



# Predictive value of change in effective arterial elastance in norepinephrine weaning: a retrospective study

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**Contributions:** (I) Conception and design: T Yang, B Du; (II) Administrative support: B Du, W Jiang; (III) Provision of study materials or patients: T Yang, H Huang, W Jiang; (IV) Collection and assembly of data: T Yang, H Huang, D Yang; (V) Data analysis and interpretation: T Yang, B Du, D Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** The weaning of vasopressors is usually an empirical choice made by clinicians. The aim of this study is to assess the predictive value of change in effective arterial elastance ( $\Delta Ea\%$ ) induced by fluid administration in early initiation of norepinephrine (NE) weaning.

**Methods:** Included were intensive care unit (ICU) septic shock patients with an indwelling pulmonary artery catheter who experienced initial resuscitation and required a fluid challenge. Reduced norepinephrine dose or maintained steady ( $\Delta NE \leq 0 \mu g/min$ ) at 6 hours after inclusion (T6) was defined as early initiation of norepinephrine weaning. Univariate and multivariate analyses were performed to assess  $\Delta Ea\%$  viability and other hemodynamic parameters in predicting the possibility of norepinephrine weaning. A receiver operating characteristic (ROC) analysis was used to confirm model predictions.

**Results:** One hundred and eight patients were assessed. Of 108 patients, 75 (69.4%) constituted the NE weaning group at T6. The multivariate analysis showed that  $\Delta Ea\%$  [odds ratios (OR): 0.95; 95% confidence interval (CI): 0.89–0.99;  $P=0.003$ ] was an independent predictive factor for norepinephrine weaning at T6. ROC analysis confirmed that  $\Delta Ea\%$  was associated with norepinephrine weaning [area under ROC curve (AUC) at 0.64; 95% CI: 0.52–0.75;  $P=0.026$ ]. To predict norepinephrine weaning, the optimum threshold for  $\Delta Ea\%$  was 5.1% (sensitivity: 61%, specificity: 67%). Notably, the combination of  $\Delta Ea\%$ , change in systemic vascular resistance ( $\Delta SVR\%$ ) and change in cardiac output ( $\Delta CO\%$ ) strengthened the predictive ability with an AUC at 0.73 (95% CI: 0.64–0.83;  $P=0.001$ ). Median (interquartile range) duration (in hours) of norepinephrine was significantly shorter in the NE weaning group compared with the NE worsening group [48 [34–89] vs. 72 [54–90] hours,  $P=0.048$ ].

**Conclusions:** Change in effective arterial elastance induced by fluid administration may assist clinicians in detecting patients who is possible to initiate norepinephrine weaning. Early initiation of norepinephrine weaning was associated with shorter duration of norepinephrine exposure.

**Keywords:** Effective arterial elastance (Ea); arterial load (AL); weaning; norepinephrine; septic shock

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## Introduction

The hemodynamic profile of septic shock is characterized by low systemic vascular resistance (SVR), high cardiac output (CO), and presents persistent low blood pressure as a clinical feature (1). Fluid therapy and vasoactive support are the cornerstones of septic shock resuscitation (2). These two main components are used to achieve target pressure and to provide adequate tissue perfusion. Meanwhile, norepinephrine is the first-choice vasopressor recommended to correct refractory hypotension due to depressed vascular tone (3). However, exposure to high dose of norepinephrine over one hour might lead to adverse events, such as myocardial cell injury, tissue ischemia, and alteration of sepsis-associated immunomodulation (4,5). Once the patient is stable and has received adequate fluid resuscitation, great effort should be directed towards decreasing the norepinephrine requirements (2,3). However, norepinephrine weaning is usually an empirical choice made by clinicians. There is insignificant published evidence on how to assess the optimal time to initiate norepinephrine weaning (6-8).

A complete description of the cardiovascular system should be considered in optimizing the norepinephrine weaning process. In this regard, the assessment of the effective arterial elastance (Ea) helps clinicians better understand the cardiovascular performance in circulatory failure and hemodynamic therapy (9-11). Ea is the net afterload, which can be acquired from the left ventricular pressure-volume loop. It integrates steady and pulsatile components of arterial load (12-14) and comprehensively reflects the left ventricular afterload better than the SVR or arterial pressure (12,15). Ea also has been regarded as the mechanical energetic aspect of heart-arterial interaction (1,16-18). The arterial system does not only act as the conduit for blood flow to provide tissue perfusion but also modulates ventricular ejection and maintains blood pressure. Analytical work revealed that the heart delivers maximal stroke work when Ea and left ventricular end-systolic elastance match (17-19).

In the past decades, a robust Ea estimate by 90% of systolic arterial pressure (SAP) over stroke volume (SV) ratio has been clinically used. Validation studies have proven that the Ea reliability acquired at bedside represented the arterial load (13,14,20). However, Ea itself has not been widely applied in clinical practice. The major reason might be the Ea's misunderstanding as a surrogate of vascular resistance, because the algorithm of Ea is similar to SVR.

