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ORIGINAL RESEARCH

The Accuracy of Dynamic Parameters for Prediction of Fluid Responsiveness in Elderly Patients with Septic Shock

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Purpose: Assessed the accuracy of stroke volume variation (SVV), pulse pressure variation (PPV), and dynamic arterial elastance (Eadyn) in predicting fluid responsiveness (FR) and mean arterial pressure (MAP) response in elderly patients with septic shock.

Patients and Methods: Mechanically ventilated patients aged over 65 with septic shock were enrolled. SVV, PPV, and Eadyn were recorded before and after FR testing (≥10% increase in cardiac output following a passive leg raise test or fluid challenge). MAP responsiveness was defined as a ≥10% increase in MAP post-fluid loading. Receiver operating characteristic curves were constructed to assess predictive parameters such as PPV, SVV for fluid responsiveness, and Eadyn for MAP response after loading. Optimal cutoff values were determined using the Youden index. Sensitivity, specificity, and area under the curve (AUC) were calculated. A p-value <0.05 indicated statistical significance.

Results: The mean age was 76 ± 8 years. Of the 104 patients, 46 were FR-positive. PPV and SVV were higher in FR-positive patients (PPV: 22.07 ± 11.02 vs 9.34 ± 7.39, p < 0.001; SVV: 20 ± 11 vs 9 ± 6, p < 0.001). The AUC was 0.875 for PPV, 95% confidence interval (CI) of 0.802–0.947, and 0.841 for SVV, 95% CI of 0.757 −0.925. Thresholds of 13.5% for PPV and 11.5% for SVV were found, with 81.8% sensitivity and 87% specificity. MAP responders had higher Eadyn (1.31 ± 0.54 vs 1.01 ± 0.93, p = 0.013). Eadyn showed an AUC of 0.844, with a threshold of 1.00 (sensitivity 85.7%, specificity 75%).

Conclusion: PV, SVV, and Eadyn are predictors of FR and MAP responsiveness in elderly septic shock patients.

Keywords: septic shock, elderly patients, pulse pressure variation, stroke volume variation, dynamic arterial elastance, fluid responsiveness

Introduction

Septic shock is one of the common causes of mortality and morbidity in critically ill patients. The sepsis pathophysiology comprises vasodilatation, increased microvascular permeability, and capillary leakage, leading to decreased intravascular volume.[1,2] Fluid administration is essential for restoring and optimizing cardiac output (CO) and organ perfusion.[1] One-half of patients with sepsis and septic shock may respond beneficially to fluid loading.[1] Fluid administration can induce deleterious pulmonary edema, compromising microvascular perfusion and oxygen delivery in patients not responsive to fluid therapy. This can occur due to overzealous fluid administration and capillary leaks, leading to overhydration and tissue edema.[3] Additionally, the impact on microcirculation and organ perfusion varies and depends on the patient's response to fluid therapy.[4] Several studies have shown that a positive cumulative fluid balance is associated with a high mortality rate in septic shock.[5,6] Thus, an accurate and reliable technique to guide fluid resuscitation is required.

Currently, none of the routinely used static variables of cardiac preload, such as central venous pressure, pulmonary artery occlusion pressure, or global end-diastolic volume index, is a reliable tool to predict fluid responsiveness.[7,8] Recent

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guidelines suggest that dynamic indicators derived from arterial pressure waveforms, such as stroke volume variation (SVV) and pulse pressure variation (PPV), can assess fluid responsiveness in mechanically ventilated patients.[7,8]

Aging is associated with an increase in the large arteries' stiffness, resulting in reduced arterial compliance.[9] Diminished arterial compliance and increased systolic blood pressure enhance pulse pressure amplitude, but the stroke volume does not change.[9] Pulse pressure was significantly related to arterial stiffness.[10] Consequently, loss of arterial elasticity in elderly patients might also affect PPV and SVV accuracy and their threshold value to predict fluid responsiveness.

