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RESEARCH PROTOCOL

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Left ventricular diastolic function compared to inferior vena cava diameter variation as predictor of fluid responsiveness in mechanical ventilated patients with shock: The research protocol

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ABSTRACT:

Background: Fluid responsiveness, defined as an increase in cardiac output by 15% after a fluid challenge, is recommended to be evaluated in-patients with shock. Left ventricular (LV) diastolic dysfunction is associated with a lower increment of cardiac output after fluid challenge. Despite being a non-invasive test, the echocardiographic evaluation of the left ventricular diastolic function was rarely studied for the prediction of fluid responsiveness. The objective of this study is to evaluate the efficacy of LV diastolic function in predicting fluid responsiveness, comparing with inferior vena cava (IVC) diameter variation method, among shock patients who required mechanical ventilation.

Methods: We plan to enroll adult patients with shock admitted to the intensive care unit (ICU). The echocardiographic hemodynamic parameters include IVC diameter variation, peak velocity of early diastolic filling of mitral valve inflow (E wave), peak early diastolic velocity of the mitral valve annulus (Ea), mitral E/Ea ratio, left ventricular ejection fraction (LVEF) and transaortic cardiac output (CO), all at baseline and after fluid therapy are measured. A fluid challenge with an infusion of 300 ml of acetate Ringer's solution within 15 minutes will be given. Patients who have an increase in systolic blood pressure of at least 10 mmHg, mean arterial pressure of at least 5 mmHg or cardiac output of at least 15% are defined as fluid responders. The primary outcome of this study is the efficacy of the mitral E/Ea ratio comparing with IVC diameter variation in predicting fluid responsiveness. The secondary outcomes include the rate of fluid responsiveness in mechanically ventilated patients and LVEF and CO in patients with shock in the intensive care units.

Conclusion: This study will evaluate the efficacy of left ventricular diastolic function measured by the echocardiography (Mitral E/Ea ratio) in predicting fluid responsiveness among mechanical ventilated patients with shock.

Trial registration: Clinicaltrials.gov NCT05066256, registered on January 10th, 2021

Keywords: Fluid responsiveness, Shock, Left ventricular diastolic function, Mitral E/Ea ratio, Fluid challenge

INTRODUCTION

Shock, a life-threatening acute circulatory failure, is one of the most common problems found among critically ill patients. Up to one-third of the patients admitted in the intensive care units (ICU) had diagnosis of shock [1,2]. One of the main treatments in patients with shock is fluid therapy to improve patient's hemodynamic by increasing stroke volume and cardiac output[2].

Factors that determine the patient's cardiac output are left ventricular end-diastolic volume (preload), heart rate, cardiac contractility, and systemic vascular resistance (afterload) which vary in each individual patient [3]. Fluid responsiveness, defined as an increase in cardiac output or stroke volume by 15% after fluid challenge, is recommended to be evaluated during shock management, according to the European Society of Intensive Care Medicine (ESICM) [1]. It can be used to evaluate the risks and benefits of a fluid challenge to avoid complications of excess fluid administration. Fluid overload can lead to interstitial edema, pulmonary edema and organ dysfunction, all of which further contribute to patient deterioration [2].

Various practices of the fluid challenge have been observed with different types of the fluid, the volume of fluid and duration of fluid infusion, in which there is no standard protocol for the fluid challenge including a method to define or evaluate a fluid responder [4,5]. In 2017, Toscani et al [5] conducted a meta-analysis on various studies of fluid challenge and reported that no aforementioned difference in practices affected fluid responsiveness except infusion duration of more than 30 minutes, which significantly decreased fluid responsiveness outcome. For a minimal volume of fluid to significantly increase cardiac output, Aya et al [6] found that the minimal volume required to increase mean systemic filling pressure (Pmsf) by 14% was at least 4 ml per kilograms of the patient's body weight.

Cardiac output measurement is often invasive or requires an expensive device[7], therefore, a test for predicting fluid responsiveness has been used to substitute the direct cardiac output measurement [8]. Transthoracic echocardiography is one of the non-invasive methods to measure fluid responsiveness and is currently available in most ICUs worldwide [9,10].

