

Mini-fluid challenge test predicts stroke volume and arterial pressure fluid responsiveness during spine surgery in prone position

A STARD-compliant diagnostic accuracy study

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Abstract

The study was designed to verify if mini-fluid challenge test is more reliable than dynamic fluid variables in predicting stroke volume (SV) and arterial pressure fluid responsiveness during spine surgery in prone position with low-tidal-volume ventilation.

Fifty patients undergoing spine surgery in prone position were included. Fluid challenge with 500 mL of colloid over 15 minutes was given. Changes in SV and systolic blood pressure (SBP) after initial 100 mL were compared with SV, pulse pressure variation (PPV), SV variation (SVV), plethysmographic variability index (PVI), and dynamic arterial elastance ($E_{a_{dyn}}$) in predicting SV or arterial pressure fluid responsiveness (15% increase or greater).

An increase in SV of 5% or more after 100 mL predicted SV fluid responsiveness with area under the receiver operating curve (AUROC) of 0.90 (95% confidence interval [CI], 0.82 to 0.99), which was significantly higher than that of PPV (0.71 [95% CI, 0.57 to 0.86]; $P=.01$), and SVV (0.72 [95% CI, 0.57 to 0.87]; $P=.03$). A more than 4% increase in SBP after 100 mL predicted arterial pressure fluid responsiveness with AUROC of 0.86 (95% CI, 0.71–1.00), which was significantly higher than that of $E_{a_{dyn}}$ (0.52 [95% CI, 0.33 to 0.71]; $P=.01$).

Changes in SV and SBP after 100 mL of colloid predicted SV and arterial pressure fluid responsiveness, respectively, during spine surgery in prone position with low-tidal-volume ventilation.

Abbreviations: AUROC = area under the receiver operating curve, BMI = body mass index, CI = confidence interval, $E_{a_{dyn}}$ = dynamic arterial elastance, MAP = mean arterial pressure, PPV = pulse pressure variation, PVI = plethysmographic variability index, SBP = systolic blood pressure, SV = stroke volume, SVV = stroke volume variation, VTI = velocity time integral.

Keywords: fluid therapy, hemodynamic monitoring, prone position, stroke volume

1. Introduction

Predicting stroke volume (SV) and arterial pressure fluid responsiveness during spine surgery is essential because such

surgery is often associated with considerable intraoperative blood loss,^[1] and the prone position reduces cardiac preload and arterial pressure.^[2] Several studies suggested that perioperative goal-directed therapy with SV optimization improves clinical outcomes.^[3] In addition, a most recent systematic review suggests that it is crucial to maintain a higher intraoperative arterial pressure [mean arterial pressure (MAP) >80 mmHg] for the avoidance of organ injuries.^[4] Because fluid therapy is often the first-line treatment to optimize SV and arterial pressure for surgical patients, predictors of fluid responsiveness are relevant to intraoperative care of patients undergoing spine surgery in prone position.

Dynamic fluid variables based on heart–lung interaction, such as pulse pressure variation (PPV), stroke volume variation (SVV), and plethysmographic variability index (PVI), reliably predict SV fluid responsiveness during surgery under mechanical ventilation.^[5] In addition, the PPV/SVV ratio, defined as dynamic arterial elastance ($E_{a_{dyn}}$), is a promising variable potentially reflecting arterial pressure response to fluid challenge in critically ill patients.^[6,7] However, intraoperative factors such as the prone position^[8] as well as low tidal volume mechanical ventilation modify the extent of heart–lung interaction and may thus reduce the utility of dynamic fluid variables for patients receiving surgery.^[9] The intraoperative ability of $E_{a_{dyn}}$ to predict arterial pressure fluid responsiveness was not observed among patients receiving surgery.^[10,11] Therefore, identification of predictors of SV and arterial pressure fluid responsiveness that are more

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reliable than dynamic fluid variables is imperative for modern anesthetic care providers.