Meanwhile, most literature has been focused on exploring Ea to predict pressure responsiveness (8,21). Therefore, this study design was to observe Ea's ability and change according to a fluid challenge in the prediction of early norepinephrine weaning among critically septic patients. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-482>).

## Methods

### Setting

This was a retrospective analysis of prospectively collected data from septic shock patients admitted to the Medical Intensive Care Unit (MICU) of Peking Union Medical College Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of Peking Union Medical College Hospital (ZS1085) and informed consent was waived because of the retrospective study design.

### Patients, hemodynamic monitoring

We screened patients who were diagnosed with septic shock from October 2015 to August 2020. Septic shock was defined according to international criteria (3). Included were patients with persistent hypotension who needed vasopressors to maintain SAP no less than 90 mmHg or mean arterial pressure (MAP) higher than 65 mmHg after initial fluid resuscitation of 30 mL/kg in accordance with sepsis campaign bundle. All patients received a fluid challenge. For the fluid challenge, 500 mL of 4% gelatin or normal saline (NS) was given over 5–10 min using a bag pressurized to 300 mmHg. The exclusion criteria included other types of diagnosed shock, the receipt of other vasopressor more than norepinephrine, the receipt of other CO monitoring tools utilizing pulse-contour analysis, such as pulse index continuous cardiac output (PiCCO), patients younger than 18, pregnancy, patients with “do-not-resuscitate” orders, and patients with a survival time of less than 24 hours after fluid challenge.

The arterial blood pressure was monitored from an arterial line (Becton Dickinson Infusion Therapy Systems Inc., Utah, USA) placed in radial artery. All patients were indwelled with a pulmonary artery catheter (PAC) and received continuous CO monitoring by thermodilution (Swan-Ganz CCOmbo CCO/SvO<sub>2</sub>, Vigilance II™ monitor,

Edwards Lifesciences, Irvine, CA, USA). Hemodynamic variables were formulated and presented by use of the IntelliVue Patient Monitor MP70 (Philips Medical System, Boeblingen, Germany).

### Data collected

Hemodynamic variables before and after fluid challenge were recorded, including heart rate (HR), SAP, MAP, central venous pressure (CVP), CO, SV and SVR. Measures of arterial load were calculated at bedside, as  $Ea = 90\%$  of  $SAP/SV$  (1,14), net arterial compliance ( $C$ ) =  $SV/\text{arterial pulse pressure}$ . Time 0 (T0) was defined as the time point before fluid challenge, Time 1 (T1) was immediately after fluid challenge, six hours (T6) and 24 hours (T24) were identified. We collected norepinephrine doses at T0, T6, T24, T48 and T72 and cumulative fluid intake, fluid output and diuresis at T6, T24, T48 and T72. There was no missing data for norepinephrine dose during the first 3 days, because it was the used crucial information in the critical care databases. Missing data for cumulative fluid output were obtained from relevant information in the medical records or calculated from the daily nursing record sheets.

### Definitions

- (I) NE weaning was defined as the dose of norepinephrine reduced or maintained stable at T6 [ $NE(T6) - NE(T0), \Delta NE \leq 0 \mu\text{g}/\text{min}$ ];
- (II) NE worsening was defined as the dose of norepinephrine increased at T6: [ $NE(T6) - NE(T0), \Delta NE \geq 1 \mu\text{g}/\text{min}$ ];
- (III)  $\Delta Ea\%$  was defined as the percentage of  $Ea$  reduction after fluid challenge: [ $[Ea(T0) - Ea(T1)]/Ea(T0)$ ];
- (IV) Preload responder was defined as an increase in CO greater than 10% after fluid challenge; meanwhile, a 10% increase in MAP was defined as pressure responder (1,22);
- (V) The discontinuation of norepinephrine was defined as a norepinephrine-free period of at least 24 h.

### Outcomes

The primary outcome was to assess the viability of  $Ea$  and other hemodynamic variables to detect norepinephrine weaning at T6. Secondary outcomes were the following: the cumulative duration of norepinephrine treatment after inclusion, the fluid intake, diuresis and fluid balance

(expressed in mL/kg) in first 6 hours until 3 days from inclusion.

