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UNDERSTANDING THE DISEASE

Understanding clinical signs of poor tissue perfusion during septic shock

Hafid Ait-Oufella[1,2*] and Jan Bakker[3,4,5]

Acute circulatory failure associated with infection, referred to as septic shock, is characterized by an inadequate tissue perfusion and oxygenation relative to metabolic requirements. This imbalance between delivery and tissue uptake is mainly due to altered microvascular blood flow regulation as a result of dysregulated and/or injured endothelial cells. Endothelial dysfunction is presumably induced by pathogenic bacterial products, inflammatory mediators, and reactive oxygen species produced by activated leukocytes [1]. Cellular and *in fine* tissue damages are related to ischemia and also to additional mechanisms that are out of the scope of this review such as mitochondria dysfunction. Direct microcirculation visualization using capillaroscopy has highlighted the heterogeneity of organ perfusion and the discrepancy between the overall hemodynamic status and local blood flow during sepsis [2]. In other words, in the presence of normal macro-hemodynamic, there may be regions of inadequate perfusion, underscoring the assessment of regional perfusion and oxygen delivery at the organ level [3]. Regional tissue perfusion has been investigated in different compartments such as the sublingual area or gastric mucosa using different devices, but in this mini-review, we will focus on skin peripheral perfusion, immediately available at the bedside (Table 1).

The rationale for peripheral perfusion monitoring is based on the fact that peripheral tissues, such as skin and muscles, are the first to suffer from impaired perfusion in severe infections. This is due to the absence of cutaneous circulation autoregulation and the early local vasoconstriction mediated by sympathetic neuroactivation [4]. In addition, several other mechanisms have shown to impair microvascular blood flow such as leukocyte adhesion, platelet activation and fibrin deposition. As the cutaneous vascular bed plays an important role in the peripheral thermoregulation, skin perfusion disorders during severe infections directly impact on skin color and/or temperature.

Skin mottling

Skin mottling, a common clinical sign in critically ill patients, is defined as patchy skin discoloration that usually manifests on the area around the knees but can extend to other peripheral circulations (fingers, ear). In the absence of diffuse intravascular coagulation causing complete microcirculatory obstruction, this phenomenon is a sign of skin hypoperfusion. Using laser Doppler imaging and NIRS (near-infrared spectroscopy) technology, both reduced perfusion and low tissue oxygen saturation in mottling areas, where demonstrated [5, 6]. In order to objectively analyse the skin mottling, a clinical scoring system based on the area of mottling discoloration from the knees to the periphery has been developed. The mottling score ranges from 0 to 5, with higher scores indicating greater areas of skin mottling (knee area to complete mottling of the leg). This simple and easy scoring system has a very good inter-observer agreement [$\kappa = 0.87$ (95 % CI (0.72–0.97)]. We reported that a high mottling score within 6 h after initial resuscitation was a strong predictor of 14-day mortality in septic shock. Moreover, this was independent of systemic haemodynamics such as mean arterial pressure or cardiac output [6]. The predictive value of the mottling score has also been reproduced in emergency departments, in non-selected critically ill patients [7] and more recently outside Europe [8]. Even in clinical conditions characterized by systemic vasodilation, mottling represents an increased risk of mortality. In patients with cirrhosis,

*Correspondence: hafid.aitoufella@sat.aphp.fr
[1] Assistance Publique-Hôpitauxde Paris, Hôpital Saint-Antoine, Servicede Réanimation Médicale, 75012 Paris, France
Full list of author information is available at the end of the article

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Table 1 Clinical methods used to measure peripheral perfusion

Method	Variable	Advantages	Limitations	Suggested cut-offs for higher mortality
Mottling of the skin	Absence/presence	Could be done by nurses	Lack of specificity	–
	Mottling score	Easy to use and learn reproducible	Not useful in patients with dark skin	Score 4–5 (scoring from 0 to 5)
Capillary refill time (CRT)	Index CRT	Easy to use and learn ± reproducible	Inter rater variability	Critically ill > 5 s Septic shock > 2.4 s
	Knee CRT	Reproducible	Not useful in patients with dark skin	Septic shock > 4.9 s
Temperature gradient	Forearm-to-finger	Validated method	Requires more complex technology	>4 °C
	Central-to-toe	Validated method		>7 °C

the mottling score remains a predictor of mortality during septic shock despite a lower sensitivity than non-cirrhotic patients. The lower sensitivity could be explained by delayed mottling given the higher baseline skin perfusion in these patients [9].