According to the Windkessel model, arterial pressure can be explained by the interplay of left ventricular stroke volume and the arterial system. The capacity of an artery to elevate pressure with rising flow is linked to its stiffness, quantified by the arterial volume–pressure relationship slope or arterial elastance. Arterial elastance, the ratio of pressure changes to volume changes, is an encompassing measure of arterial system function.[11] Recently, several studies have shown that dynamic arterial elastance (Eadyn), defined as the ratio of pulse pressure variation to stroke volume variation, serves as a dynamic parameter for assessing arterial load.[11] Eadyn can predict whether there will be an increase in mean arterial pressure (MAP) following a fluid challenge, categorizing patients as MAP responders.[11] Recent meta-analysis showed that Eadyn performs well predicting MAP increases in response to fluid expansion in mechanically ventilated hypotensive adults, especially in the ICU.[12] However, in elderly patients who tend to increase arterial stiffness,[10] the predictive value of pulse pressure variation (PPV), stroke volume variation (SVV), and Eadyn has not been explicitly evaluated. This study aimed to assess whether dynamic indexes such as PPV and SVV can reliably predict fluid responsiveness in elderly patients with septic shock who require mechanical ventilation. We also sought to investigate whether Eadyn can predict MAP responders and determine the associated thresholds for these patients.

Materials and Methods

We conducted a cross-sectional study at a medical intensive care unit in a university hospital in Bangkok, Thailand. We included the patients from two datasets: one from the prospective observational study between November 2021 and September 2022 (COA no. MURA 2021/809) and another from the study between January and December 2019 (MURA 2021/795). The Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, approved the study (MURA 2024/671). This study was conducted following the Declaration of Helsinki. Every patient or patient's next of kin is provided with informed consent.

Study Population

Inclusion Criteria

- Patients older than 65 who were diagnosed with septic shock and went to the ICU ward of Ramathibodi Hospital within 24 hours.
- Undergoing mechanical ventilation with a tidal volume of at least 8 mL/kg without spontaneous breathing effort.[13]
- Met the septic shock criteria within 24 hours following the sepsis-3 criteria, which consider meeting all of these criteria:
  - Suspected or documented infection and an acute increase of >2 SOFA points.
  - Received vasopressor therapy to keep MAP >65 mmHg.
  - Lactate >2 mmol/L (18mg/dl) despite fluid resuscitation.
- An arterial line connected to a continuous CO monitoring device (EV1000 or FloTrac®/Vigileo) is present.

Exclusion Criteria

- Patients with arrhythmias.
- Patients with a ratio of heart rate (HR) to respiratory rate of less than 3.6.
- Patients or their relatives refused to participate in the study.

Protocol Study

Initially, patients meeting the inclusion criteria were identified, while those presenting exclusion criteria were excluded from the study. The data collection includes age, gender, body mass index (BMI), vital signs at presentation, arterial lactate at presentation, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores at the time of presentation, Sequential Organ Failure Assessment (SOFA) score, dose of norepinephrine. Data collection commenced upon patient admission, with baseline hemodynamic parameters and ventilator setting recorded.

Regarding hemodynamic monitoring parameters, SVV, PPV, Eadyn, and other hemodynamic data were recorded before the fluid responsiveness test. EaDyn is defined as PPV/SVV. Tidal volume and respiratory rate were also recorded during the fluid responsiveness test. Fluid responsiveness was evaluated using one of the three methods based on clinical judgment: a passive leg-raising test, a mini-fluid challenge test involving 100 mL of colloid administered via a central line over 60 seconds, or a fluid challenge test involving 500 mL of crystalloid administered over 15–30 minutes. Hemodynamic parameters were re-recorded post-testing. Patients demonstrating fluid responsiveness were subsequently grouped based on their reaction to the fluid challenge test. The attending physician then decided on further volume expansion, typically administering 500 mL of normal saline over 30 minutes.

Definition

Fluid responsiveness: defined as CO increase of 10% or more, assessed using the noncalibrated pulse contour analysis CO monitoring devices (EV1000) after passive leg raising under deep sedation or paralysis, or mini-fluid challenge test, or fluid challenge.[8] MAP responsiveness is an increased MAP of 10% or more from baseline after fluid challenge.[11]

Outcome

The primary outcome of this study was the SVV and PPV in determining fluid responsiveness in mechanically ventilated elderly patients with septic shock. The secondary outcome involved evaluating the predictive capability of dynamic arterial elastance (Eadyn) for MAP responsiveness in the same patient population.

