CRITICAL CARE

COMMENTARY

Clinical monitoring of peripheral perfusion: there is more to learn

Alexandre Lima[*] and Jan Bakker

See related research by He *et al.*, http://ccforum.com/content/17/3/R116

Abstract

Irrespective of initiating factors, the peripheral circulation shows two general phases during the development and treatment of shock. Most published reports support earlier knowledge that the peripheral circulation is among the first to deteriorate and the last to be restored. With the advent of new and old techniques that allow us to continuously monitor peripheral perfusion, we may further shift our focus from pressure-based to flow-based resuscitation. The persisting challenge is the validation (effect on outcome parameters) of peripheral perfusion monitoring tools that can be simple and readily available worldwide.

Despite enthusiasm raised by new hemodynamic monitoring systems, a large gap still exists between what we can measure and what we would really like to measure. The report in a previous issue of *Critical Care* by He and colleagues on two techniques for peripheral perfusion monitoring adds new insights into this topic [1]. In patients with septic shock, they studied the use of continuous transcutaneous oxygen, carbon dioxide tension and peripheral perfusion index (PI) derived from the pulse oximetry signal. Although these are not new technologies, their study highlights the importance of the status of nonvital organ perfusion in the resuscitation of patients with circulatory shock.

Earlier observations on the behavior of nonvital organ perfusion have shown two phases during the shock state, irrespective of initiating factors [2]. During the initial phase, compensatory mechanisms predominate to preserve the perfusion of vital organs at expense of the peripheral tissues (nonvital organs). As blood flow variations in this phase follow a similar response pattern in the skin,

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subcutaneous tissue, muscle and gastrointestinal vascular beds, these tissues are highly sensitive for detecting occult tissue hypoperfusion during compensated circulatory shock. Although these are functionally and metabolically different organs, at a functional circulatory level they are remarkably similar. Blood flow in these organs is moderately to strongly influenced by sympathetic vasoconstrictor mechanisms. In this regard, coronary, cerebral, and renal circulations show a high degree of autoregulation with poor sympathetic control, whereas skeletal muscle, gastrointestinal and cutaneous circulations show a predominant sympathetic control with a poor degree of autoregulation. With the progression of circulatory shock and following initiation of therapy and normalization of systemic hemodynamic parameters, the association between global flow and peripheral circulation becomes less striking and ultimately disappears. Some patients enter a phase where the physiological gap between macrocirculation and microcirculation becomes more evident and intricate(Figure 1). To what extent each peripheral vascular bed expresses hypoperfusion in these stages of shock remains to be investigated. Nevertheless, most published reports support our earlier knowledge that the vascular bed of peripheral circulation is among the first to deteriorate and the last to be restored after resuscitation and, therefore, through this being a window of perfusion [3].

Poeze and colleagues observed that global hemodynamic variables and gastric tonometry variables were both different between survivors and nonsurvivors, and no superior predictor of outcome was identified at admission before ICU resuscitation was initiated [4]. However, after stabilization and normalization of global hemodynamics, gastric tonometry variables were the best predictor of outcome. Other studies have reported similar time courses in different peripheral vascular beds, such as skin, muscle and sublingual microcirculation. These studies showed that persistence of abnormal peripheral perfusion following restoration of global hemodynamics was related to an unfavorable outcome [5-9]. Our group evaluated changes in
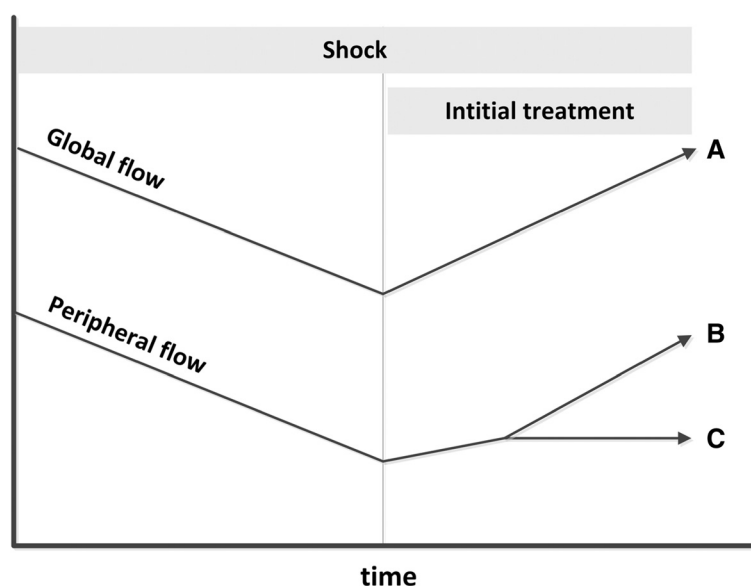
Figure 1 Clinical pattern of alterations in global and peripheral blood flow during circulatory shock. After initial treatment, restoration of global flow **(A)** is usually followed by peripheral perfusion trends towards normalization in survivors **(B)**, and remained altered in nonsurvivors **(C)**.

parameters of skin and muscle perfusion during early resuscitation of circulatory shock [8,9]. We found that patients who failed to normalize their capillary refill time, PI and peripheral tissue oxygenation during early treatment had a worse outcome. These findings could have implications for the treatment of critically ill patients with persistent abnormal peripheral perfusion, requiring additional diagnostic or therapeutic interventions.

He and colleagues explored the relationship between global and peripheral perfusion variables following initial resuscitation in septic patients [1]. The authors used two distinct but complementary methods to evaluate peripheral perfusion (PI and transcutaneous oxygen/carbon dioxide tension). The PI calculates the ratio between the arterial compartment and the nonpulsatile component and because the size of the pulsatile portion increases with vasodilation and decreases with vasoconstriction, changes in the PI reflect changes in peripheral blood flow. Transcutaneous oxygen/carbon dioxide tension, on the other hand, is a measure of oxygenation, and is related to variations in local perfusion [10]. The authors demonstrated that nonsurviving septic patients had poor peripheral perfusion characterized by lower PI and a blunted response to the oxygen challenge test (OCT; the change in transcutaneous oxygen tension relative to the change in arterial partial pressure of oxygen after 10 minutes on fraction of inspired oxygen of 1.0). The authors also showed that the PI and OCT could predict mortality with similar accuracy to arterial lactate levels, although not corrected for confounding factors.

