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Original Article / Özgün Araştırma

Reliability of Passive Leg Raising, Stroke Volume Variation and Pulse Pressure Variation to Predict Fluid Responsiveness During Weaning From Mechanical Ventilation After Cardiac Surgery: A Prospective, Observational Study

Kalp Cerrahisi Sonrası Mekanik Ventilasyondan "Weaning" Sırasında Sıvı Cevabını Öngörmek için Pasif Bacak Kaldırma, Atım Hacmi Varyasyonu ve Nabız Basıncı Varyasyonunun Güvenilirliği: Prospektif, Gözlemsel Bir Çalışma

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Abstract / Öz

Objective: During assisted ventilation and spontaneous breathing, functional haemodynamic parameters, including stroke volume variation (SVV) and pulse pressure variation (PPV), are of limited value to predict fluid responsiveness, and the passive leg raising (PLR) manoeuvre has been advocated as a surrogate method. We aimed to study the predictive value of SVV, PPV and PLR for fluid responsiveness during weaning from mechanical ventilation after cardiac surgery.

Methods: Haemodynamic variables and fluid responsiveness were assessed in 34 patients. Upon arrival at the intensive care unit, measurements were performed during continuous mandatory ventilation (CMV) and spontaneous breathing with pressure support (PSV) and after extubation (SPONT). The prediction of a positive fluid responsiveness (defined as stroke volume increase >15% after fluid administration) was tested by calculating the specific receiver operating characteristic (ROC) curves.

Results: A significant increase in stroke volumes was observed during CMV, PSV and SPONT after fluid administration. There were 19 fluid responders (55.9%) during CMV, with 22 (64.7%) and 13 (40.6%) during PSV and SPONT, respectively. The predictive value for a positive fluid responsiveness (area under the ROC curve) for SVV was 0.88, 0.70 and 0.56; was 0.83, 0.69 and 0.48 for PPV; was 0.72, 0.74 and 0.70 for PLR during CMV, PSV and SPONT, respectively.

Conclusion: During mechanical ventilation, adequate prediction of fluid responsiveness using SVV and PPV was observed. However, during spontaneous breathing, the reliability of SVV and PPV was poor. In this period, PLR as a surrogate was able to predict fluid responsiveness better than SVV or PPV but was less reliable than previously reported.

Keywords: Stroke volume variation, pulse pressure variation, passive leg raising, functional haemodynamic parameter, pulse contour analysis

Amaç: Yardımlı ventilasyon ve spontan solunum sırasında, Atım Hacmi Varyasyonu (SVV) ve Nabız Basıncı Varyasyonunun (PPV) dâhil olmak üzere fonksiyonel hemodinamik parametreler, sıvı duyarlılığını tahmin etmek için sınırlı değerdedir ve pasif bacak kaldırma (PLR) manevrası alternatif bir yöntem olarak savunulmuştur. Kalp cerrahisi sonrası mekanik ventilasyondan weaning sırasındaki sıvı yanıtı için SVV, PPV ve PLR'nin prediktif değerini araştırmayı amaçladık.

Yöntemler: Hemodinamik değişkenler ve sıvı yanıtı 34 hastada değerlendirildi. Yoğun bakım ünitesine varışta, sürekli zorunlu ventilasyon (CMV) ve basınç desteği (PSV) ile spontan solunum esnasında ve ekstübasyon sonrası (SPONT) ölçümler yapıldı. Pozitif sıvı cevabı (sıvı uygulamasından sonra atım hacmi artışı >%15 olarak tanımlanır), belirli alıcı işlem karakteristik eğrilerinin (ROC) hesaplanmasıyla test edildi.

Bulgular: Sıvı uygulamasından sonra CMV, PSV ve SPONT esnasında, atım hacimlerinde belirgin bir artış gözlendi. CMV esnasında, 19 sıvı yanıtı (%55,9) ve PSV ve SPONT esnasında sırasıyla 22 (%64,7) ve 13 (%40,6) sıvı yanıtı vardı. Pozitif sıvı cevabı (ROC eğrisinin altındaki alan) için öngörü değeri, SVV için 0,88, 0,70 ve 0,56; PPV için 0,83, 0,69 ve 0,48; PLR için CMV, PSV ve SPONT esnasında sırasıyla 0,72, 0,74 ve 0,70 idi.

Sonuç: Mekanik ventilasyon esnasında, SVV ve PPV kullanılarak, sıvı cevabı için yeterli seviyede öngörüye ulaşılmıştır. Bununla birlikte, spontan solunum esnasında, SVV ve PPV'nin güvenilirliği zayıftı. Bu dönemde, alternatif bir uygulama olarak PLR, sıvı cevabını öngörmede SVV veya PPV'den daha başarılıydı, ancak daha önce bildirilenlere göre daha az güvenilirdi.

