Capillary refill time exploration during septic shock

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Take-home message: Capillary refill time is a clinical reproducible parameter when measured on the index tip and the knee area. After initial resuscitation of septic shock, capillary refill time is a strong predictive factor of 14-day mortality.

Electronic supplementary material
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Abstract *Background:* During septic shock management, the evaluation of microvascular perfusion by skin analysis is of interest. We aimed to study the skin capillary refill time (CRT) in a selected septic shock population. *Methods:* We conducted a prospective observational study in a tertiary teaching hospital. After a preliminary study to calculate CRT reproducibility, all consecutive patients with septic shock during a 10-month period were included. After initial resuscitation at 6 h (H6), we recorded hemodynamic parameters and analyzed their predictive value on 14-day mortality. CRT was measured on the index finger tip and on the knee area. *Results:* CRT was highly reproducible with an excellent inter-rater concordance calculated at 80 % [73–86] for index CRT and 95 % [93–98] for knee CRT. A total of 59 patients were included, SOFA score was 10 [7–14], SAPS II was 61 [50–78] and 14-day mortality rate was 36 %. CRT measured at both sites was significantly higher in non-survivors compared to survivors (respectively 5.6 ± 3.5 vs 2.3 ± 1.8 s, $P < 0.0001$ for index CRT and 7.6 ± 4.6 vs 2.9 ± 1.7 s, $P < 0.0001$ for knee CRT). The CRT at H6 was strongly predictive of 14-day mortality as the area under the curve was 84 % [75–94] for the index measurement and was 90 % [83–98] for the knee area. A threshold of index CRT at 2.4 s predicted 14-day outcome with a sensitivity of 82 % (95 % CI [60–95]) and a specificity of 73 % (95 % CI [56–86]). A threshold of knee CRT at 4.9 s predicted 14-day outcome with a sensitivity of 82 % (95 % CI [60–95]) and a specificity of 84 % (95 % CI [68–94]). CRT was significantly related to tissue perfusion parameters such as arterial lactate level and SOFA score. Finally, CRT changes during shock resuscitation were significantly associated with prognosis. *Conclusion:* CRT is a clinical reproducible parameter when measured on the index finger tip or the knee area. After initial resuscitation of septic shock, CRT is a strong predictive factor of 14-day mortality.

Keywords Shock · Microcirculation · Prognosis · Capillary time refill · Intensive care medicine

Introduction

Understanding [1] and management of severe infections have greatly improved over the last decade [2]. It is now widely admitted that septic shock is characterized by heterogenous microcirculatory alterations that may contribute to organ hypoperfusion and ultimately to death [3, 4]. However, the identification of these microvascular alterations at the bedside remains challenging [5]. Recent tools, such as orthogonal spectral polarization, allow a subtle direct visualization of the microcirculation but are not yet available at the bedside [5, 6]. The exploration of peripheral perfusion through skin analysis has recently been highlighted and represents a promising clinical approach to study semiquantitatively tissue perfusion. The clinical "pale skin often covered with perspiration" during septic shock was described more than 50 years ago [7]. Altemeier [8] also reported in 1956 a moist and cool skin on septic patients with a bad prognosis. Several tools have been developed to quantify more objectively these peripheral skin alterations. Joly and Weil [9] proposed to measure skin temperature and central-to-toe temperature difference. More recently, we focused on skin discoloration called mottling and developed a clinical score based on mottling extension around the knee area. We have found that mottling extension, assessed 6 h after initial resuscitation, was a strong predictive factor of 14-day mortality during septic shock [10].

The capillary refill time (CRT) is another interesting clinical parameter. CRT measures the time required to recolor the tip of a finger, usually the index. It is an attractive tool because it is easy to learn and to use at the bedside. A number of observational studies have emphasized its relevance in the initial triage [11] of the most critical children suffering from infectious diseases such as pneumonia, gastroenteritis, and malaria [12]. In unselected pediatric and adult intensive care patients, CRT was related to tissue perfusion and organ dysfunction evaluated by the plasma lactate level and the SOFA score [13, 14]. Hernandez et al. [15] reported that in a mixed severe sepsis/septic shock population an index CRT lower than 4 s, 6 h after resuscitation was associated with a normalization of arterial lactate level 24 h later. However, CRT has never been explored specifically during septic shock. The aim of this prospective observational study was to analyze the predictive value of CRT during septic shock and to compare measurements performed at two sites, the classical index finger tip and the knee area, where mottling preferentially developed.

