

**Peripheral Perfusion in Relation
to Systemic Hemodynamics**
and its Importance in Critically Ill Patients

Michel E. van Genderen

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**Peripheral Perfusion in Relation
to Systemic Hemodynamics**
and its Importance in Critically Ill Patients

Perifere circulatie bij ernstig zieke patiënten
en de relatie met de systemische circulatie

Proefschrift

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"Only a man who knows what it is like to be defeated
can reach down to the bottom of his soul and come up with
the extra ounce of power it takes to win when the match is even."

Cassius Marcellus Clay -Muhammad Ali-

"No one is born hating another person because of the color of his skin,
or his background, or his religion."

Nelson Rolihlahla Mandela

*Voor mijn grootouders,
mijn moeder, vader en broertje*

Content

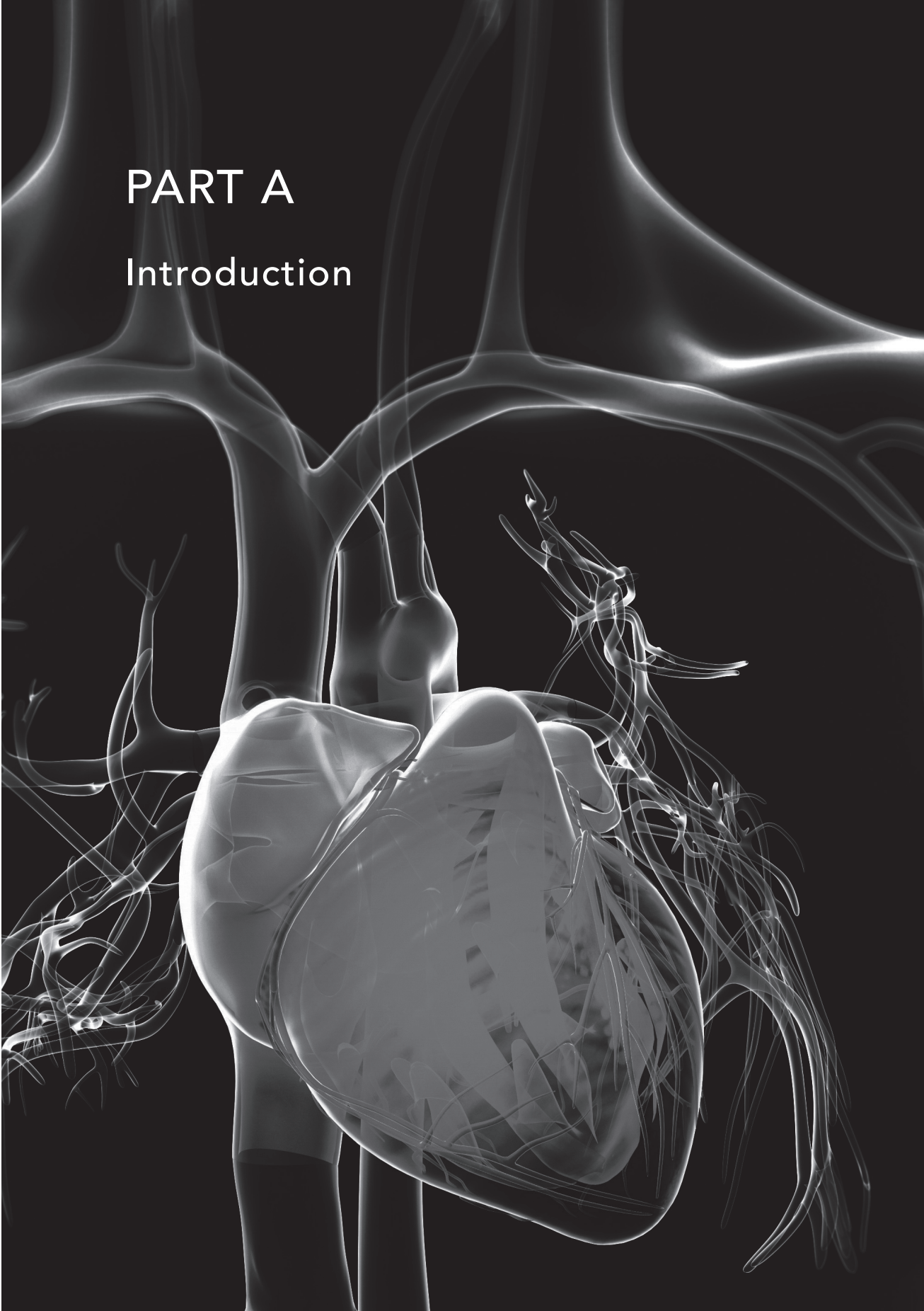
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PART A

Introduction



General introduction
and outline of the thesis

1

"To him medicine owes the art of clinical inspection and observation."

Hippocrates (460 BC – 370 BC).¹

The practice of physical examination, diagnosis and prognosis is introduced by the Egyptians and the Babylonians. The Diagnostic Handbook written by the ummânū (chief scholar) Esagil-kin-apli is known as one of the earliest and most extensive Babylonian medical texts (1069-1046 BC). In this handbook it was suggested that the patient's disease could be determined by use of clinical inspection and physical examination.² Later it was Hippocrates (460-370 BC) "father of Western medicine" who in a structured fashion, described many diseases and medical conditions. He is well known as a major contributor of descriptions of the symptomatology and physical findings of many different diseases.^{1,3} Despite this ancient knowledge, how many physicians today would have the courage to write, unaided, a text on the physical examination, diagnosis, and treatment of different diseases at the bedside? It was the Dutch physician Isidore Snapper (1889-1973), who first shared his knowledge regarding the use of *Bedside Medicine*.⁴ Before that, Jordan Furneaux, a British surgeon, gave one of the first elaborated descriptions of alterations in peripheral perfusion during 'shock' conditions (1827).

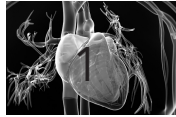
Although I feel fortunate to live in the 21st century, with incredible innovations in medical technology and progress in patient-centered care, the emphasis and dependence on technology in modern medicine has generated an unquestioned faith in this technology, which in turn may undermine the clinician's confidence in their own clinical skills. This may result in a decline of traditional bedside patient assessment at the expense of an increased use of technical diagnostic procedures. The danger of such unwavering confidence in technology (even in the absence of a solid evidence base for its benefits) may eventually reduce the status of traditional clinical bedside assessment to that of a "medical folklore".⁵

Circulatory shock

Nowadays 'shock' is best defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. It is a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysfunction. The result is cellular dysoxia, i.e. the loss of the physiological independence between oxygen delivery and oxygen consumption, associated with increased lactate levels.⁶ Circulatory shock frequently consists of inadequate tissue blood flow and if untreated, proceeds from organ dysfunction to organ failure and eventually death. It is therefore one of the most common reasons to admit patients to the Intensive Care Unit.⁷

According to Weil and Shubin,⁸ founders of the understanding and management of circulatory (dys)function, shock can be classified into four main categories: 1. Hypovolemic (decreased circulating volume), 2. Cardiogenic (cardiac pump failure), 3. Obstructive (cardiovascular circuit obstruction), and 4. Distributive (vascular dysfunction) causes (Figure 1)⁹.

Of these four types, the first three are characterized by decreased cardiac output (i.e. low flow state) and as such can be regarded typical 'shock' conditions. The last



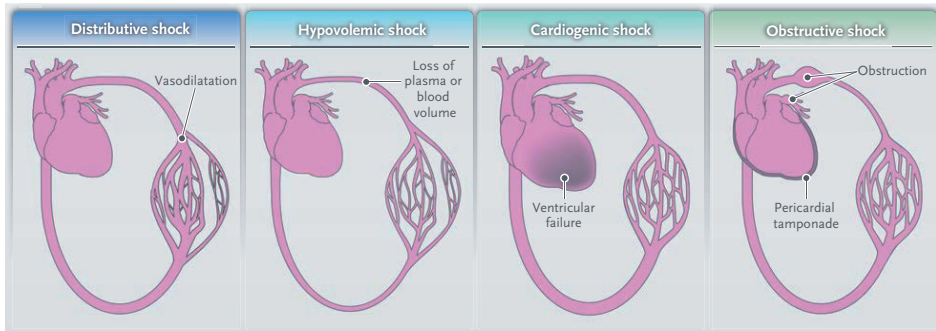


Figure 1. Schematic representation of the four types of shock. The classification of the different shock types, reproduced from Vincent et al.⁹, with permission of the NEJM.

type, distributive shock (of which septic shock is the most common example), is typically associated with high cardiac output (hyperdynamic flow) and as such provides a huge challenge in terms of understanding the underlying biologic features and identifying the 'ideal' endpoints for hemodynamic therapy. It is the result of several mediators, such as pathogen factors (i.e. microbial load and virulence) leading to a host–pathogen interaction and an exaggerated inflammation resulting in loss of autoregulation and a severe disbalance between vasodilation and vasoconstriction. Sepsis, severe sepsis, and septic shock are all used to describe the increasing severity of a systemic inflammatory response to infection accompanied by systemic symptoms (i.e. fever, leucocytosis, hyperventilation, tachycardia).¹⁰ These alterations finally cause inadequate regional oxygen delivery, tissue injury and/or refractory hypotension and acute organ dysfunction, accompanied by a normal or even of a supranormal cardiac output.^{11,12}

Hemodynamic monitoring is essential for diagnosis and management of shock. In time, many techniques have been developed: invasive or noninvasive, continuous or intermittent, and looking at different physiologic variables, directly or indirectly (through signal processing).¹³

Hemodynamic monitoring

*"Hemodynamic monitoring plays an important role in the management of today's acutely ill patient."*¹³

Hemodynamic monitoring emerged as a distinct scientific discipline late in the 19th century when Scipione Riva-Rocci developed an easy-to-use version of the sphygmomanometer to measure arterial blood pressure. Almost 70 years later in 1964, dr. Ronald Bradley introduced miniature diagnostic catheters for intravascular use.¹⁴ This inspired Jeremy Swan and William Ganz in 1968 to develop an intravascular flow-directed catheter, which could be percutaneously inserted and positioned in the pulmonary artery for the measurement of cardiac output with thermodilution.¹⁵ With their landmark study detailing the human use of this catheter, the era of modern

hemodynamic monitoring begun.¹⁶ Pulmonary artery catheterization highlighted the importance of (semi)continuous monitoring of hemodynamic parameters at the bedside. Concurrently, the introduction of monitors attached to digital computers to monitor hemodynamic measurements was a defining moment in the development of critical care medicine.¹⁷ The combination of this latter technology and pulmonary artery catheters provided intensivists with a powerful platform to (semi)continuously monitor heart function and cardiac output. Despite the widespread use of this invasive catheter in critically ill patients in the 1980's and 1990's, its use has declined in the past years and frequent complications were highlighted.¹⁷⁻²⁰ Nowadays, there is a trend toward less invasive methods of hemodynamic monitoring. Current hemodynamic monitoring tools need to be "reliable, continuous, noninvasive, operator-independent, cost-effective, and should have a fast response time (beat-to-beat)."²¹ Therefore alternative techniques have been developed, for instance: the transpulmonary thermodilution with integrated pulse contour analysis (PiCCO TM) monitoring system (PULSION Medical System, Munich, Germany).²² This device is less invasive than pulmonary artery catheterization because it allows the assessment of cardiopulmonary hemodynamics without contact between the catheter and different cardiopulmonary structures.



Despite these advanced state-of-the-art hemodynamic monitoring techniques, simply targeting parameters related to the systemic circulation does not resuscitate various organ system tissues and might lead to increased use of medical interventions and hospital mortality.²³ Surprisingly, the quest towards advanced hemodynamic monitoring techniques (central venous, arterial and pulmonary artery catheters) left a great study in 1969 unattended. In this study it was demonstrated that circulatory shock patients admitted to the Intensive Care Unit with a toe temperature $\leq 27^{\circ}\text{C}$ had more chance to die during their intensive care unit stay.²⁴ The importance of peripheral perfusion assessment at the bedside was highlighted with this study already in the 20th century.

The 21st century

Welcoming a new era of hemodynamic monitoring: Expanding from the macro to the microcirculation.*²⁵

It is known that all shock states, including distributive shock, are characterized by inadequate tissue perfusion and consequent tissue ischemia. In this latter type of shock, a combination of hypovolemia, reduced ventricular function, and pronounced vasodilation can lead to inadequate tissue perfusion. Because each of these determinants can cause hypotension, monitoring of cardiac function and volume status is essential for selecting the proper therapy. However, regional tissue hypoperfusion may persist, despite the normalization of systemic hemodynamics. During circulatory shock, blood flow is diverted from less important tissues to vital organs (heart, brain, and kidneys) to maintain vital organ perfusion at the cost of peripheral circulation, resulting in poor outcome in various pathophysiologic conditions.^{26,27} Sympathetic activity, which is induced by the baroreceptor reflex as a response to systemic hypotension, leads to increased vasomotor tone. As sympathetic neuroactivity predominates in the skin and

muscle, the sympathetic neurohumoural response-induced vasoconstriction manifests primarily as decreased peripheral perfusion.²⁸ Therefore, the rationale of peripheral perfusion monitoring is based on the concept that peripheral tissues are the first to reflect hypoperfusion during shock, and the last to reperfuse during resuscitation.²⁹

Several studies demonstrated that inadequate systemic circulation in both hypodynamic and hyperdynamic shock states can be accompanied by impaired tissue and microcirculatory perfusion. The importance of monitoring the peripheral microcirculatory tissue perfusion in different types of shock was further expanded upon by the work of Creteur, DeBacker, and their coworkers,^{30,31} who used visualization of microvessels and sublingual capnometry. These abnormalities can be determined noninvasively at the bedside using several clinical assessments. Since we now have entered an era where modern medical practitioners seek improved diagnostic techniques, that are easy to apply at the bedside, have low-risk for complications, and are non-invasive; noninvasive clinical assessment of peripheral perfusion gained interest.^{32,33} To date, many issues, to the quest that already started in 1969, remain to be elucidated. For instance, the clinical significance of the various noninvasive peripheral perfusion methods in different patient populations as well as its role as resuscitation endpoint.

Aim of the thesis

The aim of this thesis was to investigate the value of noninvasive assessment of the peripheral perfusion at the bedside for the recognition and treatment of critically ill patients.

Outline of the thesis

First, we start this thesis with a recapitulation of the currently available methods that can be used at the bedside for the noninvasive monitoring of the peripheral circulation in critically ill patients. We also discuss the potential role of peripheral perfusion monitoring for outcome prediction and resuscitation strategies, **Chapter 2A** and **Chapter 2B** (Dutch version) respectively.

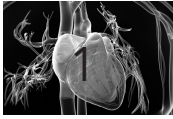
In the next part of this thesis we discuss how peripheral perfusion parameters act under different circulatory conditions. We first evaluated the effect of central hypovolemia on the pulse oximeter-derived peripheral perfusion index (PPI) in awake healthy volunteers (**Chapter 3**). Second (**Chapter 4**), as blood flow in different vascular beds is regulated by local vasomotor tone, we explored the effect of peripheral cooling on the different peripheral perfusion parameters in healthy volunteers.

The third part of this thesis focuses on the clinical value of peripheral circulation assessment at the bedside in different patient populations. In **Chapter 5** we evaluated the relative contribution of systemic blood flow and peripheral vasomotor tone (i.e., vasoconstriction) to sublingual and peripheral perfusion parameters before, during, and after therapeutic hypothermia in patients following out-of-hospital cardiac arrest, and the relation to outcome. We further explored the value of peripheral perfusion assessment for the prediction of complications following major abdominal surgery (**Chapter 6**). Finally in this part, we studied the association between the evolution of

different peripheral perfusion parameters with outcome in patients admitted to the intensive care unit, after undergoing initial septic shock resuscitation (**Chapter 7**).

In the fourth part of this thesis we aimed to answer the quintessential question: can we incorporate the different peripheral perfusion parameters into a resuscitation protocol that could benefit the patient. We therefore studied, in a prospective randomized controlled fashion, whether alterations in peripheral perfusion could be prevented in postoperative esophagectomy patients admitted to the Intensive Care Unit (**Chapter 8**). Next, we investigated in an experimental setting, whether changes in the perfusion of different regional vascular beds are dependent on the type of circulatory shock (obstructive vs. septic) and whether the different microvascular and peripheral perfusion parameters can be used to assess the adequacy of hemodynamic resuscitation during these different types of shock (**Chapter 9**). Finally, we conducted a single-center prospective randomized controlled pilot-study in septic shock patients admitted to the Intensive Care Unit. In this study our primary goal was to compare early goal directed fluid resuscitation based on clinical assessment of peripheral perfusion with standard fluid therapy, to investigate whether peripheral perfusion guided resuscitation is feasible and would lead to less fluid administration (**Chapter 10**).

In **Chapter 11, 12, and 13** we respectively discuss the main results of each chapter, provide recommendations for future work, and summarize the most important findings of this thesis.



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Monitoring peripheral
perfusion in critically
ill patients at the bedside

Curr Opin Crit Care 2012; 18:273-279

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2^a

Abstract

Purpose of review

The holy grail of circulatory monitoring is the use of an accurate, continuous and noninvasive method that can easily assess tissue perfusion under clinical conditions. As peripheral tissues are sensitive to alterations in perfusion, the noninvasive monitoring of peripheral circulation could be used as an early marker of systemic haemodynamic derangement. We therefore aim to discuss the currently available methods that can be used at the bedside as well as the role of peripheral perfusion monitoring in critically ill patients.

Recent findings

The deterioration of peripheral circulation has frequently been observed in critically ill patients with the use of subjective assessment and several optical techniques. In various patient categories, more severe and persistent alterations have been associated with worse outcomes, and these associations were independent of systemic haemodynamic parameters. Interventions aimed at systemic parameters have an unpredictable effect on peripheral circulation parameters, especially during hyperdynamic conditions. Thus, it appears that changes in peripheral perfusion reflect changes in regional vasomotor tone rather than systemic blood flow.

Summary

Subjective assessments and optical techniques provide important information regarding peripheral circulation. Moreover, these techniques are relatively easy to implement and interpret at the bedside and can be applied during acute conditions. Further research is warranted to investigate the effects of therapeutic interventions on peripheral perfusion parameters and patient outcome.

Introduction

The conventional classification for the causes of haemodynamic instability discriminates between a lack of circulating volume, insufficient pump function, obstruction of blood flow and loss of blood flow regulation.¹ Although corresponding treatment modalities have been established, selecting the correct method can be very difficult when a proper diagnosis cannot be made. Especially in patients with severe sepsis, a combination of hypovolaemia, reduced ventricular function, and pronounced vasodilation can lead to inadequate tissue perfusion. Because each of these determinants can cause hypotension, monitoring of cardiac function and volume status is essential for selecting the proper therapy. However, regional tissue hypoperfusion may persist, despite the normalization of systemic haemodynamics.



During circulatory shock, blood flow is diverted from less important tissues to vital organs (heart, brain, and kidneys) to maintain vital organ perfusion at the cost of peripheral circulation, resulting in poor outcome in various pathophysiologic conditions. Sympathetic activity, which is induced by the baroreceptor reflex as a response to systemic hypotension, leads to increased vasomotor tone. As sympathetic neuroactivity predominates in the skin and muscle, the sympathetic neurohumoral response-induced vasoconstriction manifests primarily as decreased peripheral perfusion.² Therefore, the rationale of peripheral perfusion monitoring is based on the concept that peripheral tissues are the first to reflect hypoperfusion during shock, and the last to reperfuse during resuscitation.³

It is well known that inadequate systemic circulation in both hypodynamic and hyperdynamic shock states can be accompanied by impaired peripheral circulation.⁴ These abnormalities can be determined noninvasively using simple clinical assessments,⁵ skin temperature measurements,⁵ and optical monitoring devices.^{6,7} These 'peripheral' techniques each involve the use of 'abnormal' values, which are generally associated with worse outcome in critically ill patients, do not need an intravascular catheter, and can be used directly at the bedside without entry into the body through orifices or skin or mucosal tissue punctures (Table 1). In the following section, we will discuss the currently available and commonly used techniques for assessing peripheral circulation in clinical conditions.

Clinical assessment of peripheral perfusion

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.

Capillary refill time

Capillary refill time (CRT) is defined as the time required for a distal capillary bed (i.e., the nailbed) to regain its colour after pressure has been applied to cause blanching. This concept was first introduced by Champion et al.⁸ in 1981 as a component of the international trauma severity score for the rapid and structured cardiopulmonary

Table 1. Different methods used to measure peripheral perfusion.

Method	Variable	Main advantage	Main limitation	Suggested cut-offs
Clinical assessment	Cold/warm	Depends only on the physical examination; valuable adjunct for haemodynamic monitoring in circulatory shock	Observer dependent. Digitalised and perhaps automated measurements may overcome this limitation	>4.5 seconds, related to higher morbidity and mortality
	Capillary refill time			
	Mottle score	Mottling is widely described and is an easily assessable clinical sign	The score cannot be used in patients with black skin.	Score 4-5, related to survival
Body temperature gradient	Forearm-to-finger	Validated method for estimating microcirculatory skin perfusion	Does not reflect peripheral perfusion variations in real time	>4°C, related to higher morbidity and mortality
	Central-to-toe			>7°C, related to higher morbidity and mortality
Optical monitoring	Peripheral perfusion index	Noninvasive approach to monitor the haemodynamics of critically ill patients	Not accurate during patient motion	<1.4%, related to higher morbidity and mortality
	Near-infrared spectroscopy	Can easily be repeated and can provide quantitative information on microvascular function within a few minutes	Data are reported with different devices, and the vascular occlusion test is not standardised	<70% or 75%, related to higher morbidity and mortality

assessment of critically ill patients. Because CRT assessment is an easily applicable method in many circumstances, it is most useful for assessing peripheral perfusion and predicting unfavourable outcomes in both critically ill adult and paediatric patients. For instance, in paediatric patients, Bohnhorst et al.⁹ showed that among several clinical signs present at the very first instance of suspected infection, a prolonged CRT demonstrated the most sensitive correlation with proven infection. In a recent review of clinical features that are used to confirm or exclude the possibility of serious infection in paediatric patients presented to ambulatory care, a prolonged CRT was shown to be one of the strongest indications of serious infection.¹⁰ In these patients, there may be alterations in the balance of vasoconstrictor and vasodilator substances and in the cross-talk between endothelial cells, which could result in impaired microvascular tissue blood flow regulation that is related to significant dehydration, serious infection, and severe organ dysfunction.¹¹



In a healthy adult population, Schriger and Baraff¹² reported that the upper limit of a normal CRT is 4.5 s. After applying this cutoff in critically ill patients, we demonstrated that a delayed return of normal colour (>4.5 s) can be regarded as decreased peripheral perfusion. Moreover, we found that following initial haemodynamic optimization during the first 24 h of ICU admission, the CRT could be used to discriminate patients with more severe organ dysfunction. In addition, a prolonged CRT (>4.5 s) was related to tissue hypoperfusion and a greater likelihood of worsening organ failure in the following days, compared with patients with a normal CRT.^{5,13} Although interobserver variability remains a matter of debate, an upper normality limit of more than 4.5 s appears to be highly reproducible for critically ill patients admitted to the ICU.¹⁴

Skin temperature

Skin temperature is best estimated using the dorsal surface of the hands or fingers of the medical examiner, as these areas are most sensitive to temperature perception. Patients are considered to have cool extremities if all examined extremities are considered cool by the examiner or if only the lower extremities are cool despite warm upper extremities in the absence of peripheral vascular occlusive disease.¹⁵ It has been demonstrated that subjectively determined variations in skin temperature correspond to objective measures of peripheral skin perfusion.^{13,16} Similarly, fingertip temperature estimations correlated well with objective assessments of fingertip blood flow.^{13,17} Accordingly, patients with a subjectively determined 'abnormal' peripheral perfusion following initial haemodynamic resuscitation have been associated with higher lactate levels and more severe organ dysfunction.⁵

Mottling

Mottling of the skin is easily recognized and is often encountered in critically ill patients. 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. To analyse mottling objectively, Ait-Oufella et al.¹⁸ recently developed a clinical scoring system

(from 0 to 5) based on the area of mottling from the knees to the periphery (Fig. 1). This group reported that a higher mottling score within 6h after initial resuscitation was a strong predictive factor of 14-day mortality during septic shock, and this was independent of systemic haemodynamics. This scoring system is very easy to learn, has good interobserver agreement, and can be used at the bedside.

From these studies, it is clear that the clinical assessment (Fig. 1) of peripheral perfusion is a valuable adjunct for the haemodynamic monitoring of critically ill patients and should be incorporated into future multimodal monitoring strategies to adequately monitor optimal circulatory shock resuscitation.

Body temperature gradient

Although skin temperature has been shown to be an easily accessible parameter for circulatory shock severity,¹⁹ later research demonstrated that body temperature gradients can better reflect changes in cutaneous blood flow than the absolute skin temperature itself in critically ill patients.^{20,21} 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 (T_{skin-diff}). Increased vasoconstriction during circulatory shock leads to decreased skin temperature and a diminished ability of the core

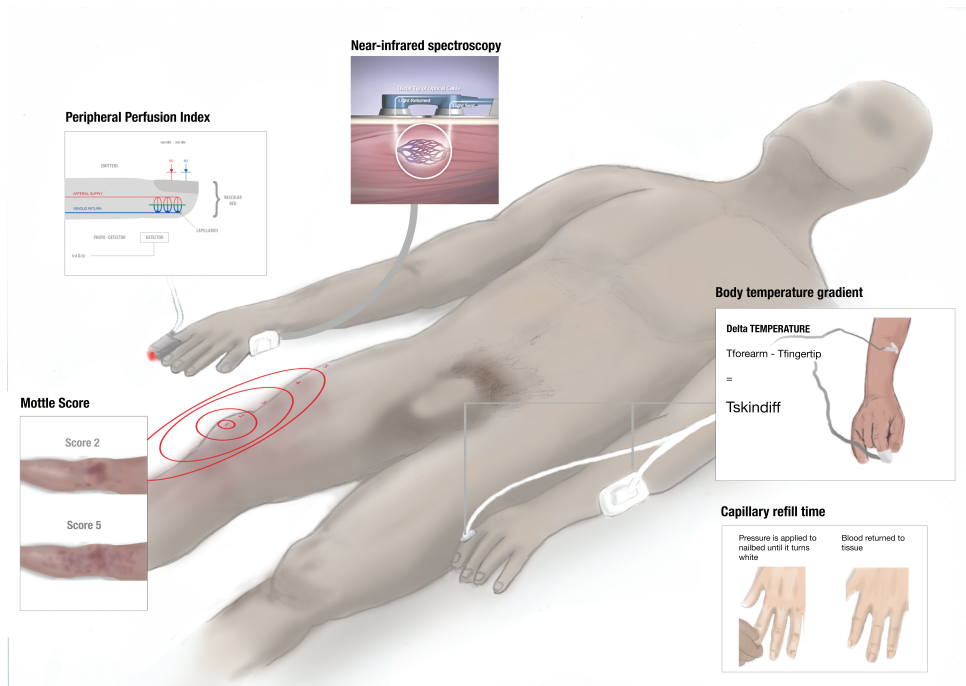


Figure 1. Peripheral perfusion methods used in clinical practice. Different methods are used to measure peripheral perfusion, and these provide quantitative real-time information regarding peripheral circulation at the bedside.

to regulate its temperature before hypothermia occurs. Consequently, core temperature is maintained at the cost of the periphery to maintain vital organ perfusion, resulting in an increased central-to-peripheral temperature difference, when vasoconstriction decreases fingertip blood flow. This concept permits the establishment of central-to-toe temperature difference as an indicator of peripheral perfusion in critically ill patients, and a normal temperature gradient of 3–7°C occurs once the patient's haemodynamics have been optimized.²² Because the effect of the operating room environment on skin and body temperature changes during surgery, especially with the use of cardiopulmonary bypass, T_{skin-diff} may be a more reliable measurement for critically ill patients.²³ The use of T_{skin-diff} is based on assumption that the reference temperature is a skin site exposed to the same ambient temperature producing little change in the gradient (Fig. 1). Experimental studies have suggested T_{skin-diff} thresholds of 0°C for initiating vasoconstriction and 4°C for severe vasoconstriction.^{23,24} In critically ill adult patients, T_{skin-diff} measurements conducted simultaneously with clinical observation have helped to address the reliability of subjective peripheral perfusion assessment, and are able to indicate abnormal peripheral perfusion in the postresuscitation period.⁵



Optical monitoring

Optical methods apply light with different wavelengths directly to the tissue to assess various tissue states. There are several research techniques (described elsewhere²⁵) that apply optical methods to visualize the microcirculation, assess oxygen availability, measure P_{co₂}, and assess microvascular function in different tissues. Commonly used optical methods in the clinical setting that are able to monitor peripheral perfusion at the bedside include finger photoplethysmography and near-infrared spectroscopy (NIRS). Although these techniques are particularly promising, as objective numerical information can be obtained within a couple of minutes, the interpretations should be considered in combination with the clinical examination and additional peripheral perfusion measurements.¹³

Peripheral perfusion index

The peripheral perfusion index (PPI) is derived from the photoelectric plethysmographic signal of the pulse oximeter. Pulse oximetry, a standard of care in the ICU, allows for the measurement of arterial haemoglobin oxygen saturation and pulse rate monitoring. This noninvasive tool uses two wavelengths of light (red and infrared) that are transmitted through the distal phalanx of the index finger, resulting in the display of a pulsatile photoplethysmographic waveform. Analogous to an arterial pulse contour analysis, several variables can be derived from the plethysmographic waveform, such as the PPI (Fig. 1). The PPI is the ratio of the pulsatile part to the nonpulsatile part of the curve, expressed as a percentage. Because the size of the pulsatile portion increases with vasodilation and decreases with vasoconstriction, changes in the PPI reflect changes in peripheral vasomotor tone. This was first demonstrated in a model of axillary plexus-induced vasodilatation, and the analgesic effect of this nerve block could be predicted within minutes using the increase in PPI as a measure of

concomitant peripheral vasodilatation in patients undergoing hand surgery.²⁶ Similarly, the PPI was shown to be rapidly reduced following sympathetic response-induced vasoconstriction after the introduction of a nociceptive skin stimulus²⁷ or an intravenous injection of epinephrine²⁸ or norepinephrine.²⁹ Furthermore, in a lower body negative pressure model, the PPI also rapidly decreased following sympathetic activation in healthy volunteers who underwent stepwise decreases in venous return.³⁰

In a large population of healthy volunteers, the median PPI value was 1.4%.⁷ In critically ill patients, the same value was found to represent a very sensitive cutoff point for determining abnormal peripheral perfusion, as defined by a prolonged CRT and an increased skin temperature difference.^{5,7,31} Therefore, this easily obtainable and noninvasive method can be used for monitoring peripheral perfusion in critically ill patients.

Near-infrared spectroscopy

NIRS is a noninvasive technique that enables the determination of tissue oxygenation based on the spectrophotometric quantitation of oxyhaemoglobin and deoxyhaemoglobin within a tissue. Although this technique can be applied to any tissue, it is primarily used to monitor peripheral oxygenation of muscle tissue in critically ill patients. The variables that are analysed using NIRS can either be directly calculated or derived from physiological interventions, such as an arterial and venous vascular occlusion test (VOT). As a result, information regarding muscle oxygen saturation (StO₂) and the absolute tissue haemoglobin index, an indicator of blood volume in the microvasculature tissue region, can be obtained.² In addition, changes in StO₂ levels during a VOT have been used to represent microvascular reactivity.^{6,32-34} The utility of NIRS for managing critically ill patients remains a matter of debate. Increasing publications using NIRS have described profound alterations in microvascular function in patients suffering from different pathophysiological conditions, such as sepsis and traumatic shock.³²⁻³⁵ In a study by Shapiro et al.³⁶, the dynamic NIRS variables collected during a VOT were strongly associated with the severity of organ dysfunction and mortality in patients with septic shock. In this study, the StO₂ recovery slope was most sensitive for the prediction of mortality. This is of special interest because there is a lack of agreement on standardization for the appropriate method for performing a VOT^{37,38}. When measured at the thenar eminence, NIRS-derived measurements are influenced by the peripheral circulation condition (Fig. 1).¹³ Nevertheless, when used in conjunction with other peripheral perfusion methods, repeated StO₂ monitoring has the potential to assess the effect of therapeutic intervention on the peripheral microvascular circulation in various shock states. Similarly, Colin et al.³⁹ investigated the dynamic response of StO₂ at different sites during the first 6h of severe sepsis resuscitation, and argued that StO₂ values measured at the masseter muscle may better relate to patient outcome and may be a more powerful indicator for monitoring the effect of resuscitation, compared with measurements taken at the thenar eminence.

Although NIRS can potentially be very useful for tissue oxygenation and perfusion assessments, additional studies are still being conducted to clarify its role in the clinical management of ICU patients.

Potential therapeutic interventions to resuscitate peripheral perfusion

Although the relationship between systemic and peripheral circulation is not always well defined, the assessment of peripheral perfusion during peripheral cooling-induced vasoconstriction in healthy volunteers has shown that profound changes in the peripheral circulation can occur independently of systemic haemodynamic parameters, such as blood pressure and cardiac output.³¹ Similar observations have been made during therapeutic hypothermia following cardiac arrest.⁴⁰ In patients with severe sepsis, this discrepancy between systemic and peripheral circulation can become even larger; regional vasoconstriction appears to be independent of systemic blood flow in these patients.⁴¹ Considering that peripheral vasoconstriction during septic shock is an effect of increased sympathetic activity, the origin of the latter is unclear; it is likely that baroreceptor reflex activity, systemic inflammatory response, and the loss of parasympathetic activity each may play a role.^{42,43}



Although the mechanism involved in sepsis resuscitation is not yet fully understood, it is clear that the persistence of impaired peripheral perfusion is associated with worse patient outcomes.^{5,6} It can be hypothesized that interventions specifically aimed at the peripheral vascular bed could resuscitate these alterations. For instance, based on the central-to-toe temperature, Boerma et al.⁴⁴ showed that the administration of nitroglycerine to septic patients following early resuscitation significantly improved peripheral perfusion, independently of systemic haemodynamics. Although there was a trend to increasing mortality, this was accompanied by reduced morbidity in the nitroglycerine-treated patient group compared with the placebo group; as a result, vasodilatory agents may be promising treatment modalities.

Although fluid resuscitation is the first line therapy for sepsis-induced hypoperfusion, few studies have evaluated its effect on peripheral perfusion. Futier et al.⁴⁵ recently showed that the administration of a fluid challenge had positive effects on peripheral tissue oxygenation in patients undergoing major abdominal surgery.

Whether these interventions are capable of resuscitating different peripheral perfusion parameters is, however, still unknown. Current studies to determine the effects of these interventions on peripheral circulation in critically ill patients are ongoing.

Conclusion

The rationale for monitoring peripheral perfusion is based on the concept that the peripheral circulation is the first to reflect a disturbance of the circulation that may lead to shock. Monitoring peripheral circulation not only provides a different point of reference for patient circulation but it also does not require invasive techniques and can be used directly at the bedside. Moreover, it is a simple approach that can be rapidly applied throughout the hospital, including the emergency department, operating room, wards, and ICU.

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Perifere circulatie bij ernstig
zieke patiënten non-invasieve
methoden voor beoordeling
van de perifere perfusie

[Peripheral circulation in critically
ill patients: non-invasive methods
for the assessment of the
peripheral perfusion]

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2^b

Abstract

Peripheral tissues, such as skin and muscles, are sensitive to alterations in perfusion. During circulatory shock, these tissues are the first to receive less blood and the last to recover after treatment. By monitoring peripheral circulation, disturbance of the systemic circulation can be detected at an early stage. Peripheral perfusion is often disturbed in critically ill patients. Peripheral perfusion may remain disturbed, even if conventional hemodynamic parameters such as blood pressure and heart frequency normalize after treatment. Persistent abnormal peripheral perfusion is related to a poorer clinical course. With current non-invasive methods, peripheral circulation in critically ill patients can easily be assessed at the bedside. Interventions that improve peripheral circulation may speed up recovery in critically ill patients.

Samenvatting

- Perifere weefsels, zoals huid en spieren, zijn gevoelig voor veranderingen in de perfusie. Tijdens circulatoire shock worden deze weefsels als eerste minder doorbloed en na behandeling herstellen ze als laatste.
- Door het monitoren van de perifere circulatie kan daarom al in een vroeg stadium een verstoring van de systemische circulatie worden opgespoord.
- Bij ernstig zieke patiënten is de perifere perfusie vaak verstoord.
- De perifere perfusie kan verstoord blijven, ook als de waarden van conventionele hemodynamische parameters, als bloeddruk en hartfrequentie, na behandeling normaliseren.
- Een blijvend afwijkende perifere perfusie is gerelateerd aan een slechter klinisch beloop.
- Met de huidige non-invasieve methoden kan de perifere circulatie bij ernstig zieke patiënten eenvoudig worden beoordeeld aan het bed.
- Mogelijk kunnen interventies die de perifere circulatie verbeteren het klinisch herstel bespoedigen bij ernstig zieke patiënten.

Introduction

Al sinds 1969 is bekend dat de temperatuur van de grote teen een maat is voor de ernst van circulatoire shock.¹ De onderzoekers lieten zien dat patiënten met een teentemperatuur $\leq 27^\circ\text{C}$ bij opname op de IC een slechtere hartfunctie en een groter risico op overlijden hadden. Anno 2013 zijn er andere methoden om de doorbloeding van de perifere circulatie te bepalen aan het bed van de patiënt. Een slechtere perifere doorbloeding, zoals bepaald met deze nieuwere methoden, is geassocieerd met een verhoogd risico op orgaanfalen en op overlijden.²⁻⁵ Mogelijk wordt het verbeteren van de perifere doorbloeding een belangrijk doel bij de behandeling van ernstig zieke patiënten.⁶



In dit artikel presenteren we de huidige non-invasieve methoden om de doorbloeding van de perifere circulatie te bepalen en de implicaties hiervan voor de kliniek.

Waarom de perifere perfusie meten

Tijdens de initiële periode van circulatoire shock vindt een herverdeling van het hartminuutvolume plaats, van de perifere weefsels (huid en spier) naar de vitale organen (hersenen en hart). Dit is het gevolg van verschillende compensatiemechanismen en heeft als doel de doorbloeding van de vitale organen te garanderen. Door een daling van de arteriële bloeddruk worden de vasomotorische centra in het ruggenmerg gestimuleerd via de arteriële baroreceptoren en de hersenstam. Dit leidt achtereenvolgens tot een sterke sympathische reflex, stimulatie van perifere chemoreceptoren, vasoconstrictie in arteriolen en venen in de niet-vitale organen en een verminderde doorbloeding van de huid en het spierweefsel. Deze mechanismen treden al in een vroeg stadium in werking, nog voordat veranderingen optreden in de waarden van conventionele hemodynamische parameters zoals bloeddruk en hartfrequentie. De perfusie van deze perifere weefsels is daarom een gevoelige indicator voor de vroege opsporing van een verstoring van de systemische circulatie, zoals tijdens acute circulatoire shock.

Als de juiste behandeling wordt gestart en de circulatie zich herstelt, zal de activiteit van de compensatiemechanismen bij de meeste patiënten verminderen. De vasoconstrictie in het perifere vaatbed neemt af en de perfusie van de huid en het spierweefsel herstelt zich weer; dit is een teken van een succesvolle behandeling. Bij sommige patiënten blijven de compensatiemechanismen – en dus de vasoconstrictie – echter actief en herstelt de perifere perfusie zich niet. Perifere vasoconstrictie kan ook optreden tijdens een gegeneraliseerde ontsteking en tijdens sepsis. Vasoconstrictie wordt dan gemedieerd door het sympathisch zenuwstelsel en is geen compensatie voor een verstoorde circulatie. De ernst en de duur van de vasoconstrictie zijn daarbij gerelateerd aan de ziekte-ernst van de patiënt; ondanks hemodynamische stabilisatie duurt de vasoconstrictie voort. Bij septische shock is de verstoorde perifere perfusie dus een weerspiegeling van de ernst van de shock en geen teken van een compensatiemechanisme zoals bij circulatoire shock.^{7,8}

Monitoring van de perifere circulatie is gebaseerd op het concept dat perifere weefsels de eerste zijn die hypoperfusie laten zien tijdens circulatoire shock en de laatste die herstellen tijdens de behandeling. Met een aantal eenvoudige klinische beoordelingen en monitoringstechnieken kan de perifere circulatie op een non-

invasieve wijze worden beoordeeld. Deze methoden worden hierna besproken en zijn ook samengevat in de tabel en de figuur.

Klinische beoordeling

Het uitgebreide huidvaatbed speelt een belangrijke rol bij de thermoregulatie van het lichaam. Veranderingen in de doorbloeding bepalen de kleur en de temperatuur van de huid: van warm en roze bij gezonde mensen tot koud, kland, wit en gevlekt bij ernstige vasoconstrictie.

