

# Effect of mean arterial pressure change by norepinephrine on peripheral perfusion index in septic shock patients after early resuscitation

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## Abstract

**Background:** The peripheral perfusion index (PI), as a real-time bedside indicator of peripheral tissue perfusion, may be useful for determining mean arterial pressure (MAP) after early resuscitation of septic shock patients. The aim of this study was to explore the response of PI to norepinephrine (NE)-induced changes in MAP.

**Methods:** Twenty septic shock patients with pulse-induced contour cardiac output catheter, who had usual MAP under NE infusion after early resuscitation, were enrolled in this prospective, open-label study. Three MAP levels (usual MAP -10 mmHg, usual MAP, and usual MAP +10 mmHg) were obtained by NE titration, and the corresponding global hemodynamic parameters and PI were recorded. The general linear model with repeated measures was used for analysis of variance of related parameters at three MAP levels.

**Results:** With increasing NE infusion, significant changes were found in MAP ( $F = 502.46, P < 0.001$ ) and central venous pressure ( $F = 27.45, P < 0.001$ ) during NE titration. However, there was not a significant and consistent change in continuous cardiac output (CO) ( $F = 0.41, P = 0.720$ ) and PI ( $F = 0.73, P = 0.482$ ) at different MAP levels. Of the 20 patients enrolled, seven reached the maximum PI value at usual MAP -10 mmHg, three reached the maximum PI value at usual MAP, and ten reached the maximum PI value at usual MAP +10 mmHg. The change in PI was not significantly correlated with the change in CO ( $r = 0.260, P = 0.269$ ) from usual MAP -10 mmHg to usual MAP. There was also no significant correlation between the change in PI and change in CO ( $r = 0.084, P = 0.726$ ) from usual MAP to usual MAP +10 mmHg.

**Conclusions:** Differing MAP levels by NE infusion induced diverse PI responses in septic shock patients, and these PI responses may be independent of the change in CO. PI may have potential applications for MAP optimization based on changes in peripheral tissue perfusion.

**Keywords:** Peripheral perfusion index; Norepinephrine; Perfusion pressure; Septic shock

## Introduction

Mean arterial pressure (MAP) plays an important role in tissue perfusion, which functions as the main driving pressure pushing blood through organs. How to optimize the target MAP for hemodynamic management of septic shock remains controversial. Restoration of macrocirculation is the priority at the early resuscitation stage. A cutoff of 65 mmHg MAP has been recommended to maintain vital organs at the beginning of resuscitation.<sup>[1]</sup> Moreover, the optimal MAP should be individualized based on the specific circumstances of each patient after early resuscitation.<sup>[2,3]</sup> Blood pressure level reported in the individual's medical history has become a common reference for defining optimal blood pressure during the

optimization stage of septic shock resuscitation. Some studies have also found that a higher MAP may protect against progression to acute kidney injury and improve microcirculation in patients with a history of hypertension.<sup>[4,5]</sup>

Moreover, highly variable effects of MAP on tissue perfusion have been observed in septic shock patients with a complex pathophysiologic status. In theory, a precise blood pressure target should be determined by the tissue perfusion-based approach.<sup>[6]</sup> Therefore, there might be room to further optimize tissue perfusion even when the patient's blood pressure has been adjusted to their usual level. The peripheral perfusion index (PI), which is defined as the ratio of the pulsatile to non-pulsatile component of

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the pulse oximetry plethysmograph (PI = pulsatile signal/non-pulsatile signal), is used as a simple and accurate indicator of the pulsation intensity of peripheral arterioles. Studies have shown that the PI can be used to reflect tissue perfusion and hypovolemia, identify the success of a regional block, and predict organ failure and outcomes in critically ill patients.<sup>[7-12]</sup> Importantly, PI could provide real-time and bedside information on peripheral tissue perfusion. Therefore, we speculated that PI might be relevant for determining optimal MAP titration with norepinephrine (NE) in septic patients.

However, no published studies have yet investigated changes in the PI during titration of blood pressure using NE based on the patient's usual blood pressure levels, as indicated in medical records. The aims of this study were, therefore, to explore the effect of MAP on PI by titrating the MAP to different levels around the level recorded in the patient's medical history using NE, and to investigate the relationship between changes in PI and changes in global circulation during blood pressure titration.