Methods

We conducted a prospective observational study in an 18-bed ICU in a tertiary teaching hospital. During a 10-month period, all consecutive patients, older than 18 years, admitted for septic shock were included. Septic shock, within 24 h after ICU admission, was defined by the 2001 international sepsis definitions conference [16]. Patients were included (H0) when vasopressor infusion was started (within 24 h of admission). Patients with dark skin were excluded because accurate clinical evaluation of CRT was not possible.

Protocol and data collection

Patients were admitted directly from the emergency department or medical wards. Circulatory support was guided by our local protocol, adapted from international guidelines [2]. Intravenous volume expansion and norepinephrine (epinephrine in case of associated systolic cardiac dysfunction) were used in a stepwise manner to achieve predefined endpoints of resuscitation from invasive hemodynamic monitoring: mean arterial pressure (MAP) greater than 65 mmHg, central venous pressure (CVP) between 8 and 12 mmHg, urinary output greater than 0.5 ml/kg/h, and $ScvO_2$ greater than 70 %. All patients were investigated with transthoracic echocardiography (Vivid 7 Dimension'06, GE Healthcare®) to assess left ventricular function and volemia. Cardiac output was measured using a third-generation FloTrac/Vigileo (Edwards). Transthoracic echocardiography was performed at admission and during acute circulatory failure management. When a cardiac dysfunction (ejection fraction less than 35 % by Simpson bi-plan) was identified, an inotropic therapy was introduced and epinephrine replaced norepinephrine. Preload was optimized and fluid infusion was stopped when the pulse pressure variation was below 13 %, or when no response to passive leg raising or no respiratory variations of the inferior vena cava diameter were observed.

General characteristics of the patients were recorded: demographic data, diagnoses, severity of illness evaluated by the sequential organ failure assessment (SOFA) score (within 6 h of inclusion) [17] and simplified acute physiology score II (SAPS II) [18]. Six hours after inclusion (H6), required for medical management and global hemodynamic restoration, we collected data that reflected macrocirculation and organ perfusion. Macrocirculation was assessed using MAP, heart rate (HR), CVP and cardiac index. Microcirculatory dysfunction and organ perfusion were assessed through arterial lactate level, urinary output and capillary refill time. Capillary refill time was measured by applying a firm pressure to the distal phalanx of the index finger (or to the center of the knee) for 15 s. The pressure applied was just enough to remove the blood at the tip of the physician's nail illustrated by appearance of a thin white distal crescent (blanching) under the nail. A chronometer recorded the time for return of the normal color. To reduce variance in measurements and improve its practical use, this was

repeated twice, and CRT was computed as the mean of the two successive readings. During the prospective observational study, CRT was measured three or four times by a senior intensivist who did not manage the patient and the mean value was recorded.

Statistical analysis

Patient characteristics were summarized as mean ± standard deviation, median (25–75th percentiles) for skewed distributions, and percentages as appropriate. Differences between groups were compared using the Student *t* test or Wilcoxon's test. Differences in 14-day survival according to initial change in CRT were tested by the Fisher's exact test. Correlations were computed using Pearson's formula. Patients' CRT associated with death by the 14th day following admission in the ICU were determined by logistic regression and results were expressed as odds ratio (OR) (95 % CI).

Interobserver agreement for the CRT was measured by the intraclass correlation coefficient [19] and the confidence interval by bootstrap resampling. We determined that 100 readings by two independent intensivists would be necessary to estimate the ICC with 10 % precision if its true value was above 80 %. The coefficient of variation was computed on log-transformed variables as variance increased with CRT. Limits of agreement, used for defining changes of interest in the CRT, were set at two standard deviations around the mean [20]. We used the CRT variance estimated in the reproducibility study to plan the number of patients to include to evidence a difference by 2 s in CRT according to outcome with 80 % power. We assessed discrimination of CRT by the area under the receiver operating characteristic curve (ROC) and determined the most discriminant threshold by maximizing the Youden index (sensitivity + specificity − 1).

Statistical significance was set at $P < 0.05$. All analyses were made using the R software (v 2.12.0; http://cran.r-project.org).

The observational protocol was approved by the ethics committee, Comité de Protection des Personnes (CPP Saint-Louis, Paris, France). This is an observational study without any specific intervention according to CRT. All patients and families were informed through the admission leaflet that anonymous data could be used for academic research and gave their consent.