### Statistical analysis

Categorical data were expressed as number (percentage). Continuous variables were expressed as the means  $\pm$  standard deviation (SD) or median with interquartile ranges (IQR) as appropriate. The Student's  $t$  or Mann-Whitney U test for the comparison of continuous data and Chi-square test for categorical data were used. The receiver operator characteristic (ROC) curves generated to describe  $\Delta Ea\%$  to predict norepinephrine weaning. The area under the ROC curves (AUCs) were calculated as well. DeLong test was used to compare the AUCs for  $\Delta Ea\%$ , a combination of  $\Delta Ea\%$  with other parameters in predicting norepinephrine weaning. Potential related factors added into the model included demographics (age and gender) and past-medical history (hypertension, diabetes mellitus, and chronic kidney disease), which might change the arterial system and affect norepinephrine weaning (23). The associations between norepinephrine weaning and potential predictive factors were initially assessed using univariate analyses. The variables associated with norepinephrine weaning in the univariate analysis with a P value  $<0.2$  in at least one comparison were included in the multivariate analysis. Multivariate analysis was performed using binary logistic regression to explore the ability of  $\Delta Ea\%$  and other indicators to predict norepinephrine weaning in sepsis resuscitation. The odds ratios (OR) was displayed with a 95% confidence interval (CI). The probability for remaining under norepinephrine was analyzed with the Kaplan-Meier method using the Gehan-Breslow-Wilcoxon test to compare between groups.

Statistical analyses were performed with SPSS 25.0 software (SPSS, Inc., Chicago, IL), MedCalc (statistical software e version 15.6.1 for Windows) and GraphPad Prism 7. A value of  $P < 0.05$  was considered to be statistically significant.

### Results

One hundred and eight patients were retrospectively screened and analyzed. All patients received norepinephrine support with a median dose of  $0.56 (0.32-1.13) \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  at T0. The most common sources of septic shock were pulmonary (67, 62.0%) and abdomen (22, 20.4%). There were 37 (34.3%), 24 (22.2%) and 18 (16.7%) patients

**Table 1** Baseline demographic and characteristics of participants

Studied parameters	NE weaning (n=75)	NE worsening (n=33)
Age (years)	62 [53–71]	63 [43–71]
Weight (kg)	65 [60–74]	68 [60–75]
Height (cm)	168 [160–172]	170 [160–174]
BSA (m <sup>2</sup> )	1.80 [1.70–1.91]	1.84 [1.74–1.95]
Gender (male/female)	46/29	18/15
Temperature (°C)	38.1 [37.4–38.7]	37.6 [36.9–38.3]
APACHE II	23 [18–29]	25 [23–31]
SOFA	13 [10–14]	12 [10–14]
ScvO <sub>2</sub> (%)	69.1 [63.5–77.9]	70.2 [59.3–77.0]
SvO <sub>2</sub> (%)	65.9 [61.6–74.5]	69.0 [60.7–76.1]
Lac (mmol/L)	2.5 [2.0–6.5]	2.7 [1.5–3.8]
Analgesia and sedative drugs		
Fentanyl, n; (µg·kg <sup>-1</sup> ·h <sup>-1</sup> )	27; 0.57 [0.50–0.67]	18; 0.59 [0.48–0.94]
Morphine, n; (mg·kg <sup>-1</sup> ·h <sup>-1</sup> )	25; 0.05 [0.03–0.07]	13; 0.07 [0.05–0.11]
Midazolam, n; (mg·kg <sup>-1</sup> ·h <sup>-1</sup> )	38; 0.06 [0.04–0.07]	19; 0.06 [0.04–0.11]
Propofol, n; (mg·kg <sup>-1</sup> ·h <sup>-1</sup> )	24; 0.59 [0.38–0.70]	15; 0.74 [0.49–0.86]
NE (µg·kg <sup>-1</sup> ·min <sup>-1</sup> )	0.57 [0.33–1.09]	0.53 [0.29–1.14]
Source of sepsis, n (%)		
Pulmonary	46 (61.4)	21 (63.6)
Abdominal	18 (24.0)	4 (12.1)
Blood	7 (9.3)	5 (15.2)
Others	4 (5.3)	3 (9.1)

Data are expressed as median [IQR] or absolute numbers (percentage) as appropriate. APACHE II, Acute Physiology and Chronic Health Evaluation II; BSA, body surface area; NE, norepinephrine; SOFA, Sequential Organ Failure Assessment; ScvO<sub>2</sub>, central venous oxygen saturation; SvO<sub>2</sub>, mixed venous oxygen saturation; Lac, lactate.

who had a prior medical history of hypertension, diabetic mellitus, and chronic kidney disease, respectively. The baseline demographic data and clinical characteristics are shown in *Table 1*.

