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Relationship between skin microvascular blood flow and capillary refill time in critically ill patients

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Abstract

Background Capillary refill time (CRT) and skin blood flow (SBF) have been reported to be strong predictors of mortality in critically ill patients. However, the relationship between both parameters remains unclear.

Methods We conducted a prospective observational study in a tertiary teaching hospital. All patients older than 18 years admitted in the intensive care unit (ICU) with circulatory failure and a measurable CRT were included. We assessed index SBF by laser doppler flowmetry and CRT on the fingertip, at T0 (Within the first 48 h from admission) and T1 (4 to 6 h later). Correlation was computed using Spearman or Pearson's formula.

Results During a 2-month period**,** 50 patients were included, 54% were admitted for sepsis. At baseline median CRT was 2.0 [1.1–3.9] seconds and median SBF was 46 [20–184] PU. At baseline SBF strongly correlated with CRT ($R^2 = 0.89$; $p < 0.0001$, curvilinear relationship), this correlation was maintained whether patients were septic or not ($R^2 = 0.94$; $p = 0.0013$; $R^2 = 0.87$; $p < 0.0001$, respectively), and whether they received norepinephrine or not ($R^2 = 0.97$; $p = 0.0035$; $R^2 = 0.92$; $p < 0.0001$, respectively). Between T0 and T1, changes in SBF also significantly correlated with changes in CRT ($R^2 = 0.34$; $p < 0.0001$). SBF was related to tissue perfusion parameters such as arterial lactate level ($p = 0.02$), whilst no correlation was found with cardiac output. In addition, only survivors significantly improved their SBF between T0 and T1. SBF was a powerful predictor of day-28 mortality as the AUROC at T0 was 85% [95% IC [76–91]] and at T1 90% [95% IC [78–100]].

Conclusion We have shown that index CRT and SBF were correlated, providing evidence that CRT is a reliable marker of microvascular blood flow.

Trial registration Comité de protection des personnes Ouest II N° 2023-A02046-39.

Keywords Blood flow, Capillary refill time, Tissue perfusion

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Background

It is now widely admitted that microcirculatory alterations are a major cause of organ hypoperfusion in various conditions affecting critically ill patients [1–6]. Studies have consistently demonstrated that the severity of these alterations and their persistence after resuscitation are independently associated with mortality [5, 7]. To develop patho-physiologically oriented resuscitation algorithms, intensivists need tools to accurately monitor microvascular blood flow. Video microscopy using Sidestream Dark Field imaging provide interesting information with a direct visualization of sublingual microvascular blood flow but remains difficult to use routinely at bedside [8]. The skin, an easily accessible organ, allows clinicians to assess peripheral tissue perfusion with noninvasive parameters such as Capillary Refill Time (CRT). This easy to use and noninvasive tool is powerful to identify patients with worse outcomes in a wide range of critical illnesses [9]. CRT also responds rapidly to resuscitation [10], making it a dynamic method to allow adjustment of therapy. The recent ANDROMEDA Shock multicentric randomized controlled trial, among patients with septic shock, has shown promising results with a resuscitation strategy targeting CRT compared to a strategy targeting serum lactate levels. Indeed, this strategy was associated with lower mortality and less organ dysfunction [11]. Therefore, the international guidelines of the latest Surviving Sepsis Campaign incorporated the monitoring of CRT [12].

CRT is related to other parameters that reflect organ perfusion [13] and notably related to sublingual microcirculation [14]. Thus, it is assumed that CRT reflects microvascular blood flow of the skin. However, this is indirect evidence, and the pathophysiology of prolonged CRT remains unknown. Several techniques have been implemented to try to quantify more precisely peripheral perfusion such as monitoring skin blood flow (SBF) using laser doppler flowmetry [15, 16]. The operating principle of this method is based on the doppler phenomenon allowing a measurement of microvascular blood flow [17]. This simple to use, noninvasive, quantitative, real-time measurement tool has been of gaining interest [16]. Recently, a prospective study has shown that in patients with circulatory shock, fingertip SBF alteration significantly correlated with serum lactate level and organ failure severity [18]. However, the relationship between SBF and CRT remains insufficiently examined.

The aim of this prospective study was to analyze the relationship between CRT and SBF in the fingertip area in a population of patients in the Intensive Care Unit (ICU) at admission and their kinetics.