Anahtar sözcükler: Atım hacmi varyasyonu, nabız basıncı varyasyonu, pasif bacak kaldırma, fonksiyonel hemodinamik parametre, nabız kontur analizi

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Introduction

There is an ongoing debate with significant controversies regarding peri-operative fluid management. The overall goal is to maintain normovolemia and to avoid hyper and hypovolemia along with their deleterious effects on patient outcome (1). It has been shown that random fluid administration improves haemodynamics in 50% of all critically ill patients and that current strategies to assess fluid status are based on weak evidence (2). In patients who require critical care, there is an urgent need to determine individual fluid status with reliable and easy-to-use monitoring tools. For optimal care, fluids should be administered only to patients who have a clear benefit, i.e. to a fluid responsive patient. Fluid administration should be goal directed, and the fluid status should be frequently re-assessed using robust and reproducible measurements (3, 4).

A major development in this regard has been the introduction of functional haemodynamic parameters (5). Derived from heart–lung interactions during mechanical ventilation, dynamic parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV) have been shown to more reliably predict response to a fluid challenge than traditional static parameters, including central venous pressure (CVP) or pulmonary artery occlusion pressure (6, 7). However, dynamic parameters are unreliable during spontaneous breathing activity. To overcome the limited accuracy of these haemodynamic parameters in this specific clinical scenario, a passive leg raising (PLR) manoeuvre has been suggested to be a reliable predictor of fluid responsiveness during spontaneous breathing (8).

Fluid therapy during weaning from mechanical ventilation is challenging as the transition from controlled ventilation to spontaneous breathing induces strong haemodynamic changes that can lead to weaning-induced cardiac failure. Cardiac patients are particularly at risk of such complications (9). Little is known about the performance of functional haemodynamic parameters as well as other haemodynamic monitoring modalities to predict the fluid status and responsiveness in this critical phase. Therefore, the aim of the present study was to evaluate how reliably SVV and PPV predict fluid responsiveness and whether PLR can be used as a surrogate for fluid loading during weaning from mechanical ventilation after cardiac surgery.

Methods

Patients

Adult patients undergoing elective cardiac surgery (off-pump coronary artery bypass grafting) were studied in the post-operative intensive care period. Emergent cardiac surgery, age <18 years, impaired left-ventricular ejection fraction (<45%), arrhythmias, intra-ventricular shunt, severe peripheral arterial occlusive disease and the need for intra-aortic balloon counter pulsation served as the exclusion criteria. The study was commenced after obtaining the local ethics committee approval; all the patients provided written informed consent prior to participation.

Monitoring

Standard monitoring (IntelliVue MP70, Philips Medical Systems, Philips Healthcare, 5680 DA Best, Netherlands) included five-lead electrocardiogram, pulse oximetry and CVP via a central venous line placed into the right internal jugular vein in all patients. Invasive arterial blood pressure was measured via a 5-French thermistor-tipped catheter (Pulsiocath, Pulsion Medical Systems, Munich, Germany) placed into the femoral artery. The arterial catheter was connected to a PiC-CO_2 monitor (Pulsion Medical System, Munich, Germany) to continuously assess the cardiac output (CO), stroke volume (SV), SVV and PPV. The PiCCO_2 monitor was calibrated by transpulmonary thermodilution according to the manufacturer's recommendations. Details of the PiCCO system have been described elsewhere (10).

Patient management and study protocol

Three haemodynamic measurement cycles were performed during routine postoperative intensive care. The first measurement was performed under continuous mandatory ventilation (CMV), the second during pressure support ventilation (PSV; allowing spontaneous breathing activities) and the last after endotracheal extubation (SPONT) of the spontaneously breathing patients without any respiratory support.

Patients were managed according to institutional standards. Initially, they remained sedated using propofol (1–2 mg kg^{-1} h^{-1}) and remifentanil (2–5 µg kg^{-1} h^{-1}); rocuronium (0.2–0.5 mg kg^{-1} h^{-1}) were administered for neuromuscular blockade. The patients were mechanically ventilated using a volume-controlled mode (tidal volume=8–10 mL kg^{-1}, respiratory frequency=12 min^{-1}) to achieve normoventilation (aimed at arterial PCO_2 4–4.5 kPa). Subsequently, weaning from the ventilator was started by PSV (pressure support 5–15 cm H_2O, positive end-expiratory pressure=5 cmH_2O) allowing spontaneous breathing efforts of the patients.

