR− of 0.23 and 0.43, respectively) (Fig. 2).

Influence of CVP increase during PLR

Among the 48 patients (16 responders) with a minimal CVP increase of 2 mmHg during PLR, $\Delta_{PLR}PP$ exhibited an AUC of 0.91 (0.79–0.97), with LR+ and LR− of 9.3 and 0.14, respectively (8% cutoff value) (Fig. 3). Otherwise, $\Delta_{PLR}PP$ disclosed a lower AUC [0.66 (0.51–0.78),
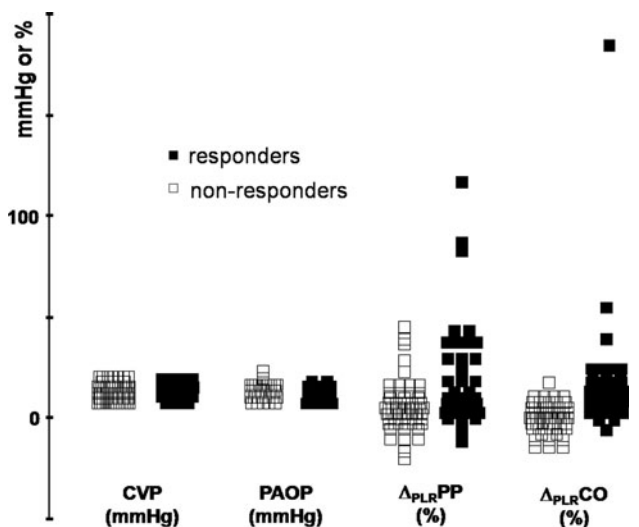
Fig. 2 Individual values of static and PLR-derived indices in responders and nonresponders of the whole study population. *PLR* passive leg-raising, *CVP* central venous pressure at baseline, *PAOP* pulmonary artery occlusion pressure at baseline, $\Delta_{PLR}PP$ PLR-induced change in pulse pressure, $\Delta_{PLR}CO$ PLR-induced change in cardiac output (thermodilution measurement). Responders are defined as patients increasing their cardiac output by at least 10% after 500-ml volume expansion
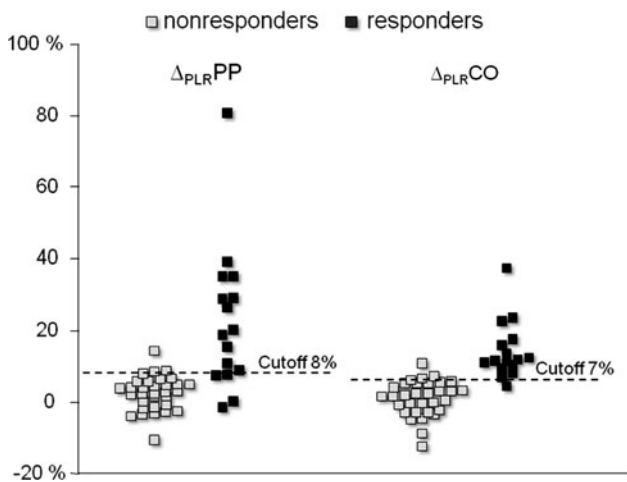

Fig. 3 Individual values of $\Delta_{PLR}PP$ and $\Delta_{PLR}CO$ in responders and nonresponders in patients with PLR-induced increase in central venous pressure ≥ 2 mmHg. *PLR* passive leg raising, $\Delta_{PLR}PP$ PLR-induced change in pulse pressure, $\Delta_{PLR}CO$ PLR-induced change in cardiac output (thermodilution)

$p = 0.002$] (Fig. 4). Hemodynamic and respiratory parameters according to CVP changes during PLR are detailed in Table 3 and ESM1.