Statistical Analysis

The sample size for the diagnostic study was calculated based on the area under the curve (AUC) method, considering a target AUC of 0.9, a null hypothesis AUC (AUCnull) of 0.7, the prevalence of sepsis and septic shock patients who are fluid responsive at 50%, a significance level (α) of 0.05, and a test power of 90% (β = 0.1). The formula used was:

$$N = (Z\alpha + Z\beta)2 \cdot [p(1 - p)]/(AUC - AUCnull)^2$$

where Zα and Zβ represent the critical values from the standard normal distribution corresponding to the significance level and test power, respectively, and p is the prevalence of the disease. Substituting the specified parameters (Zα = 1.96, Zβ = 1.28, p = 0.5, AUC = 0.9, and AUCnull = 0.7), the calculated sample size was approximately 66 participants. This method follows the recommendations for sample size estimation in diagnostic studies as outlined by Obuchowski et al (1998).[14]

All data were analyzed using the IBM SPSS program version 22. Values were expressed as the means ± standard deviation (SD) for the continuous variables with normal distribution, as the median (interquartile range, IQR) in the case of the continuous variable without normal distribution, and as a percentage for categorical variables. The mean values were compared using the Student's *t*-test. The median values were examined using the Mann–Whitney *U*-test. The categorical variables were analyzed using Chi-square or the Fisher's exact test. The receiver operating characteristic (ROC) curve was created to test the ability of PPV and SVV to predict positive fluid responsiveness and the ability of Eadyn to predict a positive MAP response after fluid loading. The optimal cutoff value was identified by selecting the point on the ROC curve that maximized the Youden index (sensitivity + specificity - 1). The sensitivity and specificity were calculated at these cutoff points. The AUC was also computed to quantify the overall accuracy of these predictive parameters. A p-value of <0.05 was considered indicative of statistical significance.

Result

A total of 127 people older than 65 years met the inclusion criteria. Twenty-three were excluded, and 104 patients (27 from an observational study between January and December 2019 and 77 from an observational study between November 2021 and November 2022) were included in the final analysis (Figure 1). Baseline patient characteristics are shown in Table 1. Of the 104 elderly patients, seventy-eight patients performed PLR, 22 performed the mini-fluid challenge test, and 4 received the

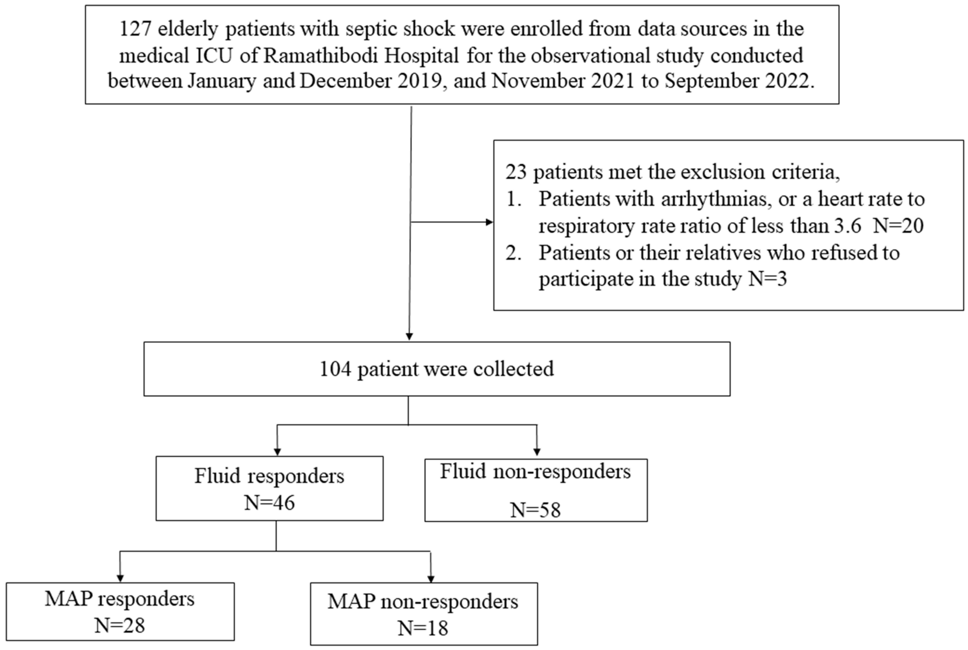

Figure 1 Patients flow and recruitment.

fluid challenge to classify fluid responsiveness. Forty-six (44.2%) were classified as positive fluid responsiveness (defined by a CO increase of 10% or more after PLR, mini-fluid challenge test, or fluid challenge). The mean age was 76 ± 8 years. The systolic, diastolic, and mean arterial pressure were significantly lower in patients with positive FR than those without FR. Patients with positive fluid responsiveness received a vasoactive agent dosage lower than the non-responders.

