Original Article

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

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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 (DO_2) 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. Spronk *et al*.[3] found microcirculatory perfusion to be disturbed in septic shock and emphasized that sepsis is a disease of microcirculation according to

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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 photoelectric 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 dermatic 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 ($Pv\text{-}aCO_2$), and superior vena

cava oxygen saturation (SvO_2), 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 consistence 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 ($[PPV_{T6} - PPV_{T0}]/PPV_{T0}$) 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 (Q_1, Q_3). 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, SvO_2, MAP, and flow index Pv-aCO_2 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.

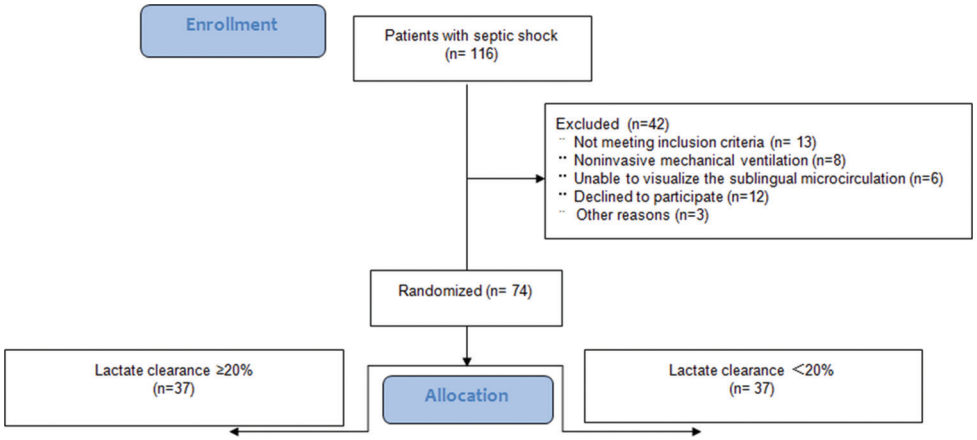

Figure 1: The flowchart of this study on septic shock patients.

However, we obtained the ΔPPV at T0 and T6 (ΔPPV = [PPV T_6 − PPV T_0]/PPV T_0). 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 0.642 (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.

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

Characteristics	LC ≥20% (n = 37)	LC <20% (n = 37)	χ^2 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)	38.5 ± 1.1	38.3 ± 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 (%). *: χ^2. –: 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; CRRT: Continuous renal replacement therapy; ICU: Intensive Care Unit; SD: Standard deviation; LC: Lactate clearance.

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). *Post hoc* tests showed significant differences in 28-day survival rates among these four groups (log rank [Mantel-Cox], 20.931; P < 0.05) [Figure 5]. Patients in the low PI and ΔPPV group had worse outcomes than those in the other three groups (P < 0.05), whereas the remaining groups were not significantly different from each other.

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

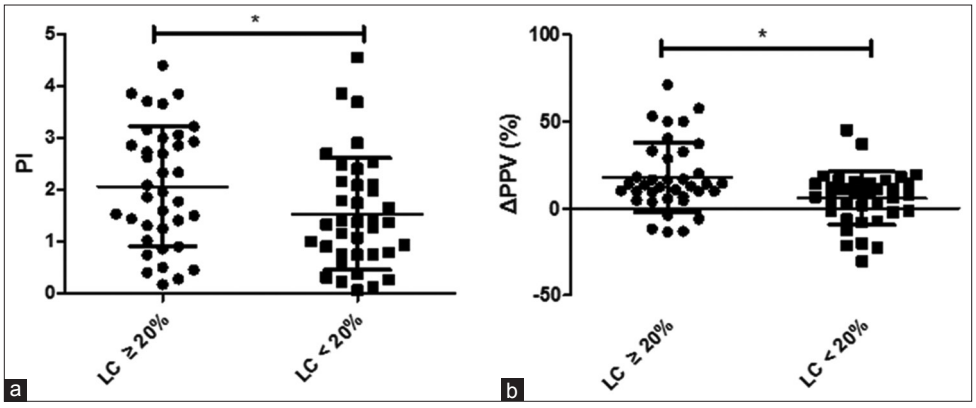

Figure 2: The distribution of PI-6 h (a) and ΔPPV (b) between different LC groups. *Significantly low levels in the LC <20% group (P < 0.05). PI: Perfusion index; ΔPPV: Proportion of perfusion vessel change rate; LC: Lactate clearance. n=37 in each group.