$\Delta_{PLR}CO$ also performed better in patients with a CVP increase ≥ 2 mmHg: AUC of 0.98 (0.89–1), and LR+ and LR− of 30 and 0.07, respectively (7% cutoff value) (Fig. 3). Otherwise, $\Delta_{PLR}CO$ disclosed a lower AUC [0.83 (0.71–0.92), $p = 0.018$].
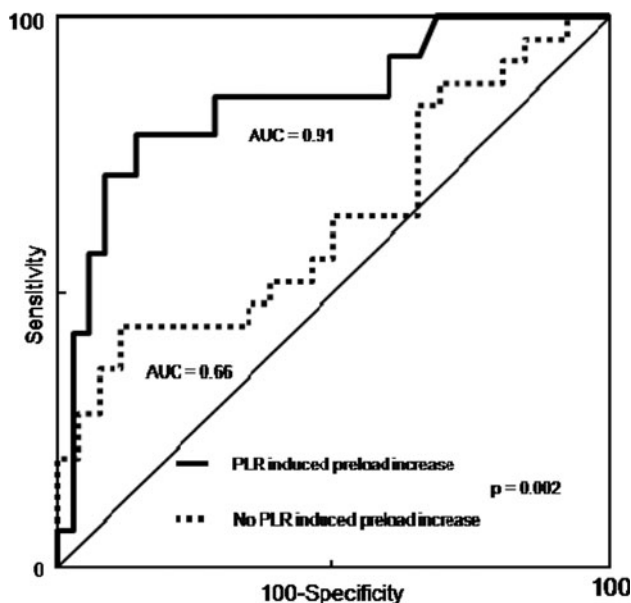
Fig. 4 Performance of $\Delta_{PLR}PP$ according to PLR-induced preload increase. Legend: Receiver-operating characteristic (ROC) curve obtained for passive leg raising (PLR)-induced increase in pulse pressure ($\Delta_{PLR}PP$) to predict a 10% increase in cardiac output after 500-ml volume expansion. PLR-induced preload increase denotes a central venous pressure increase of at least 2 mmHg during PLR compared to baseline 1. The area under the curve (AUC) in case of a marked preload increase with PLR was greater than when PLR did not sufficiently increase central venous pressure ($p = 0.002$)

Similar results were found (see ESM2):

1. when excluding (a) patients carrying either a pulmonary artery catheter with significant (grade III or IV) tricuspid regurgitation ($n = 2$) or a PiCCO^{TM} system with a significant mitral and/or tricuspid and/or aortic regurgitation ($n = 1$) and (b) patients who did not receive 500 ml fluid loading ($n = 2$) (data not shown);
2. when considering only the first PP measurement instead of averaging four measurements to calculate $\Delta_{PLR}PP$;
3. when considering end-expiratory PP measurement (as measured on paper tracing) to calculate $\Delta_{PLR}PP$;
4. when considering PLR-induced changes in SV instead of $\Delta_{PLR}CO$;
5. when using a 15% cutoff value (instead of 10%) for fluid loading-induced increase in CO to define fluid responsiveness.

Static indices

CVP, PAOP and PAOPtm disclosed an AUC of 0.61 (0.50–0.71), 0.70 (0.56–0.83) and 0.69 (0.54–0.82), respectively, with all LRs being within the weak evidence range of values (LR+ below 5, LR− above 0.2) (Fig. 2).

Table 3 Hemodynamic parameters according to CVP changes during PLR at each study phase