Interestingly, the study showed that both survivors and nonsurvivors had abnormal peripheral blood flow, as reflected by the lower PI values, when compared with healthy controls. Even more interestingly, nonsurvivors had significantly lower OCT values associated with higher arterial lactate levels. Assuming that global hemodynamic variables were optimized in all patients, the low OCT in the nonsurvivors could be explained either by a high rate of oxygen consumption or by decreased oxygen delivery, as hypothesized by the authors. Since oxygen requirements of the skin are quite low relative to other organs, we can speculate variations in peripheral blood flow as the main reason of low OCT in nonsurvivors, supported also by the low PI values. These results underscore the context of the peripheral circulation in septic shock, and provide evidence of a heterogeneous distribution of blood flow in sepsis. This phenomenon was first described by Gilbert in 1960 as 'dilation in one (vascular) bed might be accompanied by constriction elsewhere' [11]. This statement is supported by the findings of He and colleagues showing that peripheral vasoconstriction can be a hallmark of early septic shock [1]. While these abnormalities in peripheral perfusion predict an unfavorable outcome, it still needs to be proven that correcting these abnormalities results in improved outcome.

As clinicians we start shifting our focus from monitoring global pressures to monitoring flow and its determinants in order to assess adequacy of resuscitation [12,13]. With the advent of techniques that allow us to continuously monitor peripheral perfusion, we could further shift our focus to maintaining normal perfusion in nonvital organs, such as skin, subcutaneous tissue and muscle. The fundamental challenge is the validation of low-cost peripheral perfusion monitoring tools that can be readily available worldwide. The measurement of

transcutaneous and sublingual microcirculation at the bedside is still mostly used in larger research centers. Reliance on simple methods such as the capillary refill time, skin temperature, and PI must be emphasized and exploited. However, the true clinical implications of these tools should be better defined in clinical trials targeting peripheral perfusion.

Abbreviations
PI: Perfusion index; OCT: Oxygen challenge test.

Competing interests
The authors declare that they have no competing interests.

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CRITICAL CARE

The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation

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Abstract

Introduction: The peripheral perfusion index (PI) is a noninvasive numerical value of peripheral perfusion, and the transcutaneous oxygen challenge test (OCT) is defined as the degree of transcutaneous partial pressure of oxygen ($PtcO_2$) response to 1.0 FiO_2. The value of noninvasive monitoring peripheral perfusion to predict outcome remains to be established in septic patients after resuscitation. Moreover, the prognostic value of PI has not been investigated in septic patients.

Methods: Forty-six septic patients, who were receiving PiCCO-Plus cardiac output monitoring, were included in the study group. Twenty stable postoperative patients were studied as a control group. All the patients inspired 1.0 of FiO_2 for 10 minutes during the OCT. Global hemodynamic variables, traditional metabolic variables, PI and OCT related-variables were measured simultaneously at 24 hours after PiCCO catheter insertion. We obtained the 10 min-OCT (($PtcO_2$ after 10 minutes on inspired 1.0 oxygen) - (baseline $PtcO_2$)), and the oxygen challenge index ((10 min-OCT)/(PaO_2 on inspired 1.0 oxygen - baseline PaO_2)) during the OCT.

Results: The PI was significantly correlated with baseline $PtcO_2$, 10min-OCT and oxygen challenge index (OCI) in all the patients. The control group had a higher baseline $PtcO_2$, 10min-OCT and PI than the septic shock group. In the sepsis group, the macro hemodynamic parameters and $ScvO_2$ showed no differences between survivors and nonsurvivors. The nonsurvivors had a significantly lower PI, 10min-OCT and OCI, and higher arterial lactate level. The PI, 10min-OCT and OCI predicted the ICU mortality with an accuracy that was similar to arterial lactate level. A PI <0.2 and a 10min-OCT <66mmHg were related to poor outcome after resuscitation.

Conclusions: The PI and OCT are predictive of mortality for septic patients after resuscitation. Further investigations are required to determine whether the correction of an impaired level of peripheral perfusion may improve the outcome of septic shock patients.

Keywords: Peripheral perfusion index (PI), transcutaneous oxygen/carbon dioxide tensions ($PtcO_2$/$PtcCO_2$), oxygen challenge test (OCT), septic shock, prognosis

Introduction

Blood flow is diverted from the peripheral tissue to vital organs during circulation shock. It is assumed that peripheral tissue is the first tissue bed to sacrifice in shock and the last to be reperfused in resuscitation [1,2]. Tissue perfusion is commonly evaluated indirectly by subjective symptoms and imprecise signs, but they are not direct quantitative measures of peripheral tissue perfusion. With the development of new techniques, quantitatively assessment of peripheral tissue perfusion has become popular in clinical practice. The peripheral perfusion index (PI) is derived from the photoelectric plesthysmographic signal of pulse oximetry and has been shown to reflect changes in peripheral perfusion [3,4]. A PI value of 1.4 indicates the presence of poor peripheral perfusion in critically ill patients [3]. Transcutaneous oxygen/carbon dioxide tensions ($PtcO_2$/$PtcCO_2$) monitoring can provide continuous displays of data, and have been used

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in infants and premature neonates as a surrogate measure of arterial blood gases [5]. Because thicker epidermal layers cause more discrepancy between $PtcO_2$ and arterial pressure of oxygen (PaO_2), $PtcO_2$ and $PtcCO_2$ have been used to represent tissue oxygenation and perfusion in critically ill adult patients [6-8]. In addition, the oxygen challenge test (OCT) is another new method to reflect cellular O_2 deficit. Recent reports using the noninvasive $PtcO_2$ have observed a relationship between low oxygen challenge test values to mortality and new organ failure [9,10].

However, septic shock, in contrast to other forms of shock associated with peripheral vasodilation, is known as 'warm shock'. During septic shock resuscitation, perfusion assessment is difficult and usually a complex determination. The value of peripheral tissue perfusion is controversial in systemic sepsis [11]. To the best of our knowledge, no one has quantified PI to outcome in patients with septic shock. The noninvasive peripheral perfusion potential value to predict outcome remains to be established in septic patients. This study was conducted as a prospective evaluation of the predictive value of the noninvasive peripheral perfusion indicators, traditional metabolic variables, and global hemodynamic parameters in septic patients after resuscitation. This could provide valuable insights about perfusion monitoring in septic patients and help to delineate the potential role and limitations of noninvasive peripheral perfusion as a target for resuscitation.

This study has been partially presented in abstract form [12].

