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Comparison of the ability of short time low PEEP challenge and mini fluid challenge to predict fluid responsiveness in patients undergoing open pancreaticoduodenectomy: an observational cohort study

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ABSTRACT. – OBJECTIVE: **The mini-fluid challenge (MFC), which assesses the change in stroke volume index (SVI) following the administration of 100 mL of crystalloids, and the short-time low positive end-expiratory pressure (PEEP) challenge (SLPC), which evaluates the temporary reduction in SVI due to a PEEP increment, are two functional hemodynamic tests used to predict fluid responsiveness in the operating room. However, SLPC has not been assessed in patients undergoing abdominal surgery, and there is no study comparing these two methods during laparotomy. Therefore, we aimed to compare the SLPC and MFC in patients undergoing open pancreaticoduodenectomy.**

PATIENTS AND METHODS: **All patients received a standard hemodynamic management. The study protocol evaluated the percentage change in SVI following the application of an additional 5 cm-H_2O PEEP (SVIΔ%-SLPC) and the infusion of 100 mL crystalloid (SVIΔ%-MFC). Challenges that resulted in an increase of more than 15% in SVI after the 500 ml of fluid loading were classified as positive challenges (PC). Areas under the receiver operating characteristics curves (ROC AUCs) were used for the comparison of the methods.**

RESULTS: **Thirty-three patients completed the study with 94 challenges. Fifty-five (58.5%) of them were PCs. The ROC AUC of SVIΔ%-MFC was observed to be significantly higher than that of SVIΔ%-SLPC (0.97 *vs.* 0.64, $p < 0.001$). The best cut-off value for SVIΔ%-MFC was 5.6%. If we had stopped the bolus fluid administration when SVIΔ%-MFC ≤ 5% was observed (lower limit of the gray zone), we would have postponed the fluid loading in 35 (89.7%) of 39 negative challenges. The amount of fluid deferred would have corresponded to up to 40% of the total fluid given.**

CONCLUSIONS: **SVIΔ%-MFC predicts fluid responsiveness with high diagnostic performance and is better than SVIΔ%-SLPC in patients undergoing open pancreatoduodenectomy. Additionally, the use of SVIΔ%-MFC has the potential to defer up to 40% of the total fluid given.**

ClinicalTrials.gov: NCT05419570.

Key Words:
Intraoperative monitoring, Fluid therapy, Stroke volume, Pancreatoduodenectomy.

Introduction

Maintaining normovolemia during the perioperative period is crucial as both hypervolemia and hypovolemia can cause postoperative complications[1]. Therefore, goal-directed hemodynamic management (GDHM) is recommended for optimizing flow while avoiding unnecessary fluid loading (FL)[2-4].

Predicting fluid responsiveness is a vital part of GDHM. Traditional static variables, such as central venous pressure and pulmonary wedge pressure, have been shown[5] to be inadequate in predicting fluid responsiveness. Therefore, the use of dynamic parameters, such as pulse pressure variation (PPV) and stroke volume variation (SVV), have been advised when several prerequisites are ensured[6,7]. Functional hemodynamic tests (FHTs) have been developed to be used with cases for which these prerequisites cannot be achieved[8,9]. Among FHTs, mini-fluid challenge (MFC) has

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excellent accuracy in predicting fluid responsiveness in various clinical settings, including among patients undergoing open abdominal surgery and ventilated with tidal volumes (TVs) < 8 mL/kg ideal body weight (IBW)[10]. However, MFC relies on the evaluation of the change in the stroke volume index (SVI) following a small fluid volume, usually 100 mL of crystalloids[9]. When there is an increase in the frequency of a necessary fluid responsiveness assessment, the sum of these small infusions might result in a considerable fluid volume. Short-time low positive end-expiratory pressure (PEEP) challenge (SLPC) is another FHT with the potential to eliminate this limitation[8]. In this test, the temporary reduction of the SVI due to PEEP increment is evaluated. SLPC has been shown[11-13] to predict fluid responsiveness accurately in both surgical and critical care patients. However, it has not been studied in patients undergoing open abdominal surgeries, and no study has compared the abilities of MFC and SLPC to predict fluid responsiveness during laparotomy.

The primary aim of this study was to compare the abilities of MFC and SLPC to predict fluid responsiveness in patients undergoing open pancreaticoduodenectomy and ventilated with TVs < 8 mL/kg IBW. The secondary aims were to reveal the diagnostic performances of SLPC, MFC, PPV, and SVV and evaluate the potential effects of using these tests on unnecessary fluid administration.