The mini-fluid challenge test was first used to report that an increase in SV after rapid fluid challenge with 100 mL of colloid that precisely predicted fluid responsiveness in critically ill patients with low-tidal-volume ventilation.^[12] Therefore, the mini-fluid challenge test accuracy may be minimally affected by respiratory alterations resulting from the prone position and low tidal volume mechanical ventilation, rendering it a promising means of predicting fluid responsiveness during spine surgery in a prone position with protective ventilation. The primary objective of the current study is to compare the accuracy of SV fluid responsiveness prediction between the mini-fluid challenge test and dynamic fluid variables; the secondary objective is to compare the accuracy of arterial pressure fluid responsiveness prediction between variables.

2. Materials and methods

2.1. Study design and participants

This prospective single-center observational study was approved by the Research Ethics Committee of National Taiwan University Hospital (201612021RIND; date of approval: February 14, 2017) and registered at clinicaltrials.gov before patient enrollment (NCT03089710). After obtaining written informed consent, patients were enrolled between March 2017 and September 2018. Adult patients (age 20–80 years) with a body mass index (BMI) between 18.5 and 30 kg m⁻² who were scheduled for spine surgery in the prone position were included. Patients with arrhythmia, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, ongoing infectious disease, moribundity, pregnancy, and known allergy to any colloid were excluded.

2.2. Perioperative management

Each patient received general anesthesia induction consisting of fentanyl (2–3 µg·kg⁻¹), propofol (1.5–2.5 mg kg⁻¹), and rocuronium (0.6–1 mg kg⁻¹). Standard monitors comprising a Philips IntelliVue MP70 monitor (Philips Medical Systems, Suresnes, France) and Bispectral indexTM (BISTM) Quatro sensor (Covidien Inc, Mansfield, MA) connected to a Philips BIS M1034 module (Philips Medical Systems, Germany) were applied to each patient. Anesthesia was maintained by means of sevoflurane or total intravenous anesthesia (if an evoked potential test was required) at a BIS between 40 and 60. Vasopressors were administered at the discretion of the caregiving anesthesiologist during surgery. Tidal volume was set at 5 mL per ideal body weight. Positive end-expiratory pressure of 5 cm H₂O, fraction of inspired oxygen of 0.4 to 0.6 adjusted to maintain pulse oximetry above 95%, and respiratory rate adjusted to maintain end-tidal CO₂ of 35 to 45 mmHg were applied to each patient. Afterward, patients were turned into the prone position by means of longitudinal bolsters system.

2.3. Hemodynamic monitoring

Following anesthesia, a 20-G radial arterial line was inserted and connected to a fourth-generation VigileoTM/FloTracTM system (Edwards Lifesciences, Irvine, CA) to obtain hemodynamic parameters, including SV and SVV. This system analyzes the pressure waveform 100 times per second over 20 seconds,

capturing 2000 data points for analysis and calculating with data obtained from the previous 20 seconds. PPV was automatically calculated using the IntelliVue MP70 monitor, which was reported to be comparably accurate to offline-calculated PPV.^[13] The Masimo Radical-7 CO-oximeter (version 7.8; Masimo Corp., Irvine, CA) with a finger clip to measure arterial oxygen saturation noninvasively based on transcutaneous multiwavelength analysis was attached to the index finger of the hand without intravenous cannula in each patient to obtain PVI according to the manufacturer's instructions; E_{a,dyn}, measured using uncalibrated pulse contour analysis as an arterial load indicator, was then calculated as the ratio of PPV to SVV.^[14]

2.4. Study protocol and definition of fluid responder

Fluid challenge test were initiated in all patients 15 to 30 minutes after skin incision and the protocol is shown in Figure 1. If any vasopressor was administered in that period at the discretion of the caregiving anesthesiologist, we waited for at least 10 minutes for stabilization before the initiation of the fluid challenge trial, and no vasopressor was administered during the fluid challenge trial. Only the first fluid challenge test applied during surgery was used for analysis. Continuous fluid was provided by infusing 500 mL of colloid, namely, 6% tetrastarch solution (Voluven; Fresenius-Kabi, Louviers, France), over 15 minutes, with the initial 100 mL rapidly infused during the first minute. Hemodynamic parameters including heart rate, systolic blood pressure (SBP), mean arterial pressure, SV, PPV, SVV, PVI, and E_{a,dyn} were recorded prior to fluid challenge (baseline), 1 minute after infusing the initial 100 mL during the first minute (*T*₁), and 1 minute after the end of fluid challenge (*T*₂). The effects of the mini-fluid challenge test were denoted as ΔSV₁₀₀ and ΔSBP₁₀₀, calculated as percentage change of SV and SBP, respectively, after the initial 100 mL of colloid. Patients with an increase in SV or MAP of 15% or more from baseline after fluid challenge of 500 mL of colloid were classified as SV or arterial pressure responders.