Patients and methods

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study for human subjects. Informed consent was obtained from all patients or next-of-kin before data were included into the study.

When the research team was available, all adult patients within 48 h after the onset of severe sepsis or septic shock sequentially admitted to the Department of Critical Care Medicine of Peking Union Medical College Hospital, who required PiCCO-Plus cardiac output monitoring and mechanical ventilation for resuscitation, were eligible for the study. The attending intensivists decided PiCCO catheter placement according the severity of the patient's condition after the early hemodynamic support. The local reference standard of PiCCO catheter insert is: (1) tissue perfusion or organ function has not improved after early goal-directed therapy [13]; (2) according to the patient's clinical condition, it is difficult for the attending doctor to make a clinical decision of infusion fluid or pressor. Patients excluded from the study were as follows: fraction of inspired oxygen concentration (FiO_2) >80%; were pregnant; aged <18

years; were not expected to live; were brain dead; due to the decision to withhold or withdraw treatments. Septic shock was defined as severe sepsis with sepsis-induced hypotension persisting, despite adequate fluid resuscitation, and requiring the administration of vasopressors [14].

Twenty stable patients during the first 24 h of the Department of Critical Care Medicine admission who were ventilated and sedated, without infection, and admitted for postoperative monitoring were measured and considered to be the control group.

Patient management

All the patients needed mechanical ventilation and sedatives. All septic shock patients received broad-spectrum antibiotic coverage. The local hemodynamic support algorithm of septic shock patients: the early goal-directed therapy was as follows: central venous pressure was 8 to 12 mmHg; mean arterial pressure was above 65 mmHg; urine output was above 0.5 ml/kg of body weight (except in the patients with acute renal failure), and the central venous oxygen saturation ($ScvO_2$) was at 70% or more [13]. The advanced goal of hemodynamic support (after PiCCO catheter placement) was as follows: fluid loading was guided according to pulse pressure variation in ventilated patients (pulse pressure variations below 13% or lack of response to passive leg raising or no respiratory variations of the inferior vena cava diameter (Cx Cart; Phillips Ultrasound, Bothell, WA, USA)); systemic vascular resistance index >1000 dyne/sec/cm^5; after the macro hemodynamic variables were optimized, if the lactate was not decreasing, sources for the elevation of lactate were sought, and/or maneuvers to lower oxygen consumption were instituted (fever control, increase in sedation/pain medication). The intensivists were blinded for the results of the peripheral perfusion variables.

Measurements

Information collected at enrollment included demographic characteristics such as age; sex; Acute Physiology and Chronic Health Evaluation II score (APACHE II) [15]; Sequential Organ Failure Assessment (SOFA) score [16]; and primary site and type of infection. The global hemodynamic, traditional metabolic, and PI and OCT variables were measured simultaneously at 24 h after PiCCO catheter insertion.

Simultaneous basic blood gases from the arterial, central venous catheters were obtained (the placement of a central venous catheter in the superior vena cava was confirmed by chest radiography). Blood gas samples were taken anerobically in 3 ml heparinized syringes (PL67BP; BD Diagnostics, Plymouth, UK) and analyzed on blood gas bedside machines (GEM Premier 3000, model 5700; Lexington, MA, USA) or (ABL90: Radiometer,

Copenhagen, Denmark). The thermodilution cardiac output was measured by injecting 15 ml of 0.9% saline at 0°C for the PiCCO-Plus (the PiCCO system: Pulsion Medical System, Munich, Germany). Three cardiac outputs, which were within 10% of each other, were obtained and averaged. These global hemodynamic variables were recorded simultaneously.

Transcutaneous sensors (TCM4 Transcutaneous Oxygen/Carbon Dioxide Monitoring System; Radiometer, Copenhagen, Denmark) having previous validation studies were calibrated to known oxygen and carbon dioxide levels according to the manufacturer's guidelines. The sensors were attached to the patients' upper torso below the clavicle in nonbony areas, and skin was prepared with alcohol and shaved when necessary. Areas of injury such as hematomas were avoided. With a total of 15 min equilibration time, heating of the probe to 44°C required 5 min. Baseline $PtcO_2$ and $PtcCO_2$ were recorded. The OCTs were performed (FiO_2 was increased to 1.0 for 10 min), and the new $PtcO_2$ value was recorded every 1 min. The values for PaO_2 were examined on inspired of 1.0 FiO_2. PI and pulse oxygen saturation percentage (SpO_2) were measured in the index finger by using the IntelliVue MP70 monitor (Philips Medical Systems, Boblingen, Germany). The MP70 system calculates the PI as the ratio between the pulsatile component and the nonpulsatile component of the light reaching the light-sensitive cell of the pulse oximetry probe. The ambient temperature of the room was kept constant at approximately 23 to 25°C (climate controlled) during all phases of testing.

Study definitions
The $PtcO_2$ index is baseline $PtcO_2$/baseline PaO_2; 10min-OCT is ($PtcO_2$ after 10 minutes on inspired 1.0 oxygen) - (baseline $PtcO_2$); the OCI is (10min-OCT)/ ((PaO_2 on inspired 1.0 oxygen) - (baseline PaO_2)); survival is leaving the ICU alive for that admission.

Statistical analysis
A descriptive analysis was performed. All data were expressed as mean ± standard deviation, unless otherwise specified. A Mann-Whitney test was used to compare groups on continuous variables, and chi-square and Fisher's exact tests were used to compare categorical variables. Comparisons of two continuous variables were performed using a linear regression. Discrimination of values was assessed with the receiver operating characteristic analysis. All comparisons were two-tailed, and $P < 0.05$ was required to exclude the null hypothesis. The areas under the ROC curves were compared using a Hanley-McNeil test [17]. The statistical analysis was performed by using the software package SPSS version 13.0 (SPSS Inc. Chicago, IL, USA), and MedCalc 11.4.3.0 software (MedCalc, Mariakerke, Belgium).

