Hemodynamic effects of different fluid volumes for a fluid challenge in septic shock patients

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Abstract
Background: It is still unclear what the minimal infusion volume is to effectively predict fluid responsiveness. This study was designed to explore the minimal infusion volume to effectively predict fluid responsiveness in septic shock patients. Hemodynamic effects of fluid administration on arterial load were observed and added values of effective arterial elastance (Ea) in fluid resuscitation were assessed.

Methods: Intensive care unit septic shock patients with indwelling pulmonary artery catheter (PAC) received five sequential intravenous boluses of 100 mL 4% gelatin. Cardiac output (CO) was measured with PAC before and after each bolus. Fluid responsiveness was defined as an increase in CO >10% after 300 mL fluid infusion.

Results: Forty-seven patients were included and 35 (74.5%) patients were fluid responders. CO increasing >5.2% after a 200 mL fluid challenge (FC) provided an improved detection of fluid responsiveness, with a specificity of 80.0% and a sensitivity of 91.7%. The area under the ROC curve (AUC) was 0.93 (95% CI: 0.84–1.00, P < 0.001). Fluid administration induced a decrease in Ea from 2.23 (1.46–2.78) mmHg/mL to 1.83 (1.34–2.44) mmHg/mL (P = 0.002), especially for fluid responders in whom arterial pressure did not increase. Notably, the baseline Ea was able to detect the fluid responsiveness with an AUC of 0.74 (95% CI: 0.59–0.86, P < 0.001), whereas Ea failed to predict the pressure response to FC with an AUC of 0.50 (95% CI: 0.33–0.67, P = 0.086).

Conclusion: In septic shock patients, a minimal volume of 200 mL 4% gelatin could reliably detect fluid responsiveness, with a sensitivity of 91.7% and a specificity of 80.0%, whereas Ea failed to predict the pressure response to FC.

Trial registration: ClinicalTrials.gov, NCT04515511
Keywords: Cardiac output (CO); Fluid challenge (FC); Arterial load; Effective arterial elastance (Ea); Septic shock

Introduction
Fluid therapy is the cornerstone of septic resuscitation. Fluid challenge (FC) is used to assess patient’s response to fluid infusion and to avoid excessive fluid administration. However, there is no standardized process of FC, with varying fluid types, amounts of volume, and infusion rate. The concept of employing a minimum amount of fluid is to prevent the patient from overload, whereas a median volume of 500 mL was previously used (79.4%).

A minimal volume of 100 mL FC was described by Muller et al in 2011. They found that an infusion of 100 mL colloid could predict fluid responsiveness by assessing cardiac output (CO) using velocity time integral (VTi) at the aortic outflow tract. Since then, a total of seven investigations have been published that aimed to find the smallest amount of fluid required for FC. But the results differed from one another: the minimal volume varied from 50 mL to 200 mL. So, it is still unclear what the minimal infusion volume is to effectively predict fluid responsiveness.

At the same time, dynamic parameters are now recommended to guide fluid resuscitation. Assessing fluid responsiveness by Vti has been popular in recent years, but the major limitations of this parameter are technique availability and physicians’ skills. The change of stroke volume variation and pulse pressure variation can predict fluid responsiveness; however, they may be restricted to mechanically ventilated patients with the use of tidal volumes over 8 mL/kg. Thus, because of the limitations of these new approaches, the method of the rmodilution by pulmonary artery catheter (PAC), which is considered the
gold standard of CO measurement during FC of different volumes, may be preferred.

Meanwhile, fluid resuscitation is aimed at improving tissue perfusion by providing adequate CO and arterial pressures necessary. But the blood pressure is affected by the blood flow and arterial vascular tree. In this regard, the concept of the arterial load has been used to understand the net afterload, which compromises all extracardiac factors that oppose ventricular ejection, including net arterial compliance, systemic vascular resistance (SVR), aortic impedance, and the effects of arterial wave reflections.\(^{[9]}\) The effective arterial elastance (Ea) is an integrative measure of arterial load that incorporates both steady and pulsatile components. It was first proposed by Sunagawa et al.\(^{[10]}\) in 1983. The reliability of Ea to estimate arterial impedance has been demonstrated and the usefulness of Ea to characterize arterial load has been recognized.\(^{[11,12]}\)

Therefore, the primary objective of this study was to explore the minimal volume required to effectively predict fluid responsiveness in patients with septic shock. Second, to observe the hemodynamic effects of fluid administration on arterial load and to assess the predictive values of Ea during the FC.