Methods

We conducted a prospective observational study in an 18-bed ICU tertiary teaching hospital. During a 2-month period, all consecutive patients, older than 18 years with circulatory failure, admitted in the ICU were included. Circulatory failure included macro-circulatory disorders (Mean arterial pressure < 65 mmHg, heart rate > 100/min), micro-circulatory disorders (mottling, prolonged CRT, oliguria, hyperlactatemia) or therapeutic intervention (fluid challenge, vasopressor, inotropic drug). We excluded patients with dark skin or skin lesions that rendered study measurements of CRT difficult. Patients with hemorrhagic shock were also excluded because severe anemia may be a confounder for Laser Doppler analysis. The observational protocol was approved by the ethical committee, Comité de Protection des Personnes (Comité de protection des personnes Ouest II N° 2023-A02046-39). All patients were informed of the study and gave oral consent for participation.

CRT measurements

CRT was assessed by a trained physician. As previously reported and standardized by our group, CRT was measured by applying firm pressure to the distal phalanx of the index finger for 15 s. The pressure applied was just enough to remove the blood at the tip of the physician's nail, which was illustrated by the appearance of a thin white distal crescent (blanching) under the nail. A chronometer recorded the time to return to the baseline color [13]. As demonstrated in the study by Raia et al. [10], this method is highly reproducible and very accurate after training and standardization. A CRT variation larger than 0.2 s was identified as significant.

SBF measurements

SBF was evaluated using a skin laser doppler device (PeriFlux System 5000; Perimed, Jarfalla, Sweden). The emitted laser beam has a wavelength of 780 nm, allowing evaluation at 0.5 to 1 mm depth under the skin. The back-scattered light is shifted by moving red blood cells in a wavelength proportional to their velocity, providing a quantitative noninvasive measurement of SBF in perfusion units (PUs) independently from skin color and oxygen saturation.

SBF measurement was standardized by attaching the probe with a double-sided tape on the palmar surface of the index finger. Patients were asked to refrain from movement during the measurement. Data was recorded after signal stabilization, continuously for 1 min, and SBF was determined as the mean value during this period. CRT and SBF were both measured on the same finger, specifically on the hand opposite the arterial line or blood pressure cuff to avoid any potential interference. To limit

interpretation bias, CRT was measured first, followed immediately by SBF measurement on the same finger. No changes in therapeutic interventions were made between these measurements. Finally, to avoid confounders, in our ICU, room temperature was controlled and maintained at 25 °C.

Protocol and data collection

Patients were admitted directly from the emergency department or medical ward and managed by a team of intensivists different from those who performed the CRT and SBF measurements.

General characteristics of patients were recorded at admission including demographic data, reason for admission, severity of illness evaluated by the SOFA score [19] and the simplified acute physiology score II [20].

Patients were included during the 48 h following admission with data being collected at 2 time points: at inclusion (T0) and 4 to 6 h after inclusion (T1). Patients were not included during the night and the weekends. We recorded the presence of mechanical ventilation and the need for catecholamine. We also collected data reflecting macro-hemodynamics and organ perfusion. Macro-hemodynamic was assessed using mean arterial pressure, heart rate, cardiac output measured by echocardiography and the dosage of norepinephrine if required. Organ perfusion was assessed through arterial lactate level, capillary refill time and mottling score. Survival status was recorded 28 days after inclusion.

Statistical analysis

After discarding normal distribution, non-parametric tests were used. Patient characteristics were summarized as median (25–75th percentiles) and percentages as appropriate. Correlation was computed using Pearson's formula (linear relationship) or Spearman's formula (Non-linear relationship). Comparisons between groups were made with Fisher test for discrete variables and Mann–Whitney test for continuous variables. Comparisons between T0 and T1 in each group of patients were made using a paired Wilcoxon signed-rank test. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy of SBF to predict 28-day mortality. Data are presented as the area under the ROC curve (AUC–ROC) ± SD (with a 95% confidence interval), sensitivity (95% CI) and specificity (95% CI). The Youden index (sensitivity + specificity−1) was calculated to determine the best cutoff values. Statistical significance was set at a two tailed p value < 0.05. All analyses were made using Graphpad Prism softwares (Graphpad Softwares, La Joya, CA).

