Clinical assessment of peripheral circulation

Alexandre Lima and Jan Bakker

Purpose of review
Monitoring of the peripheral circulation can be done noninvasively in contrast to the more traditional invasive systemic haemodynamic monitoring in the intensive care unit. Physical examination of peripheral circulation based on clinical assessment has been well emphasized for its convenience, accessibility, and relation to the prognosis of patients with circulatory shock. The purpose of this article is to highlight the main findings according to recent literature into the clinical applications of the peripheral perfusion assessment in patient management.

Recent findings
Clinical assessment of peripheral circulation includes physical examination by inspecting the skin for pallor or mottling, and measuring capillary refill time on finger or knee. Studies have addressed the capillary refill time assessment in adults and its relation to normal range, body site, effect of skin temperature, and its reliability among examiners. These are easily applicable methods in many circumstances, and it has been used for predicting unfavourable outcomes in critically ill adult patients. Current studies are ongoing to determine the effects of different interventions on the clinical parameters of peripheral circulation in critically ill patients during shock resuscitation.

Summary
The feasibility and reproducibility of the clinical assessment of peripheral circulation are substantial, and reliance on capillary refill time, skin temperature, and mottling score must be emphasized and exploited. Incorporating therapeutic strategies into resuscitation protocols that aim at normalizing these peripheral circulation parameters are being developed to investigate the impact of peripheral perfusion-targeted resuscitation in the survival of critically ill patients.

Keywords
capillary refill time, intensive care medicine, mottling, prognosis, shock

INTRODUCTION

The recent advances in diagnostic and monitoring technologies have helped intensivists to better understand the complex pathophysiology of acute circulatory failure. The power and objectivity provided by these new technologies might cause us to think that physical examination in the intensive care setting has become obsolete. Much emphasis is given to the global variables of perfusion, whereas relatively little is said about less vital organs such as skin and/or muscle. One may argue about the clinical significance of monitoring perfusion of these nonvital organs in which blood flow is not crucial for immediate survival. As the introduction of gastric tonometry has proved to be of prognostic value, the field of regional (non)invasive monitoring gained wide interest, and studies started to address the importance of monitoring peripheral vascular beds more susceptible to hypoperfusion, such as skin, muscle, and gastrointestinal tract. Observations on the behaviour of the peripheral circulation alterations permit the recognition of two broad phases during the development of shock, irrespective of initiating factors. There is an initial period during which compensatory mechanisms predominate, when the neurohumeral response-induced vasoconstriction preserves the perfusion of the vital organs at the expense of decreased perfusion in the peripheral tissues. Blood flow variations, therefore, follow a similar response pattern in the skin, muscle, and gastrointestinal vascular beds, which makes these tissues highly sensitive for detecting occult tissue hypoperfusion during acute circulatory shock [1–4]. With the progression of

Department of Intensive Care, Erasmus MC, Rotterdam, The Netherlands

Correspondence to Professor Jan Bakker, MD, PhD, FCCP, Erasmus MC University Medical Centre, Dept Intensive Care Adults, P.O. Box 2040 - Room H625, 3000 CA Rotterdam, The Netherlands. Tel: +31 7033629; e-mail: jan.bakker@erasmusmc.nl

Curr Opin Crit Care 2015, 21:226–231

DOI:10.1097/MCC.0000000000000194

KEY POINTS

- Reliance on simple methods, such as CRT, skin temperature, and mottling score, must be emphasized and exploited.
- Studies were able to demonstrate that CRT > 5.0 s or the presence of mottling at physical exam in adult patients with either septic or nonseptic shock was of great value to predict more severe organ dysfunction.
- The effects of common resuscitation strategies (i.e., fluid resuscitation, vasopressors, or vasodilators) should take into account the dynamic assessment of peripheral circulation.
- Therapeutic strategies have been incorporated into resuscitation protocols aiming at normalizing CRT and mottling to investigate the impact of peripheral perfusion-targeted resuscitation in the survival of critically ill patients.

