

Association between Doppler snuffbox resistive index and tissue perfusion in septic patients

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Abstract

Background: Doppler snuffbox resistive index (SBRI) can be a accurate parameter at the bedside to evaluate the status of peripheral vascular. We evaluated whether SBRI could relate to tissue hypoperfusion and could predict lactate clearance in septic patients. **Methods:** We conducted a prospective observational study in a tertiary general and teaching hospital in China. From July 2019 to Decemeber 2019, all consecutive adult patients with septic shock who required ICU admission were included. At the same time, postoperative patients were studied as a control group. we recorded the hemodynamic parameters including SBRI and PI which were measured simultaneously after involved . **Results:** We evaluated 44 patients with septic shock in study group and 20 stable postoperative patients in control group. Patients with septic shock had higher SOFA scores, PCT, CI and lactate than patients in control group. The SBRI was correlated with PI and lactate. The CI was not correlated with lactate in all patients. Based on Lactate clearance in first 6 hours, the septic shock patients were divided into the Lactate clearance $\geq 20\%$ or the Lactate clearance $< 20\%$ group. CI is no significal difference between two groups. SBRI of the Lactate clearance $< 20\%$ group is higher than Lactate clearance $\geq 20\%$ group and control group. PI of the Lactate clearance $< 20\%$ group is lower than Lactate clearance $\geq 20\%$ group and control group. The cutoff of the SBRI value was ≥ 1.09 for predicting 6h-lactate clearance after resuscitation, resulting in a sensitivity of 68.8% and a specificity of 85.7%. The cutoff of the PI value was ≤ 0.99 for predicting 6h-lactate clearance after resuscitation, resulting in a sensitivity of 64.3% and a specificity of 81.2%. The SBRI was significantly better than the PI for predicting 6h-lactate clearance after resuscitation. **Conclusions:** SBRI is correlated with tissue perfusion parameters in critical ill patients. Abnormal SBRI was better than PI in suggesting disorder of lactate clearance of septic patients. SBRI is a better indicator of abnormal tissue perfusion than CI. Further investigations are required to determine whether the correction of abnormal SBRI and PI may improve success rate of resuscitation of septic shock.

Background

Hemodynamics is a science that studies the characteristics and rules of the movement of blood and its components in the body. The power of blood flow comes not only from the heart, but also from the vascular system. Septic shock is defined as progression that results in persistent hypotension requiring vasopressors to maintain adequate tissue perfusion^[1], and it is common reasons for intensive care unit (ICU) admission, responsible for high morbidity and mortality^[2]. Septic shock is main characterized by abnormal peripheral vascular resistance, thus, the management of septic shock is very important to improvement of vascular function and impaired organs. But even if conventional hemodynamic parameters such as blood pressure and heart frequency normalize after treatment, Peripheral perfusion may remain disturbed^[3]. Although the relationship between the systemic and peripheral circulation in patients with sepsis is poorly understood, the persistent impedance of peripheral tissue perfusion is associated with high mortality in these patients. Therefore, identifying and monitoring vascular

dysfunction could be of interest, and assessing regional perfusion has been validated but remains difficult to use at the bedside.

With the development of ultrasound technology in critical care medicine, more and more attention has been paid to the detection of blood flow of the peripheral circulation by ultrasound. Compared with the central circulation, the peripheral circulation is closer to tissue perfusion and microcirculation. Peripheral vascular resistance may be altered by physiologic differences or pathologic conditions^[4]. Most of the peripheral resistance is offered by arterioles because of changes in the tone of arteriolar muscles^[5]. The resistive index (RI) is a popular parameter for characterizing the arterial waveform at Doppler ultrasonography (US). Previous research has suggested that the RI to be related to vascular resistance^[6]. The waveforms obtained by the Doppler method are influenced by the angle between the ultrasound beam and blood flow direction. The incidence angle between the ultrasound beam and blood flow direction of the radial artery is smallest, so it was chosen as the target artery in the snuffbox to reduce errors^[7]. Doppler snuffbox resistive index (SBRI) has been shown to be a feasible and accurate parameter for evaluating vascular resistance and vascular compliance^[8]. En-Pei Lee et al proved a strong correlation between SBRI and SVRI as measured by invasive transpulmonary indicator dilution in septic patients^[9].

Moreover, Perfusion index (PI) is a reliable indicator of peripheral perfusion derived from the photoelectric plethysmographic signal of a pulse oximeter^[10]. PI is the ratio between the pulsatile and nonpulsatile portions of the plethysmographic waveform. The pulsatile portion decreases with vasoconstriction and increases with vasodilatation; thus, changes in PI reflect changes in peripheral vasomotor tone^[11]. Hyperlactatemia and serum lactate has been considered a marker of the severity of the septic process, alongside a guide for hemodynamic optimization^[12]. A large number of studies have confirmed that lactic acid can better reflect the index of tissue perfusion and has been widely used in clinical practice^[13]. But, the relationship between SBRI and serum lactate and PI has not been verified. During this study, we used our clinical study to answer this question.

Methods

We conducted a prospective observational study in an 30-bed ICU at a tertiary teaching hospital in China. During a 5-month period, we included all adult patients (≥ 18 years of age) who required ICU admission for septic shock (according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)) from any causes^[11]. Patients could be admitted from the emergency department or the medical wards. Patients were excluded from the present study if: (1) Patients who were younger than 18 years old, (2) pregnant women, (3) Patients with hypothermia (defined as central temperature < 35 °C), (4) they had any impairment of the upper extremity circulation, such as those who underwent radial artery harvesting for coronary artery bypass grafting or had suspected occlusion of the radial artery prior to surgery; and (5) if they had undergone an operation that involved large arteries of the aortic arch. Patients with septic shock were included when vasopressors were required (within 24 h of admission).

