PREDICTION OF FLUID RESPONSIVENESS WITH CRYSTALLOID MINI-FLUID CHALLENGE IN CRITICALLY ILL PATIENTS

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Abstract
Background: The mini-fluid challenge test is a good predictor and has minimal limitations in determining fluid responsiveness in the critically ill. However, it primarily relies on colloid infusion. The availability of colloids may vary among hospitals in resource-limited countries, and they can be more expensive than crystalloid fluids.
Objective: The study aimed to use crystalloids instead of colloids to predict fluid responsiveness.
Methods: This study was conducted from August 2022 to February 2023 among patients with shock in the medical ICU to assess fluid responsiveness. Arterial and central venous catheters were used for the intravenous infusion and monitoring. Data were collected during two consecutive crystalloid mini-fluid challenges of 50 mL each in 1 minute, 100 mL in 2 minutes, and a standard fluid challenge of 300 mL over 15 minutes. The objective was to predict a stroke volume index (SVI) increase of > 10%. Diagnostic accuracy was evaluated using the Receiver Operating Characteristic (ROC) curve, and hemodynamic variables in the positive fluid challenge group were compared for different volume expansions.
Results: Twenty-nine patients (62% males; median age, 75 years) were included, with 42 fluid challenge test events. Septic shock was the primary condition in 83% of the cases. The 50 mL crystalloid mini-fluid challenge showed an accuracy of 80% with a sensitivity of 69% and specificity of 100% at the cutoff level of SVI > 5%, Area Under ROC (AUROC)=0.79. In comparison, the 100 mL crystalloid mini-fluid challenge demonstrated an accuracy of 85% (sensitivity of 79% and specificity of 100%) at the cutoff level of SVI > 10% (AUROC= 0.89). In the positive fluid challenge group, administration of crystalloids led to a significant increase in mean arterial pressure and SVI, while other parameters remained comparable.
Conclusions: A mini-fluid challenge test with 100 mL crystalloids can predict fluid responsiveness in critically ill patients. The best cutoff level was a change in SVI > 10% from baseline.

Keywords: crystalloid; mini-fluid challenge test; fluid responsiveness; septic shock

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Introduction

Shock is a condition characterized by inadequate blood flow to tissues. It is commonly seen in the intensive care unit (ICU) and is associated with increased mortality. Initial symptoms include elevated heart rate and decreased blood pressure. Delayed treatment can lead to poor tissue perfusion and multi-organ failure.

Specific treatment for septic shock involves intravenous antibiotics and organ support; initial resuscitation includes fluid therapy.[1, 2] Despite expectations of improved healthcare systems, a US study from 2014-2015 reported a 50% mortality rate in sepsis cases, with approximately 12% potentially preventable. Delays in recognizing and treating sepsis, along with inappropriate antibiotic therapy, are significant contributors. Risk factors for sepsis-related mortality include solid cancer, chronic heart disease, dementia, and chronic lung diseases.[3]

Fluid therapy is crucial for sepsis management to address endothelial dysfunction and hypovolemia. However, excessive fluid can cause complications, such as delirium, increased intracranial pressure, pulmonary edema, bowel ileus, and acute renal failure.[4] However, inadequate fluid resuscitation impairs tissue perfusion and oxygen delivery. [5]

The fluid challenge test is a method used to assess fluid responsiveness by measuring a 10% increase in cardiac output (or stroke volume) after administering a fluid bolus of 250-500 mL.[5-7] Another approach, the mini-fluid challenge test, has accurately predicted fluid responsiveness using restricted fluid administration of a 100 mL colloid bolus.[7-10] However, it is noted that the availability of colloids varies among hospitals, and they are generally more expensive compared to crystalloids, which are more available in hospitals. Real-time cardiac output or stroke volume measurement is necessary to determine the treatment effect of a fluid bolus after a challenge test. [5, 11] A cardiac output monitor using pulse contour analysis is employed because it rapidly measures hemodynamic data and continuously monitors its changes.[2, 11, 12]

This study aimed to determine whether changes in stroke volume induced by rapid infusion of 50 and 100 mL of crystalloids can predict the effects of administering 300 mL of crystalloids in patients in a stage of shock who require predicted fluid responsiveness.

Methods

Setting and patient population

This study was conducted following the Declaration of Helsinki. Before its commencement, comprehensive ethical approval was obtained from The Institutional Review Board of the Royal Thai Army Medical Department (R148h/65).