## Methods

### Ethical approval

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study on human subjects (No. S-351), which was performed in accordance with the principles of the 1975 *Declaration of Helsinki* and its later revisions. Written informed consent was obtained from all patients or their next of kin before data were included.

### Patients

When the research team was available, all consecutive adult patients admitted to the Department of Critical Care Medicine of Peking Union Medical College Hospital with septic shock who required pulse-induced contour cardiac output (PiCCO) monitoring for resuscitation from May 2014 to December 2016, were eligible for inclusion in the study. Patient MAP levels were set to the usual levels of each patient by clinical decision. Patients with pregnancy, arrhythmia, cardiac output (CO) <2.5 L/min, ice cooling blanket therapy, peripheral artery stenosis, extracorporeal membrane oxygenation (ECMO) therapy, and intra-aortic balloon pump therapy were excluded. All patients underwent a local hemodynamic support procedure for septic shock. The early goals of this hemodynamic support are as follows: central venous pressure (CVP) of 8 to 12 mmHg; MAP above 65 mmHg; urine output above 0.5 mL/kg of body weight (except in patients with acute renal failure); and central venous oxygen saturation of 70% or more with veno-arterial carbon dioxide tension difference of 6 mmHg or less.<sup>[13,14]</sup>

The attending intensivists decided whether to place a PiCCO catheter for advanced hemodynamics therapy according to the patient's condition. Diagnosis of septic shock was as follows<sup>[15]</sup>: (1) clinical infection and systemic inflammatory response syndrome; (2) hypotension (MAP <65 mmHg or a decrease in systolic arterial pressure

≥20% from baseline) after early fluid resuscitation (CVP 8–12 mmHg), and requirement for administration of NE to maintain blood pressure; (3) tissue hypoperfusion (lactate >2 mmol/L or presence of skin mottling or urinary output <0.5 mL·kg<sup>-1</sup>·min<sup>-1</sup>).

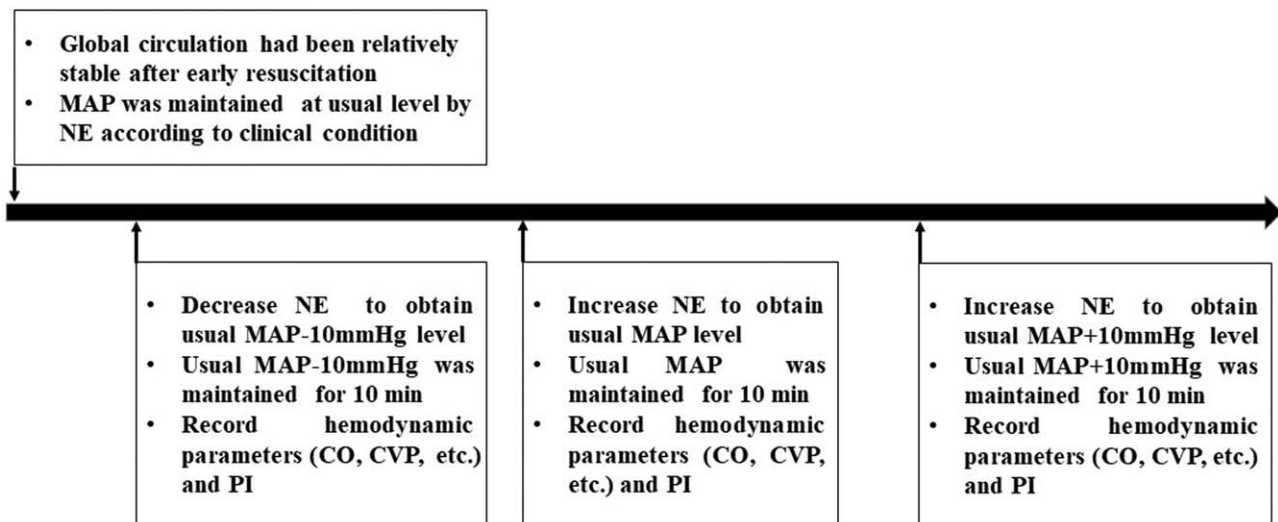
### Measurements

Information collected at enrollment included demographic characteristics such as age and sex, Acute Physiology and Chronic Health Evaluation II score,<sup>[16]</sup> and primary site and type of infection.