**Methods**

**Ethical approval**

The study was approved by the Ethical Committee of Peking Union Medical College Hospital (ZS1085). Written informed consent was obtained from the next of kin of each patient.

**Patients**

This study was conducted in the Medical Intensive Care Unit (MICU) of Peking Union Medical College Hospital, from July 2019 to September 2020. Included were patients >18 years and <80 years who were diagnosed with septic shock and required fluid resuscitation. Septic shock in this study was defined in accordance with Sepsis 3.0 criteria.\(^{[13]}\) The indication of FC was patients’ need of vasopressors to maintain systolic arterial pressure (SAP) >90 mmHg, or mean arterial pressure (MAP) >65 mmHg, or patients with evidence of tissue hypoperfusion (including but not limited to oliguria, skin mottling, altered mental status, cool peripheries, hyperlactatemia, etc.) after initial fluid administration of 30 mL/kg according to Surviving Sepsis Guidelines. The exclusion criteria included other types of shock diagnosed, such as cardiogenic shock with evidence of acute coronary syndrome, chronic cardiac dysfunction (New York Heart Association Classification III/IV), or known allergy to colloid fluids, pregnancy, or participation in another biomedical study. All patients received CO monitoring by the rmodilution of PAC during their intensive care unit (ICU) stays, and contraindications of PAC monitoring CO were excluded.

**Hemodynamic monitoring**

The arterial blood pressure was monitored from an arterial line (Becton Dickinson infusion therapy system Inc., UT, USA) placed in a radial artery. A PAC with six canals was placed in the internal jugular vein, and CO was calculated with the automatic continuous the rmodilution technique equipped with (Swan-Ganz catheter mixed venous oxygen saturation [S\(_O_2\)], Vigilance II \(^{[14]}\) monitor, Edwards Life sciences, Irvine, CA, USA). All the above-mentioned catheters are connected to pressure transducers and the IntelliVue Patient Monitor MP70 (Philips Medical System, Boeblingen, Germany).

**FC**

In this study, the FC was performed in six steps. The first set of measurements including CO, stroke volume (SV), SAP, MAP, heart rate (HR), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP) as well as SVR was recorded. CO values at each time point were calculated from the average of three measured values. Baseline sets of blood gas were collected from the arterial line (arterial blood gas), the central venous in PAC canal (venous blood gas), and the mixed venous canal in PAC canal (mixed venous blood gas) (S1). The first 100 mL of 4% gelatin (Gelofusine; B. Braun Medical [Suzhou] Company Limited, Suzhou, China) was manually infused using a 60 mL syringe (50 mL twice, within 2 min). The second set of measurements and blood gas was then recorded immediately after fluid infusion (S2). Next, we repeated the colloid injection, hemodynamic data collections, and sets of blood gas collections as described for four times (S3–S6). All the patients received a total volume of 500 mL and six sets of data were collected and analyzed. A brief study design is depicted in Figure 1. Patients were well sedated and there were no alterations in therapy during FC. However, CVP >15 mmHg or PAWP >20 mmHg indicates that the patient might be at the potential risk of overload, but a relatively high level of CVP or PAWP was not the absolute contraindication of FC since all the patients underwent a refractory shock since CVP and PAWP are subjects to a multitude of confounding variables.\(^{[14]}\) Therefore, the FC was initiated at the physicians’ discretion. Measures of arterial load were calculated before and after FC at the bedside. Ea = 90% of SAP/SV. Net arterial compliance (C) = SV/arterial pulse pressure. The arterial time constant (Tau) was the product of SVR and C.\(^{[12,13]}\) Positive fluid responsiveness (same as preload-responders [preload-R]) was defined as CO increased >10% at the end of 500 mL FC; meanwhile, a 10% increase in MAP was defined as pressure responders (pressure-R).\(^{[15,16]}\)