Left ventricular diastolic dysfunction is associated with a compromised of venous return and decreased LV preload, resulting in a lower cardiac output increment after a fluid challenge. LV diastolic function could be evaluated by measuring early (E wave) and late (A wave) peak velocity of diastolic filling of mitral valve inflow, peak early diastolic velocity of the mitral valve annulus (Ea or e') and mitral E/Ea (or E/e') ratio [11][12]. Furthermore, several previous studies demonstrated the association of high mitral E/Ea in predicting elevation of LV end-diastolic pressure [13]. Despite being a non-invasive test, echocardiographic evaluation using a mitral E/Ea ratio was rarely studied for the prediction of fluid responsiveness. One prospective study in 2019 [11] evaluated a mitral E/Ea ratio in patients receiving elective coronary revascularization before and after fluid challenge with 5% albumin solution (7 ml/kg) and found that mitral E/Ea ratio > 8 is a good indicator for predicting fluid responsiveness compared to peripheral venous pressure.

Thereby, we conducted the study to evaluate the efficacy of using a mitral E/Ea ratio to predict fluid responsiveness in patients with shock, comparing to IVC diameter variation.

KEY MESSAGES:

- We conducted a diagnostic experimental study to compare efficacy between mitral E/Ea ratio and IVC diameter variation to predict fluid responsiveness in patient requiring mechanical ventilation with shock. We hope that after the study, the result will be comparable and may contribute mitral E/Ea as one choice for fluid responsiveness test.

OBJECTIVES

This study objective is to evaluate the efficacy mitral E/Ea ratio to predict fluid responsiveness in mechanically ventilated with shock, in comparison with IVC diameter variation.

MATERIAL AND METHODS

Methodology

We conducted a diagnostic experimental study in the medical and surgical intensive care unit at Siriraj Hospital. This study was approved by Siriraj Institutional Review Board (Si 752/2020) and was registered in clinicaltrials.gov (NCT05066256).

Eligibility Criteria

Inclusion criteria

1. Age more than 18 years.
2. Diagnosis of shock as defined by systolic blood pressure < 90 mmHg or mean arterial blood pressure < 65 mmHg with clinical of tissue hypoperfusion.
3. Mechanically ventilated without ventilator dyssynchrony.
4. Presence of central venous catheter and/or arterial catheter at the time of enrollment.

Exclusion criteria

1. Patients who are under the age of 18.
2. Patients who are frankly hypovolemic, are in hypovolemic or hemorrhagic shock and required rapid fluid infusion.
3. Patients who have a clinical suspicion of cardiogenic shock.
4. Patients who have a clinical suspicion of acute decompensated heart failure.
5. Patients who have a clinical suspicion of having an acute coronary syndrome.
6. Patients who deny participation or deny informed consent.

Withdrawal Criteria

1. Patients who have sudden cardiac arrest or sudden alteration of consciousness during intervention.

2. Patients with a poor cardiac window or there is a problem in ultrasound machine causing a delay in acquiring echocardiographic parameter to more than 3 minutes.

3. Patients whose echocardiography obtained during the pre-experimental study identifies a suspicion of congestive heart failure or volume overload e.g., severely depressed LVEF, Marked IVC distention.

4. Patient's or family withdrawal from the study.

Intervention

Patients who have met the eligibility criteria and has granted informed consent will have their vital signs (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, and respiratory rate), central venous pressure (CVP) and pulse pressure variation (PPV) from arterial catheter recorded. Transthoracic Echocardiography will be performed on the patients to evaluate and record the following parameters:

- Cardiac output measures from the left ventricular outflow tract diameter (LVOT diameter) and left ventricular outflow tract velocity time integral (LVOT VTI). The LVOT diameter is obtained from the parasternal long-axis view and is measured at the aortic annulus at systole (Figure 1-A). For LVOT VTI, it is obtained from the apical five-chamber view, and the pulse-wave Doppler sample volume is placed at the level of the aortic annulus (Figure 1-B) [14]. The LVOT diameter and LVOT VTI are determined and recorded within 1 minute.

- Inferior vena cava (IVC) diameter variation calculated from maximum and minimum IVC diameters acquired from subcostal view by applying a probe to the subxiphoid area with the probe pointing to the patient's head and using a motion mode (M-mode) after IVC has been identified (Figure 1-C) [15]. The diameters are determined and recorded within 30 seconds.

- Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) determined by the Teicholz method. These parameters are obtained from the parasternal long-axis view using an M-mode to achieve perpendicular cursor alignment with the left ventricle (LV) walls (Figure 1-D) [14] and recorded within 30 seconds.

- Mitral E/Ea ratio calculated from the early mitral inflow velocity (E wave) and mitral annular early diastolic velocity (Ea wave). The peak E velocity (E wave) is obtained from the apical 4-chamber view by applying the probe at LV apex with the marker pointing toward the right side of the patient, then after the identifying LV, pulse-wave Doppler sample at the tip of mitral valve opening (Figure 1-E) [12]. The median Ea velocity (Ea Wave) is obtained from the apical 4-chamber view by using pulse-wave tissue Doppler imaging (TDI) at the septal mitral annulus (Figure 1-F) [14]. Both velocities are determined and recorded within 1 minute.

