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ORIGINAL RESEARCH

Ability of short-time low peep challenge to predict fluid responsiveness in mechanically ventilated patients in the intensive care

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Abstract
Short-time low PEEP challenge (SLPC, application of additional 5 cmH_2O PEEP to patients for 30 s) is a novel functional hemodynamic test presented in the literature. We hypothesized that SLPC could predict fluid responsiveness better than stroke volume variation (SVV) in mechanically ventilated intensive care patients. Heart rate, mean arterial pressure, stroke volume index (SVI) and SVV were recorded before SLPC, during SLPC and before and after 500 mL fluid loading. Patients whose SVI increased more than 15% after the fluid loading were defined as fluid responders. Reciever operating characteristics (ROC) curves were generated to evaluate the abilities of the methods to predict fluid responsiveness. Fifty-five patients completed the study. Twenty-five (46%) of them were responders. Decrease percentage in SVI during SLPC (SVIΔ%–SLPC) was 11.6 ± 5.2% and 4.3 ± 2.2% in responders and non-responders, respectively ($p < 0.001$). A good correlation was found between SVIΔ%–SLPC and percentage change in SVI after fluid loading ($r = 0.728$, $P < 0.001$). Areas under the ROC curves (ROC–AUC) of SVIΔ%–SLPC and SVV were 0.951 (95% CI 0.857–0.991) and 0.747 (95% CI 0.611–0.854), respectively. The ROC–AUC of SVIΔ%–SLPC was significantly higher than that of SVV ($p = 0.0045$). The best cut-off value of SVIΔ%–SLPC was 7.5% with 90% sensitivity and 96% specificity. The percentage change in SVI during SLPC predicts fluid responsiveness in intensive care patients who are ventilated with low tidal volumes; the sensitivity and specificity values are higher than those of SVV.

Keywords Monitoring · intraoperative · Fluid therapy · Positive-pressure respiration · Stroke volume

1 Introduction

Fluid therapy plays an important role in the hemodynamic management of critically ill patients [1, 2]. Positive fluid balance is an independent risk factor for morbidity and mortality in this patient group [3, 4].

Static preload assessments have been deemed inadequate in predicting fluid responsiveness in multiple studies [5–7]. Therefore, stroke volume variation (SVV) and pulse pressure variation (PPV) have been defined and used to evaluate fluid responsiveness. However, protective ventilation with low tidal volumes limits the use of these measurements in intensive care patients; thus, various functional hemodynamic tests (FHTs) have been described as alternatives to SVV and PPV [8]. Recently, a novel method named "short-time low PEEP challenge" (positive end-expiratory pressure; SLPC) has been defined and is the newest of the FHTs presented in the literature [9]. This method could predict fluid responsiveness in many clinical situations, particularly when SVV or PPV is not applicable due to low tidal volume [9].

Most fluid responsiveness studies performed under operating room conditions are conducted under general anesthesia and within the first minutes of mechanical ventilation, i.e., before its effects on lung mechanics appear [9–11]. Positive pressure ventilation inevitably causes atelectasis, fluid sequestration, surfactant dysfunction, and impaired capillary and lymphatic flow, all of which reduce respiratory system

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compliance [12]. Therefore, it is not possible to directly adapt the results obtained in this patient group to intensive care patients for two main reasons. First, because of the negative effects of prolonged mechanical ventilation, patients in intensive care units are generally expected to have lower respiratory system compliance values than recently intubated operating room patients. Since this directly affects cardiopulmonary interactions, it can change the cut-off values along with the sensitivity and specificity of the methods [11, 13]. Second, intensive care patients are followed up under sedation, whereas operating room patients are followed up under general anesthesia. For this reason, sympathetic tone differs between the two patient groups [14] and may affect patients' fluid responsiveness [15, 16]. Therefore, a method shown to be effective in operating room conditions should be safely and adequately tested for use on intensive care patients before it is broadly used in this patient group.

This study aimed to assess whether SLPC could predict fluid responsiveness better than SVV in intensive care patients followed up under controlled mechanical ventilation and ventilated with a low tidal volume (< 8 mL/kg ideal body weight [IBW]). The secondary aims were to reveal the performance of SLPC in this patient group and determine appropriate cut-off values over the receiver operator characteristics (ROC) curve.