Results

Capillary refill time reproducibility

A pilot study was conducted to assess CRT reproducibility when measured on the index and the knee area. One hundred measurements were performed on septic shock patients by two intensivists who quantified blindly CRT twice. Inter-rater concordance was 80 % [73–86] for index CRT and 95 % [93–98] for knee CRT. The coefficient of variation of the index CRT was 10 % suggesting that limits of agreement should be defined as ±20 % of a reading. On the basis of this pilot study, the standard deviation of the CRT was approximately 2.5 s. To show a difference of 2 s between 14-day survivors and non-survivors with 80 % power and a mortality estimated at 40 %, it would be necessary to include 50 patients.

Studied population

Between February and December 2013, 64 consecutive patients were eligible. Five patients were excluded, four patients because of dark skin and one because of an acute myocardial infarction associated with septic shock leaving 59 patients for the study. Baseline characteristics are summarized in Table 1. All the patients had septic shock and required vasopressors within 24 h of admission, mainly related to pneumonia (46 %) and abdominal infection (27 %). The mean SOFA score measured 6 h after vasopressor start was 10 [7–14] and the SAPS II was 61 [50–78]. Most of the patients were infused by norepinephrine [54 patients (91 %), dose at H6 0.30 [0.10–0.60] µg/kg/min] during the first 6 h of shock management and others by epinephrine [five patients (9 %), dose at H6 0.20 [0.06–0.20] µg/kg/min]. Day-14 mortality rate was 37 % (95 % CI [28–45]).

Table 1 Baseline characteristics of studied population

Patients, *n*	59
Age, years, mean (SD)	69 (14)
Gender, female, *n* (%)	21 (35)
Primary site of infection, *n* (%)	
Lung	27 (46)
Abdomen	16 (27)
Urinary tract	4 (7)
Soft tissue	5 (8)
Primary bacteriemia	7 (12)
SOFA at H6, mean (SD)	10 [7–14]
SAPS II, mean (SD)	61 [50–78]
Mechanical ventilation, *n* (%)	38 (65)
Norepinephrine, *n* (%)	54 (91)
Doses, µg/kg/min, median [25–75th percentile]	0.30 [0.1–0.6]
Epinephrine, *n* (%)	5 (9)
Doses, µg/kg/min, median [25–75th percentile]	0.2 [0.06–0.2]

Parameters and SOFA (sequential organ failure assessment) were reported within 6 h of inclusion. SAPS II (simplified acute physiology score) was calculated within 24 h of admission. Values are given as mean ± standard deviation or median [25–75th percentiles] according to data distribution

Table 2 Hemodynamic characteristics of patients according to 14-day outcome

Factor	All patients $N = 59$	Non-survivors $N = 22$	Survivors $N = 37$	P
SOFA at H6	10 [7–14]	13 [9–15]	8 [7–11]	0.005
SAPS II	61 [50–78]	77 [62–90]	55 [46–67]	0.0003
MAP (mmHg)	76 (10)	73 (10)	78 (11)	0.11
Cardiac index (l/min/m^2)	3.3 (1.3)	2.9 (0.8)	3.5 (1.4)	0.10
Urinary output (ml/kg/h)	0.41 (0.57)	0.17 (0.27)	0.56 (0.64)	0.009
Arterial lactate (mmol/l)	4.5 (4.6)	7.7 (5.8)	2.5 (1.4)	0.007
$ScvO_2$ (%)	75 (11)	73 (10)	78 (14)	0.32
Index CRT (s)	3.5 (3.0)	5.6 (3.5)	2.3 (1.8)	<0.0001
Knee CRT (s)	4.7 (3.8)	7.6 (4.6)	2.9 (1.7)	<0.0001

SOFA (sequential organ failure assessment) was calculated within 6 h of inclusion. SAPS II (simplified acute physiology score) was calculated within 24 h of admission. Values are given as mean (±standard deviation) or median [25–75th percentiles] according to distribution. Characteristics of 14-day survivors and non-survivors were compared using the Student t test or Wilcoxon test as appropriate

MAP mean arterial pressure, *$ScvO_2$* central venous saturation in oxygen, *CRT* capillary refill time

Hemodynamic parameter assessment

Hemodynamic parameters were recorded at H6 after global hemodynamic resuscitation and were compared according to the prognosis at day 14. Non-survivors had a higher SAPS II and a higher SOFA score. Macrocirculatory parameters (MAP, cardiac index) were restored and not different at H6 (Table 2). However at H6, arterial lactate level was significantly higher (7.7 ± 5.8 vs 2.5 ± 1.4 mmol/l, $P = 0.007$) and urinary output lower (0.17 ± 0.27 vs 0.56 ± 0.64 ml/kg/h, $P = 0.009$) in non-survivors compared to survivors.