Huidtemperatuur

De beoordeling van de huidtemperatuur – ‘warm’ of ‘koud’ – kan het best worden uitgevoerd met het dorsale oppervlak van de handen of vingers; deze oppervlakken zijn immers het gevoeligst voor de waarneming van temperatuur. Een afwijkende perifere perfusie bij deze manier van beoordelen is gerelateerd aan hogere lactaatspiegels en ernstiger orgaanfalen.³ Deze subjectieve waarneming van de temperatuur komt goed overeen met objectieve metingen van de huidtemperatuur en van de vingerdoorbloeding, en is daarom geschikt voor de beoordeling van de perifere circulatie.⁹

Capillaire-‘refill’-tijd

De capillaire-‘refill’-tijd is de tijd die nodig is om weer kleur te krijgen in een distaal capillair netwerk, bijvoorbeeld het nagelbed, nadat er gedurende 15 s zo veel druk op is uitgeoefend dat een bleke verkleuring is ontstaan. Bij gezonde volwassenen is de bovengrens van een normale CRT van het nagelbed 4,5 s. Bij ernstig zieke patiënten kan vertraagd herstel (> 5 s) worden beschouwd als een verminderde perifere perfusie.³ Op deze manier kunnen patiënten met een verstoorde perfusie al tijdens de eerste 24 h van opname op de IC worden geïdentificeerd. Verder is een verlengde capillaire-refill-tijd bij IC-patiënten en bij patiënten na reanimatie gerelateerd aan een verhoogd risico op orgaanfalen en op overlijden vergeleken met patiënten met een niet-afwijkende capillaire-refill-tijd (< 5 s).^{3,5} Dit risico blijft verhoogd na normalisatie van de waarden van conventionele hemodynamische parameters. De meting van capillaire-refill-tijd lijkt subjectief, maar toch komen de beoordelingen door zowel artsen als verpleegkundigen goed overeen.¹⁰

Marmering van de huid

Een marmerhuid is een reticulair, blauwrood huidaspect, meestal veroorzaakt door koude. Deze verkleuring is gemakkelijk te herkennen en komt typisch voor rondom de ellebogen of de knieën. Een marmerhuid wordt veroorzaakt door heterogene vasoconstrictie in het huidvaatbed en wordt vaak gezien bij ernstig zieke patiënten. Een recente studie bij patiënten met septische shock laat zien dat de mate van marmering – en dus de ernst van de hypoperfusie – goed kan worden beoordeeld met de ‘mottling’-score (zie figuur). Deze score loopt van 0 (‘geen marmering’) tot 5 (‘zeer ernstige marmering’). Een score van 4 (‘ernstige marmering’) of 5 binnen 6 h na de initiële behandeling is een sterk voorspellende factor voor de 14-daagse mortaliteit, onafhankelijk van de conventionele

Tabel. Non-invasieve methoden voor de beoordeling van de perifere circulatie

Methoden	Voordeel	Nadeel	Aanbevolen afkappunt
Klinische beoordeling			
huidtemperatuur	tijdens lichamelijk onderzoek; waardevolle aanvulling op hemodynamische monitoring tijdens circulatoire shock	subjectief; mogelijk zijn gedigitaliseerde of geautomatiseerde metingen wel objectief	koud, gerelateerd aan hogere morbiditeit en mortaliteit
capillaire-'refill'-tijd	tijdens lichamelijk onderzoek; waardevolle aanvulling op hemodynamische monitoring tijdens circulatoire shock	subjectief; mogelijk zijn gedigitaliseerde of geautomatiseerde metingen wel objectief	> 4,5 s, gerelateerd aan hogere morbiditeit en mortaliteit
'mottling'-score*	tijdens lichamelijk onderzoek; marmerskilt is eenvoudig te herkennen en te beoordelen	beoordeling is lastig bij patiënten met donkere of zwarte huid	score 4-5, gerelateerd aan mortaliteit
Huidtemperatuurgadiënt			
onderarm-tot-vingertop	gevalideerde methode voor beoordeling van perifere weefseldoorbloeding	geen realtime weergave van veranderingen in perifere perfusie	> 4°C, gerelateerd aan hogere morbiditeit en mortaliteit
Optische monitoring			
perifere-perfusie-index	voor hemodynamische monitoring van ernstig zieke patiënten	niet accuraat tijdens bewegingen van patiënt	< 1,4%, gerelateerd aan hogere morbiditeit en mortaliteit
'near-infrared'-spectroscopie	kwantitatieve informatie over weefseloxygenatie en microvasculaire functie binnen enkele minuten; eenvoudig te herhalen	voor de metingen zijn verschillende apparaten nodig; test voor vasculaire reactiviteit is niet gestandaardiseerd	< 70% of > 75%, gerelateerd aan hogere morbiditeit en mortaliteit

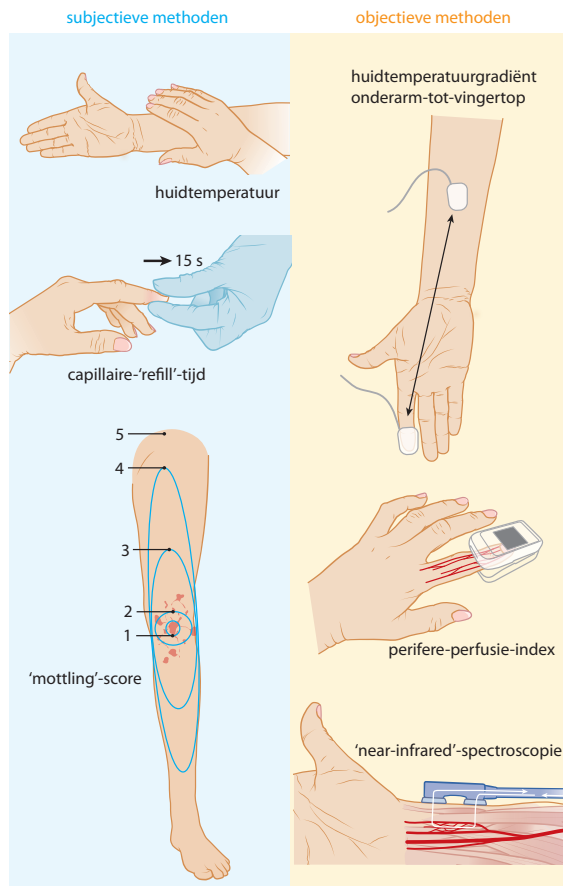
* De mate van marmering van de huid wordt bepaald met de 'mottling'-score, die loopt van 0 (geen marmering) tot 5 (zeer ernstige marmering).



hemodynamische parameters.¹¹ Dit scoringsysteem is eenvoudig te leren, heeft een goede interbeoordelaarsbetrouwbaarheid en kan aan het bed worden toegepast.

Huidtemperatuurgradiënt

Hoewel al lang bekend is dat de absolute huidtemperatuur een goede parameter is voor de ernst van circulatoire shock,¹ laat recenter onderzoek zien dat de gradiënt in de huidtemperatuur de veranderingen in lokale doorbloeding beter weergeeft.^{11,12} Deze gradiënt wordt bepaald door de temperatuurverschillen tussen een proximaal en distaal meetpunt te bepalen, zoals centraal-tot-grote-teen of onderarm-tot-vingertop, en wordt gemeten door middel van thermometer probes op de huid (zie figuur). De



Figuur. Non-invasieve methoden om de perifere circulatie te beoordelen aan het bed van de patiënt. Subjectieve methoden zijn de huidtemperatuur, de capillaire-'refill'-tijd, en de 'mottling'-score voor het bepalen van de mate van marmering van de huid. Objectieve methoden zijn de huidtemperatuurgradiënt onderarm-tot-vingertop, de perifere-perfusie-index en de 'near-infrared'-spectroscopie.

huidtemperatuurgradiënt onderarm-tot-vingertop wordt 'Tskin-diff' genoemd (afgeleid van 'skin-temperature gradient'). Het optreden van perifere vasoconstrictie tijdens circulatoire shock leidt tot een afname van de huidtemperatuur en tot een verminderd vermogen om de centrale temperatuur te regelen. Daardoor stijgt de centraal-perifere temperatuurgradiënt. Het gebruik van Tskin-diff is gebaseerd op de aanname dat de referentietemperatuur een plaats op de huid is die aan dezelfde omgevingstemperatuur is blootgesteld als de vingertop. Een andere omgevingstemperatuur heeft eenzelfde soort effect op de onderarm als op de vingertop, en heeft daardoor weinig invloed op de gradiënt.¹²

Het gebruik van Tskin-diff is gevalideerd voor het beoordelen van de perifere weefseldoorbloeding. Uit verschillende experimentele studies is gebleken dat een Tskin-diff > 4°C een teken is van een ernstige verstoring van de huidperfusie en dat deze gerelateerd is aan een verhoogd risico op orgaanfalen.^{5,13} Het is niet bekend wat de invloed van vaatvernauwende of -verwijdende medicatie is op de huidtemperatuur of op de Tskin-diff; onze groep doet momenteel onderzoek naar deze relatie.



Optische monitoring

Optische technieken maken gebruik van licht met verschillende golflengten. Met deze non-invasieve methoden kan de conditie van verschillende weefsels worden vastgesteld. De meest gebruikte optische methoden om de perfusie van de perifere circulatie te meten zijn fotoplethysmografie en 'near-infrared'-spectroscopie.

Perifere-perfusie-index

De perifere-perfusie-index is afgeleid van het plethysmografiesignaal van de pulsoximeter. Pulsoximetrie wordt in de meeste ziekenhuizen gebruikt om de arteriële zuurstofsaturatie van een patiënt te bepalen. De pulsoximeter zendt licht van 2 golflengtes door de distale falanx van de vinger. Door de pulsaties in het vaatbed resulteert dit in een pulsatiele fotoplethysmografische lichtgolf die aan de andere kant van vinger wordt opgevangen door een detector. Andere weefsels, zoals bindweefsel en bot, geven een niet-pulsatiele lichtgolf. De perifere-perfusie-index is de verhouding tussen het pulsatiele en het niet-pulsatiele deel van de opgevangen lichtgolven, uitgedrukt in een percentage. Omdat de grootte van het pulsatiele deel toeneemt bij vasodilatatie en afneemt bij vasoconstrictie, corresponderen veranderingen in perifere-perfusie-index met veranderingen in de perifere vasomotorische tonus. Dit is als eerste aangetoond met plexusblokkade tijdens locoregionale anesthesie, waarbij vasodilatatie van de extremiteit optreedt.¹⁴ Andersom neemt de perifere-perfusie-index snel af bij vasoconstrictie na toediening van (nor)adrenaline.¹⁵

Bij een grote groep gezonde vrijwilligers was de mediane perifere-perfusie-index 1,4%.¹⁶ Deze waarde was bij ernstig zieke patiënten een gevoelig afkappunt voor het bepalen van een afwijkende perifere perfusie, gedefinieerd als een verlengde capillaire-refill-tijd en een toegenomen huidtemperatuurgradiënt.³ Een perifere-perfusie-index < 1,4% is gerelateerd aan een toegenomen prevalentie van orgaanfalen.⁵ Deze eenvoudig te bepalen index kan dus worden gebruikt om de perifere circulatie te bepalen en te vervolgen.

Near-infrared-spectroscopie

Met near-infrared-spectroscopie kan de zuurstofsaturatie van hemoglobine worden bepaald in oppervlakkig gelegen weefsels zoals spierweefsel. Naast de weefselzuurstofsaturatie wordt ook de absolute weefselhemoglobine-index bepaald. Deze index is een maat voor het bloedvolume in het weefsel.¹⁷ Ook kan de mate van vasculaire reactiviteit worden weergegeven na een kortdurende vasculaire occlusie.

Bij ernstig zieke patiënten geeft een afgenomen weefselzuurstofsaturatie de aanwezigheid van een inadequate weefselperfusie weer. Zo zijn negatieve veranderingen in de weefselzuurstofsaturatie sterk gerelateerd aan de ernst van orgaanfalen en aan de mortaliteit bij patiënten met septische shock.¹⁸ Ook tijdens de eerste 6 h van de behandeling van patiënten met septische shock lijkt de weefselzuurstofsaturatie een gevoelige indicator voor het monitoren van het behandelingseffect en daardoor voor de 28-daagse mortaliteit.¹⁹ Deze parameter lijkt eerder te worden beïnvloed door veranderingen in de perifere circulatie, met name door vasoconstrictie, dan door veranderingen in de systemische circulatie.²⁰

Hoewel near-infrared-spectroscopie mogelijk geschikt is voor het bepalen van weefseloxygenatie en -perfusie, wordt nog steeds aanvullend onderzoek gedaan om het belang ervan voor de behandeling van ernstig zieke patiënten te verduidelijken.

Consequenties voor de praktijk

Perifere circulatie als waarschuwing

Uit de hiervoor beschreven studies blijkt dat een afwijkende doorbloeding van het perifere vaatbed op 2 manieren geïnterpreteerd kan worden. In de eerste plaats is het een uiting van een primair circulatoire ontregeling (shock) die nog onvoldoende behandeld is. Daarnaast lijkt het, na herstel van de circulatie, een teken van de ziekte-ernst. In dat geval is een afwijkende perifere perfusie een onderdeel van de stressreactie van het lichaam die wordt veroorzaakt door een actief ziekteproces. Dit is echter alleen nog maar aangetoond in kleine studies, waarvan de omvang niet voldoende was om een duidelijke relatie aan te tonen tussen de toestand van de perifere circulatie en de veelgebruikte scores voor ziekte-ernst. Uit deze resultaten kan wel worden afgeleid dat een blijvend afwijkende perifere perfusie gepaard gaat met een hoog risico op een ongunstiger beloop.

Het klinisch beoordelen van de perifere perfusie is eenvoudig en gaat snel. Als deze beoordeling afwijkend blijft, is dit een alarmsymptoom.

Perifere circulatie als therapeutisch doel

Op grond van bovenstaande overwegingen komt vanzelf de vraag naar voren of de perifere circulatie ook een doel van de behandeling kan zijn. Als de waarden van conventionele hemodynamische parameters zich niet herstellen na initiële therapie of de therapie niet leidt tot een toename van de perifere perfusie, ligt het voor de hand te proberen deze conventionele parameters op een andere manier te verbeteren.^{5,21} Ruim 40 jaar geleden werd al gesuggereerd dat hiervoor vaatverwijders kunnen

worden gebruikt.²² Recent bleek dat toediening van nitroglycerine aan patiënten met ernstig hartfalen een positief effect kan hebben op de weefselperfusie.²³ Ook bij patiënten met ernstige septische shock leek de perifere circulatie te verbeteren na toediening van nitroglycerine.²⁴ Deze studies waren echter te klein om een effect op het ziektebeloop aan te tonen. Ook werd niet naar de perifere circulatie gekeken op een gestructureerde manier, zoals in dit artikel beschreven.

Het kan natuurlijk niet worden uitgesloten dat het optreden van perifere vasoconstrictie ook een doel heeft als onderdeel van een autoregulatiemechanisme. Opheffing van dit mechanisme hoeft dus geen positief effect te hebben. Meer onderzoek naar dit mechanisme en naar de perifere circulatie als behandeldoel is nodig.



Aan het bed

Omdat er steeds meer verschillende diagnostische technieken beschikbaar zijn om metingen te verrichten aan het bed van de patiënt, kan men minder vertrouwen hebben in de meer traditionele methoden van lichamelijk onderzoek. In de kliniek is er een tendens om getallen op een scherm prioriteit te geven boven het lichamelijk onderzoek. Met de hier genoemde non-invasieve methoden kan de beoordeling van de perifere circulatie gemakkelijk worden meegenomen in het standaardonderzoek aan het bed. Zowel subjectieve methoden (de huidtemperatuur, de capillaire-refill-tijd en de mottling-score) als de meer objectieve methoden (de huidtemperatuurgradiënt en de perifere-perfusie-index) kunnen hiervoor worden gebruikt.

Conclusie

Tijdens circulatoire shock worden perifere weefsels als eerste minder doorbloed. Door de perifere perfusie te meten kan een verstoring van de circulatie al in een zeer vroeg stadium en op een eenvoudige wijze worden waargenomen. De relatie tussen de beoordeling van de perifere perfusie en waarden van conventionele hemodynamische parameters, zoals bloeddruk en hartfrequentie, is afhankelijk van het ziektebeeld. Toch lijkt een verstoring van de perifere circulatie gerelateerd te zijn aan een slechter klinisch beloop bij verschillende patiëntengroepen. De beoordeling van de perifere circulatie is daarmee niet alleen een referentiepunt voor de beoordeling van de circulatie, maar dient ook als waarschuwing voor de ernst van circulatoire shock. De rol van de perifere circulatie bij het bepalen van de juiste therapie bij ernstig zieke patiënten moet nog worden onderzocht.

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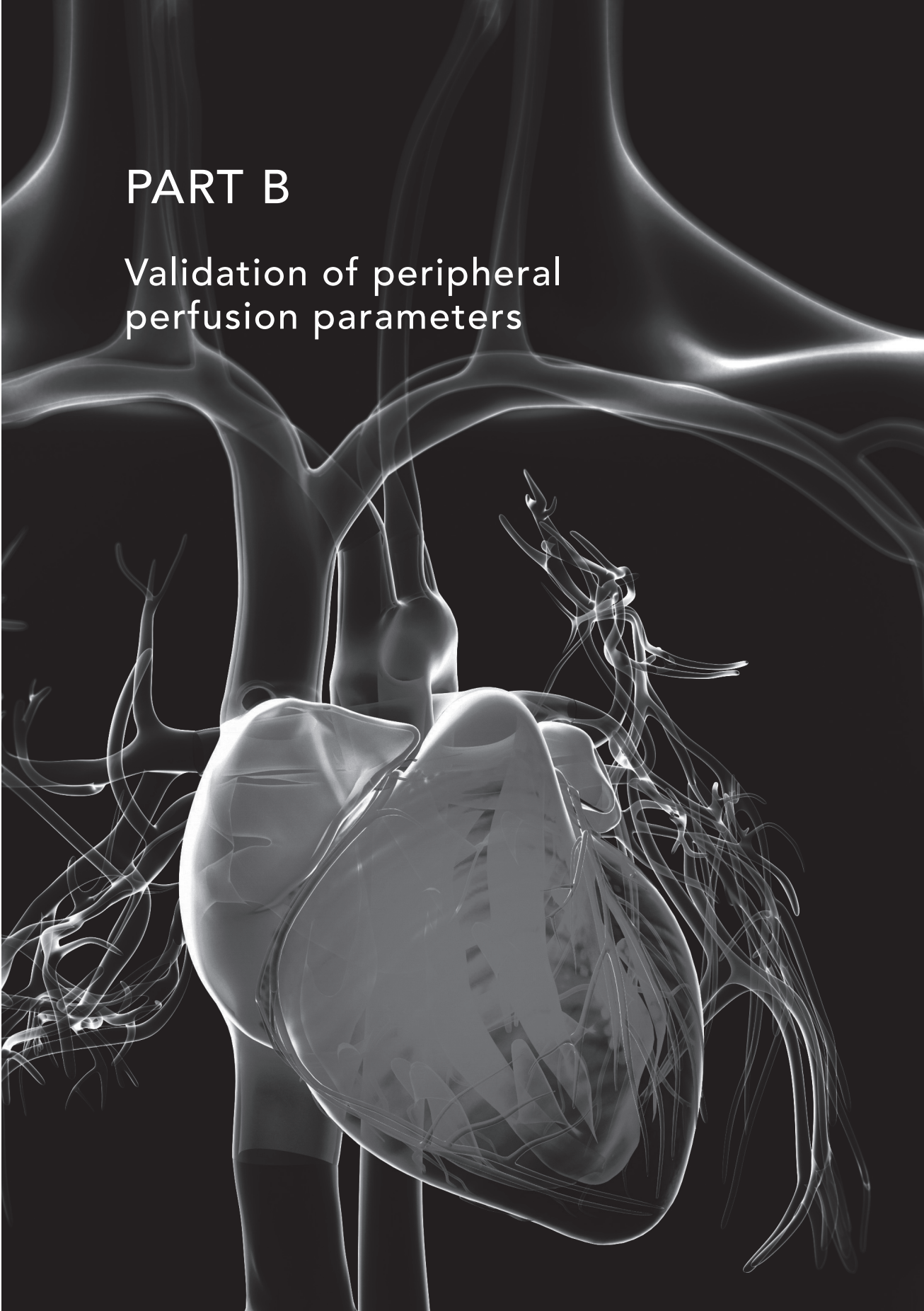
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PART B

Validation of peripheral perfusion parameters



Peripheral perfusion index
as an early predictor
for central hypovolemia

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3

Abstract

Background

In healthy volunteers, we investigated the ability of the pulse oximeter–derived peripheral perfusion index (PPI) to detect progressive reductions in central blood volume.

Methods

Twenty-five awake, spontaneously breathing, healthy male volunteers were subjected to progressive reductions in central blood volume by inducing stepwise lower body negative pressure (LBNP) with 20 mm Hg for 5 minutes per step, from 0 to –20, –40, –60, and back to 0 mm Hg. Throughout the procedure, stroke volume (SV), heart rate (HR), and mean arterial blood pressure were recorded using volume-clamp finger plethysmography. Assessment of the PPI was done by pulse oximetry. Additionally, the forearm-to-fingertip skin-temperature gradient was measured. Data are presented as mean \pm SE. PPI underwent log transformation and is presented as median (25th–75th).

Results

Of the 25 subjects, one did not complete the study because of cardiovascular collapse. After the first LBNP step (–20 mm Hg), PPI decreased from 2.2 (1.6–3.3) to 1.2 (0.8–1.6) ($P = 0.007$) and SV decreased from 116 ± 3.0 mL to 104 ± 2.6 mL ($P = 0.02$). The magnitude of the PPI decrease ($41\% \pm 6.0\%$) was statistically different from that observed for SV ($9\% \pm 1.3\%$) and HR ($3\% \pm 1.9\%$). During progression of LBNP, SV decreased and HR increased progressively with the increased applied negative pressure, whereas the PPI remained low throughout the remainder of the protocol and returned to baseline values when LBNP was released. At –60 mm Hg LBNP, SV decreased and HR increased by $36\% \pm 0.9\%$ and $33\% \pm 2.4\%$ from baseline, respectively. Mean arterial blood pressure remained in the same range throughout the experiment.

Conclusions

These results indicate that the pulse oximeter–derived PPI may be a valuable adjunct diagnostic tool to detect early clinically significant central hypovolemia, before the onset of cardiovascular decompensation in healthy volunteers.

Introduction

Peripheral vasoconstriction is an early warning sign of circulatory shock in critically ill patients, when blood flow is diverted from less important tissues to maintain vital organ perfusion at the cost of peripheral circulation.^{1,2} Because sympathetic neuroactivity predominates in the skin and muscle, the sympathetic neurohumoral response-induced vasoconstriction manifests primarily as decreased peripheral perfusion.^{3,4} Unfortunately, standard physiologic measurements, such as mean arterial blood pressure (MAP), are poor indicators for the early assessment of shock.⁵ Even standard examinations of mental status, pulse character, and heart rate (HR) provide late information about the severity of blood loss. Subsequently, the appearance of hypotension and other signs of shock do not mark the beginning of circulatory shock but rather represent the beginning of cardiovascular decompensation and do not allow for early intervention.⁶ Therefore, a more practical and convenient method to detect early circulatory shock is needed.



The peripheral perfusion index (PPI), derived from the photoelectric plethysmographic signal of the pulse oximeter, is able to monitor vascular reactivity in adult critically ill patients.^{2,7} Additionally, the PPI has been suggested to be a useful noninvasive method for the assessment of peripheral vasomotor tone in healthy volunteers, neonates, and critically ill patients.^{2,8} This index is calculated as the ratio between the pulsatile component (arterial compartment) and the nonpulsatile component (venous and capillary blood and other tissues) of the light reaching the detector of the pulse oximeter. Therefore, peripheral vasoconstriction, mainly reducing the pulsatile component, directly affects the ratio and thus decreases the PPI.⁹ Because a pulse oximeter is universally available in the operating room, emergency room, and intensive care unit, it could potentially be useful for the early detection of peripheral hypoperfusion in response to reductions in central blood volume in these settings.

In the present study, we investigated changes in PPI as an early marker of peripheral vasoconstriction induced by changes in central circulating volume, and hypothesized that PPI could be used for early detection of hypovolemia, before changes in conventional hemodynamic variables occur. To test this, we used a model of controlled central hypovolemia in healthy male volunteers by applying lower body negative pressure (LBNP). During application of LBNP, the circulating volume is progressively redistributed from the upper to the lower body, inducing central hypovolemia, which triggers similar compensatory mechanisms as during acute hemorrhage and clinical hypovolemia.¹⁰ Using this approach, we were able to study the potential use of PPI during progressive reductions in central blood volume and determine whether changes in this index precede changes in frequently monitored vital signs.

Material and methods

Subjects

This study was conducted in a research laboratory at a university-affiliated teaching hospital. We recruited 25 awake, spontaneously breathing, healthy male volunteers

without history of cardiac events nor receiving any vasoactive medication. To minimize potential confounding factors to different LBNP tolerances, all volunteers underwent an exercise electrocardiogram to determine equal physical fitness.¹¹ The volunteers were instructed not to consume caffeine-containing drinks or practice intensive exercise ≤ 12 hours before the experiments, but fluid intake was not standardized or regulated. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam, and written informed consent was obtained from all subjects.

Measurements

Subjects were placed with their lower body in an air-tight chamber with a seal applied at the level of the iliac crests. The amount of negative pressure within the chamber could be manually adjusted using a variable vacuum source. Baseline recordings were made after a 10-minute stabilization period before LBNP application. LBNP was applied progressively in a 5-minute stepwise manner from 0 to -20 , -40 , and -60 mm Hg, followed by a second baseline measurement of 0 mm Hg 10 minutes after the last LBNP step. Data were gathered at the completion of every 5-minute LBNP step when the PPI signal was adequate and subjects were hemodynamically stable. In this regard, the different LBNPs simulate different levels of beginning hypovolemia and can be categorized as "mild" (-10 to -20 mm Hg, corresponding with 400–550 mL blood loss), "moderate" (-30 to -40 mm Hg, corresponding with 500–1000 mL blood loss), and "severe" (-40 to -60 mm Hg, corresponding with >1000 mL blood loss).^{10,11} The LBNP protocol was immediately terminated if the subject developed presyncope, which was defined as a decrease in systolic blood pressure of >15 mm Hg from baseline, or if the subject experienced symptoms of impending syncope such as dizziness, light-headedness, nausea, sweating, or visual disturbances.

Global Hemodynamic Parameters

MAP, HR, and stroke volume (SV) were continuously and noninvasively measured using volume-clamp plethysmography (Nexfin; BMEYE, Amsterdam, The Netherlands) with the cuff placed around the left index finger. The Nexfin device is extensively described elsewhere and is validated technically to measure hemodynamic variables.^{12,13} In brief, this method applies variable pressure in an inflatable cuff around the finger, countering the pulsatile arterial pressure. An optical plethysmograph placed in this cuff measures arterial volume and a calibration system determines the volume at which the artery is unloaded (i.e., when transmural pressure equals zero and no interference of the arterial wall occurs). Because brachial and finger arterial pressure are physiologically different, waveform transformation and correction are applied in order to reconstruct brachial arterial pressure.

Peripheral Perfusion Index

The PPI is derived from the photoelectric plethysmographic signal of the pulse oximeter Masimo SET Radical-7 (Masimo Corp., Irvine, CA). The adhesive sensor was attached onto the right index finger (Masimo SET® LNCS Actx, adult sensor).⁷ This index signal

has been used as a noninvasive measurement of peripheral perfusion in critically ill patients.² The technique is based on 2 light sources that emit light at wavelengths of 660 and 940 nm through the cutaneous vascular bed of the distal side of the index finger. Because other tissues, such as connective tissue, bone, and venous blood, also absorb light, the pulse oximeter distinguishes the pulsatile component of arterial blood from the nonpulsatile component of venous and capillary blood, and other tissues. Using a 2-wavelength system, the nonpulsatile component is then discarded and the pulsatile component is used to calculate the arterial oxygen saturation (SpO₂). The PPI is calculated as the ratio between the amplitude of the pulsatile component (arterial compartment) and the nonpulsatile component (venous and capillary blood, and other tissues) of the light reaching the detector of the pulse oximeter. This ratio is independent of the hemoglobin oxygen saturation. Because a change in peripheral vasomotor tone primarily causes a corresponding change in the pulsatile component of the signal, the ratio changes accordingly. As a result, the PPI value reflects changes in peripheral vasomotor tone, with a median value of 1.4 for normality in healthy volunteers.² Simultaneously SpO₂ values were recorded.



Skin Temperature

We obtained the peripheral skin-temperature gradient (T_{skin-diff}) from 2 skin probes (Hewlett Packard 21078A, Palo Alto, CA) attached to the right ring finger and to the radial side of the forearm, midway between the elbow and the wrist. At constant environmental conditions, T_{skin-diff} increases during vasoconstriction and thereby provides a better measurement of peripheral vasomotor tone compared with only the local skin temperature. The ambient temperature was therefore actively set at 22°C during the entire protocol. Basically, when vasoconstriction decreases fingertip blood flow, finger skin-temperature decreases, and T_{skin-diff} increases. This temperature gradient was previously validated as an independent measurement of peripheral perfusion.¹⁴

Statistics

Unless otherwise specified, data are presented as mean ± SE. For statistical analysis, the different LBNP levels (0, -20, -40, -60, and 0 mm Hg) were plotted as points over time. Accordingly, HR, MAP, SV, T_{skin-diff}, and PPI were plotted versus the level of LBNP. PPI underwent log-transformation (Kolmogorov-Smirnov test $P < 0.05$) to achieve close to normal distribution and then qualified for longitudinal testing. Assuming equal variances and the same correlation between measures for all variables (Mauchly criterion “test for sphericity” not significant), statistical significance of differences between the progressive LBNP levels was explored using repeated-measures analysis of variance with a Bonferroni correction for multiple comparisons. Changes from baseline were computed dividing the parameter value at specific time points into the baseline value and was expressed as percentile changes (% of baseline × 100). We compared the magnitude of changes among PPI, SV, and HR at specific time points and differences were tested with the use of Mann-Whitney test for unpaired data. In case of cardiovascular collapse, data were excluded from the repeated-measurements

analysis. We used SPSS software (version 20.0; SPSS Inc., Chicago, IL) for statistical analysis. $P < 0.05$ was regarded as statistically significant.

Results

Of the 25 male subjects recruited, one did not complete the study because of cardiovascular collapse and was excluded from further analysis, but the results of this excluded subject are presented and discussed below. The mean \pm SD of age, weight, and height of the remaining 24 subjects were 23 ± 6 years, 82 ± 2 kg, and 182 ± 1 cm, respectively.

Baseline values for global hemodynamic variables, PPI, and Tskin-diff stratified by the progressive LBNP levels are presented in Table 1. The mean PPI decreased substantially from baseline during the onset of mild central hypovolemia (i.e., LBNP -20 mm Hg) and remained in the same range during the remainder of the experiment (Fig. 1). SV progressively decreased and HR progressively increased in an opposite manner to the level of negative pressure in the chamber. On average, the magnitude of PPI decreasing ($41\% \pm 6.0\%$) in the first LBNP step was statistically different from that observed for SV ($9\% \pm 1.3\%$) and HR ($3\% \pm 1.9\%$) (Fig.1). Progressive hypovolemia (i.e., LBNP = -60 mm Hg) resulted in a mean decrease in SV of $36\% \pm 0.9\%$ from baseline and a mean increase in HR of $33\% \pm 2.4\%$ from baseline. MAP did not change significantly during progressive LBNP exposure (Table 1). Accordingly, Tskin-diff and SpO_2 remained unchanged during the LBNP protocol (Table 1). Upon cessation of LBNP, all systemic hemodynamic variables and PPI returned to baseline values (Fig. 1, Table 1).

Figure 2A shows HR, SV, and PPI in the subject who experienced cardiovascular collapse during LBNP. Figure 2B shows a representative subject with a normal response. The subject who experienced cardiovascular collapse started with a low PPI (approximately 1) and displayed a lack of appropriate sympathetic baroreflex activation as reflected by an absence of an increase in HR, despite a significant decrease in SV. Directly after the start of -60 mm Hg LBNP, this volunteer already had signs of nausea

Table 1. Descriptive analysis

	LBNP level				
	0 mmHg	-20 mmHg	-40 mmHg	-60 mmHg	0 mmHg ^(2nd)
Heart rate (bpm)	63 ± 1.8	64 ± 1.5	$72 \pm 1.5^*$	$83 \pm 2.0^*$	59 ± 1.7
Mean arterial pressure (mmHg)	89 ± 1.8	92 ± 1.8	90 ± 1.4	86 ± 1.7	90 ± 1.5
Stroke volume (mL)	116 ± 3.0	$104 \pm 2.6^*$	$91 \pm 2.4^*$	$74 \pm 2.1^*$	112 ± 2.1
Tskin-diff (°C)	0.0 ± 0.2	-0.1 ± 0.3	0.1 ± 0.2	0.9 ± 0.2	0.0 ± 0.3
PPI (a.u.)	2.2 [1.6-3.3]	1.2* [0.8-1.6]	1.2* [0.9-1.8]	1.3* [0.9-1.7]	2.2 [1.4-3.4]

Systemic hemodynamic variables, skin temperature difference between finger and forearm (Tskin-diff), and peripheral perfusion index (PPI) during progressive application of lower body negative pressure (LBNP) from 0 mmHg to -60 mmHg and back to 0 mmHg^(2nd).

Data are presented as mean \pm SE and median [25th-75th] for PPI. * $P < 0.05$, vs. LBNP = 0 mmHg.

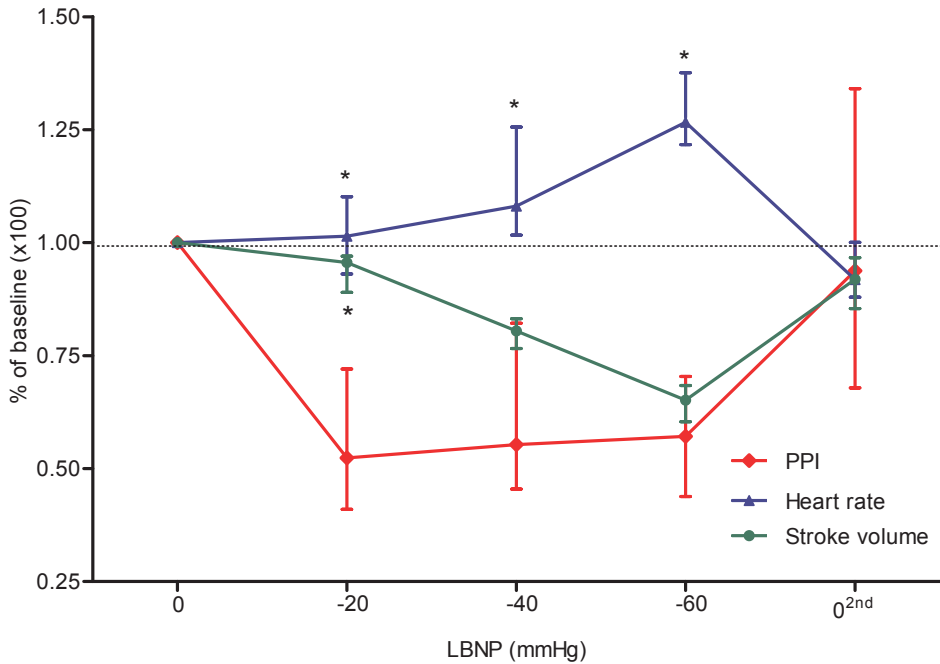


Figure 1. Peripheral perfusion index (PPI; red line), heart rate (blue line), and stroke volume (green line) plotted as proportional changes from baseline during progressive application of lower body negative pressure (LBNP) from 0 mmHg to -60 mmHg and back to 0 mmHg. Bars represent mean \pm 95% CI (n=24). Changes in PPI were statistically different from those observed for SV and HR (* $P < 0.05$ vs. PPI, by Mann-Whitney test)

and dizziness, which were followed by signs of impending cardiovascular collapse with a further decrease in SV from 82 to 57 mL, and concomitant decreases in HR from 76 to 56 bpm, systolic blood pressure from 136 to 97 mm Hg, diastolic blood pressure from 83 to 68 mm Hg, and a decrease in MAP from 88 to 63 mm Hg. Paradoxically, his PPI increased from 2.1 to 8.4 (suggesting vasodilation), simultaneous to the development of clammy skin. Thereafter, decompression was immediately initiated, followed by discontinuance of the protocol. During this collapse, T_{skin}-diff did not change.

Discussion

We induced progressive central hypovolemia by controlled application of LBNP and studied changes in PPI. We found that PPI changed significantly with the onset of mild hypovolemia, and may have reflected induced compensatory peripheral vasoconstriction. In addition, PPI changed earlier than the peripheral T_{skin}-diff, suggesting that PPI may be a useful early indicator of mild central hypovolemia in an acute setting.

Early detection of hypovolemia is of key importance in the management of circulatory shock. Circulatory changes during LBNP resemble hemodynamic responses similar to

those reported during acute hemorrhage, such as tachycardia and reductions in SV as result of a neurohumoral response.^{3,10} However, physiologic compensatory factors, such as increased HR, limit the use of blood pressure and cardiac output as indicators for mild central hypovolemia in the early setting.⁶ Thus, hypotension is a late marker

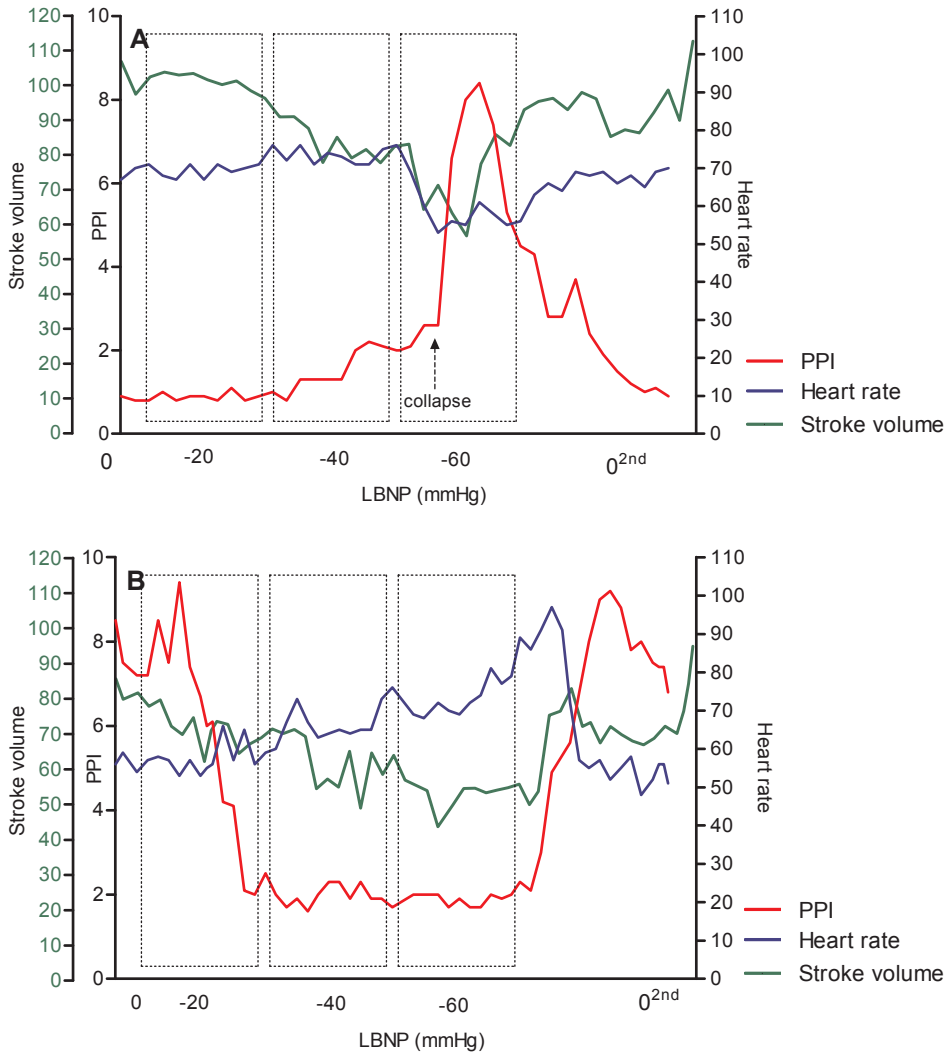


Figure 2. Heart rate, stroke volume, and peripheral perfusion index (PPI) during the application of lower body negative pressure (LBNP); (A) a subject who presented with cardiovascular collapse during progressive LBNP; and (B) a representative subject with a normal response. The subject that collapsed displayed a remarkably low PPI at baseline, indicative of peripheral vasoconstriction well before the application of LBNP. Subsequently, with progressive stroke volume reduction, collapse occurred with a simultaneous fall in heart rate and sudden rise in the PPI. LBNP was released immediately, leading to the subjects recovery and return to baseline levels (0^{2nd}) of heart rate, stroke volume, and PPI.

of hypoperfusion, and almost 30% of circulating volume may already be lost before hypotension occurs.¹⁵ Therefore, recognizing hemodynamic instability before this point is of prime importance in the prevention of hypoperfusion induced organ failure.