**Statistical analysis**

Categorical data were expressed as number (%), while continuous variables were expressed as the mean ± standard deviation (SD) or median with interquartile ranges within 25% to 75%, as appropriate. The normality of the data was tested with the Shapiro-Wilk test. Before the FC, patient characteristics between preload-R and preload-non-responders (preload-NR) were compared using the Student t test or Mann-Whitney U test for continuous data, and the chi-square test for categorical data. The Paired-Sample t test or Wilcoxon test was used for within-group comparisons. The receiver operator characteristic (ROC)
curves generated for ΔCO_{200 mL}, ΔCO_{300 mL}, ΔCO_{400 mL}, and ΔCO_{500 mL}, and the area under the ROC curve (AUCs) were calculated to assess predictive value. The DeLong test was used to compare the AUCs for different fluid volumes of FC to predict fluid responsiveness.[17] The Youden index was used to determine the optimal cutoff value of changes in CO when the AUC was >0.5. The reproducibility of CO was calculated from data obtained from 47 subjects. When the hemodynamic status was stable, five consecutive values of CO from each patient were recorded. The coefficient of variation (CV) was equal to the ratio of SD to the mean for each collection and averaged for 47 sets. The precision was calculated as two times the CV, and the least significant change (LSC) was calculated as precision time/2.[18,19] The Pearson correlation coefficient (r_p) was used to quantify the relationship between continuous variables.

Statistical analyses were performed with SPSS 25.0 software (SPSS, Inc., Chicago, IL, USA), Med Calc (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

During the study period, 152 patients with acute circulatory failure were admitted from July 2019 to September 2020. 95 patients who met the exclusion criteria were excluded, leaving 57 patients with septic shock from different sites of infection who were eligible for the study. In addition, six patients did not complete the study for various reasons. Four patients without mechanical ventilation were excluded due to their strong respiratory effort which affected the monitoring of pressure and CO. Thus, 47 patients were finally included and analyzed. The detailed information that was recorded is shown in the flow chart [Figure 2]. The median Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 24 (18–29), and all the patients received a continuous infusion of norepinephrine with a median dose of 0.69 (0.33–0.88) mcg·kg^{-1}·min^{-1} before FC (see Corrigendum, doi: 10.1097/CM9.0000000000002306).

The main reasons for initiating an FC were as follows: tachycardia over 120 beats/min cannot be explained by fever; pain, delirium in 23 (48.9%) patients; hyperlactatemia >3 mmol/L in 22 (46.8%) patients; SvO₂ <60% in 11 (23.4%) patients; oliguria without evidence of chronic kidney disease in eight (17.0%) patients and skin mottling in four patients (8.5%). Baseline demographic and clinical characteristics of participants between preload-R and preload-NR are shown in [Table 1].

Basic hemodynamic parameters change with different volumes of FC

Of the 47 patients, 35 (74%) showed positive responses to the FC. Hemodynamic variables with FC from the baseline are presented in Table 2. Except the baseline CO and CVP in preload-NR were higher than that in preload-NR, there were no significant differences between preload-R and preload-NR at baseline. The tendency of ΔCO% after FC in preload-R and preload-NR is shown in Figure 3. After fluid infusion, ΔCO% was significantly greater with preload-R compared to preload-NR (P < 0.001). HR decreased after fluid infusion in both preload-R and preload-NR, whereas SAP, diastolic arterial pressure, MAP, CVP, and PAWP all showed an upward trend in both preload-R and preload-NR [Table 2].

Reproducibility of CO

Forty-seven sets of five consecutive CO were analyzed. For CO, the CV was 1.4 ± 0.7%, precision and LSC were 2.7 ± 1.3% and 3.8 ± 1.9%, respectively.