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

Ethics approval and consent to participate

The Peking Union Medical College Hospital Ethics Committee approved the study (No. ZS-2153), and all patients were involved in the study based on the voluntary principle and had signed informed consent form. Informed consent was obtained from all patients. We would maximize the protection of the interests of patients and would not cause harm to any patients.

Protocol for the management of patients

Management of patients with septic shock was guided by our local protocol, adapted from international guidelines^[14]. We gave all the included patients of septic shock the standard 6-h bundles of treatments^[15]. 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, and again assess patient volume status, tissue perfusion, and lactic acid conditions. All patients were investigated with Color Doppler ultrasound devicing equipment (ALOKA NOBLUS, HITACHI Japan). All ultrasound (US) examinations are performed by two uniformly trained and certified operators. Glycemic control and venous thrombosis prophylaxis were provided according to Surviving Sepsis Campaign Guidelines^[10].

Data collection

The following general characteristics of the patients were recorded: age, sex, previous chronic illnesses, severity of illness evaluated by the Acute Physiology and Chronic Health Evaluation II score (APACHE II score)^[16] and the Sequential Organ Failure Assessment score (SOFA score) within 6 h of inclusion^[17], primary site of infection, Serum white blood cell (WBC) count, Procalcitonin (PCT), vasopressors use and Richmond Agitation-Sedation Scale (RASS) score were collected. We collected global hemodynamic parameters including mean artery pressure (MAP), central venous pressure (CVP), Velocity time integral (VTI), cardiac index (CI), venous-to-arterial carbon dioxide difference (Pv-aCO₂), Central-venous oxygen saturation (ScvO₂) and microcirculatory dysfunction and organ perfusion parameters [perfusion index (PI), arterial lactate level (Lac) at the first 6 h of the Department of Critical Care Medicine admission (T6h). PI was measured at T6h using a Philips Medical Systems Viridia/56S monitor.

Hemodynamic measurements

Some Hemodynamic parameters were obtained through Transthoracic echocardiography (TTE) including VTI and CI. In all cases, VTI was computed on an apical five-chamber view using pulse Doppler in the left ventricle outflow chamber. The measurement of the left ventricular outflow tract (LVOT) diameter was

made with each US device to allow area calculation. Investigators were doing the same diameter measurement in each US device. The LVOT area was calculated by US devices according to the formula: LVOT area = $3.14 \times (\text{LVOT diameter}/2)^2$ ^[18]. For each time, a VTI recording during a respiratory cycle was made. At each measure time, three VTI were measured: VTI_{max} (the VTI seemed the biggest), VTI_{min} (the VTI seemed the smallest), and VTI_{med} (a VTI seemed of medium size). An average VTI was calculated: $\text{VTI} = (\text{VTI}_{\text{max}} + \text{VTI}_{\text{med}} + \text{VTI}_{\text{min}}) / 3$. The HR, CVP, MAP and body surface area (BSA) were manually indicated in the meantime. Finally, the CI was calculated: $\text{CI} = \text{HR} \times \text{VTI} \times \text{LVOT area} / \text{BSA}$, then stroke systemic vascular resistance index (SSVRI) was calculated: $\text{SSVRI} = 80 \times \text{HR} \times (\text{MAP} - \text{CVP}) / \text{CI}$. Systemic vascular resistance index (SVRI) was calculated: $\text{SVRI} = 80 \times (\text{MAP} - \text{CVP}) / \text{CI}$.

SBRI Measurement

SBRI was measured using a ALOKA NOBLUS (HITACH) portable system with a 3-10-MHz linear probe and resolution limit of 0.01 mm. The evaluation of RI via Doppler was performed as previously described^{[4], [7]}. We measured the SBRI at one depths (1 cm) of the radial artery in the SB in one hand. The SBRI was imaged in B mode using waveform analysis, and was defined as follows: resistive index = $(\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}$ ^[4]. Two skilled intensivists conducted a total of 30 measurements on five septic patients in the ICU to evaluate interobserver reproducibility.

Statistical analysis

Descriptive analysis was performed. Results for continuous variables with normal distributions were presented as mean \pm standard deviations (SD). Results for continuous variables that were not normally distributed were presented as median (25–75th percentiles) or percentages as appropriate. For the continuous variables, depending on the data distribution and the number of variables, data were analyzed using the t-test, analysis of variance, Kruskal-Wallis test, or Mann-Whitney U-test. Correlation analyses were performed using the Spearman test. When correlation was significant, a linear regression model was fit to the data. Receiver operating characteristics (ROC) curves were constructed to compare the accuracy of SBRI in the prediction of lactate clearance. The areas under the ROC curves were compared using a Hanley-McNeil test^[19]. 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 17.0 software package (SPSS, Chicago, IL, USA).