For the primary outcome sample size calculation, with a two-sided α error of 0.05 and power of 80% and an estimated correlation r-coefficient of 0.7, only 13 patients would be required for the study. However, we considered that a proper sample size is required to address the secondary outcome of SBF-T1 diagnostic accuracy to identify 28-day mortality as well. We estimated the sample size by comparing an expected AUC–ROC of 0.75 with the null hypothesis of 0.50, assuming a 28-day mortality of 25%, two-sided α error of 0.05 and power of 80%. In total, at least 48 cases were required to be included.

Results

Studied population

During a 2 month-period, 62 consecutive patients were eligible. Twelve patients were excluded, 10 patients because of dark skin and 2 because agitation made it impossible to place the device to record SBF, leaving 50 patients for the study. Baseline characteristics are summarized in Table 1. The main reasons for admission were sepsis and septic shock 27 (54%) and the time from admission to inclusion was 5 [1–13] hours. The median SOFA score measured at inclusion was 5 [2–8] and the median SAPS II was 40 [27–51]. Fourteen (28%) patients underwent mechanical ventilation, and ten (20%) required a treatment by norepinephrine with a median dose at inclusion of 0.55 [0.22–0.79] µg/kg/min. Day-28 mortality rate was 22%.

Analysis of baseline skin blood flow

At baseline, median CRT at index was 2.0 [1.1–3.9] seconds and median SBF was 46 [20–184] PU. SBF was correlated with index CRT ($R^2 = 0.89$; $p < 0.0001$), the correlation following an exponential curve (Fig. 1A) whereas the correlation between SBF and 1/CRT was linear ($R^2 = 0.83$; $p < 0.0001$) (Supplementary Figure 1). This correlation was similar in patients receiving norepinephrine ($R^2 = 0.97$, $p = 0.0035$) or not ($R^2 = 0.92$, $p < 0.0001$) (Fig. 1B). The correlation was also identical in patients with ($R^2 = 0.94$, $p = 0.0013$) or without ($R^2 = 0.87$, $p < 0.0001$) sepsis (Fig. 1C). At baseline, there was a significant correlation between SBF and arterial lactate level ($R^2 = 0.35$, $p = 0.02$) but no significant correlation between SBF and cardiac output (Supplementary Figure 2). Finally, we also observed a significant correlation between index SBF and knee CRT ($R^2 = 0.64$, $p < 0.0001$) (Supplementary Figure 3).

Analysis of skin blood flow variations at T1

Global hemodynamic and tissue perfusion parameters were recorded at T1, 4 to 6 h after inclusion. These parameters are summarized in Table 2. Index CRT significantly decreased from 2.0 [1.1–3.9] to 1.6 [1–2.5] seconds ($p = 0.001$) while SBF significantly increased from

Table 1 Baseline characteristics of studied population. Values are shown as median (25–75th percentiles) unless stated otherwise