2 Materials and methods

2.1 Patients

This observational cohort study was conducted between May 5, 2019, and September 9, 2019, and included patients aged ≥ 18 years who were mechanically ventilated in controlled mode with 4–8 cmH_2O PEEP in the intensive care unit and were prescribed fluid therapy. All patients included in the study were followed up with a radial arterial line. Patients with arrhythmia, an ejection fraction value < 50%, static respiratory system compliance (Crs, tidal volume/driving pressure) value < 35 mL/cmH_2O, valvular heart disease, spontaneous respiratory effort, or body mass index > 40 kg/m^2 or patients positioned prone were excluded from the study. Approval was obtained from the Clinical Research Ethics Committee (2018/1685), and informed consent was provided by each of the patient's guardians.

2.2 Hemodynamic monitorization

The heart rate (HR) and systolic, diastolic, and mean arterial pressures (SAP, DAP, and MAP, respectively) of patients were measured using a CARESCAPE Monitor (B850; GE Healthcare, Helsinki, Finland). Patients were connected to the Vigileo™ system (Edwards Lifesciences) using the FloTrac™ sensor over an existing invasive radial arterial cannulation. The following hemodynamic data were obtained through this pulse contour analysis system: stroke volume (SV), stroke volume index (SVI), cardiac output, cardiac index (CI), and SVV.

2.3 Ventilation

Patients were ventilated in the volume-controlled ventilation mode (Servo-i, Maquet, Göteborg, Sweden) with a tidal volume of < 8 mL/kg IBW. IBW was calculated using Robinson's formula [17]. CRS values were automatically calculated by the ventilator after inspiratory and expiratory hold maneuvers were performed.

2.4 Protocol

Attending intensivists decided whether to apply fluid therapy to patients; the decision-making process was not standardized with a protocol. All patients were in the supine position under controlled mechanical ventilation and sedation (Richmond agitation and sedation scale scores were − 3 or − 4) throughout the protocol. Hemodynamic parameters (SVI, CI, HR, MAP, and SVV) and respiratory parameters (tidal volume, frequency, PEEP, and peak pressure) of the patients were recorded at four points of the protocol (T1, T2, T3, and T4).

After baseline measurements were taken at T1, the patient's PEEP value was increased by 5 cmH_2O for 30 s (SLPC). The aforementioned hemodynamic and respiratory parameters were recorded again at the end of the SLPC (T2). Then, the PEEP value was decreased to the patient's baseline value, and the data were recorded 3 min later (T3). For fluid loading (FL), 500 mL of isotonic sodium chloride solution was infused within 10 min. After 3 min, the data at T4 were recorded for the last time. Patients with an increase in SVI of > 15% after FL were classified as "responders." The following parameters were then calculated in relation to SVI and SVV:

- Absolute change in SVV due to SLPC (SVVΔ–SLPC)
- Percentage change in SVI due to SLPC (SVIΔ%–SLPC)
- Percentage change in SVI after FL (SVIΔ%–FL)

2.5 Statistical analysis

The primary goal of the study was to compare the ability of SVIΔ%–SLPC and SVV_{T1} to predict fluid responsiveness in patients over the areas under the ROC curve (ROC–AUC). In this context, while power analysis was performed, it was predicted that the areas under the curve for SVIΔ%–SLPC and SVV_{T1} would be a minimum of 0.9 and a maximum of 0.75, respectively. More than 40% of

the patients were predicted to be fluid responsive. With type 1 error set to 5% and type 2 error set to 20%, we aimed to include at least 54 patients to reveal the predicted difference.

The distribution of interval data was evaluated by calculating the kurtosis and skewness values. Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as median (range 25th percentile–75th percentile). Categorical data are presented as frequency and percentage rates. The effects of SLPC and FL on hemodynamic parameters were analyzed using a two-way analysis of variance followed by Bonferroni correction. Hemodynamic data between the responders and non-responders were compared using Student's t-test. The intraclass correlation between the hemodynamic parameters at two baseline measures (T1 and T3) was evaluated using random-effects models to examine the similarity and reliability of the measurements within groups over time [18]. The relationship between SVIΔ%–SLPC and SVIΔ%–FL was evaluated using linear correlation analysis. ROC curves were created for SVIΔ%–SLPC, SVV_{T1}, and SVV_{T3} to evaluate their ability to predict fluid responsiveness. The areas under the ROC curve were compared using the approach defined by DeLong et al. [19]. Cut-off values for both methods and the sensitivity and specificity percentages were calculated using the Youden index (sensitivity + specificity − 1). Statistical significance was set at $p < 0.05$.