Results

General characteristics

From July 2019 to December 2019, a total of 64 consecutive adult patients who required ICU admission were included in the study including 44 patients with septic shock (Table 1). The control group included 20 hemodynamically stable patients without sepsis admitted for postoperative monitoring. The most prevalent primary sites of infection of septic shock patients were the abdomen (23/44, 52.27%) and the lungs (18/44, 40.91%). Most of the patients had comorbidities such as hypertension or diabetes. Patients

with septic shock had higher SOFA(12.07 ± 3.34 vs. 8.25 ± 3.28 , $P < 0.001$) scores ,PCT(13 vs. 1.17, $P < 0.001$),and lactate(2.0 vs.2.9, $P < 0.001$).

Table 1
Comparison of the septic group and the control group

Variables	Control	All Septic shock	Z/F	P value
	(N = 20)	(N = 44)		
Age	57.5(25,88)	64(17,88)	-0.783	0.434
Gender (n, %)			-1.854	0.064
Male	14(70.00)	30(68.18)		
Female	6(30.00)	14(36.36)		
Comorbidities (n, %)				
HTN	7(31.82)	13(25)	-0.144	0.885
DM	5(9.09)	10(22.73)	-0.577	0.564
CAD	1(4.55)	10(22.73)	-2.303	0.021 ^a
Blood temp(°C)	36.61 ± 0.91	36.76 ± 1.09	0.991	0.585
WBCcount	13.49(9.97,16.89)	13.59(10.81,21.05)	-0.862	0.389
PCT	1.17(0.23,3.68)	13(3.65,28.25)	-4.179	0.000 ^a
APACHE II score	15.5(13,19.5)	16.5(14,24)	-1.103	0.270
SOFA score	8.25 ± 3.28	12.07 ± 3.34	0.037	0.000 ^a
RASS score	-2.80 ± 1.58	-2.45 ± 3.32	0.795	0.660
HR	91.60 ± 11.69	103.11 ± 16.94	1.785	0.006
CVP	8.74 ± 3.09	8.75 ± 4.04	0.996	0.99
VTI	17.1 ± 2.86	16.55 ± 3.47	0.432	0.535
CI	2.48 ± 0.48	3.02 ± 0.92	8.187	0.017
P _{v-a} CO ₂	4.12 ± 2.5	5.10 ± 2.97	0.093	0.275

aP < 0.05 for control group vs. septic group. HTN, hypertension; DM Diabetes Mellitus; CAD, Coronary Artery Disease; Age (years); Blood temp(°C); WBC, White Blood Cell (× 10⁹/L); PCT, procalcitonin (ng/ml); APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score; RASS Richmond Agitation-Sedation Scale; HR, heart rate; CVP, central venous pressure; VTI Velocity time integral; CI Cardiac Index (L·min⁻¹·m⁻²); P_{v-a}CO₂, venous-to-arterial carbon dioxide difference; ScvO₂, Central-venous oxygen saturation; SVRI, Systemic Vascular Resistance Index (dyn·sec·cm⁻⁵·m²); SSVRI, Stroke Systemic Vascular Resistance Index (mmHg·cm⁻¹·m²); MAP, mean arterial pressure (mmHg)

Variables	Control	All Septic shock	Z/F	P value
	(N = 20)	(N = 44)		
ScvO ₂	74.25 ± 15.42	72.95 ± 11.30	2.212	0.734
SVRI	2374.92 ± 650.04	2162.19 ± 705.60	0.332	0.257
SSVRI	214.32 ± 59.84	219.32 ± 74.07	1.042	0.792
MAP	82.5(68.25,89.75)	83(79,91)	-0.515	0.607
Lac	2.0(1.25,2.38)	2.9(2.33,3.88)	-3.764	0.000 ^a

aP < 0.05 for control group vs. septic group. HTN,hypertension;DM Diabetes Mellitus;CAD,Coronary Artery Disease; Age (years);Blood temp(°C);WBC,White Blood Cell($\times 10^9/L$);PCT,procalcitonin(ng/ml);APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score;RASS Richmond Agitation-Sedation Scale; HR,heart rate;CVP,central venous pressure;VTI Velocity time integral;CI Cadiac Index ($L \cdot \text{min} \cdot \text{m}^{-2}$); Pv-aCO₂,venous-to-arterial carbon dioxide difference; ScvO₂,Central-venous oxygen saturation;SVRI,Systemic Vascular Resistance Index ($\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^2$); SSVRI,Stroke Systemic Vascular Resistance Index ($\text{mmHg} \cdot \text{cm}^{-1} \cdot \text{m}^2$);MAP, mean arterial pressure (mmHg)

All patients with septic shock received vasopressor therapy, and the vasopressor mainly used was norepinephrine. In the whole group, the SBRI was not correlated with the CVP, CI and MAP. In contrast, the SBRI was correlated with PI ($r = 0.740, P < 0.001$) and lactate ($r = -0.517, P < 0.001$) (Fig. 1). But the lactate was not correlated with the CI ($r = 0.091, P = 0.475$), Pv-aCO₂ ($r = 0.259, P = 0.052$), and ScvO₂ ($r = 0.045, P = 0.742$) (Fig. 2).

Hemodynamics and peripheral perfusion variables in septic shock groups

Based on Lactate clearance in first 6 hours, the septic shock patients were divided into the Lactate clearance $\geq 20\%$ ($n = 28$) or the Lactate clearance $< 20\%$ ($n = 16$) group (Table 2). Parameters including age, gender, blood temperature, comorbidities, white blood cell count, procalcitonin, APACHE II score, SOFA score, and RASS score had no significant difference between the two groups ($P > 0.05$). The PCT of the Lactate Clearance $< 20\%$ group was significantly higher than the Lactate Clearance $\geq 20\%$ ($13(3.65, 28.25)$ vs. $1.17(0.23, 3.68)$, $Z = -4.179, P = 0.001$), which had statistically difference. About the hemodynamics and microcirculation perfusion targets, There were no statistical differences such as CVP, CI, SVRI, MAP in both groups (Table 2).