To this end, monitoring the early compensatory mechanisms that act on the peripheral circulation might provide a better indication of the onset of compensated shock than systemic hemodynamic variables.¹⁶ PPI is able to reflect rapid changes in the peripheral vascular diameter.⁷ We chose the LBNP model to test our hypothesis, because previous studies, including those of our own group, have shown that peripheral vasoconstriction is a frequent abnormality in peripheral perfusion of critically ill patients, and its persistence has been associated with increased lactate levels and organ failure.² Moreover, PPI has been linked to HR and the abdominal flank-to-forearm skin-temperature gradient, particularly in neonates.¹⁷ The marked decrease in PPI in our model provides evidence that PPI can be used to detect changes in peripheral vasomotor tone as an additional tool for hemodynamic monitoring. Our study expands these observations with the demonstration that PPI decreases well before the onset of cardiovascular instability. Thus, PPI seems to provide an early and continuous indication of central hypovolemia during preshock hemorrhage when arterial blood pressure and HR remain within clinically normal levels.

Except for the volunteer who collapsed, MAP was maintained around baseline levels during the entire protocol, which indicated adequate compensation of the reduced circulating volume. It should be noted, however, that PPI did not decrease further during progression of hypovolemia and did not differentiate between mild hypovolemia and progressive hypovolemia, which might be of vital importance for follow-up and resuscitation. It is important to note that there is no direct causal relation implied between hypovolemia and PPI. We demonstrated that PPI reflects the condition of peripheral vasomotor tone, such as hypovolemia-induced peripheral vasoconstriction, but one cannot predict hypovolemia looking at a single PPI value. Instead, one should look at the physiologic behavior of PPI as a marker of variations in peripheral vasomotor tone. Although changes in the PPI preceded significant changes in HR, our data demonstrate that measuring PPI together with HR can be a more elegant noninvasive technique to detect the onset of hypovolemia, and therefore can reflect hemodynamic instability earlier than arterial blood pressure. In this regard, the development of an algorithm capable of providing changes in the PPI together with HR could provide a valuable clinical tool for the early detection of hemodynamic instability in trauma and intensive care patients.

Interestingly, the subject who experienced cardiovascular collapse was already vasoconstricted at baseline (Fig. 2A). At the beginning of -60 mm Hg, his HR suddenly decreased followed by a rapid increase in PPI (vasodilation) and the actual collapse. Apparently, loss of sympathetic tone resulted in a simultaneous decrease in HR and a decrease in peripheral vasomotor tone, leading to low cardiac output and cardiovascular collapse. This observation emphasizes the value of the PPI as a monitor of sympathetic activity. Previous studies demonstrated the phenomenon of paradoxical vasodilation in patients with depressed baroreceptor unloading¹⁸ and congestive heart



failure¹⁹ during mild central hypovolemia induced by LBNP. Cardiovascular collapse becomes imminent when sympathetic activity decreases or vagal tone increases and cardiac chronotropic and peripheral vasoconstrictive mechanisms can no longer adequately compensate for progressive hypovolemia, resulting in reduced HR and vasodilation that occur at, or before, the onset of cardiovascular collapse.^{3,20}

Although *T*_{skin-diff} is associated with vasoconstriction, and is an independent indicator of peripheral blood flow,¹⁴ we found that changes in PPI occurred earlier than changes in the *T*_{skin-diff}. Because PPI is based on the photoelectric plethysmographic signal of the pulse oximeter, it can reflect real-time changes in the peripheral vasomotor tone, and therefore peripheral blood flow. In contrast, it takes much more time for the skin temperature to decrease as a result of peripheral vasoconstriction. This explains why the skintemperature gradient takes longer to reflect variations in peripheral blood flow. PPI may therefore be more suitable as an early indicator of acute changes in peripheral vasomotor tone in response to changes in central blood volume.

During hemorrhage, vasoconstriction is heterogeneous throughout the body, predominantly affecting peripheral skin and muscle and splanchnic circulation, to redirect blood flow to the heart and brain.²¹⁻²³ As previously proposed by Lima et al., changes in peripheral circulation in critically ill patients can be reflected by changes in PPI.² By using PPI in such a way, and in combination with HR, it can be used as a complementary hemodynamic monitoring technique for the early detection of conditions that can trigger variations in peripheral circulation secondary to hemodynamic instability in trauma and intensive care patients.

This study has some limitations that should be acknowledged. First, although volume redistributions with LBNP are similar to those that occur during hemorrhage, we did not induce severe hypovolemia or hypovolemic shock. Nevertheless, the LBNP model of moderate hypovolemia provides an excellent opportunity to collect physiologic data on healthy human subjects, without confounding factors such as tissue injury, anesthesia, or hypothermia. Hence, we were interested in the ability of PPI to indicate the onset of clinically significant central hypovolemia. This was clearly demonstrated, as changes in PPI occurred before systemic hemodynamic changes. Our results may be the first to strictly reflect the relationship between reduced central blood volume and PPI in humans. Second, PPI changes as local vasomotor tone changes. Vasomotor tone is not only influenced by sympathetic activity due to hypovolemia and hypotension but also due to pain, emotional stress, or local conditions such as hypothermia. Such external factors should be considered when interpreting the PPI. Furthermore, our study involved awake, young, healthy subjects, which might not exactly mimic physiologic responses in older, ill patients, especially under general anesthesia. Third, we used a commercial pulse oximeter system with the Masimo SET software incorporated to derive the PPI. The sensors in such systems are not without limitations, and pulse oximeter-derived PPI can be affected by incorrect sensor placement and motion artifacts. Last, we did not measure MAP and SV with invasive methods such as an arterial or pulmonary artery catheter, but

instead used the noninvasive Nexfin device. Although the Nexfin has been validated previously¹² and was shown to provide accurate measurements of MAP and SV during a LBNP protocol,²⁴ it still might lead to inaccuracies when compared with conventional techniques that are frequently used in the clinical setting.²⁵

In conclusion, the pulse oximeter-derived PPI may be a valuable adjunct to systemic monitoring to detect acute hemodynamic responses to central hypovolemia, even before the onset of cardiovascular decompensation. Because the pulse oximeter is used extensively in many different clinical environments, the PPI can be easily obtained and can be used as a complementary hemodynamic monitor for the early detection of hemodynamic instability in trauma and intensive care patients.



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Peripheral vasoconstriction
influences thenar oxygen
saturation as measured
by near-infrared spectroscopy

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4

Abstract

Purpose

Near-infrared spectroscopy has been used as a noninvasive monitoring tool for tissue oxygen saturation (StO_2) in acutely ill patients. This study aimed to investigate whether local vasoconstriction induced by body surface cooling significantly influences thenar StO_2 as measured by InSpectra model 650.

Methods

Eight healthy individuals (age 26 ± 6 years) participated in the study. Using a cooling blanket, we aimed to cool the entire body surface to induce vasoconstriction in the skin without any changes in central temperature. Thenar StO_2 was noninvasively measured during a 3-min vascular occlusion test using InSpectra model 650 with a 15-mm probe. Measurements were analyzed for resting StO_2 values, rate of StO_2 desaturation ($R_{dec}StO_2$, %/min), and rate of StO_2 recovery ($R_{inc}StO_2$, %/s) before, during, and after skin cooling. Measurements also included heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), capillary refill time (CRT), forearm-to-fingertip skin-temperature gradient ($T_{skin-diff}$), perfusion index (PI), and tissue hemoglobin index (THI).

Results

In all subjects MAP, CO, SV, and core temperature did not change during the procedure. Skin cooling resulted in a significant decrease in StO_2 from 82% (80–87) to 72% (70–77) ($P < 0.05$) and in $R_{inc}StO_2$ from 3.0%/s (2.8–3.3) to 1.7%/s (1.1–2.0) ($P < 0.05$). Similar changes in CRT, $T_{skin-diff}$, and PI were also observed: from 2.5 s (2.0–3.0) to 8.5 s (7.2–11.0) ($P < 0.05$), from 1.0°C (–1.6–1.8) to 3.1°C (1.8–4.3) ($P < 0.05$), and from 10.0% (9.1–11.7) to 2.5% (2.0–3.8), respectively. The THI values did not change significantly.

Conclusion

Peripheral vasoconstriction due to body surface cooling could significantly influence noninvasive measurements of thenar StO_2 using InSpectra model 650 with 15-mm probe spacing.

Introduction

Near-infrared spectroscopy (NIRS) is a noninvasive technique that allows the determination of tissue oxygenation based on spectrophotometric quantitation of oxy- and deoxyhemoglobin levels within a tissue. Since its advent as a noninvasive monitoring tool for peripheral tissue oxygenation, a relationship between the potential influences of skin circulation on tissue oxygen saturation (StO₂) signals has been debated. Numerous studies have investigated different NIRS devices in various tissues and under various experimental conditions.¹⁻⁴ These studies indicate that the StO₂ signal is widely influenced by the volume of the vascular bed in the catchment area of the probe. Current clinical NIRS studies, particularly those performed in an intensive care setting seem to neglect this relationship when monitoring peripheral tissue oxygenation. One of the reasons may be the lack of studies that address the influence of thenar skin circulation on StO₂ signal as measured with the most current commercial device available (InSpectra model 650).

We recently reported in an observational study that abnormalities in skin perfusion contribute significantly to the StO₂-derived signal measured with an InSpectra model 650 probe on the thenar, and this correlation was independent of disease condition or systemic hemodynamics.⁵ The question that remains is how important is the potential contribution of low skin blood flow, specifically of the thenar eminence, on StO₂. To answer this question, we performed StO₂-derived tissue oxygenation measurements during local vasoconstriction induced by extremity cooling. We hypothesize that the decrease in skin blood flow resulting from peripheral vasoconstriction during body surface cooling significantly influences the noninvasive measurement of thenar StO₂ using an InSpectra model 650 with 15-mm probe spacing.



Materials and methods

Study population

The study was conducted at a university-affiliated teaching hospital. We recruited healthy volunteers with no history of receiving any vasoactive medication. The volunteers were instructed to avoid caffeine-containing drinks for 24 h before the experiments. The local medical ethics committee approved this study protocol.

Measurements

StO₂-derived tissue oxygenation

StO₂-derived tissue oxygenation was continuously monitored using an InSpectra tissue spectrometer model 650 with a 15-mm probe over the thenar eminence. A vascular occlusion test (VOT) was performed by arrest of forearm blood flow using a conventional sphygmomanometer pneumatic cuff. The cuff was placed around the upper arm and was inflated to a pressure approximately 30 mmHg greater than patient systolic pressure for 3 min. On the completion of the ischemic period, the occluding cuff was rapidly deflated to 0 mmHg. VOT-derived StO₂ parameters were divided into three components: resting StO₂ values, rate of StO₂ desaturation (RdecStO₂, expressed as %/min), and rate of StO₂ recovery (RincStO₂, expressed as %/s).

Peripheral perfusion

Peripheral perfusion was evaluated using conventional physical examination with capillary refill time (CRT), forearm-to-fingertip skin-temperature gradient (T_{skin-diff}), perfusion index (PI), and tissue hemoglobin index (THI). CRT was measured by applying firm pressure to the distal phalanx of the index finger for 15 s. A chronometer recorded the time for the return of the normal color. The T_{skin-diff} was obtained with two skin probes (Hewlett Packard 21078A) attached to the index finger and on the radial side of the forearm, midway between the elbow and the wrist. T_{skin-diff} can better reflect changes in cutaneous blood flow than skin temperature itself. When being evaluated under constant environmental conditions, T_{skin-diff} increases during vasoconstriction, and a threshold of 4°C has been shown to reflect vasoconstriction in critically ill patients.⁶ The PI provides a noninvasive method for evaluating perfusion and has been shown to reflect changes in peripheral perfusion.⁷ In this study, the PI value was obtained using Masimo pulse oximetry, which displays a range from 0.02% (very weak pulse strength) to 20% (very strong pulse strength). The THI was derived from a second-derivative attenuation spectrum and is part of the StO₂ algorithm of the NIRS monitor.

Global hemodynamic parameters

Global hemodynamic parameters included heart rate (HR), stroke volume (SV), cardiac output (CO), and mean arterial pressure (MAP). Global parameters were recorded using thoracic bioimpedance, as measured by a noninvasive cardiac output monitor (NICOM; Cheetah Medical Inc., Wilmington, DE, USA). The NICOM system and technology have been described elsewhere.⁸ In summary, connecting the NICOM to the subject requires four double electrode stickers placed on the thorax, according to the manufacturer's instructions. Data are automatically recorded using a computer data logger on a minute-by-minute basis.

Cooling techniques and monitoring

Body surface cooling was achieved using circulating cold water blankets (Thermowrap, Or-Akiva Ind. Park, Israel). A cooling pump device (CSZ Blanketrol III, model 233, Cincinnati SubZero, Inc.) was connected to the blankets to pump cold water. The water temperature was set to the desired temperature. The blanket garment was attached directly to the patient's body using medically approved adhesive.

Protocol

Individuals were positioned in supine position dressed with the cooling blankets on a comfortable bed. The blanket suit covered the entire body with the exception of the head, instrumented forearm, hands, and feet. The cooling pump device permitted control of blanket water temperature by changing the temperature of water perfusing the suit. The suit was then perfused with 32°C water. Electronic measurements were obtained continuously and the values are reported as averaged data for each interval. The time points included the following: baseline measurements prior to the cooling process (T₀), after 30 min of peripheral cooling (T₁), and after 30 min of the suspension

of cooling and initiation of the rewarming process (T2). For this protocol, peripheral cooling was designed mainly to chill the skin over the entire body to induce only skin vasoconstriction without any changes in central temperature. Therefore, core temperature was measured each 5 min with an infrared tympanic thermometer (First Temp Genius model 3000A). Ambient temperature was constant during all experiments (T = 22°C). Skin vasoconstriction was defined as a minimal 50% decrease either in the T_{skin-diff} temperature or the PI signal.

Statistical analysis

The results are presented as the median (25th–75th), unless otherwise specified. A one-way repeated-measures ANOVA was conducted to compare NIRS-derived and peripheral perfusion parameters prior, during, and after rewarming. The Bonferroni post hoc test was performed if a significant main effect was observed. SPSS (version 15.0, SPSS, Chicago, IL) was used for statistical analysis. A P value less than 0.05 was considered statistically significant.



Results

Eight healthy individuals (4 male, 4 female) participated in the study. The mean age, height, and weight were 26 ± 6 years, 172 ± 5 cm, and 74.1 ± 6.2 kg, respectively. Table 1 lists the global hemodynamic variables stratified by the time points of the study. All subjects tolerated the cooling process well and did not develop shivering during the experiment. We found a nonsignificant tendency towards an increase in SV and CO during peripheral cooling at T1 (Table 1). Core temperature and heart rate did not change significantly during the experiment.

Figure 1 presents the time course of the NIRS dynamic variables and peripheral perfusion parameters before, during, and after the skin cooling process. Table 2 lists the absolute values of all peripheral parameters as stratified by time points. The peripheral

Table 1. Descriptive analysis of global hemodynamic variables and central temperature stratified by the time points

	Time point		
	T0	T1	T2
Heart rate (bpm)	76 [70;83]	67 [58;73]	70 [67;74]
Stroke volume (ml)	110 [76;125]	139 [132;147]	114 [106;164]
Cardiac output (L/min)	8.6 [8.0;9.4]	10.1 [8.9;12.2]	7.9 [7.3;10.1]
Mean arterial pressure (mmHg)	93 [88;101]	100 [92;107]	95 [87;100]
Central temperature (°C)	36,8 [36.6;36.9]	36.6 [36.4;36.9]	36.6 [36.4;36.9]

Data presented as median [25th;75th]

T0 prior to the cooling process, T1 after 30 min of peripheral cooling, T2 after 30 min of the suspension of cooling and initiation of the rewarming process

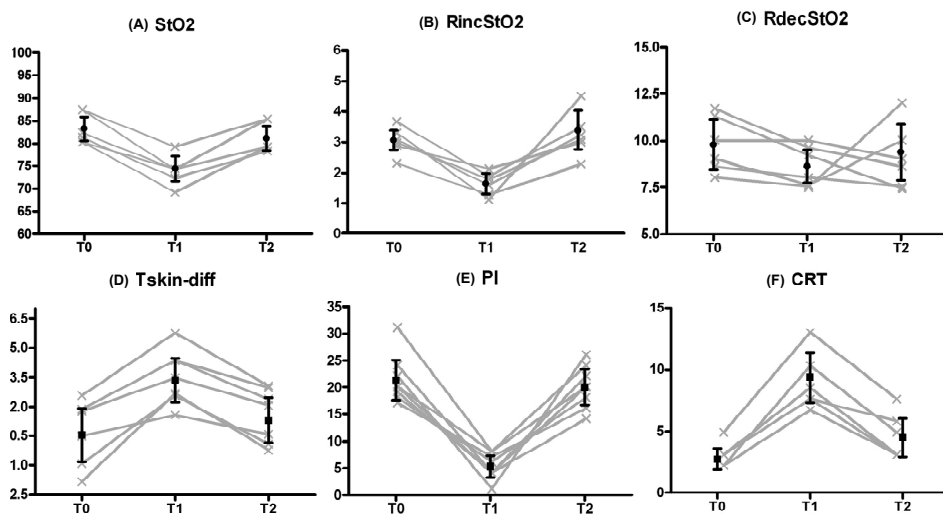


Figure 1. Time course of NIRS-derived variables and peripheral perfusion parameters. T0, prior to the cooling process; T1, after 30 min of peripheral cooling; T2, after 30 min of the suspension of cooling and initiation of the rewarming process. (A) StO₂= peripheral tissue oxygenation (%); (B) RincStO₂= rate of StO₂ recovery after arterial occlusion (%/s); (C) RdecStO₂= rate of StO₂ desaturation during arterial occlusion (%/min); (D) T_{skin-diff}= forearm-to-fingertip skin-temperature gradient (°C); (E) PI= perfusion index (%); (F) CRT= capillary refill time (s). Lines represent individual values for each healthy volunteer. Bars are mean ± 95%CI

cooling resulted in skin vasoconstriction in all volunteers with a significant decrease in the T_{skin-diff} temperature and in the PI signal: 55% (40–175) and 77% (62–83) compared with baseline, respectively. Concomitantly, we observed a significant decrease in StO₂ and RincStO₂ values but not in RdecStO₂. The rewarming process increased StO₂ and RincStO₂ values towards baseline levels. Similar changes in CRT, T_{skin-diff}, and PI were also observed. The THI values did not change significantly during the entire experiment.

We were also interested in investigating which of the NIRS variables was most affected by changes in skin circulation. Our results indicated that the magnitude of changes seem to be more prominent in RincStO₂ than StO₂ and that RincStO₂ is more sensitive to changes in peripheral perfusion than StO₂ itself. When compared with baseline values, the magnitude of the RincStO₂ decreases was larger than that observed for StO₂ [47% (30–62%) vs. 11% (9.2–13.1), $P = 0.001$].

Discussion

The key finding from this study is that changes in vasomotor tone in the skin of the thenar eminence contributed significantly to the StO₂-derived parameters as measured with a NIRS InSpectra device. The main mechanistic theory of our study is that peripheral vasoconstriction due to surface cooling results in decreased perfusion of the skin and, therefore, in parallel, changes in the StO₂ resting values and in the StO₂ recovery rate.

Table 2. Descriptive analysis of NIRS-derived variables and peripheral perfusion parameters stratified by the time points

	Time point		
	T0	T1	T2
StO ₂ (%)	82 [80;87]	72* [70;77]	80 [79;85]
RincStO ₂ (%/sec)	3.0 [2.8;3.3]	1.7* [1.1;2.0]	3.2 [3.0;4.2]
RdecStO ₂ (%/min)	9.5 [8.0;11.6]	8.6 [7.5;9.6]	8.8 [7.7;11.5]
THI (a.u.)	13.1 [12.8;13.9]	13.2 [12.6;13.9]	13.3 [12.9 ;14.2]
T _{skin} -diff (°C)	1.0 [-1.6;1.8]	3.1* [1.8;4.3]	1.2 [-0.3;2.7]
CRT (sec)	2.5 [2.0;3.0]	8.5* [7.2;11.0]	4.0 [3.0;5.7]
PI (%)	10.0 [9.1;11.7]	2.5* [2.0;3.8]	9.1 [8.2;11.7]

Data presented as median (25th;75th)

T0 prior to the cooling process, T1 after 30 min of peripheral cooling, T2 after 30 min of the suspension of cooling and initiation of the rewarming process,

RincStO₂= rate of StO₂ increase after arterial occlusion; RdecStO₂= rate of StO₂ deoxygenation during arterial occlusion; THI= tissue hemoglobine index; T_{skin}-diff = forearm-to-fingertip skin-temperature gradient; CRT= capillary refill time; PI= Perfusion Index.

* P<0.05 versus T0 and T2 (one-way repeated-measures ANOVA with Bonferroni post hoc test)



Under resting conditions, the impact of peripheral perfusion alterations on NIRS-derived measurements can be expected to be magnified as the skin temperature decreases.

This finding was not totally unexpected because light from the NIRS system must pass through the skin and some absorbance in the resistance vessels that supply subepidermal capillaries would be anticipated. The 15-mm NIRS probe mainly covers approximately an 8-mm depth of tissue and focusing on the muscle. Skin and subcutaneous layers above the muscle definitely contribute to the overall StO₂ measured. It is likely that the decreasing StO₂ effect after skin cooling is mainly due to the upper layers' compromised perfusion because of cutaneous vasoconstriction. One may argue that it is possible that the cooling device induced changes beyond that of skin circulation and that flow in skeletal muscle was also altered. Our study does not allow us to conclude which of the two components (skin or muscle) is the major contributor to the changes in StO₂-derived variables in our model. Nevertheless, we speculate that participation of muscle blood flow was not predominant because THI readings in our volunteers presented small changes during the cooling period. On the other hand, participation of skin blood flow was significant, as reflected by changes in skin temperature, PI, and CRT. The THI represents the total tissue concentration of hemoglobin in both extravascular and vascular tissue, and its physiological significance and clinical utility are still under investigation. Our model induced changes mainly on the arterial side of microcirculation and may explain why THI was not affected by the peripheral cooling device, as the sensitivity of THI is greater for vessels with high capacitance, such as post capillaries and venous compartments. This phenomenon

may explain why other NIRS researchers have reported low THI values and normal StO₂ in patients with sepsis, as this is a condition related to vascular leak and low vascular density due to microcirculatory derangements.^{9, 10} Therefore, the decreased NIRS signal from oxygenated hemoglobin is likely the result of a decrease in arterial blood volume within the peripheral vasculature as a consequence of vasoconstriction.

We chose this model to test our hypotheses because previous studies, including one by our own group, have shown that peripheral vasoconstriction is a frequent abnormality in critically ill patients.^{11, 12} For instance, studies that employed NIRS as a peripheral tissue oxygenation monitoring device have shown that the fall in StO₂ in peripheral tissues correlates well with the degree of hypotension in trauma and hemorrhagic shock.¹³⁻¹⁶ However, these findings were always related to acute shock states and the disturbance of the systemic circulation, which indicates that the pathological link between hypotension and the fall in StO₂ may be explained by increased peripheral vasoconstriction as a result of the adrenergic response that follows the neurohumoral compensatory mechanisms induced by the low-flow systemic shock state. Peripheral vasoconstriction may very well explain the fall in StO₂ levels in acute situations, such as in trauma and cardiogenic or hemorrhagic shock. In critically ill patients after resuscitation of the systemic circulation, during the stability phase, peripheral vascular tone may no longer reflect the acute compensatory mechanisms because other factors overcome this physiologic response; such factors include mechanical ventilation, vasopressors, vasodilators, sedatives, and opiate use. However, abnormalities in peripheral perfusion may persist despite patient systemic hemodynamic stability.^{11, 12, 17} The noticeable decreases in StO₂ and StO₂ recovery rate in our model provide evidence that peripheral vasoconstriction markedly influences the NIRS measurements of the tissue oxygenation and may confound interpretation of StO₂-derived parameters in critically ill patients, in whom peripheral perfusion constantly changes over time.

Another interesting finding was that we could induce significant changes in StO₂-derived tissue oxygenation values by maintaining unchanged systemic hemodynamics. We found a nonsignificant tendency towards an increase in SV and CO during peripheral cooling. This finding may be explained by the shift of blood volume from the vasoconstricted peripheral circulation to the central circulation with a subsequent increase in the cardiac preload, justifying the augmentation of cardiac output as a result of an increase in stroke volume. In one previous study conducted by our group, we found that changes in StO₂-derived parameters were correlated with parameters of peripheral perfusion in critically ill patients but were independent of the hemodynamic status of the patient.⁵ In another recent study in a model of controlled central hypovolemia, a decreased venous return with a concomitant decrease in stroke volume did not lead to clinically significant changes in StO₂ as measured on the thenar.¹⁸ These findings strongly suggest that StO₂-derived parameters are more affected by changes in peripheral vasomotor tone than by systemic hemodynamic conditions. Perhaps even more interesting to the clinician who applies NIRS for peripheral perfusion monitoring is the knowledge that abnormal StO₂-derived parameters may reflect a condition of peripheral vasoconstriction independent of systemic hemodynamics.

In conclusion, the presence of peripheral vasoconstriction due to body surface cooling could significantly influence the noninvasive measurement of thenar StO₂ using an InSpectra model 650 with 15-mm probe spacing. Depending on the condition of peripheral circulation, significant decreases in peripheral blood flow can affect StO₂-derived measurements, particularly StO₂ and StO₂ recovery rate, which are exclusively dependent on local vasodilation capacity. Therefore, careful consideration must be given when using NIRS to measure tissue oxygenation in critically ill patients, and consideration should be given to the peripheral circulation when interpreting peripheral tissue oxygenation.

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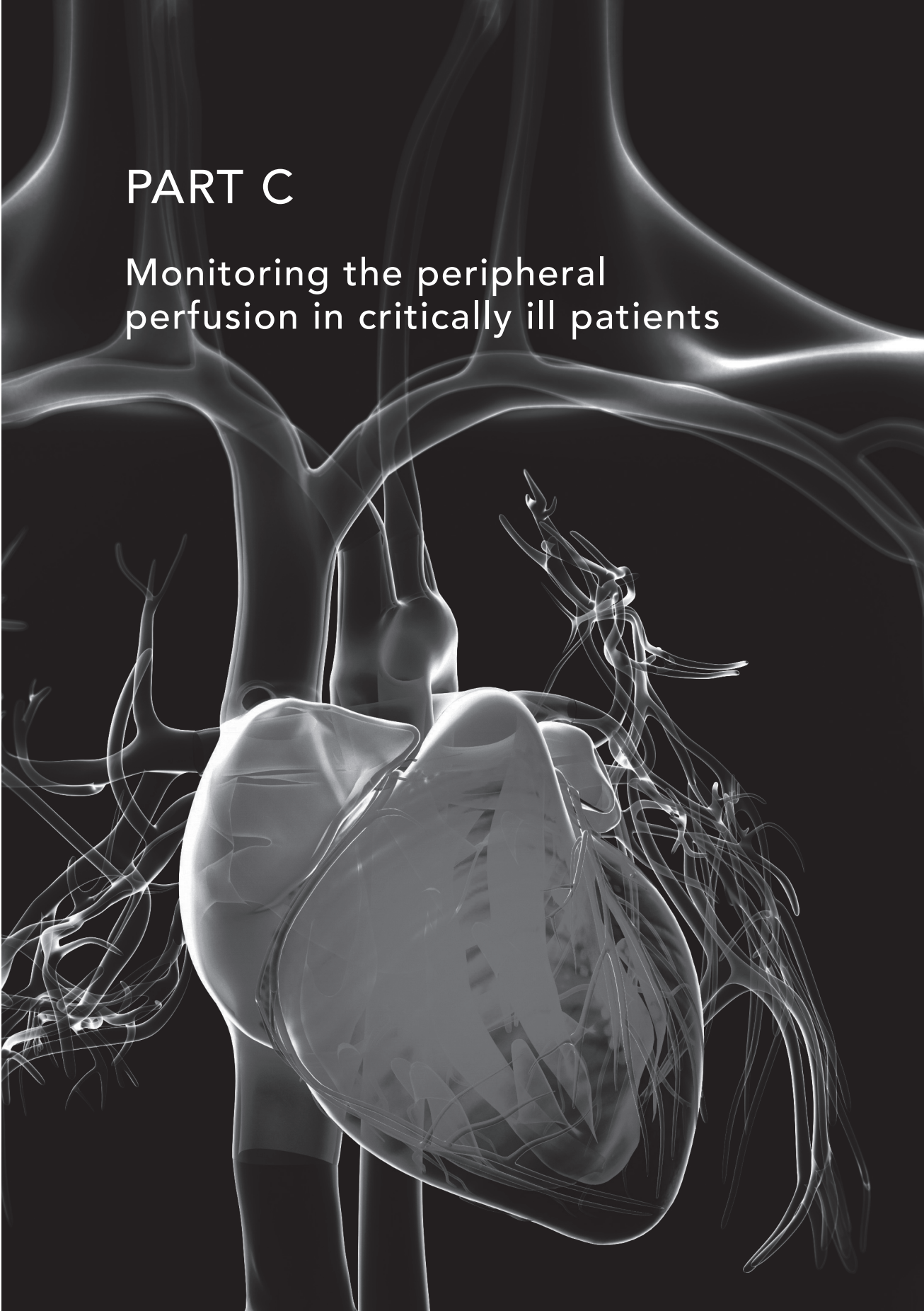
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PART C

Monitoring the peripheral perfusion in critically ill patients



Persistent peripheral and
microvascular perfusion
alterations after out-of- hospital
cardiac arrest are associated
with poor survival

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What hemodynamic and perfusion variables are we monitoring in
post-cardiac arrest patients...and why?

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5

Abstract

Objective

To evaluate sublingual microcirculatory and peripheral tissue perfusion parameters in relation to systemic hemodynamics during and after therapeutic hypothermia following out-of-hospital cardiac arrest.

Design

Prospective observational study.

Setting

Intensive Cardiac Care Unit at a university teaching hospital.

Subjects

We followed 80 patients, of whom 25 were included after out-of-hospital cardiac arrest.

Intervention

In all patients we induced therapeutic hypothermia to 33°C during the first 24 hours of admission.

Measurements and Main Results

Complete hemodynamic measurements were obtained directly on intensive cardiac care unit admission (baseline), during induced hypothermia (T1), directly after rewarming (T2), and another 24 hrs later (T3). In addition, the sublingual microcirculation was observed using sidestream dark-field imaging, and peripheral tissue perfusion was monitored with the peripheral perfusion index, capillary refill time, tissue oxygen saturation, and forearm-to-fingertip skin temperature gradient. During hypothermia, all sublingual microcirculatory parameters decreased significantly together with peripheral capillary refill time and the peripheral perfusion index, followed by a significant increase at T2. Changes in sublingual and peripheral tissue perfusion parameters were significantly related to changes in central body temperature, but not to changes in systemic hemodynamic variables such as cardiac index or mean arterial pressure. Surprisingly, these parameters were significantly lower in nonsurvivors ($n = 6$) at admission and after rewarming. Persistent alterations in these parameters were related with the prevalence of organ dysfunction and were highly predictive of mortality.

Conclusions

Following out-of-hospital cardiac arrest, the early postresuscitation phase is characterized by abnormalities in sublingual microcirculation and peripheral tissue perfusion, which are caused by vasoconstriction due to induced systemic hypothermia and not by impaired systemic blood flow. Persistence of these alterations is associated with organ failure and death, independent of systemic hemodynamics.

Introduction

Profound tissue perfusion alterations have been correlated with the development of multiorgan dysfunction and poor outcome. Recent years have witnessed the development of new techniques that can either directly visualize or indirectly evaluate microvascular tissue perfusion in critically ill patients. Using sublingual sidestream dark-field imaging¹ and different peripheral tissue perfusion parameters, such as the peripheral perfusion index (PPI),² capillary refill time (CRT)⁽³⁾, and forearm-to-fingertipskin temperature gradient (Tskin-diff),³ has described these alterations in patients suffering from different pathophysiologic conditions, such as sepsis⁴ and cardiogenic shock,⁵ apparently independent of systemic hemodynamic variables. Therefore, early detection of inadequate tissue perfusion and oxygenation is crucial to institute prompt therapy, avoiding further organ damage.

Because blood flow in different vascular beds is regulated by local vasomotor tone, it can be assumed that alterations in peripheral tissue perfusion parameters are predominantly caused by local mechanisms, i.e., vasoconstriction.³ Local vasoconstriction occurs when systemic blood flow is not sufficient to meet the body's demands (hypodynamic shock) and/or when the autoregulatory mechanisms governing the distribution of systemic blood flow over different vascular beds are disturbed (redistributive shock).⁶ Until now, the relative contribution of either systemic blood flow or peripheral vasomotor tone (i.e., vasoconstriction) to parameters of microcirculatory tissue perfusion during disease and resuscitation has not been investigated.

A group of patients in whom global and reversible vasoconstriction is induced are the patients who undergo mild systemic hypothermia following out-of-hospital cardiac arrest (OHCA) to protect their brain against ischemia-reperfusion injury.⁷ Following return of spontaneous circulation (ROSC), the extent of damage by the ischemia-reperfusion reaction seems to be the major determinant of outcome following cardiac arrest as it leads to a systemic inflammatory response syndrome, resulting in a hyperdynamic systemic circulation that is associated with the occurrence of multiorgan failure.⁸⁻¹⁰ This post-ROSC "sepsis-like" condition has recently emerged as a critical window of opportunity for impact on survival from cardiac arrest.¹¹ We hypothesized that hypothermia-induced peripheral vasoconstriction will lead to significant alterations in sublingual microcirculatory and peripheral tissue perfusion, independent of systemic hemodynamic variables. In addition, we studied the relation between the occurrence of peripheral tissue perfusion alterations and outcome following OHCA.

Material and methods

Study design, setting and population

This prospective observational study was conducted between October 2010 and February 2011 at the intensive cardiac care unit (ICCU) in patients who were treated with moderate therapeutic hypothermia after OHCA. Cardiac arrest was defined as the cessation of mechanical cardiac activity as confirmed by the absence of signs of circulation.¹² The arrest was presumed to be of cardiac etiology unless it was caused by trauma, drowning, drug overdose, asphyxia, cerebrovascular accident, hypovolemic shock, or any other noncardiac



cause. Patients were eligible for inclusion if they were comatose (Glasgow Coma Scale ≤ 6) after ROSC, older than 18 yrs, not hypothermic (temperature $>34^{\circ}\text{C}$) on study admission, and if peripheral perfusion measurements could be obtained ≤ 4 hrs after ICCU admission (Fig. 1). Patients were excluded if they, after right heart catheterization, turned out to have a persistent unstable systemic circulation, for instance due to persistent hypovolemia, severe myocardial infarction, severe aortic valve stenosis, or had an immediate indication for mechanical assistance to temporarily support heart function.¹³

Medical ethical approval was provided by the local Institutional Review Board. In all patients, written proxy consent was asked within 4 hrs after ICCU admission from a relative authorized to consent on behalf of such a patient. If possible, deferred patient consent was obtained at the moment the patient was conscious, and if it was ethically valid to do so.¹⁴

Hemodynamic monitoring

Systemic hemodynamic variables included heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, stroke volume, cardiac index, and systemic vascular resistance. All patients were monitored with a radial artery catheter and a pulmonary artery catheter (Edwards Lifesciences, Saint-Prex, Switzerland). After obtaining these measurements, arterial and mixed venous blood samples were withdrawn for the determination of blood gases, hemoglobin saturation, arterial hemoglobin, and arterial lactate concentrations (ABL700; Radiometer, Copenhagen, Denmark).

Treatment protocol

In agreement with our standard protocol, therapeutic hypothermia was induced to a target temperature of 33°C by insertion of an intravascular cooling catheter (CoolLine, Coolgard and Fortius, Alsius Corporation, Irvine, CA, USA) as soon as possible following admission. Target temperature was maintained for 24 hours while the patient continued to be sedated,¹⁵ followed by passive rewarming ($0.5^{\circ}\text{C}/\text{hr}$) to normothermia (37°C). Central body temperature was measured continuously with the thermistor of the pulmonary-artery catheter and continuously checked with a rectal temperature probe.

Propofol, midazolam, or a combination of both was used for sedation, and fentanyl was used for analgesia. Shivering was treated with a bolus dose of fentanyl and/or by increasing the dosage of sedatives. According to our local protocol, MAP was maintained above 60 mm Hg with a diuresis ≥ 0.5 mL/kg/hr with volume infusion and vasoactive medication. Additionally, patients were treated with volume infusion or inotropic medication to maintain a CI ≥ 2.0 L/min. Arterial blood gas values, corrected for temperature, were used to adjust the ventilator to maintain a PaO₂ between 8,0 and 13,3 kPa and a PaCO₂ between 4,0 and 5,0 kPa, with a FiO₂ of 40%. After cessation of cooling, sedation was stopped as soon as a core temperature of 35°C had been reached.

Microcirculatory and peripheral perfusion assessment and analysis

Sublingual microcirculatory perfusion was assessed using the sidestream dark-field imager (MicroScan; Microvision Medical, Amsterdam, The Netherlands) as described previously.¹

An investigator, blinded to the patients' clinical course and the order of the sequences, analyzed the video images semiquantitatively. Vascular flow (i.e., microcirculatory flow index) and density (i.e., perfused capillary density and proportion perfused vessels) were calculated by the following flow classification: no flow, sluggish, intermittent, continuous, or hyperdynamic¹⁶ using dedicated software (Automated Vascular Analysis, AVA 3.0; Microvision Medical). This approach has been validated previously with low inter- and intraobserver variability.¹⁷ Capillaries were defined as microvessels with a diameter $\leq 20 \mu\text{m}$.

Tissue oxygen saturation was continuously obtained from the thenar using an InSpectra Tissue Spectrometer Model 650 (Hutchinson Technology, Hutchinson, MN) with a 15-mm near-infrared spectroscopy probe placed over the thenar eminence, as described previously.^{18, 19}

Peripheral tissue perfusion was evaluated using a combination of the peripheral perfusion index (PPI), capillary refill time (CRT), and forearm-to-fingertip skin temperature gradient ($T_{\text{skin-diff}}$). The PPI (Masimo SET® pulse oximetry Perfusion Index, Radical 7, Basingstoke, Hants, UK) provides a noninvasive indicator of peripheral vasomotor tone and peripheral perfusion, and is derived from the photo-electric plethysmographic signal of the pulseoximeter.²⁰ CRT was measured by applying firm pressure to the distal phalanx of the index finger for 15 secs. The time to return of normal color was measured with a per second analog hospital clock present in every ICCU box.²¹ $T_{\text{skin-diff}}$ was obtained from two skin probes, attached to the index finger and on the radial side of the forearm, midway between the elbow and the wrist. This temperature gradient can better reflect changes in cutaneous blood flow than the absolute skin temperature itself and increases during vasoconstriction.²²



Study protocol

All systemic hemodynamic variables, temperature, metabolic state, and sublingual microcirculatory and peripheral perfusion parameters were collected within 4 hrs after admission to the ICCU (baseline). Measurements were repeated as soon as the patients reached their hypothermic core temperature and were hemodynamically stable (T1), directly after rewarming to normothermic temperature (T2), and another 24 hrs later (T3). All components of the Sequential Organ Failure Assessment (SOFA) score²³ and Simplified Acute Physiology Score II score²⁴ were collected for each patient at each time point. The total SOFA score was calculated by summing the scores for each of the components (i.e., cardiac, renal, nervous, respiratory, coagulation, and liver). Twenty-eight-day survival was registered for all patients. The response rate was 100% and no patients were lost during follow-up.

Statistical analysis

The results are presented as median (25th–75th), unless otherwise specified. To study the effect of hypothermia over time on all systemic hemodynamic variables (i.e., heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, stroke volume, and cardiac index) and all peripheral and microcirculatory perfusion variables, we used the linear mixed model

analysis.²⁵ We retrospectively divided the groups into survivors and nonsurvivors to test whether the averages were significantly different between both groups. Because microcirculation and peripheral perfusion parameters are quantitative results, cutoff values were necessary to discriminate abnormal from normal. We therefore assumed the mean response of sublingual microcirculatory and peripheral perfusion parameters over time in the nonsurvivors as appropriate cutoff to test our hypothesis. To allow determination of the accuracy of microcirculatory and peripheral perfusion parameters for prediction, we used mortality as our dichotomous outcome and abnormal microcirculation and peripheral perfusion parameters as our dichotomous predictor variables.²⁶ We then summarized our results as sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio, with their respective 95% confidence interval.

To explore the effect of abnormal sublingual microcirculatory and peripheral perfusion parameters on organ (dys)function (see Materials and Methods for definition), we compared the individual SOFA organ systems and Simplified Acute Physiology Score II score between normal and abnormal perfusion after the rewarming period (T2 and T3). Differences between group means were tested by Mann-Whitney U test. To correct for multiple testing, a p value $< .025$ was considered statistically significant. We used SPSS (version 16.0; SPSS, Chicago, IL) for the statistical analysis.

