Changes in perfusion can detect changes in the cardiac index in patients with septic shock

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Abstract

Objective: The perfusion index (PI) is usually used to assess peripheral perfusion, which can be influenced by the cardiac index (CI). CI monitoring is often needed during the treatment of patients with shock. We investigated the relationship between changes in the PI (ΔPI) and changes in the CI (ΔCI) in patients with septic shock.

Methods: This retrospective study included patients with septic shock who underwent pulse-induced continuous cardiac output monitoring. We measured the CI and PI before and after fluid loading during the first 6 hours of intensive care unit admission. Fluid responsiveness was defined as a ≥10% ΔCI after fluid loading. Other hemodynamic and oxygen-derived parameters were also collected at the exact time of each CI measurement.

Results: Fifty-five patients were included in the study (29 fluid responders, 26 fluid non-responders). In the univariate analysis, ΔPI was positively correlated with ΔCI. In the multivariable analysis, ΔPI was independently associated with ΔCI. The receiver operating characteristic curve showed that ΔPI was an appropriate marker with which to discriminate a CI increase with an area under the curve of 0.776.

Conclusion: This study showed a positive correlation between ΔPI and ΔCI during the early treatment phase of septic shock.

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Introduction

For patients with shock in whom initial treatment has failed, cardiac index (CI) monitoring is generally recommended.\(^1\) CI monitoring is particularly useful in patients with refractory septic shock, who often exhibit hemodynamic instability and/or insufficient tissue perfusion.\(^2\)

The use of a pulmonary arterial catheter or a pulse-induced continuous cardiac output (PiCCO) monitoring device each has drawbacks, such as invasiveness, the requirement for regular calibration, the risk of nosocomial infection, and lack of applicability for certain conditions.\(^3,4\) The use of ultrasound monitors for continuous echocardiographic monitoring of the CI is still controversial, and its high error rate makes it difficult to routinely apply.\(^5\) Several other parameters with which to track the changes in the CI have been discussed. Different conclusions have been reached regarding the relationship between changes in the mean arterial pressure (MAP) and changes in the CI.\(^6,7\) The central venous oxygen saturation (ScvO\(_2\)) is reportedly associated with changes in the CI.\(^8,9\) However, blood gas results are not continuous parameters.

The perfusion index (PI) refers to the ratio of pulsatile blood flow to nonpulsatile blood flow in peripheral tissues, and this index can be measured noninvasively with a pulse oximeter.\(^10\) The PI is usually used to assess peripheral perfusion dynamics due to changes in peripheral vascular tone.\(^11,12\) A previous study showed that among ventilated critically ill pediatric patients, peripheral perfusion parameters such as the capillary refill time were related to the stroke volume index.\(^13\) In a group of normal volunteers, the changes in the PI were found to be valuable diagnostic tools for detecting changes in the stroke volume induced by lower body negative pressure.\(^14\) Another study showed that the PI was associated with ScvO\(_2\) in critically ill patients with hypoperfusion, and these relationships were strengthened when the PI was \(<1.4.\)\(^15\)

However, whether the PI is associated with the CI in patients with septic shock patients has not been reported to date. The present study was performed to elucidate whether the PI can be used to detect changes in the CI in patients with septic shock.

Patients and methods

Study design and patient population

This retrospective study was conducted in the intensive care unit (ICU) of Peking Union Medical College Hospital. Patients with septic shock who underwent PiCCO and tissue perfusion monitoring from 1 May 2015 to 1 May 2017 were studied.

Septic shock was defined as follows: (1) the presence of sepsis (i.e., a suspected or confirmed infection and an acute change of \(\geq2\) points in the patient’s total Sequential Organ Failure Assessment score, the need for vasopressors to maintain an MAP of \(\geq65\) mmHg, and a serum lactate level of \(>2\) mmol/L in the absence of hypovolemia)
and (2) the need for dopamine at >15 μg/kg/minute or norepinephrine or epinephrine at >0.25 μg/kg/minute.2,16

The exclusion criteria were atrial fibrillation, severely damaged peripheral perfusion with an undetectable pulse oxygen saturation or PI, current treatment with a cool blanket, central hypothermia (core temperature of <36°C) with limb ischemia attributable to vascular occlusion, and lack of fluid loading or lack of CI measurement before and after fluid loading within the first 6 hours of ICU admission.

This study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of our institution. The requirement for informed consent was waived because of the retrospective observational nature of this study.