Patients and Methods

Study Design and Patient Selection

This single-center prospective observational trial was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Clinical Research Ethics Committee of Istanbul Basaksehir Cam and Sakura City Hospital (number: 2021.12.271; date: December 15), and the study protocol was registered on ClinicalTrials.gov (NCT05419570) prior to study initiation. Written informed consent was obtained from all participants.

The study included patients aged 18-70 years old who were scheduled to undergo pancreaticoduodenectomy in Istanbul Basaksehir Cam and Sakura City Hospital, Turkiye, between June 2022 and October 2022. The exclusion criteria were as follows: body mass index (BMI) > 35 kg/m^2, arrhythmia, left ventricle ejection fraction < 50%, tricuspid annular plane systolic excursion < 16 mm, severe valvular heart disease, compliance of the respiratory system (Crs) < 35 mL/cmH_2O, chronic obstructive pulmonary disease, American Society of Anesthesiologists (ASA) score > 3, poor arterial signal quality, and refusal to participate in the study. During the intraoperative period, patients with loss of arterial signal quality and new-onset arrhythmia were also excluded.

Anesthesia Management

After arrival in the operating room, patients' peripheral oxygen saturation, heart rate (HR; by five-channel electrocardiography), noninvasive blood pressure, and patient state index (PSI) were monitored.

Anesthesia was induced with 1% propofol to achieve PSI < 50, along with 1 µg/kg fentanyl and 0.6 mg/kg rocuronium bromide. For anesthesia maintenance, sevoflurane (1-2%) and remifentanil (0.05-0.3 mcg/kg/min) were infused with a PSI target of 25-50. Neuromuscular blockade was ensured by administering 0.1 mg/kg rocuronium bromide boluses every 30 minutes.

Mechanical ventilation included volume-controlled ventilation (Perseus A500; Drager, Lübeck, Germany) with a TV < 8 mL/kg IBW at a rate of 12-15/min and an I/E ratio of 1/2 in 40% oxygen and air with a PEEP of 4-6 cmH_2O. IBW was calculated using Robinson's formula[14].

Prior to the anesthesia machine connection, a ventilator (Hamilton-C1 Ventilator; Hamilton Medical, Bonaduz, Switzerland) capable of applying expiratory and inspiratory hold maneuvers was used to automatically calculate Crs values.

The left radial artery was catheterized using a 20-gauge arterial catheter (Vygon, Padova, Italy) dedicated to radial artery catheterization and arterial waveform analysis *via* a MostCare monitor (Vygon, Padova, Italy). The MostCare monitor analyses the arterial waveform with a sampling rate of 1,000 points per second[15]. Consequently, the points of instability profile of the arterial waveform are determined. This profile is a result of the mix-up of forward and backward forces in the arterial system and can be used to calculate the arterial impedance[15]. The arterial impedance and systolic area are then used to calculate the beat-to-beat stroke volume without the need for any calibrations. The MostCare monitor has been validated against pulmonary thermodilution[16]. This monitor was set to recalculate the dynamic variables every 10 seconds. The square-wave test was used to ensure the absence of overdamping and underdamping of the arterial pressure wave. The right internal jugular vein was catheterized using an 8.5-French central venous catheter for

monitoring central venous pressure (CVP), sampling central venous blood, and administering treatments. Lactated Ringer's solution was infused at 4 mL/kg/h as maintenance fluid from the central line, along with the other infusions, while FL protocols were performed with isotonic saline *via* a 16-gauge peripheral cannula to ensure the stability of the infusions applied *via* the central line.

Hemodynamic Management

All patients received standard hemodynamic management (**Supplementary Material 1**). Briefly, FL was indicated when a low cardiac index (CI) was noted. Dobutamine was initiated or increased when a low CI persisted despite FL. Noradrenaline was started or increased when a low mean arterial pressure (MAP) was observed despite normal CI values. The hemoglobin threshold for erythrocyte transfusion was < 8 g/dL or < 10 g/dL accompanied by cardiovascular disease. Colloids were used when hypotension occurred due to acute bleeding. The FL protocol was not initiated in such cases as it was judged to be evident hypovolemia. The protocol was canceled if new-onset bleeding occurred.

Fluid Loading Protocol

The FL protocol was applied after confirming hemodynamic stability during the surgery (MAP change of < 10% for 3 minutes). The PSI was kept at 30-50 and within ± 10% of the baseline value during the protocol. The surgical team was warned not to apply a new-onset surgical stimulus.