MAP was measured with a standard PiCCO femoral artery catheter (the PiCCO<sup>®</sup> system, PV2015L20, Pulsion Medical System, Munich, Germany), and the CVP was measured with a venous catheter inserted in the internal jugular or subclavian vein (the placement of a central venous catheter in the superior vena cava was confirmed by chest radiography). The central venous and arterial catheters were separately connected to a pressure transducer, and the central venous and arterial pressure waveform signal fidelity was checked visually using a fast-flush test to assess the adequacy of the damping of the pressure shape. The site of the phlebostatic axis was defined as the zero level (reference level), which was at the intersection of the fourth inter-costal space and midway between the anterior and posterior surfaces of the chest.

During the study interval, the patient was kept in a relatively stable condition. No other therapy was administered, such as suction, mechanical ventilation setting adjustment, or early mobilization and rehabilitation other than the NE dosage per the protocol. Moreover, all patients were hemodynamically stable without fluid resuscitation (no clinical evidence of fluid response, and MAP was stable under the vasopressor therapy). Patients were verified as having a relatively stable hemodynamic status, which was defined as no more than 5% variation in heart rate, MAP, and continuous CO for 30 min. The CO was initially calibrated by injecting 15 mL of 0.9% saline at 0°C via the PiCCO. Three COs within 10% of one another were obtained and averaged. NE was titrated to achieve the following three blood pressure levels: the patient's usual MAP –10 mmHg, the patient's usual MAP, and the patient's usual MAP +10 mmHg. The usual MAP value was obtained from the recent medical records and/or medical history of each patient. We allowed 10 min for hemodynamic adaptation at each MAP level. The heart rate, CVP, systolic/diastolic blood pressure, MAP, continuous CO, and PI were simultaneously recorded (the flow chart is shown in Figure 1).

PI and peripheral capillary oxygen saturation (SpO<sub>2</sub>) were measured in the index finger using the IntelliVue MP70 monitor (Philips Medical Systems, Boblingen, Germany). The quality of the PI signal was checked (defined as the SpO<sub>2</sub> waveform was synchronized with the QRS wave of the electrocardiogram [ECG]). The MP70 system calculates the PI as the ratio between the pulsatile component and the non-pulsatile component of the light reaching the light-sensitive cells of the pulse oximetry probe. The ambient temperature of the room was kept constant at



**Figure 1:** Flow chart of the NE titration methodology. CO: Cardiac output; CVP: Central venous pressure; MAP: Mean arterial pressure; NE: Norepinephrine; PI: Peripheral perfusion index.

approximately 23 to 25°C (climate controlled) during all phases of testing.

### Statistical analysis

This was a self-controlled, paired study, and the sample size was calculated using the following formula:

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 Sd^2 / (\mu_d)^2$$

The  $(100 \times u)$ th percentile of a standard normal distribution is denoted by  $Z_u$ , and the  $u$  was the counted area of graphic display of  $Z_u$ . Where  $\alpha$  is 0.05 and  $\beta$  is 0.1, and Sd is the standard deviation (SD) of the difference before and after the medical intervention (NE infusion adjustment).  $\mu_d$  is the difference between the follow-up and baseline groups. The sample size was calculated based on the PI value in the septic shock patients. The PI mean  $\pm$  SD was  $1.37 \pm 1.43$  in septic shock patients after early resuscitation.<sup>[10]</sup> We assumed that the expected difference of PI would be 0.14 upon intervention and that the Sd would be 0.15. The minimum sample size calculated to obtain a study power of 90% was 15.

Continuous variables with normal distribution were presented as mean  $\pm$  SD whereas those with non-normal distribution were presented as median (interquartile range). Comparisons of the related parameters according to the different blood pressure levels were performed using a general linear model with repeated measures (GLMRM).<sup>[17,18]</sup> This model is an extension of the classical analysis of variance, which allows handling of both fixed effects (blood pressure levels) and random effects (patients). The GLMRM considers the correlation between multiple measurements of one patient; thus, the estimated marginal means adjusted for the covariates, as well as the trends of related parameters corresponding to the different blood pressure levels, could be identified. When Mauchly Test of Sphericity was not appropriate ( $P < 0.05$ ), Epsilon (Greenhouse-Geisser) was used for the

corrected test. The pairwise comparisons were used to compare differences of these related variables among three MAP levels in the GLMRM, and Bonferroni correction was used to adjust the  $P$  value for multiple comparisons. Relationships between two continuous variables were assessed using a Spearman correlation and linear regression. All comparisons were two-tailed, and  $P < 0.05$  was required to indicate significance and exclude the null hypothesis. Statistical analysis was performed using the SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA).