2.5. Statistical analysis

The primary and secondary outcomes of the present study are to investigate the ability of mini-fluid challenge test to predict SV and arterial pressure fluid responsiveness respectively. To calculate the sample size, we noted that most reported dynamic fluid variables have an area under the receiver operating curve (AUROC) of approximately 0.80 and then tested the probability of rejecting the null hypothesis that AUROC is 0.5. Based on our institutional database, the number of SV responders was assumed to be twice that of nonresponders, and the number of arterial pressure responders one-fourth that of nonresponders. We therefore calculated that at least 19 SV responders and 10 nonresponders as well as at least 9 arterial pressure responders and 36 nonresponders were required. Therefore, a total of 50 patients were enrolled.

Categorical variables are presented as numbers (percentages) and compared using χ^2 or Fisher exact testing, as appropriate. Continuous variables are presented as mean (standard deviation) if normally distributed, or as median (interquartile range) if not. Comparisons between responders and nonresponders were assessed using Student *t* test or the Mann–Whitney *U* test, as appropriate. Comparisons of hemodynamic parameters during fluid challenge were assessed using Friedman test or repeated

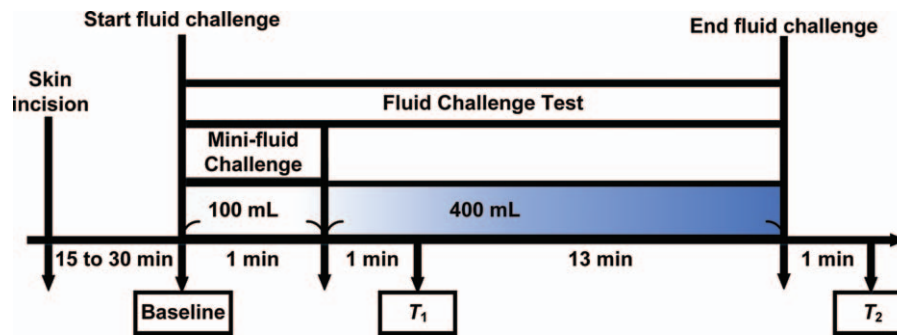


Figure 1. Fluid challenge protocol. Continuous fluid challenge was performed by infusing 500 mL of colloid solution over 15 minutes. Hemodynamic measurements including heart rate, mean arterial pressure, systolic blood pressure, stroke volume, pulse pressure variation, stroke volume variation, and plethysmographic variability index were performed before fluid challenge (baseline), 1 minute after infusing the initial 100 mL during 1 minute (T_1), and 1 minute after fluid challenge (T_2).

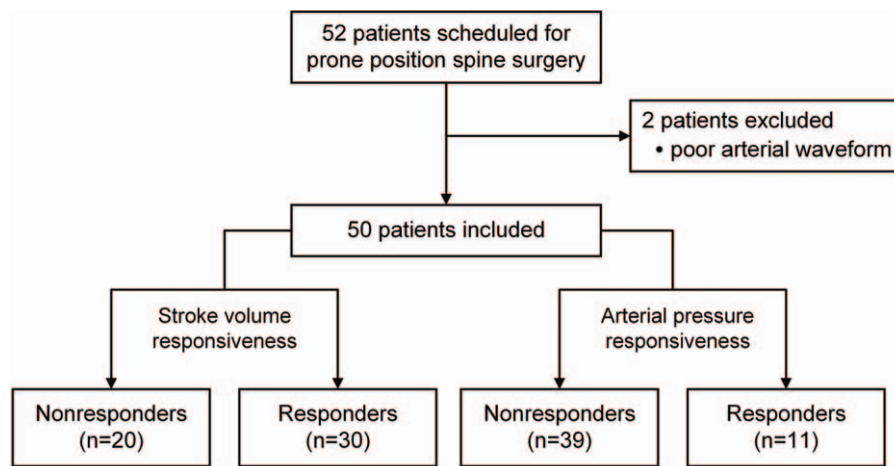


Figure 2. Study flowchart.

measures analysis of variance, as appropriate, and post hoc analyses with Bonferroni adjustment.

