

# **Noninvasive Monitoring Of Peripheral Perfusion In Critically Ill Patients**

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# Noninvasive Monitoring Of Peripheral Perfusion In Critically Ill Patients

*Beoordeling van de perifere circulatie bij  
ernstig zieke patienten*

## **Thesis**

to obtain the degree of Doctor from the  
Erasmus University Rotterdam  
by command of the  
rector magnificus

**Prof.dr. H.G. Schmidt**

and in accordance with the decision of the Doctorate Board  
The public defense shall be held on  
Thursday 14th March 2013 at 15:30 hrs

**by**

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*... to the memory of my father*



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# **Introduction**

Introduction: a historical perspective



## SHOCK

The evolution of medical knowledge over history happened more recently than advances in the art, industry and other sciences. The industrial revolution through the 18<sup>th</sup> and 19<sup>th</sup> centuries was bringing innovations and transforming life in America and Europe whereas it was widely accepted that diseases were the result of an imbalance in humours, and one of the conventional treatments to bring back the good healthy was draining blood through a phlebotomy (bloodletting) (1). Bloodletting was a common 'cure for everything' from ancient times until the nineteenth century. The practice gained wide acceptance in America in the eighteenth century with Dr. Benjamin Rush, who treated George Washington for acute laryngitis by draining one liter (nine pounds) of blood in less than 24 hours (2). George Washington died soon afterward. In that time, there was no knowledge of the association between loss of blood and circulatory shock. In fact, shock was still an abstract concept, usually described as 'sudden vital depression', 'great nervous depression', or 'final sinking of vitality'. The history of hemodynamic monitoring overlaps with the history of shock and much of the history of shock relates to the history of traumatic shock. The term *shock* only came into clinical use with *Edwin A. Morri*, who began to popularize the term using it in his 1867 Civil War text, 'A Practical Treatise on Shock After Operations and Injuries' (3). Since then, the word *shock* started to be linked with the concept of cardiovascular collapse. In the same year, a British Surgeon named Jordan Furneaux wrote what it is known to be one of the first elaborate descriptions of abnormalities in peripheral perfusion during shock conditions (4). In his description, he emphasized the cold, clammy and mottle skin associated with high heart rate (**Figure 1**). The belief held by notable physicians of that time was that those alterations in peripheral perfusion during shock were the result of a disorder of the nervous system, known as 'nervous collapse'. Despite these results, the final studies about neural regulation of cardiovascular function in shock did not occur until 1950s.

The era of modern hemodynamic monitoring begins, in many ways, with two important technological advancements: the ability to measure blood pressure noninvasively and cardiac output. After the introduction of the mercury sphygmomanometer in 1896 by Scipione Riva-Rocci, hypotension started to be used to define shock (5). Riva-Rocci introduced the now familiar instrument that collapses vessels by means of an inflatable cuff which became generally adopted (**Figure 2**). Later on, the work of German doctor Werner Frossman, with studies done of right heart catheterization, earned him the Nobel Prize in Medicine and Physiology in 1956 (6) (**Figure 3**). The primary purpose was to develop a technique for direct delivery of drugs to the heart. His success culminated later on with the development of the thermodilution cardiac output measurements with flow-directed pulmonary artery catheter by Swan and Ganz (7). The ability to measure blood pressure and cardiac output contributed to a great extent to the understanding of

THE  
**Hastings Prize Essay,**  
 1866.  
 ON  
**SHOCK AFTER SURGICAL OPERATIONS  
 AND INJURIES.\***