Predictive value of minimal volume of fluid

ROCs of ΔCO% after every 100 mL fluid bolus were analyzed for predicting fluid responsiveness [Figure 4A]. The AUCs were calculated and compared separately. In this study, a volume of 100 mL had a poor predictive ability (AUC = 0.76 [95% CI: 0.59–0.93], P = 0.004). ΔCO_{200 mL} demonstrated a predictive value for fluid responsiveness with an AUC of 0.93 (95% CI: 0.84–1.00, P < 0.001). The AUC of ΔCO_{500 mL} was 1.00 (95% CI: 1.00–1.00, P < 0.001) and 0.97 (95% CI: 0.93–1.00, P < 0.001) for ΔCO_{400 mL}. In the pairwise comparisons of ROC curves, the predictive ability of ΔCO_{100mL} was significantly different when compared with the gold standard of ΔCO_{500 mL} and ΔCO_{200 mL} in which
\[ Z = 2.727, \ P < 0.001 \text{ and } Z = 2.691, \ P < 0.001 \] respectively. There were no differences among the predictive abilities of the \( \Delta CO_{200\ mL} \), \( \Delta CO_{300\ mL} \) and \( \Delta CO_{400\ mL} \) compared with the \( \Delta CO_{500\ mL} \), even when pairwise comparisons between them were made \((P > 0.05)\). Therefore, the minimal volume of FC, which can detect fluid responsiveness as effectively as 500 mL does, was 200 mL in this study. The best cutoff value of \( \Delta CO_{200\ mL} \) was 1.9\% according to the Youden Index, but it was lower than the reproducibility of CO measurements. Taking reproducibility and the LSC into account, the cutoff value was 5.2\%, with a sensitivity of 80.0\%, and a specificity of 91.7\%. The correlations between \( \Delta CO_{100\ mL} \) and \( \Delta CO_{500\ mL} \) were all positive \((r = 0.34, \ r = 0.54, \ r = 0.72, \ r = 0.88; \ P < 0.001, \text{ respectively})\).

**Effects of FC on arterial load**

In the group of preload responders (preload-R), fluid infusion induced a decrease in \( E_a \) from 2.23 (1.46–2.78) mmHg/mL to 1.83 (1.34–2.44) mmHg/mL \((P < 0.001)\). SVR decreased from 960 (597–1361) dynes·s\(^{-1}\)·cm\(^{-5}\) to 831 (637–1134) dynes·s\(^{-1}\)·cm\(^{-5}\) \((P < 0.001)\). \( \text{Tau} \) decreased slightly from 0.72 (0.54–0.87) s to 0.70 (0.53–0.86) s \((P = 0.017)\). Net arterial compliance increased from
0.91 (0.74–1.27) mL/mmHg to 1.03 (0.81–1.40) mL/mmHg, but no significant difference was found (P = 0.556).

There were no significant changes in arterial load parameters in the group of preload-NR [Table 3]. Notably, baseline Ea was significantly higher in preload-R than Ea in preload-NR: 2.23 (1.46–2.78) mmHg/mL vs. 1.60 (1.41–1.65) mmHg/mL (P < 0.001) [Table 3].

When accounting the changes of arterial load parameters only in the preload-R, 19 patients (54.3%) were pressure-non-responders (pressure-NR). There were no differences in arterial load indices between pressure-R and pressure-NR before and after volume expansion [Table 4]. In preload-R whose arterial pressure did not increase after fluid infusion, the FC induced a reduction in arterial load: Ea decreased from 2.37 (1.63–2.91) mmHg/mL to 1.91 (1.34–2.22) mmHg/mL (P < 0.001). The SVR and Tau decreased simultaneously and net arterial compliance increased conversely (P = 0.024, P = 0.131, and P < 0.001, respectively). In preload-R who was pressure-R as well, no statistically significant difference was observed, and Ea maintained steady in pressure-R during the FC.

### Predictive values of Ea in FC

We explored the predictive values of Ea during the FC (n = 47). Ea before FC was able to predict fluid responsiveness with an AUC of 0.74 (95% CI: 0.59–0.86, P < 0.001) [Figure 4B]. The best cutoff was 1.65 with a sensitivity of 71.4% and a specificity of 83.3%. Moreover, the baseline Ea failed to predict pressure responsiveness to the FC with an AUC of 0.50 (95% CI: 0.33–0.67, P = 0.086).

### Discussion

Our study demonstrated that, in septic shock patients monitored by the modulization of PAC, the minimal volume of FC, which can effectively detect fluid responders, was 200 mL. Meanwhile, the baseline Ea may predict fluid responsiveness but not subsequent changes in arterial pressure. Furthermore, FC induced a reduction in Ea, especially in preload responders who were...
pressure non-responders. The loss of $E_a$ might be associated with the pressure response to FC.