Results
From July 2009 to May 2012, a total of 66 patients were enrolled. Fifty-five septic shock patients were screened for the study, and nine septic shock patients were not included in the analysis because of the failure of the correction of $ScvO_2$ ($ScvO_2$ <60%). Twenty-six of the 46 septic shock patients were also engaged in a previous reported study [18]. The median time between the start of the PiCCO catheter insertion and admission to the ICU was 16 h in the study group. The ICU mortality in the 46 septic shock patients was 43% (20/46). In this population, there were no differences in the using of norepinephrine (NE), the APACHE and SOFA score and white blood cell (WBC) count between the survivors and the nonsurvivors. The characteristics of the primary infection sites were as follows: 24/46 (52%) cases of lung; 10/46 (22%) cases of abdomen; 1/46 (2%) cases of urinary tract; 2/46 (4%) cases of soft tissue; 1/46 (2%) cases of bloodstream; 8/46 (17%) cases of an unknown source. Characteristics of the septic shock patients are shown in Table 1. The control group included 20 hemodynamically stable patients without sepsis admitted for postoperative monitoring. The characteristics of surgery sites were as follows: 16/20 (80%) cases of abdomen, 4/20 (20%) cases of other sites. None of these patients was treated with pressor agents. Demographics and clinical characteristics of the study groups and the control groups are shown in Table 2; the mean arterial pressure (MAP) had been corrected in all the septic shock patients at the measurement stage.

Global, metabolic, and peripheral perfusion variables in different groups
There were no differences in SpO_2, $PtcCO_2$, and arterial lactate level between the control patients and the septic patients (Table 2). The control group had a higher baseline PaO_2, baseline $PtcO_2$, PaO_2 (on FiO_2 1.0), MAP, 10 min-OCT and PI than the septic group (Table 3). There was no difference in $PtcO_2$ index and OCI between the two groups.

Table 1 Characteristics of the septic patients (*n* = 46).

Variables	Survivor *n* = 26	Nonsurvivor *n* = 20	*P* value
Age (years)	58 ± 16	67 ± 16	0.080
Sex (female/male)	8:18	8:12	0.515
APACHE II score	18 ± 6	20 ± 6	0.069
SOFA score	9 ± 2	10 ± 2	0.056
Ramsay score	5 ± 0.8	5.5 ± 0.7	0.583
NE	0.59 ± 0.67	0.74 ± 0.62	0.235
WBC	12.7 ± 7.8	9.1 ± 5.9	0.126

[a]*P* <0.05 for survivor group vs. nonsurvivor group. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score; NE, norepinephrine (μg/kg/min); WBC, white blood cell count (X 10^9/L).

Table 2 Comparison of the septic group and the control group.

Variables	Control group n = 20	Septic group n = 46	P value
Age (years)	59 ± 10	62 ± 16	0.442
Sex (female/male)	9:11	16:30	0.432
APACHE II score	12 ± 4	19 ± 6	0.000[a]
SOFA score	2 ± 2	9 ± 2	0.000[a]
Ramsay score	5.1 ± 0.3	5 ± 1	0.008 [a]
MAP	93 ± 9	87 ± 12	0.024 [a]
SpO_2 (%)	100 ± 1	99 ± 2	0.193
Lactate (mmol/L)	3.2 ± 2.2	3.8 ± 3.9	0.950

[a]$P < 0.05$ for control group vs. septic group. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score; MAP, mean arterial pressure (mmHg); SpO_2, arterial oxygen saturation measured by pulse oximetry.

Table 4 Global and metabolic variables in the septic patients according to their survival

Variables	Total n = 46	Survivor n = 26	Nonsurvivor n = 20	P value
Blood temp (℃)	38 ± 1.1	38 ± 0.9	38.1 ± 1.4	0.564
PEEP	7 ± 3	7 ± 3	7 ± 2	0.910
Basic FiO_2	49 ± 9	47 ± 8	51 ± 9	0.078
MAP	87 ± 12	88 ± 12	85 ± 12	0.513
CVP	11 ± 3	12 ± 3	11 ± 4	0.319
CI	3.7 ± 1	3.9 ± 0.8	3.6 ± 1.3	0.111
SVRI	1705 ± 559	1676 ± 474	1742 ± 664	0.982
GEDVI	805 ± 162	744 ± 125	844 ± 197	0.341
$ScvO_2$ (%)	71 ± 8	72 ± 8	69 ± 8	0.156
Pv-a CO_2	6 ± 3	5 ± 3	7 ± 4	0.144
Lactate (mmol/L)	3.8 ± 3.9	2.3 ± 2	5.6 ± 4.9	0.000[a]

[a]$P < 0.05$ for survivor vs. nonsurvivor. PEEP, positive end-expiratory pressure (cmH_2O); FiO_2, fraction of inspired oxygen concentration; MAP, mean arterial pressure (mmHg); CVP, central venous pressure (mmHg); CI, cardiac index (L/min/m^2); SVRI, systemic vascular resistance index (dyne/sec/cm^5); GEDVI, global end-diastolic volume index (ml/m^2); $ScvO_2$, central venous oxygen saturation; Pv-a CO_2 ,difference between central venous and arterial PCO_2 (mmHg).

Global, metabolic and peripheral perfusion variables after resuscitation of the septic patients according to survival are shown in Table 3 and Table 4. In this study group, the macro hemodynamic-related parameters, baseline $PtcO_2$, baseline $PtcCO_2$, PaO_2 (on FiO_2 1.0), $PtcO_2$ index and $ScvO_2$ showed no differences between survivors and nonsurvivors. Statistically significant variables between the survivors and the nonsurvivors included arterial lactate level (2.3 ± 2 vs. 5.6 ± 4.9mmol/l, $P < 0.0001$), PI (1.95 ± 1.5 vs. 0.6 ± 0.86, $P < 0.0001$), 10 min-OCT (186 ± 75 vs. 93 ± 103 mmHg, $P = 0.001$) and OCI (0.79 ± 0.28 vs. 0.49 ± 0.36, $P = 0.01$).

There were 26 patients in septic group with $ScvO_2$ ≥70% after resuscitation, and the mortality was 9/26 (35%) in this subgroup. Statistically significant variables between the survivors and the nonsurvivors included arterial lactate level (2.3 ± 1.5 vs. 5.0 ± 5.2mmol/l, $P = 0.034$), PI (2.2 ± 1.7 vs. 0.87 ± 1.1, $P = 0.013$).

In the whole group, the PI was not correlated with the baseline $PtcCO_2$, $PtcO_2$ index and $ScvO_2$. In contrast, the PI was correlated with baseline $PtcO_2$ (r = 0.298,

$P = 0.015$), 10 min-OCT (r = 0.573, $P < 0.0001$), OCI (r = 0.395, $P = 0.001$), lactate (r = -0.309, $P = 0.012$). There is a significantly positive relationship between $PaCO_2$ and $PtcCO_2$ (r = 0.874, $P < 0.0001$).