Transthoracic echocardiography parameters are obtained within 3 minutes after enrollment to prevent a harmful effect from delaying resuscitation. After the echocardiography parameters have been recorded, patients will receive a fluid infusion of 300 ml of acetate Ringer's

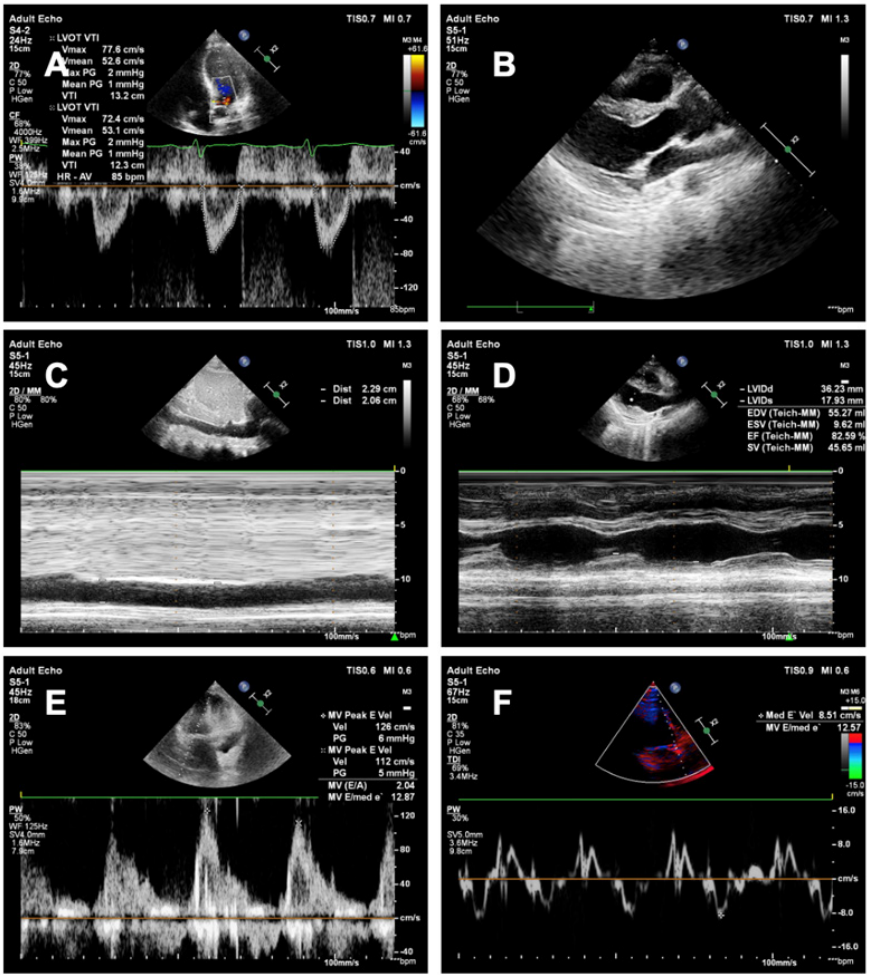

Figure 1. Echocardiographic measurement. **A**: LVOT VTI obtained from apical five-chamber view, **B**: LVOT diameter obtained from parasternal long-axis view, **C**: IVC diameter obtained from subcostal view in motion mode, **D**: LVEF obtained from parasternal long-axis view in motion mode, **E**: Mitral E/A ratio obtained from apical four-chamber view using pulse-wave doppler mode. **F**: Mitral E/Ea ratio obtained from apical four-chamber view using pulse wave tissue-doppler imaging.

solution for 15 minutes. After fluid infusion, all aforementioned parameters are remeasured to evaluate the aftereffect of a fluid challenge.

Patients who have an increase in cardiac output of more than 15%, systolic blood pressure higher than 10 mmHg or mean arterial blood pressure more than 5 mmHg will be classified as fluid responders. Total intervention time between the diagnosis of shock and the evaluation after fluid challenge must be within 30-minutes interval.

Since the data acquired from transthoracic echocardiography are operator-dependent, a hand-on echocardiography workshop will be conducted to facilitate medical doctors' competency. The intra-observer and inter-observer variability of each acquiring parameters needed in this study are evaluated at the end of the echocardiographic workshop. The variability must be less than 15% before collecting data for the study.