Each haemodynamic measurement cycle (comprising 5 haemodynamic measurement time points – before/during/after the PLR manoeuvre and before/after the fluid challenge) was initiated when the physician in charge made the decision to administer intravenous (i.v.) fluids. This was based on the presence of at least one clinical sign of acute circulatory failure or associated signs of hypoperfusion. Before fluid administration, transpulmonary thermodilution measurements were performed in a semi-recumbent, supine position (before PLR) by triplicate injection of 15 mL ice-cold normal saline. A difference of >15% in CO and global end-diastolic volume (GEDV) measurements prompted another two injections to achieve measurements below this threshold. Then, three measurements were averaged, and haemodynamic data, including heart rate (HR), mean arterial pressure (MAP), CVP, CO, SV, SVV PPV and GEDV were recorded. Thereafter, a PLR manoeuvre was performed by raising the lower limbs to a 45° angle while the patient's trunk was lowered, as previously reported by Monnet et al. (11). Changes in haemodynamics were measured, and the maximum values within the first 3

min were recorded (during PLR). After completing the PLR, patients were placed back into the semi-recumbent, supine position and another haemodynamic measurement was performed after achieving haemodynamic stability (after PLR). A fluid challenge (i.e. 500 mL of gelatine solution; Physiogel® balanced, B. Braun AG, Melsungen, Germany) was prepared and administered over a 20 min time period. Before and after fluid administration, another complete haemodynamic measurement was performed.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (version 12.3.2 for MAC 2008, Microsoft Corporation, Redmond, WA), Sigmaplot (version 12.0, Systat, San Jose CA) and SPSS® 10.0 (SPSS® Inc., Chicago, IL, USA). A sample size of >30 patients (α=0.05 and power=0.8) was calculated to detect changes in SV induced by fluid loading that were >15%. Student's t-test was used to compare haemodynamic data before and after fluid administration. To evaluate repeated measurements, analysis of variance with a Bonferroni correction was used. The prediction of fluid responsiveness was tested by calculating the area under receiver operating characteristic (ROC) curve for PLR and the following variables: SVV, PPV, CVP and GEDV. Positive fluid responsiveness was defined as an increase of SV >15% after the fluid challenge (500 mL of gelatine infusion over 20 min) Threshold values were identified as matching values with highest sensitivity and values with highest specificity. ROC curves were compared as reported by Hanley et al. (12) A p value of <0.05 was considered to be statistically significant. Data are presented as mean ±standard deviation.

Results

In total, 34 patients were included in this study (Table 1), and 510 sets of data (15 complete haemodynamic measurements per patient, 5 each per CMV, PSV and SPONT) were available for statistical analysis.

PLR resulted in significant changes of all haemodynamic parameters (Table 2). PLR induced a mean increase of 7.3% in SV during CMV, 6.0% during assisted PSV and 6.0% during spontaneous breathing after SPONT (Table 2). After PLR, an increase of >15% in SV was observed in 13 (38.4%), 12 (35.3%) and 6 (18.2%) patients during CMV, PSV and SPONT, respectively.

The fluid challenge (i.e. IV administration of 500 mL of gelatine solution over 20 min) resulted in significant haemodynamic changes during all three measurement periods (Table 3). SV increased by 18.3±14.4% during CMV, by 17.4±17.9% during PSV and by 13.9±17.7% during SPONT. According to SV changes, 19 (55.9%), 22 (64.7%) and 13 (40.6%) patients were categorised as fluid responders (SV increase >15%) during CMV, PSV and SPONT, respectively. There was a significant increase in CVP and GEDV and decrease in SVV and PPV after fluid loading. In addition, MAP only increased during CMV but not during PSV and SPONT. Results for responders and non-responders after fluid administration showed a significant difference predominantly during CMV, CVP, GEDV and CO, and the related parameters tended to be higher and SVV and PPV lower for non-responders compared to responders (Table 3).

Hemodynamic variables were also significantly different in PLR between patients who (later) showed a positive fluid responsiveness and those who did not show primarily during CMV (Table 2). Interestingly, there was also a significant increase in the MAP after PLR, and this response exceeded the increase in the MAP after the fluid challenge (Tables 2 and 3). One possible explanation could be the speed of preload increase, which was greater in PLR compared to that in the fluid challenge.

Results of the ROC curve analysis for the prediction of fluid responsiveness are summarised in Figure 1 and Table 4. During CMV, SVV (AUC=0.89) and PPV (AUC=0.84) allowed a good identification of fluid responders, but not when spontaneous breathing activities were present (i.e. during PSV and SPONT). AUC for PLR was comparable for all three measurement cycles (AUC=0.72, 0.74 and 0.70, respectively), whereas CVP and GEDV could not identify fluid responders.