Metabolic and peripheral perfusion variables as predictors of mortality

The cutoff value and areas under the receiver operating characteristic (ROC) curves for the related variables used for predicting ICU mortality are shown in Table 5. The cutoff of the PI value was ≤0.2 for predicting ICU mortality, resulting in a sensitivity of 65% and a specificity of 92.3%. The PI, 10min-OCT and OCI predicted the ICU mortality with an accuracy that was similar to arterial lactate level, and the PI was significantly better than the difference between central venous and arterial

Table 3 Peripheral perfusion related-variables in the different groups

Variables	Controls n = 20	All sepsis n = 46	Survivor sepsis n = 26	Nonsurvivor sepsis n = 20
PI	2.58 ± 0.68[a,c]	1.37 ± 1.43	1.95 ± 1.5[c]	0.6 ± 0.86
$PtcO_2$	124 ± 45[a,b,c]	73 ± 24	79 ± 21	66 ± 26
PaO_2 (on basic FiO_2)	179 ± 70[a,b,c]	119 ± 45	125 ± 51	111 ± 37
$PtcO_2$ index	0.71 ± 0.29	0.67 ± 0.22	0.69 ± 0.21	0.64 ± 0.24
$PtcCO_2$	36 ± 7	36 ± 9	38 ± 7	34 ± 12
$PaCO_2$	35 ± 6	36 ± 8	37 ± 6	35 ± 10
10min-OCT	247 ± 65[a,b,c]	145 ± 99	186 ± 75[c]	93 ± 103
PaO_2 (on 1.0 FiO_2)	489 ± 106[a,b,c]	343 ± 122	371 ± 116	307 ± 123
OCI	0.83 ± 0.2[c]	0.66 ± 0.35	0.79 ± 0.28[c]	0.49 ± 0.36

[a]$P < 0.05$ for controls vs. all sepsis; [b]$P < 0.05$ for controls vs. survivor sepsis; [c]$P < 0.05$ for controls vs. nonsurvivor sepsis. PI, peripheral perfusion index measured by pulse oximetry; FiO_2, fraction of inspired oxygen concentration; $PtcO_2$, transcutaneous partial pressure of oxygen (mmHg); PaO_2, arterial pressure of oxygen (mmHg); $PtcCO_2$, transcutaneous partial pressure of carbon dioxide (mmHg); $PaCO_2$, arterial pressure of carbon dioxide (mmHg); 10 min-OCT, 10 minute oxygen challenge test value (mmHg); OCI, oxygen challenge index.

Table 5 Comparison of the areas under the ROC curves for predicting ICU mortality in the septic patients.

	ROC area	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
Lactate	0.80	0.658-0.905	4.2	45	84.62
Pv-a CO_2	0.62[a]	0.469-0.762	7	40	88.46
PI	0.84	0.698-0.929	0.2	65	92.3
$ScvO_2$	0.62[a]	0.468-0.762	0.67	55	73.08
$PtcO_2$	0.66[b]	0.508-0.795	61	55	80.8
$PtcO_2$ index	0.54[c]	0.387-0.688	0.51	30	76.92
10min-OCT	0.81	0.662-0.907	66	65	96.2
OCI	0.74	0.588-0.857	0.55	60	88.5

[a]$P < 0.05$ for comparison of Pv-a CO_2, $ScvO_2$vs, PI; [b]$P < 0.05$ for comparison of $PtcO_2$ vs. PI, lactate; [c]$P < 0.05$ for comparison of $PtcO_2$ index vs. 10 min-OCT, OCI, PI and lactate. ROC, receiver operating characteristic; CI confidence interval; Pv-a CO_2 , difference between central venous and arterial PCO_2 (mmHg); PI, peripheral perfusion index measured by pulse oximetry; $ScvO_2$, central venous oxygen saturation; 10 min-OCT, 10 minute oxygen challenge test value (mmHg); OCI, oxygen challenge index.

PCO_2 (P(v-a)CO_2) and $ScvO_2$. In these $PtcO_2$-related parameters, the 10min-OCT and OCI were significant predictors of lethal outcome, but not baseline $PtcO_2$ and $PtcO_2$ index. For predicting ICU mortality, a threshold of 10min-OCT at 66 mmHg was associated with a sensitivity of 65% and a specificity of 96.2%, and a cutoff of OCI at 0.55 was associated with a sensitivity of 60% and a specificity of 88.5%. The ROC curves of baseline $PtcO_2$, $PtcO_2$ index, 10min-OCT and OCI are shown in Figure 1, and the ROC curves of PI, lactate, $ScvO_2$ and Pv-aCO_2 are shown in Figure 2.

Discussion

The main finding of our study was that lower peripheral perfusion and higher metabolic variables are associated with increased ICU mortality in septic patients after resuscitation. The PI, 10min-OCT and OCI predicted the ICU mortality with an accuracy that was similar to arterial lactate level. Thus, peripheral perfusion monitoring appears as a simple but powerful tool to assess global resuscitation status and outcome.

As we know, this is the first study to explore the relationship between PI and ICU mortality in septic patients after resuscitation. We found that the cutoff of the PI value was ≤0.2 for predicting ICU mortality, resulting in a sensitivity of 65% and a specificity of 92.3%. The PI, which was defined as the ratio of the pulsatile to non-pulsatile component of the pulse oximetry plethysmograph, is used as a simple and accurate indication of changes in digital blood flow. It has been suggested as a reliable and early indicator of regional block success, and known to increase due to the effect of autonomic blockade during spinal anesthesia [4,19,20]. Some studies showed that PI could be used too as a predictor of early adverse respiratory neonatal outcome after elective cesarean delivery [21].

The change of the finger PI resulted from the blood volume pulsations, the dispensability of the vascular wall and the intravascular pulse pressure, which can be complicated in critically ill adult patients [22,23]. Therefore, many factors can impact the PI value (temperature, level of consciousness, pain and other stressful stimuli, endogenous catecholamines, vasopressors). All the patients needed mechanical ventilation and sedatives, and there were no difference in temperature, Ramsay score, and the dose of NE between survivors and nonsurvivors in the study group. Therefore, the PI was relatively comparable in this study. Our study found that PI was significantly lower in the patients with septic shock than in the control group. One can argue that the using of NE may have an effect on PI in the septic patients. However, the nonsurvivors also had a significantly lower PI than survivors in the patients with septic shock. The correlation between hyperlactatemia and PI in our patients could be related to the presence of tissue hypoperfusion. We demonstrated that a value of PI below 0.2 was associated with an increased risk of ICU mortality. Recently, van Genderen and colleagues found that persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with organ failure and death, independent of systemic hemodynamics. They reported the PI value was 0.3 ± 0.28 in the nonsurvivor at 24 h after rewarming, which is similar to our results in the nonsurvivor after resuscitation [24].