## Results

### Clinical characteristics

A total of 20 septic shock patients were enrolled in this study. The age of these patients was  $58 \pm 15$  years. All patients had received mechanical ventilation and sedation. The characteristics of the primary infection sites were as follows: five (25%) cases of lung infection; six (30%) cases of abdomen infection; one (5%) case of brain infection; three (15%) cases of soft tissue infection; three (15%) cases of bloodstream infection; two (10%) cases of an unknown source of infection. Demographics and clinical characteristics of the study group are shown in Table 1.

### Evolution of hemodynamic variables and PI during MAP titration with NE

The average dose of NE was significantly increased from 0.58 to 0.71  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and again to 0.89  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  to achieve the different MAP levels defined in this study (usual MAP  $-10$  mmHg, usual MAP, and MAP  $+10$  mmHg). There were no adverse effects associated with the increased NE doses. An average increase in NE dosage of 0.13  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  induced a change in the MAP from the usual MAP  $-10$  mmHg to the usual MAP, and an average increase in NE dosage of 0.18  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  caused a change in the MAP from the usual MAP to the usual MAP  $+10$  mmHg.

**Table 1: Demographic and clinical characteristics of the patients (n = 20).**

Variables	Values
Age (years)	58 ± 15
Sex (female/male)	11/9
Admission Ward	
Internal	8
Surgical	7
Emergency	5
Medical history with hypertension	9 (45)
WBC ( $\times 10^9/L$ )	15.9 ± 6.7
Plt ( $\times 10^9/L$ )	97 (50–239)
Cr ( $\mu\text{mol/L}$ )	126 (87–234)
Tbil ( $\mu\text{mol/L}$ )	37 (17–97)
FiO <sub>2</sub> (%)	46 ± 10
PEEP (cmH <sub>2</sub> O)	7 (5–10)
ScvO <sub>2</sub> (%)	78 ± 7
P(v-a)CO <sub>2</sub> (mmHg)	4 (0–7)
Lactate (mmol/L)	3 (2–5)
Patients receiving renal replacement	9 (45)
APACHE II score	23 ± 10

Data were presented as mean ± standard deviation, median (interquartile range), *n* or *n* (%). WBC: White blood cell count; Plt: Platelet count; Cr: Creatinine; Tbil: Total bilirubin; FiO<sub>2</sub>: Fractional inspired oxygen concentration; PEEP: Positive end-expiratory pressure; ScvO<sub>2</sub>: Central venous oxygen saturation; P(v-a)CO<sub>2</sub>: Difference in veno-arterial carbon dioxide tension; APACHE II: Acute Physiology and Chronic Health Evaluation II.

The changes in the pulse contour-derived hemodynamic variables induced by this intervention are listed in Table 2. Increasing the dose of NE caused a significant and continuous increase in CVP ( $F = 27.45$ ,  $P < 0.001$ ), MAP ( $F = 502.46$ ,  $P < 0.001$ ), and SVR ( $F = 26.26$ ,  $P < 0.001$ ) from the usual MAP –10 mmHg to the usual MAP +10 mmHg. However, there was not a significant change in CO ( $F = 0.41$ ,  $P = 0.720$ ) and PI ( $F = 0.73$ ,  $P = 0.482$ ) from the usual MAP –10 mmHg to the usual MAP +10 mmHg.

A broad variability in the blood pressure level was observed with the maximum PI during NE titration. Individual PI values of the 20 patients at the three MAP levels are shown in Figure 2. Seven patients had a maximum PI value at the usual MAP –10 mmHg, three patients had a maximum PI value at the usual MAP, and ten patients had a maximum PI value at the usual MAP +10 mmHg.

### Relationship between the changes in hemodynamic parameters and the change in PI

There was no significant relationship between the  $\Delta\text{CO}$  and  $\Delta\text{PI}$  ( $r = 0.260$ ,  $P = 0.269$ ) from the usual MAP –10 mmHg level to the usual MAP level. Moreover, there was no significant relationship between  $\Delta\text{CO}$  and  $\Delta\text{PI}$  ( $r = 0.084$ ,  $P = 0.726$ ) from the usual MAP –10 mmHg level to the usual MAP level.