Results

Clinical characteristics

Of the 26 patients fulfilling the inclusion criteria, we had to discontinue measurements in one patient due to early death. Of the 25 patients in whom we completed all measurements, 19 survived (Fig. 1). Table 1 summarizes the characteristics of all patients. Main hemodynamic and biochemical variables are presented in Table 2. Cardiac index, heart rate, and lactate were significantly different after rewarming (T2) when compared to admission (baseline) or during cooling (T1). In the nonsurvivors, time to ROSC was longer and lactate was higher on admission.

Time course of microcirculatory and peripheral perfusion parameters

Figure 2A and 2B show the time course of sublingual microcirculatory (Fig. 2A) and peripheral tissue perfusion (Fig. 2B) parameters. In addition, Table 3 shows the microcirculatory and peripheral perfusion values. During hypothermia (T1), there was no difference between survivors and nonsurvivors in all peripheral and microcirculatory perfusion variables. Immediately at baseline however, all sublingual microcirculatory parameters (microcirculatory flow index, perfused capillary density, and proportion perfused vessels) were lower in the nonsurvivors. This difference persisted following rewarming (T2 and T3) when sublingual perfusion improved significantly in the survivors compared to the nonsurvivors (Fig. 2A). Similar findings were observed in the peripheral perfusion parameters (with the exception of tissue oxygen saturation): CRT was shorter in survivors at admission and improved even further directly after rewarming, whereas $T_{\text{skin-diff}}$ and PPI indicated good peripheral perfusion after rewarming compared to nonsurvivors (Fig. 2B).

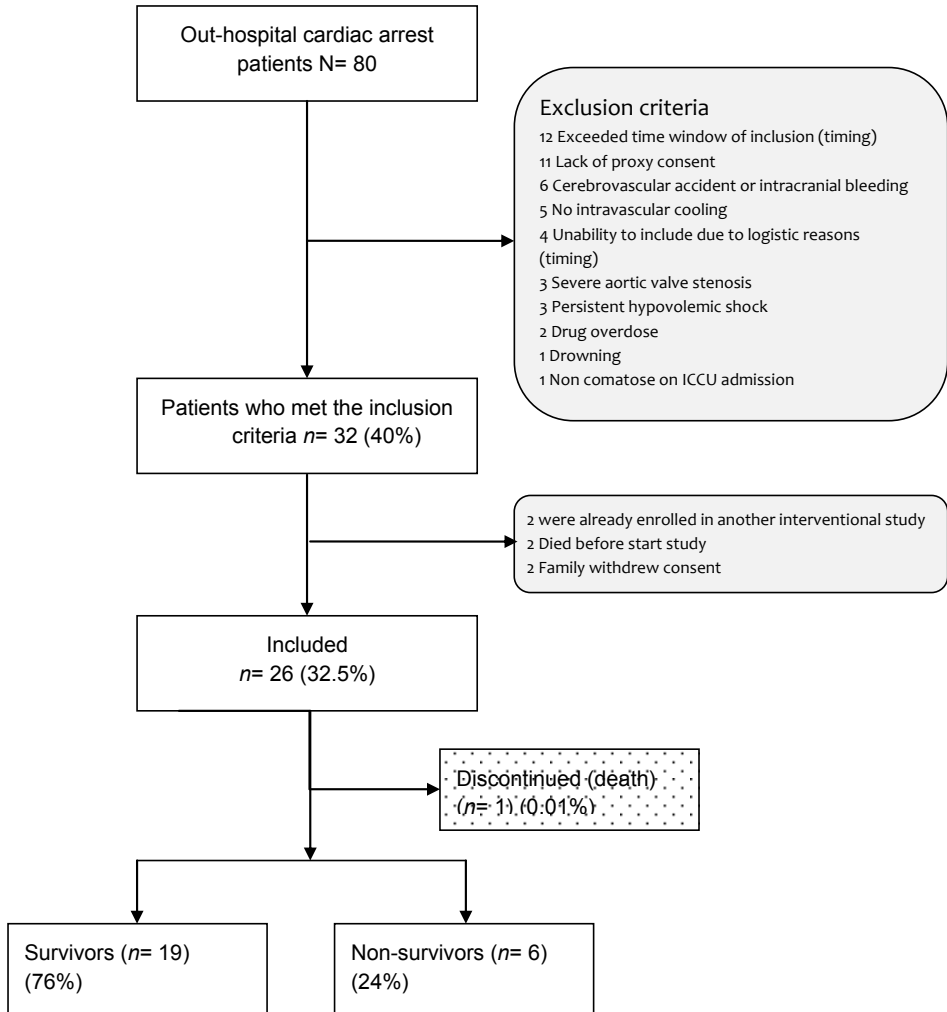


Figure 1. Study flow chart of inclusion.

Prediction of microcirculatory and peripheral perfusion levels on outcome

Based on the mean response of microcirculatory and peripheral perfusion parameters seen in the nonsurvivors (Table 3), abnormal sublingual microcirculation was defined as a microcirculatory flow index <2.8, perfused capillary density <12.6, or proportion perfused vessels <96.8; and abnormal peripheral perfusion was defined as CRT >11.5, Tskin-diff >5, or PPI < 0.4. Table 4 summarizes the accuracy of microcirculatory and peripheral parameters for mortality prediction at different time points. At admission, sensitivity indicated that approximately 93% in the nonsurvivor group had microcirculatory and peripheral perfusion abnormalities. The positive likelihood ratio obtained at both time points after rewarming indicated that the accuracy of microcirculatory and peripheral

Table 1. Baseline characteristics

	Survivors (n= 19)	Non-survivors (n= 6)
Age (years)	59 [57-76]	71 [66-79]
Male/Female, n	17/2	5/1
Body mass index (kg/m ²)	25.4 [24.1-26.9]	25.7 [24.6-27.8]
Acute Physiology and Chronic Health Evaluation II	19 [16-20]	22 [18-25]
Total Sequential Organ Failure Assessment 24h	6 [4-8]	11 [10-12]*
Return Of Spontaneous Circulation (min)	9.0 [7.0-10.0]	26.5 [13-32]*
Mechanical ventilation, n	19	6
First monitored rhythm, n	14 Ventricular fibrillation/tachycardia 2 Asystole 1 Pulseless electrical activity 2 Other/unknown	2 Ventricular fibrillation/tachycardia 2 Asystole 1 Pulseless electrical activity 1 Other/unknown
Dobutamine use, n (%)	2 (8)	4 (66)
Dobutamine dose (µg/kg/min)	2.8 [3.1-5.2]	4.2 [3.0-6.6]
Noradrenaline use, n (%)	3 (16)	3 (50)
Noradrenaline dose (µg/kg/min)	0.18 [0.08-0.31]	0.23 [0.08-0.45]
Intensive Cardiac Care Unit stay (days)	5.0 [5.0-7.0]	10.0 [3.0-12.0]

Values are expressed as median (range). Return of spontaneous circulation is defined as the time between the witnessed cardiac arrest and the actual return of spontaneous circulation. *p < .05, by Mann-Whitney test (survivor vs. nonsurvivors).

perfusion parameters improved significantly with good predictive value. Abnormalities in microcirculatory and peripheral perfusion parameters are obtained approximately 2.5–12 times more often in nonsurvivors than survivors.

Tables 5 and 6 shows the specific organ SOFA subscores and Simplified Acute Physiology Score II scores stratified by abnormal and normal sublingual microcirculatory (Table 5) and peripheral perfusion conditions (Table 6), directly after rewarming (T2), and 24 hrs thereafter (T3). At baseline and T1, there was no significant difference in individual SOFA scores between abnormal and normal microcirculatory and peripheral perfusion parameters. Total SOFA score was significantly higher at T2 and T3 for patients with abnormal microcirculatory perfusion and at T3 for patients with abnormal peripheral perfusion compared to those with normal peripheral perfusion (Table 5 and 6). Looking at the organ system subscores, this can be attributed to the significantly higher scores for respiratory, cardiovascular, and renal SOFA at T2 and to an almost overall increased organ failure score at T3. The Simplified Acute Physiology Score II organ failure assessment was higher at both time points after rewarming for patients with either abnormal microcirculation or abnormal peripheral perfusion.

Table 2. Systemic hemodynamics and metabolic variables

	Baseline		T1		T2		T3	
	S	NS	S	NS	S	NS	S	NS
Central temperature (°C)	36.0 (0.2)	36.1 (0.4)	33.1 (0.06)	32.8 (0.1)	37.5 (0.2)	37.3 (0.3)	37.4 (0.1)	37.6 (0.2)
Heart rate (beats/min)	87.5 (3.3)	73.0 (5.9)	70.0 (3.4)	62.0 (6.1)*	94.0 (4.6)	103.5 (8.3)	89.0 (3.5)	101.0 (6.3)
Mean arterial pressure (mm Hg)	85.6 (2.4)	75.3 (4.2)	74.5 (3.3)	80.0 (5.8)	88.7 (3.3)	81.3 (5.9)	92.0 (3.1)	73.0 (5.5)
Central venous pressure (mm Hg)	14.3 (0.8)	15.0 (1.5)	12.0 (0.8)	16.6 (1.4)	13.8 (0.8)	17.5 (1.5)	12.5 (1.1)	14.5 (1.9)
Pulmonary artery occlusion pressure (mm Hg)	20.3 (1.7)	23.8 (3.0)	16.0 (0.9)	16.8 (1.6)	16.4 (1.5)	17.5 (2.8)	16.0 (1.5)	18.5 (2.8)
Mean pulmonary arterial pressure (mm Hg)	33.0 (3.4)	29.0 (6.1)	23.8 (1.0)	26.8 (1.8)	28.2 (1.5)	35.3 (2.7)*	25.0 (0.9)	33.1 (1.7)*
Cardiac index (L/min · M ²)	3.6 (0.5)	2.2 (0.9)	2.5 (0.5)	2.0 (0.9)	3.9 (0.5)	3.6 (0.9)	4.0 (0.5)	3.9 (0.9)
SvO ₂ (%)	74 (2.0)	66 (3.0)	75 (2.0)	74 (3.0)	76 (1.5)	74 (2.8)	76 (2.2)	74 (4.0)
Lactate (mmol/L)	2.8 (0.4)	4.2 (0.8)*	1.2 (0.14)	1.9 (0.26)*	1.1 (0.10)	1.6 (0.19)*	1.0 (0.14)	2.3 (0.25)*
pH	7.30 (0.02)	7.23 (0.03)	7.33 (0.015)	7.27 (0.03)*	7.36 (0.10)	7.34 (0.018)*	7.40 (0.08)	7.37 (0.015)*
PaO ₂ (kPa)	22 (1.8)	19.3 (3.3)	14.8 (0.8)	15 (1.4)	13.3 (1.5)	17.6 (2.6)	13.3 (0.9)	13.5 (1.7)
PaCO ₂ (kPa)	6.14 (0.26)	6.45 (0.46)	5.62 (0.26)	6.40 (0.46)	5.37 (0.17)	5.0 (0.30)	5.5 (0.09)	4.9 (0.17)
Base Excess	-4.2 (0.95)	-7.5 (1.7)	-2.8 (0.44)	-6.0 (0.80)*	-2.0 (0.57)	-5.0 (1.0)*	0.31 (0.67)	-3.5 (1.2)*
Hemoglobin	8.7 (0.16)	8.2 (0.30)	7.86 (0.19)	7.50 (0.35)	7.60 (0.16)	7.33 (0.30)	7.37 (0.14)	6.6 (0.25)

Systemic hemodynamics and metabolic variables for the different time points compared between survivors and nonsurvivors.

T1, during induced hypothermia; T2, directly after rewarming; T3, 24 hrs after T2; S, survivors (n = 19); NS, nonsurvivors (n = 6). *p < .05, between groups (survivors and nonsurvivors) in the specific time point, by linear mixed model analysis. Data are presented as mean ± SE



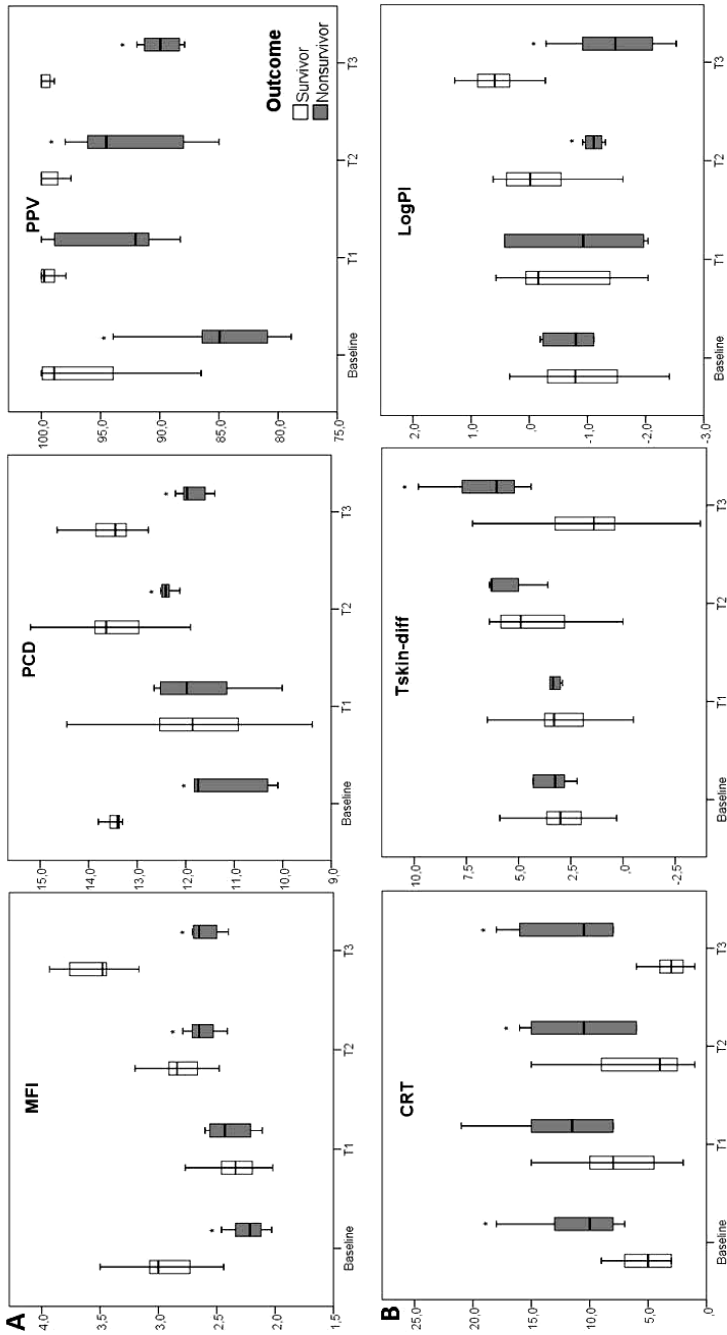


Figure 2. Box plots demonstrating the time course of (A) sublingual microcirculatory parameters (microvascular flow index [MFI], perfused capillary density [PCD, n/mm²], and proportion perfused vessels [PPV, %]) and (B) peripheral perfusion parameters (capillary refill time [CRT, secs], forearm-to-fingertip skin temperature gradient [Tskin-diff, °C], and PPI) in survivors and nonsurvivors. LogPI, log of peripheral perfusion index; baseline, within 4 hrs after admission to the intensive cardiac care unit; T1, directly after rewarming; T2, 24 hrs after rewarming; T3, 24 hrs after hypothermia. * p < .05, between groups (survivors and nonsurvivors) by linear mixed model analysis. The evolution of microcirculatory and peripheral perfusion parameters was significantly different between survivors and nonsurvivors directly after hypothermia (T2) and 24 hrs after hypothermia (T3). Already at baseline there was a difference in MFI, PCD, PPV, and CRT between survivors and nonsurvivors.

Table 3. Microcirculatory and peripheral perfusion parameters

	Baseline		T1		T2		T3	
	S	NS	S	NS	S	NS	S	NS
Microvascular flow index	2.9 (0.06)	2.3 (0.10)*	2.4 (0.06)	2.4 (0.11)	2.9 (0.04)	2.7 (0.08)*	3.6 (0.05)	2.7 (0.09)*
Perfused capillary density (n/mm ²)	13.0 (0.42)	11.2 (0.75)*	11.9 (0.41)	11.7 (0.73)	13.4 (0.29)	12.3 (0.52)*	13.8 (0.30)	12.1 (0.53)*
Proportion perfused vessels (%)	94.3 (1.7)	84.9 (2.9)*	94.8 (0.8)	93.6 (1.4)	99.1 (0.6)	92.7 (1.1)*	99.7 (0.5)	91.7 (0.8)*
Forearm-to-fingertip skin temperature gradient (°C)	2.9 (0.31)	3.3 (0.56)	2.4 (0.5)	3.3 (0.9)	3.7 (0.6)	5.6 (1.0)	1.5 (0.6)	6.5 (1.0)*
Capillary refill time (secs)	5.4 (0.6)	11.0 (1.0)*	7.9 (0.9)	12.5 (1.7)	5.5 (0.9)	10.6 (1.7)*	3.0 (0.6)	11.8 (1.0)*
Peripheral perfusion index	0.5 (0.07)	0.5 (0.12)	0.8 (0.13)	0.7 (0.23)	0.9 (0.11)	0.5 (0.20)*	1.9 (0.16)	0.3 (0.28)*

Microcirculatory and peripheral perfusion parameters for the different time points compared between survivors and nonsurvivors. T1, during induced hypothermia; T2, directly after rewarming; T3, 24 hrs after T2; S, survivors (n = 19); NS, nonsurvivors (n = 6). *p < .05, between groups (survivors and nonsurvivors) on specific time point, by linear mixed model analysis. Data are presented as mean ± SE.



Table 4. Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for abnormal sublingual microcirculation and abnormal peripheral perfusion, as predictors of mortality

		Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Abnormal microcirculation	Baseline	93 (54-99)	58 (44-64)	2.2 (1.1-2.5)	0.12 (0.01-0.8)
	T1	7 (1.0-25)	93 (90-99)	0.9 (0.1-12)	1.0 (0.7-0.1)
	T2	93 (54-99)	63 (49-65)	2.5 (1.1-2.8)	0.11 (0.1-0.9)
	T3	78 (43-85)	98 (85-99)	12.0 (1.6-99.0)	0.35 (0.17-0.86)
Abnormal peripheral perfusion	Baseline	93 (55-99)	38 (24-40)	1.4 (0.8-1.6)	0.19 (0.09-1.8)
	T1	93 (56-99)	33 (20-93)	1.4 (0.6-1.5)	0.22 (0.01-2.2)
	T2	83 (42-99)	90 (76-94)	7.9 (1.8-17.0)	0.18 (0.01-0.8)
	T3	67 (28-82)	94 (83-99)	12.6 (1.7-99.0)	0.35 (0.17-0.86)

CI, confidence interval; T1, during induced hypothermia; T2, directly after rewarming; T3, 24 hrs after T2.

Abnormal perfusion is based on the mean response in the nonsurvivors and used as cutoff (microcirculatory flow index <2.8, perfused capillary density <12.6, or proportion perfused vessels <96.8; capillary refill time >11.5, forearm-to-fingertip skin temperature gradient >5, or peripheral perfusion index <0.4). After rewarming, an abnormal peripheral perfusion increases the odds to die 7.9 (T2) and, respectively, 12.6 (T3) times more than patients who have a normal peripheral perfusion.

Table 5. Specific organ Sequential Organ Failure Assessment subscores and Simplified Acute Physiology Score II stratified by abnormal and normal sublingual microcirculatory perfusion, directly after rewarming (T2) and 24 hrs thereafter (T3)

	Sublingual Microcirculation			
	T2		T3	
	Abnormal (n=12)	Normal (n=13)	Abnormal (n=6)	Normal (n=19)
SOFA _{respiratory}	3.0 (2.0-4.0)	2.0 (1.0-2.0)	3.0 (2.0-3.0)	1.0 (1.0-2.0)
SOFA _{coagulation}	1.0 (1.0-1.7)	1.0 (0.0-1.5)	2.0 (0.7-3.0)	1.0 (1.0-2.0)
SOFA _{cardiovascular}	2.5 (1.2-3.7)	2.0 (0.0-2.0)	3.0 (2.7-3.2)	0.0 (0.0-2.0)
SOFA _{CNS}	4.0 (3.0-4.0)	3.0 (2.0-4.0)	3.5 (2.0-4.0)	1.0 (1.0-4.0)
SOFA _{Renal}	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.5 (0.0-1.2)	0.0 (0.0-1.0)
SOFA _{liver}	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
SOFA _{total}	11.0 (8.2-14.0)	6.0* (4.5-9.0)	12.0 (10.7-13.2)	5.0* (2.0-11.0)
Simplified Acute Physiology Score II	55.0 (37.8, 59.0)	40.0* (26.0, 48.5)	46.5 (38.0, 57.0)	32.0* (24.0, 45.0)

CNS, central nervous system; SOFA, Sequential Organ Failure Assessment. *p < .025, by Mann-Whitney test (abnormal vs. normal) for SOFA total and Simplified Acute Physiology Score II. Values are expressed as median (interquartile range). Patients with abnormal sublingual microcirculation (see Materials and Methods for definition) have more organ failure at both time points after rewarming than patients with normal sublingual microcirculation.

Table 6. Specific organ Sequential Organ Failure Assessment subscores and Simplified Acute Physiology Score II stratified by abnormal and normal peripheral perfusion, directly after rewarming (T2) and 24 hrs thereafter (T3)

	Peripheral perfusion			
	T2		T3	
	Abnormal (n=12)	Normal (n=13)	Abnormal (n=6)	Normal (n=19)
SOFA _{respiratory}	2.0 (2.0-3.5)	2.0 (1.0-2.7)	3.0 (2.0-3.0)	1.0 (1.0-2.0)
SOFA _{coagulation}	1.0 (0.0-1.5)	1.0 (0.3-1.7)	2.0 (0.7-3.0)	1.0 (1.0-2.0)
SOFA _{cardiovascular}	2.0 (2.0-3.5)	1.0 (0.0-2.7)	3.0 (2.7-3.2)	0.0 (0.0-2.0)
SOFA _{CNS}	4.0 (3.0-4.0)	3.0 (3.0-4.0)	3.5 (2.0-4.0)	1.0 (1.0-4.0)
SOFA _{Renal}	0.0 (0.0-0.5)	0.0 (0.0-1.0)	0.5 (0.0-1.2)	0.0 (0.0-1.0)
SOFA _{liver}	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
SOFA _{total}	11.0 (8.2-14.0)	8.0 (5.0-12.0)	12.0 (10.7-13.2)	5.0* (2.0-11.0)
Simplified Acute Physiology Score II	55.0 (37.8, 59.0)	40.0* (26.0, 48.5)	46.5 (38.0, 57.0)	32.0* (24.0, 45.0)

CNS, central nervous system; SOFA, Sequential Organ Failure Assessment. * $p < .025$, by Mann-Whitney test (abnormal vs. normal) for SOFA total and Simplified Acute Physiology Score II. Values are expressed as median (interquartile range). Patients with abnormal peripheral perfusion (see Materials and Methods for definition) have more organ failure at both time points after rewarming than patients with normal peripheral perfusion.



Discussion

Our study demonstrates that the postcardiac arrest phase is characterized by profound changes in sublingual microcirculation and peripheral tissue perfusion, independent of systemic hemodynamics. This confirms our hypothesis that the indices of both sublingual and peripheral perfusion are more influenced by changes in local vasomotor tone than changes in systemic blood flow. Although sublingual microcirculatory and peripheral tissue perfusion alterations were initially similar in all patients during hypothermia, these parameters improved toward normalization in survivors, but not in the nonsurvivors. Abnormal sublingual and peripheral microcirculatory tissue perfusion was indicative for unfavorable outcome, reflected as higher organ dysfunction score and high probability, and a good predictor of ICCU mortality as well.

Although vasoconstriction appears to be the major determinant of peripheral perfusion, the response of the different parameters to hypothermia was not similar. For instance, only sublingual microcirculatory perfusion decreases due to vasoconstriction during hypothermia, whereas the peripheral circulation is already in a vasoconstricted state at admission. Only after rewarming, when the systemic circulation becomes hyperdynamic, the lack of any relation between systemic and regional perfusion becomes apparent. Sublingual microcirculatory and peripheral perfusion parameters improved in the survivors, but remained significantly impaired in the patients who did not.

Vasoconstriction is a result of compensatory sympathetic nervous system activation, especially active in the cutaneous vascular bed, to preserve blood flow to vital organs under conditions of reduced systemic blood flow. Persistent vasoconstriction, independent of systemic hemodynamics, suggests ongoing sympathetic activity in the patients who ultimately died after OHCA.^{27, 28} A similar relation was observed in patients with septic shock.²⁹ This analogy is not surprising considering that as in sepsis, the ischemia-reperfusion phase following cardiac arrest is characterized by the release of inflammatory mediators leading to a systemic inflammatory syndrome–like response, which has been associated with loss of autoregulation and tissue perfusion alterations.³⁰ Hence, the autonomic nervous modulation in the initial phase following OHCA patients might resemble that of severe sepsis.³¹ On the other hand, it has been shown that vasoconstriction and altered microcirculation are also present in an experimental model of hypothermic circulatory arrest.³² Therefore, it is not clear whether induced hypothermia augments or inhibits these alterations, leading to respectively prolonging of impaired perfusion at admission or postponing the increase following rewarming.

Our observations are in accordance with similar observations in other patient groups. Previously, multiple studies have shown that the severity and persistence of sublingual microvascular alterations are associated with unfavorable outcome in patients with severe sepsis or septic shock,^{29, 33} cardiac failure,³⁴ cardiogenic shock,⁵ or abdominal surgery.³⁵ Although less sensitive, assessment of the peripheral perfusion is much more practical than sidestream dark-field monitoring of the sublingual microcirculation, as it is much easier to perform at the bedside and does not require elaborate analyses. In fact, the latter is an important obstacle for the practical implementation of sidestream dark-field monitoring in the daily bedside care.³⁶ In contrast, peripheral skin temperature difference and finger plethysmography are easily implemented, are part of standard monitoring techniques, and are observer independent. In addition, observations from our own group have shown that in adult critically ill patients impaired peripheral perfusion was associated with higher lactate levels, higher organ failure scores, and worse outcome.³⁷

Interestingly, the lactate levels were highest in the nonsurvivors at admission (Tables 2 and 3). Over time, lactate decreased in this group to similar levels as the survivors at T3. As such, only the admission levels can be used to predict outcome after OHCA, not the course in time. As we have shown in a previous study, this seems to be typical for this group of patients (i.e., post–low-flow state) compared to patients with sepsis, where not the lactate level at admission but the reduction over time was associated with outcome.^{38–40}

The potential role for the assessment of peripheral perfusion in an intensive care unit population applied by multiple clinicians must be further investigated to address whether aiming at normalization of peripheral perfusion will have an impact on outcome. These findings imply that if the clinician stops the resuscitation after the traditional end points have been normalized, patients might still remain in a compensatory vasoconstricted state. The presence of abnormal peripheral perfusion after initial resuscitation identifies patients with a more unfavorable outcome. Therefore,

assessment of peripheral perfusion during resuscitation has the potential to optimize vasomotor tone, microcirculatory alterations, and as such resuscitation procedures.

Some limitations of our study need to be acknowledged. First, we used different flow and density parameters as indices of sublingual microvascular perfusion. These software-derived parameters do not take into account the heterogeneity of perfusion, which can be increased in disease states⁴¹; still an interobserver variability of 5% has been reported.⁴² Second, although sublingual perfusion was significantly different between survivors and nonsurvivors, it is not clear whether this was caused by the worse condition of the nonsurvivors or by differences in the preceding resuscitation procedure, for instance, the difference in time to ROSC, which was shorter in the survivors, or by the amount of epinephrine used during resuscitation. Finally, because our study was an observational study, significant correlations between microcirculatory hypoperfusion and changes in SOFA score and mortality rates do not prove causality. Due to the small sample size, our results have to be interpreted with caution. Future studies will have to prove whether recruitment of the peripheral circulation could be a valuable addition to the resuscitation of the systemic circulation.

In conclusion, following OHCA, sublingual and peripheral microcirculatory tissue perfusion alterations are frequent, and are aggravated by induced hypothermia independent of systemic hemodynamics. Persistence of these tissue perfusion alterations is independently associated with the development of organ failure and mortality. Monitoring of peripheral tissue perfusion might therefore be a valuable adjunct to identify those patients after cardiac arrest eligible for additional therapy, aimed at recruitment of the peripheral circulation.



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Clinical assessment
of peripheral perfusion
to predict postoperative
complications after major
abdominal surgery early:
a prospective observational
study in adults

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Abstract

Introduction

Altered peripheral perfusion is strongly associated with poor outcome in critically ill patients. We wanted to determine whether repeated assessments of peripheral perfusion during the days following surgery could help to early identify patients that are more likely to develop postoperative complications.

Methods

Hemodynamic measurements and peripheral perfusion parameters were collected one day prior to surgery, directly after surgery (D0) and on the first (D1), second (D2) and third (D3) postoperative days. Peripheral perfusion assessment consisted of capillary refill time (CRT), peripheral perfusion index (PPI) and forearm-to-fingertip skin temperature gradient (T_{skin-diff}). Generalized linear mixed models were used to predict severe complications within ten days after surgery based on Clavien-Dindo classification.

Results

We prospectively followed 137 consecutive patients, from among whom 111 were included in the analysis. Severe complications were observed in 19 patients (18.0%). Postoperatively, peripheral perfusion parameters were significantly altered in patients who subsequently developed severe complications compared to those who did not, and these parameters persisted over time. CRT was altered at D0, and PPI and T_{skin-diff} were altered on D1 and D2, respectively. Among the different peripheral perfusion parameters, the diagnostic accuracy in predicting severe postoperative complications was highest for CRT on D2 (area under the receiver operating characteristic curve = 0.91 (95% confidence interval (CI) = 0.83 to 0.92)) with a sensitivity of 0.79 (95% CI = 0.54 to 0.94) and a specificity of 0.93 (95% CI = 0.86 to 0.97). Generalized mixed-model analysis demonstrated that abnormal peripheral perfusion on D2 and D3 was an independent predictor of severe postoperative complications (D2 odds ratio (OR) = 8.4, 95% CI = 2.7 to 25.9; D3 OR = 6.4, 95% CI = 2.1 to 19.6).

Conclusions

In a group of patients assessed following major abdominal surgery, peripheral perfusion alterations were associated with the development of severe complications independently of systemic hemodynamics. Further research is needed to confirm these findings and to explore in more detail the effects of peripheral perfusion-targeted resuscitation following major abdominal surgery.

Introduction

Despite reductions in postoperative mortality, the occurrence of severe complications remains high.¹ The development of postoperative complications affects the prognosis of surgical patients and substantially increases the utilization of resources and the cost of care.¹⁻³ Early recognition of patients more likely to develop postoperative complications is therefore of prime importance.

Because postoperative complications better predict short- and long-term mortality than preoperative and intraoperative factors,³⁻⁵ recent research has been focused on identifying preoperative factors that predispose patients to postoperative complications. Several scoring systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the American Society of Anesthesiologists (ASA) score and the Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) score can be applied in a general surgery population. These scores are based on preoperative and perioperative variables specific to different types of surgery. Despite the great number of identified predictors, these scores do not take into consideration the individual patient's postoperative situation, are difficult to calculate⁶, cannot be calculated over time and are still doubted for their specific predictive value for assessing the individual high-risk surgery patient.⁷ Therefore, in clinical practice, a simple, easy-to-use approach is needed to recognize patients at risk for severe complications and to ensure timely initiation of interventions to improve outcomes.



There is increasing evidence that altered tissue perfusion in high-risk surgical patients could be helpful for the detection of those at risk for complications^{8,9} and optimally improve outcomes.¹⁰ In this regard, the success of early, goal-directed hemodynamic therapy has demonstrated the importance of maintaining and improving tissue oxygenation and has shown that early detection and correction of altered tissue perfusion reduce postoperative complications.^{2,11} Accordingly, their importance is also the basis for stressing the need to monitor postoperative early warning signals for occult tissue hypoperfusion.^{2,12} Likewise, lactate level, a potential marker of occult hypoperfusion, is used as a resuscitation target, although its relationship with regional circulation is still not clear.^{13,14} Therefore, early recognition of regional tissue perfusion abnormalities remains important to avoid further organ damage and improve outcomes following major surgery. Postoperative monitoring is still based on conventional hemodynamic variables, which are known to be insensitive to determination of the presence of regional tissue hypoperfusion.

Recently, we and others have shown that assessment of perfusion of the peripheral circulation enables the identification of patients who will have unfavourable outcome. In critically ill patients,¹⁵ after out-of-hospital cardiac arrest¹⁶ and during septic shock,¹⁷ impaired peripheral perfusion has been shown to be associated with organ failure and increased mortality. By use of the capillary refill time (CRT), the peripheral perfusion index (PPI) (Masimo SET Radical-7 pulse oximeter on a rainbow and SatShare platform; Masimo UK, Basingstoke, UK) and the forearm-to-fingertip body temperature gradient (Tskin-diff), peripheral perfusion can easily and noninvasively be evaluated at the bedside and may thus be a more simple and generally useful tool for identifying

patients at risk for postoperative complications.¹⁸ In this context, we were interested in determining whether repeated assessment of the peripheral circulation in the days following surgery could help in the early identification of patients who are more likely to develop postoperative complications. We hypothesized that a disturbance of the peripheral perfusion might be present more frequently in patients who develop severe complications after major abdominal surgery.

Material And Methods

Study population

We conducted this single-centre, prospective observational study between September 2011 and June 2012. We included consecutive patients scheduled to undergo major abdominal surgery. All procedures were performed by senior surgeons and were defined as any intervention in which extensive resection was performed, a body cavity was entered, organs were removed or normal anatomy was significantly altered. Operations included colorectal, gastric, hepatic, pancreatic and oesophageal surgery for benign and malignant disease. Patients were suitable for inclusion if they met the following criteria: (1) age ≥ 18 years, (2) ASA Physical Status between 1 and 4 and (3) expected duration of surgery ≥ 120 minutes. Patients were excluded if they met the following criteria: (1) known neurologic or peripheral arterial occlusive disease, (2) refusal of consent, (3) pregnancy, (4) emergency surgery or (5) minor abdominal surgery. Medical ethical approval was provided by the Human Research Ethics Committee of the Erasmus University Medical Centre (Erasmus MC), Rotterdam, the Netherlands. Written informed consent was obtained from all patients at least 1 day prior to surgery.

Data collection

Hemodynamic variables, metabolic state and peripheral perfusion parameters were collected 1 day before surgery (BL), directly after surgery (D0) and on the first (D1), second (D2) and third (D3) postoperative days. Before surgery, basic demographic characteristics and routine biological, standard hemodynamic and peripheral perfusion parameters were recorded. Standard hemodynamic monitoring included continuous recording of electrocardiographic data, heart rate (HR), mean arterial pressure (MAP), body temperature and pulse oximetry. Concurrently at each time point, arterial blood samples were taken for blood gas analysis, arterial hemoglobin and lactate concentration (Radiometer Copenhagen ABL700 blood gas analyzer; Radiometer Medical, Copenhagen, Denmark). Additionally, surgery duration, operative blood loss, vasopressor therapy (any dose of norepinephrine), ICU and hospital length of stay, length of ventilator support and 30-day mortality were recorded.

We assessed all data needed to calculate the APACHE II score,¹⁹ Sequential Organ Failure Assessment (SOFA) score²⁰ and P-POSSUM score²¹. The total SOFA score was calculated by summing the scores for each of the components (that is, cardiac, renal, respiratory, coagulation, and liver). We did not record the data for second surgeries in patients who underwent reoperation during the same hospitalization.

Definition of complications

Complications were defined as the presence of complications within the first 10 days after surgery. We also scored in-hospital 30-day postoperative complications. Postoperative complications were graded according to the Clavien-Dindo classification system.^{22,23} In short, grades I and II complications are defined as any deviation from the normal postoperative course, without the need for surgical, endoscopic or radiological interventions (grade I) but with the need for pharmacological treatment (grade II). Grade III complications required a surgical, endoscopic or radiological intervention during local (grade IIIa) or general anaesthesia (grade IIIb). Grade IV complications include those requiring ICU care because of single organ failure (grade IVa) or multiorgan failure (grade IVb). Postoperative overnight monitoring in the ICU was routinely performed in patients after oesophagectomy with gastric tube reconstruction and after liver transplantation, and therefore was not scored as a complication *per se*, unless a complication, as described in the Clavien-Dindo classification scheme, occurred and prolonged expected ICU stay, or in cases where continuous ICU admission was necessary for treatment. Additionally, we recorded 30-day survival to evaluate grade V complications (that is, death during the postoperative period). Grades III and IV complications and death (grade V) are classified as severe complications²⁴

In addition, we defined infectious complications as one of the following infections: pneumonia (infiltrate noted on chest radiograph or positive sputum culture), sepsis and related syndromes according to the international sepsis consensus guidelines,²⁵ urinary tract infection (white blood cells in urine) and wound infection. Leakage was defined as anastomotic or chyle leakage. Pleural effusion was diagnosed by chest radiography and/or computed tomography.



Peripheral perfusion assessment

Peripheral perfusion was evaluated using the CRT, the PPI and the forearm-to-fingertip (Tskin-diff) body temperature gradient. These methods are more extensively described elsewhere.¹⁸ In short, CRT is defined as the time required for a distal capillary bed (that is, the nail bed) to regain its colour after pressure has been applied to cause blanching. The time to return of normal colour was measured with a per-second analog hospital clock, which was present in every hospital room. A delayed return to normal colour (>5 seconds) is regarded as impaired peripheral perfusion and has been related to tissue hypoperfusion and an increased likelihood of worsening organ failure.¹⁵ Additionally, to investigate the reliability of CRT, which is a subjective assessment, in terms of variability between different health-care workers, two examiners evaluated CRT in each patient—a trained researcher and a random nurse at the ward at the concurrent time point.

The PPI, which we measured using the Masimo SET Radical-7 pulse oximeter on a rainbow and SatShare platform, provides a noninvasive indicator of the peripheral vasomotor tone and peripheral perfusion and is derived from the photoelectric plethysmographic signal of the pulse oximeter, which is placed on the finger. A threshold value of 1.4 represents a very sensitive cutoff point for determining abnormal peripheral perfusion associated with vasoconstriction.²⁶

Tskin-diff values was obtained from two skin probes attached to the index finger and on the radial side of the forearm, midway between the elbow and the wrist. This temperature gradient can reflect changes in cutaneous blood flow better than the absolute skin temperature itself and is related to blood flow. Tskin-diff increases during vasoconstriction. A threshold value of 2°C has been shown to reflect intermediate vasoconstriction, and a threshold >4°C reflects severe vasoconstriction, in critically ill patients.¹⁵

Statistical analysis

Data are presented as mean \pm SE, unless otherwise specified. We used a Kolmogorov–Smirnov test to test for normality ($P > 0.05$). Differences between group means were tested by Student’s t-test or Mann–Whitney U test. To analyse changes in the different systemic hemodynamic and biological variables over time and between groups, we used linear mixed-model analysis. We retrospectively divided the groups into group A (nonsevere) and group B (severe) complications. Briefly, patients without complications and grades I and II complications were combined as group A, and grades III, IV and V complications were labelled group B. Group B complications (grades III to V) are known as severe complications because of the necessity of surgical intervention (grade III) or due to their severity (that is, organ failure (grade IV or death (grade V)) and are therefore defined as the primary outcome.^{6,24} Because peripheral perfusion parameters are quantitative results, cutoff values were necessary to determine outcome associations. We therefore used predefined cutoffs for abnormal peripheral perfusion (cutoffs: CRT >4.5 seconds, PPI <1.4 and Tskin-diff >2°C) to evaluate the relationship with outcome.^{15,18} We then constructed receiver operating characteristic (ROC) curves (plotted as continuous variables). To calculate sensitivity, specificity, positive likelihood ratio and negative likelihood ratio, we used the predefined cutoffs for abnormal perfusion. We also performed a generalized mixed-model analysis to calculate the predictive value, which was estimated using odds ratios (ORs) with 95% confidence intervals (CIs), for each postoperative day. This multivariate model was confirmed by using forward stepwise selection. We selected the variables based on differences between groups and on previous reports of prognostic factors for peripheral perfusion.^{15,27} We therefore corrected for MAP, HR, vasopressor therapy, C-reactive protein (CRP) and hemoglobin. We used severe complications as our dichotomous outcome variable and any combination of abnormal peripheral perfusion parameters as our dichotomous predictor variable. Subsequently, we performed binary logistic regression to further explore the predictive value of the more traditional predictive scores (APACHE II, ASA, P-POSSUM and SOFA scores). The Bonferroni correction was applied to correct for multiple testing, assuming an α of 0.05 for the three independent tests (CRT, PPI and Tskin-diff). Therefore, P-values <0.017 were considered statistically significant.

Interobserver variability for subjective assessment of peripheral perfusion based on CRT was assessed by calculating Cohen’s κ (clinical cutoff >5 seconds). A κ -value ≥ 0.7 was regarded as adequate. Most analyses were conducted using SPSS version 20.0 software (SPSS, Chicago, IL, USA). The ROC analyses were performed in SigmaPlot 11.0 software (Systat Software, San Jose, CA, USA).