The impact of possible therapy aimed at increasing the PI was not explored in current study. There is a need of further investigations to test such hypothesis. In our study, we investigated the relationship between PI and $PtcO_2$-related parameters in critically ill patients. The PI was significantly correlated with baseline $PtcO_2$, 10min-OCT and OCI. We concluded that all these parameters are dependent on peripheral blood flow, and reflect peripheral tissue perfusion.

$PtcO_2$/$PtcCO_2$ is the direct measurement of the local partial pressure of oxygen/carbon dioxide, achieved by placing a Clark polarographic oxygen/carbon dioxide electrode on the skin surface. When the circulation is normal, the $PtcO_2$ reflects PaO_2, but in low flow state, it always
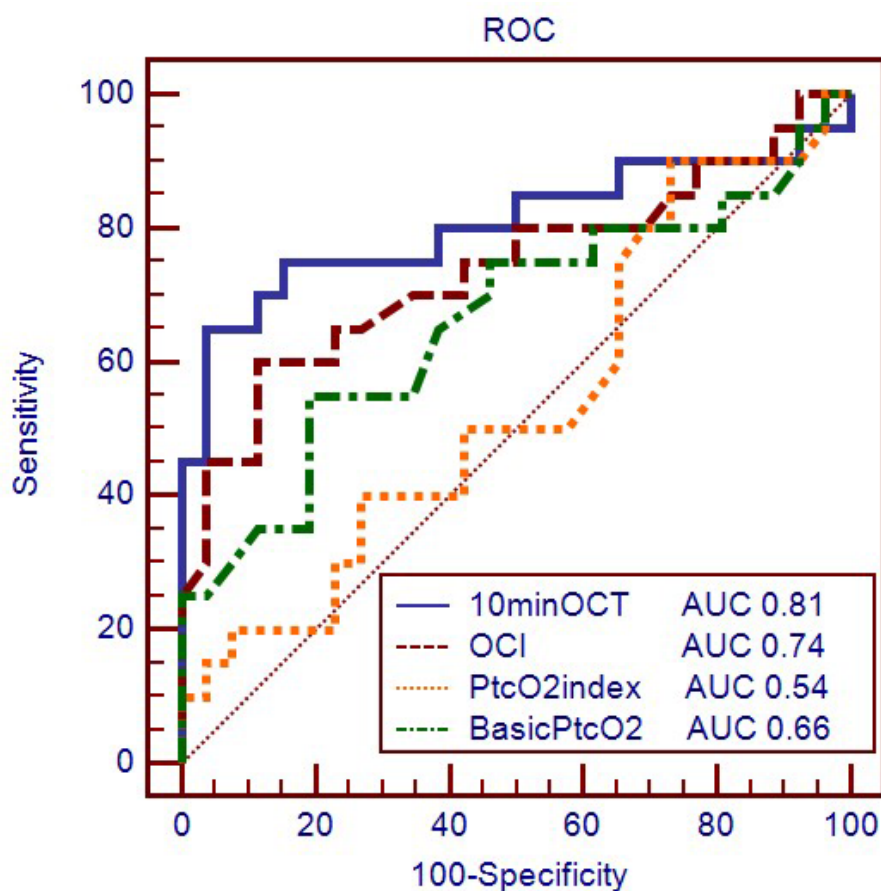
Figure 1 ROC curves comparing the ability of 10 min-OCT, OCI, baseline PtcO$_2$ and PtcO$_2$ index to discriminate ICU mortality. 10 min-OCT, 10 minute oxygen challenge test value (mmHg); OCI, oxygen challenge index; PtcO$_2$, transcutaneous partial pressure of oxygen (mmHg); PtcO$_2$ index, transcutaneous partial pressure of oxygen index; AUC, area under the receiver operating characteristic (ROC) curve.

underestimates PaO$_2$. Shoemaker *et al.* attempted the translation of PtcO$_2$ values to cardiac hemodynamics, when they explored the dependence of PtcO$_2$ on PaO$_2$ using a PtcO$_2$ index (PtcO$_2$/PaO$_2$) to assess the severity of low flow shock [6]. A PtcO$_2$ index below 0.7 has been associated with hemodynamic failure in adult patients [25,26]. The PtcO$_2$ index has been used to estimate the adequacy of cardiac output and peripheral blood flow. The OCT is another method to determine the situation of circulation using the noninvasive PtcO$_2$ technique. In non-shock states, PtcO$_2$ correlates with PaO$_2$ to strongly increase response to the FiO$_2$. When peripheral perfusion severely decreases, the PtcO$_2$ values will deviate from their relationship with the arterial tensions and lack of response to a FiO$_2$ of 1.0. In our previous study, we showed that an OCT could improve the diagnostic accuracy of the PtcO$_2$ in estimating the cardiac index (CI) value, and a cutoff 10 min-OCT value of 53 mmHg has a good positive predictive value and positive likelihood ratio for predicting low CI value [18].