Receiver operating characteristic curves were obtained to evaluate the fluid responsiveness predictive ability of each variable. AUROC were presented with 95% confidence intervals (CIs) and compared using the method proposed by DeLong et al.^[15] The cutoff value was determined as the point with the maximal Youden index (sensitivity + specificity - 1). A gray zone approach was introduced to determine the range of each examined variable with inconclusive information regarding ability to precisely discriminate between fluid responders and nonresponders.^[16] All statistical analyses were performed using MedCalc version 18.6 (MedCalc Software Inc., Mariakerke, Belgium).

3. Results

3.1. Patient characteristics

A total of 52 patients were assessed for inclusion, among whom two were excluded because of poor arterial wave form (Fig. 2). Patient characteristics of the remaining 50 patients are summarized in Table 1. None of the included patients received any vasopressor before or during the fluid challenge trial. Among the 50 included patients, thirty SV responders and 11 arterial pressure responders were identified.

3.2. Hemodynamics during fluid challenge

Hemodynamic parameters in 30 SV responders and 20 non-responders prior to fluid challenge (baseline), after mini-fluid challenge (T_1), and at the end of fluid challenge (T_2) are reported in Table 2. SVV and PPV before fluid challenge were significantly

Table 1
Patient characteristics.

	All patients (n = 50)
Age (y)	63 (10)
Sex, male/female (n)	55 / 45
Weight (kg)	64.9 (11.1)
BMI (kg·m ⁻²)	25.2 (2.7)
Surgery type (n)	
Cervical	14
Thoracic	3
Lumbar	33
Peak airway pressure (cm H ₂ O)	
Supine	15.3 (1.9)
Prone	18.4 (2.9)
Respiratory compliance (mL·cm H ₂ O ⁻¹)	
Supine	28.3 (6.3)
Prone	22.0 (3.9)

Variables are presented as mean (standard deviation). BMI = body mass index.

Table 2
Hemodynamic parameters before and after 100- and 500-mL fluid challenge in SV responders and nonresponders.

	Responder (n=30)			Nonresponder (n=20)		
	Baseline	100 mL	500 mL	Baseline	100 mL	500 mL
HR (bpm)	72 (12)	69 (12) [†]	67 (11) [†]	69 (8)	68 (9)	67 (8)
SV (mL)	46 (14) [*]	51 (13) [†]	60 (15) [†]	59 (14)	61 (14) [†]	63 (14) [†]
SVV (%)	12 (4) [*]	11 (4) [†]	9 (4) [†]	9 (4)	8 (4)	7 (3) [†]
PPV (%)	10 (4) [*]	8 (4) [†]	6 (3) [†]	8 (3)	7 (4)	5 (2) [†]
PVI (%)	14 (10 to 18)	12 (9 to 18)	12 (7 to 16)	11 (6 to 13)	11 (5 to 13)	10 (6 to 14)
SBP (mmHg)	111 (19)	114 (21)	114 (22)	107 (19)	107 (18)	112 (22)
MAP (mmHg)	83 (14)	85 (15)	84 (15)	80 (13)	80 (12)	83 (14)
Ea _{dyn}	0.9 (0.3)	0.7 (0.2) [†]	0.8 (0.2) [†]	0.9 (0.3)	0.9 (0.3)	0.9 (0.5)

Variables are presented as mean (standard deviation) if normally distributed, or as median (interquartile range) if not. SV responder was defined as a 15% or greater increase in SV from baseline after fluid challenge with 500 mL of colloid. Baseline was just before fluid challenge, 100 mL was 1 minute after infusing the initial 100 mL within the first minute; 500 mL was 1 minute after the end of fluid challenge. Ea_{dyn} = dynamic arterial elastance, HR = heart rate, MAP = mean arterial pressure, PPV = pulse pressure variation, PVI = plethysmographic variability index, SBP = systolic blood pressure, SV = stroke volume, SVV = stroke volume variation.