**Data collection**

All patients underwent sedation and mechanical ventilation and were treated with a local hemodynamic support protocol for critically ill patients with tissue hypoperfusion. The early goals of hemodynamic support were a central venous pressure of 8 to 12 mmHg, MAP of >65 mmHg, urine output of >0.5 mL/kg (except in patients with acute renal failure), and ScvO2 of ≥70%. Treatment was administered at the discretion of the attending physician. The PI was not the target of the protocol but was a necessary item that was documented with each CI measurement to maintain the feasibility of this study.

A central catheter was placed in the internal jugular vein or subclavian vein to allow for central venous pressure (CVP) measurement and central venous blood sampling. A thermodilution catheter was placed in the femoral artery (PULSION Medical Systems, Feldkirchen, Germany). The PI was obtained with an IntelliVue MP70 monitor (Philips Medical Systems, Amsterdam, Netherlands). The ambient temperature of the room was consistent at approximately 25°C (climate-controlled). The blood temperature was measured from the femoral arterial catheter. The CI was measured by the thermodilution method, which involved injecting a bolus of iced saline and determining the average of three measurements. The PI was obtained during five respiratory cycles and averaged. Blood gases were measured immediately after each measurement of the CI (GEM Premier 4000; Instrumentation Laboratory, Bedford, MA, USA).

**Definitions**

We measured the CI before and after fluid loading within the first 6 hours after ICU admission. The heart rate, MAP, CVP, PI, global end-diastolic volume index (GEDI), norepinephrine dosage, and ScvO2 were collected at the exact time of each CI measurement by the thermodilution method. The dose of vasoactive agents remained the same during the process of fluid loading.

Fluid loading was performed by infusing 250 to 750 mL of crystalloid within 30 minutes. Fluid responsiveness was defined by a ≥10% increase in the CI after fluid loading.6,17 The change in each parameter was calculated according to the following equation:

\[
\text{value change (\%) = } \frac{\text{post-measurement value} - \text{pre-measurement value}}{\text{pre-measurement value}} \times 100%.
\]

**Statistical analysis**

Statistical analysis was performed using the SPSS 25.0 statistical software package (IBM Corp., Armonk, NY, USA). The normal distribution of continuous values was assessed by the Kolmogorov–Smirnov test. Normally distributed continuous data are expressed as mean ± standard deviation. Non-normally distributed variables are expressed as median and interquartile
range. Categorical variables are presented as number and percentage. Differences within groups were assessed by Student’s paired t-test or the nonparametric Wilcoxon rank-sum test for paired observations, when appropriate. The Spearman correlation test was used to assess univariate relations. A multivariate linear regression analysis including all parameters from the univariate analysis was performed to assess the independent associations of these variables with changes in the CI. Receiver operating characteristic (ROC) curves were analyzed, and the area under each respective curve was calculated and compared. All p-values were two-tailed and considered significant at \( p < 0.05 \).

### Results

#### Patients’ general characteristics

In total, 104 patients with septic shock who underwent PiCCO and tissue perfusion monitoring were screened for enrollment. Of these, 55 patients were included in the study; 29 were fluid responders, and the remaining 26 were non-responders. Forty-nine patients were excluded because of atrial fibrillation (n = 17), a lack of PI data (n = 5), cool blanket therapy or hypothermia (n = 8), and a lack of fluid loading or lack of corresponding CI measurement with fluid loading (n = 19).

The patients’ general characteristics are shown in Table 1. The main diagnoses were