Capillary refill time assessment

CRT was recorded on the index finger and on the knee area at H6 and was significantly longer in non-survivors (respectively 5.6 ± 3.5 vs 2.3 ± 1.8 s, $P < 0.0001$ for index CRT and 7.6 ± 4.6 vs 2.9 ± 1.7, $P < 0.0001$ for knee CRT) (Table 2). In univariable analysis, the OR of 14-day mortality significantly increased with CRT: index CRT (<2.5 s OR 1 (ref.), [2.5–5 s] OR 5.4 (1.3–22.3), >5 s OR 18.0 (3.6–89.6), $P < 0.001$) and knee CRT (<2.5 s OR 1 (ref.), [2.5–5 s] OR 5.1 (0.5–51.3), >5 s OR 61.2 (6.5–578.9), $P < 0.001$). In addition, adjusting on an overall severity index (SOFA score), a global hemodynamic parameter (MAP) and the dose of vasopressor did not substantially alter the association between CRT and death at day 14 (supplemental table).

At the bedside, we analyzed the prognosis of patients according to CRT changes between H0 and H6. The coefficient of variation of the index CRT was 10 %, leading to limits of agreement of 20 % around a measurement. Therefore, a change by 20 % between CRTs was considered of interest. Among the patients who died, both knee and index CRT did not change and remained large in 18 (82 %) patients despite resuscitation (Chi squared test, $P = 0.002$ for index and $P = 0.004$ for knee) (Fig. 1). We did not observe any significant relation between CRT changes and cardiac index changes between H0 and H6 ($P = 0.10$, $r = 0.22$; supplemental figure).

The CRT at H6 was strongly predictive of 14-day mortality as the area under the curve was 84 % [75–94] for the index measurement and the AUC was 90 % [83–98] for the knee area. A threshold of index CRT at 2.4 s predicted 14-day outcome with a sensitivity of 82 % (95 % CI [60–95]) and a specificity of 73 % (95 % CI [56–86]). A threshold of knee CRT at 4.9 s predicted 14-day outcome with a sensitivity of 82 % (95 % CI [60–95]) and a specificity of 84 % (95 % CI [68–94]) (Figs. 2, 3).

We also analyzed correlations between CRT and other hemodynamic variables both measured at H6, after initial resuscitation. The CRT did not correlate with cardiac index and $ScvO_2$. In contrast, we observed a significant relation between CRT and parameters related to organ perfusion such as arterial lactate level (index $P < 0.0001$, $r = 0.53$; knee $P = 0.0005$, $r = 0.36$) and SOFA score (index $P < 0.0001$, $r = 0.50$; knee $P = 0.01$, $r = 0.31$). The relationship between CRT and SOFA score remained significant when we removed the neurological (index $P < 0.0001$, $r = 0.53$; knee $P = 0.001$, $r = 0.41$) or the hemodynamic parameter (index $P < 0.0001$, $r = 0.54$; knee $P = 0.001$, $r = 0.40$) from the organ failure score.

Discussion

CRT is a classical clinical sign of hypoperfusion taught in medical school and several studies have reported on its interest. In pediatric units, index CRT helps to identify the most severe children suffering from infectious diseases such as pneumonia, gastroenteritis, and malaria [11, 12]. However, few studies have been done in critically ill patients. Tibby et al. [13] explored CRT in a mixed ICU population of children that included post-cardiac surgery (50 %) and septic shock (46 %) patients. Recently, Lima