3 Results

3.1 Patient characteristics and general hemodynamic data

A total of 101 patients were eligible for inclusion in the study; 62 patients were included, and 55 patients finished the study with complete data (Fig. 1). The demographic and clinical characteristics of the patients are presented in Table 1. Twenty-five (46%) patients were responders and 30 (54%) patients were non-responders. The HR, MAP, SVI, and SVV values of responders and non-responders are shown in Table 2.

3.2 Similarity of baseline hemodynamic data

The intraclass correlations of baseline I (T1) and baseline II (T3) measurements were 0.994 (95% confidence interval 0.989–0.997) for HR, 0.977 (95% confidence interval 0.959–0.987) for MAP, 0.997 (95% confidence interval 0.995–0.998) for SVI, and 0.960 (95% confidence interval 0.932–0.976) for SVV.

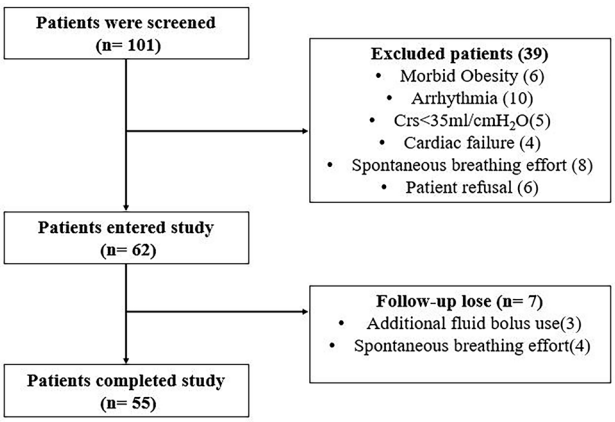

Fig. 1 Study flow-chart

3.3 Changes in SVI after SLPC and FL

After the SLPC, a decrease of 11.6 ± 5.2% and 4.3 ± 2.2% was found in SVI in responders and non-responders, respectively. A higher percentage decrease in SVI was observed after SLPC in responders than in non-responders ($p < 0.001$).

After FL, there was an increase in SVI of 27 ± 11% and 7.2 ± 4% in responders and non-responders, respectively. A higher percentage increase in SVI was observed after FL in responders than in non-responders ($p < 0.001$).

There was a good correlation between SVIΔ%–SLPC and SVIΔ%–FL ($p < 0.001$, $r = -0.728$).

3.4 Changes in SVV after SLPC

After the SLPC, an increase of 2% (1%–3%) and 1% (0%–2%) was found in SVV in responders and non-responders, respectively. A higher percentage increase in SVV was observed after SLPC in responders than in non-responders ($p = 0.02$).

There was no statistically significant correlation between SVVΔ–SLPC and SVIΔ%–FL ($p = 0.09$, $r = 0.25$).

3.5 Evaluation of fluid responsiveness

ROC curves were created to compare the abilities of SVIΔ%–SLPC, SVV_{T1}, and SVV_{T3} in predicting fluid responsiveness (Fig. 2). The value of the ROC–AUC for SVIΔ–SLPC (0.951, 95% confidence interval 0.857–0.991) was significantly higher than that for SVV_{T1} (0.747, 95% confidence interval 0.611–0.854) ($p = 0.0045$) and SVV_{T3} (0.752, 95% confidence interval 0.617–0.859) ($p = 0.006$).

The optimal cut-off values, sensitivity and specificity percentages, and negative and positive predictive values of both parameters for predicting fluid responsiveness are given in Table 3.