We mainly explored the correlation between the outcome and the OCT in this study. We found that the control group had a higher baseline PaO$_2$, PaO$_2$ (on FiO$_2$ 1.0), 10 min-OCT than the septic shock group. Therefore, we speculated the control group had a better lung function. However, there were no difference of baseline PaO$_2$ and PaO$_2$ (on FiO$_2$ 1.0) between the survivors and nonsurvivors. Hence, PtcO$_2$ showing a poor response of FiO$_2$ 1.0 in the nonsurvivor was not due to the lung function, but due to a poor peripheral tissue flow. Moreover, the 10 min-OCT and OCI as a predictor of lethal outcome were more sensitive and specific than baseline PtcO$_2$ and PtcO$_2$ index in the patients with septic shock. For predicting ICU mortality, a threshold of 10 min-OCT at 66 mmHg was associated with a sensitivity of 65% and a specificity of 96.2%, and a cutoff of the OCI at 0.55 was associated with a sensitivity of 60% and a specificity of 88.5%. In addition, there is another hypothesis for the OCT to determine tissue perfusion. If there is a cellular oxygen deficit, then
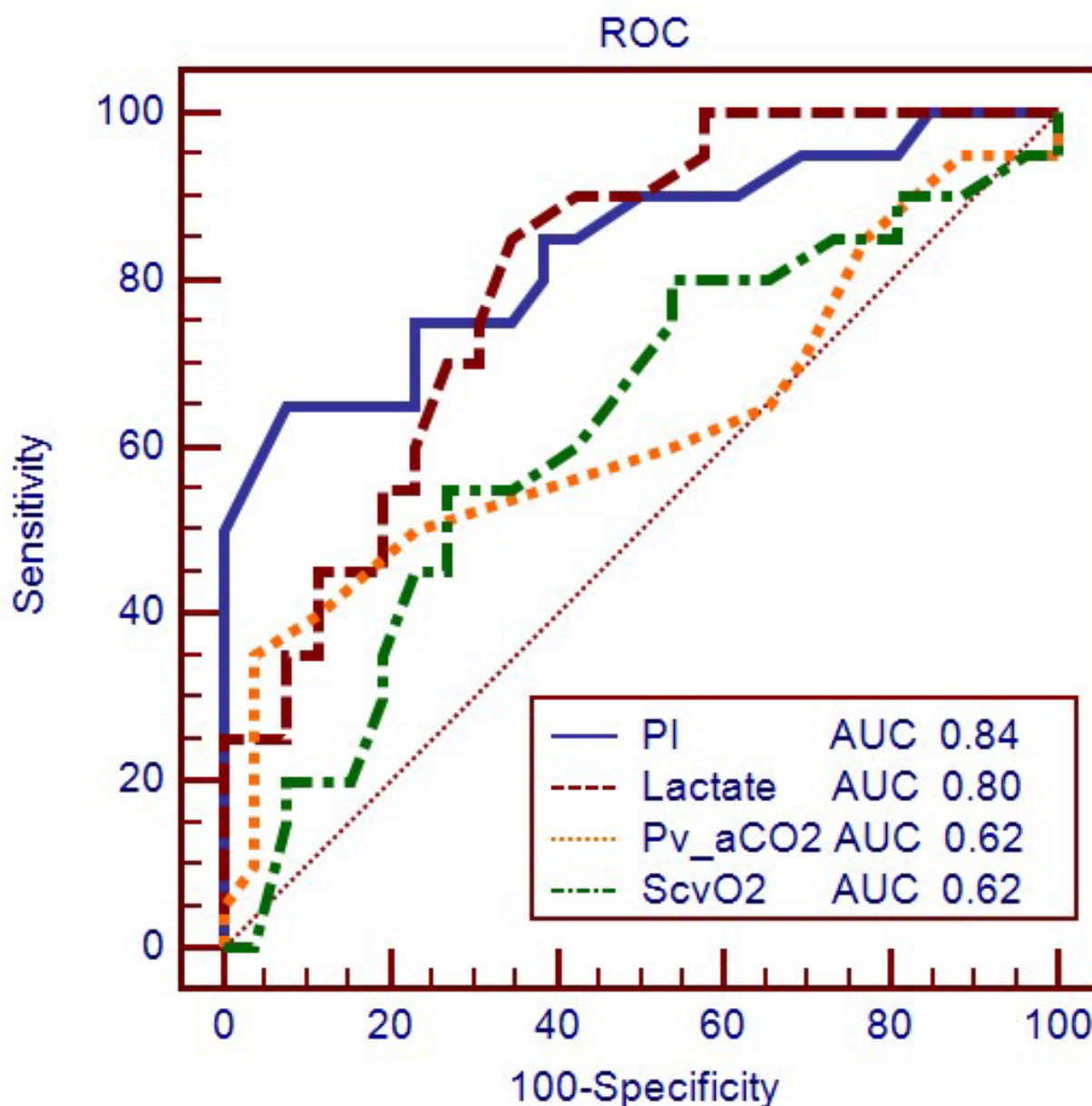
Figure 2 ROC curves comparing the ability of PI, lactate, Pv-a CO$_2$ and ScvO$_2$ to discriminate ICU mortality. PI, peripheral perfusion index measured by pulse oximetry; Pv-aCO$_2$, difference between central venous and arterial PCO$_2$ (mmHg); ScvO$_2$, central venous oxygen saturation; AUC, area under the receiver operating characteristic (ROC) curve.

the additional dissolved oxygen after the oxygen challenge would be utilized, resulting in a minimum rise in PtcO$_2$. The OCT as a method to assess tissue perfusion mainly described in adult patients by using intramuscular PO$_2$, as in the previous study [27,28]. Yu *et al.* reported an incremental change of less than 21 mmHg in PtcO$_2$ in response to a 1.0 FiO$_2$ has been associated with mortality reports during 5min-OCT [9]. Our previous study found that there were substantial differences

between the oxygen challenge at 5 minutes and 10 minutes, with the PtcO$_2$ value at 10 minutes always being higher than at 5 minutes [18]. The ideal response time of PtcO$_2$ on OCT is not well established in critically ill adult patients. Shah *et al.* suggested that the ideal time for the OCT is at least 10 minutes in the evaluation of patients with hypoxic wounds [29]. Further studies are necessary to identify which is the ideal time interval for the OCT. In addition, a multitude of factors can impact

$PtcO_2$, and the regulation of skin microcirculation during increasing normobaric oxygen is complex [30]. Therefore, the application of an OCT to assess cellular oxygen deficit still needs further investigation.

There are several advantages of the PI and OCT in comparison with the current global endpoints of resuscitation: (1) the peripheral perfusion indicators may provide a specific endpoint of resuscitation rather than the average survival values of $ScvO_2$; (2) the peripheral perfusion monitors may provide information on internal organ perfusion with the assumption that the peripheral tissue is the last to perfuse during shock resuscitation; (3) the techniques are noninvasive, and the equipment is readily available and inexpensive. Its importance will be affirmed if peripheral perfusion monitoring during shock resuscitation becomes routine, and if the critical values defined in this paper are validated by further study.

In recent years, tissue oxygen saturation (StO_2) has been applied to estimate regional perfusion by near-infrared spectroscopy (NIRS), and the changes of StO_2 during a vascular occlusion test (VOT) have been used as a marker of microvascular reactivity [31-35]. Lima showed that PI correlates with StO_2, and that peripheral circulation influences StO_2 resting values and the StO_2 reoxygenation rate [36,37]. In addition, the changes of PI and $PtcO_2$ could be used to evaluate microvascular reactive hyperemia as during a VOT [38,39]. Therefore, we infer that all three (StO_2, PI, and $PtcO_2$) indicators are used to assess regional perfusion and reactive hyperemia with close values.