A prospective experimental study was conducted, including patients admitted to the medical intensive care unit ((ICU), Phramongkutklao Hospital, between August 2022 and February 2023, who met the shock stage criteria and a requirement for predicted fluid responsiveness. Patients had to be over 20 years old to be eligible for the study. They had a central catheter inserted either in the jugular or subclavian vein, an arterial catheter, and cardiac output monitoring by pulse contour analysis. All patients provided informed consent, either personally or through a first-degree relative. Additionally, they were in the supine position and exhibited clinical signs of pulmonary edema. The study excluded pregnant women and those receiving palliative care.

Data collection

Patients who met the inclusion criteria underwent non-calibrated cardiac output monitoring using pulse contour analysis (FloTrac sensor on EV1000 monitor, Edwards Lifesciences), positioned with a 30-degree head elevation. We prepared two syringes containing 50 mL of crystalloid fluid in each crystalloid bag containing 200 mL (total volume, 300 mL). As the initial step preceding the experimental process, we collected baseline demographic data, including illness severity (assessed using the APACHE II score), comorbidities, vasopressor type, and dosage, as well as vital signs and respiratory parameters such as tidal volume, positive end-expiratory pressure (PEEP), and respiratory compliance. Following administering a 50 mL and 100 mL crystalloid fluid bolus within 20 sec-

onds, we collected cardiac output parameters and vital signs. Subsequently, we collected additional cardiac output parameters and vital signs after 300 mL crystalloid fluid loading for 15 minutes (**Figure 1, data supplement**). During the experi mental process, we engaged a well-trained critical care physician to oversee vital signs and cardiac output parameters obtained from the EV1000 monitor, including stroke volume (SV), stroke volume index (SVI), stroke volume variation (SVV), cardiac output (CO), and cardiac index (CI), and to follow the protocol. An ICU nurse was also responsible for adjusting crystalloid fluid boluses and loading them.

Outcomes

The primary objective was to assess the accuracy of fluid responsiveness by comparing the crystalloid mini-fluid challenge test with the standard fluid challenge test. The secondary outcomes aimed to evaluate the SVI's sensitivity and specificity, that is, SV per body surface area (BSA), and SVT was automatically displayed during cardiac output monitoring. This evaluation was to predict fluid responsiveness using the crystalloid mini-fluid challenge compared with the standard fluid challenge test. Additionally, the study sought to analyze trends in hemodynamic parameters during positive fluid challenges identified by the crystalloid mini-fluid challenge test.

Statistical analysis

Based on previous research findings, which indicated a change of over 6% in SVI following the administration of 100 mL of crystalloid to predict fluid responsiveness in the operating room with a sensitivity of 93% and specificity of 85%, a sample size estimation was conducted to determine the number of events required to predict fluid responsiveness accurately. The analysis determined that approximately 42 events were necessary, with a power of 80% and a two-tailed type I error rate of 5%.[13]

This study defined a positive fluid challenge as a 10% or more significant increase in the SVI from the baseline following a 300 mL infusion. Mean ± SD was reported for normally distributed variables and median (interquartile range: 25^{th}–75^{th} percentile) for non-normally distributed variables. A receiver operating characteristic (ROC) curve analysis was employed to evaluate the SVI's accuracy, sensitivity, specificity, and Youden index and determine the optimal cutoff values for comparing the crystalloid mini-fluid challenge with the standard fluid challenge test. Wilcoxon signed-rank tests assessed whether statistically significant differences in the mean hemodynamic parameters were observed before and after administering 50, 100, and 300 mL fluid challenges.

Additionally, Pearson correlation tests were performed to examine the relationship between SVI after 50 mL (ΔSVI 50), 100 mL (ΔSVI 100), and 300 mL (ΔSVI 300) fluid administration. All *p*-values were two-tailed, and a significance level of $p < 0.05$ was deemed statistically significant.Statistical analyses were conducted using STATA, Version 17.