Table 1 Characteristics of patients

Variables	n = 55
Sex (male/female)	31 (56%)/24 (44%)
Age (years)	53 ± 15
Height (cm)	168 ± 10
Weight (kg)	72 ± 12
BMI (kg/m^2)	25.7 ± 4.3
IBW (kg)	63 ± 8
Tidal volume (mL)	410 ± 50
Tidal volume/IBW (mL/kg)	6.6 ± 0.3
Frequency	14 ± 1
PEEP (cmH_2O)	6 ± 1.3
Pdriving (cmH_2O)	8.7 ± 1.9
Crs (mL/cmH_2O)	48.7 ± 8.9
SOFA score	4 (2–6)
Horowitz ratio	1 (1–2)
MAP	1 (1–3)
Platelet count	0 (0–1)
Creatinine	0 (0–1)
Bilirubin	0 (0–1)
GCS	0 (0–0)
Noradrenaline ≤ 0.1 mcg/kg/min	12 patients (23%)
Responders	8 patients (32% of responders)
Non-responders	4 patients (13% of non-responders)
Noradrenaline > 0.1 mcg/kg/min	4 patients (8%)
Responders	2 patients (8% of responders)
Non-responders	2 patients (7% of non-responders)
Comorbidities	
Hypertension	18 (%33)
Coronary artery disease	12 (%22)
Diabetes	11 (%20)
Pulmonary disease	10 (%18)
Endocrine disease, other	5 (%9)
Renal disease	4 (%7)
Other	9 (%16)
Reason for admission to intensive care unit	
Respiratory reasons	4 (%7)
Cardiologic reasons	4 (%7)
Neurologic reasons	6 (%11)
Sepsis	4 (%7)
Trauma	6 (%11)
Other	3 (%5)
Postoperative care (ASA score ≥ 3)	28 (%51)
Cystectomy	2 (%7)
Retropubic radical prostatectomy	3 (%12)
Total esophagectomy	2 (%7)
Tracheal resection + reconstruction	2 (%7)
Mandibulectomy + free flap surgery	5 (%18)
Right hepatectomy + caudate lobectomy	4 (%14)
Debulking surgery for ovarian cancer	4 (%14)

Normally distributed data are expressed as mean ± SD. Non-normally distributed data are expressed as median (25th to 75th percentile). Qualitative data are expressed as number and percentage of case. *BMI* body mass index, *IBW* ideal body weight, *Pdriving* driving pressure, *Crs* static respiratory system compliance, *MAP* mean arterial pressure, *GCS* Glasgow coma score

Table 2 Hemodynamic variables during study period

	Baseline 1 (T1)	SLPC (T2)	*P1* values	Baseline 2 (T3)	After FL (T4)	*P*2 values
HR (beat/min)						
Responders	88 ± 22	88 ± 22	0.797	88 ± 22	86 ± 22	0.011*
Nonresponders	77 ± 24	76 ± 25	0.627	76 ± 25	76 ± 25	0.424
P intergroup	0.089	0.077		0.087	0.164	
MAP (mmHg)						
Responders	72 ± 14	70 ± 15	< 0.001*	72 ± 14	84 ± 15	< 0.001*
Nonresponders	77 ± 20	75 ± 19	0.009*	75 ± 20	80 ± 20	0.001*
P intergroup	0.415	0.326		0.541	0.455	
SVI (mL/m^2)						
Responders	37 ± 12	32 ± 10	< 0.001*	37 ± 11	46 ± 16	< 0.001*
Nonresponders	47 ± 12	45 ± 11	< 0.001*	47 ± 12	51 ± 13	< 0.001*
P intergroup	0.003*	< 0.001*		0.003*	0.293	
SVV (%)						
Responders	9.5 (6–13)	12 (9–14.3)	< 0.001*	9.5 (7–14)	5.5 (4.8–8)	< 0.001*
Nonresponders	6 (4–8)	8 (6.5–9)	< 0.001*	7 (5–8)	5 (3.5–6)	< 0.001*
P intergroup	0.002*	< 0.001*		0.001*	0.076	

Normally distributed data are expressed as mean ± SD. Non-normally distributed data are expressed as median (25th to 75th percentile). P1 = comparison between T1 and T2 with two-way repeated measures ANOVA with Bonferroni correction. P2: comparison between T3 and T4 with one-way repeated measures ANOVA with Bonferroni correction. P intergroup: comparison between responders and nonresponders with independent-sample T test. *HR* heart rate, *MAP* mean arterial pressure, *SVI* stroke volume index, *PPV* pulse pressure variation, *SVV* stroke volume variation. *SLPC* short-term low PEEP challenge, *FL* fluid loading