^{*} Denotes a significant difference between baseline values for responders and nonresponders ($P < .05$).

[†] Denotes a significant difference compared with the baseline value ($P < .016$ from post hoc analysis with Bonferroni adjustment).

higher in SV responders than in nonresponders. ΔSV_{100} was 10% (6%–13%) in SV responders, which was significantly greater than that of nonresponders (2% [1%–5%], $P < .001$).

3.3. Prediction of SV responsiveness

The ability of ΔSV_{100} , baseline SV, baseline SVV, baseline PPV, and baseline PVI to predict SV fluid responsiveness is summarized in Table 3. The AUROC of ΔSV_{100} (0.90 [0.82–0.99]) was significantly higher than that of PPV (0.71 [0.57–0.86]), SVV (0.72 [0.57–0.87]), and PVI (0.67 [0.51–0.82]) (Fig. 3). The cutoff value of ΔSV_{100} was 5% or more, with a gray zone between 5% and 9%, which was narrower than that of SV, PPV, SVV, and PVI (Table 3). Moreover, fewer fluid challenges were in the gray zone of ΔSV_{100} (20%) than in that of SV (52%), PPV (62%), SVV (66%), and PVI (66%).

3.4. Prediction of arterial pressure responsiveness

Hemodynamic variables in 11 arterial pressure responders and 39 nonresponders before fluid challenge (baseline), after mini-fluid challenge (T_1), and at the end of fluid challenge (T_2) are shown in Supplemental Content 1, <http://links.lww.com/MD/D704>. A more than 4% increase in SBP after 100 mL (gray zone 3%–6%) predicted arterial pressure fluid responsiveness (sensitivity 82%, specificity 85%). The AUROC of ΔSBP_{100} (0.86 [0.71–1.00]) was higher than that of ΔSV_{100} (0.65 [0.44–0.86]; $P = .07$) and baseline Ea_{dyn} (0.52 [0.33–0.71]; $P = .01$) (Fig. 4).

4. Discussion

The major finding of our study is that an increase in SV of $\geq 5\%$ and in SBP of $>4\%$ after rapid infusion of 100 mL of colloid during 1 minute predicted the fluid responsiveness of SV and arterial pressure, respectively, in patients undergoing spine surgery in a prone position with low tidal volume.

Our findings indicate that the mini-fluid challenge test has high reproducibility in different surgical settings and is promising for application in patients requiring surgery. Guinot et al reported that the mini-fluid challenge predicted SV fluid responsiveness, with a narrow gray zone of 3% to 8% in spontaneously breathing patients under spinal anesthesia in supine position.^[17] Bias et al also demonstrated that the mini-fluid challenge predicted fluid responsiveness in SV index more reliably than PPV in neurosurgical patients in supine position, with a threshold value of 6% and a narrower gray zone of 4% to 7%.^[18] In line with these studies, our results demonstrated the effectiveness of the mini-fluid challenge test in predicting SV fluid responsiveness during spine surgery, despite the prone position causing a significant airway pressure increase and reduced pulmonary compliance. Similarly, the mini-fluid challenge test had a narrower gray zone (5%–9%) in our study than that of all three dynamic fluid variables. Because the smallest detectable SV change for each monitoring system may limit the feasibility of mini-fluid challenge,^[19] the best cutoff value found in the present study (5%) exceeded the previously reported least significant change for SV of 1.3% (0%–4.2%) when using pulse contour analysis.^[20] Studies indicate that PPV, SVV, and PVI during

Table 3
Ability of variables to predict SV fluid responsiveness.

	AUROC (95% CI)	Best cutoff value, %	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Gray zone, %	Patients in gray zone, %
ΔSV_{100}	0.90 (0.82–0.99)	≥ 5	87 (69–96)	85 (62–97)	5–9	20
SV	0.78 (0.65–0.91)	≤ 46	60 (41–77)	90 (68–99)	46–65	52
PPV	0.71 [*] (0.57–0.86)	> 8	70 (50–85)	60 (41–85)	5–11	62
SVV	0.72 [*] (0.57–0.87)	> 8	87 (69–96)	60 (36–81)	6–14	66
PVI	0.67 [*] (0.51–0.82)	> 13	53 (34–72)	80 (56–94)	6–17	66

SV fluid responsiveness was defined as a 15% or greater increase in SV from baseline after fluid challenge with 500 mL of colloid; ΔSV_{100} represented the increase in SV induced by mini-fluid challenge. AUROC = area under the receiver operating curve, CI = confidence interval, PPV = pulse pressure variation, PVI = plethysmographic variability index, SV = stroke volume, SVV = stroke volume variation.