#### *ΔEa% predicts early initiation of norepinephrine weaning*

Patients were allocated into two groups according to NE weaning ( $\Delta\text{NE} \leq 0$  µg/min, n=75) and NE worsening ( $\Delta\text{NE} \geq 1$  µg/min, n=33). The hemodynamic variables at T0 and T1 were assessed (*Table 2*). In the univariate analysis, Ea at T0 (OR =0.52; 95% CI: 0.29–0.93; P=0.029),  $\Delta\text{Ea}\%$  (OR =0.98; 95% CI: 0.98–1.00; P=0.049), and  $\Delta\text{CO}\%$  (OR

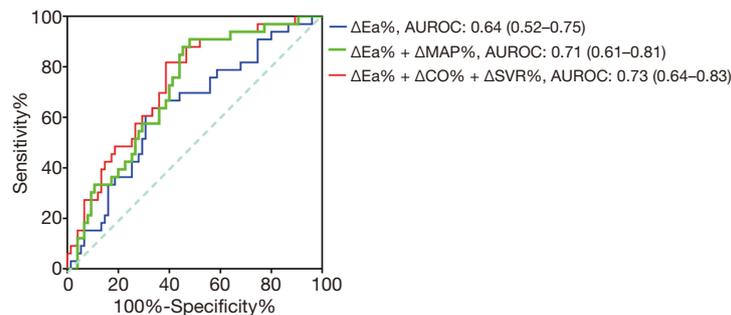
=0.96; 95% CI: 0.93–0.99; P=0.011) were associated with norepinephrine weaning, while  $\Delta\text{MAP}\%$  (OR =0.55; 95% CI: 0.23–1.32; P=0.183),  $\Delta\text{SVR}\%$  (OR =0.99; 95% CI: 0.97–1.02; P=0.188) were not associated with norepinephrine weaning.

The multivariate analysis showed that  $\Delta\text{Ea}\%$  (OR =0.95; 95% CI: 0.89–0.99; P=0.003),  $\Delta\text{CO}\%$  (OR =0.94; 95% CI: 0.91–0.99; P=0.015),  $\Delta\text{SVR}\%$  (OR =0.92; 95% CI: 0.87–0.98; P=0.013) and  $\Delta\text{MAP}\%$  (OR =0.94; 95% CI: 0.89–0.98; P=0.010) were independent predictive factors for norepinephrine weaning at T6. The AUCs of  $\Delta\text{Ea}\%$  to predict norepinephrine weaning was at 0.64 (95% CI: 0.52–0.75; P=0.026). To predict norepinephrine weaning,

**Table 2** Changes in effective arterial elastance and hemodynamic variables categorized according to NE weaning or NE worsening at T6

Hemodynamic variables	NE weaning (n=75)		NE worsening (n=33)		P	
	Before	After	Before	After	Before FC	After FC
Ea, mmHg/mL	2.26±0.94	2.06±0.88*	1.85±0.62	1.84±0.66	0.025	0.207
CO, L/min	6.3±2.4	7.2±2.7*	7.2±2.8	7.8±2.7*	0.063	0.245
SV, mL	55.8±23.0	66.1±23.4*	67.3±23.9	72.4±24.3*	0.021	0.206
HR, bpm	116±22	112±21*	111±22	109±20*	0.243	0.598
SAP, mmHg	121±18	135±27*	126±20	135±20*	0.201	0.999
DAP, mmHg	64±9	68±10*	61±8	64±10	0.089	0.064
MAP, mmHg	82±10	89±14*	80±8	84±10*	0.452	0.077
CVP, mmHg	10±4	11±4*	11±4	15±4*	0.212	0.048
SVR, dynes·s·cm <sup>-5</sup>	1,005±441	845±363*	1,089±514	770±296*	0.071	0.054
C, mL/mmHg	1.04±0.45	1.07±0.45	1.09±0.36	1.06±0.33	0.635	0.839

Data are summarized as mean ± SD. The P value refers to a comparison between the NE weaning group and the NE worsening group. \*P<0.05 refers to comparison of hemodynamic parameters before and after fluid challenge in subgroup of NE weaning or NE worsening. CO, cardiac output; C, net arterial compliance; CVP, central venous pressure; DAP, diastolic arterial pressure; Ea, effective arterial elastance; FC, fluid challenge; HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine; SAP, systolic arterial pressure; SV, stroke volume; SVR, systemic vascular resistance.



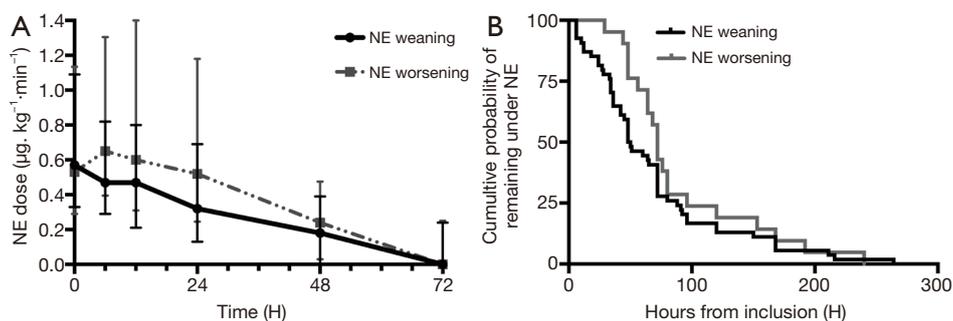
**Figure 1** Receiver operating characteristics curves generated for  $\Delta Ea\%$ ,  $\Delta Ea\% + \Delta MAP\%$ ,  $\Delta Ea\% + \Delta CO\% + \Delta SVR\%$  to predict norepinephrine weaning at T6 from inclusion.