We recorded the hemodynamic and ventilatory parameters at five time points (T1-T5) (Figure 1). Following the baseline measurement (T1), we applied an additional 5 cmH_2O PEEP for 30 seconds (SLPC). T2 measurement was performed prior to PEEP lowering. T3 measurement was performed 1 minute after PEEP decreased to its initial value and was recorded as the second baseline. Thereafter, 100 mL of isotonic saline was infused over 1 minute (MFC). T4 measurement was performed 30 seconds after MFC was completed. Lastly, the T5 measurement was taken 1 minute after infusing an additional 400 mL of isotonic saline within 9 minutes, completing 500 mL of fluid. Challenges that resulted in an increase in the SVI of more than 15% after FL were classified as positive challenges. The following parameters were also calculated:

Percentage change in SVI due to SLPC (SVIΔ%-SLPC):

[(SVI-T1 – SVI-T2)/SVI-T1] × 100.

Percentage change in SVI due to MFC (SVIΔ%-MFC):

[(SVI-T4 – SVI-T3)/SVI-T3] × 100.

Percentage change in SVI due to FL (SVIΔ%-FL):

[(SVI-T5 – SVI-T3)/SVI-T3] × 100.

Statistical Analysis

The primary outcome was the difference between the areas under the receiver operating characteristic curves (ROC AUCs) of SVIΔ%-SLPC and SVIΔ%-MFC. Considering previous results, sample size calculation was performed by assuming that the ROC AUCs of SVIΔ%-SLPC and SVIΔ%-MFC would be < 0.70 and > 0.90, respectively. The expected ratio for fluid responders was > 40%. Accordingly, at least 60 measurements were required (type I and II errors of 5% and 20%, respectively). Our clinical practice suggests that, generally, at least two FL procedures are performed during pancreaticoduodenectomy. Therefore, we decided to recruit 35 patients, taking into account the possible losses during follow-up.

Interval data distribution was evaluated by the d'Agostino-Pearson test. Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are presented as median (25^{th}-75^{th} percentile). Categorical data are presented as number and frequency. The hemodynamic parameters of responders and non-responders were compared with the Student's *t*-test or Mann-Whitney U test, whereas hemodynamic changes within the groups during the protocol were analyzed using

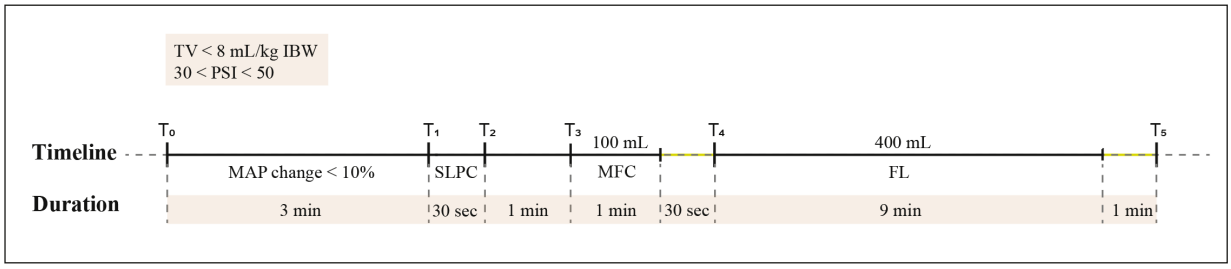

Figure 1. Study protocol. TV: tidal volume, IBW: ideal body weight, PSI: patient state index, MAP: mean arterial pressure, SLPC: short time low PEEP challenge, MFC: mini fluid challenge, FL: fluid loading.

repeated measures one-way analysis of variance or the Friedmann test, as appropriate. The Bonferroni or Dunn methods were applied for post-hoc pairwise comparisons, respectively.

Owing to the nature of the study, multiple challenges were performed on the same patient. Therefore, to assess the cluster effect on hemodynamic changes, intraclass correlation coefficients (ICCs) were calculated using random effects models[17]. The cluster effects on the predictive abilities of SVIΔ%-SLPC and SVIΔ%-MFC were assessed by constructing both a generalized linear model (GLM) and a generalized linear mixed model (GLMM, using the logit link function for both) and then comparing these models using the Akaike information criterion (AIC) and Bayesian information criterion (BIC)[18].