During CMV, the optimal threshold values predicting fluid responsiveness given by the ROC curves were 11.5% for SVV (sensitivity: 94%; specificity: 80%), 10% for PPV (sensitivity: 94%; specificity: 80%) and ΔSV of 10% for PLR (sensitivity: 84%; specificity: 79%). There were only significant differences between the AUC of SVV, PPV and PLR compared to CVP and GEDV during CMV as well as the AUC of SVV, PPV and PLR compared to GEDV during PSV (Table 5).

Discussion

During weaning from mechanical ventilation after cardiac surgery, functional haemodynamic parameters, such as PPV and SVV, only showed adequate prediction of fluid responsiveness during the period of CMV. After transition to assisted PSV and during spontaneous breathing after SPONT,

Table 1. Characteristics of study participants

Female/male ratio n/n	6/28
Age years	65.8±8.9
BMI kg m^{-2}	27.9±4.5
Euroscore	3.4±1.9
LVEF %	64.8±6.1
Hypertension n (%)	28 (82)
Diabetes n (%)	4 (11.8)
COLD n (%)	12 (35.3)

BMI: body mass index; COLD: chronic obstructive lung disease; LVEF: left ventricular ejection fraction

Table 2. Haemodynamic parameters before, during and after the PLR manoeuvre

	CMV			PSV			SPONT		
	Before	**During**	**After**	**Before**	**During**	**After**	**Before**	**During**	**After**
HR beats min^{-1}	84±9	85±7	86±8	87±9	86±9	86±8	85±8	85±8	85±8
HR_{Resp} beats min^{-1}	87±6	86±3	86±7	87±9	85±8	87±8	88±6	88±5	88±6
$HR_{Non\text{-}Resp}$ beats min^{-1}	82±8§	82±10§	81±10§	83±10	84±10	83±8	83±8§	83±8	83±8
MAP mmHg	77.3±10.1	86.9±10.3*	73.8±9.0*	78.4±10.8	81.1±11.8*	59.9±99.0*	78.0±8.3	80.9±8.2*	76.0±8.0*
MAP_{Resp} mmHg	77.1±12.3	89.4±10.7*	74.0±9.8*	76.3±11.6	79.9±11.7*	57.5±8.1*	77.3±9.9	81.2±11.1*	76.4±11.3*
$MAP_{Non\text{-}Resp}$ mmHg	77.4±8.9	83.7±9.1*	73.5±9.9*	82.4±8.2	83.4±11.9	61.9±10.3*	78.1±7.3	80.7±5.8	75.6±5.0*
CVP mmHg	9.0±3.1	11.2±4.1*	9.0±3.3*	11.1±4.0	13.9±4.4*	11.3±4.0*	8.2±4.1	11.6±4.2*	7.9±4.0*
CVP^{Resp} mmHg	8.1±2.9	9.9±3.2*	8.1±3.3*	11.4±4.4	14.0±4.9*	11.3±4.2*	6.4±3.4	9.5±3.6*	5.9±3.3*
$CVP^{Non\text{-}Resp}$ mmHg	10.0±3.0§	12.8±4.5*§	10.0±3.0*	10.5±3.2	13.8±3.7*	11.0±3.4*	9.8±4.2§	13.0±4.0*§	9.4±3.7*§
CO L min^{-1}	5.1±1.1	5.3±1.3*	4.8±1.3*	5.4±1.4	5.5±1.5	5.4±1.5	6.2±1.9	6.2±1.8*	5.9±1.8*
CO_{Resp} L min^{-1}	4.5±0.7	4.9±0.8*	4.3±0.9*	5.3±1.1	5.4±1.2	5.1±1.1	5.6±1.5	5.8±1.5*	5.3±1.3*
$CO_{Non\text{-}Resp}$ L min^{-1}	5.9±1.2§	6.0±1.1*§	5.8±1.4*§	5.9±1.8	5.9±1.9	5.9±2.1	6.4±2.1§	6.4±1.9§	6.3±2.1§
CI L min^{-1} m^{-2}	2.6±0.5	2.7±0.6*	2.5±0.6*	2.8±0.6	2.9±0.7	3.1±0.7	3.2±0.8	3.2±0.7*	3.0±0.8
CI_{Resp} L min^{-1} m^{-2}	2.3±0.2	2.6±0.4*	2.3±0.4*	2.7±0.5	2.8±0.5	2.9±0.7	3.0±0.6	3.1±0.7*	2.8±0.5
$CI_{Non\text{-}Resp}$ L min^{-1} m^{-2}	2.9±0.6§	3.0±0.6*§	2.8±0.6§*	2.9±0.8	3.0±0.9	3.3±0.8	3.3±0.9	3.3±0.8*	3.2±0.9
SV mL	60.0±17.4	63.3±18.4*	58.0±19.0*	63.9±21.2	64.5±21.3*	69.7±19.7	71.8±23.2	74.1±23.8*	70.2±23.1*
SV_{Resp} mL	50.4±8.3	53.6±8.9*	48.9±10.9*	59.5±13.4	61.3±14.6*	66.4±19.0*	62.0±15.0	66.6±16.8*	60.4±15.6*
$SV_{Non\text{-}Resp}$ mL	71.5±18.9§	75.6±22.3*§	69.5±21.2*§	71.6±29.0§	70.4±29.9§	70.9±20.3§	78.4±26.3§	79.2±26.7§	76.9±25.3§
SVV %	18.4±7.0	11.7±5.2*	19.7±7.4*	13.8±5.4	11.7±3.8*	14.6±6.0*	14.0±5.5	11.6±4.6*	15.8±5.6*
SVV_{Resp} %	22.4±6.0	13.7±4.7*	23.3±6.6*	15.1±5.9	12.5±3.6*	15.9±6.6*	14.6±5.1	11.2±4.6*	15.7±5.1*
$SVV_{Non\text{-}Resp}$ %	13.5±4.8§	9.2±4.8*§	15.2±5.6*§	11.3±3.4§	10.3±3.9*	12.3±93.6*	13.7±5.9§	11.8±4.7*	15.9±6.0*
PPV %	17.1±6.8	11.7±5.9*	18.1±6.4*	13.8±6.7	10.3±4.6*	13.9±7.1*	12.8±4.2	11.5±4.6*	15.6±5.4*
PPV_{Resp} %	20.6±6.5	14.4±6.1*	20.8±6.5*	15.2±7.4	11.2±5.0*	15.5±8.1*	12.8±3.9	11.0±4.0*	15.9±4.5*
$PPV_{Non\text{-}Resp}$ %	12.6±4.0§	8.0±3.0*§	14.8±4.6*§	10.4±3.8	8.4±2.8*§	11.2±3.7*§	12.9±4.4	11.9±5.0	15.4±6.0*