to provide sufficient flow to ensure adequate oxygen delivery to reduce anaerobic glycolysis, but also need 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, Kanoore Edul *et al*.[2] 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.[20] In other words, PI reflects the flow of peripheral small-vessel perfusion.[21] 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.[22] 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,[23] 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)

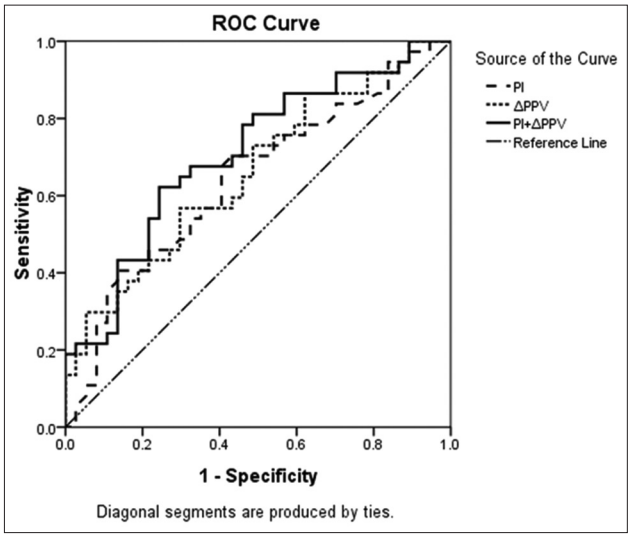

Figure 3: A cutoff for PI and ΔPPV was calculated from a ROC curve, PI = 1.41, sensibility = 0.703, specificity = 0.568 ($P < 0.05$); ΔPPV% = 12.1, sensibility = 0.568, specificity = 0.703 ($P < 0.05$). The cutoff value for the combined indicators was 1.379 according to the Logistic regression. AUC demonstrated 0.709 ($P < 0.05$); sensibility and specificity of using combined indicators were 0.622 and 0.757, respectively. PI: Perfusion index; ΔPPV: Proportion of perfusion vessel change rate; ROC: Receiver operating characteristic; AUC: Area under the curve.

Table 2: Tissue perfusion indicator and microcirculation index of septic shock at ICU admission

Characteristics	LC ≥20% (n = 37)	LC <20% (n = 37)	t or Z	P
CVP				
0 h	10.1 ± 2.8	9.4 ± 3.4	−0.868	0.388
6 h	11.1 ± 1.5	10.6 ± 2.6	1.158	0.253
SvO_2				
0 h	68.3 ± 7.8	69.2 ± 12.3	0.330	0.742
6 h	71.4 ± 3.6	72.5 ± 8.4	−0.038	0.292
Gap				
0 h	6.5 ± 3.2	6.3 ± 3.7	−0.189	0.850
6 h	4.6 ± 3.5	4.8 ± 2.1	2.513	0.530
MAP				
0 h	83.4 ± 11.6	80.9 ± 11.8	0.935	0.353
6 h	91.3 ± 7.1	94.2 ± 9.3	−1.640	0.084
PI				
0 h	1.9 ± 0.7	1.3 ± 0.9	−2.040	0.173
6 h	1.52 (0.89, 1.98)	0.79 (0.44, 1.81)	2.514*	0.012
PPV				
0 h	71.7 ± 12.9	70.5 ± 15.8	−0.777	0.280
6 h	75.2 ± 14.0	72.4 ± 17.4	−2.806	0.440
PVD				
0 h	13.21 ± 4.6	12.64 ± 1.7	−1.578	0.163
6 h	11.35 ± 2.7	10.3 ± 2.9	−2.376	0.119
TVD				
0 h	17.2 ± 3.7	17.8 ± 3.3	0.790	0.357
6 h	17.2 ± 3.7	17.8 ± 3.3	0.797	0.432
ΔPPV	13.73 (6.28, 30.79)	8.82 (−1.82, 14.41)	−2.914	0.030

