Role of Combining Peripheral with Sublingual Perfusion on Evaluating Microcirculation and Predicting Prognosis in Patients with Septic Shock

Pan Pan, Da-Wei Liu, Long-Xiang Su, Hualu-He, Xiao-Ting Wang, Chao Yu
Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

Abstract

Background: Measurement of general microcirculation remains difficult in septic shock patients. The peripheral perfusion index (PI) and sublingual microcirculation monitoring are thought to be possible methods. This study was performed to determine whether assessing microcirculation by PI and a new parameter, proportion of perfusion vessel change rate (ΔPPV) from sublingual microcirculation monitoring, can be associated with patients’ outcome.

Methods: A prospective observational study was carried out, including 74 patients with septic shock in a mixed intensive care unit. Systemic hemodynamic variables were obtained at T0 and 6 h after (T6). PI and sublingual microcirculation indicators were obtained using a bedside monitor and a sidestream dark-field device, respectively. The t-test, analysis of variance, Mann-Whitney U-test, Kruskal-Wallis test, receiver operating characteristic curve analysis with the Hanley-McNeil test, survival curves using the Kaplan-Meier method, and the log-rank (Mantel-Cox) test were used to statistical analysis.

Results: Systemic hemodynamics and microcirculation data were obtained and analyzed. Patients were divided into two groups based on whether the first 6 h lactate clearance (LC) was ≥20%; PI and ΔPPV were lower at T6 in the LC <20% group compared with LC ≥20% (PI: 1.52 [0.89, 1.98] vs. 0.79 [0.44, 1.81], Z = −2.514, P = 0.012; ΔPPV: 5.9 ± 15.2 vs. 17.9 ± 20.0, t = −2.914, P = 0.005). The cutoff values of PI and ΔPPV were 1.41% and 12.1%, respectively. The cutoff value of the combined indicators was 1.379 according to logistic regression. Area under the curve demonstrated 0.709 (P < 0.05), and the sensitivity and specificity of using combined indicators were 0.622 and 0.757, respectively. Based on the PI and ΔPPV cutoff, all the participants were divided into the following groups: (1) high PI and high ΔPPV group, (2) high PI and low ΔPPV group, (3) low PI and high ΔPPV group, and (4) low PI and low ΔPPV group. The highest Sequential Organ Failure Assessment score (14.5 ± 2.9) was in the low PI and low ΔPPV group (F = 13.7, P < 0.001). Post hoc tests showed significant differences in 28-day survival rates among these four groups (log rank [Mantel-Cox], 20.931; P < 0.05).

Conclusion: PI and ΔPPV in septic shock patients are related to 6 h LC, and combining these two parameters to assess microcirculation can predict organ dysfunction and 28-day mortality in patients with septic shock.

Key words: Microcirculation; Sepsis; Shock

INTRODUCTION

Septic shock, which is a life-threatening circulatory failure with inadequate tissue perfusion, is a clinical emergency that occurs in millions of patients each year.[1] It is widely known that the crucial procedure is the exhaustion of the circulatory system to provide adequate oxygen delivery (DO₂) to meet oxygen demand in shock. Consequently, anaerobic metabolism ensues.[2] Despite the progress that is made over the past decades in the treatment of septic shock, mortality remains high. Sprock et al.[3] found microcirculatory perfusion to be disturbed in septic shock and emphasized that sepsis is a disease of microcirculation according to...
their research. Microcirculation plays an essential role in nutrition and gas exchange; it can be adjusted by constantly controlling vascular tone.[4] According to the latest sepsis guideline, we can use quick Sequential Organ Failure Assessment (SOFA) to judge patients’ condition rapidly and make resuscitation with a large amount of fluid.[5] However, clinicians have difficulty in assessing patients’ tissue perfusion condition when they still have severe illness with normal macrocirculation. Microcirculation exhibits a feature that is quite dissociated from systemic hemodynamics. It is hard to simultaneously assess these different aspects of microcirculation as indicators such as blood pressure, heart rate, and central venous oxygen saturation cannot reflect microcirculation exactly.