Receiver operating characteristic (ROC) curves were created to compare the abilities of SVIΔ%-SLPC and SVIΔ%-MFC to predict fluid responsiveness using the approach defined by DeLong et al[19]. The best cutoffs for the variables were calculated using the Youden index (sensitivity + specificity – 1). A p-value < 0.05 was considered statistically significant. Gray zone analysis was performed for SVIΔ%-SLPC and SVIΔ%-MFC as described by Coste and Pouchot[20]. The upper and lower cutoffs determining the gray zone were defined with the values associated with a positive likelihood ratio = 0.1, ensuring a post-test probability < 0.05, and a negative likelihood ratio = 10, ensuring a post-test probability > 0.90, respectively.

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA), MedCalc version 16.1 (MedCalc Software Ltd., Ostend, Belgium), and RStudio version 2023.03.0 (Posit Software, Boston, MA, USA) as appropriate.

Results

Patients' Characteristics and Hemodynamic Data

Thirty-three patients completed the study with 94 successful challenges (Figure 2). The patients' characteristics are shown in Table I.

FL resulted in an increase in the SVI of at least 15% in 55 (58.5%) challenges (positive challenges). The HR, MAP, SVI, CVP, SVV, and PPV of positive and negative challenges are shown in Table II. Both positive and negative challenges induced significant differences in all aforementioned hemodynamic variables. However, the effect sizes were greater in positive challenges than in negative challenges. There were no significant differences between the groups in terms of the HR, MAP, and SVI before FL, and only the SVI differed at the end of the challenges (Table II).

Cluster Effect

ICC corresponds to the percentage of data variety that can be explained by clustering, and it was calculated by defining the patients as the cluster effect. The ICCs for SVIΔ%-SLPC, SVIΔ%-MFC, and SVIΔ%-FL were 0.08, 0.02, and 0, respectively, indicating minimal or zero patient effect on the data.

GLMMs (by defining the patients as the cluster effect) were created for SVIΔ%-SLPC and SVIΔ%-MFC to predict fluid responsiveness and were compared with GLMs (without cluster definition).

GLMs were favored over GLMMs for SVIΔ%-MFC (AIC: 43.1 *vs.* 49.1, BIC: 48.2 *vs.* 61.9) and SVIΔ%-SLPC (AIC: 128.1 *vs.* 134.1, BIC: 133.2 *vs.* 146.8), thereby indicating the absence of a patient effect on the predictive abilities of the variables.

Predicting Fluid Responsiveness

ROC curves were created to determine the abilities of SVIΔ%-MFC, SVIΔ%-SLPC, and baseline PPV and SVV to predict fluid responsiveness (Figure 3). The ROC AUC of SVIΔ%-MFC was significantly higher than that of SVIΔ%-SLPC (0.97 *vs.* 0.64, p < 0.001). Moreover, the ROC AUC of SVIΔ%-MFC was significantly higher than the ROC AUCs of baseline PPV and SVV (both p < 0.001). However, there were no significant differences between the ROC AUC of SVIΔ%-SLPC and the ROC AUCs of baseline PPV and SVV (all p > 0.05). The ROC AUC, best cutoff, sensitivity, and specificity values for all variables are shown in Table III.

We performed gray zone analysis for SVIΔ%-MFC. The lower and upper gray zone thresholds were 5% and 5.56%, and five measurements (5.3%) were inside the gray zone.

Potential Effect of MFC on Unnecessary Fluid Administration

If we had stopped the bolus fluid administration when SVIΔ%-MFC was ≤ 5%, we would have canceled or postponed FL in 35 (89.7%) of 39 negative challenges. The number of boluses avoided would have been 1 in 16 patients, 2 in 5 patients, and 3 in 3 patients. The amount of fluid postponed would have corresponded to up to 40% of the total fluid administered, with an average ratio of 13.3%. Despite these results, four false-negative and seven false-positive decisions would have been inevitable.

Table I. Characteristics of patients.

Patients (n = 33)	
Gender (m/f)	14/19
Age (years)	58 (48-63)
BMI (kg/m^2)	27.1 ± 5.6
IBW (kg)	59.4 ± 8.9
PEEP (cmH_2O)	5 (5-5)
Plateau pressure (cmH_2O)	14 (13-16)
Tidal volume (mL)	420 ± 63
Tidal volume (mL/kg of IBW)	7.08 ± 0.49
Static compliance (mL/cmH_2O)	56 ± 17
Duration of anesthesia (min)	358 ± 88
Duration of surgery (min)	323 ± 90
Total volume infused (mL)	3,725 ± 1,256
Patients needed transfusion	7 (21%)
Patients needed catecholamine infusion	13 (39%)
Number of challenges performed in patients	
1 challenge	4 (12%)
2 challenges	7 (21%)
3 challenges	14 (43%)
4 challenges	6 (18%)
5 challenges	2 (6%)
Challenges under catecholamine infusion (PC/NC)	12/8
ASA Scores (I/II/III)	11/17/5
Comorbidities	
Diabetes mellitus	11 (33%)
Hypertension	15 (45%)
Cardiovascular disease	7 (21%)
Thyroid dysfunction	3 (9%)
COPD	2 (6%)