	Baseline 1 CVP increase during PLR				During PLR CVP increase during PLR				After volume expansion CVP increase during PLR			
	<2 mmHg		≥2 mmHg		<2 mmHg		≥2 mmHg		<2 mmHg		>2 mmHg	
	R $n = 27$	NR $n = 27$	R $n = 16$	NR $n = 32$	R $n = 27$	NR $n = 27$	R $n = 16$	NR $n = 32$	R $n = 27$	NR $n = 27$	R $n = 16$	NR $n = 32$
Heart rate (bpm)	98 ± 19	105 ± 23	103 ± 25	88 ± 22	95 ± 18[‡]	102 ± 23[‡]	101 ± 27	88 ± 22	93 ± 17[‡]	99 ± 25[‡]	100 ± 25[‡]	87 ± 21[‡]
Mean arterial pressure (mmHg)	68 ± 12	69 ± 12	72 ± 11	74 ± 14	78 ± 16[‡]	75 ± 12[‡]	84 ± 12[‡]	78 ± 14[‡]	81 ± 15[‡]	78 ± 15[‡]	86 ± 15[‡]	79 ± 16[‡]
Arterial pulse pressure (mmHg)	52 ± 17	53 ± 13	48 ± 10	57 ± 15	61 ± 17[‡]	56 ± 13	59 ± 14[‡]	59 ± 16[‡]	70 ± 19[‡]	58 ± 16	64 ± 18[‡]	58 ± 16
CVP (mmHg)	9.5 ± 3.9	11.7 ± 4.0	9.9 ± 4.5	11.5 ± 4.3	9.2 ± 3.6	11.8 ± 4.0	13.0 ± 3.9[‡]	14.6 ± 5.0[‡]	11.2 ± 3.8[‡]	15.4 ± 3.8[‡]	14.6 ± 4.7[‡]	16.1 ± 5.3[‡]
PAOP (mmHg) ($n = 50$)	9.9 ± 3.1	11.0 ± 3.7	10.6 ± 4.0	14.3 ± 3.6[‡‡]	10.8 ± 3.7	13.0 ± 4.2[‡]	14.1 ± 3.2[‡]	16.3 ± 3.4[‡]	12.8 ± 5.1[‡]	16.3 ± 3.8[‡]	17.6 ± 4.7[‡]	18.2 ± 3.0[‡]
Cardiac output (l/min)	5.7 ± 2.1	6.6 ± 2.9	5.6 ± 4.3	5.8 ± 2.1	6.5 ± 2.1[‡]	6.7 ± 3.2	6.4 ± 2.5[‡]	5.8 ± 2.1	7.4 ± 2.1[‡]	6.5 ± 3.0	7.2 ± 2.9[‡]	5.7 ± 2.2
Cardiac index (l/min/m²)	3.3 ± 1.3	3.9 ± 1.6	3.3 ± 1.6	3.2 ± 1.1	3.8 ± 1.3[‡]	4.0 ± 1.8	3.7 ± 1.7[‡]	3.2 ± 1.2	4.3 ± 1.4[‡]	3.8 ± 1.6	4.2 ± 2.0[‡]	3.2 ± 1.2

CVP central venous pressure, *PAOP* pulmonary artery occlusion pressure, *PEEPt* total positive end-expiratory pressure, *R* responders, *NR* nonresponders

[‡] $p < 0.05$ compared to baseline

[‡‡] $p < 0.05$ compared to responders in subgroup of patients with CVP increase during PLR ≥ 2 mmHg

Values are expressed as mean ± standard deviation

Discussion

The main finding of this multicenter study of 102 patients in shock is that it highlights a physiological limitation of PLR-derived indices, i.e., the lack of PLR-induced change in preload. Thus, provided that CVP increases by at least 2 mmHg during PLR, $\Delta_{PLR}CO$ and, remarkably, $\Delta_{PLR}PP$ appear to be useful tools to predict fluid responsiveness in our population.

Our study showed that $\Delta_{PLR}CO$ was the best index in our population. This strongly supports the validity of the physiological rationale of PLR to predict volume responsiveness.

Most other studies addressing PLR did not measure CO using the thermodilution technique and therefore did not evaluate this index, but showed results compatible with ours: $\Delta_{PLR}PP$ is, overall, of low performance for detecting fluid responsiveness, whereas other left ventricular SV surrogates (aortic blood flow as assessed by esophageal Doppler, iliac artery pulse contour-derived CO) perform better [2, 10, 24–26].