Limitations

Several limitations should be acknowledged. First, the study period may be considered not long enough to evaluate other relevant clinical outcomes and the selected time points are relatively arbitrary. A small number of subjects at a single time point is an important issue and our findings should be confirmed in a larger multicenter study before being translated into regular clinical practice. Second, one can argue that the assessment of these objective parameters requires stability of a number of factors that might affect tissue perfusion and oxygenation. To reduce those uncertainty factors, we strictly stabilized the related parameters (ambient temperature, level of consciousness, hemodynamic status). Third was our failure to directly determine skin microcirculation, local blood flow and subjective peripheral tissue perfusion indicators in this study. Fourth, one can argue that this chest skin circulation is not representative of other site circulations. Recently, some studies have been done to explore the value of evaluating peripheral tissue perfusion of other sites in septic shock patients, such as thenar, deltoid, masseter, and ear sites [40,41]. Peripheral tissue

perfusion monitoring from different parts may have different values. According to previously published studies on critically ill patients [8-10], we chose the chest site as a relatively standard location for $PtcO_2$ monitoring. Moreover, the PI could be considered as a method to assess the finger tip circulation in this study. We found that the two site-related parameters were both predictive for outcome, and there was a significant relationship between chest and finger tip site-related parameters. Further studies should be done to test the clinical worth of $PtcO_2$ in other sites in critically ill patients. Fifth, MAP had been corrected in all the septic shock patients at the measurement stage, but not for $ScvO_2$. It is difficult for an observational study to guarantee the $ScvO_2 \geq 70\%$ in clinical practice after resuscitation. In our study, 57% of the septic patients' $ScvO_2$ were equal or greater than 70% after resuscitation. We excluded nine septic patients in the analysis with low $ScvO_2$ (<60%) after resuscitation, and these patients had high lactate and poor peripheral perfusion. We acknowledge that the using of $ScvO_2$ <60% to reveal the imbalance between oxygen delivery and oxygen consumption is relatively arbitrary. According to early goal-directed therapy, $ScvO_2 \geq 70\%$ is used to reflect the balance between oxygen delivery and oxygen consumption. Therefore, we analyzed a subgroup of septic shock patients with $ScvO_2 \geq 70\%$, and we found these peripheral indicators still work. This revealed that peripheral perfusion parameters may provide a specific endpoint of resuscitation after $ScvO_2 \geq 70\%$.

Conclusions

The PI and OCT are predictive of mortality for septic patients after resuscitation, comparable to arterial blood lactate. Further investigations are required to determine whether the correction of an impaired peripheral tissue value may improve the outcome of these patients.

Key messages

• The PI and OCT are predictive of mortality for septic patients after resuscitation, comparable to arterial blood lactate.
• For predicting ICU mortality, the cutoff of the PI value was ≤0.2 resulting in a sensitivity of 65% and a specificity of 92.3%, and a threshold of 10 min-OCT at 66 mmHg was associated with a sensitivity of 65% and a specificity of 96.2%.
• The peripheral perfusion indicators may provide a specific endpoint of resuscitation.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; CI: cardiac index; CVP: central venous pressure; FiO_2: fraction of inspired oxygen concentration; GEDVI: global-heart end-diastolic volume index; ICU: intensive care unit; MAP: mean arterial pressure; NE: norepinephrine; NIRS: near-infrared

spectroscopy; OCI: oxygen challenge index; OCT: oxygen challenge test; $PaCO_2$: arterial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; PEEP: positive end-expiratory pressure; PI: peripheral perfusion index; $PtcCO_2$: transcutaneous partial pressure of carbon dioxide; $PtcO_2$: transcutaneous partial pressure of oxygen; Pv-aCO_2: difference between central venous and arterial PCO_2; ROC: receiver operating characteristic; $ScvO_2$: central venous oxygen saturation; SpO_2: pulse oxygen saturation percentage; SOFA: Sequential Organ Failure Assessment; StO_2: tissue oxygen saturation; SVRI: systemic vascular resistance index; VOT: vascular occlusion test; WBC: white blood cell count; 10min-OCT: 10 minute oxygen challenge test value.

Authors' contributions
DL conceived and designed the study, interpreted data and helped draft the manuscript. HWH participated in the study conception and design, recruited patients, collected data, performed the statistical analysis, interpreted the data and drafted the manuscript. YL and XTW participated in patient recruitment, data collection, technical support and contributed to the critical review of the manuscript. All of the authors read and approved the final manuscript.

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CRITICAL CARE

LETTER

Clinical monitoring of peripheral perfusion: perspective on ProCess

John PR Moore[1,2*] and John F Fraser[2]

We read with interest the commentary by Lima and Bakker [1]. The authors note that there are two phases in the shock state that differ in the degree of uncoupling of macrocirculatory and microcirculatory function. They suggest that a shift to flow-based resuscitation may offer benefit for the critically ill by prioritising microcirculatory perfusion. This commentary is of particular interest when viewed in the context of ProCess [2], the recent negative early goal-directed therapy study.

The absence of a treatment effect in this trial from the therapies one would normally expect to resuscitate the microcirculation warrants consideration. Resuscitation attempts that reverse microcirculatory dysfunction early in the shock state appear to offer clinical benefit [3]. Conversely, in the phase of established shock the primary function of the microcirculation may be limiting damage by preventing spread of infection [4] and harmful excess oxygen delivery in parallel with mitochondrial shutdown and reduced oxygen consumption [5]. Microcirculatory dysfunction in established organ failure may therefore in fact be adaptive. Re-recruitment as a result of zealous resuscitation could hence be predicted to result in detrimental tissue effects. The ProCess trial utilised aggressive resuscitation strategies, without an endpoint that reflected microcirculatory perfusion in the context of ongoing metabolic need. This could be predicted to result in successful resuscitation of some patients and harm to others, dependent on their individual phase of illness.

We offer caution that despite the negative results from the ProCess trial, the concept of early goal-directed therapy should not yet be discounted, but should be revisited once valid clinical measures of microcirculatory and metabolic function are available.

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Competing interests
The authors declare that they have no competing interests.

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