Characteristics	Total (n = 50)	Survivors (n = 39)	Non survivors (n = 11)	*p*-value
Age, years	66 (48–73)	58 (48–73)	69 (66–73)	0.12
Body mass index, kg/m^2	28 (24–31)	28 (24–32)	27 (23–28)	0.24
Gender, female, n (%)	21 (42)	16 (42)	5 (45)	> 0.99
Comorbidities, n (%)				
Diabetes	12 (24)	9 (23)	3 (27)	> 0.99
Chronic hypertension	22 (44)	17 (44)	5 (45)	> 0.99
Coronary disease	9 (18)	5 (13)	4 (36)	0.09
Stroke	6 (12)	3 (8)	3 (27)	0.11
Time from admission, hours	5 (1–13)	10 (2–13)	4 (2–6)	0.11
Reason for admission, n (%)				
Sepsis	16 (32)	14 (36)	2 (18)	0.27
Septic shock	11 (22)	6 (15)	5 (45)	0.03
Hypovolemia	6 (12)	5 (13)	1 (1)	0.74
Cardiogenic shock	4 (8)	3 (7)	1 (1)	0.88
Other*	13 (26)	11 (28)	2 (18)	0.5
SAPS II	40 (27–51)	38 (23–46)	53 (46–65)	0.002
SOFA	5 (2–8)	4 (2–7)	7 (5–8)	0.07
Norepineprhine				
N (%)	10 (20)	7 (17)	3 (27)	0.7
Dose, µg/kg/min	0.55 (0.22–0.79)	0.4 (0.17–0.72)	0.8 (0.5–2.6)	0.27
Mechanical ventilation, n (%)	14 (28)	12 (31)	5 (45)	0.47
Mean arterial pressure, mmHg	86 (75–94)	87 (80–98)	70 (64–82)	0.003
Heart rate, beats/min	96 (80–114)	89 (79–107)	112 (102–121)	0.02
Cardiac output, L/min	5.6 (4.4–6.4)	5.8 (4.6–6.5)	4.4 (3.8–5.9)	0.06
Temperature, °C	36.5 (36.2–37.2)	36.7 (36.2–37.3)	36.1 (35.5–36.5)	0.1
Lactate, mmol/l	1.9 (1.2–4.6)	1.8 (1.1–2.8)	2.1 (1.5–7.5)	0.21
Hemoglobin, g/dl	11.7 (8.7–13.1)	12.2 (8.7–13.1)	10.7 (8.2–11.4)	0.09
Creatininemia, µmol/l	98 (60–190)	86 (58–159)	125 (82–300)	0.15
Capillary refill time, s				
Index	2.0 (1.1–3.9)	1.5 (1.1–2.8)	4.3 (4.1–5.5)	< 0.0001
Knee	3.0 (1.6–4.6)	2.1 (1.5–3.9)	4.9 (4.2–5.2)	0.002
Skin blood flow, Perfusion Units	46 (20.3–184)	74 (27–205)	16 (11–22)	0.0002

SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment

* Other main reasons for admission were acute pancreatitis, self-poisoning and cytokine release syndrome after CAR T cell therapy

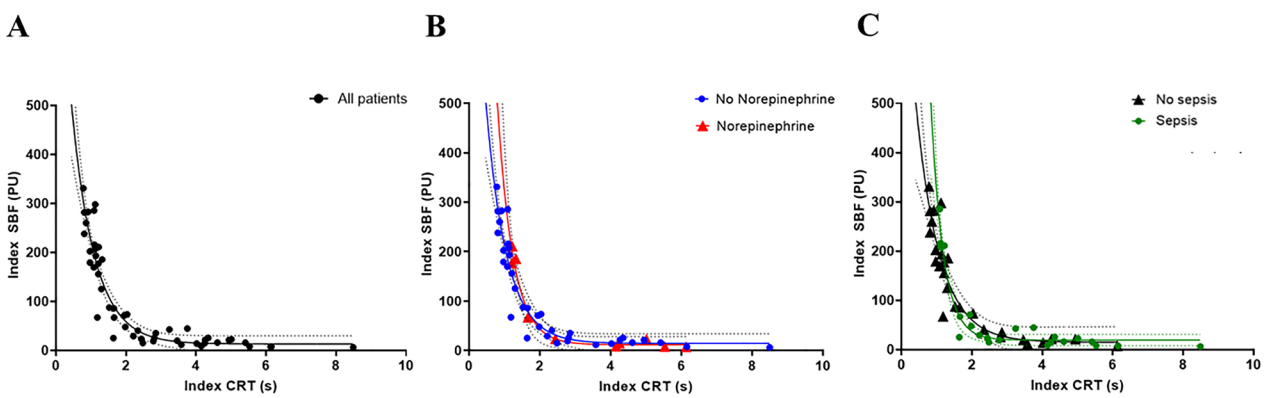

Fig. 1 Correlation between capillary refill time and skin blood flow at baseline. **A** Correlation between CRT and SBF measured on the index, **B** in patients with (red) or without norepinephrine (blue) **C** in patients with (green) or without sepsis (black). Spearman test. CRT, capillary refill time; SBF, skin blood flow; PU, perfusion units