Outcome Measurement

Primary Outcome

The primary outcome is the efficacy of the mitral E/Ea ratio in predicting fluid responsiveness demonstrated as sensitivity, specificity and positive and negative predictive values compared to IVC variation, central venous pressure, and pulse pressure variation.

Secondary Outcome

The secondary outcomes include the rate of fluid responsiveness in mechanically ventilated patients with shock, assessment of fluid responsiveness in mechanically ventilated patients with shock requiring vasopressors and/or inotropic agents, a comparison of stroke volume measured by transthoracic echocardiography using left ventricular ejection fraction and left ventricular outflow tract velocity time integral, and left ventricular ejection fraction and cardiac output in patients with shock in the medical and surgical intensive care units at Siriraj hospital.

STATISTICAL ANALYSIS

Sample size calculation

This study aims to compare hemodynamic parameters before and after a fluid challenge. The sample size was calculated based on Marques et al [11] study in 2019, in which mean mitral E/Ea ratios before and after a fluid challenge are 10.7 and 12.6, respectively with a standard deviation of 5.5. A significance level of 0.05 and a power of 80% is assumed. Using sample size calculation for mean difference, the estimated sample size will be 66. With an additional 20% sample size, the calculated sample size needed in this study is 80.

OUTCOME ANALYSIS PLAN

1. General data will be analyzed with descriptive statistics, show as mean (standard deviation, SD), or median (interquartile range, IQR) when suitable.

2. Compare mitral E/Ea ratio, IVC variability, CVP and PPV before and after fluid challenge with paired student's t-test or Wilcoxon test.

3. Compare mitral E/Ea ratio, IVC variability, CVP and PPV between fluid responders and non-fluid responders with independent sample t-test.

4. Create a receiver operating characteristic (ROC) curve with a 95% confidence interval with the best diagnostic threshold at the highest Youden index and compare an area under the ROC curve (AUROC) with the Hanley-Mcneil test.

DATA MANAGEMENT AND DATA MONITORING

Data collection and monitoring

The case record form is used to assess the eligibility and exclusion criteria, baseline patient characteristics and outcome of the intervention. Details on each variable and their collection method are shown in Table 1-3.

An interim analysis will be evaluated to ensure patient's safety after 50% of the sample size has been collected.
Confidentiality

Confidentiality

The result of this study may be published in medical journals. The participant's information will be presented as a unique number. The information of subjects will be maintained confidential as required.

Table 1. Patient's baseline characteristic variable and data collection plan.

Baseline characteristic	Collection method
Age	Chart review
Sex	Chart review
Underlying disease - Hypertension - Diabetes mellitus - Dyslipidemia - Chronic kidney disease - Coronary artery disease - Valvular heart disease - Stroke - COPD/Asthma - Cirrhosis - Malignancy	
Diagnosis	Chart review
Sepsis	Chart review
Weight/Height	Chart review
APACHE II Score	Chart review
SOFA score	Chart review
Electrocardiogram	Chart review
Mechanical ventilation parameter at enrollment - Tidal volume, ml - Tidal volume, ml/kg - Peak inspired pressure - PEEP - Respiratory rate	Data collection from ventilator
Vasoactivea agent - Received vasopressors - Received inotrope - Total vasopressor dose	Chart review

Table 2. Variable collected before and after fluid challenge, and data collection plan.

Variable before and after fluid challenge	Collection method
Vital signs - Body temperature - Heart rate - Systolic blood pressure - Diastolic blood pressure - Mean arterial pressure - Respiratory rate	Collect from real time monitoring
Hemodynamic parameter - Central venous pressure - Pulse pressure variation	Collect from real time monitoring
Echocardiographic parameter - LVEF - LVEDV - LVESV - Stroke volume from biplane method - Minimal IVC diameter - Maximal IVC diameter - IVC variability index - Mitral E/A ratio - Mitral E/Ea ratio - Cardiac output - Stroke volume from LVOT VTI	Echocardiographic report

DISCUSSION

This study is the first study to evaluate the efficacy of left ventricular diastolic function measured by the transthoracic echocardiography (mitral E/Ea ratio), in predicting fluid responsiveness in critically ill patients with shock. A similar technique was employed in a previous study by Quintard et al [16] to examine the physiologic effect of acute preload changes to the hemodynamic parameters acquired from transesophageal echocardiography. The study was conducted in critically ill patients with shock requiring mechanical ventilation and vasopressors. The result showed that despite significant changes in the peak E velocity and median Ea velocity after infusion of 500 ml of colloid solution the change in the mitral E/Ea ratio was insignificant. The patients enrolled in this study were assumed to be fluid responders due to their need of fluid infusion as required by the physician in charge. Similar results were also found by Marques et al [11] in the efficacy study of LV diastolic function compared to peripheral venous pressure in predicting fluid responsiveness in patients undergoing cardiac surgery. A significant change in the mitral E/Ea ratio is observed only in non-fluid responders. However, this study was performed on patients under general anesthesia without shock.