CI: cardiac index; CMV: continuous mandatory ventilation; CO: cardiac output; CVP: central venous pressure; HR: heart rate; Non-Resp: fluid non-responder (negative fluid responsiveness); MAP: mean arterial pressure; PPV: pulse pressure variation; PSV: pressure support ventilation; Resp: fluid responder (positive fluid responsiveness); SV: stroke volume; SVV: stroke volume variation; SPONT: spontaneous breathing after endotracheal extubation; PLR: passive leg raising n=34 patients; *p<0.05 comparing before and after, §p<0.05 comparing Resp and Non-Resp

the ability of these parameters to predict fluid responsiveness was poor. The PLR manoeuvre could predict a positive response to fluid administration throughout the weaning period and even during spontaneous breathing activity. However, PLR was less accurate in our patients during all the phases of weaning compared to previous reports that showed pooled sensitivity and specificity ≥85% and AUC=0.95 (13, 14).

Dynamic parameters of fluid responsiveness, including PPV and SVV, have been shown to be superior to traditional static parameters in predicting rise in stroke volume following a fluid challenge (6, 7). These parameters are displayed by most of the currently available haemodynamic monitoring devices, and their use is recommended by several treatment guidelines of authorities (15). A prerequisite for their accurate performance is a passive patient, i.e. the patient is ventilated in a fully controlled mode with a tidal volume ≥8 mL kg^{-1}. However, these parameters proved to be unreliable in most real-life clinical situations, i.e. in the presence of spontaneous breathing activity, arrhythmias, small tidal volumes and a low respiratory rate (16, 17). In our study, the performance of PPV and SVV is in agreement with these findings. Recent observational data also suggest that in the majority of critically ill patients, the use of dynamic parameters is precluded for these reasons (18).