Table 2
 Characteristics of the septic patients (n = 44)

Variables	Lactate clearance ≥ 20%	Lactate clearance < 20%	Z/F	P value
	(N = 28)	(N = 16)		
Age	63(52.5,68.75)	64(56.25,71.25)	-0.745	0.456
Gender (n, %)			-0.775	0.439
Male	18(90.00)	12(68.18)		
Female	10(10.00)	4(36.36)		
Comorbidities (n, %)			-1.935	0.053
HTN	6(21.43)	8(50)		
DM	5(17.86)	6(37.50)		
CAD	4(14.25)	5(31.25)		
Primary site of infection (n, %)			-1.965	0.062
Lung	6(30.00)	12(27.27)		
Abdomen	10(50.00)	13(29.55)		
Blood tract	4(20.00)	8(18.18)		
Blood temp	36.96 ± 1.13	36.41 ± 0.93	1.323	0.106
WBC count	14.21(11.22,24.49)	13.59(10.81,21.04)	-1.513	0.130
PCT	18.13 ± 26.10	34.41 ± 35.56	4.800	0.089
APACHE II score	16.5(13,24)	16.5(14,24)	-0.538	0.591
SOFA score	12.11 ± 3.37	12.00 ± 3.40	0.220	0.920
RASS score	-3.1 ± 1.32	-2.31 ± 1.13	11.017	0.085
HR	102.57 ± 18.99	104.06 ± 13.10	2.658	0.783
CVP	9.75 ± 4.34	9.0 ± 2.78	2.98	0.098

HTN,hypertension;DM Diabetes Mellitus;CAD,Coronary Artery Disease;Age (years);Blood temp($^{\circ}$ C);WBC,White Blood Cell;PCT,procalcitonin;APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score;RASS Richmond Agitation-Sedation Scale;HR,heart rate;CVP,central venous pressure; MAP,mean arterial pressure (mmHg);VTI Velocity time integral;CI Cadiac Index ($L \cdot \text{min} \cdot \text{m}^{-2}$); Pv-aCO₂,venous-to-arterial carbon dioxide difference; ScvO₂,Central-venous oxygen saturation;SVRI,Systemic Vascular Resistance Index ($\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{m}^2$); SSVRI,Stroke Systemic Vascular Resistance Index ($\text{mmHg} \cdot \text{cm}^{-1} \cdot \text{m}^2$);NE, norepinephrine ($\mu\text{g}/\text{kg}/\text{min}$).

Variables	Lactate clearance ≥ 20%	Lactate clearance < 20%	Z/F	P value
	(N = 28)	(N = 16)		
MAP	86(80,96)	83(79,91)	-1.734	0.083
VTI	16.93 ± 3.45	15.88 ± 3.52	4.504	0.339
CI	3.06 ± 0.95	2.96 ± 0.89	0.037	0.746
P _{v-a} CO ₂	4.97 ± 3.25	5.30 ± 2.50	0.196	0.733
S _{cv} O ₂	72.04 ± 11.03	74.45 ± 11.93	0.935	0.502
SVRI	2162.41 ± 749.44	2161.8 ± 645.25	0.555	0.998
SSVRI	217.84 ± 80.39	221.91 ± 63.93	1.035	0.855
Lac	2.45(2.3,3.6)	2.9(2.3,3.9)	-2.224	0.026

HTN,hypertension;DM Diabetes Mellitus;CAD,Coronary Artery Disease;Age (years);Blood temp(°C);WBC,White Blood Cell;PCT,procalcitonin;APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score;RASS Richmond Agitation-Sedation Scale;HR,heart rate;CVP,central venous pressure; MAP,mean arterial pressure (mmHg);VTI Velocity time integral;CI Cadiac Index (L·min·m⁻²); Pv-aCO₂,venous-to-arterial carbon dioxide difference; ScvO₂,Central-venous oxygen saturation;SVRI,Systemic Vascular Resistance Index (dyn·sec·cm⁻⁵·m²); SSVRI,Stroke Systemic Vascular Resistance Index (mmHg·cm⁻¹·m²);NE, norepinephrine (µg/kg/min).

SBRI and PI variables of the septic patients according to lactate clearance and control group are shown in Table 3 and Fig. 3. They had statistically difference.SBRI of the Lactate clearance < 20% group is higher than Lactate clearance ≥ 20% group and control group(1.15 ± 0.09 vs. 0.88 ± 0.14,P < 0.01;1.15 ± 0.09 vs 0.79 ± 0.12,P < 0.01). PI of the Lactate clearance < 20% group is lower than Lactate clearance ≥ 20% group and control group(0.75 ± 0.69 vs.2.22 ± 1.20,P < 0.01;0.75 ± 0.69 vs 2.5 ± 1.66,P < 0.01).