the optimum thresholds for  $\Delta Ea\%$  was 5.1% [sensitivity: 61%, specificity: 67%, positive likelihood ratio (+LR) 1.84, negative likelihood ratio (-LR) 0.58]. Notably, the combination of  $\Delta Ea\%$ ,  $\Delta SVR\%$  and  $\Delta CO\%$  was associated with norepinephrine weaning [AUC at 0.73 (95% CI: 0.64–0.83); P=0.001] whereas the combination of  $\Delta Ea\%$  and  $\Delta MAP\%$  was at 0.71 (95% CI: 0.61–0.81); P<0.001 (Figure 1). In the pairwise comparison of ROC curves, the AUC of  $\Delta Ea\% + \Delta CO\% + \Delta SVR\%$  was higher than that of  $\Delta Ea\%$  along (Z=1.968; P=0.049), whereas no difference was observed when comparison was made between  $\Delta Ea\%$  and  $\Delta Ea\% + \Delta MAP\%$ , or between  $\Delta Ea\% + \Delta MAP\%$  and  $\Delta Ea\%$

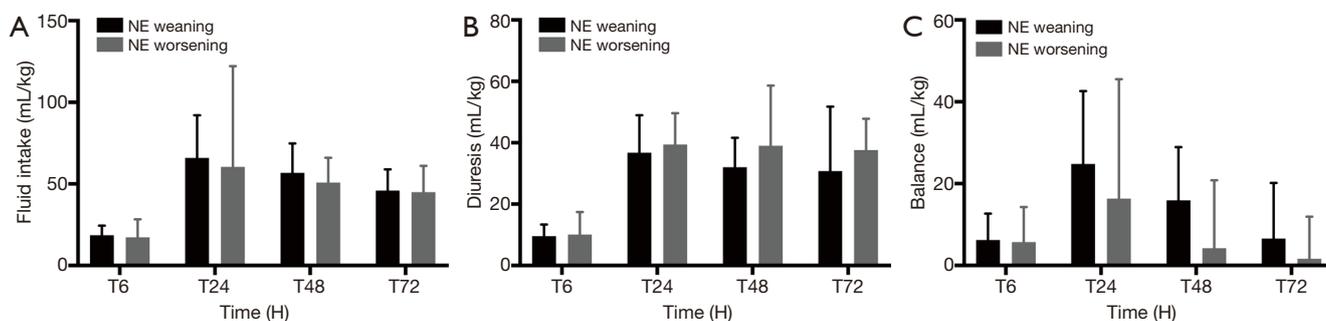
+  $\Delta CO\% + \Delta SVR\%$  (Z=1.519, P=0.129 and Z=0.896, P=0.371, respectively).

### *Norepinephrine weaning and cumulative use of norepinephrine*

The norepinephrine dose at T0 was similar between the two groups: 0.57 (0.33–1.09) vs. 0.53 (0.29–1.14)  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , P=0.971. In groups of NE weaning, norepinephrine dose decreased to 0.47 (0.29–0.82)  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  at T6, whereas a value of 0.65 (0.40–1.30)  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  was shown in the NE worsening group at T6, P=0.013. The tendency of



**Figure 2** Evolution of norepinephrine dose over time and the Kaplan-Meier plot of the cumulative probability of remaining under norepinephrine. (A) Evolution of norepinephrine dose over time; (B) the duration of norepinephrine use. NE, norepinephrine.



**Figure 3** Evolution of fluid administration over time. (A) Evolution of fluid intake over time; (B) evolution of diuresis over time; (C) evolution of fluid balance over time. NE, norepinephrine.

norepinephrine weaning during the first 72 hours from inclusion is displayed in *Figure 2A*. A discontinuation of norepinephrine was achieved in 50 (66.7%) of the 75 NE weaning group and in 18 (54.5%) of 33 NE worsening group. Forty patients did not achieve discontinuation of norepinephrine due to they died before norepinephrine weaning (no significant difference between groups). Median (IQR) duration (in hours) of norepinephrine was significantly shorter in the NE weaning group: 48 [34–89] *vs.* 72 [54–90] hours,  $P=0.048$ . The median time of cumulative probability remaining under norepinephrine of the two groups is shown by the Kaplan-Meier plot in *Figure 2B*.