The PLR manoeuvre has been suggested in such situations as an alternate modality to assess fluid responsiveness (19). By

Table 3. Haemodynamic parameters before and after fluid administration

	CMV		PSV		SPONT	
	Before	After	Before	After	Before	After
HR beats min^{-1}	85±8	86±7	87±9	86±9	85±8	84±7
HR_{Resp} beats min^{-1}	88±5	82±3	86±9	86±9	89±7	86±6
$HR_{Non-Resp}$ beats min^{-1}	81±9	81±10	84±10	85±10	82±8§	83±8
MAP mmHg	77.4±10.5	85.0±10.7*	78.4±10.8	78.0±7.6	78.0±8.3	77.9±7.4
MAP_{Resp} mmHg	77.2±12.1	85.5±11.1*	76.3±11.6	77.6±7.3	77.3±9.9	80.3±9.5
$MAP_{Non-Resp}$ mmHg	77.6±8.8	82.2±9.4*	82.5±8.2§	78.8±8.5	78.1±7.3	76.3±5.2
CVP mmHg	9.0±3.1	10.9±3.7*	11.1±4.1	13.6±3.9*	8.2±4.1	11.6±4.2*
CVP_{Resp} mmHg	8.1±2.9	9.6±3.3*	11.5±4.3	14.0±4.1*	6.4±3.4	9.5±3.6*
$CVP_{Non-Resp}$ mmHg	10.0±3.0§	12.5±3.5*§	10.5±3.3	12.8±3.4*	9.8±4.2§	13.0±4.0*§
GEDV mL	658±152	718±181*	719±199	762±224*	759±178	787±177*
$GEDV_{Resp}$ mL	618±168	702±214*	867±199	753±247*	713±162	765±121*
$GEDV_{Non-Resp}$ mL	708±114§	738±132*§	813±169§	780±185*	781±187§	802±209*§
CO L min^{-1}	5.1±1.1	6.0±1.2*	5.5±1.4	5.8±1.5*	6.2±1.8	6.3±1.7*
CO_{Resp} L min^{-1}	4.5±0.7	6.4±1.4*	5.2±1.1	5.7±1.4*	5.7±1.5	5.9±1.3*
$CO_{Non-Resp}$ L min^{-1}	5.8±1.2§	5.7±1.1*§	5.8±1.9	6.0±1.9*	6.4±2.1§	6.6±1.9*
CI L min^{-1} m^{-2}	2.6±0.5	3.1±0.5*	2.8±0.7	3.3±0.8*	3.2±0.8	3.3±0.7*
CI_{Resp} L min^{-1} m^{-2}	2.4±0.3	3.0±0.4*	2.7±0.5	3.1±0.9*	3.0±0.6	3.2±0.5*
$CI_{Non-Resp}$ L min^{-1} m^{-2}	2.9±0.6§	3.3±0.6*§	3.0±0.8	3.3±0.7*	3.3±0.9	3.4±0.8*
SV mL	60.0±17.4	63.8±21.1*	63.8±21.1	68.4±21.5*	71.9±23.3	77.2±22.7*
SV_{Resp} mL	50.4±8.3	57.9±9.6*	59.6±14.4	66.1±16.5*	62.0±15.1	68.8±16.4*
$SV_{Non-Resp}$ mL	71.5±18.9§	78.3±25.5*§	71.7±29.1§	72.2±29.1*§	78.5±26.4§	81.5±25.2*§
SVV %	18.4±7.0	11.7±5.2*	14.0±5.4	11.2±4.7*	14.2±5.5	11.6±4.6*
SVV_{Resp} %	22.4±6.0	13.7±4.7*	15.2±5.9	11.6±5.0*	14.9±5.1	11.2±4.6*
$SVV_{Non-Resp}$ %	13.5±4.8§	9.2±4.8*§	11.3±3.4§	10.5±4.4*	13.9±5.9	11.8±4.7*
PPV %	17.1±6.8	10.6±4.6*	13.4±6.6	10.3±4.3*	12.7±4.1	11.5±4.3
PPV_{Resp} %	20.6±6.5	12.1±5.1*	15.0±7.4	10.7±4.4*	12.7±3.9	11.4±3.9
$PPV_{Non-Resp}$ %	12.6±4.0§	8.7±3.3*§	10.4±3.8§	9.4±4.2*	12.9±4.4	11.6±4.6

CI: cardiac index; CMV: continuous mandatory ventilation; CO: cardiac output; CVP: central venous pressure; GEDV: global end-diastolic volume; HR: heart rate; Non-Resp: fluid non-responder (negative fluid responsiveness); MAP: mean arterial pressure; PPV: pulse pressure variation; PSV: pressure support ventilation; Resp: fluid responder (positive fluid responsiveness); SV: stroke volume; SVV: stroke volume variation; SPONT: spontaneous breathing after endotracheal extubation
n=34 patients; *p<0.05 comparing preceding measurement, §p<0.05 comparing Resp and Non-Resp