Results

A total of 29 patients and 42 events were included in the study and analyzed for both primary and secondary outcomes. **Table 1** shows baseline characteristics and mechanical ventilator data. Most patients were male (62.0%), with a median age of 75. The average APACHE II score was 32.6. The average body mass index (BMI) was 22.6 kg/m², and the average body weight was 59 kg. Septic shock was the most common diagnosis, accounting for 83% (24/29). Pneumonia was the leading cause, accounting for 24.1%, followed by upper urinary tract infection (10.3%), cellulitis (6.9%), and other causes (40.7%). All patients received norepinephrine as a vasopressor with a median dose of 0.34 mcg/kg/min. Most patients had comorbidities, including hypertension (69.0%), diabetes mellitus (48.3%), chronic kidney disease (44.8%), and atrial fibrillation (55.2%). Furthermore, all patients in this study were mechanically ventilated, with a median tidal volume of 7.5 ml/kg and driving pressure of 14 cmH_2O. After a complete fluid bolus, 300 mL of crystalloid and 28 (66.7%) events met the fluid-responsive criteria, whereas 14 (33.3%) events did not. All baseline characteristics in this study showed no difference between the positive and negative challenge groups.

Table 1. Baseline characteristics of enrolled participants

Character	Total (N = 29)
Age (years)[+]	75 (64-81)
Male, n (%)	18 (62.0)
Height (cm)*	161.0 ± 7.0
Actual body weight (kg)*	59 ± 9.3
Body mass index (kg/m^2)*	22.6 ± 3.1
APACHE II score[#]	32.6 ± 7.9
Comorbidity, n (%)	
Diabetes mellitus	14 (48.3)
Hypertension	20 (69.0)
Chronic kidney disease	13 (44.8)
Atrial fibrillation	16 (55.2)
Chronic liver disease	4 (13.8)
Chronic heart failure	2 (6.9)
Diagnosis (%)	
Septic shock	24 (83.0)
Hypovolemic shock	3 (10.0)
RV failure	2 (7.0)
ARDS	8 (27.6)
Norepinephrine dose (mcg/kg/min)[+#]	0.34 (0.2-0.6)
Tidal volume/predicted body weight (mL/kg)[+#]	7.5 (7-8.5)
Positive end-expiratory pressure (cmH_2O)[+#]	5 (5-8)
Driving pressure (cmH_2O)[+#]	14 (13-16)

* mean ± SD; [+] median (IQR)
All characters were collected at the first event, [#]while specific dynamic parameters were collected on average at each subsequent event.
APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, Acute Respiratory Distress Syndrome

Table 2. Diagnostic accuracy test to predict an increase in SVI greater than 10% after 300 mL of saline infusion over 10 minutes.

Index	Best threshold (%)	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)
ΔSVI 50	> 5	0.79 (0.64-0.93)	69	100	80
ΔSVI 100	> 10	0.89 (0.78-0.99)	79	100	85

The best threshold value was determined using the Youden index. Data show the specificity (95% confidence interval). AUROC = area under receiver operating characteristics curves;
ΔSVI 50 = changes in stroke volume index induced by rapid 50-mL volume expansion;
ΔSVI 100 = changes in stroke volume index induced by rapid 100-mL volume expansion.

Table 3 . Hemodynamic variables at baseline and after 50, 100, and 300 ml of saline infusion in positive fluid challenges (n = 28) and negative fluid challenges (n = 14)

	Baseline	50 mL	100 mL	300 mL
MAP (mmHg)				
Positive fluid challenges	72 (62-84)	76.5 (67-90)*	82.5 (72-96)*	92 (88, 100)*
Negative fluid challenges	71.5 (68-84)	73 (69-80)	75 (69-84)	75 (70-85)
SVI (mL/m^2)				
Positive fluid challenges	27 (20-33)	30 (22-34)*	32 (25-39)*	35 (27-40)*
Negative fluid challenges	41 (32-60)	39.5 (32-57)	39 (32-55)	39 (31-51)
Heart rate (bpm)				
Positive fluid challenges	95 (84-124)	97 (81-123)	91 (81-123)	95 (82-126)
Negative fluid challenges	100 (91-141)	98 (86-139)	99 (93-133)	99 (89-137)

Values are median (25th to 75th percentile). Positive fluid challenges were defined as an increased stroke volume index by 10% or higher after 300 ml intravascular volume expansion. The baseline was before volume expansion, 50 mL was after 50 mL saline infusion, 100 mL was after 100 mL saline infusion, and 300 mL was after 300 mL saline infusion. Using the Friedman test for repeated measures, the p-value shows multiple comparisons among baseline, 50 mL, 100 mL, and 300 mL.
*$p < 0.0125$ *versus* T0 using Wilcoxon signed ranks test.
bpm = beats per minute; SVI = Stroke volume index; MAP = Mean Arterial Pressure.