The goal of microcirculatory monitoring is to use a noninvasive, accurate, and continuous method that can easily evaluate tissue perfusion under clinical conditions. Peripheral perfusion acting as a fundamental part of microcirculation clinical evaluation is becoming a hot issue.[6] As we know, the peripheral vascular bed is the first place where blood flow is sacrificed and the place where it is finally perfused. The peripheral perfusion index (PPI), an indicator reflecting peripheral perfusion changes, is derived from the photonic electric plethysmographic signal of the pulse oximeter.[7] This is a noninvasive technique that can use two different wavelengths of light (red and infrared) that are transmitted through the distal phalanx of the finger, resulting in the exhibition of a pulsatile photoplethysmographic waveform.[8] In addition, the ratio of pulsatile and nonpulsatile components shown on the pulse oximetry signal has been related to peripheral perfusion.[9] Another technique suggested to be an evaluation of microvascular perfusion is sidestream dark field (SDF). It is a noninvasive video-microscopic imaging technique that uses reflected polarized green light to produce real-time images of the microcirculation at bedside.[10] As it can only be used on organs that are covered by a thin epithelial layer, clinicians handle the probe in the sublingual mucosa area, which has been most investigated. From this tool, capillaries and venules of tiny size can be visualized.[11] Red blood cells are identified as flowing black bodies, and microcirculation perfusion can be characterized in individual vessels. Manifestations of acrocyanosis, mottled skin, and increased central to toe temperature gradient, decreased PI, and the sublingual microcirculation all partly reflect impaired microcirculation. However, we are always lack of quantitative evaluation criterions, and these symbols of impaired perfusion signs lack specificity and sensitivity for disclosing more central microcirculatory alterations. The sublingual mucosa originates from the intestinal mucosa, and it is the most representative indicator of the whole microcirculation. Studies show that persistently deteriorate sublingual microcirculation is an independent risk factor for the death of patients in septic shock.[12] The PI that lasts throughout the shock process is also a good indicator of the patient’s peripheral microcirculatory status, and it is closely related to the organ dysfunction in septic shock patients.[13] Different microcirculation monitoring methods are complementary to each other based on their mechanism. Therefore, in this study, we addressed if combining the two most commonly used methods (PI and SDF techniques) can predict organs dysfunction and evaluate microcirculation changes in septic shock.

**Methods**

**Ethics approval and consent to participate**

The Peking Union Medical College Hospital Ethics Committee approved the study (No. S-351), and all patients were involved in the study based on the voluntary principle and had signed informed consent form. We would maximize the protection of the interests of patients and would not cause harm to any patients.

**Patient selection**

We performed a prospective study among patients admitted to the department of Critical Care Medicine of Peking Union Medical College Hospital from February 2017 to June 2017. All consecutive patients fulfilled the diagnostic criteria of Sepsis 3.0 and were elected by the professional clinicians to use a central venous catheter. Patients who were younger than 18 years old, pregnant women, or patients who had been admitted to the Intensive Care Unit (ICU) for <24 h were excluded from the study. For the assessment of microcirculation, we did not include patients who were under noninvasive mechanical ventilation or patients who were agitated or not collaborative when we first attempted to visualize sublingual microcirculation. According to the 2016 updated guideline, we gave all the included patients the standard 6-h bundles of treatments.[14] We have to complete the following procedures within 3 h: measure lactate level, obtain blood cultures before administration of antibiotics, administer broad-spectrum antibiotics, and administer 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L. Complete the following procedures within 6 h: patients with hypotension after initial fluid resuscitation or lactic acid ≥4 mmol/L need to use vasoactive drugs to make mean arterial pressure (MAP) >65 mmHg (1 mmHg = 0.133 kPa) and again assess patient volume status, tissue perfusion, and lactic acid conditions.

**Basic measurements**

Baseline data were collected for selected patients, such as age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, SOFA score, time of mechanical ventilation, continuous renal replacement therapy (CRRT), and 28-day mortality rate.

**Hemodynamic measurements**

Arterial blood gas and central venous blood gas were obtained at T0 and T6 simultaneously (bedside chest X-ray was used to assess the central venous catheter position). We tested the blood gas using a bedside blood gas machine (GEM Premier 3000, Model 5700; Lexington, MA, USA, or ABL90, Radiometer). Hemodynamic parameters such as central venous pressure (CVP), MAP, venous-to-arterial carbon dioxide differences (Pv-aCO2), and superior vena
cava oxygen saturation (SvO₂), lactate, and 6-h lactate clearance (LC) at the time of T0 and T6 were observed.

**Microcirculatory measurements**

PPI was measured at T0 and T6 using a Philips Medical Systems Viridia/56S monitor. We used an SDF imaging device (Microscan, Microvision Medical, Amsterdam, The Netherlands) to evaluate microcirculation at T0 and T6. After gentle removal of secretions with gauze, the SDF probe was lightly applied to one side of the tongue, covering an area of approximately 2.5–4.0 cm from the tip of the tongue. At each measurement time, we recorded five fragments of video from different adjacent mucosae for at least 10 s in each area. These fragments of video were saved with a random number and later analyzed by two skilled investigators blinded to their origin. These videos were analyzed by specific software (AVA 3.0 Microscan, Microvision Medical, Amsterdam, The Netherlands). Microvessels with high speed, continuous and sluggish flows were considered normal, and while stopped, intermittent flows were considered abnormal. In accordance with consistency for the assessment of microcirculation,[15] we calculated the proportion of small perfused vessels (identified 20 μm diameter) and the microvascular flow index (MFI).