circulatory shock and after initiation of appropriate therapy, the active participation of the peripheral circulation in supporting tissue perfusion becomes less striking and ultimately disappears. Some patients enter a phase of stability, and peripheral circulation alterations may no longer reflect the acute compensatory mechanisms. Other factors, such as mechanical ventilation, the use of vasopressors or vasodilators, sedatives, and opiates, can distort the neurohumoral physiologic response. Nevertheless, abnormalities in peripheral circulation may still persist, although systemic haemodynamic stability has been reached. Moreover, the persistence of these alterations has been associated with worse outcomes [5,6]. Therefore, some argue that following normalization of perfusion parameters, global systemic parameters are of less importance [7]. Today, monitoring of the peripheral circulation can be done noninvasively in contrast to the need of intravascular catheters, transoesophageal probe insertion, or blood analysis used in more traditional haemodynamic monitoring in the ICU. Space limitations prevented us from discussing all noninvasive techniques available; however, we provide a more detailed description of the commonly used noninvasive methods of monitoring peripheral perfusion elsewhere [8].

From all these noninvasive techniques available, physical examination of peripheral perfusion based on clinical assessment has been well emphasized for its convenience, accessibility, and relation to the prognosis of patients with circulatory shock. The purpose of this article, therefore, is to highlight the main developments into the clinical assessment of peripheral perfusion as reflected in recent literature.

CLINICAL EXAMINATION OF PERIPHERAL CIRCULATION

Clinical examination of peripheral circulation allows rapid and repeated assessment of critically ill patients at the bedside. Peripheral circulation can be easily assessed performing a careful physical examination by touching the skin or measuring capillary refill time (CRT). The cutaneous vascular bed plays an important role in the thermoregulation of the body, and this process can result in skin perfusion alterations that have direct effects on skin temperature and colour, that is, a cold, clammy, white, and mottled skin, associated with an increase in CRT. In particular, CRT is defined as the time required for a distal capillary bed (i.e., the nail bed) regaining its colour after pressure has been applied to cause blanching. This concept was first introduced by Champion *et al.* [9] in 1981 as a component of the international trauma severity score for the rapid and structured cardiopulmonary assessment of trauma patients. As CRT assessment is an easily applicable method in many circumstances, it has been used for assessing peripheral perfusion and for predicting unfavourable outcomes in both critically ill adults and paediatric patients. Over the past 30 years, the definition of a delayed CRT has been debated in the literature [10]. Most of what we know, however, about this simple clinical test comes from studies performed in the paediatric population. For instance, in paediatric patients, several systematic reviews of clinical predictors of severe cardiovascular dysfunction have highlighted the CRT as a warning signal of a cardiovascular distress [11▪]. Although much has been published in paediatrics, these findings cannot be transferred easily to adult critically ill patients. In addition, very few studies have addressed the CRT assessment in adults and its relation to normal range, body site, effect of ambient or skin temperature, and its reliability among examiners.

Effect of skin temperature on capillary refill time

Assessing the skin temperature will assist in evaluating the cause of sluggish capillary refill. Maintaining the same heart rate, cardiac output, and core temperature in a healthy population of eight volunteers, our group showed that the presence of peripheral vasoconstriction as a result of body surface cooling could significantly increase the CRT to a magnitude of more than 150% (>11.0 s) [12]. Thus, assuming normal core temperature, decreased skin blood flow as cause of delayed CRT can be estimated by measuring skin temperature, as cold extremities reflect constriction of

cutaneous vessels that ultimately decreases the amount of blood volume within peripheral vasculature. By contrast, peripheral vasodilation has the opposite effect. Inducing peripheral vasodilation with nitroglycerin infusion in patients with shock after haemodynamic stabilization and with much delayed CRT resulted in significant decrease in CRT in 51% toward normal compared with baseline values [13]. One should pay attention to how to evaluate skin temperature. In this regard, a temperature gradient can better reflect changes in cutaneous blood flow than the absolute skin temperature itself [8]. Body temperature gradients are determined by the temperature difference between two measurement points such as peripheral-to-ambient, central-to-toe, and forearm-to-fingertip (Tskin-diff). Increased vasoconstriction leads to decreased skin temperature and limited ability to regulate core temperature before hypothermia occurs. Consequently, core temperature is maintained at the cost of low skin blood flow, resulting in an increased central-to-peripheral temperature difference. As peripheral temperature may be influenced by ambient temperature, Tskin-diff may be a more reliable measurement, as the two skin temperatures are exposed to the same ambient temperature [14]. Experimental studies have suggested a Tskin-diff threshold of 0°C for initiating vasoconstriction and of 4°C for severe vasoconstriction [15,16]. Therefore, assessing skin temperature by touching the extremities or measuring a body temperature gradient can assist a physician to recognize a clinically acceptable CRT. If the extremities are cold, one should expect a delayed CRT. On the contrary, warm extremities indicate adequate cutaneous blood flow and one should expect a normal CRT, whereas a delayed CRT in this condition suggests cutaneous microcirculatory derangement [17].