Date were presented by mean ± SD. *: Z value. CVP: Central venous pressure; SvO_2: Superior vena cava oxygen saturation; Gap: Pv-aCO_2; MAP: Mean arterial pressure; PI: Perfusion index; PPV: Proportion of perfused vessels; PVD: Perfused vessel density; TVD: Total vessel density; ΔPPV: Proportion of perfused vessels change rate; SD: Standard deviation; ICU: Intensive Care Unit; LC: Lactate clearance.

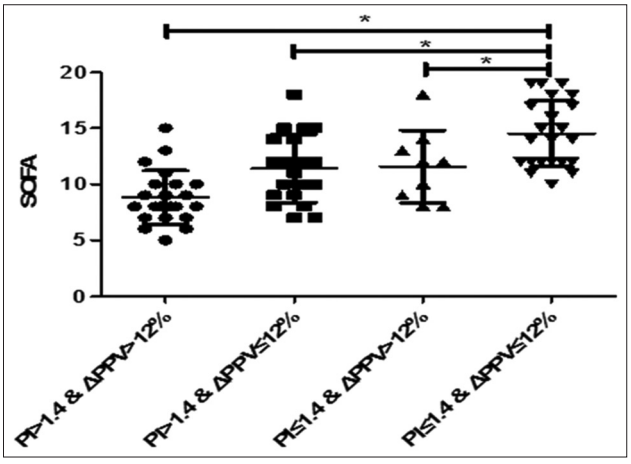

Figure 4: SOFA score in the four different groups. Among these groups, the high PI and ΔPPV group (n = 22) and the low PI and ΔPPV group (n = 20) had the lowest and highest SOFA scores, respectively. The PI > 1.4 and ΔPPV ≤12.1 group (n = 20), and PI ≤1.4 and ΔPPV > 12.1 group (n = 12) had intermediate SOFA scores and had no significant difference between the two groups. *: $P < 0.05$ PI: Perfusion index; ΔPPV: Proportion of perfusion vessel change rate; SOFA: Sequential Organ Failure Assessment.

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

Variable	*B*	SE	Wald	*P*	*OR*	95% *CI* for *OR*	
						Lower	Upper
PI	−0.432	0.219	3.869	0.049	0.649	0.422	0.992
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.

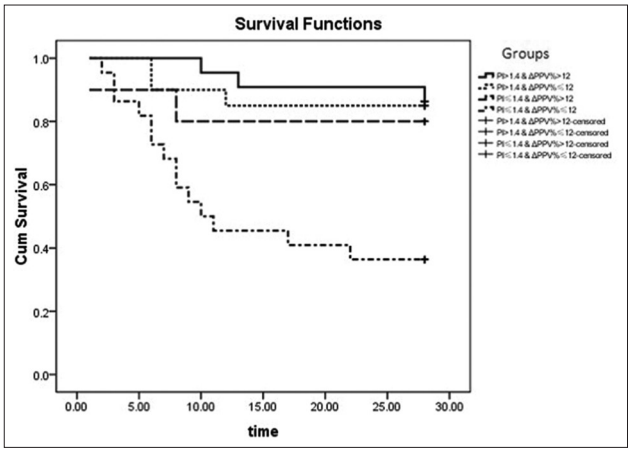

Figure 5: The survival curves of the four groups. The 28-day mortality in the low PI and ΔPPV group was the highest among all groups ($P < 0.05$). PI and ΔPPV values were used to determine the prognostic significance. PI: Perfusion index; ΔPPV: Proportion of perfusion vessel change rate.