Results

From among the 137 patients who were eligible for inclusion during the study period, 111 patients were ultimately included (Figure 1). There were no other discontinuations or patients lost to follow-up. Table 1 summarizes the demographic, biochemical and surgical characteristics of all patients. There was no significant difference between groups.

Postoperative outcomes

Of the 111 patients included, 19 patients (18%) developed severe complications (grade III, IV or V) (Table 2 and Figure 1). The mean occurrence of severe postoperative complications was 5.2 (± 0.7) days. Importantly, 87% of the patients developed complications after the last peripheral perfusion measurement was obtained. The overall postoperative mortality rate was 3.6%, and the overall morbidity rate was 38.7%. Of the nonsurvivors, one patient died due to liver failure and three patients died due to infectious complications. Operative blood loss tended to be greater in patients who developed severe complications compared to patients who developed nonsevere complications, although this difference was not significant ($P = 0.245$). Fluid balance at D0 did not differ between groups (724 ± 83 ml vs. 829 ± 170 ml). ICU and hospital lengths of stay were significantly longer in patients who developed severe complications

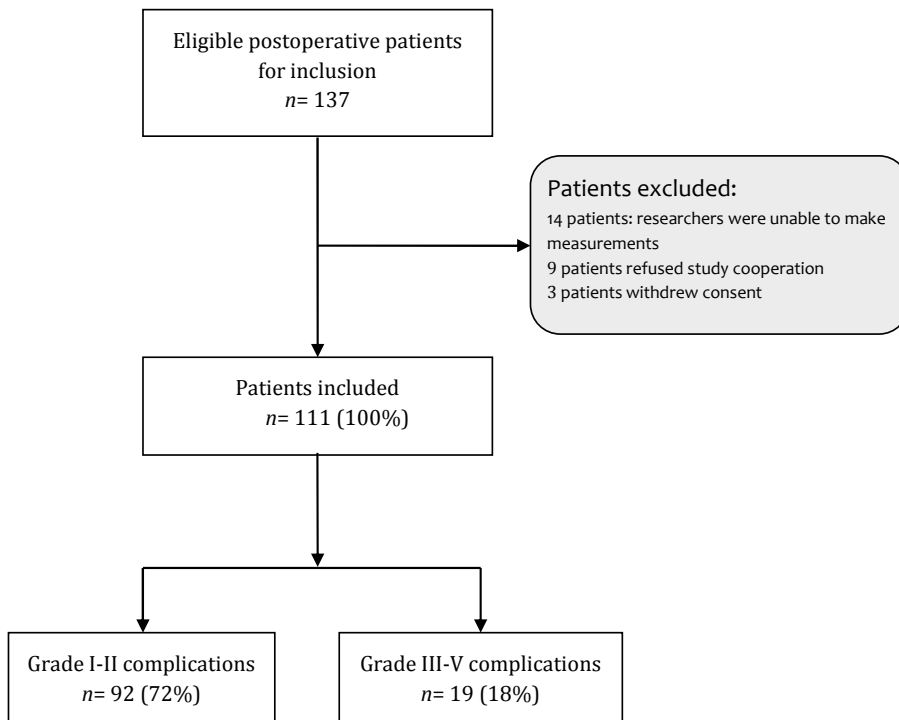


Figure 1. Flowchart of patient inclusion in the study.

Table 1. Patients' characteristics

Characteristics	All patients (n=111)	Nonsevere complications (n=92)	Severe complications (n=19)
Age (years), median [IQR]	60 [54-69]	60 [52-69]	61 [55-72]
Sex (Male/Female), n	76/35	62/30	14/5
Body mass index (kg/m ²)	26.4 (0.7)	26.6 (0.8)	25.0 (1.3)
APACHE II	13.8 (0.4)	13 (0)	15 (1)
Total SOFA D0	4.8 (0.3)	5 (0)	6 (1)
P-POSSUM	31.6 (0.6)	31.0 (0.7)	33.6 (1.7)
Blood Loss (mL)	1068 (149)	971(174)	1493 (234)
Surgery time (min)	324 (12)	322 (13)	337 (32)
ASA score			
- Grade I	11	11	0
- Grade II	59	48	11
- Grade III	40	32	8
- Grade IV	1	1	0
Type of surgery, n			
- Transthoracic esophagectomy	22	16	6
- Transhiatal esophagectomy	13	11	2
- Pancreaticoduodenectomy	23	18	5
- Kidney transplantation	24	23	1
- Liver transplantation	7	4	3
- Hemihepatectomy	7	6	1
- Partial gastrectomy	4	4	0
- Hepatico-jejunostomy	2	2	0
- Gastroenterostomy	2	2	0
- Pancreatico-jejunostomy	1	1	0
- Aortic bypass	1	1	0
- Colon interposition	1	0	1
- Colorectal surgery	1	1	0
- Distal pancreaticotectomy	2	2	0
- Subtotal colectomy	1	1	0

APACHE II, Acute Physiology and Chronic Health Evaluation II; ASA, American Society of Anesthesiologists; P-POSSUM, Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; SOFA, Sequential Organ Failure Assessment. Data are presented as the number of patients, n (%), or as the mean (SE), unless otherwise specified. Nonsevere complications category comprises no complications to grade II complications. Severe complications category comprises grades III to V complications.

Table 2. Postoperative complications

	All patients (n=111)	Nonsevere complications (n=92)	Severe complications (n=19)	P-values
ICU stay (days), median (IQR)	2 [2-4]	2 [0-3]	6 [3-9]	<0.001
Hospital stay (days), median [IQR]	13 [11-20]	12 [10-17]	27 [17-36]	<0.001
Highest complication grade				
- No complications	68	68	-	-
- Grade I	11	11	-	-
- Grade II	13	13	-	-
- Grade IIIa	3	-	3	-
- Grade IIIb	4	-	4	-
- Grade IVa	6	-	6	-
- Grade IVb	2	-	2	-
- Grade V (death)	4	-	4	-

According to the Clavien-Dindo classification scheme, the most severe complication is scored when those of lesser severity are clearly a step in the process leading to the serious event. Data are presented as the number of patients, unless otherwise specified. P-values represent differences between groups, and the statistical significance threshold was set at $P < 0.017$. Dash (-) indicates not applicable. Nonsevere complications category comprises no complications- to grade II complications. Severe complications category comprises grades III to V complications.



Systemic and peripheral perfusion parameters over time and relationship to outcomes

Hemodynamic and biological data are presented in Table 3. On the different postoperative days, there was no difference in cardiac index ($n = 39$), MAP or central venous pressure between patients who developed severe complications and those who did not. Immediately after surgery (D0), however, HR was higher in patients who developed severe complications and persisted over time until D3. In patients who received vasopressor therapy postoperatively, the dose of vasopressor did not differ between groups in linear mixed-model analysis. Overall fluid balance during the study period did not differ between groups ($2,462 \pm 155$ ml vs. $2,879 \pm 334$ ml).

Table 4 shows the time course for the different peripheral perfusion parameters. Before surgery there were no differences between groups in these parameters. However, at D0, CRT was significantly longer in patients who subsequently developed severe complications ($P = 0.005$). This difference persisted over time until D3. Similarly, there was a downward trend for PPI (increasingly altered), which reached a significant difference between groups on D2. Concurrently on D3, there was a significant difference between groups in Tskin-diff. Importantly, mean CRT exceeded the clinical cutoff for delayed refill time (>5 seconds) at D0, whereas mean PPI and mean Tskin-diff values did not exceed the cutoff for abnormality.

Table 3. Systemic hemodynamic and biological data

Systemic hemodynamics	Baseline		D0	
	Nonsevere complications	Severe complications	Nonsevere complications	Severe complications
Heart rate (beats/min)	74 (1)	76 (4)	77 (1)	87 (5)*
Mean arterial pressure (mmHg)	96 (2)	95 (4)	89 (2)	85 (3)
pH	7.36 (0.02)	7.41 (0.02)	7.36 (0.01)	7.37 (0.01)
PaO ₂ (kPa)	10.5 (5.8)	11.1 (0.05)	17.6 (0.9)	15.8 (1.3)
Base Excess	-4 .0 (2.08)	-3.0 (3.0)	-2.92 (0.29)	-2.69 (1.08)
Lactate (mmol/L)	1.3 (0.2)	1.6 (0.01)	1.3 (0.1)	1.6 (0.3)
Hemoglobin (g/dL)	7.7 (0.2)	8.0 (0.3)	7.1 (0.1)	6.9 (0.3)
Creatinine (µmol/L)	81 (7)	85 (12)	84 (6)	94 (13)*
C-reactive protein mg/L	8 (2)	21 (18)	35 (9)	96 (33) *
White blood cells (10 ⁹ /l)	6.7 (0.3)	9.7 (2.5)	8.7 (0.4)	10.8 (1.4)
Central temperature (°C)	36.7 (0.1)	36.7 (0.1)	36.7 (0.1)	36.7 (0.1)
Vasopressor use, n (%)	-	-	36 (39)	11 (58)
Vasopressor dose, (µg/kg.min)	-	-	0.17 (0.12)	0.07 (0.03) *

Baseline, Prior to surgery; D0, Directly after surgery; D1 First postoperative day; D2, Second postoperative day; D3, Third postoperative day; PaO₂, Arterial blood gas oxygen tension. Dash (-) indicates not applicable. Nonsevere complications category comprises no complications- to grade II complications. Severe complications category comprises grades III to V complications.

Table 4. Peripheral perfusion parameters

Measurement parameters	Baseline		D0	
	Nonsevere complications	Severe complications	Nonsevere complications	Severe complications
CRT (s)	2.4 (0.1)	2.8 (0.2)	3.6 (0.2)	5.2 (0.5) *
PPI (a.u.)	3.9 (0.3)	2.9 (0.3)	3.5 (0.4)	2.7 (0.8)
Tskin-diff (°C)	2.1 (0.2)	2.5 (0.5)	2.7 (0.2)	3.1 (0.4)

a.u., Arbitrary units; Baseline, Prior to surgery; CRT, Capillary refill time; D0, Directly after surgery; D1 First postoperative day; D2, Second postoperative day; D3, Third postoperative day; PPI, Peripheral perfusion index; Tskin-diff, Forearm-to-fingertip skin temperature gradient. Nonsevere complications category comprises no complications to grade II complications.

D1		D2		D3	
Nonsevere complications	Severe complications	Nonsevere complications	Severe complications	Nonsevere complications	Severe complications
80 (2)	91 (5)*	83 (1)	91 (4)*	81 (2)	92 (3)*
90 (2)	87 (5)	93 (2)	93 (4)	96 (1)	91 (4)
7.39 (0.01)	7.39 (0.02)	7.40 (0.02)	7.43 (0.01)	7.40 (0.02)	7.43 (0.01)
12.7 (0.5)	11.7 (0.7)	11.3 (0.5)	13.6 (2.3)	10.2 (0.6)	11.4 (1.1)
-2.20 (0.34)	-2.0 (1.06)	-0.59 (0.47)	-0.36 (1.59)	-0.22 (0.85)	0.5 (1.29)
1.2 (0.1)	1.5 (0.2)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.3 (0.2)
6.8 (0.1)	6.5 (0.3)	6.5 (0.1)	5.9 (0.3)*	6.4 (0.1)	5.8 (0.3)
76 (5)	89 (10)*	69 (5)	86 (9)	68 (6)	82 (10)
86 (10)	121 (26) *	135 (15)	156 (24)	120 (15)	153 (29)
11.6 (0.5)	11.5 (0.7)	11.3 (0.4)	11.3 (0.4)	10.2 (0.5)	9.7 (0.5)
37.1 (0.1)	37.3 (0.1)	37.0 (0.1)	37.2 (0.1)	37.0 (0.1)	37.2 (0.1)
25 (27)	10 (52)	9 (10)	7 (37)	3 (3)	3 (16)
0.05 (0.33)	0.04 (0.02)	0.01 (0.05)	0.01 (0.07)	0	0.18 (0.01)

Data are presented as mean (SE). *P < 0.05 indicates statistical significance between groups (nonsevere complications vs. severe complications) at the specific time point. Differences between groups on the different postoperative days were assessed by linear mixed-model analysis



D1		D2		D3	
Nonsevere complications	Severe complications	Nonsevere complications	Severe complications	Nonsevere complications	Severe complications
2.9 (0.2)	6.2 (0.7)*	2.7 (0.1)	5.9 (0.6)*	2.8 (0.2)	5.7 (0.7)*
4.9 (0.0)	2.4 (0.7)	3.9 (0.3)	1.7 (0.4)*	4.4 (0.3)	2.2 (0.5)*
2.3 (0.2)	3.3 (0.5)	2.2 (0.2)	3.9 (0.6)*	2.2 (0.2)	3.6 (0.7)*

Severe complications category comprises grades III to V complications. Data are presented as mean ± SE for the total patient sample (N = 111). *P < 0.017 indicates significant difference between groups at specific time point by linear mixed-model analysis.

Peripheral perfusion parameters were treated as continuous variables and analysed accordingly over time. Amongst these different parameters, the diagnostic accuracy of predicting severe postoperative complications on D1 was highest using CRT (ROC area under the curve (AUC) = 0.79 (95% CI = 0.66 to 0.90); $P < 0.001$) (Figure 2A). This value increased marginally and had the largest AUC on D2 (0.91 (0.83 to 0.92); $P < 0.001$) (Figure 2B). Moreover, CRT was a significantly better predictor than PPI ($P = 0.001$) and Tskin-diff ($P < 0.001$) at D1.

For discriminatory analyses of the individual assessment of peripheral perfusion, we used predefined cutoff values for abnormal peripheral perfusion on each independent parameter. Table 5 shows the diagnostic accuracy of the different peripheral perfusion parameters for the early identification of patients with severe complications. For testing on D2, the sensitivity (0.79, 95% CI = 0.54 to 0.94) for CRT was very good, with a specificity of 0.93 (95% CI = 0.86 to 0.97). Similarly, PPI and Tskin-diff had the highest sensitivity (0.74 (95% CI = 0.49 to 0.91) and 0.84 (95% CI = 0.60 to 0.97), respectively) on D2 compared to the other postoperative days. Subsequently, the positive likelihood ratio obtained on D1 and D2 indicated that the accuracy of peripheral perfusion parameters improved significantly, respectively 1 and 2 days, after surgery with good predictive value. Abnormalities in peripheral perfusion parameters were already predictive on D1, and over time these abnormalities were present approximately two to twelve times more often in patients with severe complications.

Interrater reliability of CRT between observers at the different postoperative days demonstrated a good overall agreement. Cohen's κ analyses demonstrated κ -values

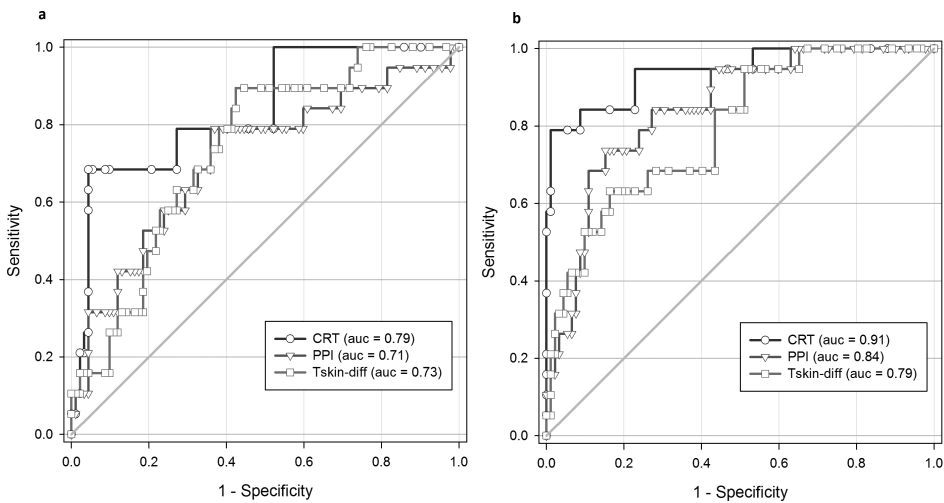


Figure 2. Receiver operating characteristic curves of peripheral perfusion parameters for prediction of severe complications. Receiver operating characteristic curves for capillary refill time (CRT), peripheral perfusion index (PPI) and forearm-to-fingertip skin temperature gradient (Tskin-diff) to predict severe complications on the first postoperative day (D1) (a) and the second postoperative day (D2) (b). Full details, including sensitivity and specificity values of the curves, are given in Table 5.

Table 5. Predictive value after surgery for the different peripheral perfusion parameters, when altered, as predictors of severe complications.

		AUC (95% CI)	P-values	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood Ratio	Negative likelihood Ratio
CRT	D0	0.76 (0.65-0.80)	0.31	0.63 (0.38-0.83)	0.79 (70-87)	3.06	0.46
	D1	0.79(0.66-0.90)	< 0.001	0.68 (0.43-0.87)	0.91 (0.83-0.96)	7.42	0.35
	D2	0.91 (0.83-0.92)	< 0.001	0.79 (0.54-0.94)	0.93 (0.86-0.97)	11.71	0.23
	D3	0.88 (0.78-0.93)	< 0.001	0.71 (0.46-0.89)	0.93 (0.85-0.98)	10.15	0.34
PPI	D0	0.59 (0.45-0.70)	0.19	0.42 (0.20-0.67)	0.64 (0.53-0.74)	1.17	0.90
	D1	0.71 (0.57-0.82)	0.43	0.58 (0.34-0.80)	0.76 (0.66-0.84)	2.42	0.55
	D2	0.84 (0.75-0.91)	< 0.001	0.74 (0.49-0.91)	0.84 (0.75-0.91)	4.52	0.31
	D3	0.81 (0.70-0.91)	< 0.001	0.53 (0.29-0.76)	0.90 (0.82-0.95)	5.21	0.53
Tskin-diff	D0	0.59 (0.44-0.70)	0.23	0.73 (0.49-0.91)	0.50 (0.40-0.61)	1.54	0.50
	D1	0.73 (0.62-0.83)	0.14	0.82 (0.57-0.95)	0.58 (0.47-0.68)	1.91	0.36
	D2	0.79 (0.68-0.81)	< 0.001	0.84 (0.60-0.97)	0.52 (42-63)	1.76	0.30
	D3	0.72 (0.60-0.80)	0.31	0.68 (0.43-0.87)	0.58 (0.48-0.69)	1.64	0.52

AUC, Area under the receiver operating characteristic curve; CI, Confidence interval; D0, Directly after surgery; D1, First postoperative day; D2, Second postoperative day; D3, Third postoperative day; PPI, Peripheral perfusion index; Tskin-diff, Forearm-to-fingertip skin temperature gradient. P < 0.017 is considered significant.



of 0.91 (95% CI = 0.80 to 0.97) on D0, 0.81 (95% CI = 0.65 to 0.93) on D1, 0.74 (95% CI = 0.52 to 0.89) on D2 and (95% CI = 0.70 to 0.98) on D3. Importantly, the interrater reliability of CRT at D2, which had the best predictive value for severe complications (see Table 5), showed good agreement between the different observers.

Accuracy of peripheral perfusion for predicting postoperative complications

We performed a generalized linear mixed-model analysis to further explore the association of abnormal peripheral perfusion with outcomes. After adjusting for hemodynamic variables (MAP and HR), vasopressor therapy, CRP and hemoglobin, the condition of abnormal peripheral perfusion was found to have a major predictive effect. The predictive value for severe complications was calculated for each postoperative day separately, and the results are presented in Table 6. Postoperatively, abnormal peripheral perfusion was predictive for development of severe complications. Notably, abnormal peripheral perfusion on D2 had the best predictive value; patients with abnormal peripheral perfusion were almost nine times more likely to develop postoperative complications (OR = 8.40 (95% CI = 2.72 to 25.87); $P < 0.001$). More importantly, this effect persisted over time. When we scored the occurrence of 30-day postoperative complications, abnormal peripheral perfusion was still predictive at the different subsequent time points: D1 (OR = 2.87 (95% CI = 1.23 to 6.71); $P = 0.015$), D2 (OR = 3.46 (95% CI = 1.46 to 8.23); $P = 0.005$) and D3 (OR = 3.34 (95% CI = 1.40 to 7.96); $P = 0.007$).

The following commonly used risk stratification scores had no predictive value for the occurrence of complications in our population: ASA score (OR = 2.62 (95% CI = 0.71 to 9.56); $P = 0.14$), P-POSSUM score (OR = 1.04 (95% CI = 0.92 to 1.18); $P = 0.52$), APACHE II score (OR = 1.11 (95% CI = 0.94 to 1.32); $P = 0.24$) and SOFA score on D0 (OR = 1.08 (95% CI = 0.81 to 1.43); $P = 0.62$).

Table 6. Predictive value of abnormal peripheral perfusion for severe complications

Abnormal peripheral perfusion measurement	Odds Ratio	(95% CI)	P-value
D0	4.49	1.38-14.56	0.013
D1	3.70	1.29-10.63	0.015
D2	8.40	2.72-25.87	<0.001
D3	6.43	2.11-19.64	0.001

CI, Confidence interval; D0, Directly after surgery; D1, First postoperative day; D2, Second postoperative day; D3, Third postoperative day. Abnormal peripheral perfusion is defined as at least one abnormal peripheral perfusion variable capillary refill time >4.5 seconds, peripheral perfusion index <1.4 or a forearm-to-fingertip skin temperature gradient >2°C. We used a generalized mixed-model analysis to calculate the predictive value of abnormal peripheral perfusion for severe complications at each postoperative day. Mean arterial pressure, heart rate, vasopressor therapy, C-reactive protein and hemoglobin were used to adjust the predictors in the multivariate analysis. $P < 0.017$ is considered significant.

Discussion

The principal findings in the present study illustrate that, following elective major abdominal surgery, peripheral perfusion alterations were more marked in patients who were more likely to develop severe complications. Peripheral perfusion alterations were already present in these patients immediately after surgery and became even more predictive on D1 and D2. Further research is required to confirm these findings and to investigate whether targeted treatment based on peripheral perfusion assessment could improve outcomes.

Surprisingly, the diagnostic accuracy of peripheral perfusion assessment was highest using CRT, as compared to PPI and Tskin-diff. This finding has major clinical implications. First, this parameter provided high levels of accuracy and discrimination, as soon as D2, in the prediction of patients more likely to develop severe complications. Second, the subjective inspection and palpation of peripheral perfusion is safe, noninvasive, cheap and easy to perform at the bedside and enables physicians to identify early on those patients more likely to deviate from the normal postoperative course and have severe complications, even before continuing to invasive procedures. Moreover, despite the current questions raised about the clinical utility of CRT, we found that it had very good interrater reliability between observers. The results of our study extend the findings of a recent single-centre study¹⁵ which showed that subjective assessment of peripheral perfusion with CRT could identify early on those critically ill patients with more severe organ dysfunction.

Since the introduction of the Clavien-Dindo classification system in 2004²³, an increasing consensus has been formed on how to define and grade adverse postoperative events and evaluate surgical procedures.²² Early identification of patients who subsequently develop life-threatening complications or who are at risk for longterm disability due to postoperative complications enables timely recognition of patients who may benefit from early intensive management. Several prediction models, such as the Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity²⁸, the Rotterdam score²⁹ and a new score described by Braga et al.⁶ have been proposed to predict standardized complications based on several physiological and operative measurements. These prediction models are usually organ- and surgery-specific, however, and tend to overestimate poor outcomes in a surgical case mix population, and are even outranked by a surgeon's intuition.³⁰ Therefore, an individual assessment, such as the assessment of peripheral perfusion, to predict postoperative patients at risk for severe adverse postoperative events could be very useful in comparing the postoperative performance of patients in a heterogeneous population. Maybe more importantly, we observed peripheral perfusion alterations before the clinical occurrence of postoperative complications, with a mean occurrence on the fifth postoperative day. Because of the preliminary nature of our findings, comparison with other measures of individual surgical risk assessment, such as exercise testing or plasma biomarkers, could confirm our observations.

From an etiological perspective, compromised peripheral circulation in the postoperative course may resemble the early, initial period of that in both septic and



nonseptic shock. In the latter case, increased sympathetic activity, as a response to circulatory shock, leads to increased vasomotor tone and is usually induced by the baroreceptor reflex. During this period, in which compensatory mechanisms predominate, the neurohumoral response-induced vasoconstriction preserves the perfusion of the heart and brain at the expense of perfusion of the skin, muscle and gastrointestinal vascular beds.^{27,31} On the other hand, this increased adrenergic response could also well be the result of inflammation-induced vasoconstriction due to intraoperative stress and surgical trauma, independent of systemic hemodynamics.^{32,33} For instance, Boerma et al. showed that severe inflammation affects intestinal and sublingual tissue perfusion.³⁴ Furthermore, using an experimental model of abdominal surgery, Hildebrand et al. found that treatment of hypotension with norepinephrine had no adverse effects on microcirculatory perfusion or tissue oxygen tension in the intestinal tract, proving that administering low to moderate doses of norepinephrine to increase perioperative blood pressure does not adversely affect peripheral tissue perfusion.³⁵

Others have confirmed that this postsurgical systemic inflammatory response syndrome (SIRS)-induced vasoconstriction could be seen as a surrogate marker for impaired tissue healing, increased metabolic demands and organ hypoperfusion.^{36,37} In our patient population, the observed delayed CRT and increased $T_{\text{skin-diff}}$ in patients who developed severe complications may similarly reflect the release of inflammatory mediators, leading to SIRS,³⁸ loss of autoregulation, increased endothelial damage and tissue perfusion alterations.

Although the presence of abnormal peripheral perfusion identifies patients at increased risk for unfavourable outcomes, no study has been conducted to date, to the best of our knowledge, that has been focused on resuscitation based on these parameters. Current perioperative 'goal-directed therapy' studies have been focused mainly on systemic hemodynamic parameters^{11,39} and may contribute to improvements in survival after major surgery by using perioperative plasma volume expansion^{12,39} or a more restricted fluid approach.⁴⁰ Moreover, there is to date no uniform goal-directed strategy aimed at resuscitation of regional peripheral blood flow. Some researchers have shown positive effects of regional perfusion-based resuscitation,^{41,42} whereas others have reported contrasting findings.⁴³ Our findings in the present study have important clinical implications, however, as our results demonstrate the importance of adequate tissue perfusion and thus may provide a foundation for developing a tissue perfusion-based approach for use even before critical illness.^{44,45} The role of individual peripheral perfusion assessment as a potential additional tissue perfusion endpoint must be investigated further to address whether aiming at normalization has an impact on outcome. Given the results we report here, one can imagine that serial peripheral perfusion measurements in a postoperative population could provide an additional window to monitoring and treating occult hypoperfusion caused by inflammation or infection. As such, these measurements might be used for earlier treatment of surgical or infectious postoperative complications and thereby result in a reduction of organ failure and mortality. However, a large multicentre trial, preferably randomized and

controlled, is needed to demonstrate the effect of interventions based on impaired peripheral perfusion parameters.

Some limitations of our study need to be acknowledged. First, because our study was an observational study, significant correlations between peripheral perfusion alterations and the occurrence of complications do not prove causality. It has been shown previously, however, that persistent vasoconstriction, independently of systemic hemodynamics, suggests ongoing sympathetic activity associated with organ dysfunction after out-of-hospital cardiac arrest,¹⁶ and during septic shock.^{17,46} As such, there is now evidence that an elevated SIRS response before and directly after major surgery (within 24 hours) is associated with increased morbidity^{9,47} and mortality⁴⁸ and is an independent predictor of survival.

Second, in this study we chose to correlate peripheral hypoperfusion to clinical outcomes according to the Clavien-Dindo grading system.²³ Although this grading system is relatively new, it is not unfamiliar amongst surgeons and it is considered more reliable by observers.²² This classification system is simple and reproducible, correlates with treatment cost and length of stay and can be used to semiquantitatively score postoperative complications in severity in varying fields of surgery. Although 30-day follow-up is often used, we focused on a 10-day time window. We believe that the scoring of complications within 10 days after surgery better permits distinctions between procedure-related complications and those related to disease progression, especially when related to perioperative perfusion abnormalities. Nevertheless, we found that the predictive effect of impaired peripheral perfusion persisted over 30 days as well.

Third, paired measurements of global blood flow (cardiac output) were not done in all postoperative patients. Our main focus in this study was to assess the relationship between abnormal peripheral perfusion and the occurrence of severe complications. It remains to be elucidated to what extent peripheral perfusion alterations reflect systemic hemodynamics, as others have reported that peripheral circulation behaves independently of systemic hemodynamic resuscitation, even despite early goal-directed therapy.^{18,46} Despite this knowledge, we observed a significant difference in HR between groups at the different postoperative time points. Although HR is indeed an important prognostic parameter, our objective in this study was to examine whether peripheral perfusion assessment could improve risk stratification, and we therefore corrected for HR in the multivariate analysis.

We did not include other methods of peripheral blood flow monitoring, such as cutaneous laser Doppler flowmetry. We previously showed that CRT, PPI and Tskin-diff are well validated methods of estimating cutaneous blood flow¹⁵ and provide a ready to use, simple, cheap instrument at the bedside. Moreover, real-time evaluation of the (subjective) assessment of peripheral perfusion is easily obtainable by using noninvasive monitoring techniques, and it can be rapidly applied throughout the hospital under different circumstances and by different health-care workers.



Conclusions

By simple clinical assessment of peripheral perfusion immediately after surgery, clinicians are able to discriminate patients at high risk for developing severe complications. These findings suggest that assessment of peripheral perfusion can be used for early identification of postoperative patients in need of additional therapy and open a perspective on new (tissue perfusion) goal-directed therapies. Further research designed to confirm these findings, and to explore them in more detail, is needed. Such research needs to be conducted in a powered, randomized, controlled fashion to assess the effects on outcome of a peripheral perfusion targeted resuscitation following major abdominal surgery.

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Evolution of capillary refill
time and the peripheral
perfusion index after septic
shock resuscitation

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7

Abstract

Purpose

Recently, noninvasive assessment of the peripheral perfusion has been shown to be strongly predictive of poor outcome in septic shock patients. The predictive value of the evolution over time of these different peripheral perfusion parameters has however not been studied. To address this matter we evaluated whether repeated assessment of the peripheral perfusion, with parameters readily available at the bedside, could reflect response to initial standard treatment and could predict outcome in septic shock patients.

Materials and Methods

Thirty-five septic patients admitted to the intensive care unit (ICU) undergoing protocolized resuscitation between March and June 2011 were included in this retrospective cohort analysis. Study entry was after initial resuscitation at the ICU at the first day of admission (D0) and on the second day of ICU admission (D1). Peripheral perfusion assessment consisted of the CRT and the peripheral perfusion index (PPI). Abnormal peripheral perfusion was predefined as CRT > 5 seconds, PPI < 1.4 %.

Results

Overall APACHE II score was 25 (1); ICU mortality rate was 40%. Unfavorable evolution of the peripheral perfusion was associated with higher odds ratio for mortality, respectively, OR 7.33 (95% CI 1.53 - 35.11) for CRT and OR 7.65 (95% CI 1.64 - 35.80) for PPI. Generalized mixed model analysis demonstrated that the odds of unfavorable evolution over time were more predictive for mortality compared to a single observation of abnormal peripheral perfusion.

Conclusions

Unfavorable evolution of the peripheral perfusion in the first days following initial resuscitation is strongly predictive of poor outcome in septic shock patients. These results indicate that serial peripheral perfusion assessment could be incorporated as additional target during septic shock resuscitation. Further research is needed to confirm these findings and to explore in more detail the effects of peripheral perfusion targeted resuscitation.

Introduction

Circulatory failure is associated with an impairment in tissue perfusion which can contribute to the development of organ dysfunction. Until recently, adequacy of tissue perfusion

has been determined from systemic hemodynamic variables such as mean arterial pressure, cardiac output, and biochemical variables such as lactate. However, the peripheral circulation is one of the few windows of circulatory dysfunction that is readily available at the bedside in almost every patient.[1]

The rationale of peripheral perfusion monitoring is based on the concept that peripheral tissues are the first to reflect vasoconstriction and hypoperfusion during shock, and the last to reperfuse during resuscitation. In different patient populations we and others have demonstrated that peripheral perfusion assessment enables the identification of patients with unfavorable outcomes.[2-7] The capillary refill time (CRT) [2] and the peripheral perfusion index (PPI) [8] both adequately represent the state of the peripheral circulation. Both parameters are readily available and can easily be obtained at the bedside. Especially in septic shock patients single observations of the peripheral circulation demonstrated that profound alterations are associated with the development of organ failure and poor outcome, independent of initial systemic hemodynamic parameters.[4,9]

These observations however ignore the evolution over time during the course of an Intensive Care Unit (ICU) stay. Although Hernandez et al. nicely demonstrated that early recovery of the peripheral perfusion 24 hours after ICU admission anticipates a successful resuscitation in septic shock patients, they did not analyze trends over time. [10] In fact, to date no study has evaluated patient specific peripheral perfusion changes over time in septic shock patients. This could provide valuable insights about the role of peripheral perfusion as a target for resuscitation to optimize tissue perfusion.

Our aim was therefore to evaluate patient specific peripheral perfusion evolution in septic shock patients following initial standardized resuscitation during the first two days of ICU admission. In particular, we investigated whether unfavorable evolution over time for each individual peripheral perfusion parameter could identify an inadequate response to initial treatment in terms of outcome.



Materials and Methods

Study design, setting, and patient population

We conducted a retrospective observational cohort analysis of prospectively collected data in septic shock patients admitted between March and June 2011 of whom peripheral perfusion measurements were available. The local Institutional Review Board approved the protocol and waived the need for informed consent for an retrospective analysis of an observational study without any specific intervention with parameters already assessed in critically ill patients.

Adult patients with septic shock were considered eligible for study analysis. Septic shock, at ICU admission, was defined according to the most recent International Sepsis guidelines.[11] Patients were included in the analysis if they were hemodynamically stable (mean arterial pressure >65 mm Hg, no change in vasopressor infusion rate for at least

2 hours, and core temperature >35.5 °C) during peripheral perfusion assessment and if peripheral perfusion measurements were available for two consecutive days. Patients with subarachnoid hemorrhage (SAH), stroke in the cerebellum or brainstem, isolated brain trauma, known neuromuscular disease, severe peripheral vascular disease, severe arrhythmias, liver failure, and comatose patients (Glasgow Coma Scale ≥ 7) were excluded.

Hemodynamic management

Systemic hemodynamic resuscitation was guided by our local protocol, adapted from the international Surviving Sepsis Campaign Guidelines.[12,13] In short, patients were equipped with an arterial and central venous catheter if the treating physicians considered it clinically indicated. Hemodynamic support in all patients – including vasopressor therapy (noradrenaline) and volume infusion (repeated fluid challenges with crystalloid or colloid solutions) based on fluid responsiveness – was aimed to maintain HR <100 /minute, MAP ≥ 60 mmHg, central venous pressure of 8 to 12 mmHg, urinary output ≥ 0.5 ml/kg/hour and ScvO₂ $\geq 70\%$. In mechanically ventilated patients arterial blood gas values corrected for temperature were used to adjust the ventilator to maintain PaO₂ between 8.0 and 13.3 kPa and a PaCO₂ between 4.0 and 5.0 kPa.

Data collection and measurements

General characteristics and data on the first (D1) and second (D2) of ICU admission were collected. Peripheral perfusion data were collected once patients were hemodynamically stable at the first and second day of ICU admission, respectively D1 and D2. Simultaneously, different systemic hemodynamic parameters were collected, i.e. heart rate (HR), mean arterial pressure (MAP), and central venous pressure (CVP). If available, data of arterial and central venous blood samples were collected for the determination of hemoglobin saturation, arterial hemoglobin and arterial lactate concentrations (ABL700; Radiometer, Copenhagen, Denmark). Additionally we collected the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Sequential Organ Failure Assessment (SOFA), and ICU mortality to further evaluate outcome.

Peripheral perfusion measurements

Peripheral perfusion was evaluated using a combination of the CRT and the PPI.

CRT is defined as the time required for a distal capillary bed (i.e. the nailbed) to regain its color after pressure has been applied for 15 seconds to cause blanching. The time to return of normal color is standardly measured with a per second analog hospital clock present in every ICU box.(21) A delayed return of normal color (>5 seconds) can be regarded as decreased peripheral perfusion and has been related to tissue hypoperfusion and a greater likelihood of worsening organ failure.[4] A CRT ≥ 15 seconds was accounted as 15 seconds.

The PPI (Masimo SET® pulse oximetry Perfusion Index, Radical 7, Basingstoke, Hants, UK) provides a noninvasive indicator of peripheral vasomotor tone and peripheral perfusion, and is derived from the photo-electric plethysmographic signal of the pulseoximeter, used routinely. A PPI $< 1.4\%$ represent a very sensitive cutoff point for determining abnormal peripheral perfusion related with vasoconstriction. [14]

Statistical analysis

Data is presented as mean (SE), unless otherwise specified. We used a Kolmogorov-Smirnov test to test for normality ($p > 0.05$). We retrospectively divided the patients into survivors and non-survivors and tested differences between group means by Student's t tests or Mann-Whitney U test if not normally distributed. Correlations were computed using Kendall's tau-b formula. Because peripheral perfusion parameters are quantitative results, cutoff values were necessary to discriminate abnormal from normal peripheral perfusion. We therefore used predefined cut-offs for abnormal peripheral perfusion in intensive care unit patients (cut-offs: CRT > 5 seconds, PPI < 1.4%) to evaluate the relationship with outcome.[15]

To evaluate the peripheral perfusion evolution over time and its relationship with outcome, we first determined whether the peripheral perfusion was normal or abnormal (based on cut-offs) per time point for each parameter and subsequently calculated differences between groups. To analyze trends over time for each individual peripheral perfusion parameter (T0–T1), we defined unfavorable peripheral perfusion evolution as a combination of worsening (normal-abnormal) and persistent abnormal (abnormal-abnormal) peripheral perfusion for each individual patient. We then used a generalized linear model procedure to evaluate the predictive value, estimated as odds ratios with 95% confidence intervals, using abnormal peripheral perfusion evolution as binary to predict ICU mortality and organ failure (Δ -SOFA ≥ 0). This multivariate model was confirmed by using the forward stepwise selection. We selected the variables based on differences between groups and on previous reports on prognosticating factors of peripheral perfusion.[4,16] We therefore corrected for SOFA admission, MAP and HR.

A p value < .05 was considered statistically significant. We used SPSS (version 20.0, SPSS, IBM, Chicago, IL) for statistical analysis.



Results

During the study period, 154 patients had documented peripheral perfusion assessment of whom 146 had subsequent peripheral perfusion assessment. Of these patients, thirty-five patients had septic shock. Of this cohort, 14 patients (40%) died during their ICU stay. Clinical characteristics of the patients are presented in Table 1. The mean SOFA score on admission was mean, SE: 11 (1), obviously, SOFA score was significantly higher in the non-survivors compared to the survivors. All patients were treated with norepinephrine at the time of peripheral perfusion assessment on the first day of admission (mean vasopressor dose 0.30(0.06) $\mu\text{g}/\text{kg}/\text{min}$). There was no overall difference in vasopressor dosage used between survivors and non-survivors (Table 2).

Systemic and peripheral perfusion parameters

Systemic hemodynamic and biochemical variables are presented in Table 2. On both days of ICU stay, there was no difference in the systemic hemodynamic and biochemical parameters between survivors and non-survivors.

Table 1. Demographic characteristics

	All (n=35)	Survivors (n=21)	Nonsurvivors (n=14)
Age, years	61 (2)	58 (3)	66 (4)
Gender, [Male; n (%)]	24 (69)	12 (50)	12 (50)
Acute Physiology and Chronic Health Evaluation II	25 (1)	23 (1)	28 (2)
Sequential Organ Failure Assessment score at admission	11 (1)	10 (1)	13 (1)*
Length of Intensive Care Unit stay, days	12 (2)	10 (2)	16 (3)
Admission category			
Source of sepsis	21 Abdomen 10 Lung 2 Urinary tract 2 Primary bacteremia		

Data is presented as mean (SE) unless otherwise stated.

Both CRT and PPI were not significantly different in the non-survivors compared to the survivors at D1. However at D2, both CRT and PPI were significantly different in the non-survivors compared to the survivors ($P = 0.005$). Interestingly, mean CRT did not exceed the clinical cut-off for abnormality (>5 seconds) in the survivors. Additionally, CRT exceeded the clinical cut-off for an abnormal capillary refill time (>5 seconds) on this day in the non-survivors. The same accounted for the PPI, which exceeded the clinical cut-off for abnormality (<1.4) in non-survivors in contrast to the survivors whom had a normal PPI.