Table 2 Changes of hemodynamic and skin perfusion parameters

Characteristic	Baseline	T1	*p*-value
Mean arterial pressure, mmHg	86 (75–94)	80 (72–94)	0.43
Heart rate, beats/min	96 (80–114)	98 (82–113)	0.54
Cardiac output, L/min	5.6 (4.4–6.4)	5.7 (4.2–6.3)	0.08
Norepinephrine			
N (%)	10 (20)	11 (22)	> 0.99
Dose, µg/kg/min	0.55 (0.22–0.79)	0.25 (0.11–0.70)	0.06
Lactate, mmol/l	1.9 (1.2–4.6)	1.9 (1.2–2.3)	0.54
Capillary refill time, s			
Finger	2 (1.1–3.9)	1.6 (1–2.5)	0.001
Knee	3 (1.6–4.6)	2.5 (1.5–3.5)	0.004
Finger CRT > 3 s	17 (34)	8 (16)	0.06
Skin blood flow, Perfusion units	46 (20–184)	112 (29–200)	0.02

CRT, capillary refill time

46 [20–184] to 112 [30–200] PU ($p=0.02$). There was no significant change in mean arterial pressure, heart rate or cardiac output between T0 and T1. Changes in CRT and SBF between T0 and T1 were significantly correlated ($R^2=0.34$, $p<0.0001$) (Fig. 2). There was no significant correlation between variations of SBF and variations of cardiac output ($R^2=0.12$; $p=0.06$) (Supplementary Figure 4A). However, changes in SBF and lactate level were significantly correlated ($R^2=0.41$; $p=0.02$) (Supplementary Figure 4B).

Relationship between skin blood flow and outcome

Day-28 mortality rate was 22%. At baseline, when compared to survivors, non-survivors had higher SOFA ($p=0.07$), SAPS II ($p=0.002$), heart rate ($p=0.02$), index and knee CRT ($p<0.0001$ and $p=0.002$) (Table 1). Interestingly, we found that T0 index SBF was significantly lower in non-survivors 16 (11–22) vs 74 (27–205) ($p=0.0002$). As shown on Fig. 3, the AUROC for predicting day-28 mortality of T0 SBF was 0.85 [0.74–0.96] ($p=0.0004$). A threshold of T0 SBF < 27 PU predicted 28-day mortality, with a sensitivity of 0.93 IC 95% [0.70–0.99] and a specificity of 0.85 IC 95% [0.76–0.91].

In addition, the kinetics of SBF are of interest. When focusing on patients with baseline impaired tissue perfusion (defined by CRT > 3 s), survivors significantly improved their SBF between T0 and T1 ($p=0.02$) (Fig. 4A–B), whereas non-survivors did not ($p=0.15$) (Fig. 4C–D). The AUROC for predicting day mortality of SBF at T1 was 0.90 [0.78–1.00] ($p=0.0003$). A Threshold of T1 SBF < 28 PU predicted 28-day mortality with a specificity of 0.93 IC 95% [0.78–0.99] and a sensitivity of 0.78 IC 95% [0.45–0.96] (Supplementary Figure 5).

Discussion

In this prospective study, we observed that index CRT and SBF measured by laser doppler flowmetry were strongly and exponentially correlated. This correlation remains robust whether patients were septic or not, and whether patients required norepinephrine or not. After 4 to 6 h, the changes in CRT and SBF were also correlated.

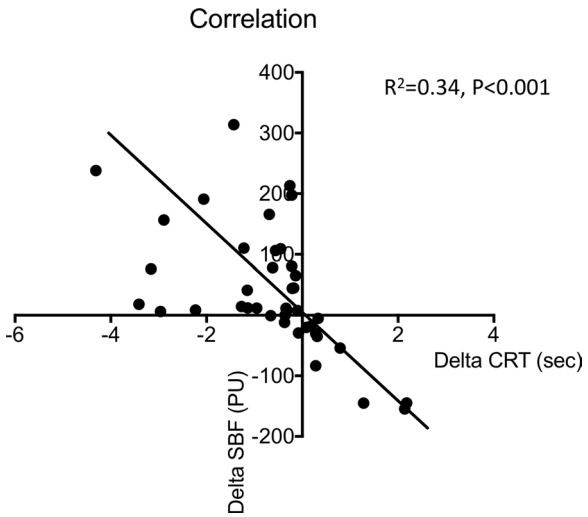

Fig. 2 Correlation between capillary refill time and skin blood flow variations. Correlation of changes between T0 and T1 in CRT and SBF, ΔCRT = CRT T1–CRT T0, ΔSBF = SBF T1–SBF T0. Pearson test. CRT, capillary refill time; SBF, skin blood flow; PU, perfusion units