**Outcome measures**

ΔPPV (Δ[PPV<sub>T6</sub> − PPV<sub>T0</sub>]) could be obtained according to the microcirculation technique, and its cutoff was based on LC ≥20% at T6. We divided the patients into four groups: PI >cutoff value and proportion of perfusion vessel change rate (ΔPPV) >cutoff value, PI >cutoff value and ΔPPV ≤cutoff value, PI ≤cutoff value and ΔPPV >cutoff value, and PI ≤cutoff value and ΔPPV ≤cutoff value; 28-day mortality was the final outcome.

**Statistical analysis**

The unreasonable values, such as abnormal outliers, were considered as missing values. Descriptive analysis was performed. Results for continuous variables with normal distributions were presented as mean ± standard deviations (SD). Results for continuous variables that were not normally distributed were presented as median (Q₁, Q₃). For the continuous variables, data were analyzed using the t-test, analysis of variance, Mann-Whitney U-test, or Kruskal-Wallis test depending on the data distribution and the number of variables. Discrimination of values was performed using receiver operating characteristic (ROC) analysis with the Hanley-McNeil test. Survival curves up to day 28 were estimated using the Kaplan-Meier method, and the log-rank (Mantel-Cox) test was used to estimate the differences among the predefined groups. All comparisons were two tailed, and a value of P<0.05 was required to exclude the null hypothesis. Statistical analyses were performed using the SPSS 13.0 software package (SPSS, Chicago, IL, USA).

**RESULTS**

**General characteristics**

From February 2017 to June 2017, a total of 74 patients were enrolled in the study according to the inclusion criteria, and all of them received mechanical ventilation. The flowchart is shown in Figure 1. General characteristics are presented in Table 1. Based on LC ≥20%, the patients were divided into the LC ≥20% (n = 37) or the LC <20% (n = 37) group. Parameters including age, gender, temperature, heart rate, respiratory rate, white blood cell count, APACHE II score, SOFA score, and CRRT had no significant difference between the two groups (P > 0.05).

**The hemodynamics and microcirculation perfusion targets between the different lactate clearance groups at Intensive Care Unit admission**

There were no statistical differences in the systemic hemodynamic parameters such as CVP, SvO₂, MAP, and flow index Pv-aCO₂ at T0 and T6 in both groups [Table 2]. There was no significant difference between PI and sublingual microcirculation parameters at T0 (1.3 ± 0.9 vs. 1.9 ± 0.7, t = −2.040, P = 0.173). After treatment, at the time of T6, the PI of the LC <20% group was significantly lower than the LC ≥20% (0.79 [0.44, 1.81] vs. 1.52 [0.89, 1.98], Z = −2.514, P = 0.012), which had statistically difference [Figure 2]. In the sublingual microcirculation indicators, we found no statistical differences among total vessel density (TVD), perfused vessel density (PVD), PPV, and MFI at T0 and T6.

![Figure 1: The flowchart of this study on septic shock patients.](image-url)
However, we obtained the ΔPPV at T0 and T6 (ΔPPV = [PPV T6 − PPV T0]/PPV T0). We found that the ΔPPV in the LC <20% group was lower than the LC ≥20% group (5.9 ± 15.2 vs. 17.9 ± 20.0) with statistical significance (t = 2.914 P = 0.03), as shown in Figure 2.

**Risk factors for lactate clearance and their relevant values**

The univariate logistic regression analysis was performed to select possible risk factors for LC ≥20% [Table 3]. The variables considered included PI and ΔPPV. PI and ΔPPV were entered into the regression equation (P < 0.05). The odds ratios of PI and ΔPPV were 0.649 (95% confidence interval CI: 0.42–0.99) and 0.959 (95% CI: 0.93–0.99), respectively. An ROC curve was drawn based on LC [Figure 3]. The area under the curve (AUC) demonstrated that PI and ΔPPV were 0.66 (95% CI: 0.516–0.769) and 0.66 (95% CI: 0.536–0.783), respectively. The cutoff value for PI and ΔPPV was 1.41% and 12.1%, respectively, based on the maximum Youden index. As these two indicators need to be used together in clinical assessment, the cutoff value of the combined indicators was 1.379 according to the logistic regression. AUC demonstrated 0.709 (P < 0.05), and the sensibility and specificity of using combined indicators were 0.622 and 0.757, respectively.

**Influence of perfusion index and proportion of perfusion vessel change rate on the Sequential Organ Failure Assessment score and 28-day survival**

Based on the cutoff of the PI and ΔPPV, the participants were divided into the following groups: (1) high PI and ΔPPV group, (2) high PI and low ΔPPV group, (3) low PI and high ΔPPV group, and (4) low PI and ΔPPV group. Figure 4 shows the specific SOFA score (calculated at T0) in the different groups. The SOFA score in the high PI and ΔPPV group (8.8 ± 2.4) was the lowest and had significant differences from the other three groups (F=13.7, P < 0.001). The highest score (14.5 ± 2.9) was in the low PI and ΔPPV group and had significant differences from the high PI and ΔPPV group and high PI and low ΔPPV group (F=13.7, P < 0.001). The SOFA scores in the high PI and low ΔPPV group and low PI and high ΔPPV group were 11.4 ± 3.1 and 12.3 ± 3.9, respectively, and there was no significant difference between these two groups (P = 0.435).

