Review

Predictors of fluid responsiveness in the operating room: a narrative review

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Prediction of fluid responsiveness has been considered an essential tool for modern fluid management. However, most studies in this field have focused on patients in intensive care unit despite numerous research throughout several decades. Therefore, the present narrative review aims to show the representative method's feasibility, advantages, and limitations in predicting fluid responsiveness, focusing on the operating room environments. Firstly, we described the predictors of fluid responsiveness based on heart-lung interaction, including pulse pressure and stroke volume variations, the measurement of respiratory variations of inferior vena cava diameter, and the end-expiratory occlusion test and addressed their limitations. Subsequently, the passive leg raising test and mini-fluid challenge tests were also mentioned, which assess fluid responsiveness by mimicking a classic fluid challenge. In the last part of this review, we pointed out the pitfalls of fluid management based on fluid responsiveness prediction, which emphasized the importance of individualized decision-making. Understanding the available representative methods to predict fluid responsiveness and their associated benefits and drawbacks through this review will aid anesthesiologists in choosing the most reliable methods for optimal fluid administration in each patient during anesthesia in the operating room.

Keywords: Cardiac output; Fluid therapy; Hemodynamic monitoring; Intensive Care Units; Operating rooms; Stroke volume.

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INTRODUCTION

Fluid administration is a first-line treatment for hemodynamically unstable patients in the operating room to increase cardiac output and improve tissue oxygenation. However, many classical methods that seem to determine the need for fluid bolus infusion failed to increase cardiac output according to fluid administration [1], which means fluid had been inadvertently loaded into the patients who did not need fluid administration [2,3]. Therefore, the need for predicting fluid responsiveness has been raised to avoid unnecessary fluid administration and improve the patient's outcomes because fluid overload is associated with postopera-

tive complications, including pulmonary edema [4], acute kidney injury [5], and increased risk of mortality [6].

Historically, so-called "static" parameters of cardiac preload, such as central venous pressure and pulmonary artery occlusion pressure, have been used for decades. But those variables cannot accurately predict fluid responsiveness in many previous studies [7,8]. After the first study of systolic pressure variation in patients with sepsis-induced hypotension who required mechanical ventilation in the surgical intensive care unit (ICU) [9], numerous studies have demonstrated many parameters that can predict fluid responsiveness in various conditions. So, at present, a variety of predictors of fluid responsiveness such as pulse pressure variation

(PPV), stroke volume variation (SVV), respiratory variation of inferior vena cava diameter, end-expiratory occlusion (EEO) test, passive leg raising (PLR) test, mini-fluid challenge test, and many other parameters have been widely used in daily clinical practice.

However, many previous studies have been performed in the ICU patients. Considering that the environments of the operating room (OR) and the ICU are different in many ways, a parameter that is helpful in the ICU to predict fluid responsiveness can be challenging or even unavailable for the prediction of fluid responsiveness during the surgical procedure under anesthesia in the OR. Therefore, in the present review, we summarized the existing and recently updated results and limitations of the representative parameters for fluid responsiveness prediction, focusing on the OR environment. The pitfalls in fluid management based on the predictors of fluid responsiveness were also addressed.

PARAMETERS BASED ON HEART-LUNG INTERECTION

Pulse pressure and stroke volume variations

PPV and SVV are some of the firstly verified predictors of fluid responsiveness in mechanically ventilated patients [10]. The physiology of those parameters is based on heart-lung interaction according to positive pressure ventilation, which means the changes in intrathoracic pressure during mechanical ventilation affect the cardiac preload and afterload differently between the left- and right-sided hearts, leading to the circulated changes in pulse pressure and stroke volume in continuous arterial pressure waveforms (Fig. 1) [11]. Many studies in the ICU and the OR have confirmed the validity of PPV and SVV as a predictor of fluid responsiveness, and they have been widely used to guide fluid management in daily clinical practice [10,12,13]. A meta-analysis showed that PPV could predict fluid responsiveness with a sensitivity of 88%, a specificity of 89%, and an area under the receiver operating characteristic curve (AUROC) of 0.94 [13]. Zhang et al. [14] also demonstrated SVV has an odd diagnostic ratio of 18.4 in predicting fluid responsiveness with a sensitivity of 81% and specificity of 80%.