Table 3
Peripheral vascular related-variables in the different groups

Variables	Control	All Septic shock	Lactate clearance ≥ 20%	Lactate clearance < 20%
	N = 20	N = 44	N = 28	N = 16
PI	2.22 ± 1.20 ^{a,c}	1.87 ± 1.63	2.50 ± 1.66 ^b	0.75 ± 0.69 ^c
SBRI	0.79 ± 0.12 ^{a,c}	0.94 ± 0.15	0.88 ± 0.14 ^b	1.15 ± 0.09 ^c

aP < 0.05 for controls vs. all septic shock; bP < 0.05 for Lactate clearance > 20% vs. Lactate clearance < 20%.; cP < 0.05 for controls vs. Lactate clearance < 20%.PI,Perfusion Index;SBRI snuffbox resistive index.

SBRI and PI as predictors of 6 h-lactate clearance

The cutoff value and areas under the receiver operating characteristic (ROC) curves for the related variables used for predicting 6 h-lactate clearance after resuscitation are shown in Table 4. The cutoff of the PI value was ≤ 0.99 for predicting 6 h-lactate clearance after resuscitation, resulting in a sensitivity of 64.3% and a specificity of 81.2%. The cutoff of the SBRI value was ≥ 1.09 for predicting 6 h-lactate clearance after resuscitation, resulting in a sensitivity of 68.8% and a specificity of 85.7%.The SBRI was significantly better than the PI for predicting 6 h-lactate clearance after resuscitation(AUC:0.805 vs.0.703, P < 0.05) (Table 4, Fig. 4).

Table 4
Comparison of the areas under the ROC curves for predicting 6 h-Lactate clearance in the septic patients.

Variable	Cut point	AUC	SE	P	Sensitivity	Specificity	95% CI	
							Lower	Upper
PI	0.99	0.703	0.082	0.010	0.643	0.812	0.542	0.864
SBRI	1.09	0.805 ^a	0.067	0.000	0.688	0.857	0.673	0.937

aP < 0.05 for comparison of SBRI vs, PI. PI,Perfusion Index;SBRI snuffbox resistive index.

Discussion

The main finding of our study was that higher SBRI and lower PI are associated with lower 6 h-lactate clearance after resuscitation in septic patients. The SBRI predicted 6 h-lactate clearance with an accuracy that was better than PI. SBRI is a better indicator of abnormal tissue perfusion than CI in septic

shock. Thus, using SBRI monitoring appears as a simple but powerful tool to assess global resuscitation status.

Based on blood-flow monitoring by Doppler ultrasonography, recent advances in ultrasound technology have enabled both morphological analysis and functional assessment of various diseases. In patients with extreme hemodynamics, including those who have had following an emergency and open-heart surgery, it is very important to know the impairment of the peripheral circulation. Resistive index (RI) is a parameter that not only indicates the absolute value of blood flow velocity but also reflects changes in Doppler waveforms^[7]. Previous studies have shown that it has mainly been to evaluate blood flow to a target organ. The combination of renal RI and CVP was valuable in the early prediction for sepsis-induced AKI^[20]. Lindsay R Clark et al found that index of cerebrovascular resistance is a potential vascular biomarker and it suggest that regionally-specific vascular changes may contribute to cognitive decline, particularly in the very-old^[21]. But, RI can also associate with hemodynamics^[9]. If RI could be used simply to quantify peripheral blood vessel resistance, based on a different perspective from that of cardiac output and oxygen saturation of mixed-venous blood, it could be an important parameter for circulation control. Because the waveforms obtained by the Doppler method are influenced by the angle between the ultrasound beam and blood flow direction, the incidence angle is critical in the Doppler analysis of blood flow, and an angle smaller than 60° is required to reduce the error to less than 20%. The SB denotes the site of depression located at the base of the thumb. The artery crossing this region connects the dorsal branch of the radial artery and deep palmar arch, and runs perpendicularly to the body surface. Therefore, a very small incidence angle of the Doppler beam is obtained, showing the SB to be ideal for Doppler analysis of blood flow. Kochi et al suggested that SB blood flow monitoring is useful to examine the patency of both radial and ulnar arteries before harvesting for coronary artery bypass grafting, and it can be applied clinically as a reliable alternative to Allen's test^[22]. Koji Ban et al studied Fifteen patients after cardiac surgery, and these findings show that SBRI measured may serve as an indicator of peripheral vascular resistance, and may be effective for the evaluation of peripheral circulatory disturbance^[7]. Hence, it's very reliable using SBRI to evaluate the peripheral vascular function.

The evidence that lactate is a marker of illness severity in all situations of physiological stress is overwhelming^[23]. It can powerful predicte outcome or mortality of septic patients. In the recent ARISE trial, data were prospectively collected on lactate levels at randomization^[24]. one-third of patients were approximately randomized because of isolated hyperlactatemia and compared with patients randomized because of isolated hypotension. Despite similar age and sources of infection, patients with isolated hyperlactatemia were less likely to be discharged alive form ICU and hospital and had 1.7 times the risk of 90-day mortality. So in our study, based on whether the 6 h-lactate clearance rate was greater than or equal to 20%, septic patients were devided two groups. During shock resuscitation, if the low tissue perfusion did not improve after the large circulation index became normal, it suggests that further indexes were needed to clarify the problem. Our study found that Parameters including CI, Pv-aCO₂, and ScvO₂ had no significant difference between the Lactate clearance ≥ 20% and the Lactate clearance < 20% group (P > 0.05), but SBRI and PI were significant statistical differences between two groups. Combined with their

association with lactate, they suggest that the peripheral circulation is closer to tissue perfusion and microcirculation compared with the central circulation. Our study also found that SBRI was significantly higher in the patients with septic shock than in the control group. Most published reports support that the peripheral circulation is among the first to deteriorate and the last to be restored, therefore, in the process of circulatory resuscitation, more attention to the improvement of peripheral circulation is more conducive to the improvement of tissue perfusion. As we know, this is the first study to explore the relationship between SBRI and tissue perfusion and lactate clearance in septic patients after resuscitation. We found that the cutoff point of the SBRI value was ≥ 1.09 for predicting 6 h-lactate clearance after resuscitation, resulting in a sensitivity of 68.8% and a specificity of 85.7%. The SBRI was significantly better than the PI for predicting 6 h-lactate clearance after resuscitation. So it may be suggested as a reliable and early indicator of resuscitation success.