There was no significant relationship between  $\Delta(\text{MAP-CVP})$  and  $\Delta\text{PI}$  ( $r = 0.367$ ,  $P = 0.111$ ) from the usual MAP level to the usual MAP level +10 mmHg. Furthermore,

there was no significant relationship between  $\Delta(\text{MAP-CVP})$  and  $\Delta\text{PI}$  ( $r = -0.327$ ,  $P = 0.159$ ) from the usual MAP level to the usual MAP level +10 mmHg.

### Discussion

The main findings of our study are as follows: (1) A broad variability in the maximum PI obtained at different MAP levels reinforces the need for precise titration based on tissue perfusion when the MAP has been set to the patient's usual level. (2) The change in PI may be independent of the change in macrocirculation during MAP titration with NE after early resuscitation in septic shock patients.

How to titrate an optimal perfusion pressure with NE during resuscitation after septic shock remains in debate. Previous studies have shown inconsistent results regarding the effect of NE-induced increases in MAP on tissue perfusion. Jhanji *et al*<sup>[19]</sup> found that patients with septic shock exhibited an increase in cutaneous microvascular flow and tissue oxygenation when a higher MAP was induced by incremental administrations of NE. In contrast, Dubin *et al*<sup>[20]</sup> reported that increasing arterial blood pressure with NE did not improve microcirculatory blood flow in septic shock patients. Moreover, inter-individual variations in the microcirculatory perfusion response to NE-induced increases in MAP have been noted previously.<sup>[20,21]</sup> Recently, the controversial optimal perfusion pressure target has shifted away from a standardized value toward individualized values. In order to reduce the individual variations in perfusion pressure, the patient's previous history of blood pressure has been considered an important indicator for determining perfusion pressure targets.

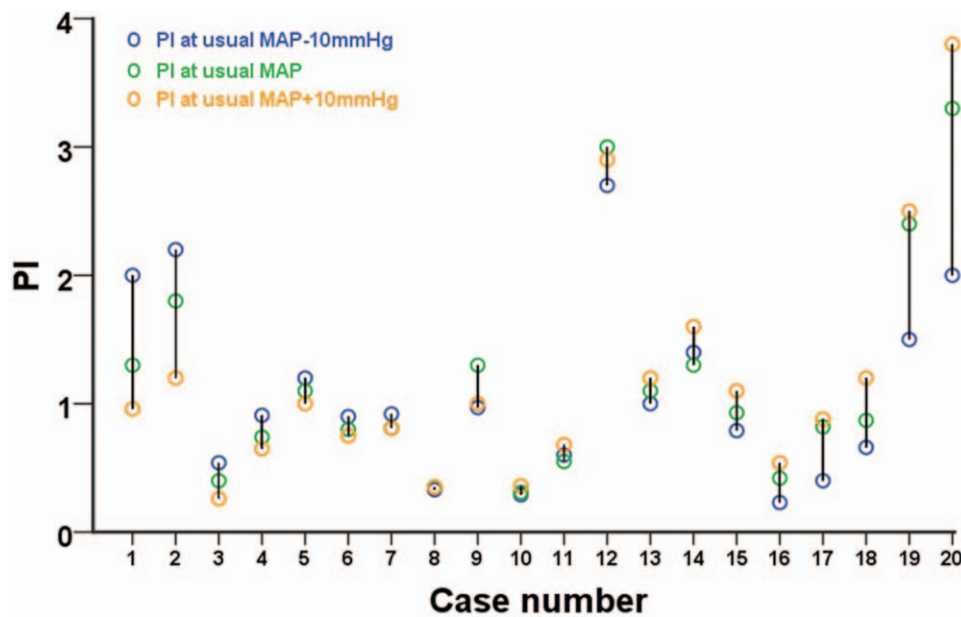
However, few trials have been performed to validate the response of tissue perfusion to changes in MAP using the value from the patient's previous history. To the best of our knowledge, this study is among the first to report the impact of changes in MAP, using values around that from the patient's medical history, on PI during septic shock. The effects of NE-induced increases in MAP on tissue perfusion are complicated. On one hand, it is well known that an over-vasoconstricting effect could independently impair peripheral perfusion even when a higher MAP has been maintained with NE. On the other hand, an insufficient perfusion pressure could also result in poor tissue perfusion. Rasmy *et al*<sup>[22]</sup> found that a low PI was associated with the NE requirement during early resuscitation in patients with hypotension. In the present study, a broad variability was observed in the maximum PI obtained at different MAP levels during MAP titration using NE. Only three patients had a maximum PI value at the usual MAP level, while 17 patients had a maximum PI value at other MAP levels. Decreases or increases in NE infusion could, therefore, achieve an increase in PI after early resuscitation. In other words, the optimal MAP, determined by the patient's usual level, might not be an adequate approach to improve peripheral perfusion. Monitoring the PI could be helpful to set an optimal perfusion pressure target. Some studies have focused on the peripheral tissue goal-directed approach in resuscitation from shock. Van Genderen *et al*<sup>[23]</sup> found that early