| Categories                      | Responders (n = 29) | Non-responders (n = 26) | t or Z or \( \chi^2 \) | p   |
|--------------------------------|---------------------|-------------------------|-------------------------|-----|
| **Age, years**                 | 53.3 ± 17.7         | 57.1 ± 17.6             | −0.796                  | 0.922|
| **Male sex**                   | 13 (44.8)           | 17 (65.4)               | 2.337                   | 0.126|
| **APACHE II score**            | 25.0 ± 4.9          | 23.3 ± 6.0              | 1.047                   | 0.301|
| **SOFA**                       | 12.0 ± 3.4          | 12.1 ± 3.2              | −0.006                  | 0.995|
| **Diagnosis**                  |                     |                         |                         |     |
| Intra-abdominal infection      | 8 (27.6)            | 11 (42.3)               | 1.314                   | 0.252|
| Bacteremia                     | 9 (31.0)            | 5 (19.2)                | 1.007                   | 0.316|
| Pneumonia                      | 7 (24.1)            | 6 (23.1)                | 0.009                   | 0.926|
| UTI                            | 3 (10.3)            | 1 (3.8)                 | 0.859                   | 0.354|
| Others*                        | 2 (6.9)             | 3 (11.5)                | 0.221                   | 0.638|
| **NE dose**                    | 0.33 (0.26–0.85)    | 0.42 (0.28–0.88)        | −0.661                  | 0.509|
| **Inotrope**                   | 15 (51.7)           | 19 (73.1)               | 2.648                   | 0.104|
| **Lactate, mmol/L**            | 3.1 (1.9–4.8)       | 3.9 (2.1–5.6)           | −1.046                  | 0.296|
| **Blood temperature, °C**      | 37.2 ± 1.0          | 36.9 ± 0.9              | 1.052                   | 0.298|
| **Volume of fluid loading**    | 496 ± 125           | 480 ± 130               | 0.557                   | 0.580|
| **Prognosis**                  |                     |                         |                         |     |
| ICU stay, days                 | 5 (5–9)             | 6 (5–8)                 | 0.069                   | 0.945|
| In-hospital mortality          | 8 (27.6)            | 9 (34.6%)               | 0.317                   | 0.573|

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; UTI, urinary tract infection; NE, norepinephrine; ICU, intensive care unit.

*Other infections included skin and soft tissue infection, biliary tract infection, central nervous system infection, and infection of unknown origin.
intra-abdominal infection, bacteremia, pneumonia, urinary tract infection, and other infections (skin and soft tissue infection, biliary tract infection, central nervous system infection, and infection of unknown origin). No differences in demographics, severity of illness, diagnosis, blood temperature, vasoactive agents, or prognosis were found between the two groups.

**PI and other hemodynamic variables before and after fluid loading**

The CI, PI, and GEDI increased significantly after fluid resuscitation in responders ($p = 0.001$, $p = 0.011$, and $p = 0.008$, respectively). No significant change in the CI, PI, or GEDI was found after fluid resuscitation in non-responders. The CVP increased significantly after fluid loading in both responders and non-responders ($p = 0.015$ and $p = 0.001$, respectively) (Table 2).

The value change in each variable after fluid loading was calculated. The value changes in the PI, CVP, and GEDI ($\Delta$PI, $\Delta$CVP, and $\Delta$GEDI, respectively) were much higher in responders than non-responders ($p < 0.001$, $p = 0.016$, and $p < 0.001$, respectively). The value change in ScvO2 ($\Delta$ScvO2) was also higher in responders, but the difference was not statistically significant (Table 3).

**Correlation between $\Delta$CI and value changes in other variables**

In the univariate analysis, $\Delta$PI, $\Delta$GEDI, and $\Delta$ScvO2 were positively correlated

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### Table 2. Perfusion index and hemodynamic variables in fluid responders and non-responders.

| Categories   | Responders (n = 29) | Non-responders (n = 26) | t or z | p     |
|--------------|---------------------|------------------------|--------|-------|
| CI, L/minute/m² | 2.27 ± 0.54         | 2.92 ± 0.76            | -3.567 | 0.001|
| PI           | 0.40 (0.28–0.79)    | 0.62 (0.51–1.30)       | -2.551 | 0.011|
| HR, bpm      | 105 ± 17            | 104 ± 16               | 0.859  | 0.797|
| MAP, mmHg    | 81 ± 13             | 84 ± 14                | -0.838 | 0.405|
| CVP, mmHg    | 9 (7–10)            | 10 (9–12)              | -2.435 | 0.015|
| GEDI, mL/m²  | 696 (634–726)       | 743 (686–913)          | -2.636 | 0.008|
| ScvO2, %     | 65.4 ± 8.9          | 69.4 ± 9.1             | -1.699 | 0.095|

Data are presented as mean ± standard deviation or median (interquartile range).

CI, cardiac index; PI, perfusion index; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; GEDI, global end-diastolic volume index; ScvO2, central venous oxygen saturation.