Table 1 Baseline Characteristics and Hemodynamic Parameters in Fluid-Responders and Fluid Non-Responders

Variables	All (n=104)	Fluid Responsiveness		P value
		Non-Responders (n=58)	Responders (n=46)	
Age, years (SD)	76 (8)	75 (8)	77 (9)	0.287
Female, n (%)	52 (50.0)	30 (51.7%)	22 (47.8%)	0.693
BMI, kg/m^2 (SD)	34.46 (6.55)	33.32 (7.98)	33.72 (3.06)	0.887
APACHE II score, mean (SD)	23 (8)	25 (7)	22 (9)	0.052
SOFA score, mean (SD)	10 (4)	10 (4)	9 (4)	0.108
Lactate level, mmol/L (SD)	5.0 (3.7)	4.5 (3.3)	5.8 (4.0)	0.075
Vasoactive agent dosage, mcg/kg/min (IQR)	0.15 (0.05,0.39)	0.22 (0.05,0.50)	0.08 (0.04,0.24)	0.014
FIO2, mean (SD)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.444
TV, mL/kg of predicted BW (SD)	9.3 (1.6)	9.5 (1.8)	9.0 (1.1)	0.111
RR, breath/min (SD)	22 (5)	21 (5)	23 (6)	0.070

(*Continued*)

Table 1 (Continued).

Variables	All (n=104)	Fluid Responsiveness		P value
		Non-Responders (n=58)	Responders (n=46)	
MV, L/min (SD)	9.9 (2.9)	10.1 (3.2)	9.6 (2.4)	0.676
Heart rate, beat/min (SD)	100 (23)	97 (23)	105 (22)	0.097
SBP, mm Hg (SD)	106 (25)	115 (25)	95 (21)	<0.001
DBP, mm Hg (SD)	56 (11)	59 (11)	51 (9)	<0.001
MAP, mm Hg (SD)	71.99 (13.92)	76.97 (13.80)	65.71 (11.39)	<0.001
PPV, % (SD)	14.94 (11.11)	9.34 (7.39)	22.07 (11.02)	<0.001
SVV, % (SD)	14 (10)	9 (6)	20 (11)	<0.001
SV, mL (SD)	46.01 (17.29)	50.58 (15.86)	40.25 (17.44)	0.002
CO, L/min (SD)	4.5 (1.7)	4.8 (1.7)	4.1 (1.7)	0.045
Eadyn, mmHg/mL (SD)	2.19 (0.92)	1.89 (0.59)	2.70 (1.17)	0.024

Notes: Values are expressed as mean (SD), median (25^{th}, 75th percentile), or absolute numbers (%), as appropriate.
Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA score, Sequential Organ Failure Assessment score; IQR, Interquartile range; FIO2, fraction of inspired oxygen; TV, tidal volume; RR, respiratory rate; MV, minute ventilation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPV, pulse pressure variation; SVV, stroke volume variation; SV, stroke volume; CO, cardiac output; Eadyn, dynamic arterial elastance.

Primary Outcome

PPV and SVV were significantly higher in patients with positive FR than those without FR (22.07± 11.02 vs 9.34± 7.39; P < 0.001 and 20 ± 11 vs 9 ± 6; P < 0.001, respectively). The area under the PPV and SVV ROC curves was 0.875 [95% confidence interval (CI) 0.802–0.947] and 0.841 (95% CI 0.757 −0.925), respectively. The optimal threshold values for discrimination between FR and non-FR were 13.5% for PPV (sensitivity 81.8%, specificity 87.0%) and 11.5% for SVV (sensitivity 81.8%, specificity 87.0%) (Figure 2). Table 2 shows hemodynamic variables before and after the fluid responsiveness test in fluid-responder and fluid-non-responders.