Despite the high accuracy and reliability of PPV and SVV, they cannot be accurately served as a predictor of fluid responsiveness in many conditions, such as patients with spontaneous breathing activity [15], cardiac arrhythmias [11], low tidal volume (< 8 ml/kg) [16], low lung compliance
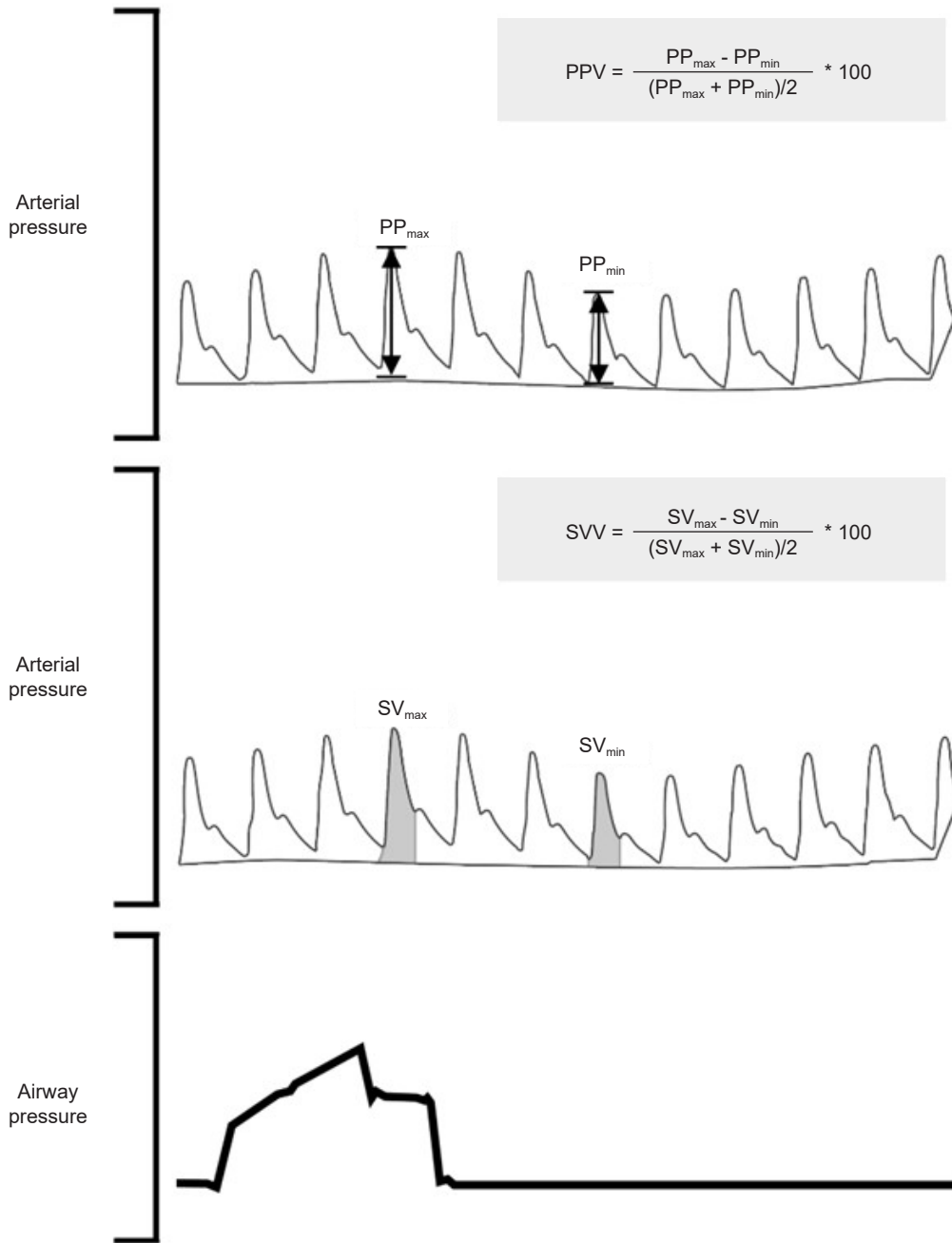
[15], open-chest condition [17], increased intra-abdominal pressure (Table 1) [18,19]. Currently, the patients in the ICU have been less sedated and frequently ventilated using low tidal volume. So, the reliability and use-frequency of PPV and SVV for fluid responsiveness prediction seem to be decreasing in the ICU environment. On the contrary, PPV and SVV are still used a lot in the OR because they can retain the predictive value accurately, as the required conditions their applicability are generally fulfilled during general anesthesia for surgical procedures.