moving the patient from a semi-recumbent to a supine position with legs raised to 45°, approximately 300 mL of venous blood can be mobilised. This endogenous fluid challenge as a surrogate method for intravascular fluid infusion sufficiently increases the mean systemic pressure to result in an increase of venous return and subsequent SV increase (8). The clinical performance of this procedure has recently been summarised by two meta-analyses which showed excellent accuracy (pooled sensitivity and specificity ≥85% and AUC=0.95) in predicting fluid responsiveness across a range of clinical conditions, if the response to PLR was monitored by the continuous measurement of SV (13, 14). Most importantly, the accurate performance of PLR persisted during spontaneous breathing. However, in the present study, the accuracy of PLR in predicting fluid responsiveness was considerably below that reported in previous studies. The following factors have been implicated to influence the accuracy of PLR: the conduct of the PLR manoeuvre itself (20), insufficient mobilisation of blood during PLR (i.e. increased abdominal pressure (21), compression stockings (22), increased sympathetic activity (23) and the

Table 4. Prediction of fluid responsiveness

	CMV					PSV					SPONT				
	AUC	95% CI	P	R	P	AUC	95% CI	P	R	P	AUC	95% CI	P	R	P
SVV	0.89	0.76/1.00	0.01	0.42	0.02	0.70	0.52/0.88	0.05	0.33	0.10	0.56	0.35/0.76	0.61	0.11	0.57
PPV	0.84	0.70/0.97	0.03	0.39	0.04	0.69	0.52/0.87	0.06	0.29	0.21	0.48	0.28/0.69	0.86	0.18	0.47
PLR	0.72	0.55/0.89	0.02	0.44	0.01	0.74	0.57/0.91	0.02	0.49	0.01	0.70	0.50/0.90	0.05	0.70	0.01
CVP	0.45	0.25/0.64	0.58	0.27	0.12	0.55	0.34/0.76	0.63	0.11	0.56	0.47	0.27/0.66	0.76	0.19	0.29
GEDV	0.44	0.24/0.64	0.59	0.13	0.48	0.46	0.25/0.69	0.69	0.09	0.93	0.49	0.26/0.67	0.70	0.14	0.59

AUC: area under the curve; CI: confidence interval; CMV: continuous mandatory ventilation; CVP: central venous pressure; GEDV: global end-diastolic volume; PLR: passive leg raising manoeuvre; PPV: pulse pressure variation; PSV: pressure support ventilation; R: Pearson correlation coefficient (correlation with changes of SV due to fluid loading); SPONT: spontaneous breathing after extubation; SVV: stroke volume variation

Table 5. Comparison of ROC curves (p values)

	CMV					PSV					SPONT				
	SVV	PPV	PLR	CVP	GEDV	SVV	PPV	PLR	CVP	GEDV	SVV	PPV	PLR	CVP	GEDV
SVV	-	0.29	0.06	<0.01	<0.01	-	0.47	0.38	0.13	0.04	-	0.28	0.15	0.26	0.31
PPV	0.29	-	0.15	<0.01	<0.01	0.47	-	0.35	0.15	0.05	0.28	-	0.05	0.47	0.48
PLR	0.06	0.15	-	0.02	0.02	0.38	0.35	-	0.08	0.02	0.15	0.05	-	0.05	0.06
CVP	<0.01	<0.01	0.02	-	0.47	0.13	0.15	0.08	-	0.26	0.26	0.47	0.05	-	0.44
GEDV	<0.01	<0.01	0.02	0.47	-	0.04	0.05	0.02	0.26	-	0.31	0.48	0.06	0.44	-

CMV: continuous mandatory ventilation; CVP: central venous pressure; GEDV: global end-diastolic volume; PLR: passive leg raising manoeuvre; PPV: pulse pressure variation; PSV: pressure support ventilation; SPONT: spontaneous breathing after extubation; SVV: stroke volume variation; ROC: receiver operating characteristics