Values are expressed as numbers, mean ± SD, median (25th to 75th percentile). m: male, f: female, BMI: body mass index, IBW: ideal body weight, PEEP: positive end-expiratory pressure, PC: positive challenges, NC: negative challenges, COPD: chronic obstructive pulmonary disease.

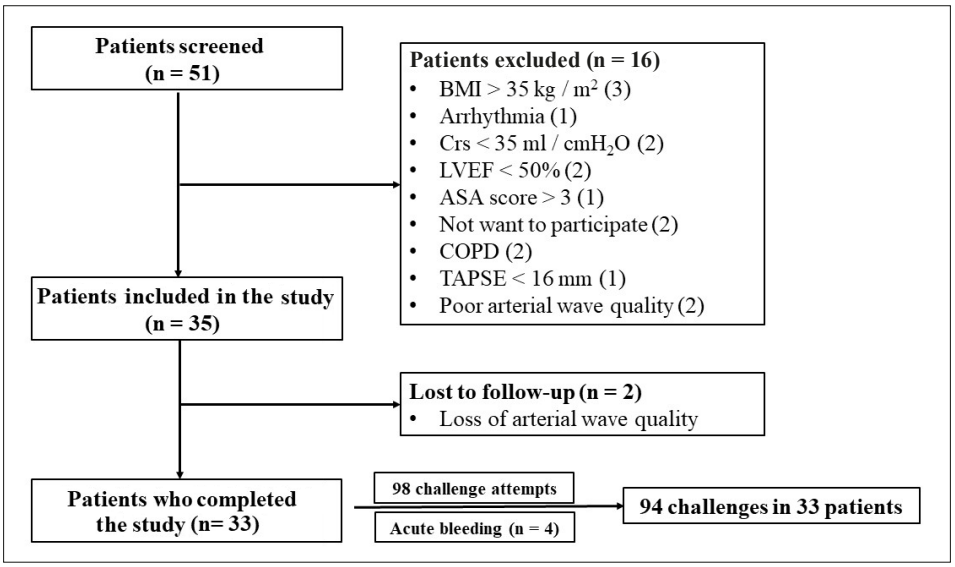

Figure 2. Study flowchart. BMI: body mass index, Crs: static respiratory system compliance, LVEF: left ventricle ejection fraction, COPD: chronic obstructive pulmonary disease, TAPSE: tricuspid annular plane systolic excursion.

Table II. Hemodynamic variables during the study period.