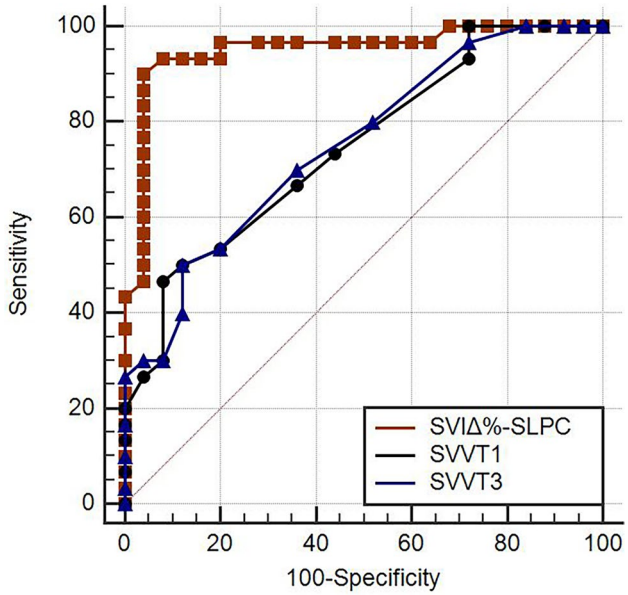

Fig. 2 Receiver operating characteristics curves generated for SVIΔ%–SLPC, SVV_{T1} and SVV_{T3} for showing to the ability to predict fluid responsiveness. *SVIΔ%–SLPC* Stroke volume index change percentage due to short-term low PEEP challenge, *SVV* stroke volume variation

4 Discussion

The findings of this study showed that during ventilation with < 8 mL/kg IBW tidal volume in the intensive care unit, SVI changes after SLPC and FL were well correlated. We also found a 7.5% decrease in SVI after SLPC predicted fluid responsiveness with higher sensitivity and specificity than SVV.

The results obtained in this study are in line with other studies showing that SVV does not work under protective ventilation [9, 20, 21]. Low tidal volumes and an average driving pressure below 9 cmH_2O were the main reasons for this. The performance of SVV is based on cardiopulmonary interactions. As in ventilation with low tidal volume (< 8 mL/kg IBW) or low driving pressure, when the change in pleural and transpulmonary pressures during inspiration is insufficient, the effects of these pressure changes on SV may not reach an accurately measurable level due to decreased signal-to-noise ratio even in the case of hypovolemia [20, 22]. As a result, SVV loses its predictive ability in such situations [23].

The most accepted cut-off value for SVV in patients ventilated with > 8 mL/kg IBW tidal volume is 10% and is

Table 3 Ability of variables to predict fluid responsiveness

Variable	Best cut-off values (%)	Sensitivity (%) (CI 95%)	Specificity (%) (CI 95%)	PPV (%) (CI 95%)	NPV (%) (CI 95%)
SLPC	> 7.5	90 (87–100)	96 (80–100)	95 (77–99)	92 (78–97)
SVV_{T1}	> 10	46 (21–71)	92 (30–72)	83 (58–95)	67 (58–75)
SVV_{T3}	> 9	50 (31–69)	88 (69–98)	78 (56–91)	67 (58–76)

Best cut-off values were determined using Youden index (J = sensitivity + specificity − 1). *SLPC* short-time low PEEP challenge, *SVV* stroke volume variation, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

expected to decrease when tidal volumes are lowered [24]. In contrast, our study revealed the best cut-off value to be 10%, but with poor sensitivity. One explanation for the aforementioned discord could be as follows. The best cut-off values for SVV have been shown to vary between 10 and 15% in different patient groups [24, 25]. It is therefore possible that if we had ventilated the patients with sufficient tidal volumes for the use of SVV, the cut-off values would have been closer to 15% with high sensitivity, contrary to our results. This variation between studies possibly results from the difference in overall fluid status and the quality of cardiopulmonary interactions between the patient groups.

Studies have shown that an increase in PEEP causes a decrease in SV [26, 27]. The reduction in SV is explained by the decrease in venous return as a result of an increase in pleural pressure [28]. In addition, the afterload of the right ventricle increases as a result of the change in transpulmonary pressure due to the increase in PEEP [29]. The level of reduction in SV depends on the patient's location in the Frank-Starling curve, the amount of PEEP applied, and the lung's ability to transmit the applied pressure to the pleura [27].