**Discussion**

Our observations reveal that PI and ΔPPV are related to LC, and combining these two indices can predict organ dysfunction and mortality in septic shock patients with microcirculation dysfunction. Indeed, peripheral perfusion and sublingual mucosa perfusion are abnormal in sepsis and septic shock, and these changes are usually inconsistent and synchronize with systemic hemodynamic changes.[16,17] These parameters improve toward normalization in survivors, but not in nonsurvivors.[18,19] From the perspective of pathophysiology, LC must rely on the macrocirculation

---

**Table 1: Baseline clinical and biological data of septic shock patients at ICU admission**

| Characteristics | LC ≥20% (n = 37) | LC <20% (n = 37) | χ² or t | P |
|-----------------|------------------|-----------------|--------|---|
| Age (years)     | 64.4 ± 10.0      | 62.7 ± 14.0     | −0.575 | 0.567 |
| Gender, n (%)   |                  |                 | 0.057* | 0.812 |
| Male            | 22 (51.1)        | 14 (48.3)       |        |    |
| Female          | 15 (48.9)        | 23 (51.7)       |        |    |
| Temperature (°C)| 35.7 ± 1.1       | 38.5 ± 1.1      | −1.150 | 0.254 |
| Heart rate (beats/min) | 104.4 ± 15.4 | 101.9 ± 12.0 | −0.775 | 0.441 |
| Respiratory rate (breaths/min) | 22.6 ± 2.8 | 22.7 ± 2.4 | 0.044 | 0.965 |
| WBC count (×10⁹/L) | 14.4 ± 5.5 | 14.5 ± 5.9 | 0.127 | 0.899 |
| APACHE II score | 23.5 ± 5.5       | 24.2 ± 6.3      | 0.490  | 0.625 |
| SOFA score      | 11.2 ± 3.5       | 12.1 ± 3.8      | 1.019  | 0.312 |
| MV, n (%)       | 37 (100.0)       | 37 (100.0)      |        | 1.000 |
| CRRT, n (%)     | 10 (47.6)        | 11 (52.4)       | 0.066* | 0.797 |

Date were presented by mean ± SD or n (%). *, t: Not available. WBC: White blood cell; MV: Mechanical ventilation; APACHE II scores: Acute Physiology and Chronic Health Evaluation II; SOFA score: Sequential Organ Failure Assessment score and 28-day survival.

**Figure 2:** The distribution of PI-6 h (a) and ΔPPV (b) between different LC groups. *Significantly low levels in the LC <20% group (P < 0.05).
PI: Perfusion index; ΔPPV: Proportion of perfusion vessel change rate; LC: Lactate clearance. n=37 in each group.
to provide sufficient flow to ensure adequate oxygen delivery to reduce anaerobic glycolysis, but also need to normalize microcirculatory function to achieve lactate metabolism. Therefore, it is not enough merely restoring macrocirculation hemodynamic parameters, but restoring microcirculation tissue metabolism as well. In 2015, Kanore Edul et al. have found that the essence of sepsis shock is actually microcirculation shock. Therefore, microcirculation is as important as the major circulation in the recovery of sepsis shock and requires extensive attention from clinicians.

From studies in recent years, it is known that PI and sublingual microcirculation parameters are the most commonly used indicators reflecting microcirculation. The difference between these indicators is that PI reflects the proportion of pulsatile blood flow in nonfluctuating blood flow, reflecting the patient’s peripheral perfusion. Peripheral skin perfusion is first decreased in septic shock, resulting in a decrease in pulsatile blood flow and a decrease in PI. In other words, PI reflects the flow of peripheral small-vessel perfusion. However, there is still a lack of high-level evidence to clarify that changes in PI can represent the central tissue perfusion and oxygenation of the body, and the relevant mechanisms may be related to changes in sympathetic nerve activity during shock that can cause heterogeneity in skin blood flow regulation. With the deeper understanding of sepsis shock, we have found that the continuous deterioration of microcirculation in patients with sepsis is directly related to the death of patients, and how to observe or find suitable indicators to assess the whole-body microcirculation is essential. In the late 1920s, the appearance of orthogonal polarization spectral (OPS)


Table 3: Univariate logistic regression analysis for possible risk factors for LC ≥20%

| Variable | B      | SE  | Wald | P    | OR  | 95% CI for OR       |
|----------|--------|-----|------|------|-----|---------------------|
| PI       | -0.432 | 0.219 | 3.869 | 0.049 | 0.649 | 0.422 - 0.959       |
| ΔPPV     | -0.041 | 0.301 | 2.486 | 0.01  | 0.959 | 0.93 - 0.99        |

SE: Standard error; CI: Confidence interval; OR: Odds ratio; LC: Lactate clearance; PI: Perfusion index; ΔPPV: Proportion of perfused vessels change rate.