technology marked the possibility of microcirculation imaging visualization. According to the constant updating of technology, SDF technology makes clinicians to hold the detector at the bedside to see real-time microcirculation. Changes in patient microcirculation are observed at time.[10,24] It is easy to observe at the site of the sublingual mucosa, and studies have shown that the sublingual mucosa has homology with intestinal mucosa. It is proved that sublingual microcirculation changes can represent changes in visceral microcirculation and predict patient mortality.[25] At present, the four types of microcirculatory abnormalities can be identified by real-time monitoring of microcirculation images, including (1) abnormal oxygen transport caused by allogeneic red blood cells, (2) reduced oxygen-carrying capacity of red blood cells due to hemodilution, (3) arteriolar contraction or increased pressure on posterior vein causes a microcirculatory blood flow arrest, and (4) edema leads to increased oxygen diffusion distance.[26] Therefore, combining the above two methods to assess the patient's microcirculation at the bedside can fully evaluate the perfusion from the center to the periphery, which helps discover and initiate microcirculation resuscitation.

PI and the sublingual microcirculation index are direct indicators reflecting general microcirculation. According to the updating bundles,[14] we use the first 6-h LC as the initial resuscitation endpoint.[27] We can get the PI and ΔPPV cutoff in line with the LC. Lima *et al*.[9] has found that a PI of 1.4 can be used to detect abnormal peripheral perfusion in critically ill patients. He *et al*.[28] 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.[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.[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.[11,31] PPV is the ratio of PVD and TVD, and being a relative value, large differences can occur with different individuals and different detecting areas.[32] There exists no standard value of PPV, and clinicians usually compare measured values to a basic value.[33] PPV is quite low on admission to the ICU and improves after resuscitation.[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.[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.[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.[37-39] Therefore, we propose the concept ΔPPV to determine the ratio of microvascular vascular 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.[40,41]

Van Genderen *et al*.[42] have proved that persistent peripheral and sublingual microcirculatory perfusion alterations after out-of-hospital cardiac arrest were associated with poor survival. As vasoconstriction appears to be the exact determinant of peripheral perfusion,[7] 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.[40,43] All in all, peripheral and sublingual perfusion parameters are improved in the survivors, but they remains 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.[42]

The choice of a therapeutic endpoint in septic shock is a critical, but relatively unexplored aspect of care. New guideline lets us not have 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.[18] 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.[44,45] Professors are firmly convinced that microcirculation resuscitation is as important as macrocirculation resuscitation or even much more essential.[46] From our point of view, different types of patients need different resuscitation endpoints based on our four groups. High PI and ΔPPV means that the patient has preferable microcirculation, and doctors can provide management such as conservative fluid treatment with a de-escalation phase.[47] For patients with low PI and ΔPPV, clinicians should ensure successful macrocirculation resuscitation and consider a potential predisposing cause (e.g., an infected lesion that was not found).[48] Patients in the other groups should have treatment adjusted correspondingly. For example, patients with high PI and low ΔPPV may indicate gastrointestinal ischemia, and patients with low PI and high ΔPPV 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.[36,49,50] Microcirculatory alterations have previously been proved to have prognostic value independently with respect to morbidity and mortality in septic shock.[17,51-53] 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 ΔPPV 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, ΔPPV, 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 ΔPPV. 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.

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Conflicts of interest

There are no conflicts of interest.

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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，ΔPPV）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ΔPPV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; ΔPPV: 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ΔPPV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ΔPPV的临界值，我们将入组病人分为四组。组1：PI ≥1.4且ΔPPV ≥12.1%，组2：PI ≥1.4且ΔPPV ＜12.1%，组3：PI ＜1.4且ΔPPV ≥12.1%，组4：PI ＜1.4且ΔPPV ＜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ΔPPV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。