Different mechanisms may explain the poor performance of PP as a SV surrogate during PLR, none of which can be firmly incriminated or excluded based on the data of our study or of others: (1) PLR may induce sympathetic or cardiac reflex stimulation, but this is unlikely in our deeply sedated patients as we did not observe significant HR changes during PLR [27, 28]. (2) Using PP as a surrogate of SV assumes a constant arterial tree compliance, which may not always be the case during PLR (see ESM3 for details). In our study, as the performance of $\Delta_{PLR}PP$ has been shown to be good in a subgroup of patients, one may consider that PLR-induced changes in compliance were insufficient to downplay the performance of $\Delta_{PLR}PP$ significantly. (3) The transferred blood from the legs towards the central compartment by our PLR technique may be insufficient in some patients to alter cardiac preload (e.g., in case of profound hypovolemia). Of note, this confounding factor can be controlled in the clinical setting by ascertaining that the Frank-Starling mechanism of the heart has been tested by PLR. Indeed, in patients fulfilling a change of CVP of at least 2 mmHg during PLR, the performance of PLR-derived indices was significantly higher than in other patients. This validity criterion was underlined in recent international guidelines [6], but surprisingly has never been reported in order to improve the performance of PLR-derived indices. In this favorable circumstance, $\Delta_{PLR}PP$ >8% or <8% provides good evidence in favor of (LR+ = 9.3) or against (LR− = 0.14) fluid responsiveness, respectively.

Maximizing blood transfer during PLR may be another way to improve $\Delta_{PLR}PP$ performance. Another technique for PLR has been proposed, consisting of a postural change from a semi-recumbent to a supine position [2, 10]; this causes a higher increase in cardiac preload [29]. However, the performance of $\Delta_{PLR}PP$ was similar in our whole population compared to studies using this semi-recumbent-to-supine PLR technique [2, 10]. Both PLR techniques need to be compared within one population of responders and *nonresponders* to draw definite conclusions about their relative performances.

We considered that changes in CVP reflect changes in preload and, as recommended [6], that a PLR-induced change in CVP of at least 2 mmHg denotes that the Frank-Starling mechanism has been tested [11–13, 30]. Actually, right ventricle preload assessment is controversial and complex [31], and a basic measurement of CVP is clearly not a good indicator of cardiac preload [31]. However, transmural CVP, i.e., the CVP relative to the pressure surrounding the heart (the pleural pressure), is an important determinant of cardiac preload [13]. We did not measure transmural CVP, but one can reliably hypothesize that PLR-induced *changes* in CVP (measured with a device that is zeroed relative to atmospheric pressure) reflect changes in transmural CVP (and then in right ventricle preload), provided that changes in pleural pressure did not occur. Interestingly, PLR-induced changes in the plateau pressure and PEEPt were negligible in our population (mean change of 0.6 ± 0.5 and 0.2 ± 0.2 cmH$_2$O, respectively), suggesting that PLR-induced changes in pleural pressure were clinically insignificant. Further, the significant difference we observed for the performance of PLR-derived indices according to the PLR-induced changes in CVP strongly supports our hypothesis.

$\Delta_{PLR}CO$ was the best performing index in our study as it allowed a very strong prediction of fluid responsiveness (LR+ = 30) and a strong prediction against it (LR− = 0.07) in case of an increase of CVP ≥2 mmHg during PLR. Nevertheless, CO measurement during PLR is cumbersome to carry out (bolus injections), and even if simpler means of CO determination exist, none is readily available at the bedside like $\Delta_{PLR}PP$. Indeed, the latter only requires an arterial and a central venous line, and is simply performed by direct reading of the displayed value of CVP and PP at baseline and after 1 min of PLR. Of note, one of the main results of our study is that $\Delta_{PLR}PP$ is useful to predict fluid responsiveness provided that one ascertains that the PLR maneuver has altered the patient preload (increase in CVP ≥2 mmHg). The use of a "blind" PLR maneuver, i.e., with no concurrent CVP measurement, may explain the poor performance reported until now for $\Delta_{PLR}PP$ [2, 10].

Of note, the best cutoff value for $\Delta_{PLR}CO$ (7%, derived from ROC curve analysis) is lower than the cutoff value we used to discriminate between responders and nonresponders (10%). However, it was higher than our mean least significant change for thermodilution CO measurements (close to 6%), and when choosing a cutoff value of 10% for $\Delta_{PLR}CO$, we found similar results (LR+

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