These physiological facts have also been demonstrated by Tusman et al. who conducted a study where they evaluated fluid responsiveness based on the change in carbon dioxide excretion with a PEEP increment in patients scheduled to undergo cardiovascular surgery. In this study, Tusman et al. examined the effect of the PEEP increment on CI as well [30]. They showed that with the PEEP increment from 5 to 10 cmH_2O, there was a significantly greater decrease in CI in the responders than in the non-responders, and that fluid responsiveness could be evaluated in this way. The best cut-off value for predicting fluid responsiveness was a 12% decrease in CI. Ali et al. studied this method in patients scheduled to undergo neurosurgery in the supine position and achieved similar results. They found that a 14.2% reduction in SVI after the application of additional 5 cmH_2O PEEP predicted fluid responsiveness with a ROC–AUC value of 94.4% [9]. To the best of our knowledge, our study is the first to demonstrate similar efficacy in intensive care patients. However, the best cut-off value for our patient group was 7.5%. This difference between the cut-off values can be explained in two ways. First, while the mean static compliance of the patients was found to be 59 mL/cmH_2O in the study conducted by Ali et al., the average static compliance of the patients in our study remained at the level of 48.7 mL/cmH_2O. In contrast to newly intubated patients in Ali et al.'s study, our patient group had been followed up under prolonged mechanical ventilation. This is one of the explanations for the difference between compliance values as mechanical ventilation impairs compliance by causing atelectasis and fluid sequestration as stated previously. This situation may have affected the transfer of pressure from the alveoli to the pleural and pericardial areas. Second, baseline PEEP values were less than 5 cmH_2O in the aforementioned study, while the mean PEEP of our patient group was 6 cmH_2O. In a study conducted on pigs by Lambert et al., when the PEEP value was increased from 0 to 10 cmH_2O, SVI decreased by 11 units, and when PEEP was increased from 10 cmH_2O to 20 cmH_2O, SVI decreased by another 6 units [31]. Therefore, the impact of PEEP increment on SVI is also related to the baseline PEEP value; as this value increases, the impact of the additional PEEP applied is likely to decrease. It is thought that the use of higher baseline PEEP values in intensive care patients may have lowered the cut-off value for this method.

The three widely accepted FHTs defined for patient groups for which SVV is not effective are as follows: the end-expiratory occlusion test (EEO), the passive leg raise test (PLR), and the mini fluid challenge (MFC) [5, 8]. With this study, SLPC is presented as another FHT that could be used on intensive care patients. Since the EEO includes a 15-s expiratory hold maneuver, it may worsen the condition of patients with high carbon dioxide pressure values [32, 33]. PLR loses its effect in increased intra-abdominal pressure [34] and cannot be used in cases where lower extremity elevation cannot be performed. MFC is the only method that does not rely on cardiopulmonary interactions and is the only choice when Crs is severely decreased. Yet, MFC requires 100 mL of fluid infused at each evaluation, thereby contributing less to the fluid balance. SLPC has not yet been validated in patients with > 8 cmH_2O PEEP values. Therefore, when SVV cannot be used, the alternative method should be chosen on a patient-by-patient basis.

This study had several limitations. First, 51% of the patient population consisted of patients who needed intensive care during the postoperative period, and the median SOFA score of the population was 4. Therefore, these data do not specifically reflect patient groups with conditions such as shock, septic shock, acute respiratory distress syndrome, or polytrauma. These patient groups have an important place in intensive care practice and have higher organ failure scores. Therefore, this method needs to be validated separately in the aforementioned clinical scenarios. Second, best cut-off, sensitivity, and specificity values may differ in patients ventilated with higher PEEP values. Third, while designing the study, patients with compliance values below 35 mL/cmH_2O were excluded. Therefore, it is not possible to comment on the effectiveness of SLPC in this particular patient group based on the results from this study. Fourth, SVI measurements were performed using uncalibrated pulse contour analysis technology. The use of calibrated technologies or echocardiographic parameters may lead to different results.

5 Conclusion

The percentage change in SVI during SLPC predicts fluid responsiveness in intensive care patients ventilated with low tidal volumes; the sensitivity and specificity values are higher than those of SVV. In this patient group, when other FHTs are not applicable, SLPC is a good alternative with high efficacy for evaluating fluid responsiveness.

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Data availability The data that support the findings of this study are available from the corresponding author, [TA], upon reasonable request.

Declarations

Conflict of interest The Authors declare that there is no conflict of interest/competing interests.

Ethical approval Approval was obtained from the Istanbul University, Istanbul Medical Faculty, Clinical Research Ethics Committee (2018/1685).

Informed consent Informed consent was provided by each of the patient's guardians.

Consent for publication All authors read and approved the final version of the manuscript.

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