Peripheral perfusion to predict outcome

We performed a generalized linear mixed-model analysis to explore the association of abnormal peripheral perfusion with outcomes. Both abnormal CRT and abnormal PPI on D1 were not predictive for either organ dysfunction or for ICU mortality. However regarding the evolution over time for each independent parameter, unfavorable evolution was found to have a major predictive value for outcome (Table 3). Patients with unfavorable evolution over time (day 1 vs day2) were roundabout seven to eight times more likely to die compared to patients with a favorable evolution. Additionally, generalized linear model analysis showed that the odds ratio for progressive organ failure (Δ -SOFA ≥ 0) was 4.74 ((1.14–5.87 ; $p = 0.03$) for CRT) times higher for a patient with abnormal peripheral perfusion than for a patient with normal peripheral perfusion at T0, independent of systemic hemodynamics and vasopressor therapy. Contrastingly, changes of PPI over time were not associated with progressive organ failure.

We also analyzed correlations between peripheral perfusion and systemic hemodynamics. CRT did not correlate with any systemic hemodynamic or biochemical parameter. In contrast, we observed a weak correlation between unfavorable PPI evolution and arterial lactate level ($r=0.32$, $p=0.03$). There was no significant correlation between PPI and systemic hemodynamics.

Table 2. Systemic hemodynamic and peripheral perfusion parameters

	D1		D2	
	Survivors	Nonsurvivors	Survivors	Nonsurvivors
Systemic hemodynamic and biochemical parameters				
Central temperature (°C)	37.0 (0.2)	37.0 (0.2)	37.0 (0.1)	37.0 (0.2)
Heart rate (bpm)	101 (5)	101 (8)	101 (5)	98 (6)
Mean arterial pressure (mmHg)	76 (4)	69 (2)	79 (3)	77 (11)
Central venous pressure (mmHg)	14 (2)	18 (7)	15 (3)	15 (4)
ScvO ₂ (%)	74 (4)	74 (2)	75 (3)	73 (4)
Lactate (mmol/L)	2.9 (0.6)	3.6 (0.9)	1.7(0.2)	4.5 (1.9)
Hemoglobin	7.0 (0.3)	6.4 (0.4)	6.0 (0.3)	5.9 (0.4)
Vasopressor use, n (%)	16 (55)	13 (45)	11 (55)	9 (45)
Vasopressor dose, µg/kg/min ^a	0.30 (0.09)	0.30 (0.08)	0.18 (0.09)	0.44 (0.17)
Peripheral perfusion parameters				
CRT	6.7 (1.2)	9.0 (1.8)	4.5 (0.6)	9.8 (1.4)*
PPI	2.9 (0.6)	2.0 (0.6)	3.2 (0.6)	1.4 (0.4)*

D1, first day of ICU admission; D2, second day of ICU admission; Survivors (n = 21 ; Nonsurvivors (n = 14); CRT, capillary refill time; PPI, peripheral perfusion index.

* $P < .05$, between groups (survivors and nonsurvivors) in the specific time point, using the students T-test or Chi-square test.

^avasopressor use (norepinephrine or epinephrine) at the time of peripheral perfusion assessment.



Discussion

The main finding of the present study is that unfavorable evolution of the peripheral perfusion following initial resuscitation is independently associated with poor outcome in septic shock patients. Interestingly, these peripheral perfusion alterations are independent of initial systemic hemodynamic resuscitation goals.

Recently several studies addressed the importance of peripheral perfusion assessment in septic shock patients. In a large database study, de Backer et al [9] demonstrated that sublingual microcirculatory alterations are stronger predictors of outcome than global hemodynamic variables in septic shock patients. Additionally non-invasive bedside parameters of peripheral perfusion demonstrated to have a similar predictive power for mortality, as sublingual microcirculatory assessment.[6] In septic shock patients, impaired peripheral perfusion demonstrated to be predictive of mortality after systemic hemodynamic resuscitation.[2,17,18] The main difference between the previous studies and the current study is the focus on patient specific dynamic peripheral perfusion changes over time after initial guideline targeted resuscitation.

We found that serial assessment of peripheral perfusion, i.e. unfavorable evolution of both CRT and PPI, was more predictive for mortality when compared to a single assessment of peripheral perfusion at the first or second day of

Table 3. Sequential peripheral perfusion parameters as predictor of mortality

D1		
A	Odds Ratio	(95% CI)
CRT	1.83	0.38 – 8.78
PPI	2.95	0.72 – 11.91
D2		
B	Odds Ratio	(95% CI)
CRT	5.96	1.26 – 28.10
PPI	5.76	1.31 – 25.42
Unfavorable evolution over time		
C	Odds Ratio	(95% CI)
CRT	7.33	1.53 -35.11
PPI	7.65	1.64 – 35.80

D1, first day of ICU admission; D2, second day of ICU admission; CRT, capillary refill time; PPI, peripheral perfusion index. Odds ratios are calculated using generalized mixed model analysis (see material and methods).

admission. Surprisingly, despite the current questions raised about the clinical utility of CRT, CRT assessment is reliable in septic shock patients and unfavorable CRT evolution was, besides ICU mortality, also predictive for progressive organ failure.[2] CRT has gained widespread acceptance as one of the strongest red flags to identify infection and tissue hypoperfusion in pediatric patients and interest is recently shifted to determine its usefulness in critically adult patients [19,20].

A recent study by He et al.[18] showed that a single measurement of lower PPI was associated with increased ICU mortality in septic patients after resuscitation. In addition to their study we demonstrated that unfavorable evolution of PPI is independently associated with increased odds to die. In contrast to their findings, we however did not find a predictive value for mortality of a single assessment of PPI at T0. This could be due to differences in study design and sample size. Nevertheless our patient population was sufficient to highlight significant results and therefore the probability of a type I error is fairly low independent of the included number of patients. One can also argue that this difference could be due to the use of different cut-off values for abnormality: they used a cut-off of 0.2 to distinguish between survivors and nonsurvivors, whereas we used a previously defined cut-off of 1.4 to define abnormality. Interestingly, they reported a similar cut off to discern critically ill patients (mean PPI: 1.4 ± 1.4) from non-critically ill patients (mean PPI: 2.6 ± 0.7).

We found a significant but weak negative correlation between PPI and the arterial lactate level. In addition, He et al [18] also reported an association between abnormal peripheral perfusion and hyperlactatemia. The correlation between hyperlactatemia and

abnormal PPI in our patients is not surprising, as hyperlactatemia in sepsis is associated with the presence of organ dysfunction and poor outcome. Interestingly we found no correlation between systemic hemodynamics and peripheral perfusion. It could be hypothesized that the combination of hyperlactatemia and abnormal peripheral perfusion following resuscitation is a reflection of (persistent) occult hypoperfusion [21]. Noninvasive bedside assessment of the peripheral perfusion could therefore provide the clinician with important additional information during and after initial resuscitation.

Despite the clinical evidence of the additional value of peripheral perfusion, the place of these parameters in resuscitation is still not clear. Although recovery of the peripheral perfusion during initial resuscitation is associated with improved outcome and worsening thereafter is associated with poor outcome[5,10]currently, goal directed hemodynamic resuscitation is still solely aimed at conventional systemic hemodynamic parameters.[13,22]. It can be hypothesized that peripheral perfusion measurements during resuscitation could provide an additional window to monitor and treat occult hypoperfusion, as assessment of peripheral perfusion during resuscitation has the potential to optimize vasomotor tone, microcirculatory alterations, and as such resuscitation procedures.[6] One next logical step would be to study the capability of peripheral perfusion as a target of resuscitation, to strive towards a more tissue perfusion-based approach [20,22].

This study has some limitations. First, we defined abnormal evolution as a combination of persistent abnormal peripheral perfusion and peripheral perfusion that evolved from normal to abnormal over 24 hours. Due to the small sample size, calculations of odds ratios for each individual course was not possible. Further research is indicated to investigate which individual course has the highest predictive value for poor outcome. Second, measurements of global blood flow (cardiac output) were not made in this study. Recent studies have however shown that peripheral perfusion alterations persist, even when systemic hemodynamics are resuscitated to satisfactory goals [15,23]. Third, observations were made in a single center and do not truly represent care across other centers. However initial resuscitation was guided by our local protocol, adapted from international guidelines and represent current national and international care.

In conclusion, serial evaluation of the peripheral perfusion during the first two days of ICU admission has profound implications on outcome in septic shock patients. Unfavorable evolution of the peripheral perfusion, following initial systemic hemodynamic optimization, is associated with progressive organ failure and higher odds to die. These findings add important knowledge to the discussion whether or not we should focus on a more tissue perfusion based fluid resuscitation approach.

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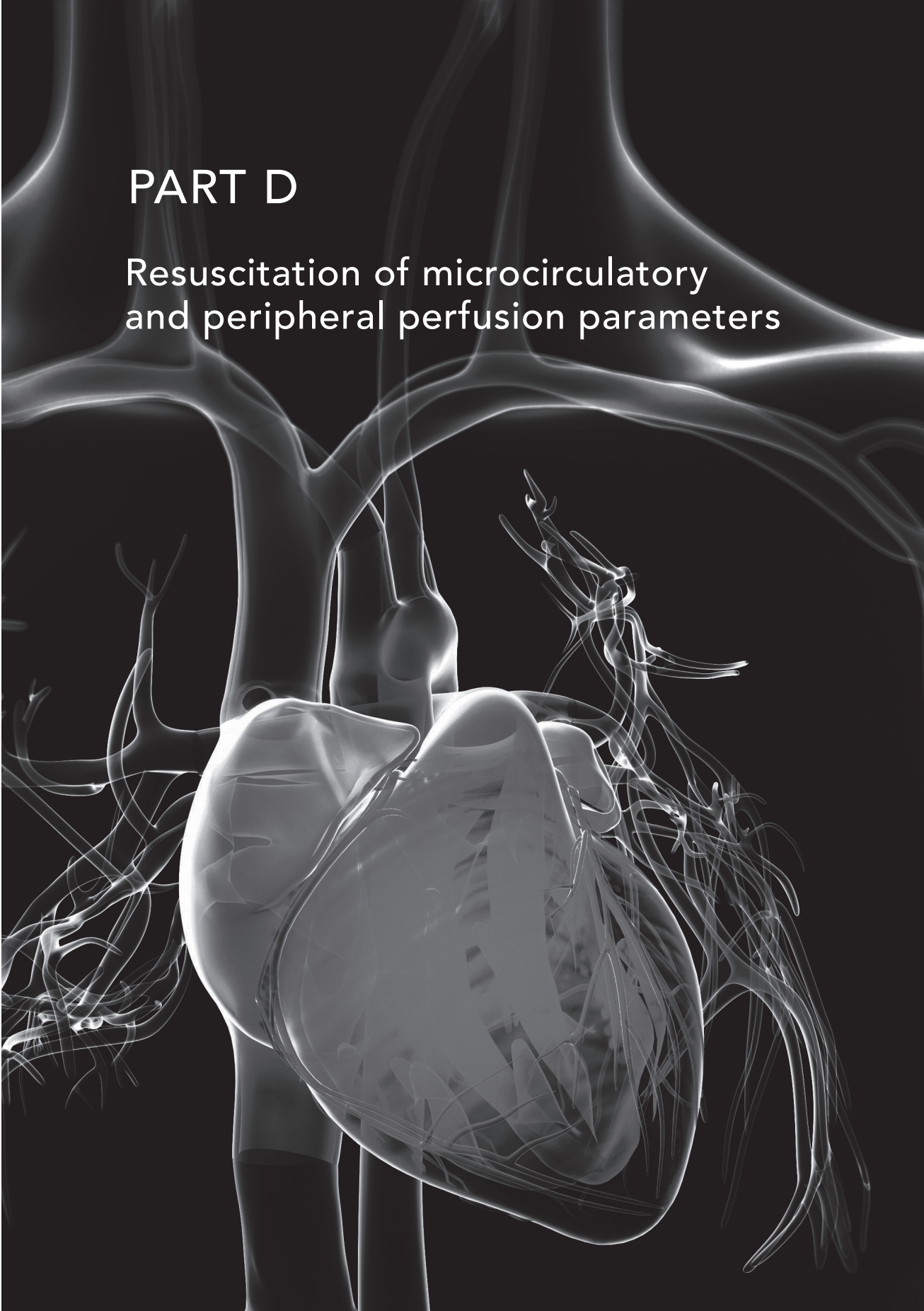
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PART D

Resuscitation of microcirculatory and peripheral perfusion parameters

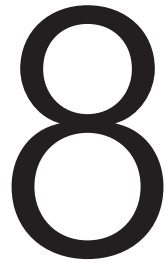


Postoperative sublingual
microcirculatory derangement
following esophagectomy
is prevented with dobutamine

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Abstract

Introduction

Esophagectomy with gastric tube reconstruction is characterized by high postoperative morbidity rates. Recently it was shown that decreased sublingual microvascular blood flow (MBF) preoperatively was associated with increased rate of complications after abdominal surgery. Similar observations in severely septic patients could be treated with dobutamine, independent of cardiac output. Based on these considerations we hypothesized that sublingual MBF derangements are more likely to be found in patients undergoing high risk surgery such as esophagectomy, and if present, might be prevented with administration of low dose dobutamine.

Methods

In this single-centre, prospective, double-blinded study, we randomized 20 patients admitted to the Intensive Care Unit following esophagectomy with gastric tube reconstruction into two groups. The intervention group (D) received a small dose of dobutamine (2.5 µg/kg/min) directly postoperative until two days postoperatively, whereas the placebo group (P) received a similar volume of saline. A subset of patients undergoing pancreaticoduodenectomy surgery was included as control group (C) for comparison with the study group. Sublingual MBF was determined one day prior to surgery until two days postoperatively.

Results

At the first postoperative day, patients in the esophagectomy/placebo group (P), showed a significant lower microvascular flow index, perfused vessel density and proportion of perfused vessels compared to baseline ($p < 0.001$) and the pancreaticoduodenectomy group (C) ($p < 0.001$). Administration of dobutamine significantly prevented the overall decrease in microvascular blood flow the first postoperative day.

Conclusion

Postoperative sublingual MBF is markedly impaired in esophagectomy patients compared to patients who underwent a pancreaticoduodenectomy and could be prevented by early administration of a small dose dobutamine.

Introduction

Esophagectomy with gastric tube reconstruction remains the most successful therapy for esophageal cancer, but is still associated with high morbidity rates. Typical surgical complications are leakage and stenosis of the cervical anastomosis, which have been attributed to decreased gastric tissue blood flow.^{1,2} Recently, we have demonstrated that decreased gastric tube tissue blood flow could be improved with topical administration of nitroglycerin, but not with a low dose of intravenous nitroglycerine.^{3,4}

Recently, Jhanji and coworkers have shown that preoperative impairments in sublingual microvascular blood flow (MBF) in patients who underwent major abdominal surgery, were associated with the occurrence of postoperative complications independent from global hemodynamic parameters.⁵ Similar changes in sublingual MBF (i.e. obstructed, stagnant blood flow in the smallest capillaries with near to normal flow in the larger microvessels) have been observed in septic patients, and were also associated with poor outcome.^{6,7} Administration of dobutamine in these septic patients was able to improve sublingual MBF independent of outcome, and again independent from systemic hemodynamic parameters.⁸

Based on these considerations we hypothesized that similar sublingual MBF derangements are more likely to be found in patients undergoing high risk surgery such as esophagectomy, and if present, might be prevented with administration of low dose dobutamine.

Material and methods

After receiving approval of the local institutional human review board, and after obtaining written informed consent from every patient, this study was conducted. The study was officially registered as a clinical trial (NTR2279, 10-apr-2010–22-apr-2010).

This was a single-centre, prospective, double-blinded study, conducted in the adult intensive care unit (ICU) at Erasmus Medical Centre, Rotterdam. Between March and June 2010, patients who underwent esophagectomy with gastric tube reconstruction were included. All patients were postoperatively admitted to the mixed ICU and were in physical status I and II, according to the American Society of Anesthesiologists classification.⁹ Previous cardiac events, diabetes mellitus and drug abuse were contraindications for enrollment.

Furthermore, one subset of patients was included as control group for comparison with the study group on the days pre- and postoperatively (group C). These patients underwent a pancreaticoduodenectomy, according to the Whipple procedure and were postoperatively admitted to the post anesthetic care unit.

Protocol

After the initial surgical procedure with the gastric tube reconstruction, patients were directly admitted to the ICU. By protocol, patients were randomly assigned, in a 1 : 1 ratio, to receive either a low dose of dobutamine directly after admission at the ICU (2.5 µg/kg/min) (group D) or a placebo (2.5 µg/kg/min of isotonic saline; Group P)



according to a computer-generated random list. To ensure masking of treatment allocation during the SDF measurements, patients randomly assigned to the placebo group were given a similar volume of saline. To make sure that the investigator was not aware of the randomization of each patient, both study infusions were prepared as identical syringes by a research nurse who was not involved in the measurements. A subset of patients undergoing pancreaticoduodenectomy surgery was included as control group (C). Age, gender, ICU-days, complications and systemic hemodynamic data during ICU stay were documented.

Anesthesia and surgery

In all patients, general anesthesia was standardized and consisted of a combination of propofol, sufentanil and rocuroniumbromide for induction and isoflurane for maintenance of anesthesia. Before induction of general anesthesia, a thoracic epidural catheter was placed to provide perioperative and postoperative analgesia. Epidural blockade started with a bolus of ropivacaine before the operation, followed by continuous administration of a mixture of ropivacaine and fentanyl after 90 minutes. Standard hemodynamic monitoring consisted of continuous arterial blood pressure and right atrial pressure. The attending physicians administered intravenous fluids and vasoactive medication in order to maintain blood pressure, right atrial pressure, heart rate and urine output within the normal range. If necessary, measures were taken to ensure adequate oxygenation, body temperature and hemoglobin levels. Following surgery, all patients were transferred to the ICU or to the post anesthetic care unit.

Esophagectomy was performed either through a transthoracic or a transhiatal approach. Although these methods differ, the construction of the gastric tube was similar and performed by the same surgical team according to the classical method.^{10,11} Another surgical team was responsible for all pancreaticoduodenectomy surgeries, which was carried out according to the standard method described by Whipple.¹²

Microvascular measurements

Sublingual MBF was performed at four time points, the day before surgery (BL), directly postoperative (T0), and on the first and second day after surgery (T1 and T2 respectively), using the SDF imager. The SDF technique, as described in detail by Goedhart et al.¹³ is a technique that allows observation of the human microcirculation at the bedside. In short, after removal of saliva and other secretions with a sponge, the device was applied without pressure on the lateral side of the tongue. If a good image (adequate focus and contrast adjustment) was seen on the screen, sequences of 20 seconds from five adjacent areas were recorded. Due to heterogeneity of flow of microvascular alterations, images were made for a total of 5 different sublingual areas. Hereafter, images were randomly assigned for the evaluating investigator; analysis was performed using the semiquantitative method described in international guidelines.¹⁴ All microvascular scores were calculated for two different vessel cohorts, divided as medium and large (> 20 μm , mainly venules) and small vessels (\leq 20 μm , mainly capillaries). Microvascular flow index (MFI) was calculated after dividing each image

into four equal quadrants. Quantification of flow was determined using an ordinal scale (0, no flow; 1, intermittent flow; 2, sluggish flow; 3, normal flow). MFI is the average score of all quadrants for a given time point. The vascular density (VD; defined as the number of vessels containing red blood cells independent of flow) was calculated as the number of vessels crossing the lines divided by the total grid length (mm). Vessel perfusion (PPV; defined as the proportion of perfused vessels) was calculated as the number of vessels continuously perfused during this period, divided by the total number of vessels of the same type. This score is based on the determination of the predominant type flow in 4 quadrants. Finally, perfused vessel density (PVD) was calculated by measuring total length of perfused vessels divided by the image area.

SDF-imaging was performed according to the described guidelines.¹⁴ This analysis score has been validated previously with an inter- and intra-observer variability of around 5%.^{15,16} Analysis was performed using the MAS analysis system (MicroVision Medical; Amsterdam, The Netherlands 2007, v3.0). SDF-images were randomized for all groups by computer-generated random sequence, so analysis was blind for the evaluating investigator.

Statistical analysis

Data are shown as mean \pm SD. For evaluating changes over time between groups, two way repeated measures analysis of variance (ANOVA) was used. Post hoc two sided Student's t tests were performed at the different time points using the Bonferroni correction for multiple testing. Analysis was performed using GraphPad Prism version 3.0 (GraphPad Software, San Diego, USA). P values $<$ 0.05 were considered statistically significant.

Results

Baseline characteristics and physiological variables between the study groups were comparable (Tables 1 and 2). All postoperative esophagectomy patients were mechanically ventilated directly after surgery, normally followed by extubation at the first postoperative day by protocol. All control patients were extubated prior to admission to the post anesthetic care unit. Mean arterial blood pressure, heart rate



Table 1. Patient characteristics

	D (n = 10)	P (n = 10)	C (n = 10)
Male/female (n)	8/2	8/2	7/3
Age (years)	66 \pm 6	62 \pm 9	67 \pm 11
Bodyweight (kg)	81 \pm 10	82 \pm 21	74 \pm 29
Length (cm)	176 \pm 10	176 \pm 8	167 \pm 10
Fluid balance during operation or ICU stay or both (L)	3.2 \pm 2.0	3.8 \pm 1.3	3.1 \pm 2.4
Operation time (min)	409 \pm 88	416 \pm 63	365 \pm 85

D, esophagectomy patients with dobutamine; P, esophagectomy patients with placebo; C, pancreaticoduodenectomy/control patients.

Table 2. Physiological variables

Parameter	Group	Time point		
		T0	T1	T2
MAP (mmHg)	D	80 ± 10	84 ± 19	82 ± 15
	P	75 ± 11	88 ± 17	94 ± 18
	C	72 ± 7	79 ± 16	80 ± 10
HR (beats/min)	D	85 ± 13	76 ± 10	78 ± 12
	P	82 ± 12	86 ± 13	90 ± 12
	C	80 ± 24	81 ± 15	82 ± 9
SaO ₂ (%)	D	99 ± 1	97 ± 2	97 ± 2
	P	99 ± 1	98 ± 2	96 ± 4
	C	99 ± 1	96 ± 4	99 ± 0
PaO ₂ (kPa)	D	19 ± 4	12 ± 5	10 ± 3
	P	17 ± 4	11 ± 4	11 ± 2
	C	19 ± 5	12 ± 4	18 ± 2
Hb (mmol/L)	D	6.8 ± 0.8	6.8 ± 0.9	6.2 ± 0.8
	P	7.3 ± 0.9	7.3 ± 0.8	6.6 ± 1.1
	C	6.9 ± 1.2	7.1 ± 1.1	6.8 ± 1.0
Lactate (mEq/L)	D	1.5 ± 0.8	1.1 ± 0.2	0.9 ± 0.3
	P	1.5 ± 0.6	1.1 ± 0.3	1.0 ± 0.3
	C	1.4 ± 1.0	1.0 ± 0.3	1.0 ± 0.3
Norepinephrine (no. pts)	D	5	5	1
	P	5	5	1
	C	0	0	0

D, esophagectomy patients with dobutamine; P, esophagectomy patients with placebo; C, pancreaticoduodenectomy/control patients.

and blood lactate concentrations were similar and did not change significantly in either group during the postoperative stay.

At the first postoperative day, patients in the placebo group (P) showed a significant decrease in microvascular flowindex, perfused vessel density and proportion of perfused vessels compared to baseline ($p < 0.001$). These parameters were significantly lower compared to the dobutamine (D) ($p < 0.001$) and to the control group (C) ($p < 0.001$) (Table 3). Despite these derangements in microvascular parameters at the first postoperative day, at the second postoperative day most of the parameters recovered. Perfused vessel density was the only parameter which was not yet recovered at the second postoperative day.

Table 3. Effects on microcirculatory perfusion (n = 30)

		Sublingual small vessels (<20 μ m)			
Parameter	Group	Time point			
		Baseline (T-1)	T0	T1	T2
VD (n/mm ²)	D	11.74 \pm 1.43	11.17 \pm 0.72	11.56 \pm 0.43	11.10 \pm 0.88
	P	11.51 \pm 0.47	10.73 \pm 1.45	10.77 \pm 1.20	10.71 \pm 1.44 ^C
	C	12.25 \pm 2.55	11.45 \pm 1.57	11.62 \pm 1.84	12.10 \pm 1.03
PPV %	D	100 \pm 0	99 \pm 1	99 \pm 1	100 \pm 0
	P	100 \pm 0	97 \pm 1	68 \pm 8 ^{A, D, E}	98 \pm 2
	C	100 \pm 0	97 \pm 2	99 \pm 1	100 \pm 0
PVD (n/mm ²)	D	11.74 \pm 1.43	11.13 \pm 0.72	11.83 \pm 0.47	11.37 \pm 0.86
	P	11.51 \pm 0.47	10.45 \pm 1.33	7.42 \pm 1.50 ^{A, D, E}	8.84 \pm 1.56 ^{A, D, E}
	C	12.06 \pm 2.02	11.07 \pm 1.37	11.49 \pm 1.85	12.68 \pm 0.97
MFI	D	2,94 \pm 0,09	2,91 \pm 0,12	2,80 \pm 0,20	2,90 \pm 0,12
	P	2,97 \pm 0,04	2,89 \pm 0,12	1,52 \pm 0,56 ^{A, D, E}	2,74 \pm 0,15
	C	2,97 \pm 0,06	2,91 \pm 0,09	2,88 \pm 0,16	2,96 \pm 0,07

D, esophagectomy patients with dobutamine; P, esophagectomy patients with placebo; C, pancreaticoduodenectomy/control patients; VD, vascular density; PPV, proportion perfused vessels; PVD, perfused vessel density; MFI, microvascular flow index.

^A: P<0.05 vs. baseline, ^B: P<0.05 vs. C, ^C: P<0.05 vs. D, ^D: P<0.001 vs. D, ^E: P<0.001 vs. C.

Administration of dobutamine significantly prevented the overall decrease in microvascular blood flow the first postoperative day. Compared to the placebo group the dobutamine group had a higher proportion of perfused vessels (p < 0.001) (Fig. 1A), perfused vessel density (p < 0.001) (Fig. 1B) and microvascular flow index (p < 0.001) (Fig. 1C) at the first postoperative day.

All venules (vessels > 20 μ m) showed no change in perfusion nor density, independent of the time point, and were not affected by dobutamine administration. Parameters of sublingual MBF were not related to systemic hemodynamic parameters, at baseline or after dobutamine administration (data not shown).

Discussion

The principle finding of the present study is that in esophagectomy patients sublingual MBF was markedly impaired compared to patients who underwent a pancreaticoduodenectomy. In addition, early administration of a low dose of dobutamine could prevent this overall microvascular impairment in patients undergoing esophagectomy with gastric tube reconstruction.

Our findings are consistent with the results of a previous study that observed impairment of microvascular blood flow during gastrointestinal surgery and that this



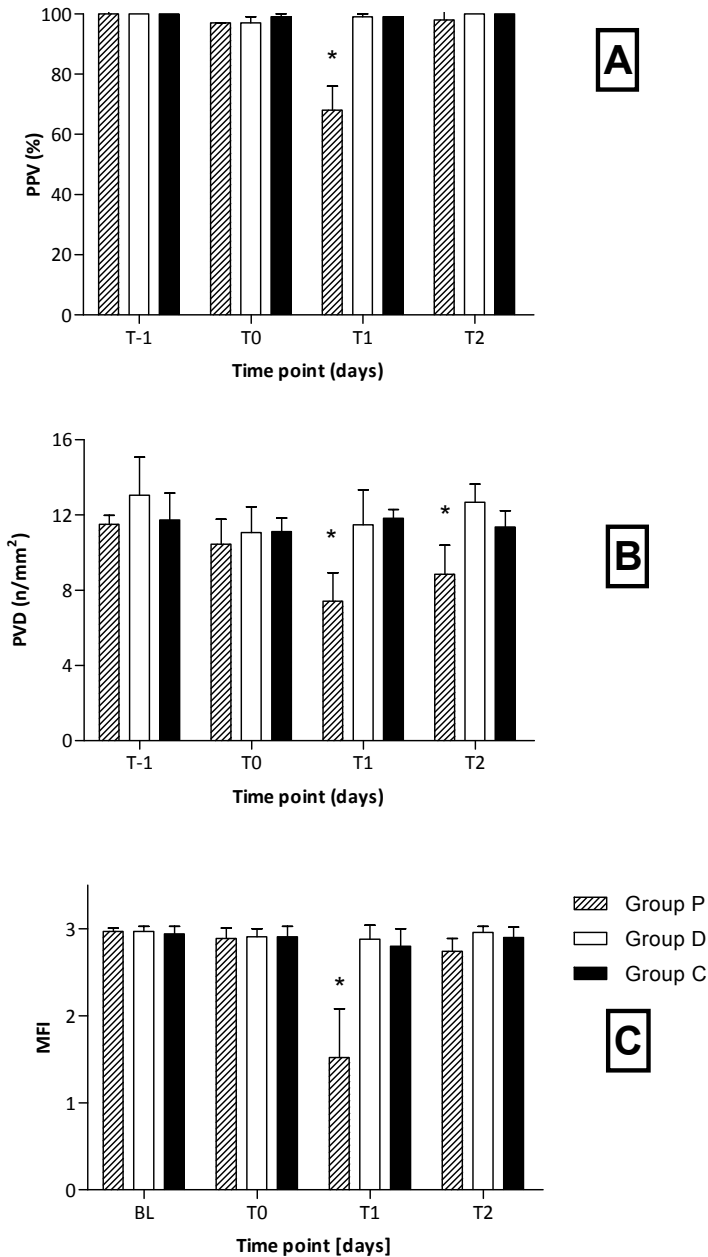


Figure 1. A: Proportion of perfused vessels (PPV) is expressed as percentage and is calculated as the number of vessels continuously perfused divided by the total number of vessels of the same type. **B:** Perfused vessel density (PVD) is expressed as the number of vessels per square millimeter and is calculated as; $VD \times PPV$. **C:** Bar plot of microvascular flow index (MFI) of small vessels ($<20 \mu m$) at BL, directly postoperative (T0) until 2 days postoperatively (T1, T2). Group C, pancreaduodenectomy group; Group P, placebo group; Group D, dobutamine group. All Values are expressed as mean \pm SD, * $p < 0.001$

was associated with an increased incidence of postoperative complications. In patients undergoing colorectal cancer surgery, intraoperative MBF reduction at the rectal stump was associated with an increased risk of anastomotic leak.¹⁷ In patients undergoing thoracic esophagectomy, decreased tissue blood flow of the gastric tube during the intraoperative period was associated with more postoperative anastomotic insufficiency.¹⁸

It has been suggested that adequate perioperative global oxygen delivery might play an important role in anastomotic healing. Although this has yet to be demonstrated, it is well established that high-risk surgical patients,¹⁹ especially esophagectomy patients,^{20,21} who fail to mount an postoperative adequate global oxygen delivery will more frequently develop postoperative complications. Additionally, a number of investigators have described abnormalities in gastro-intestinal mucosal blood flow in patients who developed postoperative complications, associated with an increased incidence of anastomotic leakage following esophagectomy.¹⁸

Recently, Sakr et al.⁶ demonstrated that microcirculatory alterations were present in patients with septic shock, which is also a profound pro-inflammatory state, and that persistence of these alterations was associated with organ dysfunction and death. It has been shown that the stress-response after esophagectomy with gastric tube reconstruction is also profound.²² Although it can be assumed that in our postoperative patients the stress response was less severe than in septic shock patients, there could be a role for a low dose of dobutamine in order to prevent the impairment of sublingual MBF.

A recent report about the effects of dobutamine in septic shock on microcirculatory alterations, independent of systemic hemodynamic changes, seems to be in accordance with our presented data.⁸ On the first postoperative day, sublingual MBF was recruited by a small dose of dobutamine independent of systemic hemodynamic values. Whether this is a true effect due to recruitment itself, or a net result of a complex of therapeutic interventions, remains to be established. Our observation provides however additional confirmation on the beneficial effects of dobutamine on microvascular perfusion, not only in sepsis but also following high-risk surgery with a severe inflammatory response. Although we did not determined cardiac output, several studies have already shown that microvascular alterations are present during sepsis, regardless of cardiac output^{6,23} and other systemic hemodynamic variables.²⁴ In surgical patients the occurrence of decreased sublingual MBF and its relation to complications were also shown to be independent of blood pressure and cardiac output.^{5,25}



Conclusion

Dobutamine was able to prevent the microvascular disturbances observed in the first two days postoperatively after esophagectomy surgery. These disturbances were not seen after other large abdominal surgery, i.e. pancreateoduodenectomy. Further research is warranted to establish the clinical effects of these microvascular derangements after high risk surgery and whether preventing this with dobutamine could decrease complication rate and improve clinical outcome.

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Microvascular perfusion as a target for fluid resuscitation in experimental circulatory shock

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The right target at the right time: the microcirculation in
circulatory shock.

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Abstract

Objective

To study regional perfusion during experimental endotoxemic and obstructive shock and compare the effect of initial cardiac output-targeted fluid resuscitation with optimal cardiac output-targeted resuscitation on different peripheral tissues.

Design

Controlled experimental study.

Setting

University-affiliated research laboratory.

Subjects

Fourteen fasted anesthetized mechanically ventilated domestic pigs.

Interventions

Domestic pigs were randomly assigned to the endotoxemic ($n = 7$) or obstructive shock ($n = 7$) model. Central and regional perfusion parameters were obtained at baseline, during greater than or equal to 50% reduction of cardiac output (T1), after initial resuscitation to baseline (T2), and after optimization of cardiac output (T3).

Measurements and Main Results

Regional perfusion was assessed in the sublingual, intestinal, and muscle vascular beds at the different time points and included visualization of the microcirculation, measurement of tissue oxygenation, and indirect assessments of peripheral skin perfusion. Hypodynamic shock (T1) simultaneously decreased all regional perfusion variables in both models. In the obstructive model, these variables returned to baseline levels at T2 and remained in this range after T3, similar to cardiac output. In the endotoxemic model, however, the different regional perfusion variables were only normalized at T3 associated with the hyperdynamic state at this point. The magnitude of changes over time between the different vascular beds was similar in both models, but the endotoxemic model displayed greater heterogeneity between tissues.

Conclusions

This study demonstrates that the relationship between the systemic and regional perfusion is dependent on the underlying cause of circulatory shock. Further research will have to demonstrate whether different microvascular perfusion variables can be used as additional resuscitation endpoints.

Introduction

Systemic hemodynamic variables, such as blood pressure, heart rate, and cardiac output, are routinely used as indicators of shock severity and target for intervention. Accordingly, it is well known that inadequate systemic circulation in hypodynamic and hyperdynamic shock states may also be accompanied by impaired tissue perfusion.¹ Especially in septic shock, impaired vasomotor tone and the disturbed regulation of regional tissue perfusion lead to microcirculatory dysfunction and a regional mismatch of tissue oxygenation.^{2,3} Even when systemic hemodynamics are normalized, microcirculatory alterations can be present and may impair tissue perfusion and oxygenation.⁴ Monitoring of regional tissue perfusion is therefore of prime importance to assess the adequacy of resuscitation. The development of new techniques that directly visualize the microcirculation,⁵ measure tissue oxygenation (Sto_2),⁶ or determine peripheral perfusion⁷ has improved the evaluation of the effect of various hemodynamic interventions in different peripheral tissues. The current Surviving Sepsis Campaign guidelines recommend early structured resuscitation that targets systemic hemodynamic variables, which underscores the importance of the early identification and resuscitation of tissue perfusion alterations.⁸ Although early fluid resuscitation protocols have been demonstrated to improve outcomes in patients with severe sepsis,⁹⁻¹¹ still little is known about the use of regional tissue perfusion variables as a direct target for resuscitation. This is remarkable because microcirculatory abnormalities are more prevalent in nonsurvivors after circulatory shock due to cardiac arrest,¹² following cardiogenic shock,¹³ and after septic shock.¹⁴ Because these abnormalities recover over time only in survivors,¹⁵ the question rises if early optimization of circulatory conditions (i.e., cardiac output) could exert a beneficial effect on microvascular perfusion. This is supported by the positive effects of early goal-directed therapy on outcome in acute sepsis patients¹⁶ However, it is as yet unknown whether microvascular perfusion abnormalities in the early phase of circulatory shock are caused by relatively insufficient systemic hemodynamic resuscitation or by local microvascular pathology. For this purpose, we examined the effect of cardiac output resuscitation on different microvascular perfusion and peripheral perfusion variables during different endotoxemic and obstructive shock states. We hypothesized that only in endotoxemic shock, microvascular and peripheral perfusion abnormalities would persist after the resuscitation of systemic hemodynamics to preshock levels and that these abnormalities would be remedied with additional resuscitation of cardiac output in a different magnitude for the different peripheral tissues and the different regional perfusion variables.



Material and methods

The local animal experimental committee approved these studies in accordance with the National Guidelines for Animal Care and Handling. Fourteen female pigs (Yorkshire, Landrace or Durok) with a mean body weight \pm SD of 30.2 ± 2.1 kg were included in our study.

Animal preparation

Animals were fasted overnight with free access to water and premedicated with intramuscular ketamine (30 mg/kg) and midazolam (1 mg/kg). IV access was obtained by cannulation of an ear vein. Anesthesia was maintained with a combination of IV midazolam (0.2 mg/kg bolus followed by 0.3 mg/kg/hr) and propofol (2 mg/kg/hr). Analgesia was provided with continuous administration of fentanyl (20 µg/kg/hr) and supplemented with bolus doses (20–50 µg) when needed. Muscle relaxation was obtained with pancuronium bromide (0.1 mg/kg bolus followed by 0.2 mg/kg/hr).

Through a midline cervical tracheostomy, an endotracheal tube (9.0F) was placed in the trachea. Ventilation was performed in a volume-controlled mode (Servo 300; Siemens-Eléma, Solna, Sweden) with a minimal oxygen-in-air fraction of 0.40, frequency adjusted to achieve normocapnia, and a positive end-expiratory pressure of 5 cm H₂O to prevent atelectasis. Core temperature was monitored by the thermistor at the tip of the pulmonary artery catheter and was maintained at approximately 37°C with a heating pad or external cooling if necessary. Normoglycemia (arterial blood glucose level 4.5–7 mmol/L) was maintained throughout the whole experiment using 20% glucose infusion as needed.

Catheters were placed in the right carotid artery to measure arterial blood pressure and collect arterial blood samples and in the right jugular vein to administer fluid. A pulmonary artery thermodilution catheter (Edwards Lifesciences, Irvine, CA) was positioned in the pulmonary artery. With the pig in supine position, a urinary catheter was placed into the bladder for drainage of urine. In the animals randomized to the obstructive shock group, the pericardial sac was accessed through the midline incision, after removal of the xiphoid. After making a small opening in the pericardium, a purse-string suture was placed with polydioxanone 4.0 and a 8.0F tube. Urinary catheter was inserted in the pericardium. The purse-string suture was knotted watertight, fixing the catheter to the pericardium. When all surgical procedures were completed, the abdominal wall was closed and the animal was covered in blankets to minimize heat loss.

Different regional perfusion measurements

Regional perfusion was assessed using different microvascular perfusion and peripheral perfusion variables. Accordingly we evaluated microvascular perfusion in the sublingual, intestinal, and muscle vascular beds using a sidestream dark field (SDF) imager (Microscan; Microvision Medical, Amsterdam, the Netherlands) as described previously. The SDF imager contains a × 5 stroboscopic light-emitting diode whose light is absorbed by hemoglobin of the RBCs, making the capillaries of the microcirculation visible in different tissues. To obtain access to the intestinal tissue, a loop of the ileum was exteriorized through a 5-cm lateral abdominal incision, and a small ileum segment was opened along its antimesenteric border using electrocautery. With the mucosal surface facing upward, the edges of the opened intestinal segment were fixed at the skin, creating a double-lumen ileostomy. In the proximal part of this ileostomy, the microcirculation was visualized with the SDF imager at 5–7 cm from the margin of the loop. In between measurements, the ileostomy was protected with moisturized wet gauze to prevent desiccation. To obtain a view on muscle microcirculation, a

skin incision was made in the lateral side of the upper hind leg, and the tip of the SDF imager was cautiously positioned on the exposed muscle tissue. Muscle tissue was protected with moisturized wet gauze to prevent desiccation. The sublingual microcirculation was assessed by placing the tip of the SDF imager gently on the sublingual mucosa, avoiding the midline region and the salivary glands.

An investigator, blinded to the study model and the order of sequences, analyzed the video images semiquantitatively.¹⁷ Vascular flow (i.e., microcirculatory flow index, MFI) and density (i.e., perfused capillary density, PCD and; proportion of perfused vessels, PPV) were calculated by the following flow classification: no flow, sluggish, intermittent, or continuous using dedicated software (Automated Vascular Analysis, AVA 3.0, Microvision Medical, Amsterdam, the Netherlands).¹⁸ This approach has been validated previously with low interobserver and intraobserver variability. Capillaries were defined as microvessels with a diameter less than or equal to 20 μm .

Using near-infrared spectroscopy (NIRS), Sto_2 was continuously monitored using an InSpectra Tissue Spectrometer Model 650 (Hutchinson Technology, Hutchinson, MN) in the different peripheral vascular beds. Sublingual and intestinal Sto_2 were assessed with a 15-mm probe. Simultaneously, sublingual Sto_2 was determined by placing the NIRS probe under the base of the tongue and the intestinal Sto_2 by inserting the probe into the distal part of the ileostomy, which was closed and reinserted into the abdominal cavity afterward. Muscle Sto_2 was assessed with a multidepth NIRS probe attached over the biceps femoris muscle eminence.