What is a normal capillary refill time in healthy persons?

The normal range of CRT in adults is still debated. Only two studies have addressed the normal range of CRT in the adult population. Schriger and Baraff [18] reported that the upper limit of a normal CRT is 4.5 s. In a more recent study, Anderson *et al.* [19] assessed the difference in normal range of CRT with age in an adult population. The study included 1000 participants, and CRT was found to be strongly dependent on age, sex, and ambient temperature, with the upper limit of normal (defined by the 95th percentile) of 3.5 s. The authors also emphasized that using 2.0 s as the upper limit of normal would have misclassified 45% of participants in their study. Taken together, these findings show that the delayed return of more than 2.0 s seems to be of limited value in adult critically ill patients and not specific enough to identify patients in cardiovascular distress.

What is normal capillary refill time in critically ill patients?

Many studies already showed that a CRT >5.0 s following initial haemodynamic optimization discriminated haemodynamically stable patients with more severe organ dysfunction and higher odds for worsening organ failure [20–23].

Serial evaluations of CRT have more prognostic value than one time point measurement. In a population of 111 postoperative patients, delayed CRT was more often seen in patients with severe complications (grade III–V Clavien–Dindo classification system) [23]. Before surgery, there were no differences between groups in CRT. However, at first day after surgery, CRT was significantly longer (CRT > 5.0 s) in patients who subsequently developed severe complications, and this difference persisted over time until the fourth day. In another recent study, Hernandez *et al.* [20] reported that in a population of 41 critically ill patients with sepsis-related circulatory dysfunction, 34 (85%) who were successfully resuscitated exhibited normal CRT (<5.0 s) within 6 h, even before normalization of lactate levels.

In severe cardiovascular dysfunction, an even longer CRT may have more prognostic value. Van Genderen *et al.* [22] performed a controlled observational study of mild systemic hypothermia in patients following out-of-hospital cardiac arrest. In this study, CRT was shorter in survivors at admission and improved even further directly after rewarming, whereas in nonsurvivors a prolonged CRT persisted during the rewarming period. A positive likelihood ratio was calculated after rewarming and indicated that CRT response exceeding 11.5 s was obtained at least 1.8–17.0 times more often in nonsurvivors than survivors. In addition, the authors also found that after rewarming to achieve normal core temperature, SOFA score was significantly higher in patients who had a CRT > 11.5 s. This was largely attributed to the significantly higher scores for respiratory, cardiovascular, and renal system, although this of course does not indicate causality.

Similar observations were reported in septic shock patients. In a recent article, Ait-Oufella *et al.* [24▪▪] investigated the skin CRT in a selected group of septic shock patients. CRT was evaluated in 59 patients at intensive care admission and after

initiation of vasopressor therapy within 24 h. Skin CRT of finger and knee was a strong predictor of 14-day mortality. Patients who persisted with CRT > 5.0 s had an odds ratio of dying in 14 days of 9 [95% confidence interval (CI) 1–61] when measured in the finger and odds ratio of 23 (95% CI 11–1568) when measured in the knee. Among patients who died, both knee and index CRTs did not change and remained prolonged in 82% of the patients despite resuscitation, demonstrating that abnormal signs of peripheral perfusion in patients with no other clinical signs of shock are predictive of progressing organ dysfunction. These results align with two previous findings of the same group. To analyse mottling objectively, Ait-Oufella *et al.* [25] recently developed a clinical scoring system (from 0 to 5) based on the area of mottling from the knees to the periphery. This group reported that a higher mottling score within 6 h after initial resuscitation was a strong predictive factor of 14-day mortality during septic shock, and this was independent of systemic haemodynamics. In a second study, applying the same mottling score system, the same group found that tissue oxygen saturation measured around the knee in septic shock was associated with an increase of the mottling score [26].