#### **Fluid administration and fluid balance in both groups**

The data regarding fluid administration and fluid balance are displayed in *Figure 3* and *Table 3*. The fluid intake and fluid balance reduced day-by-day in both groups from inclusion to 72 h, and there was no significantly difference between groups. Meanwhile, the daily administered fluid amounts were higher in the NE weaning group (*Figure 3A*);

on the contrary, the daily amounts of diuresis were lower in the NE weaning group (*Figure 3B*), but no statistical difference was observed between groups. As a result, the fluid balance in the NE weaning group was insignificantly higher than that of the NE worsening group, but there was no significant difference between two groups at each time points ( $P>0.05$ , *Figure 3C*).

#### **Effect of fluid type: gelatin vs. normal saline**

Except  $\Delta\text{CO}\%$ , there was no significant difference in the blood pressure and arterial load changes after fluid challenge between the gelatin group and the normal saline group (*Table 4*).

#### **Effective arterial elastance in fluid challenge**

Of the 108 patients, 62 (57.4%) were preload responders (R) to the fluid challenge, whereas 46 (42.6%) were pressure responders (NR). Only 28 (25.9%) patients were both preload responders and pressure responders. Changes in

**Table 3** NE dose and fluid administration at first 6 hours after inclusion

Variable	NE weaning (n=75)	NE worsening (n=33)	P
NE dose T0 ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	0.57 [0.33–1.09]	0.53 [0.29–1.14]	0.971
NE dose T6 ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	0.47 [0.29–0.82]*	0.65 [0.40–1.30]*	0.013
Fluid intake (mL/kg)	18.5 [13.5–24.5]	17.3 [13.3–28.3]	0.996
Diuresis (mL/kg)	9.6 [5.5–13.4]	10.1 [3.8–17.4]	0.831
Fluid output (mL/kg)	10.9 [6.9–14.9]	12.5 [5.9–18.2]	0.434
Fluid balance (mL/kg)	6.2 [1.3–12.7]	5.7 [–2.0 to 14.2]	0.808

Data are summarized as median [IQR]. The P value refers to a comparison between the NE weaning group and the NE worsening group; \*P<0.05 refers to comparison between NE dose at T6 and NE dose at T0 in subgroup of NE weaning or NE worsening. NE, norepinephrine.

**Table 4** Relative changes induced by FC in hemodynamic parameters according to type of fluid administrated

Changes after FC	Gelatin (n=89)	Normal saline (n=19)	P
$\Delta\text{Ea}$ , %	–6.3 [–18.5 to 4.0]	–0.3 [–9.3 to 12.2]	0.163
$\Delta\text{CO}$ , %	14.5 [4.4 to 24.4]	4.9 [–2.6 to 10.7]	<0.001
$\Delta\text{MAP}$ , %	7.7 [0.6 to 16.3]	1.2 [–3.4 to 10.6]	0.201
$\Delta\text{SVR}$ , %	–5.5 [–11.4 to 2.9]	–7.9 [–21.2 to 6.7]	0.650
$\Delta\text{C}$ , %	1.9 [–9.2 to 15.5]	0.2 [–18.3 to 9.9]	0.273

Data are summarized as median [IQR]. The P value refers to a comparison between the Gelatin group and Normal saline group. CO, cardiac output; C, net arterial compliance; Ea, effective arterial elastance; FC, fluid challenge; MAP, mean arterial pressure; SVR, systemic vascular resistance.

hemodynamic variables before and after fluid challenge in R and NR categorized according to CO are shown in *Table 5*. Fluid responsive individuals had expected changes in CO, SV, and SVR over the study interval. Fluid infusion decreased Ea from  $2.36\pm 0.94$  to  $2.03\pm 0.89$  mmHg/mL for preload-R, whereas Ea of patients with negative preload response increased from  $1.84\pm 0.67$  to  $1.94\pm 0.72$  mmHg/mL.

## Discussion

Our study explored that  $\Delta\text{Ea}\%$  induced by fluid challenge was able to predict the early initiation of norepinephrine weaning. A combination of  $\Delta\text{Ea}\%$ ,  $\Delta\text{SVR}\%$  and  $\Delta\text{CO}\%$  provided an increased level of prediction. In addition, a significant reduction in Ea after fluid challenge was a predictive factor to norepinephrine weaning, although this reduction has also been used to explain why preload responders without increasing blood pressure. We

highlighted that timely application of Ea strengthened the clinical decision to promote norepinephrine weaning as early as possible, particularly at bedside in septic shock patients.

Once the patient is hemodynamically stable following a thorough assessment of perfusion status, vasopressor weaning should commence. The early goal-directed therapy (EGDT) takes account of the infusion vasopressor's early initiation to achieve a predefined hemodynamic goal; subsequent hemodynamic management is left to the clinician's discretion (8). The optimum method for weaning vasopressors is subject to much controversy, although the classical method recommends titration of the vasopressors by monitoring the MAP (3,6,7). Ea in some way explains the arterial system's performance in hemodynamic resuscitation. In the NE weaning group, early initiation of norepinephrine weaning was associated with a shorter duration of vasopressor exposure, while a similar fluid intake and balance were applied. This study was the first to evaluate Ea as a means to assess the early initiation possibilities of norepinephrine weaning. Further studies are needed to validate the clinical value of Ea, while an individualized approach could be applied in order to improve patient's management.