Table 2 demonstrates the ability of ΔSVI 50 and ΔSVI 100 to predict the effect of volume expansion **(Figure 2**, **data supplement**). The accuracy of the crystalloid mini-fluid challenge with a 50 mL bolus in predicting fluid responsiveness (stroke volume index > 10%) was 80%, with a sensitivity of 69% and a specificity of 100%. In contrast, the accuracy of the crystalloid mini-fluid challenge with a 100 mL bolus in predicting fluid responsiveness was 85%, with a sensitivity of 79% and a specificity of 100%.

Table 3 and **Figure 3 in the data supplement** show the hemodynamic variables in the positive and negative fluid challenge groups at different stages of volume expansion. The positive fluid challenge group comprised 66.7% of the participants and exhibited increased mean arterial pressure (MAP) and SVI, while the heart rate remained unchanged. The median baseline MAP of 72 mmHg increased to 76.5 mmHg, 82.5 mmHg, and 92 mmHg after fluid boluses of 50 mL, 100 mL, and 300 mL, respectively, with a $p < 0.05$. Similarly, the median baseline SVI of 27 mL/m² increased to 30 mL/m², 32 mL/m², and 34.5 mL/m² after fluid boluses of 50 mL, 100 mL, and 300 mL, respectively, with a $p < 0.05$. However, the heart rate did not change significantly and remained at a median baseline of 95.5 beats/min after fluid boluses of 50 mL, 100 mL, and 300 mL. In contrast, the negative fluid challenge group did not exhibit any changes in MAP, SVI, or heart rate compared with the baseline values.

Furthermore, a strong correlation was observed between ΔSVI 50, ΔSVI 100, and ΔSVI 300 ($r = 0.912$, $p < 0.001$; $r = 0.875$, $p < 0.001$), as shown in **Figures 4A** and **4B in the data supplement.**

Discussion

This study illustrated that in predominantly patients with septic shock undergoing mechanical ventilation in the ICU, a 100 mL crystalloid mini-fluid challenge showed very good accuracy in predicting fluid responsiveness compared with the standard fluid challenge test with an AUROC of 0.89. ΔSVI 100 performed better than ΔSVI 50 in predicting the effect of volume expansion. When ΔSVI 100 exceeded 10%, an 85% accuracy in predicting a positive response to volume expansion occurred. Furthermore, ΔSVI 50 and ΔSVI 100 significantly correlated with ΔSVI 300

($p < 0.001$); this suggested that changes in SVI after administering a small amount of fluid might be sufficient to predict the response to standard fluid administration. Due to the very high specificity (100%) of the test for administering 50 ml and 100 ml of fluid in predicting fluid response, further fluid boluses should be avoided if a patient does not respond.

The accuracy of the crystalloid mini-fluid challenge, which involved administering a 100 mL bolus within 2 min, was found to be 85% compared with the fluid challenge test using a 300 mL crystalloid bolus over 15 min. Furthermore, we observed a sensitivity of 79% and specificity of 100% when considering a more than 10% SVI increase from the baseline. Biais et al. found that the crystalloid mini-fluid challenge had a sensitivity of 93% and a specificity of 85% when considering an SVI increase of over 6% from the baseline compared with the standard fluid challenge.[13] Similarly, Guinot et al. reported that the crystalloid mini-fluid challenge showed a sensitivity of 89% and specificity of 89% when assessing an SVI increase of over 7% from the baseline compared with the fluid challenge. [14] Our study utilized a different cutoff value and showed a lower sensitivity in predicting fluid responsiveness. This difference was likely attributed to the inclusion of predominant patients with septic shock receiving moderate doses of vasopressors, whereas previous studies were conducted in an operating room setting.

Two previous studies explored the use of crystalloid mini-fluid challenges to predict fluid responsiveness in the ICU. Wu et al. reported a sensitivity of 75% and a specificity of 95% for crystalloid mini-fluid challenge compared with fluid challenge. [15] They considered a Velocity Time Integral (VTI) increase of > 9% from the baseline. In this study, echocardiography was employed to measure VTI, and the study protocol involved the administration of a 50 mL crystalloid fluid bolus for 10 sec to predict fluid responsiveness. Wang Xiao Ting et al. also reported a sensitivity of 73% and a specificity of 60% for the crystalloid mini-fluid challenge when compared with the fluid challenge. [16] They considered a CI increase of > 5.4% from the baseline. Calibrated invasive cardiac output monitoring (PiCCO) was utilized, and the study protocol involved administering a 100 mL crystalloid bolus over 60 sec to predict fluid responsiveness. Our study exhibited differences in cutoff values, sensitivity, and specificity for predicting fluid responsiveness, primarily attributable to variations in the study design. These differences encompassed factors such as the quantity and duration of fluid bolus administration and the tools employed to assess fluid responsiveness.