According to the latest surviving sepsis campaign, balanced crystalloid solutions should be considered as the first-line fluid for resuscitation[17]. In recent studies, the administration of normal saline solution in critically ill patients can lead to more adverse kidney outcomes compared to the balanced crystalloids solution [18,19].

Compared to colloid solutions, crystalloid solutions have a shorter context-sensitive half-time [20]. However, according to the volume kinetics study [21], the short-term effect of crystalloid solutions on expanding plasma volume expansion can be as high as 50% to 80% compared to colloid solution. In addition, the context-sensitive half-time of the crystalloid solutions can be much longer in the setting of arterial hypotension or hypovolemia [21,22]. As mentioned earlier, the amount of fluid infused is not associated with the rate of fluid responsiveness [5] but at least 4 ml/kg of fluid should be used in a fluid challenge to evaluate fluid responsiveness [6]. Therefore, in our study, a 15-minute infusion of 300 ml of acetated Ringer's solution is used for the fluid challenge. The use of acetated Ringer's solution is effective, and the solution is easier to access than colloid solutions. The infusion rate employed is the highest achievable via our currently in-use infusion pumps.

Changes in cardiac output or cardiac index are used to identify a fluid responder [5,23]. However, due to difficulty in obtaining the parameters, a mean arterial pressure is often a key target in fluid resuscitation [23]. There is a significant increase in arterial pressures (systolic, diastolic, and mean arterial pressure) observed after a fluid challenge in fluid responders, but for predicting fluid responsiveness, these changes may have a high false negative rate [24] and a poor correlation with changes in the cardiac index [23]. On the other hand, increase in cardiac output after fluid challenge may not be accurately predict increase in mean arterial pressure, therefore, the term pressure responder is also being used in predicting arterial pressure increment after a fluid challenge [25]. Though there are no single MAP value recommended, maintaining MAP are usually recommended for maintaining adequate tissue perfusion [17] Thus, in our study, both arterial blood pressure and cardiac output are used to identify fluid responder. Concern in fluid responder criteria including blood pressure changes has been raised, therefore, we plan to analyze the outcome based on using our criteria and using cardiac output increment as a fluid responder criterion in comparison. For the method for obtaining cardiac output, the mini fluid challenge study [26] demonstrates that, an increase in LVOT VTI from echocardiography after a fluid challenge can be used as a predictor of fluid responsiveness. Therefore, we use a 15% change in cardiac output [24,26] obtained from echocardiography as a key criterion to identify a fluid responder.

Respiratory variations of the inferior vena cava have been extensively studied and are frequently used in clinical practices due to being noninvasive test for fluid responsiveness prediction. The efficacy of IVC variation index to predict fluid responsiveness in mechanically ventilated patients varies in each study, with sensitivity from 67% to 90% and specificity from 70% to 90% [27]. In our study, we aimed to study efficacy of mitral E/Ea as a noninvasive fluid responsiveness prediction. Therefore, we decided to compare the efficacy with mitral E/Ea with a widely used noninvasive parameter which can acquired from echocardiography, which is IVC diameter variation index.

We conducted this diagnostic experimental study to compare efficacy of two non-invasive methods to predict fluid responsiveness. Though mitral E/Ea is a static parameter which are not currently recommended as fluid responsiveness test, we hope that the study result may contribute to some clinical practice or may warrant further clinical trials to test efficacy of mitral E/Ea as a dynamic parameter.

CONCLUSION

Though physiologically, left ventricular diastolic dysfunction is associated with decreased LVEDP and results in less fluid responsiveness, the left ventricular diastolic function from transthoracic echocardiography is rarely studied for fluid responsiveness despite being a non-invasive test. We conduct the study to evaluate the usefulness of mitral E/Ea ratio from echocardiography as both static and dynamic parameters in the fluid responsiveness test in patients with shock.

Ethics

This study was approved by Siriraj Institutional Review Board (Si 752/2020) and was registered in clinicaltrials.gov (NCT05066256).

DISSEMINATION POLICY

When the study is complete. We planned to disseminate the result for peer-review internationally with critical care medicine related journals.

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AUTHORS' CONTRIBUTIONS

Every author in this study has equally contributed to the study. Including conceptualization, data collection, methodology, writing and editing.

SUPPLEMENTARY MATERIALS

none

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