In our study, SBRI and CI showed the largest difference between septic shock group and control group. We analysed the relationship between SBRI and the hemodynamic parameters. There was no relationship between SBRI and cardiac index. This may be related to a heterogeneous distribution of blood flow in sepsis. Previous studies provide evidence for this^[25]. He and colleagues explored the relationship between global and peripheral perfusion variables following initial resuscitation in septic patients, showing that peripheral vasoconstriction can be a hallmark of early septic shock^[26]. We identified a significant correlation between SBRI and tissue perfusion variables such as arterial lactate level and PI. This suggests that SBRI reflects more the peripheral tissue perfusion than the global hemodynamic status.

Because the snuffbox radial artery is one of the nearest arteries to the tip of the finger, many factors may impact the SBRI value and PI value (temperature, level of consciousness, vasopressors and endogenous catecholamines)^{[26],[27]}. Since central aortic vessels have little smooth muscle relative to their vascular walls whereas peripheral vasculature has much reactive smooth muscle architecture it is reasonable that they may be differentially affected by vasodilating substances during endotoxemic shock^[28]. In this study, all the patients needed mechanical ventilation and sedatives, and there were no differences in temperature and RASS score between Lactate clearance $\geq 20\%$ group and the Lactate clearance $< 20\%$ group. Thus, the SBRI and PI were relatively comparable in this study.

In our study, the SBRI was correlated with PI ($r = -0.740, P < 0.001$) and lactate ($r = 0.517, P < 0.001$). So we think that there are several advantages of the SBRI in comparison with the current global endpoints of resuscitation: (1) the SBRI indicators may provide a specific endpoint of resuscitation rather than the average survival values of Pv-aCO₂ and ScvO₂; (2) Assumption that the peripheral tissue is the last to perfuse during shock resuscitation, the SBRI monitors may provide information on internal organ perfusion; (3) the techniques of ultrasound are noninvasive, and the equipment is readily available and simple operation. If Peripheral vascular function monitoring during shock resuscitation becomes routine, and if the critical values defined in this paper are validated by further study, the importance of SBRI monitoring will be affirmed.

The limitations of this study include the small sample size and the prospective design conducted at a single center. Therefore, there is a risk of information bias. In this study, we investigated the predictive value of 6 h-lactate clearance, but we did not analyse the underlying mechanisms leading to SBRI changes according to outcome of septic shock. In the context of severe infection, sympathetic activation and endothelial dysfunction could both participate to impairment of distal blood flow and in fine to changes in peripheral vascular tension.

Conclusions

In a prospective observational study of critically ill patients with severe infections, SBRI correlated with tissue perfusion parameters. Abnormal SBRI was better than PI in suggesting disorder of lactate clearance. SBRI is a better indicator of abnormal tissue perfusion than CI. Further investigations are required to determine whether the correction of abnormal SBRI and PI may improve success rate of resuscitation of septic shock.

Abbreviations

PI, Perfusion Index; SBRI snuffbox resistive index; HTN, hypertension; DM Diabetes Mellitus; CAD, Coronary Artery Disease; WBC, White Blood Cell; PCT, procalcitonin; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment score; RASS Richmond Agitation-Sedation Scale; HR, heart rate; CVP, central venous pressure; VTI Velocity time integral; CI Cardiac Index; Pv-aCO₂, venous- to-arterial carbon dioxide difference; ScvO₂, Central-venous oxygen saturation; SVRI, Systemic Vascular Resistance Index; SSVRI, Stroke Systemic Vascular Resistance Index; MAP, mean arterial pressure. LVOT, left ventricular outflow tract; ROC, receiver operating characteristic; TTE, Transthoracic echocardiography; BSA, body surface area.

Declarations

Ethics approval and consent to participate

The Peking Union Medical College Hospital Ethics Committee approved the study (No. ZS-2153), and all patients were involved in the study based on the voluntary principle and had signed informed consent form. Informed consent was obtained from all patients. We would maximize the protection of the interests of patients and would not cause harm to any patients.