More recently, Coudroy *et al.* [27▪] conducted an observational study applying this same mottling score to investigate the incidence of mottling in a large cohort of 791 critically ill patients and its impact on ICU mortality. Skin mottling was defined as a red-violaceous discoloration of the knee visually assessed by the nurses regardless of skin temperature or CRT. This study also included an interobserver agreement assessment between the nurse and the principal investigator. Although the authors studied the nurse–investigator agreement in only 16 patients, the reliability of qualitative assessment of mottling in patients with nonextensive mottling (mottling score <2) was very good (Cohen κ of 0.87, 95% CI 0.63–1.0). The authors reported a mottling incidence of 29% in all patients and 49% in patients admitted for acute circulatory failure. Patients with skin mottling had more severe disease with higher SOFA and higher SAPS II score. In addition, patients with mottling had significantly more organ support (mechanical ventilation, vasopressor infusion, or renal replacement therapy). Using multivariate analysis, the occurrence of at least one skin mottling episode (mottling score > 1) over the knee was associated with ICU mortality independent from SAPS II [27▪].

These studies suggest that mottling of the skin is easily recognized and is often encountered in critically ill patients. Pallor, mottling, and cyanosis are key visual indicators of reduced skin circulation. It is defined as a bluish skin discoloration that typically manifests near the elbows or knees and has a distinct patchy pattern. Mottling is the result of heterogenic small vessel vasoconstriction and is thought to reflect abnormal skin perfusion. This scoring system is very easy to learn, has good interobserver agreement, and can be used at the bedside.

Reliability of capillary refill time

One concern among physicians is the suspected lack of reproducibility of CRT within and between observers. In the study by Ait-Oufella *et al.* [24▪▪], skin CRT of finger and knee was evaluated in 59 patients at intensive care admission and after initiation of vasopressor therapy within 24 h. Two intensivists blinded to patient treatment quantified the CRT, and the interrater concordance was 80% (73–86) for finger CRT and 95% (93–98) for knee CRT. In another recent study, van Genderen *et al.* [23] evaluated 1038 consecutive daily CRT measurements in 173 postoperative patients, reporting a substantial overall agreement between trained observers, instructed intensivists, and ICU nurses to determine prolonged CRT (CRT > 5.0 s) with a Cohen κ between-rater correlation coefficient of 0.91 (95% CI 0.80–0.97) on first postoperative day, 0.81 (95% CI 0.65–0.93) on the second postoperative day, and 0.74 (95% CI 0.52–0.89) on the third postoperative day. With a substantial interrater agreement of CRT measurement, these complementary studies provide convincing evidence of CRT reproducibility and support the strategy of bedside evaluation of peripheral perfusion with CRT.

CLINICAL APPLICATIONS IN PATIENT MANAGEMENT

From the above, we can conclude that conventional haemodynamic parameters must be combined with the clinical assessment of peripheral circulation to continually monitor a critically ill patient as an attempt to optimize resuscitation. Although the mechanisms involved in shock resuscitation are not yet fully understood, it is clear that the persistence of abnormal peripheral circulation is associated with worse patient outcomes. It is likely that interventions specifically aimed at the peripheral vascular bed would have a greater effect on regional perfusion. However, before developing specific therapy that targets peripheral perfusion, it is essential to evaluate the effect of different therapeutic strategies in critically ill patients, such as fluid resuscitation, vasopressor, or vasodilator therapy. The concept of treating peripheral perfusion in critically

ill patients originated in the 1990s with clinical trials of different types of therapy, including vasodilators (prostacyclin and *N*-acetylcysteine), targeting splanchnic perfusion as assessed by gastric tonometry [28]. These studies demonstrated an improvement in gastric perfusion suggesting that successful microcirculatory recruitment had occurred. More recently, studies have evaluated sublingual microcirculation during short-term infusions of nitroglycerin in septic or nonseptic shock and demonstrated significant improvements in microcirculation capillary density [29–31]. A randomized controlled trial in 70 patients with septic shock failed to show significant differences in the evolution of the sublingual microcirculation between the control and the protocol groups treated with a constant dose of nitroglycerin [30]. Although this study precluded the effectiveness of nitroglycerin in the sublingual microvascular flow, cutaneous circulation as measured by central-to-toe temperature significantly improved in the nitroglycerin-treated group compared with the placebo group. This finding highlights the need for additional studies to identify the best peripheral vascular bed to target during and after resuscitation therapy of shock, as well as the type of patient population who may benefit from such an intervention. In this line of thought, our group recently performed a crossover study to investigate the effect of intravenous nitroglycerin on clinical parameters in shock patients with abnormal peripheral circulation following initial resuscitation [13]. This study showed that the use of a stepwise increase in the dose of nitroglycerin (starting 2 mg/h to maximum 8 mg/h) normalized the abnormal CRT in all 15 patients. These changes occurred in parallel with changes in Tskin-diff suggesting that the improvement in cutaneous microcirculation was likely the result of increase in cutaneous blood flow. The noticeable changes in CRT during nitroglycerin infusion provide evidence that clinical assessment of peripheral perfusion can be used to titrate vasodilator therapy to improve tissue perfusion. However, whether this therapeutic strategy results in better clinical outcome still has to be determined in randomized clinical trials.