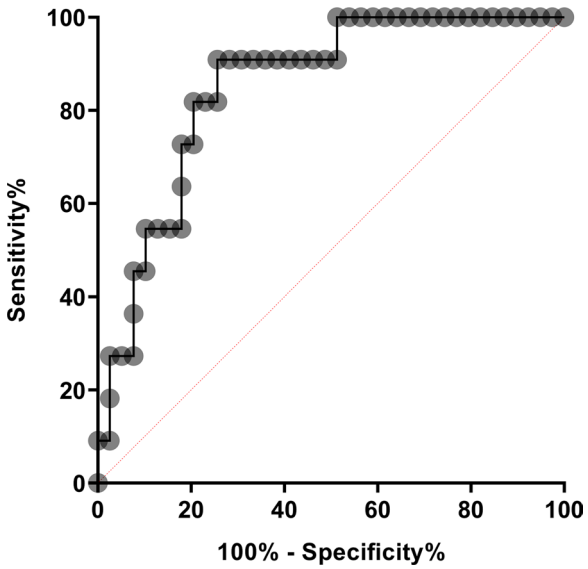

Fig. 3 Prediction of day-28 mortality by baseline skin blood flow

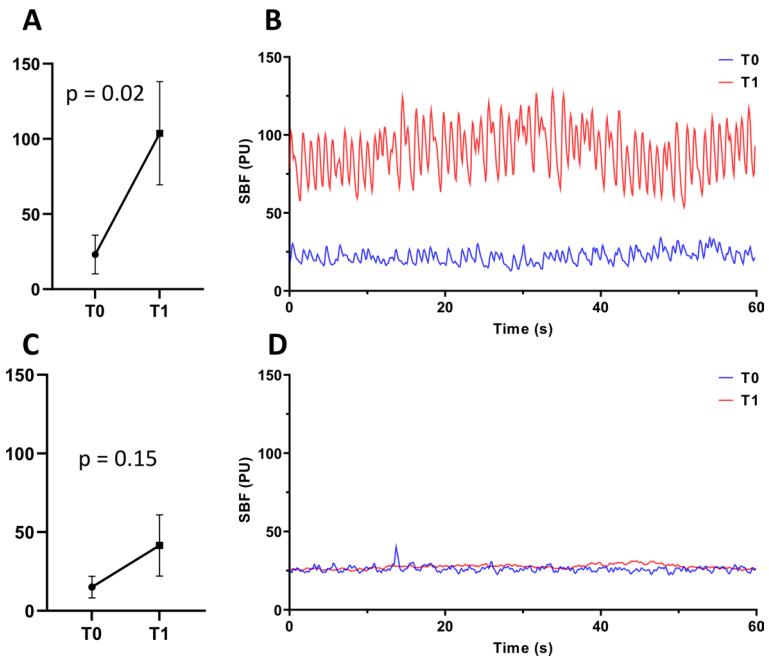

Fig. 4 Variations of skin blood flow in survivors and non survivors. Variations between T0 and T1 of SBF in survivors with initial CRT > 2.5 s **A** and in non survivors **C** Example of variations between T0 (blue) and T1 (red) of SBF in a survivor **B** and a non-survivor **D**. CRT, capillary refill time; SBF, skin blood flow; PU, perfusion units

Finally, baseline as well as SBF variations were significantly different according to the outcome.

CRT is a powerful tool used by physicians to assess the severity of an acute illness [13, 21, 22]. It is assumed that CRT reflects microvascular peripheral perfusion. However, a causal association had never been established. Our results support the direct relationship between prolonged CRT and microvascular blood flow impairment. Indeed, the baseline value of CRT was correlated to baseline SBF with an R^2 value of 0.89. This direct relationship is reinforced by the observation that variations of SBF in time were also correlated with CRT variations, though the correlation was less important ($R^2 = 0.34$), suggesting that additional parameters may impact CRT changes during resuscitation. The relationship remained statistically significant regardless of baseline circulatory failure type, vasopressor requirement. There is a clear break in the slope of the relationship for values of CRT around 2.5 s, and the magnitude of SBF value variations differs when the CRT value is below or above 2.5 s. The physiological mechanisms driving this phenomenon warrant further research. Nevertheless, the relationship between CRT and SBF remains statistically significant whatever the baseline CRT value, suggesting SBF could be a useful tool for all patients. Our results are in line with the study by Contreras et al. [23] performed on 11 selected patients with septic shock which also found a strong correlation between CRT and SBF, but expands this association to a wider non-selected ICU population. This allowed us to explore the relationship between both parameters in a broader range of CRT values and across a variety of acute conditions. These results are consistent with the fact that CRT has been reported to be predictive of outcome in a wide range of acute illnesses including septic shock [13], cardiogenic shock [24] and severe dehydration in children [9].