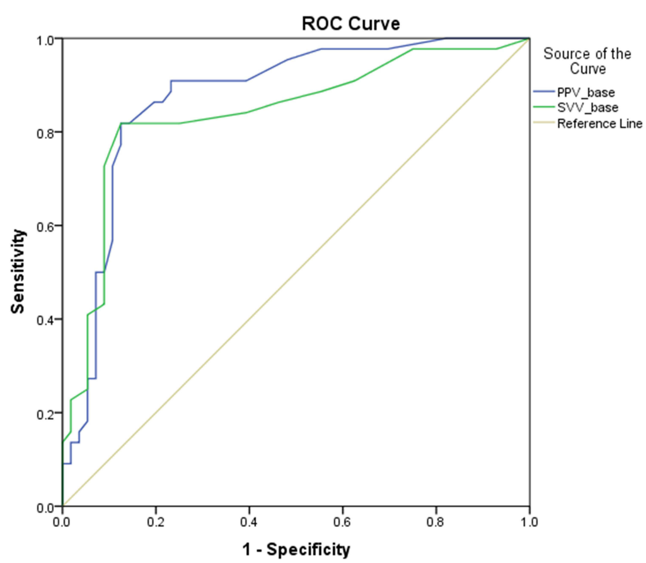

Figure 2 The receiver operating characteristic curves for testing the ability of pulse pressure variation or stroke volume variation to predict fluid responsiveness in elderly patients with septic shock.
Abbreviations: PPV, pulse pressure variation; SVV, stroke volume variation; ROC receiver operating characteristic.

Table 2 Hemodynamic Variables Before and After Fluid Responsiveness Test in Fluid-Responder and Fluid Non-Responders

	Fluid-Responders (N=46)		P value	Fluid Non-Responders (n=58)		P value
	Before	After		Before	After	
Heart rate, beat/min (SD)	105 (22)	98 (20)	0.002	97 (23)	94 (21)	0.018
SBP, mm Hg (SD)	95 (21)	109 (24)	0.000	115 (25)	117 (26)	0.051
DBP, mm Hg (SD)	51 (9)	59 (12)	0.000	59 (11)	59 (9)	0.988
MAP, mm Hg (SD)	66 (11)	75 (13)	0.000	77 (14)	78 (13)	0.249
PPV, % (SD)	22.1 (11.0)	9.9 (4.4)	0.000	9.3 (7.4)	8.4 (6.2)	0.049
SVV, % (SD)	20.0 (11.0)	10.0 (4.0)	0.000	9.0 (6.0)	8.0 (5.0)	0.006
CO, L/min (SD)	4.1 (1.7)	4.5 (1.8)	0.001	4.8 (1.7)	4.7 (1.7)	0.459
SV, ml (SD)	40.3 (17.4)	47.4 (21.8)	0.000	50.6 (15.9)	51.4 (17.9)	0.394
Eadyn, mmHg/mL (SD)	1.3 (0.7)	1.2 (0.6)	0.002	1.0 (0.4)	1.1 (0.4)	0.675

Note: Values are expressed as mean (SD).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPV, pulse pressure variation; SVV, stroke volume variation; SV, stroke volume; CO, cardiac output; Eadyn, dynamic arterial elastance.

Secondary Outcome

Among 46 patients who were positive for FR, 28 were MAP responders. Baseline hemodynamic variables in the subgroup of patients with fluid responders are shown in Table 3. Baseline Eadyn was higher in the MAP-responder group than in the MAP non-responder group (1.31 ± 0.54 vs 1.01 ± 0.93 P = 0.013). The area under the ROC curve of Eadyn for predicting MAP responsiveness is 0.844 (95% CI 0.704–0.984) (Figure 3). The threshold value of Eadyn to predicting MAP-responder was 1.00 (sensitivity 85.7% and specificity 75%).

Table 3 Baseline Hemodynamic Variables in the Subgroup of Patients with Fluid Responders (n = 46)

	MAP Responsiveness		P value
	MAP Non-Responders	MAP Responders	
Heart rate, beat/min (SD)	99(22)	108(22)	0.028
SBP, mm Hg (SD)	102(25)	90(16)	<0.001
DBP, mm Hg (SD)	53(10)	51(9)	<0.001
MAP, mm Hg (SD)	69.09(13.43)	63.54(9.50)	<0.001
PPV, % (SD)	16.72(5.18)	25.12(12.32)	0.001
SVV, % (SD)	21(11)	19(11)	0.098
CO, L/min (SD)	4.2(1.9)	4(1.6)	0.366
SV, mL (SD)	43.84(20.99)	37.94(14.68)	0.025
Eadyn, mmHg/mL (SD)	0.98(0.93)	1.40(0.57)	0.013

Note: Values are expressed as mean (SD).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PPV, pulse pressure variation; SVV, stroke volume variation; SV, stroke volume; CO, cardiac output; Eadyn, dynamic arterial elastance.