^{*} Denotes a significant difference between the AUROC of variables and that of ΔSV_{100} ($P < .05$).

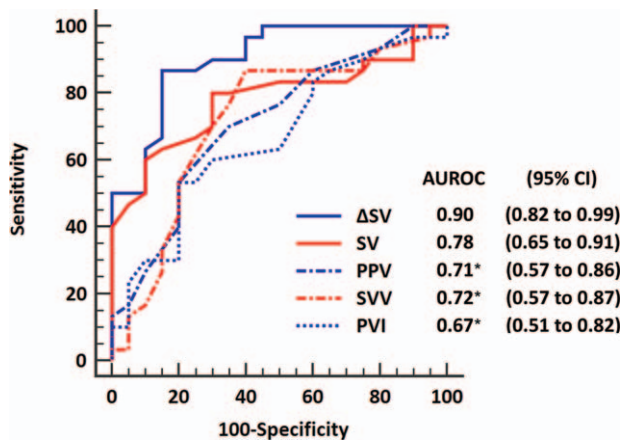


Figure 3. Prediction of SV fluid responsiveness. Receiver operating characteristic curves were calculated for ΔSV_{100} (increase in SV induced by mini-fluid challenge) and baseline SV, PPV, SVV, and PVI. SV fluid responsiveness was defined as a 15% or greater increase in SV from baseline after fluid challenge with 500mL of colloid. *denotes a significant difference between the AUROC of variables and that of ΔSV_{100} ($P < .05$). AUROC=area under the receiver operating curve, CI=confidence interval, PPV=pulse pressure variation, PVI=plethysmographic variability index, SV=stroke volume, SVV=stroke volume variation.

surgery in the prone position may be reliable only under mechanical ventilation set with a high tidal volume.^[21–23] Because evidence increasingly supports the notion that lower tidal volume is a vital component of intraoperative protective ventilation for reducing postoperative pulmonary complications,^[24] the feasibility of dynamic preload variables is highly limited. The mini-fluid challenge test, less influenced by tidal volume setting,^[25] may therefore be preferred for surgery in the prone position with a low tidal volume mechanical ventilation. In

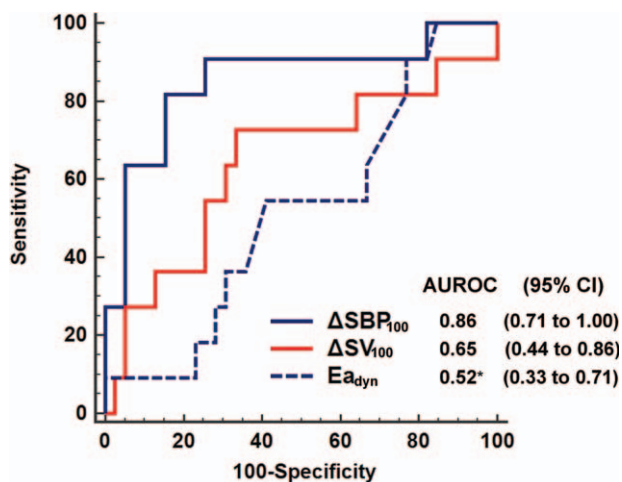


Figure 4. Prediction of arterial pressure fluid responsiveness. Receiver operating characteristic curves were calculated for ΔSBP_{100} (increase in SBP induced by mini-fluid challenge), ΔSV_{100} (increase in SV induced by mini-fluid challenge), and baseline Ea_{dyn} . Fluid responsiveness in arterial pressure was defined as a 15% or greater increase in MAP from baseline after fluid challenge with 500mL of colloid. *denotes a significant difference between the AUROC of variables and that of ΔSBP_{100} ($P < .05$). AUROC=area under the receiver operating curve, CI=confidence interval, Ea_{dyn} =dynamic arterial elastance, MAP=mean arterial pressure, SBP=systolic blood pressure, SV=stroke volume.

addition, we found that baseline SV was significantly lower in SV responders than in nonresponders, suggesting that it is a potential predictor with acceptable discrimination. However, a study reported that a pulse contour analysis device could not reliably estimate the absolute value of cardiac output, especially in critically ill patients, but had reliable trending ability in tracking cardiac output response to fluid.^[26] This fact may limit the clinical use of absolute SV in predicting fluid responsiveness when using a pulse contour analysis device.