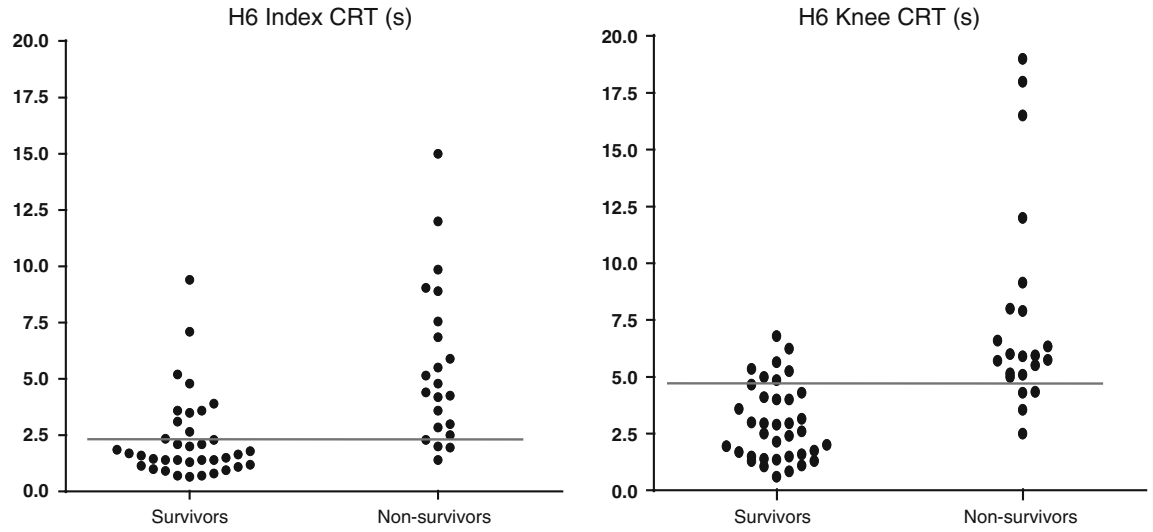

Fig. 1 Individual knee CRT changes between H0 and H6, expressed as percentage, according to H0 knee CRT (seconds). 14-day survivors (*black circles*) and non-survivors (*white squares*). A reduction of CRT higher than 20 % was considered as significant (*grey area*)

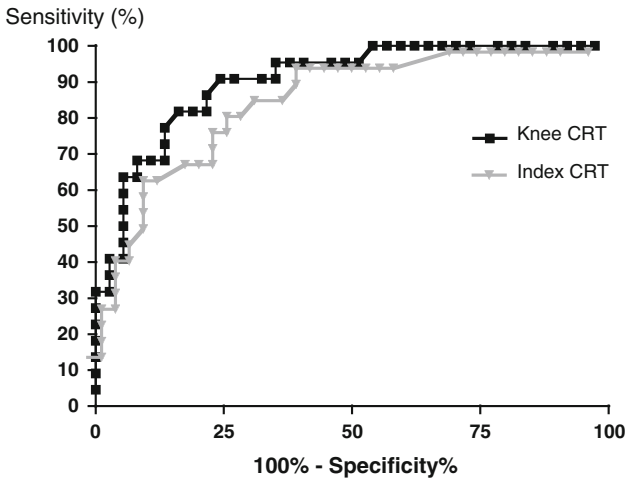

Fig. 2 Receiver operating characteristic curves. Index (*grey line*) and knee (*black line*) capillary refill time according to 14-day survival. The area under the curve was 84 % [75–94] for the index measurement and 90 % [83–98] for the knee area. Data were recorded 6 h after inclusion and septic shock management

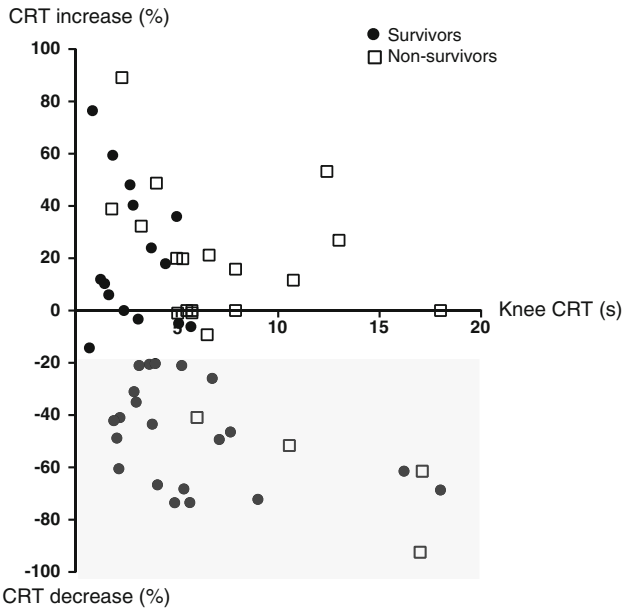

Fig. 3 Individual CRT values according to 14-day prognosis. *Left* CRT was measured on the index finger tip, *right* CRT was measured on the knee area. Data were recorded at H6 after inclusion and septic shock management

et al. [14] analyzed index CRT among other peripheral microcirculatory parameters in a mixed ICU adult population suffering from infections, trauma, and neurological disorders. Among them, 21 patients (42 %) had septic shock. For the first time, we explored CRT in a selected population of adult septic shock patients. We decided to assess the CRT measured on the classical index tip and on the center of the knee because it is the preferential site of mottling extension [10] that matches with skin hypoperfusion during septic shock [21].