	Baseline 1 (T1)	SLPC (T2)	p_1	Baseline 2 (T3)	MFC (T4)	p_2	FL (T5)	p_3	*p*-value
HR (beat/min)									
Pos. Challenges	81 ± 13	80 ± 12	*1*	80 ± 13	79 ± 13	***0.005***	77 ± 11	***0.006***	**< 0.001**
Neg. Challenges	77 ± 11	77 ± 11	*0.38*	77 ± 11	77 ± 11	*0.67*	76 ± 10	***0.047***	**0.009**
p intergroup	*0.21*	*0.16*		*0.34*	*0.49*		*0.55*		
MAP (mmHg)									
Pos. Challenges	71 ± 11	69 ± 12	***< 0.001***	70 ± 12	73 ± 13	***< 0.001***	80 ± 14	***< 0.001***	**< 0.001**
Neg. Challenges	71 ± 12	70 ± 13	***0.02***	71 ± 12	73 ± 13	*0.46*	76 ± 12	***0.002***	**< 0.001**
p intergroup	*0.92*	*0.78*		*0.73*	*0.92*		*0.12*		
SVI (mL/m^2)									
Pos. Challenges	27.6 ± 6.4	26.7 ± 6.3	***0.001***	27.6 ± 64	31.1 ± 6.9	***< 0.001***	35.8 ± 7.6	***< 0.001***	**< 0.001**
Neg. Challenges	29.5 ± 7.6	29.2 ± 7.6	*1*	29.5 ± 7.5	30.3 ± 8.1	***< 0.001***	31.4 ± 8.5	***< 0.001***	***< 0.001***
p intergroup	*0.18*	*0.08*		*0.19*	*0.61*		***0.009***		
CVP (mmHg)									
Pos. Challenges	4.9 ± 2.3	6 ± 2.5	***< 0.001***	4.9 ± 2.2	5.5 ± 2.4	***< 0.001***	6.6 ± 2.9	***< 0.001***	**< 0.001**
Neg. Challenges	6 ± 2.9	7 ± 3.2	***< 0.001***	6.1 ± 3.1	6.6 ± 3.1	***0.01***	7.4 ± 2.8	***< 0.001***	***< 0.001***
p intergroup	***0.039***	*0.08*		***0.032***	***0.048***		*0.18*		
PPV (%)									
Pos. Challenges	12 (9-15)	14 (10-17)	***< 0.001***	11 (9-15)	9 (6-12)	***< 0.001***	6 (4-8)	***< 0.001***	**< 0.001**
Neg. Challenges	8 (7-11)	10 (8-13)	***0.003***	8 (7-11)	7 (5-10)	***0.006***	5 (4-8)	***< 0.001***	
p intergroup	***0.003***	***0.002***		***0.001***	*0.05*		*0.52*		
SVV (%)									
Pos. Challenges	9 (5-14)	12 (8-16)	***0.02***	9 (5-14)	8 (5-11)	***0.01***	5 (4-9)	***< 0.001***	**< 0.001**
Neg. Challenges	8 (4-10)	10 (6-11)	***0.003***	7 (5-10)	6 (4-9)	*0.15*	5 (4-9)	***0.009***	**< 0.001**
p intergroup	*0.05*	*0.05*		*0.12*	*0.07*		*0.65*		

Values are expressed as mean ± SD or median (25th to 75th percentile). *p* intergroup: comparison between the positive and negative challenges with the student's *t*-test or Mann-Whitney U test. *p*-value: comparison of time points within the groups with the repeated measurements one-way ANOVA or Friedman test. *p*-values for post-hoc comparisons with Bonferroni or Dunn methods: p_1: T1 *vs.* T2 p_2: T3 *vs.* T4, p_3: T3 *vs.* T5. Pos. Challenges: Positive Challenges, Neg. Challenges: Negative Challenges, SLPC: short-term low PEEP challenge, MFC: mini fluid challenge, FL: fluid loading, HR: heart rate, MAP: mean arterial pressure, SVI: stroke volume index, CVP: central venous pressure, PPV: pulse pressure variation, SVV: stroke volume variation.

Table III. Best cut-off values and diagnostic performances of the variables.

Variable	ROC AUC	95% CI	Best cut-off (%)	95% CI	Sensitivity (%)	95% CI	Specificity (%)	95% CI
SVIΔ%-MFC	0.97	0.91-0.99	5.56	4.35-7.5	91	80-97	92	79-98
SVIΔ%-SLPC	0.64	0.53-0.74	3.45	-3.57-5	58	44-71	72	55-85
PPV	0.68	0.58-0.77	9	8-14	65	51-79	67	50-81
SVV	0.62	0.51-0.72	10	3-11	45	32-59	82	67-93

The best cut-off values were determined using the Youden index (J = sensitivity + specificity − 1). ROC AUC: area under the receiver operating characteristics curve, CI: confidence interval, SVIΔ%-MFC percentage change in stroke volume index due to mini fluid challenge, SVIΔ%-SLPC: percentage change in stroke volume index due to short-term low PEEP challenge, PPV: pulse pressure variation. SVV: stroke volume variation.

Discussion

There were several findings regarding the use of MFC and SLPC in patients undergoing pancreaticoduodenectomy with TVs < 8 ml/kg IBW: first, MFC predicts fluid responsiveness with excellent diagnostic performance and is better than SLPC. Second, SLPC fails to demonstrate the same predictive ability reported previously in the literature[11-13]. Lastly, MFC use throughout surgery as part of a standardized hemodynamic management protocol has the potential to defer up to 40% of the total fluid administered.