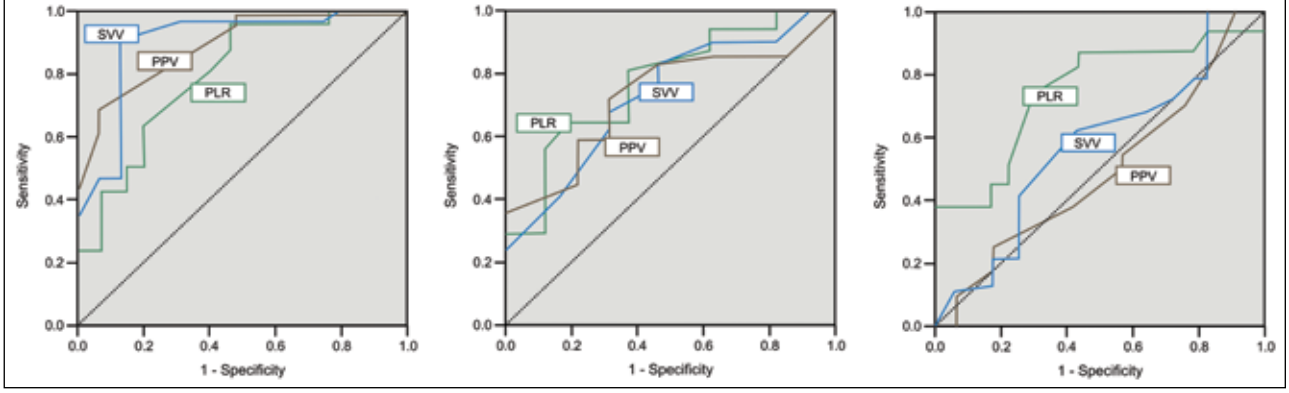

Figure 1. Prediction of fluid responsiveness and ROC curves
AUC: area under the curve; CI: confidence interval; CMV: continuous mandatory ventilation; SPONT: spontaneous breathing after endotracheal extubation; PLR: passive leg raising manoeuvre; PPV: pulse pressure variation; PSV: pressure support ventilation; SV: stroke volume; SVV: stroke volume variation; ROC: receiver operating characteristic, numeric data see Table 4.

accuracy of the monitoring device used to display changes in SV in response to PLR (11). In the present study, PLR was performed starting from a semi-recumbent position following cardiac surgery, as recommended by Monnet et al. (11). The amount of mobilised blood may have been limited by the presence of compressive dressings covering the vein graft harvesting sites at the lower extremities. Further, with transition to spontaneous breathing and decrease in the level of sedation, increased sympathetic activity may have counteracted the haemodynamic effect of PLR. The irritating effect of indwelling pleural and/or mediastinal drains during the procedure and postural change itself may have further provoked changes in HR and vascular tone mediated by the sympathetic drive.

The PiCCO system used in the present study has been shown to accurately display changes in SV following PLR and fluid

challenges (24, 25). However, only a small number of published studies actually investigated the performance of PLR as a surrogate method to predict fluid responsiveness in cardiac surgical patients (26, 27). These investigations mostly used bioreactance as a technology to measure SV changes rather than the devices based on pulse wave analysis, including PiCCO, rendering comparison with our results difficult (28, 29). In a rigorous investigation of PLR to detect fluid responsiveness in patients after cardiac surgery, Benomar et al. (27) determined the least minimum significant change (LMSC), i.e. the level above which SV changes can be expected not to occur because of random errors, specifically with regard to the NICOM bioreactance device. Defining the thresholds of SV change for fluid responsiveness on the basis of LMSC, the authors determined sensitivity of 68% and specificity of 95% in predicting fluid responsiveness for PLR (AUC=0.84), which is below the pooled performance data suggested by recent meta-analyses. This may indicate that PLR performance is generally limited in cardiac surgery settings compared to other clinical circumstances, e.g. sepsis, in which most studies investigating PLR performance have been conducted. In fact, previous studies performed after cardiac surgery have not assessed PLR in extubated, non-sedated patients.

The present study has several limitations, which need to be addressed. This investigation was performed in a small and highly selected group of cardiac surgery patients, which precludes the generalizability of our results. Any assumptions regarding the limiting effects on PLR performance have to remain speculative, as no measurements of vascular tone, abdominal pressure or venous compression were performed. Data collection was performed on site in the intensive care unit and in real time, as opposed to previous studies using continuous data recording with consecutive averaging of SV data for offline analysis. Whether the latter practise has an effect on the accuracy of measured SV response to fluid administration has not been established.

The present study has focused on a common clinical scenario that has not been systematically addressed by previous research: haemodynamic stabilization during ongoing weaning from ventilator support. PLR may be a useful tool to assess fluid responsiveness in this situation avoiding the need for *a priori* IV fluid infusion, although it is less accurate after cardiac surgery than previously reported. Alternative estimates of fluid responsiveness have been suggested, such as the end-expiratory occlusion test during mechanical ventilation (25) or a mini fluid challenge, applicable in non-ventilated patients (30). However, the value of these methods in the postoperative care of cardiac surgical patients has yet to be established.

Conclusion

In patients after cardiac surgery, fluid responsiveness can be predicted using SVV and PPV as long as they are mechanically ventilated. Conversely, during spontaneous breathing activity, the reliability of SVV and PPV is poor. As an alternative, the PLR manoeuvre is suggested to be a reliable test even during spontaneous breathing. Our data in post-operative cardiac surgical patients however show that PLR is less reliable than previously reported.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kantonale Ethikkommission des Kantons Zürich.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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