Consent for publication

All authors agree to publish in this journal.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

Xiaoting Wang and Dawei Liu conceived and designed the study, interpreted data and helped draft the manuscript. Cui Wang participated in the study conception and design, recruited patients, collected data, performed the statistical analysis, interpreted the data and drafted the manuscript. Hongmin Zhang and Wei Huang 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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Figures

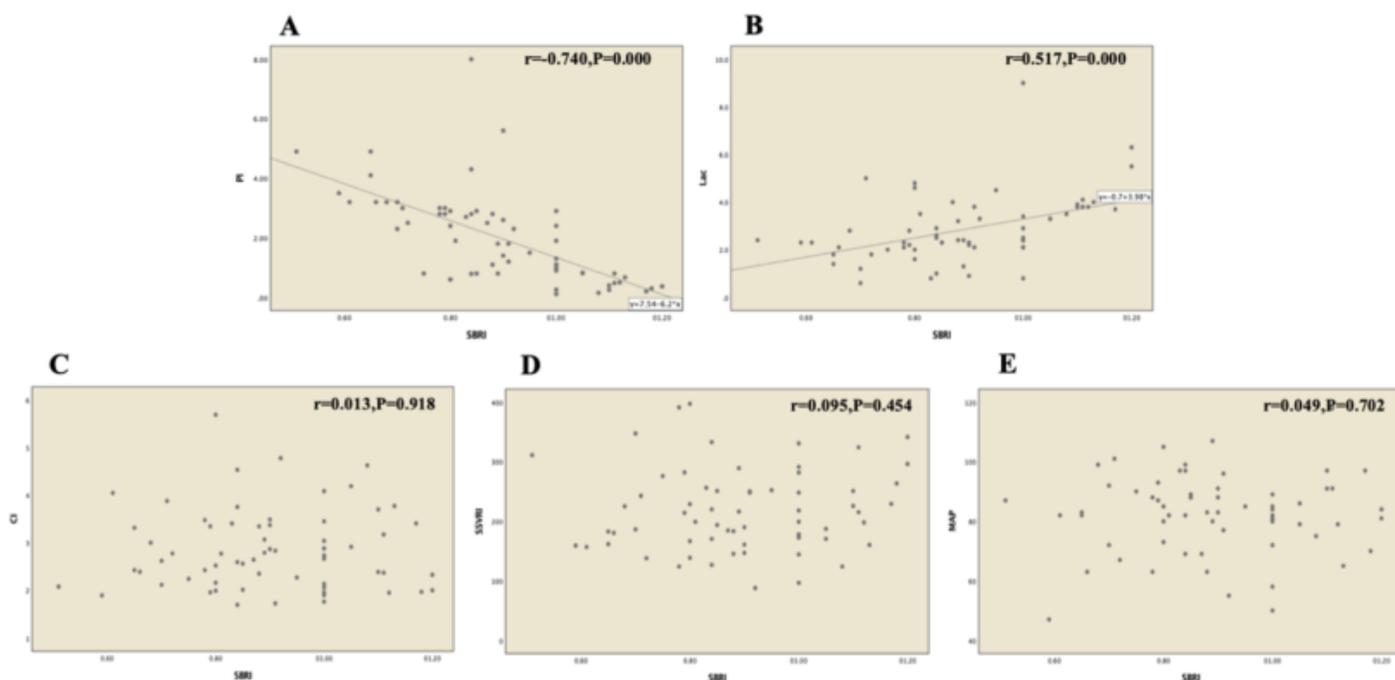


Figure 1

Relationship between SBRI and hemodynamic parameters in a pooled analysis of patient with control group and septic shock group. A: PI, Perfusion Index (PI); B: arterial lactate level; C: cardiac index (CI, L·min⁻¹·m⁻²); D: Stroke Systemic Vascular Resistance Index (SSVRI, mmHg·cm⁻¹·m²); E: mean arterial pressure (MAP, mmHg).

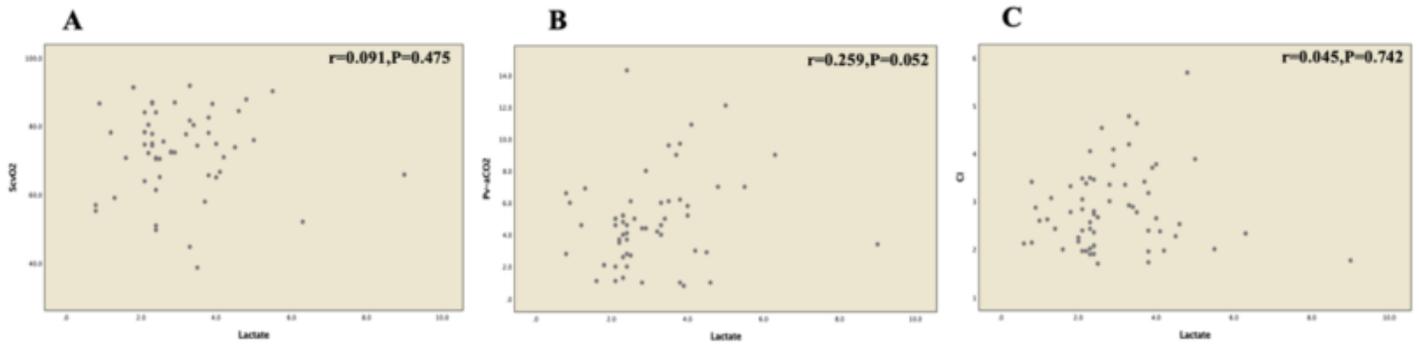


Figure 2

Relationship between Lactate and hemodynamic parameters in a pooled analysis of patient with control group and septic shock group. A: Central-venous oxygen saturation (ScvO₂); B: venous-to-arterial carbon dioxide difference (Pv-aCO₂, mmHg); C: cardiac index (CI, L·min·m⁻²).