Among FHTs, MFC is unique owing to its independence from cardiopulmonary interac-

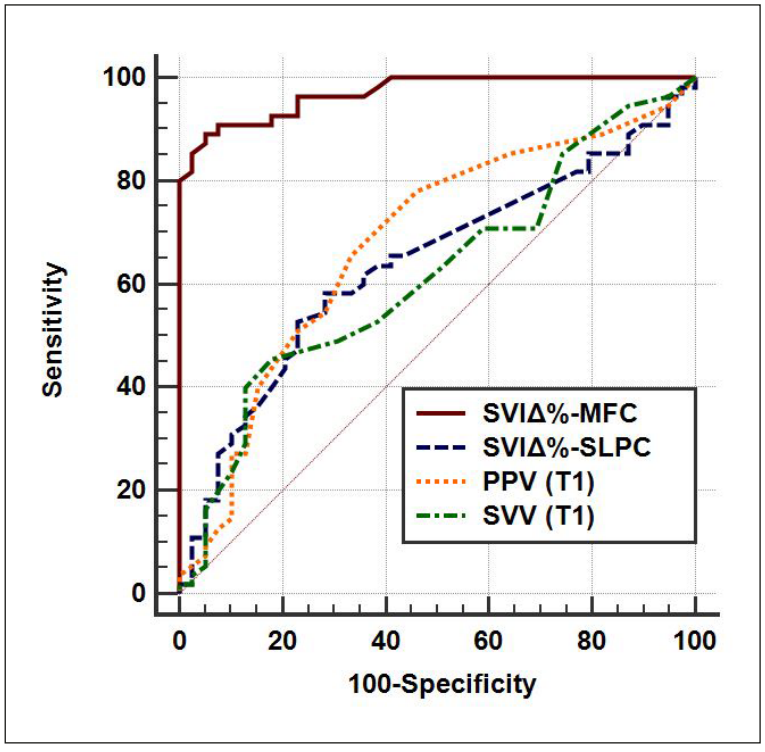

Figure 3. Receiver operating characteristics curves generated for SVIΔ%-MFC, SVIΔ%-SLPC, PPV and SVV for showing the ability to predict fluid responsiveness. SVIΔ%-MFC: percentage change in stroke volume index due to mini fluid challenge, SVIΔ%-SLPC: percentage change in stroke volume index due to short-term low PEEP challenge, PPV: pulse pressure variation, SVV: stroke volume variation.

tions[8]. Therefore, this method can predict fluid responsiveness in patients with spontaneous breathing, low Crs, and high BMI and those ventilated with TVs < 8 mL/kg IBW[10,21-24]. A meta-analysis[9] evaluating 368 fluid challenges from different clinical settings revealed a pooled ROC AUC of 0.91, with a cutoff of 5% for SVIΔ%-MFC. Despite this strong evidence, clinicians have prioritized other FHTs, such as the passive leg raise test (PLR), end-expiratory occlusion test (EEO), SLPC, and the assessment of the inferior vena cava owing to the constant need for infusing small volumes when MFC is applied continuously[5,8]. The EEO was recently compared with MFC in patients undergoing open abdominal surgery and was shown[10] to have a significantly lower and clinically insufficient accuracy in predicting fluid responsiveness. Taking into account that the PLR and inferior vena cava assessment are not suitable options for the operating room, SLPC is left as the only FHT with the potential to be an alternative to MFC.

Three studies[11-13] have evaluated SLPC in terms of predicting fluid responsiveness, with ROC AUCs higher than 0.90. However, unlike the current study, the previous studies[11-13] were performed in the intensive care unit or with a protocol adopted after anesthesia induction but before surgery initiation in the operating room. To our knowledge, this is the first study to evaluate SLPC during an open abdominal surgery and compare this method with MFC in this patient group. However, the ROC AUC of SLPC in this study (0.64, 95% CI: 0.53-0.74) was severely impaired compared to the values in previous studies[11-13]. This inconsistency can be explained by the loss of transdiaphragmatic pressure following laparotomy. Since transdiaphragmatic pressure works as a driving force for blood through the inferior vena cava toward the right ventricle, the loss of this force impairs the effects of cardiopulonary interactions on the right vetnricle preload, causing insufficient changes in the preload for predicting fluid responsiveness[25]. A further study[26] demonstrated the attenuating effects of the open abdomen on right ventricle preload changes caused by cardiopulmonary interactions by revealing reductions in dynamic indices following laparotomy (50% and 40% reductions in SVV and PPV, respectively). Consequently, neither dynamic indices nor FHTs that rely on cardiopulmonary interactions (i.e., SLPC and EEO) are capable of predicting fluid responsiveness in patients undergoing open abdominal surgery, leaving MFC as the only alternative.