Several recent studies have suggested that temporally increasing tidal volume can restore the predictability of PPV and SVV in various clinical situations of the ICU and OR. Myatra et al. [20] showed that the increases in PPV and SVV related to the transient increase in tidal volume from 6 to 8 ml/kg for 1 min could be a reliable predictor of fluid responsiveness in ICU patients. Min et al. [21,22] also demonstrated that augmentation of PPV using a temporary increase in tidal volume from 8 to 12 ml/kg and the Valsalva maneuver could restore its predictability of fluid responsiveness in the anesthetized patients in the "gray zone" and with the open-chest condition, respectively. So, employing a temporary increase in tidal volume can be an alternative option to overcome some limitations of PPV and SVV.

Respiratory variation of inferior vena cava diameter

Respiratory variation in the diameter of the inferior vena cava has been suggested as a non-invasive parameter to predict fluid responsiveness and is widely used in ICU patients [23]. This method does not require arterial catheterization and can be easily obtained using ultrasound with minimal training. However, based on the recent results, it seems to need more studies to confirm the diagnostic accuracy of respiratory variation of inferior vena cava to predict fluid responsiveness.

Initial small-scaled validation studies in the ICU reported that respiratory variation of inferior vena cava diameter could be a reliable parameter for predicting fluid responsiveness in mechanically ventilated patients [24-26] and even spontaneously breathing patients with cardiac arrhythmia [27]. A systematic review also suggested that respiratory variation in the diameter of the inferior vena cava had diagnostic accuracy higher than central venous pressure, lower than the PLR test, and equivalent to SVV and PPV [28]. However, in a recent study of 540 patients in the ICU, respiratory variation of inferior vena cava diameter showed lower diagnostic accuracy in predicting fluid responsiveness than the

$$PPV = \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min})/2} * 100$$

$$SVV = \frac{SV_{max} - SV_{min}}{(SV_{max} + SV_{min})/2} * 100$$

Fig. 1. PP variation and SV variation. During inspiration in positive-pressure mechanical ventilation, the increase in intrathoracic pressure leads to an increase in cardiac preload, which results in the largest PP and SV at the end of inspiration. Conversely, intrathoracic pressure decreases during expiration, resulting in a decrease in PP and SV. Consequently, PP and SV are smallest at the end of expiration. PP: pulse pressure, SV: stroke volume, PPV: pulse pressure variation, SVV: stroke volume variation.

initial validation studies (threshold value: 8%, AUROC: 0.635, sensitivity: 55%, and specificity: 70%) [29]. Two recent meta-analyses reported that the pooled AUROCs, sensitivities, and specificities of respiratory variation of inferior vena cava diameter in mechanically ventilated patients were 0.75, 79%, and 70% [30] and 0.82, 69%, and 88% [31], respectively.

Although the exact reasons for those divergent results have not been fully explained, it seems to play a role in those discrepancies that the compliance of inferior vena cava depends on many factors, such as volume status, intra-abdominal pressure, and measurement location [29,32].