**Table 2: Changes in hemodynamic and PI variables as MAP was increased from the usual MAP –10 mmHg to the usual MAP +10 mmHg using NE (n = 20).**

Variables	Usual MAP –10 mmHg	Usual MAP	Usual MAP +10 mmHg	F	P value
SBP (mmHg)	118±10	135 ± 10*	153 ± 10*,†	240.16	<0.001
MAP (mmHg)	82 ± 9	95 ± 9*	107 ± 10*,†	502.46	<0.001
DBP (mmHg)	64 ± 8	74 ± 10*	82 ± 12*,†	98.18	<0.001
HR (bpm)	101 ± 16	101 ± 16	100 ± 17	0.93	0.437
CVP (mmHg)	9 ± 3	10 ± 3*	12 ± 3*,†	27.45	<0.001
MAP–CVP (mmHg)	73 ± 8	85 ± 9*	95 ± 10*,†	293.00	<0.001
CO (L/min)	5.0 ± 1.5	5.2 ± 1.5	5.2 ± 1.8	0.41	0.720
SVR (dyne/s)	1262 ± 93	1429 ± 467*	1650 ± 135*,†	26.26	<0.001
PI	0.92 (0.56–1.48)	0.90 (0.60–1.30)	0.98 (0.66–1.20)	0.73	0.482
NE (µg·kg <sup>-1</sup> ·min <sup>-1</sup> )	0.34 (0.13–0.98)	0.43 (0.23–1.09)*	0.57 (0.31–1.21)*,†	26.10	<0.001

Data were presented as mean ± standard deviation or median (interquartile range). \*P < 0.05 as compared with usual MAP –10 mmHg. †P < 0.05 as compared with usual MAP. PI: Peripheral perfusion index; MAP: Mean arterial pressure; NE: Norepinephrine; SBP: Systolic brterial pressure; DBP: Diastolic brterial pressure; HR: Heart rate; CVP: Central venous pressure; CO: Cardiac output; SVR: Systemic vascular resistance.



**Figure 2:** Individual changes in PI caused by NE at different MAP levels in the 20 cases. MAP: Mean arterial pressure; NE: Norepinephrine; PI: Peripheral perfusion index.

peripheral perfusion-targeted fluid resuscitation tended towards less fluids compared with a conventional regimen, based on systemic hemodynamic parameters in 30 septic shock patients. A randomized controlled trial is on-going in critically ill patients to compare peripheral perfusion-targeted resuscitation and lactate-targeted resuscitation.<sup>[24]</sup> Our investigation should be regarded as an initial study for the design of a larger trial to validate a rapid MAP titration test based on PI.

Importantly, the PI has several advantages for achieving optimal NE-induced perfusion pressure. First, equipment for PI measurement is readily available (bedside ECG monitor device) in an intensive care unit and is relatively inexpensive. Second, PI could provide non-invasive, real-time, and continuous information on peripheral perfusion. Third, measurement of PI is easy, direct, and objective. Although assessment of sublingual microcirculation by

side stream darkfield device can obtain more information on microcirculatory perfusion (such as microcirculation density and perfusion flow), it is operator-dependent, not real-time, and is time-consuming. Moreover, several limitations of PI should be taken into consideration at the bedside. Several other factors, including room temperature, ice cooling blanket therapy, peripheral artery stenosis, and intra-aortic balloon pump, could independently impact the PI value. PI should be interpreted with caution in cases of arrhythmia in which there is broad variation in PI. Finally, PI does not reflect non-pulsatile perfusion (such as veno-arterial ECMO).