Figure 5: The survival curves of the four groups. The 28-day mortality in the low PI and ΔPPV group was the highest among all groups (P < 0.05). PI and ΔPPV values were used to determine the prognostic significance. PI: Perfusion index; ΔPPV: Proportion of perfused vessels change rate.

cutoff in line with the LC. Lima et al.\cite{9} has found that a PI of 1.4 can be used to detect abnormal peripheral perfusion in critically ill patients. He et al.\cite{26} have suggested that the critical value of PI is 0.6 and have defined it as the best cutoff value related to 28-day mortality in the study population. Acting as an indicator of flow in peripheral arterioles, PI is related to oxygen transport and anaerobic metabolism.\cite{29,30}

Thus, in our research, getting a PI cutoff value of 1.4 as a result for LC is reasonable, as in the previous study. SDF technique is a real-time monitoring method at bedside that provides high-contrast images of the microvasculature.\cite{15}

Due to hemodynamic theory, we emphasize the continuous and dynamic changes of microvasculature after treatment, especially the vascular opening condition, but not the single instantaneous state. The most typical pathological feature of microcirculation in septic shock is heterogeneity.\cite{11,31} PPV is the ratio of PVD to TVD, and being a relative value, large differences can occur with different individuals and different detecting areas.\cite{32}

There exists no standard value of PPV, and clinicians usually compare measured values to a basic value.\cite{33} PPV is quite low on admission to the ICU and improves after resuscitation.\cite{34,36}

Here, we propose another concept, ΔPPV, which can provide information on changes of vascular opening and flow heterogeneity in a certain period. In addition, mistakes due to individual differences may be avoided. However, there is little other research investigating this indicator. In our study, we estimate a ΔPPV cutoff value of 12.1% in line with LC, leading to a novel treatment target in clinics. According to the theory of hemodynamics, we want to emphasize the continuous and dynamic changes of microvascular after treatment, especially the open state of blood vessels, rather than just a single-transient state. The most typical pathological feature of septic shock microcirculation is heterogeneity.\cite{31} PPV is the ratio of PVD to TVD. As a relative value, different individuals and different detection areas may make it have large differences.\cite{32}

Until now, there is still no standard value of PPV. The researchers have found that patients with septic shock experienced microcirculatory disturbances and patients who responded well after treatment could recover gradually even if the microcirculation was still abnormal\cite{37,39}.

Therefore, we propose the concept ΔPPV to determine the ratio of microvascular changes after treatment and to provide information on changes in vascular patency and blood flow inhomogeneity over a certain period of time. In other words, we need to judge the potential resuscitation in patients.

Based on the cutoff of the PI and ΔPPV ROC curve, all the participants are assigned to a low PI and low ΔPPV group, a high PI or high ΔPPV group, or a high PI and high ΔPPV group. We can learn from Figures 3 and 4 that low PI and ΔPPV suggested higher SOFA scores and poor prognosis for 28-day mortality in adult critically ill patients. Meanwhile, the sensitivity and specificity are better when using the combined index than using the single index. PI reflects stroke volume in microvessels, while ΔPPV represents the opening of microvessels. Both are parts of microcirculation perfusion so that using these two indicators together is reasonable.\cite{40,41}
Van Genderen et al. have proved that persistent peripheral and sublingual microcirculatory perfusion alterations after out-of-hospital cardiac arrest were associated with poor survival. As vasocostriction appears to be the exact determinant of peripheral perfusion, the responses of the peripheral and sublingual perfusion are not similar. For instance, the peripheral perfusion is in a vasoconstricted state during hypothermia, whereas the sublingual microcirculation index can decrease after rewarming. All in all, peripheral and sublingual perfusion parameters are improved in the survivors, but they remain significantly depressed in the patients who did not. Moreover, any single indicator has a limited ability to reflect the general microcirculation, and combining two different indicators can increase the sensitivity and specificity of predicting the prognosis.

The choice of a therapeutic endpoint in septic shock is a critical, but relatively unexplored aspect of care. New guideline lets us not to stick to the indicator like CVP or central venous oxygen saturation. However, we cannot judge some of the hidden harm only through clinical manifestations. It is important to find the proper indicators to help clarify the patient’s situation. Lactate acting as an anaerobic metabolism parameter can be affected by macrocirculation, microcirculation, and cell metabolism. The upstream endpoints of resuscitation are hemodynamic and oxygen-derived variables that can be modulated by circulatory support interventions. The downstream variables are markers of tissue perfusion and effectiveness of resuscitation. Professors are firmly convinced that microcirculation resuscitation is as important as macrocirculation resuscitation or even much more essential. From our point of view, different types of patients need different resuscitation endpoints based on our four groups. High PI and ∆PPV means that the patient has preferable microcirculation, and doctors can provide management such as conservative fluid treatment with a de-escalation phase. For patients with low PI and ∆PPV, clinicians should ensure successful macrocirculation resuscitation and consider a potential predisposing cause (e.g., an infected lesion that was not found). Patients in the other groups should have treatment adjusted correspondingly. For example, patients with high PI and low ∆PPV may indicate gastrointestinal ischemia, and patients with low PI and high ∆PPV may require attention to the dose of vasopressor agents or rewarming therapy. Early resuscitation of microcirculation is associated with reduced multiorgan failure and SOFA score. Microcirculatory alterations have previously been proved to have prognostic value independently with respect to morbidity and mortality in septic shock. In our study, peripheral and sublingual perfusions have close associations with prognosis and provide a feasible view and experimental data for a microcirculation resuscitation endpoint.