In addition, the respiratory variation of inferior vena cava

Table 1. Summary of Available Tests to Predict Fluid Responsiveness with Main Advantages and Limitations in the Operating Room

Test	Monitoring techniques	Advantages	Limitations
Heart-lung interaction indices			
Pulse pressure variation/ Stroke volume variation	Arterial catheter	• No requirement for the direct measurement of cardiac output	• Cannot be used in patients with spontaneous breathing, cardiac arrhythmia, intra-abdominal hypertension, and open chest
			• False negative in low-tidal volume ventilation/low lung compliance
Inferior vena cava diameter	Transthoracic echocardiography	• Applicable in patients with spontaneous breathing and cardiac arrhythmia	• Transthoracic approach may not be feasible due to operation field
			• Not reliable in intra-abdominal hypertension
End-expiratory occlusion test	Pulse contour analysis	• Easy to perform	• Requires precise and real-time measurement
			• Cannot be used in spontaneous breathing patients
			• Limited evidence in the operating room
Fluid loading methods			
Passive leg raising test	Pulse contour analysis	• Applicable in patients with spontaneous breathing and cardiac arrhythmia	• Positional change cannot be feasible during surgery
	Echocardiography		• Not reliable in intra-abdominal hypertension
	Oesophageal Doppler	• Mimics fluid challenge without actual fluid administration	
	Pulse oximeter		
	Bioreactance		
Mini-fluid challenge	Pulse contour analysis	• Applicable in patients with spontaneous breathing and cardiac arrhythmia	• Requires a very precise measurement due to low cut-off values
	Echocardiography		• Repeated use may cause fluid overload

diameter shares most limitations of PPV and SVV except for cardiac arrhythmia and spontaneous breathing activity because those parameters are based on the same physiology that is heart-lung interactions [27]. Moreover, because the diameter of the inferior vena cava is measured in the subcostal region [25], measurement of the inferior vena cava using ultrasound is sometimes impossible in certain types of procedure (i.e., intra-abdominal surgery) because performing that method can interfere with the operation and contaminate the surgical field (Table 2). Therefore, respiratory variation in the diameter of the inferior vena cava seems to play a limited role in predicting fluid responsiveness in the OR.

End-expiratory occlusion test

The EEO test is based on the simple physiology that insufflation during mechanical ventilation can decrease cardiac preload [33]. Eliminating the rise in intrathoracic pressure during the inspiratory phase increases venous return, which acts as a fluid challenge to predict fluid responsiveness. The EEO test can be performed simply to stop the mechanical ventilation at the end-expiration and to measure the resulting changes in cardiac output for longer than 12 seconds [34]. This method is very easy-to-perform and reliable in certain conditions where PPV and SVV can be unreliable, such as low tidal volume ventilation, low pulmonary compliance (i.e., acute respiratory distress syndrome), and cardiac arrhythmia [15,35,36]. Because of its brevity, the EEO test requires a precise, continuous, and real-time hemodynamic assessment to detect the changes in cardiac output properly [34].

Since the first report by Monnet et al. [35] in 2009, several studies showed that hemodynamic response to an EEO test could accurately predict fluid responsiveness in ICU patients [20,36]. But it would be hard to conclude whether the EEO test has a diagnostic accuracy to predict fluid responsiveness in the OR. Biais et al. [37] showed that changes in stroke volume index induced by the EEO test could predict fluid responsiveness in patients with low tidal volume ventilation (6.9 ml/kg of ideal body weight). Whereas the EEO test failed to discriminate fluid responders during laparotomic surgery [38,39] and in a prone position during neurosurgery [40], which may affect venous return by involving alterations in intra-abdominal pressure and vena cava pressure [41,42]. In addition, even a recent meta-analysis that stated the EEO

Table 2. Overview of Monitoring Devices Available for the Prediction of Fluid Responsiveness