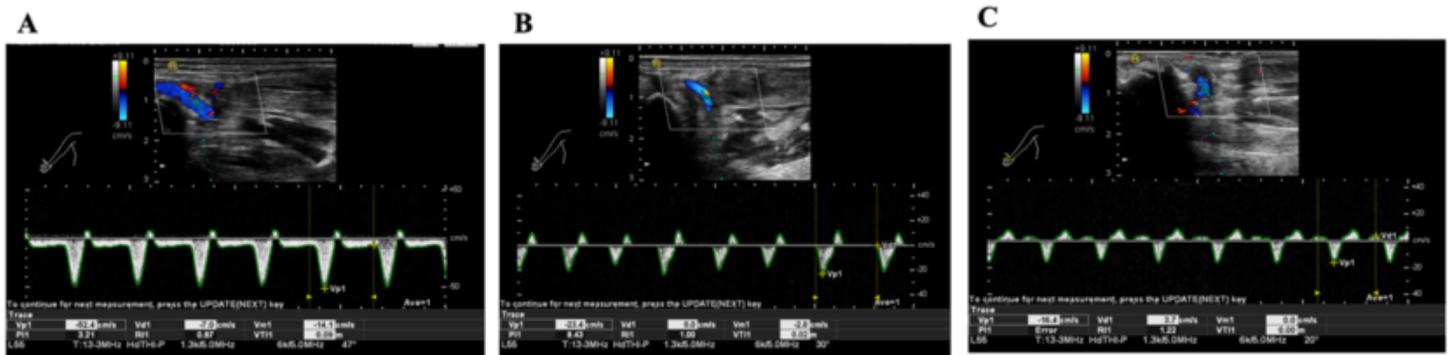


Figure 3

The Doppler waveforms of the radial artery in the snuffbox (SB). A: Normal snuffbox resistive index (SBRI) from control group, resistive index (RI)=0.87; B: High SBRI from septic shock group: Doppler waveforms without diastolic flow at the SB (RI=1.0); C: High SBRI from septic shock group: Doppler waveforms with reverse end-diastolic flow at the SB (RI=1.22).

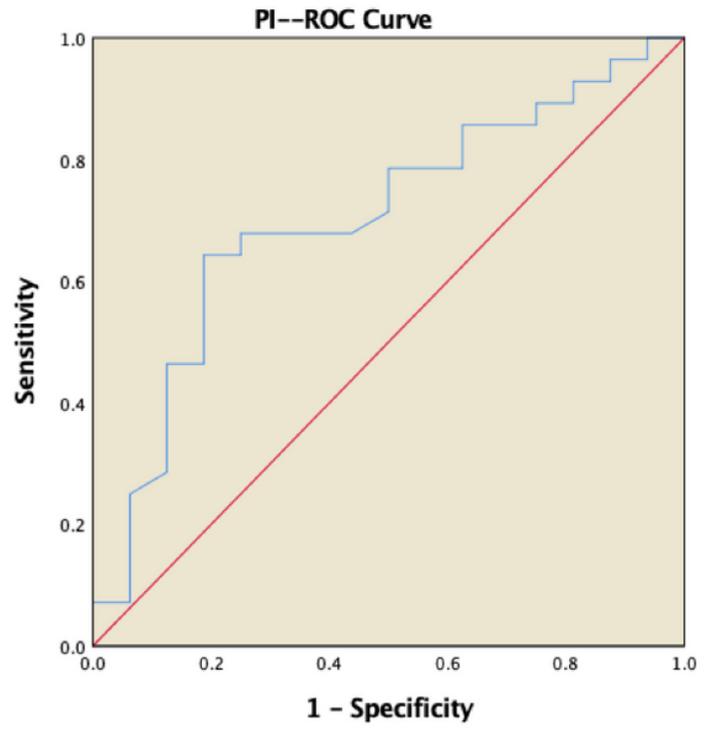
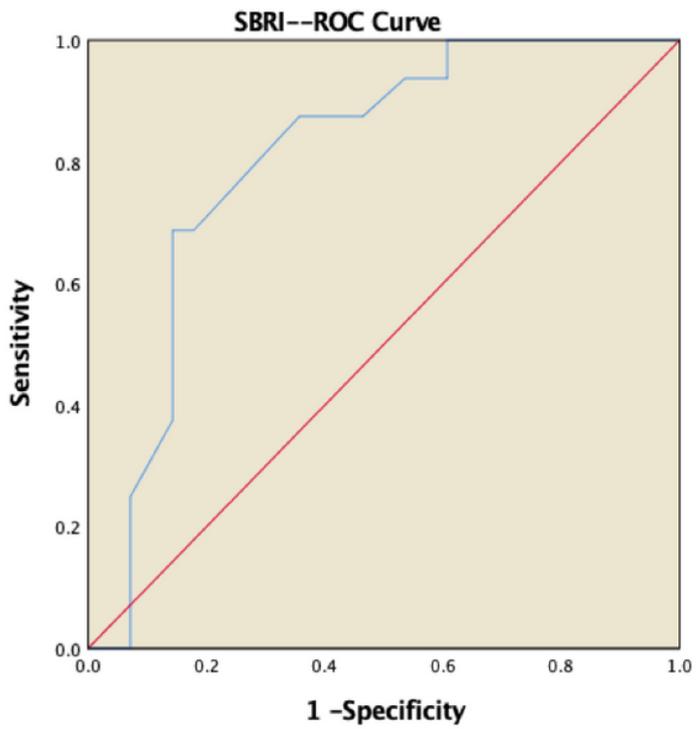


Figure 4

ROC curves comparing the ability of SBRI and PI to discriminate 6h-lactate clearance of septic patients