Some limitations of our study need to be acknowledged. First, the time of this study is short, and the number of patients is less. Second, we have not compared PI or ∆PPV to other indicators such as lactate. We think we can do a deeper research in the future. Finally, our study is an observational one; significant correlations between microcirculatory hypoperfusion and changes in SOFA score and mortality rates do not prove causality. Due to the small sample size, our results should be interpreted with caution.

In this study, we utilize a new indicator, ∆PPV, the changing rate of PPV (proportion of perfusion vessels), which provides information on changes of vascular opening and flow heterogeneity in sublingual microcirculation monitoring. According to 6 h LC, we calculated a cutoff value for PI and ∆PPV. Peripheral and sublingual microcirculatory tissue perfusion alterations are frequent, and they are aggravated by induced septic shock independent of systemic hemodynamics. Persistence of these tissue perfusion alterations is independently associated with the development of organ failure and mortality. Monitoring of peripheral and sublingual microcirculation might therefore be a valuable adjunct for identifying those septic shock patients with microcirculation dysfunction who are eligible for additional therapy aimed at microcirculation recruitment.

Acknowledgments
We thank Ms. Xing Liu and the company Microscan BV., Amsterdam, The Netherlands, for helping us to provide equipment support and solve technical problems.

Financial support and sponsorship
This study was supported by a grant from the National Natural Science Foundation of China (No. 81671878).