It is generally believed that patients with both preload and pressure positive response might have prospects of a better outcome. There can be no argument that the reserve of cardiac function, expressed as fluid infusion leading to a greater increase in CO, is a protective factor of norepinephrine weaning, but the change in Ea ( $\Delta\text{Ea}\%$ ) demonstrates an attractive result. Previous studies have reported that maintaining Ea stability was associated with positive pressure responsiveness during fluid challenge, hypothesizing that the loss of arterial load is the primary

**Table 5** Hemodynamic variables changes during fluid challenge in preload-R and preload-NR

Hemodynamic variables	Preload-R (n=62)		Preload-NR (n=46)		P	
	Before	After	Before	After	Before FC	After FC
CO, L/min	6.1±2.3	7.5±2.5*	7.3±2.3	7.3±2.4	0.012	0.687
SV, mL	53.5±22.1	67.5±23.4*	67.3±24.4	68.7±24.5	0.003	0.808
HR, bpm	117±23	114±19*	111±20	109±19*	0.131	0.227
SAP, mmHg	121±18	136±27*	123±19	133±22*	0.574	0.567
DAP, mmHg	65±8	69±10*	61±10	64±10*	0.041	0.024
MAP, mmHg	82±9	90±14*	80±11	85±11*	0.317	0.028
CVP, mmHg	10±4	13±4*	11±4	15±4*	0.057	0.014
SVR, dynes·s·cm <sup>-5</sup>	1,066±458	914±408*	808±323	818±304	0.001	0.180
Ea, mmHg/mL	2.36±0.94	2.03±0.89*	1.84±0.67	1.94±0.72	0.002	0.570
C, mL/mmHg	1.00±0.43	1.09±0.47*	1.13±0.39	1.05±0.34*	0.117	0.597

Data are summarized as mean ± SD. The P value always refers to a comparison between the preload-R group and the preload-NR group. \*P<0.05 refers to comparison of hemodynamic parameters before and after fluid challenge in subgroup of preload-R and preload-NR. CO, cardiac output; C, net arterial compliance; CVP, central venous pressure; DAP, diastolic arterial pressure; Ea, effective arterial elastance; FC, fluid challenge; HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure; SV, stroke volume; SVR, systemic vascular resistance; R, responders; NR, non-responders.

reason for an exhibited a CO increase in septic patients after fluid administration without an improvement in blood pressure (6,19,24,25). Therefore, one can hypothesize that an unchanged Ea, performed in fluid administration, was a predictive factor of norepinephrine weaning. Meanwhile, according to the concept of ventriculoarterial coupling (VAC), Ea was assumed to concomitantly contribute to a preload increase in order to match a maximal stroke work (13,17,26). However, other studies found that fluid administration induced an Ea reduction. There are several possible explanations. First, the sympathetic nervous system contributes to vasoconstriction in response to hypovolemia and hypotension. After fluid infusion, the baroreflex changes, and a Ea decrease is the response in order to adapt the modulation of blood volume, arterial tone, and ventricular work. Sakamoto *et al.* has demonstrated that the vascular properties predominantly contribute to baroreflex regulation of arterial pressure, rather than ventricular properties (26,27). Second, fluid loading during a short-time period may stimulate the production of nitric oxide and endothelial shear stress, leading to a reduction of arterial tone (28). Third (and a related possibility) is that the increased resistance and impedance were triggered by intravenous fluid replacement. In Sagawa's analytical model, the ratio of Ea and end-systolic elastance of 50%

was thought to reach the maximal mechanical efficiency of ventricular contraction (16). The following considerations need further study: (I) determining whether an appropriate therapeutic approach is the restoration of the vascular system's autoregulation and (II) whether a decrease in Ea induced by fluid loading indicates VAC optimization (18).

We used a combination of these markers to provide a better level of prediction. The combination of  $\Delta Ea\%$ ,  $\Delta SVR\%$  and  $\Delta CO\%$ , which include the factors of the cardiac system, arterial load, and the major vascular system, demonstrated better prediction ability. A significant reduction in Ea and an increase in CO and SVR following fluid challenge predicted a higher chance of norepinephrine weaning. It is worth noting that although Ea and SVR included the component of vascular resistance, the small and large vessels presented different responses to increased flow (29). An opposite trend in changes of Ea and SVR has therefore, been established in this predictive equation. Moreover, the baseline Ea, was able to predict NE weaning, but in critically ill patients with septic shock, a norepinephrine infusion increases arterial pressure through vasoconstrictive effects (30-32). Thus, some patients presented normal SVR and higher Ea, especially in severe septic shock. It is troublesome to use a normal range of SVR and Ea to predict hemodynamic performance

at bedside. Therefore, we selected the changes in Ea and SVR in this prediction model. Actually, they were found to be more reliable and useful as predictors due to their adjustment by baseline value. Additionally, considering that demographics and characteristics might affect the efficiency and therapy outcome, we selected data for analysis based on the patients' age and gender, having received concurrent doses of norepinephrine infusion, along with their medical history including prior hypertensive disease, chronic kidney disease and diabetes mellitus. The clinical improvement was independent of concurrent norepinephrine and other factors mentioned above.