Predicting fluid responsiveness is to test whether the patient was in the ascending part of the Frank-Starling curve and may benefit from fluid treatment. Therefore, the primary aim of the FC is to evaluate how preload affects CO. In previous studies exploring the minimal volume required to predict fluid responsiveness, PAC, the commonly used reference method to measure CO, was not used. This may be due to two reasons. Firstly, PAC is an invasive technique. In a multicenter randomized controlled trial (PAC-Man) of 1014 patients, PAC insertion was attempted in 486 patients, but only 46 (10%) patients were reported with one or more direct complications. The most common direct complication was hematomata at the insertion site (4%), and arrhythmias needing treatment within 1 h of insertion (3%), none of which was fatal. PAC is the device we know the best in our center. Only three (6.4%) patients met with arrhythmias during insertion but treatment was not required. There were no direct severe adverse events associated with PAC insertions in our center. Thus, under proper use and quality control, the invasiveness of PAC is acceptable. Secondly, PAC is not the best choice to conduct a complete assessment of cardiac structure and function. In this respect, echocardiography is a good choice. Nevertheless, it is hard to consider echocardiography as a method for continuous hemodynamic monitoring because it is time-consuming. However, despite the limitations mentioned above, PAC is still the gold standard of CO monitoring and is irreplaceable. Moreover, PAC is the major CO monitoring in our center, we have actually answered the clinical question, whether a small empirical fluid volume really can predict fluid responsiveness in clinical practice. Our study showed that the smallest administered volume of 100 mL increased CO by 5% (1.6–8.8%) in preload responders, while 200 mL induced an increase in CO of 12.2% (5.6–18%).

When considering the predictive ability, previous studies demonstrated that 100 mL could predict fluid responsiveness, but the predictive abilities varied from 0.78 (0.64–0.88) to 0.95 (0.90–0.99). According to the understanding of the use of AUC to assess a biomarker diagnostic ability, there is a broad range of AUC in which a biomarker possesses a good diagnostic value (AUC 0.75–0.90) to an excellent diagnostic value (AUC >0.90). In our study, $\Delta CO_\%$
after a volume of 200 mL FC showed an excellent predictive ability with an AUC of 0.93 compared to the 100 mL fluid infusion (AUC of 0.76). On the other hand, although the AUC of $\Delta CO_{100\text{ mL}}$ was > 0.5 with significant statistical significance, when applying the DeLong test of pairwise comparisons to ensure the diagnostic reliability, the predictive value of $\Delta CO_{100\text{ mL}}$ could not match with the predictive value of $\Delta CO_{500\text{ mL}}$. Moreover, an advanced Swan-Ganz catheter using thermal energy to calculate CO was applied in our study. We assessed the LSC to be 3.8 ± 1.9%. Thus, the cutoff value of 5.2% of $\Delta CO_{200\text{ mL}}$ was acceptable. Furthermore, caution should be taken that if the predictive ability is not strong enough, responders may be misclassified as non-responders. A multicenter, prospective study in 19 French ICU showed that the median number of FCs surveyed per patient was three.[27] Negative responsiveness might lead to repeated FCs in clinical practice because the physicians expect patients to benefit from fluid administration in septic shock resuscitation. Therefore, experiments that aim to determine the minimal volume required to detect fluid responsiveness are not only focused on the “smallest” volume, but also on reproducibility and reliability. Above all, we suggest that the minimal volume required to effectively predict fluid responsiveness is 200 mL.

Interestingly, the FENICE[28] study demonstrated that the trigger for FC was mainly low blood pressure (BP, 58.7%). This is a common practice around the globe, and it illustrates that most physicians intend to increase BP with FC. However, BP is the product of the interaction between the heart and the arterial load, whereas Ea is a good index integrating all elements of arterial load, and represents the capability of the vascular system responsiveness to SV change.[15] Meanwhile, the hemodynamic profile of septic shock is classically characterized by generalized vasodilatation and a significant increase in Ea. In our study, more than half of the preload-R were pressure-NR (19/35). The baseline Ea of pressure-NR was higher than that of preload-R, which differed. In the study of Monge Garcia et al.[29] and Guarracino et al.[30] However, when previous studies attempted to explore the arterial load indices’ predictive ability of the FC, the results differed. In the study of Monge Garcia et al.[31] in 2011, the results demonstrated that dynamic arterial elastance (Eadyn) > 0.89 could predict a MAP increase after FC, but similar findings were not duplicated a subsequent by Monge Garcia et al.[29] nor by our study, where the Ea was used to represent arterial load. Caution should be taken when assessing the arterial load by using the Ea or Eadyn. Another attractive finding of our study was that pre-infusion Ea of > 1.65 mmHg/mL might be able to predict fluid responsiveness. Nevertheless, the AUC of 0.74 is at the marginal value to be regarded as a good predictor. This potential correlation between Ea and preload responsiveness was likely not by chance, since a recent study has explored the possibility of dynamic arterial elastance as a potential marker of cardiovascular efficiency.[32] Moreover, the previous experimental study suggested that aortic wall edema caused by sepsis could contribute to a persistent elevation in aortic characteristic impedance.
leading to an impaired arterial load and ventriculoarterial decoupling.\(^\text{[33]}\) Whether an \(E_a\) decrease after FC indicates a better optimization of the arterial load and left ventricular workload match needs further study.