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Seymour CW, Rosengart MR. Septic shock: Advances in diagnosis and treatment. JAMA 2015;314:708-17. doi: 10.1001/jama.2015.7885.
2. Kanoore Edul VS, Ince C, Dubin A. What is microcirculatory shock? Curr Opin Crit Care 2015;21:245-52. doi: 10.1097/MCC.0000000000000196.
3. Sprok PE, Zandstra DF, Ince C. Bench-to-bedside review: Sepsis is a disease of the microcirculation. Crit Care 2004;8:462-8. doi: 10.1186/cc2894.
4. Scheeren TW. Monitoring the microcirculation in the critically ill patient: Reflectance spectroscopy. Intensive Care Med 2011;37:1045-6. doi: 10.1007/s00134-011-2197-1.
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10. doi: 10.1001/jama.2016.0287.
6. van Genderen ME, van Bommel J, Lima A. Monitoring peripheral perfusion in critically ill patients at the bedside. Curr Opin Crit Care 2012;18:273-9. doi: 10.1097/MCC.0b013e3283533924.
7. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med 2005;31:1316-26. doi: 10.1007/s00134-005-2790-2.
8. Sakr Y. Techniques to assess tissue oxygenation in the clinical setting. Transfus Apher Sci 2010;43:79-94. doi: 10.1016/j.transci.2010.05.012.
9. Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002;30:1210-3.
10. Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ,
Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42:211-21. doi: 10.1007/s00134-015-4133-2.
25. Donati A, Damiani E, Botticelli L, Adario E, Lombrano MR, Domizi R, et al. The aPC treatment improves microcirculation in severe sepsis/septic shock syndrome. BMC Anesthesiology 2013;13:25. doi: 10.1186/1471-2253-13-25.
26. Ince C, McCoy JV, Philip Dellingier R, Arnold RC, Rizzuto M, Abate NL, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 2016;34:2210-7. doi: 10.1007/s00134-008-1193-6.
27. Dubin A, Pozo MO, Casabella CA, Pálizas F Jr, Muriás G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: A prospective study. Crit Care 2009;13:892. doi: 10.1186/cc8722.
28. Trzeciak S, De Backer D, Durand A, Monitoring the microcirculation in critically ill patients. Best Pract Res Clin Anaesthesiol 2014;28:441-51. doi: 10.1016/j.bpa.2014.09.005.
29. Ospina-Tascón GA, Umana M, Bermúdez WF, Bautista-Rincón DF, Valencia JD, Madrühñ J, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42:211-21. doi: 10.1007/s00134-015-4133-2.
30. Miranda M, Balarini M, Caixeta D, Bouskela E. Microcirculatory targets for hemodynamic optimization in resuscitation of circulatory shock. Curr Opin Crit Care 2017;23:348-54. doi: 10.1097/MCC.000000000000423.
31. Verdant CL, De Backer D, Bruhn A, Dubin A, Shapiro NI, et al. International study on microcirculatory shock occurrence in acutely ill patients. Crit Care Med 2015;43:48-56. doi: 10.1097/CCM.0000000000000553.
32. Galvin EM, Niehof S, Verbrugge SJ, Maisan I, Jahn A, Klein J, et al. Peripheral flow index is a reliable and early indicator of regional block success. Anesth Analg 2006;103:239-43. doi: 10.1213/01.ane.0000220947.02689.9F.
33. De Backer D, Hollenberg S, Boerma C, Goodhart P, Büchele G, Ospina-Tascon G, et al. How to evaluate the microcirculation: Report of a round table conference. Crit Care 2007;11:R101. doi: 10.1186/cc6118.
34. Messmer K, et al. Orthogonal polarization spectral imaging: A new method for study of the microcirculation. Nat Med 1999;5:1209-12. doi: 10.1038/13529.
35. Miranda M, Balarini M, Caixeta D, Bouskela E. Microcirculatory dysfunction in sepsis: Pathophysiology, clinical monitoring, and potential therapies. Am J Physiol Heart Circ Physiol 2016;311:H24-35. doi: 10.1152/ajpheart.00034.2016.
36. Peters JK, Nishiyasu T, Mack GW. Reflex control of the cutaneous microcirculation. Crit Care 2015;19 Suppl 3:S8. doi: 10.1186/cc6118.
37. De Backer D, Balarini M, Caixeta D, Bouskela E. Microcirculatory dysfunction and biomarker dilemma in early septic shock diagnosis and treatment. Curr Vasc Pharmacol 2016;14:330-44.
38. Trzeciak S, Dellingier RP, Schorr CA, Levy MM. A user’s guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med 2017;43:299-303. doi: 10.1007/s00134-017-4681-8.
39. Broch O, Bein B, Gruenewald M, Höcker I, Schöttler J, Meybohm P, et al. Accuracy of the pleth variability index to predict fluid responsiveness depends on the perfusion index. Acta Anaesthesiologica Scandinavica 2011;55:686-93. doi: 10.1111/j.1399-6576.2011.02453.x.
40. Messmer K, et al. Orthogonal polarization spectral imaging: A new method for study of the microcirculation. Nat Med 1999;5:1209-12. doi: 10.1038/13529.
41. Morlet T, Guérin L, Joziwak M, Bataille A, Julien F, Richard C, et al. Pleth variability index is a weak predictor of fluid responsiveness in patients receiving norepinephrine. Br J Anaesth 2013;110:207-13. doi: 10.1093/bja/aes373.
42. Al-Asrhi H, Abuazid A, Asim M, El-Menayar Y. Microcirculation alteration and biomarker dilemma in early septic shock diagnosis and treatment. Curr Vasc Pharmacol 2016;14:330-44.
43. De Backer D, Ospina-Tascon G, Salgado D, Favory R, Creteret J, Vincent JL, et al. Monitoring the microcirculation in the critically ill patient: Current methods and future approaches. Intensive Care Med 2010;36:1815-25. doi: 10.1007/s00134-010-2005-3.
44. De Backer D, Durand A. Monitoring the microcirculation in critically ill patients. Best Pract Res Clin Anaesthesiol 2014;28:441-51. doi: 10.1016/j.bpa.2014.09.005.
45. Ospina-Tascón GA, Umana M, Bermúdez WF, Bautista-Rincón DF, Valencia JD, Madrühñ J, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42:211-21. doi: 10.1007/s00134-015-4133-2.
46. Donati A, Damiani E, Botticelli L, Adario E, Lombrano MR, Domizi R, et al. The aPC treatment improves microcirculation in severe sepsis/septic shock syndrome. BMC Anesthesiology 2013;13:25. doi: 10.1186/1471-2253-13-25.
47. Dubin A, Pozo MO, Casabella CA, Pálizas F Jr, Muriás G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: A prospective study. Crit Care 2009;13:892. doi: 10.1186/cc8722.
48. De Backer D, Creteret J, Dubois MJ, Sakr Y, Koch M, Verdant C, et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med 2006;34:403-8.
49. Hernandez G, Bruhn A, Luengo C, Regueira T, Kattan E, Fuentalba A, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: A randomized, placebo-controlled, double-blind, crossover study. Intensive Care Med 2013;39:1435-43. doi: 10.1007/s00134-013-2992-0.
50. Boerma EC, Kuiper MA, Kingma WP, Egbers PH, Gerritsen RT, Ince C, et al. Disparity between skin perfusion and sublingual microcirculatory alterations in severe sepsis and septic shock: A prospective observational study. Intensive Care Med 2008;34:1294-8. doi: 10.1007/s00134-008-1007-x.
51. Oliver JJ, Bowler A, Beudeker Q, Cate T, Webb DJ. Dose-response relationship of sublingual nitroglycerin with brachial artery dilatation and change in central and peripheral augmentation index. Clin Pharmacol Ther 2005;77:337-8.
52. van Genderen ME, Lima A, Akkerhuis M, Bakker J, van Bommel J. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012;40:2287-94. doi: 10.1097/CCM.0b013e31825333b2.
53. Boerma EC. The microcirculation as a clinical concept: Work in progress. Curr Opin Crit Care 2009;15:261-5. doi: 10.1097/MCC.0b013e328230ef04.
54. Hernandez G, Luengo C, Bruhn A, Kattan E, Friedman G, Ospina-Tascon GA, et al. When to stop septic shock resuscitation: Clues from a dynamic perfusion monitoring. Ann Intensive Care 2014;4:30. doi: 10.1186/s13613-014-0030-z.
55. Trzeciak S, Dellingier RP, Parrillo JE, Guglielmì M, Bajaj B, Abate NL, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 2007;49:88-98, 98.e1-2. doi: 10.1016/j.annemergmed.2006.08.021.
56. Büchele GL, Ospina-Tascon GA, De Backer D. How microcirculation...
data have changed my clinical practice. Curr Opin Crit Care 2007;13:324-31. doi: 10.1097/MCC.0b013e3280c1e5c5.