Other less specific therapeutic approaches have shown to have positive effects on peripheral circulation. For instance, Futier *et al.* [32] recently showed that the administration of a fluid challenge improved peripheral tissue oxygenation in patients undergoing major abdominal surgery. Taken one step further, van Genderen *et al.* [33▪▪] have explored the effects of peripheral perfusion-guided fluid therapy in patients with septic shock. In a randomized, controlled pilot trial, 30 patients were randomly assigned to fluid management either targeting peripheral perfusion parameters or mean arterial pressure >65 mmHg. The primary study parameter was the daily fluid balance. In the intervention group, patients received less fluids during the treatment period, 4227 (±1081 ml) vs. 6069 (±1715 ml), and almost 2.5 l less in the following days, 7565 (±982 ml) vs. 10 028 (±941 ml). Interestingly, patients in the control group stayed longer in the hospital compared with the intervention group and had higher odds for organ failure. The conclusion of the authors was that fluid administration in the intervention group worked as a safety limit rather than a resuscitation target. Whether these interventions are capable of resuscitating different peripheral vascular beds remains to be determined. Current studies are ongoing to determine the effects of different interventions on peripheral circulation in critically ill patients.

CONCLUSION

The feasibility and reproducibility of the clinical assessment of peripheral circulation are substantial, and involved physicians and nurses judge this diagnostic tool to be easy to use. Perhaps the most obvious reason why the physical examination will endure is convenience. Reliance on simple methods, such as CRT, skin temperature, and mottling score must be emphasized and exploited. To what extent these abnormalities reflect tissue hypoperfusion in shock remains to be investigated. Nevertheless, most of published reports support our earlier knowledge that the vascular bed of peripheral circulation is among the first to deteriorate and the last to be restored after resuscitation. The true clinical implications of this strategy may be better defined in the next clinical trials of peripheral perfusion-targeted resuscitation. One next logical step, therefore, would be incorporating therapeutic strategies into resuscitation protocols that aim at normalizing (peripheral) perfusion parameters to investigate the impact of peripheral perfusion-targeted resuscitation in the survival of critically ill patients. Thoughtfully integrated with the new technology, the clinical assessment of peripheral perfusion should and will continue to be central to intensive care clinical practice.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the Department of Intensive Care, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Guzman JA, Dikin MS, Kruse JA. Lingual, splanchnic, and systemic hemodynamic and carbon dioxide tension changes during endotoxic shock and resuscitation. J Appl Physiol 2005; 98:108–113.
2. Guzman JA, Lacoma FJ, Kruse JA. Relationship between systemic oxygen supply dependency and gastric intramucosal P_{CO_2} during progressive hemorrhage. J Trauma 1998; 44:696–700.
3. Shepherd AP, Kiel JW. A model of countercurrent shunting of oxygen in the intestinal villus. Am J Physiol 1992; 262 (4 Pt 2):H1136–H1142.
4. Schlichtig R, Kramer DJ, Pinsky MR. Flow redistribution during progressive hemorrhage is a determinant of critical O_2 delivery. J Appl Physiol 1991; 70:169–178.
5. Chien LC, Lu KJ, Wo CC, Shoemaker WC. Hemodynamic patterns preceding circulatory deterioration and death after trauma. J Trauma 2007; 62:928–932.
6. Poeze M, Solberg BC, Greve JW, Ramsay G. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: what is a better predictor of outcome in critically ill septic patients? Crit Care Med 2005; 33:2494–2500.
7. Dunser MW, Takala J, Brunauer A, Bakker J. Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. Crit Care 2013; 17: 326.
8. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med 2005; 31:1316–1326.
9. Champion HR, Sacco WJ, Carnazzo AJ, *et al.* Trauma score. Crit Care Med 1981; 9:672–676.
10. Pickard A, Karlen W, Ansermino JM. Capillary refill time: is it still a useful clinical sign? Anesth Analg 2011; 113:120–123.
11. ■ Fleming S, Gill P, Jones C, *et al.* Validity and reliability of measurement of capillary refill time in children: a systematic review. Arch Dis Child 2013; 98:265–268.