Monitoring devices	Requirement	Advantages	Limitations
Invasive method			
Pulmonary artery catheter	• Central venous catheter	• Direct measurement of hemo-dynamic parameters, including pulmonary artery pressure, cardiac output	• Delay in determining cardiac output • Invasiveness and complications (bleeding, infection, arrhythmias, and vessel damage)
Less-invasive methods			
Pulse contour analysis	• Arterial catheter	• Continuous cardiac output monitoring	• Lack of accuracy in hemodynamically unstable patients or during use of vasoactive drugs • Not reliable in patients with arrhythmia
Transesopahgeal echocardiography		• Real-time measurement of hemodynamic parameters and cardiac function • Acquirement of quantitative and qualitative data (ejection fraction, stroke volume...)	• Time and resource-intensive (equipment, trained personnel...) • Operator dependency • Not suitable for patients with esophageal pathology
Esophageal doppler		• Real-time monitoring of cardiac output	• Risk of dislocation, misplacement • Not suitable for patients with esophageal pathology
Non-invasive methods			
Transthoracic echocardiography		• Real-time measurement of hemodynamic parameters and cardiac function	• Time and resource-intensive (equipment, trained personnel...) • Operator dependency • Limited acoustic window due to patient position and operative field
Bioimpedance		• Simple, easy-to-use • Real-time monitoring of cardiac output	• Lack of reliability in patient movement, adipose tissue, edema, or the presence of electrical interference

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test successfully predicted fluid responsiveness in the ICU and OR was based merely on two previous studies: One that the EEO test could predict fluid responsiveness in patients with protective ventilation in the OR [37] and the other that EEO test failed to predict fluid responsiveness in patients undergoing laparotomic surgery [38]. Therefore, to ascertain the diagnostic accuracy of the EEO test as a predictor of fluid responsiveness in the OR, further studies conducted in the OR environment will be needed.

TESTS THAT ASSESS FLUID RESPONSIVENESS BY MIMICKING CLASSIC FLUID LOADING

Passive leg raising test

The PLR test involves positional changes from the semi-recumbent position to the position of the 45° of leg elevation with the horizontal trunk, which causes transferring blood from the lower limbs and splanchnic territory towards the intrathoracic compartment, thus increasing circulatory volume around 150–300 ml [43,44]. This reversible "self-transfusion" allows the assessment of fluid responsiveness without actual fluid infusion to the patient [43]. Also, the PLR test is independent of the heart-lung interaction; therefore, it can be successfully used to assess fluid responsiveness in patients with spontaneous breathing activity, cardiac arrhythmia, low tidal volume ventilation, and low pulmonary compliance [45]. Numerous studies have repeatedly established the high reliability of the PLR test as a predictor of fluid responsiveness in a wide variety of clinical situations [45,46]. A meta-analysis also demonstrated that PLR-induced changes in cardiac output ≥ 10% very reliably predict fluid responsiveness with good AUROC, sensitivity, and specificity (0.95, 85%, and 91%, respectively) [45]. Therefore, the Surviving Sepsis Campaign has involved the PLR test in the hemodynamic management of septic shock [47].

Because the effects of the PLR test should be measured

using cardiac output, not arterial pressure [48] and usually reach the maximum within 1 minute and then diminish, a real-time cardiac output monitoring device, such as arterial pulse contour analysis, echocardiography, and esophageal Doppler, should be used for assessing the changes in PLR-induced cardiac output [45,49]. More recently, less-invasive and easy-to-use cardiac output measuring devices such as perfusion index from plethysmography and bioreactance-based cardiac output have been suggested as the alternative methods to assess the changes in cardiac output by PLR. Beurton et al. [50] showed that an increase in perfusion index during a PLR test ≥ 10% could predict fluid responsiveness with a sensitivity of 91% and a specificity of 79% (AUROC = 0.89) in ICU patients with acute circulatory failure. Galarza et al. [51] also reported that changes in bioreactance-based cardiac output during PLR test ≥ 10% successfully discriminated fluid responders with a sensitivity of 92% and a specificity of 80% (AUROC = 0.88) in critically ill patients in the ICU. The previous study found that the bioreactance monitor, which averaged cardiac output over a 30-s period, was not able to measure the effects of PLR accurately due to its longer averaging time [52]. However, the latest version of the Starling-stroke volume system, which only takes 8 seconds to average cardiac output, allows for a more accurate assessment of the PLR effects [51]. This highlights the significance of utilizing a real-time cardiac output monitor to effectively monitor the effects of a brief test like PLR.