In the present study, there was no significant relationship between ΔCO, Δ (MAP–CVP), and ΔPI during MAP titration. Loss of hemodynamic coherence is most frequently found in septic patients in whom a lack of microcirculatory recruitment is observed despite successful macrocirculatory

resuscitation.<sup>[2,5]</sup> The potential pathophysiologic mechanisms include an extensive cascade of inflammation, a major influx of cytokines, generation of reactive oxygen species, glycolyx degradation and shedding, capillary leaking due to endothelial dysfunction, and mitochondrial dysfunction.<sup>[26,27]</sup> Moreover, lack of global circulation-tissue perfusion coupling could occur during medical interventions, resulting in unnecessary fluid challenge and transfusion. Pranskunas *et al*<sup>[28]</sup> found that improved sublingual microcirculatory flow was not restricted to patients with a rise in stroke volume  $\geq 10\%$  during fluid challenge. Tanaka *et al*<sup>[29]</sup> found that red blood cell transfusion improved sublingual microcirculation independently of both macro-circulation and hemoglobin in hemorrhagic shock patients. Our data also suggest that the variation in PI was not related to the variation in CO in our study. However, the absence of a relationship between PI and CO should be interpreted with caution in clinical practice. We stress that the independent effect of NE on regional microcirculation (PI, sublingual microcirculation, urine output, etc) and dependent effect of NE on macro-circulation (CO and MAP) should be taken into consideration when using PI to guide MAP titration using NE.

Several limitations to this study should be acknowledged. The sample size was estimated based on the PI variation in septic shock patients, and a large sample study is required to validate the identified relationship between change in macro-circulation and change in PI. Our study was conducted in a single center and included a small number of patients. Thus, our investigation should be regarded as an initial study for the design of a larger trial to validate using the PI to optimize perfusion pressure. Moreover, there is always the risk of a selection bias.

The study period may not have been long enough to evaluate other relevant clinical outcomes, such as lactate clearance, organ function, and mortality. Further studies are required to validate the clinical benefit of the optimized blood pressure target based on the PI value.

Finger perfusion may not reflect perfusion of other organ tissues. Kanoore *et al*<sup>[30]</sup> found that there was a dissociation between sublingual and gut tissue microcirculation during fluid challenge. Hence, different tissue/organ perfusion must be considered when defining the optimum blood pressure. Nevertheless, a low PI has been considered to be a strong and independent predictor of outcome in critically ill adult patients.<sup>[10,12]</sup> Therefore, evaluating the PI remains clinically relevant during MAP titration with NE.

Changes in the finger PI result from blood volume pulsations, the dispensability of the vascular wall, and the intravascular pulse pressure, which can be complicated in critically ill adult patients. Some may argue that many factors can impact the PI value. To reduce uncertainty due to extra factors, we strictly controlled the patients' conditions (all patients received mechanical ventilation and sedatives; a constant ambient temperature was maintained; the PI value was obtained without finger movement, suction, or other stimulation).

Because the patients were in a stable condition with normal blood pressure, the present research should be taken as a physiologic primary study. Selection of a 10 mmHg MAP variation might be arbitrary. All patients in the study had received early resuscitation, and were in a relatively stable condition. Thus, titration with a higher variation of MAP  $\pm 20$  mmHg may have been detrimental to the patient, and mild adjustment of MPA may, therefore, be more appropriate. Attention should be paid to the broad variability in the PI response to increasing NE. Assessment of resuscitation incoherence and dynamic circulation-perfusion coupling might provide useful information for the setting of individual MAP target after early resuscitation.<sup>[31]</sup>

In the present study, only NE infusion was adjusted during the experiment; other vasopressors, such as epinephrine or dobutamine, will, therefore, have had limited confounding effects on the results. Moreover, titration of other vasopressors may have different effects on PI, and further investigation is required to clarify this. Dopamine is used as an alternative vasopressor agent to NE only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia), according to the guidelines.<sup>[2]</sup> Epinephrine is also suggested as the second-line vasopressor to maintain MAP during septic shock resuscitation. NE, as the first-choice vasopressor, is the most commonly used agent for maintaining perfusion pressure in septic shock. Hence, investigation of NE is relevant from a clinical perspective.

In this study, differing MAP levels using NE induced a diverse PI response in septic shock patients, which reinforces the need for a precise titrated approach based on peripheral tissue perfusion. The PI may have potential application for MAP optimization based on changes in peripheral tissue perfusion. Further investigations are required to determine whether using a maximum PI value to guide setting of the MAP target may improve the outcome of septic shock patients after early resuscitation.

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### Conflicts of interest

None.

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