### Table 3. Value changes of variables in fluid responders and non-responders.

| Categories   | Responders (n = 29) | Non-responders (n = 26) | Z     | p   |
|--------------|---------------------|------------------------|-------|-----|
| $\Delta$CI, %| 22.3 (15.6–40.2)    | -4.1 (–6.4 to 0.4)     | -6.356| <0.001|
| $\Delta$PI, %| 55.2 (31.4–123.8)   | -19.3 (–32.5 to 47.9)  | -3.507| <0.001|
| $\Delta$HR, %| 1.1 (–4.0 to 2.4)   | -1.3 (–5.4 to 5.3)     | -0.185| 0.853|
| $\Delta$MAP, %| 0.0 (–6.0 to 14.5)  | 2.7 (–4.6 to 8.5)      | -0.093| 0.926|
| $\Delta$CVP, %| 14.3 (0.0–31.0)    | 29.3 (17.5–44.6)       | -2.041| 0.016|
| $\Delta$GEDI, %| 10.9 (6.1–15.5)    | 3.1 (–3.6 to 5.9)      | -4.130| <0.001|
| $\Delta$ScvO2, %| 5.7 (–3.9 to 14.7) | -2.1 (–5.7 to 5.9)     | -1.787| 0.074|

CI, cardiac index; PI, perfusion index; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; GEDI, global end-diastolic volume index; ScvO2, central venous oxygen saturation.
with ΔCI (r = 0.486, p < 0.001; r = 0.539, p < 0.001; and r = 0.282, p = 0.013, respectively). In the multivariate analysis, ΔPI and ΔGEDI were independent variables associated with ΔCI (standard coefficient: 0.342, p = 0.003 and standard coefficient: 0.461, p = 0.001, respectively) (Figure 1, Table 4). In the univariate analysis, ΔCVP was negatively associated with ΔCI (r = −0.333, p = 0.013). However, no significant association was found between ΔCVP and ΔCI in the multivariate analysis.

ROC curves were calculated to evaluate the sensitivity and specificity of the parameters to assess fluid responsiveness (Figure 2, Table 5). In the ROC analysis, ΔPI was selected as an appropriate marker for determining increases in CI with an area under the curve (AUC) of 0.776 (95% confidence interval, 0.645–0.907; p < 0.001). We also found that ΔGEDI had an AUC of 0.825 (95% confidence interval, 0.712–0.938; p < 0.001). No difference was found in the AUC between ΔPI and ΔGEDI (Z = −0.557). For ΔPI, the optimum cutoff value for the diagnosis of fluid responsiveness was a 33.1% increase, resulting in a sensitivity of 75.9%, specificity of 73.3%, positive predictive value of 76.0%, and negative predictive value of 80.1%.

Table 4. Significant independent relation of ΔCI with value changes in other variables.

| Variables   | Univariate analysis | Multivariate analysis |
|-------------|---------------------|-----------------------|
|             | r   | 95% CI                  | p         | Standard coefficient (β) | p     |
| ΔPI         | 0.486 | 0.254 to 0.666         | <0.001    | 0.343                  | 0.003 |
| ΔCVP        | −0.333 | −0.549 to −0.074      | 0.013    | −0.021                 | 0.871 |
| ΔGEDI       | 0.539 | 0.319 to 0.704        | <0.001   | 0.461                  | 0.001 |
| ΔScvO2      | 0.282 | 0.017 to 0.510        | 0.037    | 0.154                  | 0.184 |

CI, cardiac index; 95% CI, 95% confidence interval; PI, perfusion index; CVP, central venous pressure; GEDI, global end-diastolic volume index; ScvO2, central venous oxygen saturation.
This study showed that ΔPI was associated with ΔCI and was capable of detecting changes in CI after fluid loading in patients with septic shock with tissue perfusion. Other easily achievable bedside parameters, including the heart rate, MAP, CVP, and ScvO2, displayed much weaker relationships with CI in these patients.

In the present study, PiCCO monitoring was initiated during early resuscitation if the patients were still hemodynamically unstable or if tissue hypoperfusion was not fully resolved. Therefore, all patients should be in the treatment phase of optimization when ScvO2, lactate level, and CI measurements should be considered. However, both the use of PiCCO monitoring and pulmonary arterial catheter placement are invasive techniques. In addition, focused cardiac ultrasound is operator-independent and cannot provide continuous cardiac output monitoring. In contrast, the PI, which is derived from a pulse oximeter, is readily available for routine use and can be used for continuous monitoring without increasing the financial burden or the risk of complications.

In a group of patients who underwent selective coronary surgery and whose baseline PI was 4.8, no difference in PI was detected in responders before and after volume expansion. However, van Genderen et al. found that the PI of healthy volunteers decreased significantly from 2.2 to 1.2 after inducing central hypovolemia. The patients in the two abovementioned studies had a significantly different baseline PI. Lima et al. noted that the PI distribution was highly skewed in the normal population but that changes in the PI correlated well with core-to-toe temperature differences in critically ill patients. In our group of patients with septic shock with tissue perfusion, we found that the median PI in both fluid responders and non-responders was <1.0 and that the PI changed accordingly with the CI. We hypothesized that the PI might have a closer relationship with the CI in patients with shock.