We highlight that when using a minimal volume to perform an FC, it is not the case that a “smaller” volume leads to a better outcome. If a mini FC does not effectively detect the patient who is preload-dependent, this would increase the risk of under-resuscitation. On the other hand, if physicians repeat the FC due to the previous negative responsiveness, the value of preventing patients from overload is lost. Furthermore, a deeper study of \(E_a\) could help physicians improve their understanding of the hemodynamic effects of fluid administration, and decide if a hypotensive patient requires only fluids, or vasoressors in combination with the fluid infusion.

Several limitations of this study need to be discussed. First, the primary aim of this study was to explore the minimal required fluid volume in FC using PAC and to guide clinical practice. But the analysis of the suitable FC volume may depend on the hemodynamic measurement technique employed.\(^\text{[24]}\) Our findings may not be extrapolated to other methods of CO monitoring. Second, the volume of 500 mL was completely infused in 40 min, because we calculated CO by taking an average of 3 measurements with each 100 mL bolus of fluid to avoid measurement errors. The meta-analysis by Toscani et al.\(^\text{[5]}\) demonstrated that the duration of the fluid infusion affects the proportions of fluid responders (PR). The PR of an FC given over 30 min was lowest at 49.9% compared with 59.2% when the duration was <15 min. Interestingly, the PR in this study was 74.5%. We hypothesized that the colloid remaining in the intravascular compartment longer contributed to the high PR. Thirdly, we only performed the FC with colloids, we did not test the predictive ability of crystalloids. Although, a systematic review and meta-analysis which included 85 studies (3601 patients) demonstrated that, if the fluid responsiveness is assessed immediately after FC, the type of fluid used will not affect the PR to an FC.\(^\text{[3]}\) Future studies may be conducted to investigate the diagnostic value of crystalloids. Moreover, there was no risk of using a little volume of colloid to perform an FC. The potential risk of acute renal failure is based on long-term use during fluid resuscitation. Meanwhile, the potential adverse events of crystalloids are hyperchloremia and overload. Lastly, neither the transthoracic nor transesophageal echocardiography was employed concurrently; thus, there were no data to compare and to explain the different findings explored by previous studies when CO was monitored by echocardiography. However, our study was in agreement with the studies of Wang et al.,\(^\text{[34]}\) Aya et al.,\(^\text{[35]}\) and Smorenberg et al.\(^\text{[36]}\) that 100 mL was not a superior minimal volume to perform an FC. In these studies, PiCCO, LiDCO\(\text{pai}/\text{ws}, \text{Modelflow}^\text{R} (\text{COm}),\) and PulseCO\(^\text{R} (\text{COli})\) were applied to monitor CO. In addition, our \(E_a\) assessment is based on an integrative simplification. More precise and complete characterization of the cardiovascular system is required to reveal the arterial pressure-flow relationship. Furthermore, future studies may be conducted to investigate the pharmacodynamic and pathophysiological mechanisms of ventricular arterial coupling induced by FC.

Conclusions
A minimal volume of 200 mL gelatin given within 10 min can effectively detect fluid responders in septic shock patients using thermodilution of PAC. Fluid administration reduced \(E_a\), especially in preload responders who increase CO without increasing blood pressure, whereas the steady maintenance of \(E_a\) was associated with positive pressure responsiveness to an FC. A baseline \(E_a\) of \(>1.65 \text{mmHg/mL}\) before FC may be able to predict preload responsiveness. Further studies are needed to confirm this result and to optimize the fluid resuscitation of patients with septic shock and acute circulatory failure.

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Conflicts of interest
None.

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