For the first time in the literature, we evaluated MFC as part of a hemodynamic management protocol and throughout a specific high-risk surgery. Only one study[22] evaluated the potential effect of MFC on limiting unnecessary fluid infusion, reporting that 73% of negative challenges would have been avoided if the infusion had been stopped when SVIΔ%-MFC was smaller than the lower limit of the gray zone. Nevertheless, neither a hemodynamic management protocol nor any predefined indications for FL were presented in the aforementioned study. The current study revealed that approximately 90% of FL would have been cancelled if FL had been stopped when SVIΔ%-MFC was ≤ 5% (lower limit of the gray zone). Up to 40% of the total fluid administered would have been deferred, with an average ratio of 13.3%. These ratios correspond to a considerable amount of fluid volume, especially for high-risk cases (e.g., pancreatoduodenectomy), where fluid balance is related to negative outcomes[27]. Moreover, a more positive fluid balance alone may not guarantee better hemodynamic indices throughout surgery, as the accurate timing of FL is as important as the total amount of fluids administered. Regarding this, GDHM and conventional hemodynamic management were compared in a study[28] conducted on patients undergoing pancreatoduodenectomy, and the GDHM group had higher MAP values despite a lower fluid balance (49.7 *vs.* 61.7 mL/kg). In another study[29], a standardized GDHM protocol (SVV ≥ 13 was the indication for FL) was compared with a clinical decision support system that evaluates patients' responses to fluid challenges and individualizes fluid management by using these data. The latter group had a shorter duration of time with SVV ≥ 13 and a longer duration with CI ≥ 2.5 L/min/m^2. Yet, the fluid balance was more positive in the GDHM group (1.725 *vs.* 1.010 mL), indicating the importance of individualized fluid management. Considering these results and the results of the current study, adopting a GDHM protocol with predefined CI and MAP targets and individualizing FL by using MFC have the potential to increase the accuracy of fluid management in terms of amount and timing.

Limitations

The present study has several limitations. First, the MFC infusion rate and total FL were 100 mL in 1 minute and 500 mL in 10 minutes,

respectively. Different infusion rates and times may result in different outcomes. Second, we used a 1-minute time window between SLPC and MFC to guarantee the return to baseline. Although different time windows might lead to different results, the hemodynamic data at the two baselines were comparable both statistically and clinically. Third, we used the MostCare monitor, a device without the need for calibration, to evaluate the arterial waveform. The use of externally or internally calibrated alternative devices may result in different cutoffs and diagnostic performances. Fourth, this study was conducted in patients undergoing open pancreatoduodenectomy in the 30-degree reverse Trendelenburg position. Our results should be extrapolated carefully for different clinical scenarios. Fifth, we used TVs < 8 mL/kg IBW and PEEP values of 4-6 cmH_2O. Different TV and PEEP settings may affect the ROC AUCs and cutoffs of SLPC, PPV, and SVV. Sixth, this was an observational study with a single-center design. Studies with multi-center designs are needed to affirm the current results.

Conclusions

SVIΔ%-MFC predicts fluid responsiveness with high diagnostic performance and is better than SVIΔ%-SLPC as well as SVV and PPV in patients undergoing open pancreatoduodenectomy and ventilated with TVs < 8 mL/kg IBW. SLPC, PPV, and SVV should not be used in this clinical setting. SVIΔ%-MFC use throughout surgery as part of the GDHM protocol has the potential to defer up to 40% of the total fluid administered.

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Authors' Contributions
Taner Abdullah: designed the study, collected the data, performed the analysis, and wrote the paper. Huru Ceren Gokduman: conceived the study, collected the data, interpreted the results, and wrote the paper. Nazli Bahar Ozbey: conceived the study, collected the data, interpreted the results, and wrote the paper. Onur Sarban: conceived the study, interpreted the results, drafted manuscript preparation, and wrote the paper. Achmet Ali: performed the analysis, interpreted the results, and supervised. Funda Gumus Ozcan: designed and conceived the study and supervised it. All authors read and approved the final version of the manuscript.

Presentation of Findings
The study's findings were solely communicated verbally at the 57th National Turkish Anesthesiology and Reanimation Congress, organized by the Turkish Anesthesiology and Reanimation Association (2-5 November 2023).

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013). Ethical approval was obtained from the Clinical Research Ethics Committee of Istanbul Basaksehir Cam and Sakura City Hospital (number: 2021.12.271; date: December 15, 2021.

Informed Consent
The authors declare that they obtained written informed consent from the patients and/or volunteers included in the article and confirm that their personal details have been removed.

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