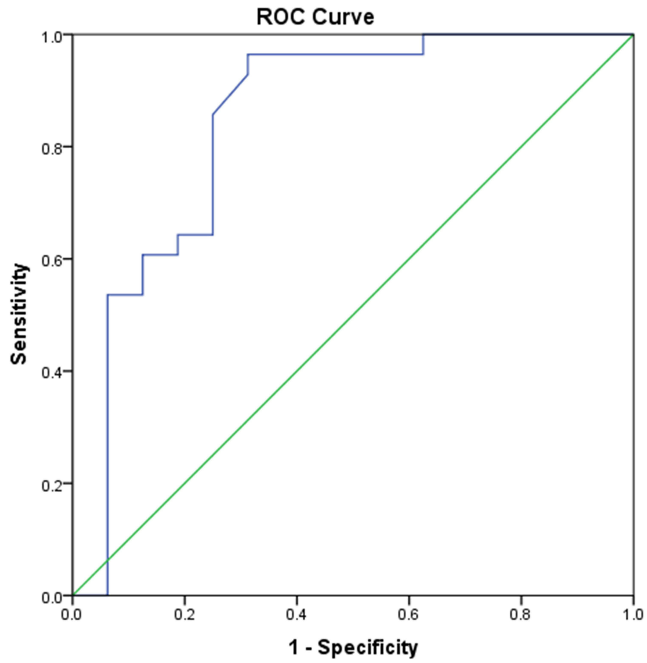

Figure 3 The receiver operating characteristic curve generated for dynamic arterial elastance (Eadyn) showing the ability to predict an increase in mean arterial pressure (MAP) after fluid challenge. MAP responsiveness defined as an increase in MAP by 10%.
Abbreviation: ROC, receiver operating characteristic.

Discussion

In mechanically ventilated elderly patients with septic shock, the main findings of our study are: 1) PPV and SVV were significantly higher in patients with positive fluid responsiveness than those without fluid responsiveness; 2) In the elderly, cuff-of value for predicting fluid responsiveness of PPV was 13.5 (sensitivity 81.8% and specificity 87.0%), and of SVV was 11.5 (sensitivity 81.8% and specificity 87.0%). 3) The area under the PPV and SVV ROC curves was 0.875 (95% CI 0.802–0.947) and 0.841 (95% CI 0.757 −0.925), respectively. And 4) The baseline Eadyn was higher in the MAP-responder group than in the MAP-non-responder group. The cuff of a threshold value of Eadyn for prediction of MAP-responder was 1.0016 (sensitivity 85.7% and specificity 75%).

Presently, dynamic parameters monitored by noninvasive CO have become the standard method for monitoring septic shock patients in the ICU. The interpretation of those parameters uses heart–lung interactions during mechanical ventilation to assess fluid responsiveness.[1,15] Among the functional hemodynamic parameters, PPV and SVV were quickly and accurately obtained by online assessment of the arterial waveform.[1] Nonetheless, data on elderly patients with septic shock are lacking.

As individuals age, arterial compliance, essentially the elasticity of the arteries—decreases significantly. This reduction in arterial compliance is primarily due to structural changes in the arterial walls, including increased collagen deposition and decreased elastin.[16] These changes cause the arteries to stiffen, which has a direct impact on pulse pressure. Pulse pressure is the difference between systolic and diastolic blood pressure. As arterial compliance decreases, systolic blood pressure tends to increase due to the stiffer arteries, while diastolic pressure may remain relatively stable or even lower. This leads to an increase in pulse pressure.[10] The stiff arteries also cause an earlier reflection of the pressure wave from the periphery back toward the heart. This earlier return increases systolic pressure further, exacerbating the increase in pulse pressure.[16] The increase in vascular stiffness directly affects ventricular-arterial coupling (interaction of the heart with the systemic vasculature).[9,10] These may affect the interpretation of parameters derived from pulse contour analysis, namely, PPV and Eadyn.[9] Thus, we performed this study in mechanically ventilated elderly patients with septic shock to evaluate the efficacy of the dynamic hemodynamic parameters, namely SVV and PVV, for predicting fluid responsiveness and MAP responsiveness.