Five rules should be followed when accurately implementing the PLR test because the performing method fundamentally affects the hemodynamic effects and reliability of the PLR test as follows [53]. First, the PLR test must start from the semi-recumbent position. Second, cardiac output, not arterial pressure, should be measured to assess the effect of the PLR test. Third, real-time cardiac output monitoring devices should be used. Forth, the cardiac output should be reassessed after returning to the semi-recumbent position after the PLR test and should return to the value before the PLR test. Fifth, any confounding factors that provoke adrenal stimulation, such as pain, cough, discomfort, and awakening, should be avoided during the PLR test.

Considering those rules when performing the PLR test and their effect on the reliability of the PLR test in predicting fluid responsiveness, it seems to be questionable whether the PLR test can be performed accurately during surgery in the OR. First, the presence of surgical equipment or the surgical procedure can make the positional change impossible or not allowed. In addition, the patients should be in a later-al or prone position in some operations. Second, each time the PLR test is performed, the operation should be stopped because a precise surgical procedure is impossible when changing the patient's position. The surgical procedure can also be a potential confounding factor that causes adrenal stimulation. Third, applying elastic compression stockings, frequently used to prevent venous thromboembolism in the OR, may compromise the reliability of the PLR test to predict fluid responsiveness by reducing returning blood volume [54]. Last, the reliability of the PLR test has been questioned in cases of intra-abdominal hypertension [55], which may restrict applying the PLR test in a specific type of surgical procedure that increases intra-abdominal pressure, such as laparoscopic surgery with intra-abdominal carbon dioxide insufflation. So, despite the proven safety and accuracy in predicting fluid responsiveness, it seems that the PLR test can merely be used in very limited cases during surgical procedures in the OR.

Mini-fluid challenge

From decades ago, the fluid challenge technique has been suggested for fluid management [56] because infusing fluid bolus and measuring its effect on cardiac is the most definite way in practice to determine the presence of fluid responsiveness. However, the "classic" fluid challenge with the administration of 300–500 ml of fluid is irreversible and can lead to fluid overload, especially if repeated, in case of the absence of fluid responsiveness, which occurs in about half of the patients. Therefore, the classic fluid challenge seems to be considered the treatment rather than the challenge. Thus, a "mini-fluid challenge" with rapid infusion (1–2 min) of a small amount (100–150 ml) of crystalloid or colloid has been introduced as an alternative method [48,57]. The mini-fluid challenge is also independent of heart-lung interaction, like the PLR test, so it can be used to predict fluid responsiveness in various clinical conditions where PPV and SVV cannot be applied.

Since the first report in 2011 [57], which reported an increase in the variation of subaortic velocity time index after 100 ml of colloid infusion over 1 min could predict fluid responsiveness with a sensitivity of 95% and a specificity of 78% (AUROC = 0.92) in mechanically ventilated patients in the ICU, several studies have shown the reliability of mini-fluid challenge to predict fluid responsiveness in the ICU [20,58,59] and the OR [60,61]. A recent meta-analysis has confirmed the reliability of mini-fluid challenge as a pre-

dictor of fluid responsiveness by demonstrating that the pooled AUROC for the mini-fluid challenge was 0.91 with the best threshold of 5% and that pooled sensitivity and specificity were 82% and 83%, respectively [62]. In addition, a multi-center trial has shown that the mini-fluid challenge of 100 ml over 1 min successfully predicted fluid responsiveness with a sensitivity of 98% and specificity of 87% for cut off value of 4% (AUROC = 0.95) in patients undergoing laparotomy [63]. Considering those results, the mini-fluid challenge can be an attractive option if the other predictors of fluid responsiveness are not feasible or applicable.

However, the mini-fluid challenge has several limitations as follows. First, critical methodological issues have been recently raised regarding the existing results of the mini-fluid challenge, in which the predictor parameters after the mini-fluid challenge of 100 ml and the outcome parameters after 500 ml of fluid administration were calculated from the same baseline, leading to potential mathematical coupling and overestimation of the observed predictive power [64]. Second, even in cases where preload responsiveness is present, a small volume of fluid administration will elicit small changes in cardiac output [65]. Therefore, a precise device to measure cardiac output should be needed to detect a relatively small diagnostic threshold for the mini-fluid challenge (around 5%) [48]. Last, the mini-fluid challenge entails the administration of fluid which cannot be removed. Although the risk is lower compared to a traditional fluid challenge, there is still a potential for fluid overload if the mini-fluid challenge is repeated.