To optimize CRT reproducibility, we standardized the finger pressure. We recommended to apply a pressure just enough to remove the blood at the tip of the physician's nail illustrated by appearance of a thin white distal crescent (blanching) under the nail. We found that interobserver reproducibility of CRT was good at both sites but seems to be better on knee area.

After global hemodynamic resuscitation, we did not observe any difference regarding mean arterial pressure and cardiac output between survivors and non-survivors,

whereas arterial lactate level was significantly higher and urinary output lower in non-survivors as previously reported by our group [22] and others [23–25]. We have shown that CRT was significantly longer in non-survivors in comparison to survivors at both sites, values being higher in the knee area. Regarding the index CRT a cutoff at 2.4 s was predictive of mortality but was different from the threshold at 4.5 s proposed by Schriger et al. [26] 25 years ago. However, in this study, the authors did not include critically ill patients with shock but compared only subjects before and after cold water immersion. The temperature is a parameter that affects CRT. Unfortunately, we did not record skin temperature; but when we analyzed central temperature, we did not observe any difference between survivor and non-survivors. Moreover, we did not find any relation between central temperature and CRT. Others factors could modify CRT such as vasopressors. At H6 we observed a significant relation between the vasopressor doses and the CRT measured on the index or the knee area (data not shown); but after adjustment based on vasopressor dose, the association between CRT and 14-day death remained significant. The association of mortality with CRT was also unaffected by stratification on known arterial disease (defined as a previous vascular event, symptomatic or requiring therapeutic intervention). We recorded four (18 %) patients with a known vascular disease in the non-survivor group, and nine (24 %) in the survivor group.

CRT changes during resuscitation also provided interesting information. In some cases, CRT decreased, suggesting that improvement of macrocirculation contributed to microcirculatory perfusion improvement. However, in other patients, CRT remained high despite correction of macrocirculatory parameters, suggesting that persistent microcirculatory alterations are independent of macrocirculation and could promote organ hypoperfusion per se, thereby worsening outcome. Hernandez et al. [15] also found that index tip CRT "normalization" at H6 after resuscitation is associated with a good prognosis. The relation between changes of microvascular perfusion during shock management and outcome was previously reported by our group using mottling score [10] and others like De Backer's group with sublingual orthogonal polarization spectral imaging [27].

We found a significant but weak negative correlation between CRT and the arterial lactate level. Interestingly, Tibby's and Lima's studies also reported an association between abnormal peripheral perfusion and high arterial lactate level in a mixed ICU population [13]. Moreover, we observed a positive relation between CRT and the SOFA score; Lima et al. [14] also showed that patients with clinical signs of hypoperfusion had a significant lower SOFA improvement compared to patients with normal peripheral perfusion.

Thus, according to our results, CRT could be proposed as a reliable and integrative clinical marker of perfusion during septic shock. CRT is useful to identify the most critical patients after global hemodynamic management. This noninvasive tool, which is easy to learn, could also be an important contribution to prehospital and emergency department management. CRT should not replace the mottling score [10], but could be used as a complementary tool for several reasons. First, the mottling score is a semiquantitative parameter whereas CRT is a quantitative parameter, leading to more accurate monitoring during resuscitation. Moreover, in the mottling group (0–1) and (2–3), knee CRT improved patient discrimination according to their outcome, with non-survivors presenting a significantly higher knee CRT (data not shown).

Our study has several limitations. It is a monocentric study and results need to be confirmed in a larger population. Nevertheless while the size of this preliminary study was not very large, it was sufficient to highlight significant results. Also, our conclusion was based on patients with severe septic shock and can probably not be extrapolated to patients with severe sepsis not requiring vasopressors. We did not include patients with dark skin because knee CRT could not be measured. In these situations, others clinical signs of peripheral hypoperfusion could be used such as central-to-toe temperature difference.

Conclusion

CRT is a clinical reproducible parameter when measured on the index tip and the knee area. After initial resuscitation of septic shock, this parameter is a strong predictive factor of 14-day mortality.

Conflicts of interest The authors had no conflict of interest.

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