Peripheral perfusion was assessed using the proximal-to-distal leg (peripheral Tskin-diff) and central-to-distal leg (central Tskin-diff) skin temperature gradients, which were obtained from two skin probes that were attached to the proximal and distal leg as estimates of peripheral skin perfusion. Central temperature was observed by inserting the tip of the thermistor into the rectum. Temperature gradients can better reflect changes in cutaneous blood flow than the absolute skin temperature itself, and they increase during vasoconstriction.¹⁹



Hemodynamic measurements

Heart rate, mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery occlusion pressure, mean pulmonary artery pressure, and cardiac output were measured. Cardiac output was continuously monitored using a thermodilution method (Vigilance; Edwards Lifesciences), indexed to body surface area, and presented as a cardiac index.²⁰ Mixed venous hemoglobin oxygen saturation (SvO_2) from the pulmonary catheter and arterial blood gases were measured using a blood gas analyzer (ABL 825FLEX, Radiometer, Copenhagen, Denmark). Systemic oxygen delivery, systemic oxygen consumption, and the oxygen extraction ratio were calculated using standard equations.²¹

Experimental procedure

The pigs were randomly assigned to the endotoxemic or obstructive shock model after baseline measurements were obtained (Fig. 1). Shock initiation (T1) was defined as a decrease in cardiac output of approximately 50% compared with baseline in both

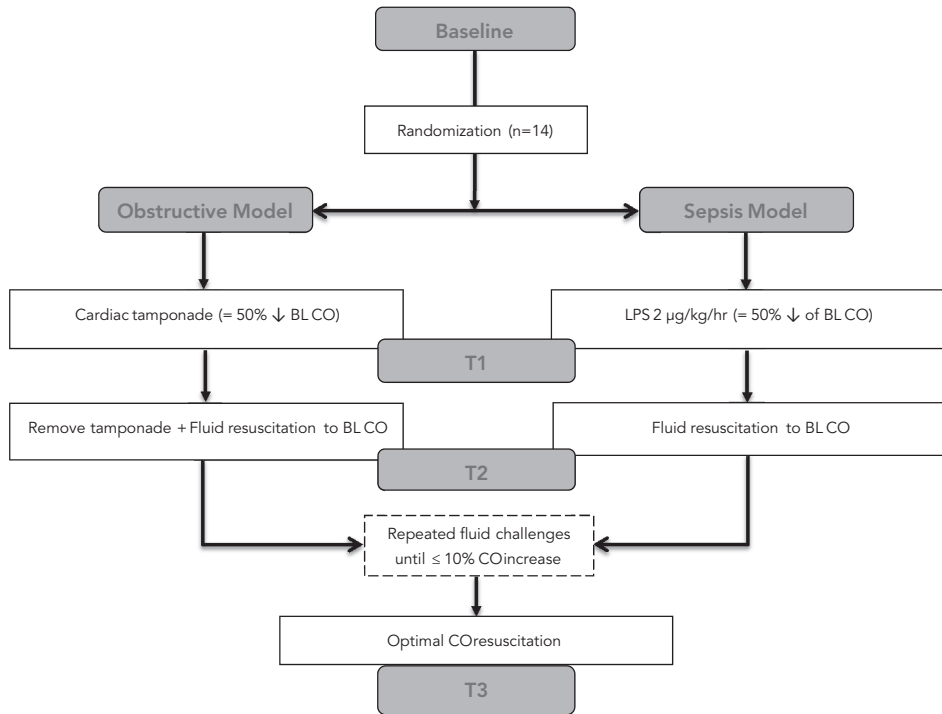


Figure 1. Overview of model classification and hemodynamic support. Obstructive shock is induced with cardiac tamponade, and endotoxemic shock is induced with lipopolysaccharide (LPS). BL = baseline, CO = cardiac output, T1 = 60 minutes after shock state, T2 = 60 minutes after successful resuscitation back to BL, T3 = 60 minutes after CO was optimized.

models. Endotoxemic shock was induced by an IV infusion of a bolus of 5 µg/kg lipopolysaccharide (LPS—*Escherichia coli* O127:B8, L-3880; Sigma, St. Louis, MO) in 1 minute, followed by a continuous infusion of 2 µg/kg/hr during the rest of the experiment. Obstructive shock was induced by infusing 0.9% saline solution of 37°C (via knotted catheter in the pericardium) into the pericardial space.²²

Initial resuscitation (T2) was performed by the withdrawal of pericardial fluid content and additional fluid administration in the obstructive model, if necessary, and with continuous fluid administration to achieve baseline cardiac output values in the endotoxemic model. Finally, in both models, optimal fluid resuscitation was continued with repeated fluid challenges until cardiac output increased no more than 10% (T3). Fluid resuscitation was performed with an infusion of colloidal fluids (Voluven, Fresenius-Kabi, Belgium). All systemic hemodynamic variables, metabolic state, and peripheral microcirculatory perfusion variables were collected after a stable 60-minute period once each physiological endpoint was reached in both models.

Statistical analysis

Data are presented as mean \pm SD unless otherwise specified. After logarithmic conversion of not normally distributed data (Kolmogorov-Smirnov test $p > 0.05$) to normalize distributions where appropriate, data were suitable for mixed-model analysis. Accordingly, we used a linear mixed-model analysis to assess differences in the different systemic hemodynamic variables and between the different microvascular perfusion and peripheral perfusion variables, over time (BL, T1, T2, and T3), and between models (endotoxemic shock vs obstructive shock). Changes from baseline were computed dividing the variable value at specific time points into the baseline value and expressed as percentile changes (% of baseline \times 100). We then compared the magnitude of changes between models (endotoxemic shock vs obstructive shock) for cardiac output and the different microvascular perfusion variables (i.e., MFI, PCD, and PPV) for the different vascular beds at specific time points to evaluate the effect of resuscitation on these variables. Differences between model means were compared using nonparametrical Mann-Whitney U test or Student t test, if normally distributed. A p value of less than 0.05 was considered statistically significant. Note that because the distribution of the percentile changes often showed differences in the variances between the groups and considerable skewness, these results have to be interpreted cautiously. Statistical analysis was performed using SPSS (version 20.0; IBM, SPSS, Chicago, IL).

Results

Systemic hemodynamics

Systemic hemodynamic and oxygenation variables at each of the three equivalent time points in both models are presented in Table 1. The baseline characteristics were similar in both models, and shock initiation (T1) produced a similar decrease in cardiac output in both models (Fig. 2). Accordingly, MAP and Svo₂ decreased at T1 ($p < 0.05$ vs all time points). This was paralleled by a marked reduction in systemic oxygen delivery and an increase in oxygen extraction rate. Concurrently, lactate concentrations increased almost five-fold, and urine output decreased significantly in both models (Tables 1 and 2).

Initial volume resuscitation (T2) normalized cardiac output, MAP, and Svo₂ in both models. Systemic oxygen delivery and oxygen extraction rate returned to pre-shock levels. Following additional fluid resuscitation (T3) however, cardiac output reached significantly higher values in the endotoxemic model compared with the obstructive model (+65% vs +22% of baseline, respectively, $p = 0.001$) (Fig. 2). As a result, systemic oxygen delivery increased ($p = 0.007$) and the oxygen extraction rate decreased further compared with T2. Notably, systemic oxygen consumption, which had remained unchanged as yet, increased as well at this point. Lactate clearance was comparable between both models after initial resuscitation (obstructive shock, -18% [0.01] vs endotoxemic shock, -20% [0.14]). After additional resuscitation, lactate persisted to elevate in the endotoxemic model, whereas in the obstructive model, lactate decreased further with 50% (0.06); ($p = 0.007$ vs endotoxemic shock). Additional fluid had been administered to achieve optimal cardiac output, although this fluid did not produce a significantly higher cumulative fluid balance



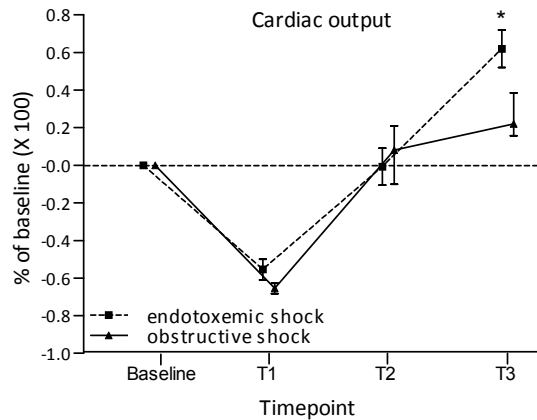


Figure 2. Behavior of cardiac output during the experimental procedure. Cardiac output plotted as proportional changes from baseline for each time point for both models. Following T2, IV fluid resuscitation was maintained to maximize cardiac output, until no more than 10% increase in cardiac output was observed (T3). At this stage, cardiac output reached significant higher values in the endotoxemic shock model (dashed line) compared with the obstructive shock model (continuous line) (* $p < 0.05$ vs obstructive shock by Mann-Whitney test). Initial volume resuscitation (T2) normalized cardiac output in both models. Following additional fluid resuscitation (T3) however, cardiac output reached significantly higher values in the endotoxemic model compared with the obstructive model.

compared with the obstructive model (3.110 [1.035 mL] vs 2.100 [528 mL]; $p = 0.062$, respectively). Still, CVP increased in both groups.

Regional perfusion

The time course of the different microvascular perfusion variables, observed with the SDF imager, is presented in Figure 3. At baseline, there was no statistical difference between the different microvascular perfusion variables and between both models. All these variables decreased simultaneously in a similar magnitude during shock in both models and increased toward baseline levels in the obstructive model at T2 and remained in this range after T3. However, in the endotoxemic model, microvascular variables increased after initial resuscitation, and they did not reach baseline values. These variables improved toward baseline levels only after additional resuscitation of cardiac output at T3. Hence, although the PCD (n/mm^2) increased significantly during this stage compared with T2, this index was lower than the baseline values in the intestinal tissue (T3, 21.8 [1.22] vs baseline, 23.2 [0.64]; $p = 0.040$) (Fig. 3B) and for PPV (%) in the sublingual (T3, 98.5 [0.47] vs baseline, 99.8 [0.13]; $p = 0.034$) and intestinal tissue (T3, 93.2 [1.72] vs baseline, 99.2 [0.32]; $p = 0.014$) (Fig. 3C).

Changes in the peripheral Tskin-diff and central Tskin-diff are presented in Table 3. Similar to the different microvascular perfusion variables (i.e., MFI, PCD, and PPV), these different peripheral perfusion variables exhibited the same magnitude of change at T1 in both models (Table 3). Peripheral Tskin-diff returned to baseline values after T2 and remained in this range after T3 in the obstructive model but not in the endotoxemic

Table 1. Evolution of systemic hemodynamic variables over time in the endotoxemic shock model (n = 7) and the obstructive shock model (n = 7)

Variables	Shock model	Baseline	T1	T2	T3
Cardiac index (L/min·m ²)	Endotoxemic	2.6 (0.5)	1.2 (0.3) ^a	2.6 (0.5)	4.4 (0.6)
	Obstructive	2.3 (0.3)	0.9 (0.2) ^a	2.4 (0.3)	2.8 (0.5) ^{a,b}
Heart rate (beats/min)	Endotoxemic	106 (29)	200 (12) ^a	150 (29) ^a	137 (23) ^a
	Obstructive	98 (17)	215 (31) ^a	137 (28) ^a	90 (48) ^b
Mean arterial pressure (mm Hg)	Endotoxemic	110 (16)	71 (27) ^a	95 (22)	118 (30)
	Obstructive	112 (18)	61 (15) ^a	95 (17)	108 (18)
Central venous pressure (mm Hg)	Endotoxemic	8 (2)	8 (4)	10 (2) ^a	14 (3) ^a
	Obstructive	8 (3)	15 (6) ^{a,b}	10 (6)	13 (6) ^a
Pulmonary artery occlusion pressure (mm Hg)	Endotoxemic	9 (3)	16 (6) ^a	13 (8)	13 (9)
	Obstructive	10 (3)	11 (7)	11 (6)	11 (8)
Mean pulmonary artery pressure (mm Hg)	Endotoxemic	24 (9)	39 (7) ^a	41 (6) ^a	43 (3) ^a
	Obstructive	23 (7)	25 (5) ^b	23 (3) ^b	26 (7) ^b
Fluid volume (mL)	Endotoxemic	688 (74)	223 (127) ^a	778 (112)	1425 (117) ^a
	Obstructive	1022 (171)	190 (74) ^a	398 (114) ^{a,b}	492 (78) ^{a,b}
Urine output (mL)	Endotoxemic	121 (51)	57 (45) ^a	20 (31) ^a	35 (23) ^a
	Obstructive	262 (108) ^b	55 (19) ^a	90 (54) ^{a,b}	88 (74) ^a

T1 = during $\geq 50\%$ reduction of cardiac output, T2 = after initial resuscitation to baseline, T3 = after the optimization of cardiac output.

^ap < 0.05 versus baseline.

^bp < 0.05 between models (endotoxemic and obstructive) in the specific time point, by linear mixed-model analysis.

Data are presented as mean \pm SD.



model. In this model, peripheral T_{skin-diff} only increased toward baseline levels after additional fluid resuscitation of cardiac output. Central T_{skin-diff} followed the same pattern of changes as peripheral T_{skin-diff} during resuscitation, but these changes were not significant. Additionally, St_{O₂} followed an identical pattern of change as the other microvascular perfusion and peripheral perfusion variables in the obstructive shock model (Table 3). In the endotoxemic model however, St_{O₂} was similarly decreased during shock but persisted following initial resuscitation and additional resuscitation of cardiac output.

Discussion

This experimental study demonstrated that the correction of cardiac output to normal levels is adequate for resuscitation of the peripheral circulation in different tissues after obstructive shock but not after endotoxemic shock. In the endotoxemic model, only

Table 2. Oxygenation and metabolic variables in endotoxemic and obstructive shock

Variables	Shock model	Baseline	T1	T2	T3
Hemoglobin concentration (mmol/mL)	Endotoxemic	6.8 (0.3)	8.5 (0.6) ^a	6.3 (0.7)	5.3 (0.9) ^a
	Obstructive	7.2 (0.4)	8.8 (0.5) ^a	7.2 (1.0)	5.6 (1.2) ^a
Lactate (mmol/L)	Endotoxemic	1.1 (0.6)	5.5 (1.6) ^a	4.0 (2.1) ^a	3.6 (1.6) ^a
	Obstructive	0.7 (0.1)	5.1 (1.5) ^a	4.2 (1.2) ^a	2.1 (0.8) ^{a,b}
Oxygen delivery (ml/min/m ²)	Endotoxemic	501.5 (144.6)	331.3 (100.5) ^a	513.3 (125.3)	731.9 (183.6) ^a
	Obstructive	521.6 (48.1)	211.9 (24.7) ^{a,b}	546.9 (75.6)	505.5 (86.7) ^b
Oxygen consumption (ml/min/m ²)	Endotoxemic	173.6 (77.7)	177.7 (20.2)	231.2 (128.3)	267.0 (102.2) ^a
	Obstructive	195.4 (47.6)	180.1 (27.5)	218.4 (33.9)	183.1 (54.1)
Oxygen extraction rate (ml/min/m ²)	Endotoxemic	0.33 (0.15)	0.56 (0.11) ^a	0.44 (0.14)	0.36 (0.07)
	Obstructive	0.37 (0.08)	0.85 (0.06) ^{a,b}	0.40 (0.03)	0.38 (0.09)
Arterial pH	Endotoxemic	7.52 (0.05)	7.30 (0.05) ^a	7.32 (0.06) ^a	7.36 (0.02) ^a
	Obstructive	7.50 (0.03)	7.36 (0.09) ^a	7.37(0.05) ^a	7.42 (0.05) ^{a,b}
P _a O ₂ (mm Hg)	Endotoxemic	229 (102)	103 (29) ^a	104 (32) ^a	121 (43) ^a
	Obstructive	214 (41)	149 (53)	183 (20) ^b	184 (24) ^b
P _a CO ₂ (mm Hg)	Endotoxemic	34 (5)	44 (9) ^a	43 (5) ^a	42 (6) ^a
	Obstructive	34 (4)	34 (9)	36 (6)	36 (6) ^b
Bicarbonate concentration (mmol/L)	Endotoxemic	27.9 (0.9)	20.7 (1.3) ^a	20.8 (2.0) ^a	22.0 (2.5) ^a
	Obstructive	27.7 (0.7)	21.0 (2.9) ^a	21.8 (1.2) ^a	23.2 (1.1) ^a
Mixed venous oxygen saturation (%)	Endotoxemic	61 (7)	42 (12) ^a	53 (12)	60 (10)
	Obstructive	63 (9)	14 (4) ^{a,b}	60 (3)	62 (7)
Central temperature (°C)	Endotoxemic	38.8 (0.3)	38.8 (0.3)	39.0 (0.3)	38.7 (0.5)
	Obstructive	38.9 (0.4)	38.6 (0.2)	38.8 (0.3)	38.5 (0.3)

T1 = during $\geq 50\%$ reduction of cardiac output, T2 = after initial resuscitation to baseline, T3 = after the optimization of cardiac output.

^a $p < 0.05$ versus baseline.

^b $p < 0.05$ between models (endotoxemic and obstructive) in the specific time point, by linear mixed-model analysis.

Data are presented as mean \pm SD.

additional cardiac output-targeted fluid resuscitation could further improve microvascular and peripheral perfusion abnormalities. These data confirm our hypothesis and highlight that additional resuscitation at the microcirculatory level might be a complementary target if the conventional global resuscitation goals have been achieved.

Despite success associated with the implementation of early resuscitation during sepsis, the value of microcirculatory abnormalities as resuscitation target

Table 3. Tissue perfusion variables in three different vascular beds.

Variables	Shock model	Baseline	T1	T2	T3
Tissue oxygen saturation					
Sublingual Sto ₂	Endotoxemic	66 (9)	33 (16) ^a	44 (9) ^a	52 (9) ^a
	Obstructive	74 (7)	29 (9) ^a	64 (12) ^b	66 (6) ^b
Intestinal Sto ₂	Endotoxemic	78 (12)	53 (14) ^a	64 (16) ^a	66 (15) ^a
	Obstructive	76 (12)	37 (6) ^{a,b}	72 (13)	77 (9)
Muscle Sto ₂	Endotoxemic	69 (2)	37 (6) ^a	53 (4) ^a	56 (7) ^a
	Obstructive	68 (6)	27 (9) ^{a,b}	61 (8) ^{a,b}	63 (9)
Tskin-diff					
Tskin-diff peripheral	Endotoxemic	1.3 (1.63)	3.3 (1.48) ^a	3.3 (1.04) ^a	0.7 (2.42)
	Obstructive	2.2 (1.71)	4.7 (2.25) ^a	3.7 (1.09)	3.2 (2.00)
Tskin-diff central	Endotoxemic	9.2 (2.42)	11.2 (3.52) ^a	10.3 (3.25)	7.1 (2.78)
	Obstructive	9.5 (1.43)	11.0 (1.57) ^a	11.6 (2.40)	9.8 (2.69)

T1 = during $\geq 50\%$ reduction of cardiac output, T2 = after initial resuscitation to baseline, T3 = after the optimization of cardiac output, Tskin-diff = body temperature gradient (*Materials and Methods* section).

^a $p < 0.05$ versus baseline.

^b $p < 0.05$ between models (endotoxemic and obstructive) in the specific time point, by linear mixed-model analysis.

Data are presented as mean \pm SD.

remains uncertain.^{23;24} Obstructive shock, unlike septic shock, maintains intact autoregulatory mechanisms that preserve vital organ perfusion and ensure that the depressed microcirculation can be adequately resuscitated with normalized systemic hemodynamics.^{25;26} However, compensatory autoregulatory mechanisms are severely disrupted during sepsis. This disruption, rather than systemic hemodynamic depression, results in impaired microvascular perfusion, characterized by endothelial dysfunction and heterogeneous flow patterns in otherwise homogeneously perfused microvascular beds.^{1;27;28} Preservation or loss of autoregulation explains why the different microvascular perfusion variables returned to normal in the obstructive model even when slightly resuscitated and why they could be restored only after supranormal resuscitation during endotoxemic shock.

Several experimental and clinical studies have demonstrated that early goal-directed cardiac output fluid resuscitation is associated with improved outcomes prior to high-risk surgery,²⁹ directly after surgery,³⁰ after trauma,³¹ and in sepsis.³² However, these studies did not take the microcirculation into account. This is important, because persistent microvascular perfusion abnormalities during sepsis are associated with increased organ failure and mortality independent of systemic hemodynamic variables.^{7;14;33} Retrospective¹⁵ and prospective³⁴ studies suggest that these abnormalities can be



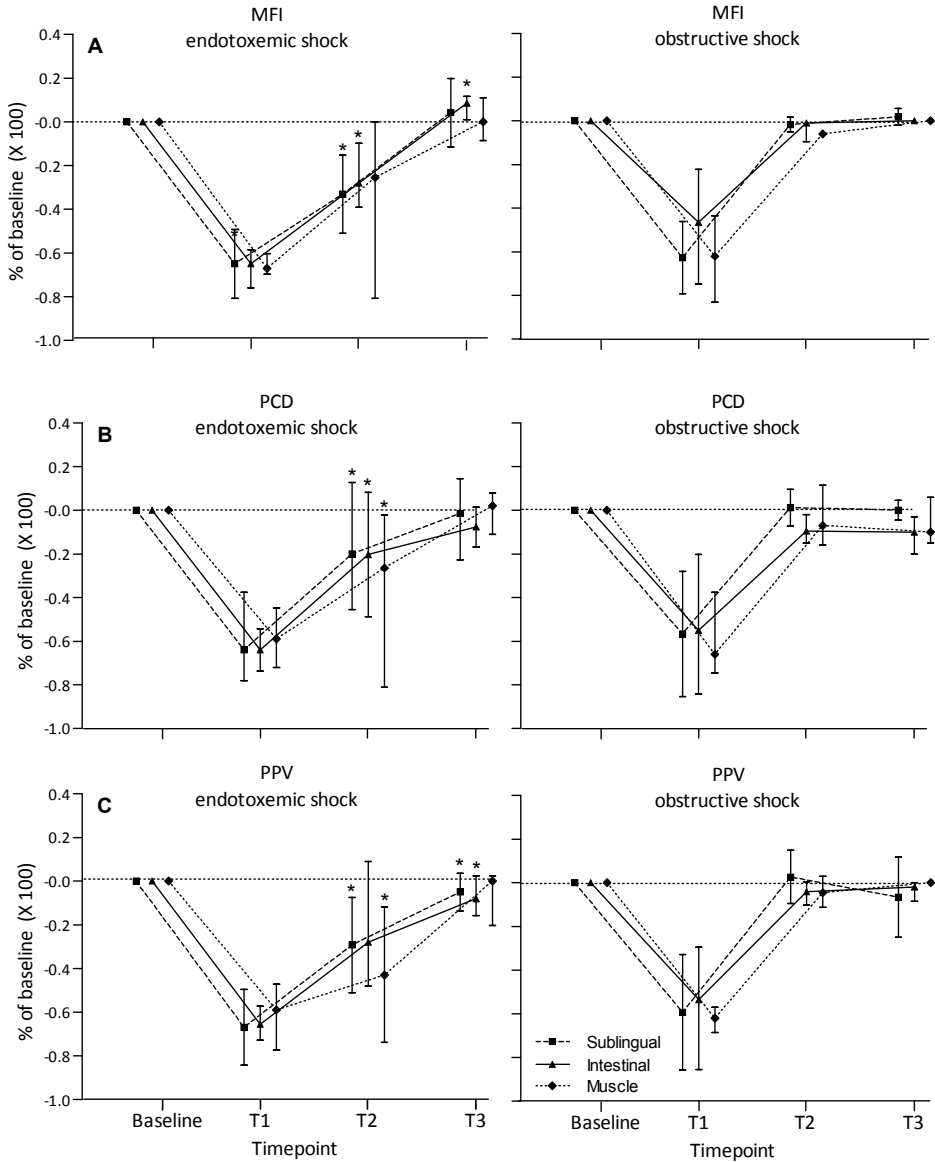


Figure 3. Relative changes (plotted as proportional changes from baseline) of different microvascular perfusion variables visualized with the sidestream dark field imager in different vascular beds. This graph demonstrates the relative changes of the microvascular flow index (MFI) (A), perfused capillary density (PCD, n/mm^2) (B), and the proportion of perfused vessels (PPV, %) (C) for the three vascular beds at each time point for the endotoxemic shock and obstructive model. Bars represent median \pm interquartile range. *p value of less than 0.05 versus obstructive shock. All microvascular perfusion variables decreased simultaneously in a similar magnitude during shock in both models and only increased toward baseline levels in the obstructive model after initial resuscitation (T2) and remained in this range at T3. In the endotoxemic model however, microvascular perfusion variables only improved toward baseline levels after additional resuscitation of cardiac output. Dashed line = sublingual, continuous line = intestinal, dotted line = muscle.

additionally resuscitated independent of cardiac output or blood pressure. Furthermore, a previous study showed that a surrogate of gut mucosal perfusion, the intramucosal-arterial Pco₂ gradient, is only corrected by supranormal increases of intestinal blood flow and not by its normalization.³⁵ Our study complements these investigations by demonstrating that persistent microvascular perfusion abnormalities in different peripheral tissues during endotoxemic shock were only improved after additional systemic resuscitation compared with obstructive shock.

Clearly, our data show that the early phase of sepsis is characterized by a generalized perfusion deficit: the impairment of the global circulation (i.e., cardiac output) has a major impact on microvascular perfusion. This is in agreement with observations in patients with acute sepsis¹⁵ and with the beneficial effect of early goal-directed therapy in patients.¹⁶ In the later phase of sepsis, the development of mitochondrial dysfunction and impaired cellular energy metabolism are most likely the predominant causes of organ dysfunction^{36,37} This is supported by our own observation that the lactate levels in the endotoxemic model remained elevated despite restoration of microvascular perfusion. This can very well explain the poor effect of “late” supranormal cardiac output therapy.³⁸

As such, the relation between microvascular perfusion and organ dysfunction at this stage remains unclear. Although the landmark study by Sakr et al¹⁴ has associated the persistence of microvascular hypoperfusion in late-phase sepsis with poor outcome, the early intervention study by Boerma³⁹ suggested that outcome was not related to differences in microvascular perfusion. Additionally, in an observational study in our own department we found no differences between survivors and non-survivors when comparing microvascular perfusion during the first week of admission.⁴⁰

Of special interest is the comparison of the microvascular perfusion (SDF) and St_{o2} (NIRS) data. In obstructive shock, both microvascular perfusion and St_{o2} were restored with the resuscitation of cardiac output, whereas during endotoxemic shock, a disparity occurred. At hyperdynamic cardiac output levels, microvascular perfusion was restored, but tissue hemoglobin saturation remained below baseline levels in all tissues. Because low St_{o2} has been associated with decreased local blood flow,⁴ it must be concluded that recovery of local microvascular perfusion was not sufficient to completely restore oxygen delivery during sepsis, resulting in increased local oxygen extraction. This is supported by the elevated lactate levels. Most likely this is due to a difference between SDF and NIRS in terms of catchment area: SDF provides an image of only the superficial microvascular bed, whereas the NIRS signal reaches a depth of 15–25 mm. It can be hypothesized that especially during sepsis, where increased heterogeneity of regional blood flow occurs, this difference in technical features becomes apparent.

Based on our observations, it is difficult to identify the microvascular bed or monitoring technique that is most suitable as target during resuscitation. Especially in the obstructive shock model, all microvascular perfusion variables displayed a rather similar pattern, whereas in the endotoxemic group, patterns were a little more heterogeneous. As a result, no microvascular bed stood out as more sensitive to the changes during shock or resuscitation. This is in accordance with a previous study, showing that sublingual and gut microvascular perfusion were significantly related



during experimental sepsis.⁴¹ As such, the sublingual microvascular bed might be the most useful for monitoring under clinical conditions.

On the other hand, from a practical point of view, the lack of bedside, real-time information, and the dependency on experienced observer analysis do not favor the use of SDF imaging. Because changes in peripheral skin temperature difference and SDF were comparable in our study, it is easily hypothesized that real-time assessment of peripheral skin perfusion at the bedside could very well be a more valuable monitor of the effect of resuscitation in the clinical setting. If so, the underlying cause of shock might have to be taken into account: a correlation between microvascular perfusion and skin perfusion was observed in cardiogenic shock¹⁰ but not in septic shock patients.⁴²

Although we found no significant difference in the cumulative fluid balance between the models after optimal resuscitation, the administered volume of fluids was almost 50% higher in the endotoxemic model compared with the obstructive model. This can be explained by the underlying pathophysiological mechanism of endotoxemic shock, that is, the decreased vasomotor tone and endothelial leakage, contributing to a hyperdynamic circulation. The beneficial effect of fluid resuscitation on the microvascular perfusion was recently demonstrated in patients with sepsis.^{43;44} In addition, because excessive fluid administration may be harmful and can potentially cause pulmonary fluid overloading, we administered repeated fluid challenges based on cardiac fluid responsiveness so that fluid overloading was most likely avoided.

Following the restoration of cardiac output to baseline levels in the endotoxemic animals, microcirculatory perfusion did not completely restore to baseline levels. The sharp increase in cardiac output from T2 to T3 (almost 70%), reaching the state of fluid unresponsiveness, is probably related to the normalization of the microcirculatory variables. The multiple insult of the endotoxemic/septic shock not only induces ischemia/reperfusion injury like in the obstructive shocked animals but also induces tissue and endothelial injury, which might result in much higher global blood flow levels when the microcirculation is restored. So, the increased cardiac output could therefore very well present the severity of the damage and is not at much directly the consequence of fluid resuscitation. A causal relationship between the increase in cardiac output and the normalization of the microcirculation can however not be made from these experiments.

This study has some limitations that should be acknowledged. First, the endotoxemic shock and resuscitation model consisted of a continuous but relatively short-term endotoxin infusion. A more clinically oriented model of sepsis might have more adequately represented the inflammatory and metabolic derangements that occur during septic shock.^{45;46} However, profound hyperlactatemia (as a sign of anaerobic tissue metabolism or catecholamine-stimulated aerobic glycolysis) was present during shock in both models, and the lactate clearance was clearly altered in the endotoxemic model compared with the obstructive model. Therefore, we concluded that our models had sufficient analogy with clinical conditions.

Second, because we did not perform a time control, an adaptive effect of the animals to LPS infusion cannot be ruled out. However, we do not think this is an explanation for our observations. The severity of the shock state was not likely to

resolve spontaneously within the time frame of the experiment. Especially because we continued the LPS infusion, to mimic clinical conditions and prevent spontaneous recovery of a short lasting insult, we believe the increase in regional perfusion can be attributed to the increase in cardiac output. Nevertheless, the time frame of our model might have been too short for the development of profound tissue edema, which is a very common problem in patients and as such might hamper the translation of our results to clinical practice.

Third, SDF imaging is a valuable technique, but it is based on semi-quantitative analyses. Therefore, data reliability may be affected by technical expertise and interobserver bias despite the use of standardized analysis software. Finally, we recognize that the sample size was limited for a multivariate analysis between the two groups. However, the sample size was adequate to address the specific aims of this study. Definitive determinations of the relationship between microcirculatory and systemic variables in sepsis require a more robust sample of longitudinal data.

Conclusions

Resuscitation of cardiac output to preshock levels produced a full recovery of the peripheral circulation in obstructive but not in endotoxemic shock. Apparently, the relationship between the systemic circulation and different microvascular and different peripheral perfusion variables is dependent on the underlying cause of circulatory shock. Our data show that different microvascular and peripheral perfusion variables can be used to assess the adequacy of hemodynamic resuscitation during different types of shock. Supranormal optimization of cardiac output is needed to restore these different variables in sepsis but might still not lead to full recovery of tissue oxygenation. Further research is required to assess the reproducibility of our findings in a clinical setting and further elucidate the relationship between systemic and different peripheral circulation and oxygenation variables as targets for systemic therapeutic interventions during the early phase of septic shock.



Acknowledgements

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Early peripheral perfusion -guided fluid therapy in patients with septic shock

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Electronic supplement:

This article has an online supplement, which will be accessible
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To the Editor

Septic shock remains the most frequent cause of death in patients admitted to the intensive care unit (ICU).¹ Careful titration of therapy is essential: undertreatment results in persistence of impaired tissue oxygenation, whereas overtreatment leads to a positive fluid balance which can result in pulmonary edema, prolonged mechanical ventilation and finally death.²⁻⁶ Although peripheral perfusion alterations are stronger predictors of outcome than systemic hemodynamic variables in septic shock patients, end points to guide volume resuscitation are still based on systemic parameters and little is known about resuscitation guided by endpoints of peripheral tissue perfusion.⁷⁻⁹ We therefore undertook a proof-of-concept randomized controlled study comparing early goal directed fluid resuscitation based on clinical assessment of peripheral perfusion with standard fluid therapy to investigate whether peripheral perfusion guided resuscitation is feasible and would lead to less fluid administration in septic shock patients. Some of the results of these studies have been previously reported in the form of an abstract.¹⁰

Materials and Methods

This trial was approved by the institutional review board and was registered at clinicaltrials.gov (NCT01397474). Deferred proxy consent was obtained from a relative authorized to consent on behalf of each patient.

In brief, we performed a prospective randomized controlled pilot study in septic shock patients admitted to the ICU, more details are listed in the electronic supplement. Directly after ICU admission patients were randomized into the control group or the intervention group (Peripheral Perfusion Targeted Fluid Management – PPTFM group) to determine the resuscitation strategy during the first 6 hours. In the PPTFM group, fluid management was based on peripheral tissue perfusion parameters: the capillary refill time (CRT), the peripheral perfusion index (PPI), the forearm-to-fingertip (T_{skin-diff}) body temperature gradient and thenar tissue oxygenation (StO₂).¹¹ Only patients with “poor peripheral perfusion” (i.e. 3 out of 4 parameters altered) were considered suitable for fluid repletion (Figure 1). In the control group, hemodynamic goals were based on the 2012 Surviving Sepsis guidelines¹². We assessed protocol adherence at 2, 4, and 6 hours after study entry. Thereafter, data was collected daily until 72 hours after study entry (observation period). More details are provided in the electronic data supplement

We used linear mixed-model analyses to calculate differences between groups in systemic hemodynamics, peripheral perfusion parameters, laboratory variables, and fluid therapy over time (see electronic supplement).

Results

30 patients were included, of which 15 were allocated to each group. Baseline characteristics of all patients are shown in Table E1. Both groups were well matched and there were no statistical differences between groups at baseline. During the



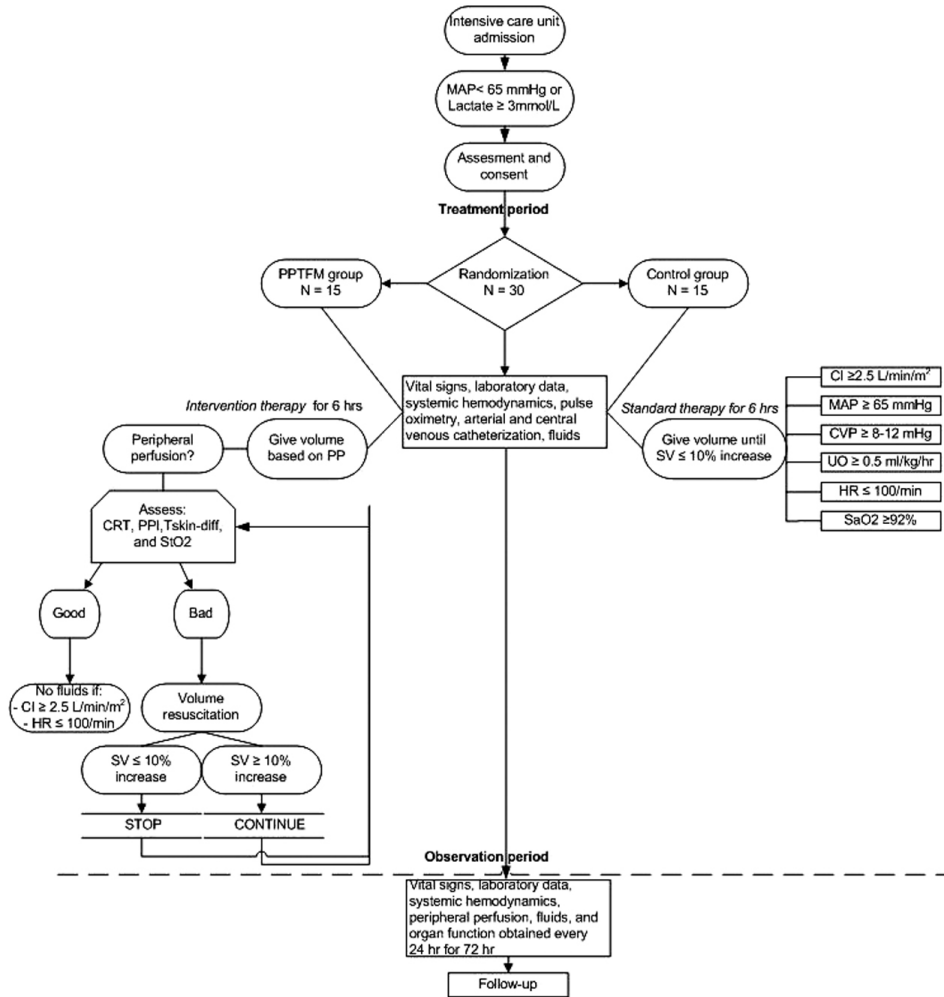


Figure 1. Study algorithm for the first 6 hours of ICU admission (control vs PPTFM group). In the control group fluid resuscitation was based on systemic hemodynamic parameters. In the intervention group, treatment was based on peripheral perfusion parameters: if 3 out of 4 parameters were considered impaired a fluid challenge (250 ml colloids in 15 mins) was administered, aiming at an increase in peripheral perfusion. If peripheral perfusion parameters did not improve following 2 consecutive challenges, fluid administration was stopped. PPTFM, Peripheral Perfusion Targeted Fluid Management; CI, Cardiac Index; MAP, Mean arterial pressure; CVP, central venous pressure; UO, urine output; SaO₂, arterial oxygenation; SV, stroke volume; HR, heart rate; CRT, capillary refill time; PPI, peripheral perfusion index; Tskin-diff, forearm-to-fingertip skin temperature gradient; StO₂, tissue oxygenation saturation.

study period we observed no significant difference between groups in systemic hemodynamic parameters and peripheral perfusion parameters. Importantly, the two groups had similar lactate concentrations and central venous oxygen saturation

values over time. PPTFM patients received less mean (SE) fluids during the treatment period, 4227 (1081 ml) vs. 6069 (1715 ml) ($P = .39$) and almost 2.5 liters less during the observation period: 7565 (982 ml) vs. 10028 (941 ml) ($P = .08$) in the control group (Table 1). Interestingly, patients in the control group stayed longer in the hospital compared to PPTFM patients with 43 (8) vs. 16 (3) days ($P = .05$) and had a higher organ failure scores (SOFA total scores and neurologic subscores).

Discussion

This proof-of-concept study shows that early peripheral perfusion targeted fluid resuscitation leads to a trend towards less fluids when compared to a conventional regimen based on systemic hemodynamic parameters.

Although the difference in fluid administration was not significant, PPTFM patients received almost 2 liters less in the first 6 hours already, leading up to 2.5 liters less 72 hours after ICU admission. If performed on a larger scale, this could have important clinical implications as large volumes of fluids are associated with pulmonary – and

Table 1. Fluid therapy and outcome variables.

Variables	Groups	Study period	
		0-6 h	7-72 h
Cumulative Fluids (ml)	Control	6069 (1715)	10028 (941)
	PPTFM	4227 (1081)	7565 (982)
Urine output (mL)	Control	520 (160)	2469 (542)
	PPTFM	332 (84)	1680 (527)
SOFA _{total}	Control	12.8 [10.0-16.8]	11.0 [5.3-15.3]
	PPTFM	11.5* [8.0-13.0]	8.3 [5.5-13.1]
		Outcome	
Mechanical ventilation free days (days)	Control	2 [2 – 6]	
	PPTFM	2 [1 – 5]	
Intensive care unit mortality, n (%)	Control	6 (40)	
	PPTFM	7 (47)	
Intensive care unit stay (days)	Control	8 [3 – 8]	
	PPTFM	10 [2 – 10]	
Hospital stay (days)	Control	43 [8 – 45]	
	PPTFM	16 [5 – 28]*	

Data are presented as mean (SE) or mean [IQR], unless otherwise stated.

Dash (-) indicates the mean value between subsequent time points during the study periods; for the period from 0 hours to 6 hours and for the period from 7 to 72 hours.

Sum of crystalloid and colloid fluids over time

* $P < 0.05$ between groups (Control vs PPTFM).



renal failure and adverse outcomes.¹³ One can hypothesize that using our algorithm for targeting the peripheral circulation less fluids are administered because infusion is stopped earlier: as soon as peripheral perfusion is not impaired (anymore) or when perfusion remains impaired although maximum cardiac output is reached. Surprisingly, we observed that PPTFM patients have a significantly shorter hospital length of stay and significantly lower organ failure scores. It must however be noted that our study was not powered to for this purpose so these results should be interpreted with caution. A larger trial is needed to confirm and elaborate our findings.