In addition to SV optimization, recognizing arterial pressure fluid responsiveness is also crucial because intraoperative hypotension is common adverse event which increasing the risk of organ injury.^[27] Although Guinot et al reported that ΔSV_{100} predicted arterial pressure response after 500-mL fluid challenge,^[28] we did not observe this in the prone position. We instead found that ΔSBP_{100} had adequate validity in predicting arterial pressure fluid responsiveness. The prone position not only increases cardiac afterload but also reduces cardiac preload and diastolic function,^[29] and the complex effects of the prone position on ventriculo-arterial coupling may also contribute to the superiority of ΔSBP_{100} to ΔSV_{100} in predicting arterial pressure responsiveness. According to the Windkessel model, arterial pressure is the result of the interaction between SV and arterial system factors, including ventricular inotropy, ventriculo-arterial coupling, and vasomotor tone^[30,31], rather than of the preload state alone. Therefore, ΔSV_{100} may not reflect the true ventricular elastance ($\Delta P/\Delta V$) in the prone position; the rapid SBP change induced by rapid fixed-volume infusion (100 mL; fixed ΔV) may be closer to the true ventricular elastance.^[32] Ea_{dyn} is a functional index of vasomotor tone and represents the result of arterioventricular interactions, including arterial compliance, resistance, impedance, and pulse wave velocity,^[33] making Ea_{dyn} more complex than ventriculoarterial coupling.^[34] Accordingly, the ability of Ea_{dyn} to predict arterial pressure response to vasopressor adjustment was recognized among critically ill patients in the intensive care unit.^[14] However, in our study, Ea_{dyn} failed to predict arterial pressure fluid responsiveness among patients receiving surgery.^[10] In addition, the best reported cutoff values of Ea_{dyn} to predict arterial pressure fluid responsiveness have varied between 0.74 and 1 among different patient populations.^[7,35,36] The variation reflects the complicated nature of Ea_{dyn} and implies that it should be interpreted with caution, especially in different clinical settings.

This study has a number of limitations. First, no consensus has been reached regarding the optimal methodology for mini-fluid challenge protocol, particularly the selection of the baseline SV value. Artificially enhancing the predictive power of the mini-fluid challenge is a concern because the effects of ΔSV_{100} and ΔSV_{500} can be mathematically coupled.^[37] Despite the potential to statistically enhance the predictive value, applying the mini-fluid challenge remains possibly advantageous for avoiding excessive fluid administration. Second, various prone positioning systems are used in spine surgery worldwide and may have different hemodynamic or cardiac effects. All patients enrolled in this study were in the raised-leg prone position with longitudinal bolsters, a method that has the least effect on cardiac performance.^[29] Because our findings suggested that the mini-fluid challenge test was less influenced by cardiopulmonary alteration than were dynamic fluid variables, we believe that its accuracy in predicting fluid responsiveness would apply to other prone positioning systems as well. Third, the selection of a colloid

or crystalloid for the fluid challenge may raise concern regarding its effects on immediate hemodynamic response after the fluid challenge. Joosten et al found no significant difference between the use of a crystalloid or colloid in a mini-fluid challenge test in terms of responder rate or cumulative distribution fractions; this supports the fact that the immediate hemodynamic response after a mini-fluid challenge is independent of the choice of fluid.^[38]

In conclusion, our study indicated that the mini-fluid challenge test was more accurate than dynamic fluid variables and Ea_{dyn} in predicting SV and arterial pressure fluid responsiveness, respectively, in patients undergoing spine surgery in the prone position with low-tidal-volume mechanical ventilation.

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