Ea shares the same units of ventricle end-systolic elastance (Ees). Ea therefore, has been most often applied to assess cardiovascular efficiency. Ea, taken in isolation, is commonly considered as an index of arterial load (12,33), which compromises different arterial properties and the effects of arterial wave reflections. Although Ea is a complex lumped parameter, Ea plays an important role in physiological regulation of the heart and arterial system. Since the estimation of Ea by 90% of SAP over SV ratio has been clinically used, the Ea calculation leads to confusion when trying to understand changes in Ea. Mathematically, Ea is calculated from arterial pressure and stroke volume; from a physiological point, Ea integrates arterial properties both in steady and pulsatile components. The Ea, arterial pressure, and blood flow value are actually the independent variables (three components) of cardiovascular system. Therefore, Ea, along with the Ea changes, should not be considered as a spurious mathematical coupling effect (24). We should keep this in mind when analyzing Ea during hemodynamic therapy.

To enhance the Ea's understanding in clinical practice, we analyzed the data before and after fluid infusion. Generalized vasodilation is the septic shock's typical hemodynamic profile, leading to refractory hypotension. In our study, the vascular system's manifestation was an increase in Ea but a decrease in SVR. Previous experimental studies suggested that aortic wall edema caused by sepsis could contribute to a persistent elevation in aortic characteristic impedance, whereas the pharmacological vasoconstriction induced by the fluid infusion or exogenous vasoactive drug might also be a major factor in inducing an Ea increase (21,26,33,34). Ea has been regarded as a product of the vascular system's response to an SV increase (1). Still, caution should be taken to ensure that a higher pre-infusion Ea did not instigate an improved pressure response to fluid challenge—no significant difference in pre-infusion

Ea was observed between pressure-R and pressure-NR. In this respect, our findings displayed similarities to previous studies (24,25). Simultaneously, we found that prior to fluid challenge, Ea was higher in preload-R than in preload-NR, and a baseline Ea greater than 1.97 mmHg/mL can predict preload responsiveness. However, the baseline value of Ea differed in previous studies due to the different measurements given (19,24,25). Moreover, recent studies reported that a higher  $Ea_{dyn}$  might indicate greater efficiency of the cardiovascular system in delivering energy to the arterial system for sustaining blood flow (35,36). Based on this, we were only able to suggest that a higher pre-infusion Ea might indicate a positive preload response to fluid challenge, without using an accurate predictive value.

Several limitations of this study require discussion. First, it is a retrospective analysis of previously collected data, although we documented the data before and after fluid challenge and also evaluated the added value of Ea in assessing fluid challenge and further therapy. The most important hemodynamic data, including Ea and CO, were not completely recorded at T6 and T24. Therefore, even though the sample size was not small, it was hard to continuously trace Ea changes across 24 h and provide more valuable clinical evidence. Second, the blood pressure was obtained from the radial artery. Although arterial load indices derived from the radial artery have been verified as similar to aortic (20,37), Jozwiak demonstrated that a femoral estimate of Ea was supposed to be more accurate and precise than the radial estimate (38). However, our study used the changes in Ea and cardiac vascular variables induced by fluid in the prediction model; the dynamic changes in hemodynamic indicators were more meaningful than the baseline value itself. Third, we did not validate the potential use of Ea to titrate norepinephrine weaning at bedside, which was the major reason why the long-term prognosis of the two group patients were similar in this study. Fourth, this study excluded patients who received vasopressors other than norepinephrine - the different receptors of dobutamine or epinephrine would affect the heart pump and arterial load. Further validation studies are needed to confirm the value of Ea in constituting an approach to infusion and weaning off norepinephrine and other vasopressors.

## Conclusions

The assessment of arterial load by effective arterial elastance in septic shock patients may assist clinicians in detecting

patients with whom it is possible to initiate norepinephrine weaning at the early phase of resuscitation. Early initiation of norepinephrine weaning was associated with shorter duration of norepinephrine exposure. A combination of Ea, CO and SVR according to fluid challenge provided an improved prediction ability. Further studies are needed to confirm the results and to optimize the hemodynamic treatment of patients with septic shock and acute circulatory failure.

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