In particular, conditions to predict fluid responsiveness, such as acute respiratory distress syndrome (ARDS), are limited in using heart-lung interaction due to low tidal volume and lung compliance. Additionally, caution is needed when employing a fluid challenge test due to the increased risk of volume overload. In this study, we encountered ARDS in approximately 30% of cases, with the majority, around 80%, classified as mild severity. These mild cases utilized low PEEP and a tidal volume of about 8 mL/kg, factors that did not influence the threshold of SVI change in predicting fluid responsiveness.

Our study's secondary outcome involved examining hemodynamic variables in the positive fluid challenge group after the fluid challenge. We observed an increase in mean MAP and SVI while the heart rate remained unchanged. When comparing our findings with those of a previous study conducted by Biais et al.[13], we noticed similar increases in MAP and SVI in the positive fluid challenge group. However, our study differed from the previous study in that we did not observe a decrease in the heart rate. The difference could be due to our emphasis on patients with septic shock characterized by heightened sympathetic activity and relative hypovolemia; this suggested that the fluid administered might not have adequately addressed the sympathetic tone during the early stages of septic shock.

Our study encountered some limitations. First, we utilized uncalibrated cardiac output monitoring to predict fluid responsiveness. While cardiac output data from an uncalibrated device might not be accurate, it demonstrated good precision, meaning that a change in the parameter rather than a static value could predict

the response to intervention. In assessing fluid responsiveness, the reference criteria involved an increase in cardiac output of >10-15% from the baseline following a fluid bolus. Therefore, having an exact cardiac output value was not imperative, and we aimed to mitigate this limitation by collecting data 20 sec after the fluid bolus, given that the device collected data every 20 sec. Second, our sample size was small, and some patients contributed to repeated data, which could have introduced selection bias. Nevertheless, no more than three events were used to predict fluid responsiveness in each patient, and data collected from all patients were on different days. Third, most data were obtained from patients with septic shock. Thus, the outcomes could vary for other types of shocks, which needs further investigation. Finally, the interpretation of the data depended on the expertise required to operate the cardiac output monitoring machine and the availability of central venous and arterial catheters. It is important to note that not all hospitals in resource-limited countries have the necessary monitoring types of equipment. This limitation may affect the generalizability of the results. However, our study had notable strengths. First, using crystalloid fluid, readily available in all hospitals, reduced treatment costs compared to colloids such as albumin. Second, we opted for uncalibrated cardiac output monitoring, a minimally invasive alternative to calibrated cardiac output monitoring, or a pulmonary artery catheter.

Conclusion

The study showed that administering 100 mL of crystalloid mini-fluid challenge over 2 min could effectively predict fluid responsiveness in critically ill patients during shock. The most effective cutoff level for predicting fluid responsiveness was a change in SVI exceeding 10% from baseline.

Conflict of Interest

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

Authors' Contributions

Conceptualization: WT, PA. Data curation: WT, PA Formal analysis: WT, PA. Methodology: WT, DS, AL, PA. Project administration: WT, PA. Visualization: WT, DS, AL, PA Writing – original draft: WT. Writing – review & editing: WT, PA.

Supplementary Material

The Supplementary Material for this article can be found online at: https://jseamed.org/index.php/jseamed/article/view/190

Supplementary Figure 1: Flow chart of the study protocol Flow chart of the study protocol

Supplementary Figure 2: Receiver operating characteristics curves were generated for ΔSVI 50 (changes in stroke volume index induced by a rapid 50 ml volume expansion) and ΔSVI 100 (changes in stroke volume index induced by a rapid 100 ml volume expansion).

Supplementary Figure 3: Mean arterial blood pressure (MAP) at baseline, after 50 ml, 100 ml, and 300 ml of crystalloid infusion stratified by fluid responsive status.

Supplementary Figure 4A: Correlation between stroke volume index after 100 mL crystalloids infusion (SVI 100) and stroke volume index after 300 mL crystalloids infusion (SVI 300)

Supplementary Figure 4B: Correlation between stroke volume index after 50 mL crystalloids infusion (SVI 50) and stroke volume index after 300 mL crystalloids infusion (SVI 300)

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