Capillary refill time

Capillary refill time (CRT) measures the time required for skin's colour to return to baseline on the tip of a finger, usually the index, after application of blanching pressure. The CRT reflects blood flowing back to the distal capillary bed. A number of observational studies have emphasised its interest in the initial triage of the most critically ill children suffering from infectious diseases. In non-selected paediatric and critically ill adult patients, CRT was related to tissue perfusion, which was correlated to the plasma lactate level [10]. Using a cutoff of 4.5 s as described by Schriger in a healthy adult population, Lima et al. reported that, in non-selected critically ill patients, a high CRT reflects decreased peripheral perfusion and could be used to discriminate patients with more severe organ dysfunction [11]. In patients following abdominal surgery, the finger tip CRT (cutoff 5 s) has been associated with post-operative complications and death [12]. In septic shock patients, after initial resuscitation, CRT is a strong predictor of 14-day mortality with an area under the curve of 84 % (75–94) for the index tip measurement and 90 % (83–98) for the knee area measurement. In this study, a threshold of 2.4 s (index tip CRT) predicted mortality with a sensitivity of 82 % and a specificity of 73 %. When applied at the knee area, a CRT of 4.9 s predicted mortality with a sensitivity of 82 % and a specificity of 84 %. Most importantly, this study reported a good correlation between CRT and other parameters of tissue perfusion like urinary output and lactate levels [13]. Finally, in a recent study in septic shock survivors, Hernandez et al. showed that survival was characterised by normalisation of the CRT [14].

Temperature gradients

Although a few studies have related the subjective assessment of skin temperature to outcome, one of the problems of this approach, on top of the subjectiveness of this assessment, is that the temperature of the skin is affected by the outside (room temperature). Therefore, a difference between two temperatures is frequently used. Weil and co-workers have popularised the use of the central-to-toe temperature difference and also related this variable, like others, to outcome parameters. The use of central-to-toe temperature differences is limited by hypothermia of the patient or low ambient temperature. As the main focus of peripheral temperature assessment is skin perfusion, the difference between distinct peripheral skin temperature differences has been used in different studies. Frequently, the difference between forearm and fingertip (Tskin-diff) is used to assess peripheral perfusion. Despite some discrepancies, several studies have shown that a Tskin-diff 0 °C is indicative of vasoconstriction whereas a Tskin-diff of more than 4 °C is associated with severe vasoconstriction. The advantage of this technique is that both spots of skin are similarly affected by room temperature. Tskin-diff has been shown to be related to laser Doppler flow of the skin. In clinical studies, Tskin-diff has been related to outcome of various groups of patients. In patients with circulatory failure, Lima et al. showed increased Tskin-diff to be related to outcome [11], whereas van Genderen et al. showed that a complicated post-operative trajectory following major abdominal surgery was associated with differences in Tskin-diff [12].

Perspectives

In general, signs of abnormal peripheral perfusion such as mottling, prolonged CRT, a cool skin or increased skin temperature gradients should be a significant warning signal to clinicians, leading to therapeutic

interventions. The choice of the complementary haemodynamic tool that could help to guide fluid infusion or inotrope administration remains a subject of controversy. In parallel, the identification of persistent tissue hypoperfusion after initial resuscitation could prompt to use specific vascular treatment [15]. For example, in a preliminary study, Lima et al. reported that nitroglycerin infusion normalised peripheral perfusion (maximal dose 16 mg/h). Twelve of the 15 patients (80 %) required a low dose (8 mg/h or less) to correct abnormal peripheral perfusion. Tskin-diff has also been used prospectively to guide fluid resuscitation in septic shock patients [16]. The main assumption in this study was that patients with abnormal peripheral perfusion, as assessed by CRT in addition to Tskin-diff and other parameters of skin perfusion, were very likely to benefit from additional fluid resuscitation if a clinical problem persisted following the resuscitation including fluid boluses. In this safety study including only 30 patients, it seemed that limiting the use of fluids in patients with normal peripheral perfusion was not only safe but was also associated with improved outcome parameters. The intervention group received less fluid in the treatment period as well as in the follow-up totalling almost 5 l less net positive fluid balance over the total study period of 72 h. Although all of this strongly links abnormal peripheral perfusion parameters (temperature, colour and perfusion) to important outcome parameters, and correction of these parameters is possible by clinical interventions, the number of patients included in the relevant studies is rather small. The use of peripheral perfusion parameters as guidelines in clinical resuscitation is a very promising result; however, we need studies including a significantly higher number of patients to assure safety and improved outcome.

Author details
[1] Assistance Publique-Hôpitauxde Paris, Hôpital Saint-Antoine, Servicede Réanimation Médicale, 75012 Paris, France. [2] Sorbonne Universités, UPMC Univ Paris 06, Paris, France. [3] Department of Intensive Care, Erasmus MC University Medical Center, Rotterdam, Netherlands. [4] Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. [5] Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University Medical Center, New York, NY, USA.

Compliance with ethical standards

Conflicts of interest
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