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Previous studies have shown that guided fluid management based on SVV and PPV will result in improved outcomes in septic shock patients. In our study, SVV and PPV are good predictors of fluid responsiveness in elderly patients. The recent meta-analysis by Chaves et al reported that the mean threshold of PPV and SVV in predicting fluid responsiveness was 11.5% (95% CI 10.5–12.4) and 12.1% (95% CI 10.9–13.3), respectively.[17] Khwannimit et al demonstrated that the optimal threshold values in predicting fluid responsiveness were 10% for SVV, obtained by FloTrac/Vigileo, and, (sensitivity 91.7% and specificity 83.3%) and 12% for the automated PPV (sensitivity 83.3% and specificity 83.3%.[11] Cuff-of value for predicting fluid responsiveness of PPV in our study was 13.5 (sensitivity 81.8% and specificity 87.0%), and of SVV was 11.5 (sensitivity 81.8% and specificity 87.0%). The results of our study align with recent studies, in the general adults population affirming the values of SVV and PPV could also predict fluid responsiveness in elderly patients. This study demonstrated that both the SVV and the automated PPV could be used to predict fluid responsiveness in elderly patients with septic shock patients. We also found that fluid responder patients had received lower doses of vasoactive agents than fluid non-responders. The high dose of norepinephrine (≥0.3 mcg/kg/min) of norepinephrine was reported to be related to the improvement of performance of PLR and the end-expiratory occlusion test in predicting fluid responsiveness.[18] Previous research has indicated a correlation between norepinephrine use and fluid responsiveness.[19] The probability of a positive fluid response is closely influenced by mean systemic filling pressure and the dynamic balance between stressed and unstressed blood volumes.

Garcia et al investigated using Eadyn to predict arterial pressure response following fluid administration in patients. The study aims to validate whether Eadyn, can be an effective indicator for predicting the increase in arterial pressure after fluid resuscitation. The study found that Eadyn predicts arterial pressure response significantly in fluid responder patients. Patients with higher Eadyn values before fluid administration were likelier to experience increased arterial pressure post-intervention.[11] Our study found that baseline Eadyn was higher in the MAP-responder group than in the MAP-non-responder group. The cuff of a threshold value of Eadyn for the prediction of MAP-responder was 1.00 (sensitivity 85.7% and specificity 75%). A recent meta-analysis from 6 studies reported that the cut-off value of Eadyn ranged from 0.65 to 0.89, which was lower than the cut-off value in our study.[12] The mean ages of patients in this meta-analysis ranged from 57 to 69 years. The pathophysiological mechanisms differ significantly between adult and elderly populations, influencing arterial tone and potentially resulting in varying cut-off values. This study supports using PPV, SVV, and dynamic arterial elastance as reliable metrics for predicting which elderly patients will benefit from fluid resuscitation, thereby enhancing the precision of fluid therapy in critical care settings in the aging society.

Limitations

Our study has several limitations; first, the gold standard of positive fluid responsiveness in our population was defined as a CO increase of 10% or more, assessed using the pulse contour analysis CO monitoring devices after passive raised leg raising test or mini-fluid challenge test or fluid challenge, which may affect the threshold cut-off value of PPV and SVV. We used previously mentioned techniques rather than fluid challenge because we are concerned about the ethical issue of performing a large amount of fluid loading on the elderly population. Second, because we used different devices to measure PPV and SVV, although we set the time in both machines simultaneously, the timing of PPV and SVV acquisition may not be real-time; however, the values of each variable were averaged from the three data collected three minutes apart.

Conclusion

Despite the increased arterial stiffness of the elderly, PPV and SVV can predict fluid responsiveness in elderly patients with septic shock who underwent mechanical ventilators; furthermore, Eadyn can predict MAP responsiveness in elderly patients.

Data Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Approval

The Faculty of Medicine's Human Research Ethics Committee approved the study, Ramathibodi Hospital, Mahidol University (COA no. MURA 2024/671).

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Disclosure

The authors report no conflicts of interest in this work.

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