47. Ragaller M. Microcirculation in sepsis and septic shock – Therapeutic options? Anesthesiol Intensivmed Notfallmed Schmerzther 2008;43:48-53. doi: 10.1055/s-2008-1038091.

48. Schuster HP. Infection and septic shock. Pathophysiology (microcirculation and the clinical picture). Verh Dtsch Ges Inn Med 1987;93:336-43.

49. Scheeren TW. Journal of clinical monitoring and computing 2015 end of year summary: Tissue oxygenation and microcirculation. J Clin Monit Comput 2016;30:141-6. doi: 10.1007/s10877-016-9846-4.

50. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 2004;32:1825-31.

51. Zhao MY, Li A, Zhuang HZ, Dong L, Li J, Liu C, et al. The clinical significance of determining the severity and prognosis by monitoring the changes in sublingual microcirculation in patients with severe sepsis (in Chinese). Chin Critic Care Med 2012;24:158-61.

52. Kara A, Akin S, Ince C. Monitoring microcirculation in critical illness. Curr Opin Crit Care 2016;22:444-52. doi: 10.1097/MCC.0000000000000335.

53. Ostergaard L, Granfeldt A, Secher N, Tietze A, Iversen NK, Jensen MS, et al. Microcirculatory dysfunction and tissue oxygenation in critical illness. Acta Anaesthesiol Scand 2015;59:1246-59. doi: 10.1111/aas.12581.
联合外周灌注指数与舌下微循环监测脓毒症休克微循环障碍与预后

摘要

背景：对于脓毒症休克患者而言，休克时微循环的变化与监测至关重要。外周灌注指数（peripheral perfusion index，PI）及舌下微循环监测是目前临床上较为直接且便捷的监测手段。本研究通过联合外周灌注指数（PI）及舌下微循环监测衍生指标灌注血管比例变化率（proportion of perfusion vessel change rate，△PPV）对脓毒症休克患者器官损伤情况及28天病死率进行预测。

方法：本研究为前瞻性观察性研究，采用t检验、方程分析(ANOVA)、Mann-Whitney U检验、Kruskal-Wallis检验、ROC曲线、Kaplan-Meier生存曲线结合Mantel-Cox检验。本实验中共纳入74名脓毒症休克患者。于收入重症医学科时（T0）及第6小时（T6）分别监测患者大循环血流动力学参数、舌下微循环相关参数及外周灌注指数（PI）。

结果：根据患者6h乳酸清除率（lactate clearance，LC）是否≥20%，将入组病人分为两组，分别为LC<20%组与LC≥20%组。LC<20%组患者T6时刻的PI及6小时后△PPV均低于LC≥20%组（PI：1.52 [0.89, 1.98] vs. 0.79 [0.44, 1.81], Z=-2.514, P=0.012; △PPV：5.9±15.2 vs. 17.9±20.0, t=-2.914, P=0.005）。因此根据6h的LC是否≥20%，分别得到PI临界值1.41与△PPV临界值12.1%。

通过逻辑回归分析可得联合应用两个指标的临界值为1.379，曲线下面积为0.709，敏感性和特异性分别为0.622及0.757（P<0.05）。根据PI及△PPV的临界值，我们将入组病人分为四组。组1：PI≥1.4且△PPV≥12.1%，组2：PI≥1.4且△PPV<12.1%，组3：PI<1.4且△PPV≥12.1%，组4：PI<1.4且△PPV<12.1%。其中，组4患者SOFA评分最高（14.5±2.9），Post hoc分析显示组1患者生存率最高，而组4患者生存率最低（log rank [Mantel-Cox], 20.931; P<0.05）。

结论：PI和△PPV与脓毒症休克患者6小时乳酸清除率相关，联合应用两个指标可早期预测患者病情危重程度（器官功能异常情况）与28天病死率。