Although it was performed in a paediatric population, this study has helped shed light on questions related to the optimum method of measurement of CRT. This systematic review should be a reference study for future investigations in the adult population.

12. Lima A, van Genderen ME, Klijn E, *et al.* Peripheral vasoconstriction influences thenar oxygen saturation as measured by near-infrared spectroscopy. Intensive Care Med 2012; 38:606–611.
13. Lima A, van Genderen ME, van Bommel J, *et al.* Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock. Crit Care 2014; 18:R126.
14. Carrillo AE, Cheung SS, Flouris AD. A novel model to predict cutaneous finger blood flow via finger and rectal temperatures. Microcirculation 2011; 18:670–676.
15. Sessler DI. Skin-temperature gradients are a validated measure of fingertip perfusion. Eur J Appl Physiol 2003; 89:401–402.
16. House JR, Tipton MJ. Using skin temperature gradients or skin heat flux measurements to determine thresholds of vasoconstriction and vasodilatation. Eur J Appl Physiol 2002; 88:141–145.
17. Lima A, van Bommel J, Sikorska K, *et al.* The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients. Crit Care Med 2011; 39:1649–1654.
18. Schriger DL, Baraff L. Defining normal capillary refill: variation with age, sex, and temperature. Ann Emerg Med 1988; 17:932–935.
19. Anderson B, Kelly AM, Kerr D, *et al.* Impact of patient and environmental factors on capillary refill time in adults. Am J Emerg Med 2008; 26:62–65.
20. Hernandez G, Pedreros C, Veas E, *et al.* Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation. A clinical-physiologic study. J Crit Care 2012; 27:283–288.
21. Lima A, Jansen TC, van Bommel J, *et al.* The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. Crit Care Med 2009; 37:934–938.
22. van Genderen ME, Lima A, Akkerhuis M, *et al.* Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012; 40:2287–2294.
23. van Genderen ME, Paauwe J, de Jonge J, *et al.* Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. Crit Care 2014; 18:R114.
24. ■■ Ait-Oufella H, Bige N, Boelle PY, *et al.* Capillary refill time exploration during septic shock. Intensive Care Med 2014; 40:958–964.

The first study to demonstrate the prognostic value of CRT concomitantly measured in two different places in patients with septic shock.

25. Ait-Oufella H, Lemoinne S, Boelle PY, *et al.* Mottling score predicts survival in septic shock. Intensive Care Med 2011; 37:801–807.
26. Ait-Oufella H, Joffre J, Boelle PY, *et al.* Knee area tissue oxygen saturation is predictive of 14-day mortality in septic shock. Intensive Care Med 2012; 38:976–983.
27. ■ Coudroy R, Jamet A, Frat JP, *et al.* Incidence and impact of skin mottling over the knee and its duration on outcome in critically ill patients. Intensive Care Med 2015; 41:452–459.

This study is interesting and valuable as it includes a large cohort of 791 critically ill patients.

28. Lima A. Circulatory shock and peripheral circulatory failure: a historical perspective. Neth J Crit Care 2014; 18:14–18.
29. Spronk PE, Ince C, Gardien MJ, *et al.* Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 2002; 360:1395–1396.
30. Boerma EC, Koopmans M, Konijn A, *et al.* Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. Crit Care Med 2010; 38:93–100.
31. den Uil CA, Caliskan K, Lagrand WK, *et al.* Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. Intensive Care Med 2009; 35:1893–1899.
32. Futier E, Christophe S, Robin E, *et al.* Use of near-infrared spectroscopy during a vascular occlusion test to assess the microcirculatory response during fluid challenge. Crit Care 2011; 15:R214.
33. ■■ van Genderen M, Noel E, van der Valk RJ, *et al.* Early peripheral perfusion-guided fluid therapy in patients with septic shock. Am J Respir Crit Care Med 2015; 191:477–480.

This is the first clinical trial to demonstrate the impact of fluid therapy targeting CRT during resuscitation of patients with septic shock.