PITFALLS IN FLUID MANAGEMENT

Gray zone: Uncertainty exists in every test

No single test or value is perfect for predicting fluid responsiveness tests or for any diagnostic tests. There are inherent limitations in every test. In statistical analysis, fluid responsiveness is typically described in a dichotomous manner as either present or absent. But the response to fluid administration is a continuous parameter. Thus, the diagnostic threshold derived from the quantitative test is arbitrary and does not reflect the full range of potential responses. So, the "gray zone," which represents a zone of uncertainty, has been introduced as a complement to the binary constraint of ROC curve analysis [66]. Cannesson et al. [67] first reported that the gray zone of PPV to predict fluid responsiveness was between 9% and 13% in approximately 24% of patients. In addi-

tion, previous studies have shown that 17% and 19% of patients were included in the gray zone for the EEO test [37] and mini-fluid challenge [61], respectively. Therefore, anesthesiologists should recognize that relying solely on a single parameter within the gray zone may not provide definitive guidance for fluid administration decisions.

Fluid responsiveness is not an omnipotent rule

The decision to administer fluid should not be solely based on the presence of fluid responsiveness. While fluid responsiveness indicates the likelihood of a patient's potential to increase cardiac output in response to fluid administration, it does not necessarily mean that fluid should always be given. It is crucial to consider the patient's overall fluid status, underlying pathology, and potential risks associated with fluid overload. Although fluid administration may be necessary to optimize hemodynamics in some patients, excessive fluid administration may lead to complications such as pulmonary edema and impaired organ function in certain conditions, such as congestive heart failure, chronic kidney disease, or acute respiratory distress syndrome [4]. Alternative treatments, such as vasopressors or inotropes, may be more appropriate in these cases. Therefore, fluid therapy should always be individualized based on careful evaluation of the patient's clinical condition, focusing on achieving adequate tissue perfusion while avoiding complications associated with fluid overload.

No need to determine fluid responsiveness in every patient

In the OR, the ultimate goal of fluid management is to optimize the patient's hemodynamic status by promptly addressing blood volume depletion or other contributing factors to hemodynamic instability. Therefore, immediate fluid loading will be more effective than testing fluid responsiveness if the clinical situation corresponds to the obvious hypovolemia (i.e., massive bleeding). However, it should be remembered that in most other cases, fluid administration increases cardiac output sufficiently in around half of patients.

CONCLUSION

For the optimal fluid management in each patient, it is crucial to determine fluid responsiveness accurately before fluid administration to prevent unwanted fluid overload and

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the related risks. However, several well-known existing methods for assessing fluid responsiveness, such as respiratory variation of inferior vena cava diameter, the EEO test, and the PLR test, require numerous prerequisites, and even when certain limitations are addressed, their applicability in the operating room remains restricted. So, despite its inevitable limitations resulting from the heart-lung interaction, PPV and SVV will be the first choice as a test for fluid responsiveness prediction in the OR environments if the patient is not in a situation where PPV and SVV cannot be applied, such as the presence of spontaneous breathing or cardiac arrhythmia. If PPV and SVV are not applicable, a mini-fluid challenge seems helpful for predicting fluid responsiveness in the OR. Further studies will be needed to evaluate the optimal method for determining fluid responsiveness focusing on OR environments.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conceptualization: Ah Ran Oh, Jong-Hwan Lee. Methodology: Ah Ran Oh, Jong-Hwan Lee. Writing - original draft: Ah Ran Oh, Jong-Hwan Lee. Writing - review & editing: Ah Ran Oh, Jong-Hwan Lee. Investigation: Ah Ran Oh, Jong-Hwan Lee. Resources: Ah Ran Oh, Jong-Hwan Lee. Supervision: Ah Ran Oh, Jong-Hwan Lee. Validation: Ah Ran Oh, Jong-Hwan Lee.

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