In our study both baseline SBF value and its variations through resuscitation were correlated with outcome. This is consistent with the recent study of Mongkolpun [18], however our results need to be interpreted cautiously since we included a mixed population of critically ill patients and the number of death was limited in our study (N = 11). We also found a correlation between both baseline values and kinetics of arterial lactate level and SBF. This reinforces the hypothesis that assessment of microcirculatory skin perfusion, is a "window" on the microcirculatory perfusion of other organs. Indeed we have previously reported that skin perfusion significantly correlates with both urinary output and arterial lactate levels [13, 25], while prolonged CRT has been associated with abnormal sublingual microcirculation [14].

ANDROMEDA-SHOCK was a convincing trial showing that resuscitation could be managed using peripheral tools and more specifically CRT [11]. Recent international guidelines recommend the use of CRT to

guide sepsis management [12]. However, CRT has several limitations. Firstly, without training, interobserver variability of CRT is high [26]. Secondly, factors such as skin pigmentation affect its measurement. Finally, CRT can be measured repetitively but not monitored continuously. A monitoring tool whose value and variations would have a similar association with outcome as CRT, while lacking its inherent limitations could be a valuable alternative to guide resuscitation. Unfortunately, no device is yet routinely available to measure SBF at the bedside.

In our study, we have shown the correlation between changes in SBF and 1/CRT, and the association of SBF and its variations with outcome. SBF provides a precise, objective, quantitative measure, independent from skin pigmentation as well as the possibility of continuous monitoring and could be a powerful alternative to CRT to guide resuscitation. The impact of resuscitation strategies such as fluid expansion on SBF needs further assessment.

Our study has several limitations. It is a monocentric study, and results need to be confirmed in a larger population. Nonetheless, while the size of this study was relatively small, it was powerful enough to highlight significant results. The time from admission to inclusion in our study was short highlighting that analysis were performed at early stages but the impact of initial resuscitation on skin blood flow was probably not fully explored. Finally, we investigated global microvascular blood flow, but we did not analyze the precise mechanisms leading to alteration of skin perfusion such as endothelial dysfunction, alteration of vasomotor tone or changes in blood viscosity [27].

Conclusion

Using laser doppler flowmetry, we have shown that, in a non-selected population of ICU patients, index skin blood flow was correlated with capillary refill time, suggesting that CRT is an accurate reflection of microvascular blood flow. Their variation during resuscitation is also related, and predictive of mortality.

Abbreviations

CRT	Capillary refill time
SBF	Skin blood flow
PU	Perfusion unit
ICU	Intensive care unit
SAPS II	Simplified acute physiology score II
SOFA	Sequential organ failure assessment
CPP	Comité de protection des personnes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05285-y.

Additional file1

Author contributions

Study concept and design, all authors. Acquisitions of data, all authors. Drafting of the manuscript, AM and HAO. Critical revision of manuscript, all authors. Statistical analysis, AM, JJ, EK and HAO. All authors read and approved the final manuscript.