Still, to our knowledge this is the first randomized controlled study that incorporates peripheral perfusion parameters as target for fluid resuscitation in septic shock patients. In our opinion this approach provides an important complement to currently targeted systemic hemodynamic parameters. From a physiological point of view, peripheral tissues are the first to reflect hypoperfusion during shock and are the last to reperfuse during resuscitation, as a result of compensatory sympathetic nervous system activation.¹⁴ If this response is adequate, restored peripheral perfusion indicates that enough fluid has been administered and a conservative strategy can be followed. It therefore makes sense to strive towards a more tissue perfusion based approach that allows the physician to titrate therapy in a way conventional targets such as blood pressure and urine production do not provide. These considerations, as well as the limitations of our study, are elaborated in the electronic supplement.

Further research is needed to confirm our findings and definitely demonstrate whether the use of peripheral perfusion parameters as resuscitation targets can benefit outcome in critically ill patients.

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Electronic supplement

Data Safety Monitoring Board (DSMB):

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Material and methods

This trial was approved by the institutional review board, was conducted under the auspices of an independent Data Safety Monitoring Board (DSMB), and was registered at clinicaltrials.gov (NCT01397474). For all patients deferred proxy consent was obtained from a relative authorized to consent on behalf of such a patient.

Between October 2011 and November 2013 we performed a prospective randomized controlled pilot-study in septic shock patients that were admitted to the ICU who met two or more criteria for systemic inflammatory response syndrome¹, with hypotension and/or a blood lactate level at or above 3.0 mEq/L on ICU admission. Exclusion criteria are listed in the electronic supplement.

Study protocol

Fluid repletion was guided using fluid challenges in both groups (i.e. bolus of 250 ml fluid [hydroxyl-ethyl starch 6% 130/0.4 [Fresenius Kabi, Germany] 130/0.4]), yet targeted by different endpoints. In the PPPTM group, after each fluid challenge, peripheral perfusion was re-evaluated to assess further need of fluid challenges. To ensure normovolemia, fluid was also targeted at a minimum cardiac index of 2.5 L/min/m², irrespective of peripheral perfusion (Figure 1). When additional fluid infusion was no longer accompanied by a response in peripheral perfusion, fluid administration was cancelled to prevent fluid overloading.

Cardiac output index and its related variables were measured with transpulmonary thermodilution catheter (PiCCO; Pulsion Medical Systems AG, Munich, Germany) using a femoral artery catheter and a central venous catheter (subclavian or internal jugular vein). Cardiac output measurements were performed with bolus injections of 20-mL saline (4°C) and were obtained in triplicate and averaged. We aimed for a minimum arterial blood pressure of 65 mmHg, according to the Surviving Sepsis Guidelines. In case of hypotension (i.e. MAP < 65 mmHg) at admission this was treated in both groups with the administration of noradrenaline, while immediate fluid resuscitation was started for the following 6 hours (intervention period) according to the study protocol

Inclusion criteria

All adult patients (≥ 18 years) with hemodynamic instability due to severe sepsis or septic shock on ICU admission were eligible for inclusion. Septic shock was defined as hypotension (mean arterial pressure <65 mm Hg) requiring the administration of a vasopressor (norepinephrine at any dose) or a blood lactate level at or above 3.0 mEq/L on ICU admission in patients in whom infection was suspected.¹ We excluded patients with preexisting conditions precluding peripheral perfusion assessment, such as hypothermia, Raynaud disease, or known severe peripheral vascular disease, acute coronary syndrome, acute pulmonary edema, burn or trauma, liver failure (prothrombin time > 15 seconds or international normalized ratio equal to or greater than 1.5 and any hepatic encephalopathy, after liver surgery, a contraindication for central venous catheterization, an evident aerobic cause of hyperlactatemia (at the discretion of the treating physician), any neurological insult (stroke, subarachnoid hemorrhage, brain



trauma, epileptic seizures prior to admission, a do-not-resuscitate status, pregnancy, or recent participation in another biomedical study. Patients were also excluded if they had an inability to start the study within 4 hours after ICU admission.

Systemic inflammatory response syndrome criteria according to Bone et al.¹ Patients were required to have >2 of the following 4 criteria:

- i.) temperature >38° C or <36° C;
- ii.) heart rate >90 beats per minute;
- iii.) respiratory rate >20 breaths per minute, intubation or a PaCO₂ <32Mm Hg; and,
- iv.) white blood cell count >12,000/mm³, <4,000/mm³,

Randomization

The start of the study was defined as the opportunity to include a patient and start the study protocol within 4 hours after ICU admission. Randomization was done with the use of opaque sealed envelopes randomly shuffled by an investigator not involved in patient inclusion. The randomization was performed using block randomization containing 3 blocks with a block size of ten. The first two authors enrolled all patients and opened the envelopes. By immediately filling out name and date on the randomization-patient form, the connection between the patient and the outcome of the randomization was safeguarded. The random allocation sequence was generated with the use of the Random Allocation Software. The treating physicians were unaware of the randomization block size. To ensure that the treating physicians were following the protocol, complying with fluid procedures and data collection, a researcher was present during the treatment period in patients randomized to the PPTFM group.

Data collection time points

Our protocol is based on different 6-hour early goal-directed landscape studies.^{2,3} We therefore assessed adherence to the PPTFM and control group protocol at 2, 4, and 6 hours after study entry. We defined these first 6 hours as intervention period because during this time frame patients were actively resuscitated based on either protocol. We subsequently repeated these measurements daily until 72 hours after study entry and defined this as the observation period. For patients in the control group, the treating physicians directed all care based on protocolized clinical decision making.

Organ failure assessment

All components of the Sequential Organ Failure Assessment (SOFA) score were collected for each patient at each time point to assess the presence of organ failure. The total SOFA score was calculated by summing the scores for each of the components (i.e., cardiac, renal, nervous, respiratory, coagulation, and liver). SOFA total and subscores were compared between groups.

Statistical analysis

Data are presented as mean ± SE unless otherwise specified. The results were analyzed according to an intention-to-treat principle, which was defined as all patients who had

undergone randomization except for those who did not provide consent for the use of their data. We used a Kolmogorov-Smirnov test and stratified distribution plots to verify the normality of distribution of continuous variables ($P > .05$). Differences between model means were compared using Student t test or Mann-Whitney U test if not normally distributed. Accordingly, we used a linear mixed-model analysis to assess differences between groups (controls vs. PPTFM) to calculate differences in fluid administration/balance during the first 72 hours of ICU admission, Secondary we analyzed differences between groups in systemic hemodynamics, peripheral perfusion parameters, laboratory variables, fluid therapy, and SOFA scores over time; i.e. for the intervention period and the observation period (7-72 hours), corrected for the following predefined covariables: age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and baseline SOFA score.

Statistical analysis was performed using SPSS (version 20.0; IBM, SPSS, Chicago, IL). A p value $< .05$ was considered statistically significant. No correction for multiple testing was performed due to planned comparisons ⁴

Results

Table E1. Baseline characteristics at admission

	Control group	PPTFM group	P-value
Age (years)	67 [55 - 74]	63 [58 -73]	0.78
Male sex, n (%)	9 (60)	9 (60)	0.94
Body mass index (kg/m ²)	24.0 (1.3)	26.3 (1.9)	0.33
Median time from ICU admission to enrollment (minutes)	89 (21)	118 (35)	0.46
Acute Physiology and Chronic Health Evaluation II	24 (3)	26 (3)	0.59
Total Sequential Organ Failure Assessment at inclusion	13 (1)	11 (1)	0.89
Central temperature (°C)	36.5 (0.2)	36.8 (0.3)	0.45
Referring department, n			
- Postoperative (acute)	1	3	
- Postoperative (elective)	8	4	
- Ward or emergency department	5	6	
- Other ICU	1	2	
Source of sepsis, n			
- Abdomen	10	8	
- Lungs	1	2	
- Vascular	1	2	
- Other	3	3	
Noradrenaline use, n (%)	15 (100)	13 (87)	0.48
Noradrenaline dose (µg/kg/min)	0.35 (0.08)	0.27 (0.09)	0.34

Unless otherwise specified values are expressed as mean (SE) or median [interquartile range]; n = 15 for each group.

There were no significant differences between groups in any of the variables.

Data presented is at study admission.



Discussion

In combination with arbitrary minimum cardiac index values, early peripheral perfusion-targeted resuscitation is easy to perform, feasible, and safe.

The current guidelines still suggest targeting a mean arterial blood pressure \geq 65 mmHg in septic shock patients. Recently, a large randomized trial however demonstrated that increasing mean arterial pressure (MAP) did not predict global tissue perfusion nor improved organ perfusion in septic shock patients.⁵ This arbitrary value can be debated since pressures around 45 -50 mmHg are adequate to maintain cardiac and cerebral blood.⁶

Urine output is conventionally used as a target for resuscitation. Understandably, when systemic blood flow fails and hypotension induced sympathetic nervous system activity leads to different compensatory mechanisms such as stimulation of the kidney to retain fluid, resulting in (prerenal) oliguria. Restoring systemic blood flow will result in decreased sympathetic activity and return of urine production. However, during septic shock restoring cardiac output will typically not lead to a decreased sympathetic outflow and renal fluid retention will persist. Depending on the course of the disease this might transform in acute kidney injury (AKI). It has been shown repeatedly that improving systemic hemodynamic parameters during severe sepsis does not result in recovery of urine production or kidney function, recently by Asfar et al.⁵ For this reason we decided not to incorporate urine production in the PPTFM algorithm. It should be noted however that a similar mechanism might be responsible for the changes in peripheral perfusion during severe sepsis. Persistent sympathetic activity despite recovery of systemic hemodynamic parameters might be responsible for impaired peripheral perfusion in severe sepsis.

This proof-of-concept study shows that early peripheral perfusion targeted fluid resuscitation might lead towards less fluid administration. Although this effect did not reach significance, we hypothesized that fluid administration in the PPTFM group was limited in two ways. First, if peripheral perfusion was considered good, no more fluids were given irrespective of systemic hemodynamic parameters. Second, if peripheral perfusion was considered bad, fluid administration was continued only if peripheral perfusion improved as well as stroke volume. If one of these did not improve, no more fluids were administered. In this way, peripheral perfusion parameters worked as a safety limit rather than a resuscitation target. A secondary aim of our study was to test the feasibility of a peripheral perfusion targeted resuscitation protocol. For this purpose we designed a simple algorithm that was easy to interpret and left little room for mistakes.

Limitations

Naturally, our study has some limitations. First, we included patients that were admitted to the ICU with suspected sepsis. Septic shock occurs in a heterogeneous population, and care before randomization can be variable. Because this is a single center study, this may limit the generalizability of our results. A future randomized trial should better monitor pre-inclusion resuscitation strategies. Secondary, this study is performed as

an open-label trial design.^{7,8} First, as blinding of the treatment team in a study like this is impossible, this imposes a great risk of bias. The study was however intended to mimic everyday bedside practice and such a design provides a closer reflection of everyday clinical practice compared to double-blind trials. Moreover, to minimize the risk of bias and protocol violation, all treating physicians were aware of the treatment protocol before the start of the study and were accompanied by a researcher, fully aware of the protocol, during the treatment period in patients randomized to the intervention group. Additionally, we chose to randomize patients after collection of baseline data, to minimize the likelihood of bias.⁹

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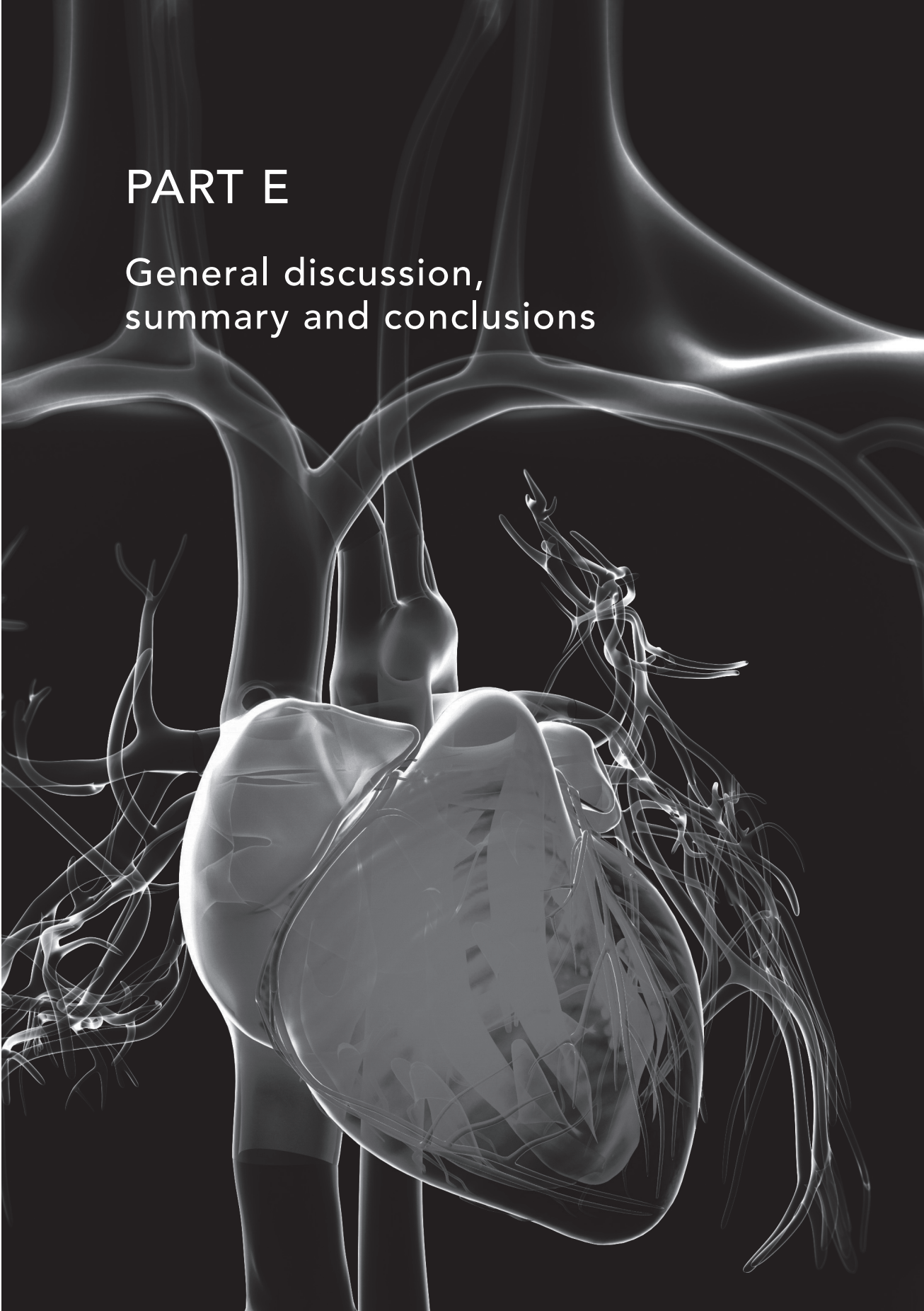
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PART E

General discussion,
summary and conclusions



General discussion
and future research
perspectives

11

*“Hemodynamic monitoring can be particularly helpful in the early stages of resuscitation, but is less useful when organ failure is established. Most importantly, one must never forget that it is not the monitoring itself that improves outcomes but the changes in therapy guided by the data obtained.”*¹

Jean-Louis Vincent as part of a consensus regarding hemodynamic monitoring, 2011. Professor Vincent is Professor of Intensive Care, Université Libre de Bruxelles and the Department of Intensive Care, Erasme University Hospital (Belgium). He is a member of the editorial board of more than 30 international journals, including the New England Journal of Medicine.

Already in 1947 the noninvasive assessment of peripheral perfusion was advocated as a valuable parameter to grade circulatory shock in the early phase.² Nowadays, physical examination has gained more skepticism: clinicians are more trained to evaluate scans and x-ray images even before they start talking to a patient or perform physical examination. This trend leads to an increased reliance on technology and consequently has reduced health carer’s confidence in traditional methods of physical examination. Consequently, when making clinical judgments there is a tendency to value numbers on a screen and an urge to perform further examination instead of relying on our own manual examination of a patient. Even when the latter might provide more useful information. For instance, a recent report by America’s national health insurance political advocacy regarding the use of diagnostic imaging claimed that 20- 50 % of all “high-tech” imaging provided no useful information and could be considered unnecessary.³ This suggests a widespread perception among many branches of medicine that today’s health care modalities are overused. This is surprising since there is an unsustainable rise in health care costs throughout the world.⁴ Surprisingly, increased health care costs per patient do not necessarily lead to better outcomes. To reduce the increase in health care costs and to warrant high-value, cost-conscious health care, the American College of Physicians convened a workgroup of physicians to identify, valuable screening and diagnostic tests in different clinical situations. It is therefore striking that examination of clinical skills is argued to be a poor value investment.⁵ Especially since warranting quality of physical examination of different physicians might improve health care quality and could lead to a decrease in costs and strengthen the physician–patient relationship.⁶

In this thesis we aim to demonstrate that a reliable assessment of the circulation of a patient can be obtained with physical examination. Using simple tests or non-invasive techniques, the peripheral perfusion (i.e. perfusion of skin and muscle of hand or foot) can be evaluated at the bedside, is easy to interpret, and is able to identify critically ill patients. In **Chapter 2A & 2B** we discuss several subjective assessments and optical techniques that could be used to monitor the peripheral perfusion.



Validation of peripheral perfusion parameters

The peripheral perfusion index (PPI) is derived from the photoelectric plethysmographic signal of the pulse oximeter. This index is calculated as the ratio between the pulsatile component (arterial compartment) and the nonpulsatile component (venous and capillary blood and other tissues) of the light reaching the detector of the pulse

oximeter. Peripheral vasoconstriction reduces the pulsatile component and thus decreases the PPI. Because a pulse oximeter is universally available in the operating room, emergency room, and intensive care unit (ICU), it could potentially be useful for the early detection of peripheral vasoconstriction in response to reductions in central blood volume. In **Chapter 3** we therefore investigated the ability of the PPI to reflect early peripheral vasoconstriction during controlled stepwise central progressive hypovolemia in twenty-five healthy male volunteers by applying lower body negative pressure (LBNP). During application of LBNP, the circulating volume is progressively redistributed from the upper to the lower body, inducing central hypovolemia, which triggers similar compensatory mechanisms as during acute hemorrhage and clinical hypovolemia, i.e. activation of the sympathetic nervous system. Already after the first LBNP step (-20 mm Hg), the mean PPI decreased substantially from baseline ($41\% \pm 6.0\%$). During this step stroke volume significantly decreased, while heart rate remained unaltered. The magnitude of the PPI decrease was statistically different from the changes in stroke volume and heart rate. With progressive LBNP, SV decreased and HR increased progressively. The PPI was low throughout the remainder of the protocol and returned to baseline values when LBNP was released. Mean arterial blood pressure remained in the same range throughout the experiment. These results indicate that the pulse oximeter-derived PPI may be a valuable diagnostic tool for the early detection of hypovolemia, before the onset of cardiovascular decompensation.

To further explore the effect of peripheral vasoconstriction on the different peripheral perfusion parameters, we performed a study in eight healthy volunteers in which we induced peripheral vasoconstriction by body surface cooling (**Chapter 4**). Cooling resulted in peripheral vasoconstriction in all volunteers with a significant decrease in the forearm-to-fingertip skin-temperature gradient ($T_{\text{skin-diff}}$) and the PPI. Subsequently we found that capillary refill time (CRT) changed similarly. CRT changed from 2.5 s (2.0–3.0) before cooling to 8.5 s (7.2–11.0) after 30 minutes of cooling and returned to normal after initiation of the rewarming process. Different systemic hemodynamic parameters, such as cardiac output, mean arterial pressure and heart rate did not change during cooling. We concluded that changes in the peripheral perfusion parameters reflect changes in peripheral vasomotor tone, independent of the systemic hemodynamic parameters.

Monitoring and resuscitation of the peripheral perfusion in critically ill patients

Supported by the findings in Chapter 4, we were curious to find out whether central hypothermia-induced peripheral vasoconstriction would have a similar effect on the different peripheral perfusion parameters. We therefore performed in **Chapter 5** a prospective observational study in patients who were treated with therapeutic hypothermia after out-of-hospital cardiac arrest. In addition to the previously mentioned methods we also used a Sidestream dark-field imager to visualize the sublingual microcirculation. We found that the early post resuscitation hypothermia phase is characterized by vasoconstriction in both the sublingual microcirculation

and the peripheral circulation. The impaired perfusion is aggravated by induced hypothermia and not by impaired cardiac output. Persistence of these tissue perfusion alterations after hypothermia is independently associated with the development of organ failure and mortality in this group of patients.

As early identification of critical illness is widely acknowledged as a vital step towards improving survival,⁷⁻⁹ we aimed to determine whether repeated assessment of the peripheral circulation in the days following surgery could help to early identify patients that develop postoperative complications. In **Chapter 6** we present the results of a prospective observational study in which we followed 111 consecutive patients who underwent elective major abdominal surgery. We found that peripheral perfusion alterations are associated with the development of severe complications, independently of systemic hemodynamics. Notably, peripheral perfusion alterations were already present in these patients immediately after surgery and became even more predictive over time. These abnormalities were present approximately 2–12 times more often in patients with severe complications.

Although CRT has gained widespread acceptance as one of the strongest red flags to identify infection and tissue hypoperfusion in pediatric patients,¹⁰ its reproducibility and thus its reliability is still doubted in critically adult patients. For the first time in a postoperative population we studied CRT reproducibility and found a good overall agreement between different observers. It can thus be concluded that manual assessment of the peripheral perfusion is reliable, improves risk stratification independently of systemic hemodynamics, and can be used immediately after surgery to discriminate patients at high risk for developing severe complications. Early identification of patients at risk could help the surgeon to early adopt postoperative strategies tailored on individual basis and opens the perspective of new goal directed therapies.

In view of goal directed therapies, the predictive value of the course of peripheral perfusion parameters over time has not been studied. For this purpose we evaluated the additional value of repeated assessment of the peripheral perfusion in septic shock patients (**Chapter 7**). We retrospectively analyzed thirty-five septic shock patients that were admitted to the ICU. In these patients, unfavorable evolution of the peripheral perfusion in the first days following initial resuscitation is strongly predictive of mortality in septic shock patients. Moreover serial assessment of peripheral perfusion, i.e. unfavorable evolution of both CRT and PPI, was more predictive for mortality when compared to a single assessment of peripheral perfusion.

The chapters above describe the potential additional value of peripheral perfusion assessment in critically ill patients. Its use in resuscitation is however still unknown. In light of this findings we conducted a prospective double-blinded study in postoperative esophagectomy patients admitted to the ICU (**Chapter 8**). These patients are known for their postoperative systemic “sepsis-like” inflammatory response and high morbidity and mortality rates. To observe microcirculatory peripheral perfusion, we visualized sublingual microvascular perfusion using SDF-imaging. We randomized 20 postoperative esophagectomy patients in two groups: the intervention group (received a small dose of dobutamine: 2.5 µg/kg/min) directly postoperative and the placebo



group (syringe with saline). At the first postoperative day, patients in the placebo group, showed altered sublingual microvascular perfusion, which could be prevented in the dobutamine group. These disturbances were not seen when we compared these findings with controls, patients after pancreaticoduodenectomy.

This study was however limited in providing pathophysiological rationale as we could not establish whether dobutamine showed a true effect of recruitment itself, or whether this was the result of a complex of therapeutic interventions. Moreover, little was known about the use of regional tissue perfusion parameters as a direct target for resuscitation. We therefore designed an experimental study to examine the effect of cardiac output resuscitation on different microvascular perfusion and peripheral perfusion parameters during endotoxemic and obstructive shock states in pigs (**Chapter 9**). The main finding of this study was that the relationship between the systemic circulation and regional perfusion is dependent on the underlying cause of circulatory shock. The correction of cardiac output to normal levels is adequate for resuscitation of the regional perfusion parameters after obstructive shock but not after endotoxemic shock. In the latter model, only additional cardiac output-targeted fluid resuscitation to supranormal values could further improve the regional perfusion. These findings highlight that additional resuscitation at the regional (microcirculatory) perfusion level might be a complementary target if the conventional global resuscitation goals have been achieved during endotoxemic shock. It also raises the question whether we should aim at full recovery of microcirculatory disturbances in septic shock.^{11,12}

In the last part of my thesis, **Chapter 10**, we performed a prospective randomized controlled pilot-study in 30 septic shock patients admitted to the Intensive Care Unit between October 2011 and November 2013. In this study we investigated whether peripheral perfusion guided fluid resuscitation is feasible and would lead to less fluid administration compared to the currently used hemodynamic endpoints. Patients were randomized into two groups, i.e. the control group (standard fluid therapy) or the intervention group (Peripheral Perfusion Targeted Fluid Management – PPTFM group) in whom peripheral perfusion parameters were taken into consideration before each fluid challenge. We found that patients randomized to the PPTFM group received less mean fluids compared to the control group. Although the difference in fluid administration was not significant, PPTFM patients received almost 2 liters less in the first 6 hours after ICU admission, leading up to 2.5 liters less 72 hours after ICU admission. These findings support our hypothesis that peripheral perfusion parameters can both be used as diagnostic tool and as a target in the resuscitation of critically ill patients.

Altogether, peripheral perfusion can be assessed at the bedside by physical examination and simple objective tools. It is reliable, and can be repeated as often as necessary.

Future research perspectives

Although this thesis demonstrated that evaluation of the peripheral perfusion provides an inexpensive good prognosticator for organ failure and outcome in different patient populations, several questions still remain unanswered.

We have demonstrated that, despite systemic hemodynamic optimization, tissue perfusion alterations can persist in different patient populations. Additionally it has been demonstrated that microcirculatory perfusion can be improved by some inotropes but not by others.¹³ It can be hypothesized that interventions directed at the regional tissue perfusion level may help bridging the gap between improved hemodynamics and patient outcome. In patients with septic shock, dose-dependent infusion of nitroglycerin reverted abnormal peripheral perfusion and poor tissue oxygenation in patients following circulatory shock resuscitation.¹⁴ Contrastingly Boerma and colleagues failed to show significant differences in the evolution of the sublingual microcirculation between septic shock patients treated without and those treated with nitroglycerin.¹⁵ Although this study precluded the effectiveness of nitroglycerin in the sublingual microvascular flow, the fixed dose of nitroglycerin used (2 mg/hour) was able to significantly increase skin blood flow as measured by central-to-toe temperature gradient in the treatment group. In addition to that finding, the authors reported lower Sequential Organ Failure Assessment (SOFA) scores in patients who received nitroglycerin compared with the placebo group. Therefore it still needs to be proven whether these abnormalities in peripheral perfusion when incorporated in a diagnostic/treatment plan do improve patient outcome.

A large powered randomized controlled multicenter trial is warranted to investigate whether peripheral perfusion assessment could help in a (postoperative) patient tailored treatment. Moreover recent publications give increasing awareness of the potential for harm due to the excessive fluid administration in patients with septic shock. This future randomized trial should be taken the previous into account and therefore should target (fluid) resuscitation in a goal-directed manner and targeted to physiologic needs of individual patient, to avoid the risk of over-resuscitation. We hypothesize that early goal-directed fluid resuscitation guided by endpoints of peripheral tissue perfusion might lead to less fluid administration and might result in improved outcome in different patient populations. Currently, protocols are being designed to conduct such a study.

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Summary and conclusions

12

Hemodynamic monitoring is a cornerstone in the care of the critically ill patient. Monitoring techniques have greatly improved over the last decade and technologies have evolved from invasive to non-invasive monitoring devices. The rationale of peripheral perfusion monitoring is based on the concept that peripheral tissues are the first to reflect a disturbance of the circulation that frequently characterizes shock*, independent of systemic hemodynamics. Peripheral perfusion monitoring not only provides a different point of reference for patient circulation, but is also non-invasive and can be used directly at the bedside.

In patients after out-of-hospital cardiac arrest, after major abdominal surgery, and in a heterogeneous intensive care unit population, persistence of these alterations is associated with organ failure and death, independent of systemic hemodynamics (i.e., heart rate, blood pressure, and cardiac output). Moreover, in septic shock patients, early peripheral perfusion targeted fluid resuscitation leads to a trend towards less fluids when compared to a conventional regimen based on systemic hemodynamic parameters. These findings demonstrate that assessment of the peripheral perfusion could be used to early identify specifically those patients in need of additional therapy and open the perspective of peripheral perfusion targeted resuscitation.

It can thus be concluded that assessment of the peripheral perfusion can be easily performed at the bedside, can be rapidly instituted throughout the hospital, and could be a potential target to optimize the circulation. Still, its role as an efficient target for resuscitation warrants further investigation.



*Circulatory shock is a life-threatening syndrome resulting in multiorgan failure and a high mortality rate.

Cecconi M, De Backer D, Antonelli M, et al.: Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med.* 2014;40:1795-815.

Samenvatting en conclusie

13

Monitoring van de perifere circulatie is gebaseerd op het concept dat perifere weefsels de eerste zijn die hypoperfusie laten zien tijdens circulatoire shock en de laatste die herstellen tijdens de behandeling. De beoordeling van de perifere circulatie is daarmee niet alleen een referentiepunt voor de beoordeling van de circulatie, maar kan met eenvoudige klinische beoordelingen en monitoringstechnieken op een non-invasieve wijze aan het bed van de patiënt worden uitgevoerd. Bovendien is het klinisch beoordelen van de perifere perfusie eenvoudig, snel, goedkoop en uitvoerbaar in vrijwel iedere patiënt. Bij patiënten na reanimatie, na grote chirurgische buikoperatie en bij ernstig zieke patiënten opgenomen op de Intensive Care is een blijvend afwijkende perifere perfusie gerelateerd aan een verhoogd risico op orgaanfalen en overlijden, ook als de waarden van conventionele hemodynamische parameters, zoals bloeddruk en hartfrequentie, na behandeling normaliseren. Bij patiënten met ernstige septische shock (een aandoening die wordt veroorzaakt door een infectie in de bloedbaan, waarbij de bloeddruk gevaarlijk daalt en tot orgaanfalen kan leiden), leidt een op de perifere circulatie getitreerd vochtbeleid tot toediening van minder vocht wanneer deze wordt vergeleken met een vochtbeleid dat alleen gebaseerd is op verschillende conventionele hemodynamische parameters. Mogelijk kunnen interventies die de perifere circulatie verbeteren het klinisch herstel bespoedigen bij ernstig zieke patiënten.

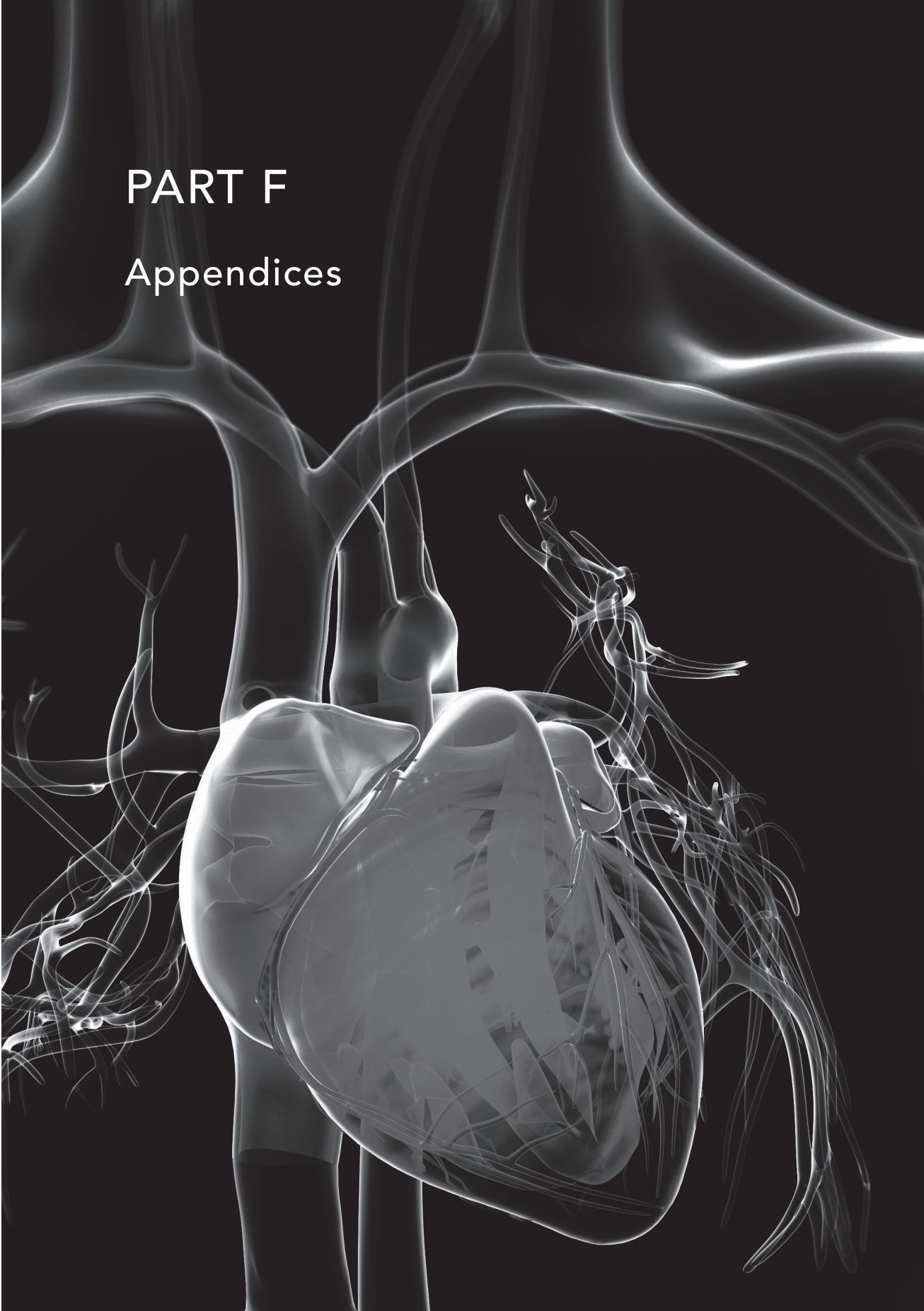
De perifere circulatie kan met de huidige non-invasieve methoden eenvoudig aan het bed van elke ernstig zieke patiënt, waar ook in het ziekenhuis, worden beoordeeld. Interventies die de perifere circulatie gebruiken als doel van therapie zouden het klinisch herstel van ernstig zieke patiënten kunnen bespoedigen. Alhoewel we positieve effecten hebben gezien van een dergelijke aanpak moet een definitieve gerandomiseerde studie dit nog bevestigen.





PART F

Appendices



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List of publications
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B

Publications related to this thesis

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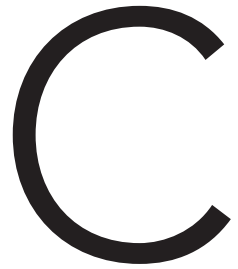
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Book contributions

- Lima A, **van Genderen ME**, Bakker J: Clinical significance of peripheral circulation abnormalities in critically ill patients. *33rd ISICEM - Annual Update in Intensive Care and emergency Medicine* 2013; 200-12



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Acknowledgements - Dankwoord

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PhD Portfolio

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PhD Portfolio

Summary of PhD training and teaching activities.

Erasmus MC Department: Intensive Care
 Research School: COEUR
 PhD period: July 2010- December 2012
 Promotor: Prof.dr. J. Bakker
 Supervisor: Dr. J. van Bommel

1. PhD TRAINING	Year	Workload (ECTS)
General courses		
– Course in statistics in Intensive Care – prof. E. Lesaffre	2009	0.5
– Biomedical English Writing and Communication	2011	4
In-depth COEUR courses		
– Research seminars (Friday afternoon)	2009-2011	1.2
– Cardiovascular Medicine	2011	1
– Intensive Care Research	2012	1.5
Specific courses		
– Postgraduate course on microcirculation and mitochondrial dysfunction, Lisbon, Portugal	2008	1.0
– “The understanding and clinical use of StO ₂ ”, Rotterdam, The Netherlands	2011	0.5
Presentations		
– “The microcirculation in critically ill” COEUR research seminar	2009	0.5
– “Microcirculatory resuscitation” COEUR Intensive Care Research	2012	0.5
National conference – participation and presentation		
– Nederlandse Intensivistendagen (NVIC), Ede, Netherlands <i>Oral presentation</i>	2013	0.5
International conferences – participation and presentations		
– 21 th ESICM, Lisbon, Portugal <i>Two poster presentations</i>	2008	1.5
– 30 th ISICEM, Brussels, Belgium <i>Poster presentation</i>	2010	0.9
– 23 th ESICM, Barcelona, Spain <i>Poster presentation</i>	2010	1.2
– 31 th ISICEM, Brussels, Belgium <i>Two poster presentations</i>	2011	1.2
– 24 th ESICM, Berlin, Germany <i>Two poster presentations</i>	2011	1.5
– 25 th ESICM, Lisbon, Portugal <i>Two oral presentations</i>	2012	1.5
– 27 th ESICM, Barcelona, Spain <i>Oral presentation</i>	2014	1.2
Seminars and workshops		
– “Lactate in goal directed therapy”, Rotterdam, the Netherlands	2010	0.25
– PhD day 2010	2010	0.25
– Photoshop illustrator workshop	2010	0.25
– CPO Minicursus	2011	0.25
– PhD day 2011	2011	0.25
– Intensive Care Adults research meetings (weekly)	2011-2012	1
– Various intensive care (evening) symposia	2011-2012	0.5
– 10 th Winter Workshop Intensive Care, Alpbach, Austria	2012	1.5
– ‘Hemodynamiek “How we do it”’, Rotterdam, the Netherlands	2012	0.5



2. TEACHING

Lecturing

- Esophagectomy patients at the Intensive Care Unit	2010	0.5
- Monitoring of microcirculation and peripheral perfusion in the Intensive Care Unit	2010-2011	2
- Quantification of microcirculation using MAS software	2011	1
- Abnormal StO ₂ in critically ill patients: clinical relevance	2011	1

Supervising practicals

- Assisting circulation practitioner D. Beach	2010-2011	0.5
- Assisting circulation practitioner L. Zang	2010-2011	0.5
- Various classes 'anaesthesia and intensive care' minor students	2010-2011	1

Supervising Master's theses

- Co-supervision of T. Boerstra	2011	1
- Co-supervision of J. Paauwe	2012	1
- Co-supervision of N. Engels	2013	1

Writing

- "Cordiaal", the journal for cardiac care nurses Contribution: " <i>Monitoring van de perifere perfusie</i> "	2011	1
- 33 rd ISICEM - Annual Update in Intensive Care & Emergency Medicine Book contribution: book chapter " <i>Clinical significance of peripheral circulation abnormalities in critically ill patients</i> "	2013	1

ECTS: European Credit Transfer and Accumulation System. 1 ECTS credit represents 28 hours

COEUR: Cardiovascular Research School Erasmus University Rotterdam

ESICM: Annual Congress of the European Society of Intensive Care Medicine

ISICEM: International symposium on Intensive Care and Emergency Medicine

Curriculum Vitae

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Curriculum Vitae

Michel Egide van Genderen was born on the 22th of January 1986 in Rotterdam, the Netherlands. In 2005, he completed secondary school at Zadkine College, Capelle aan den IJssel. That same year he attended medical school at the Erasmus MC - University Medical Center, Rotterdam, The Netherlands. In 2006 he started working as a medical student-assistant in the department of Intensive Care Adults, Unit I. From 2007 onwards, he combined his medical training and work as a medical student-assistant by supporting in several research projects for the department of Intensive Care Adults (all units). These projects led to an increased interest in circulation research – a subject he dedicated his research elective to obtain his master's degree (doctoraal examen). This work resulted in a publication regarding postoperative sublingual microcirculatory perfusion in patients following esophagectomy, chapter 8 respectively.

Under the supervision of Prof.dr. J. Bakker and Dr. J. van Bommel he commenced his PhD work in July 2010, studying the importance of peripheral perfusion assessment in critically ill patients. During the final year of his PhD training, Michel was a board member of the Co-Raad Rotterdam, which organizes seminars, workshops, and activities for medical interns at the Erasmus MC.

In February 2013, Michel commenced his internships at the Erasmus MC - University Medical Center, Rotterdam. During this time period he also worked on the last chapters of this manuscript. Michel will complete his final examination in medicine on the 20th of March 2015. Beginning May 2015, Michel will begin as a resident in the department of Internal Medicine at the Sint Franciscus Gasthuis, Rotterdam. Per January 1, 2016 Michel will start his specialty training in the department of Internal Medicine at the Sint Franciscus Gasthuis under the supervision of Dr. S.C.E. Klein Nagelvoort-Schuit (Erasmus MC, Rotterdam, the Netherlands) and Drs. A.P. Rietveld (Sint Franciscus Gasthuis, Rotterdam, The Netherlands).