Changes in the PI are caused by pulsatile changes in the arterial blood volume and changes in the venous and non-pulsatile arterial blood volume. Apart from low cardiac output, a variety of factors can influence the sympathetic innervation, including vascular disease, hypothermia, various vasoactive drugs, and even the feeling of pain. In the present study, patients with shock with tissue perfusion were maintained in a sedated condition, and the ambient temperature was set at 25°C. The norepinephrine dosage was not tapered between the pre- and post-measurement time periods.

The MAP can increase or remain stable while the CI significantly decreases due to sympathetic stimulation or vasopressor administration. Furthermore, the MAP tends to be constantly maintained while cardiac output varies through sympathetic modulation of arterial tone, rendering changes in MAP dissociated from changes in cardiac output.
in cardiac output.\textsuperscript{23} Pierrakos et al.\textsuperscript{6} found that changes in MAP did not reliably track changes in the CI after fluid challenge in patients with septic shock. Although a previous study revealed that blood pressure could be used to monitor changes in cardiac output after fluid challenge, the criterion for changes in cardiac output was set as high as 15\%,\textsuperscript{7} In the present study, we chose 10\% as the criterion for CI change and found that changes in MAP and changes in the CI were not well correlated. The results indicated that changes in blood pressure might not be ideal surrogate markers of changes in CI in these patients.

Theoretically, ScvO\textsubscript{2} should be correlated with the CI. However, the correlation may be altered by oxygen consumption and disrupted microcirculation.\textsuperscript{9,24} No correlation was observed between ScvO\textsubscript{2} and cardiac output in patients with acute decompensated heart failure.\textsuperscript{25} In the present study, we observed changes in ScvO\textsubscript{2} in fluid responders, but the correlation between ΔScvO\textsubscript{2} and ΔCI was poor. Because we included patients with septic shock with tissue perfusion, changes in ScvO\textsubscript{2} may have been obscured by oxygen consumption in some patients, and disrupted microcirculation may have also existed in some other patients.

Investment in securities has been proposed to reflect the quality of skin perfusion, especially in anesthesia. Nonetheless, every time the heart beats, the stroke volume should also affect the PI by increasing the finger arterial blood volume. The relationship between the PI and CI cannot be straightforward because it is also affected by venous blood flow. Decreased venous blood flow may result in stagnation of finger venous blood, an increase in non-pulsatile components, and eventually a decrease in the PI, which is not related to changes in arterial blood flow.\textsuperscript{31}

Some studies have shown that changes in the PI reflects changes in the CI or arterial pressure amplitude in different environments. McGrath et al.\textsuperscript{32} demonstrated that changes in the PI measured on the forehead can accurately detect fluid-induced changes in cerebral infarction after anesthesia induction. Differences in results have also been reported. In particular, Cannesson et al.\textsuperscript{33} found no significant changes in PI manipulation during passive leg raising. Nonetheless, in all of these studies with negative findings, the quality of the PI was not mentioned.

**Limitations**

Our study has some limitations. First, this was a retrospective study and the sample size was limited. Thus, a larger population with unequivocal interventions is needed to confirm the results. However, we believe that this study was a useful pilot study. Second, the loading doses could not be standardized because of the retrospective nature of the study. However, no difference was found between the loading volumes in the two groups. Prior studies demonstrated that the GEDI and changes in the GEDI were significantly correlated with the CI and reflected volume responsiveness.\textsuperscript{26–28} We also found that the GEDI changed accordingly with the CI in the responders and that no such relationship existed in the non-responders. Third, we only determined the relationship between the PI and CI within the first 6 hours after ICU admission. Because the cardiac function, norepinephrine dosage, and peripheral vascular tone invariably change, whether the PI is still a reliable predictor of changes in the CI after the first 6 hours remains unknown. The final limitation is that because almost half of the patients with septic shock were excluded from the present study, the results are difficult to generalize.\textsuperscript{29,30} In further investigations, we might use the PI to assess fluid responsiveness instead of monitoring the stroke volume to ascertain that these results would be better for clinical application.
Conclusion

Changes in the PI are positively correlated with changes in the CI in patients with septic shock with tissue perfusion during the early treatment phase.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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