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None.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The protocol was approved by a national IRB (Comité de protection des personnes Ouest II N° 2023-A02046-39). All patients were informed of the study and gave oral consent for participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Vincent JL, De Backer D. Microvascular dysfunction as a cause of organ dysfunction in severe sepsis. Crit Care. 2005;9:S9-12.
2. Top APC, Ince C, de Meij N, van Dijk M, Tibboel D. Persistent low microcirculatory vessel density in nonsurvivors of sepsis in pediatric intensive care. Crit Care Med. 2011;39(1):8–13.
3. Tachon G, Harrois A, Tanaka S, Kato H, Huet O, Pottecher J, et al. Microcirculatory alterations in traumatic hemorrhagic shock. Crit Care Med. 2014;42(6):1433–41.
4. Scorcella C, Damiani E, Domizi R, Pierantozzi S, Tondi S, Carsetti A, et al. MicroDAIMON study: microcirculatory DAIly MONitoring in critically ill patients: a prospective observational study. Ann Intensive Care. 2018;8(1):64.
5. 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(9):1825–31.
6. den Uil CA, Lagrand WK, van der Ent M, Jewbali LSD, Cheng JM, Spronk PE, et al. Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. Eur Heart J. 2010;31(24):3032–9.
7. 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(8):2287–94.
8. Duranteau J, De Backer D, Donadello K, Shapiro NI, Hutchings SD, Rovas A, et al. The future of intensive care: the study of the microcirculation will help to guide our therapies. Crit Care. 2023;27(1):190.
9. Hariri G, Joffre J, Leblanc G, Bonsey M, Lavillegrand JR, Urbina T, et al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. Ann Intensive Care. 2019;9(1):37.

10. Raia L, Gabarre P, Bonny V, Urbina T, Missri L, Boelle PY, et al. Kinetics of capillary refill time after fluid challenge. Ann Intensive Care. 2022;12(1):74.
11. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019;321(7):654–64.
12. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.
13. Ait-Oufella H, Bige N, Boelle PY, Pichereau C, Alves M, Bertinchamp R, et al. Capillary refill time exploration during septic shock. Intensive Care Med. 2014;40(7):958–64.
14. Huang W, Xiang H, Hu C, Wu T, Zhang D, Ma S, et al. Association of sublingual microcirculation parameters and capillary refill time in the early phase of ICU admission. Crit Care Med. 2023;51(7):913–23.
15. Roustit M, Cracowski JL. Non-invasive assessment of skin microvascular function in humans: an insight into methods. Microcirculation. 2012;19(1):47–64.
16. Roustit M, Blaise S, Millet C, Cracowski JL. Reproducibility and methodological issues of skin post-occlusive and thermal hyperemia assessed by single-point laser Doppler flowmetry. Microvasc Res. 2010;79(2):102–8.
17. Rajan V, Varghese B, van Leeuwen TG, Steenbergen W. Review of methodological developments in laser Doppler flowmetry. Lasers Med Sci. 2009;24(2):269–83.
18. Mongkolpun W, Orbegozo D, Cordeiro CPR, Franco CJCS, Vincent JL, Creteur J. Alterations in skin blood flow at the fingertip are related to mortality in patients with circulatory shock. Crit Care Med. 2020;48(4):443–50.
19. Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective multicentre study. Working group on sepsis related problems of the ESICM. Intensive Care Med. 1999;25(7):686–96.
20. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270(24):2957–63.
21. Gove S, Tamburlini G, Molyneux E, Whitesell P, Campbell H. Development and technical basis of simplified guidelines for emergency triage assessment and treatment in developing countries. WHO integrated management of childhood illness (IMCI) referral care project. Arch Dis Child. 1999;81(6):473–7.
22. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med. 2009;37(3):934–8.
23. Contreras R, Hernández G, Valenzuela ED, González C, Ulloa R, Soto D, et al. Exploring the relationship between capillary refill time, skin blood flow and microcirculatory reactivity during early resuscitation of patients with septic shock: a pilot study. J Clin Monit Comput. 2023;37(3):839–45.
24. Merdji H, Curtiaud A, Aheto A, Studer A, Harjola VP, Monnier A, et al. Performance of early capillary refill time measurement on outcomes in cardiogenic shock: an observational, prospective multicentric study. Am J Respir Crit Care Med. 2022;206(10):1230–8.
25. Bourcier S, Pichereau C, Boelle PY, Nemlaghi S, Dubée V, Lejour G, et al. Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. Ann Intensive Care. 2016;6(1):63.
26. Alsma J, van Saase JLCM, Nanayakkara PWB, Schouten WEMI, Baten A, Bauer MP, et al. The power of flash mob research: conducting a nationwide observational clinical study on capillary refill time in a single day. Chest. 2017;151(5):1106–13.
27. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. Am J Respir Crit Care Med. 2020;202(3):361–70.

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