BY  
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**SYMPTOMS OF SHOCK.**

IN describing shock, it is desirable to select a case where the intensity of the condition is of a striking and well marked character; for shock, like other deviations from health, presents every degree of intensity, from a condition so slight that its existence may be doubted, to one in which it can scarcely be distinguished from death. Suppose, then, that a limb has been crushed—possibly the knee-joint opened, or a large portion of the skin of the trunk has been burnt, or the uterus has been extensively ruptured, or a small hernia has become suddenly strangulated, or the thigh has been amputated in the upper third or at the hip-joint: on examining the recipient of any such severe injury, we should find him as pale, as motionless, as indifferent to the outward world, as if the injury had already terminated in death. The pallor of the skin has the sickly white hue which only bloodless human skin is capable of presenting. The ruddiness of the lip has gone, and is replaced by a clearer and whiter tinge than that of the skin. The cornea, in severe cases, are directed upwards, so that the whites of the eyes only are seen; but the altered axis of the eye is more apparent than real, because the upper lid is more or less depressed. The conjunctiva is lustreless, or even "glazed". The features are smaller, especially the nose, the tip of which is constricted, and occasionally of a dusky colour, presenting a singular contrast to the rest of the face. The nostrils appear dilated. The lips are parted, and thin as well as pale. The whole countenance is so much changed, that recognition may be difficult to near relatives and friends. The surface of the body is everywhere cold to the touch; and, if consciousness be partially present, cold is also complained of. Small drops of moisture lie on the skin, especially of the forehead. The hands are blanched like the face; the fingers and nails exhibit a bluish colour, and are shrunk, so that the skin on the palmar aspect lies in loose folds. Those parts of the body which are usually covered, though presenting less change of colour, are perceptibly whiter. There is marked inaction of the whole muscular system, the position of the body being either on the back, or, in extreme cases, in the position in which bystanders have placed it. In less severe cases, muscular action is impaired, but not absent. In cases where the shock is due to

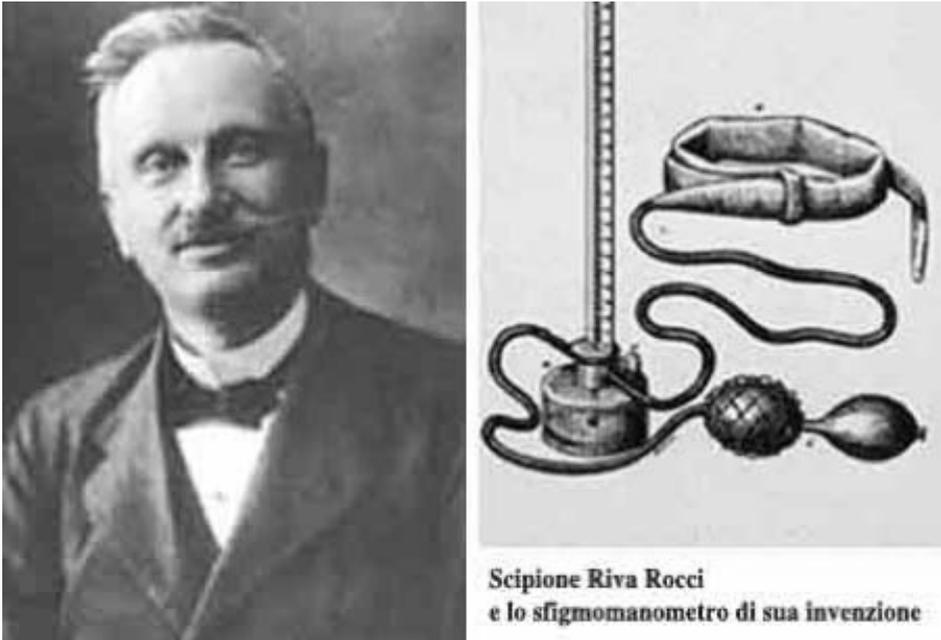
great but not sudden loss of blood, the stillness of the muscular system will be replaced by the tossing restlessness, and possibly delirium, so characteristic of unchecked hæmorrhage, either internal or on the surface of the body. It is commonly said, that the action of the heart is accelerated; it is certainly enfeebled, the pulse being also irregular and intermittent. But the pulse is not rapid in all cases. (I do not hesitate to say—and this question I shall examine later—that in every case of shock there is at first, and for a longer or shorter time, diminished frequency of the heart's action.) In strangulated hernia commonly, and in some injuries of the head, the pulse is often remarkably slow, descending to 40 or even 30 beats; yet in these cases we have the purest examples of shock, as regards the depression of the nervo-muscular force. The action of the heart may be so feeble, that neither it nor the pulse at the wrist can be detected. Consciousness, the intellect, and the sensibilities, are blunted, and the will paralysed; or it may be that consciousness, the intellect, the sensibilities, and the will, are extinguished for a time. Deglutition may be difficult, and the contractility of the sphincters lost. The urinary secretion and glandular activity generally is arrested or retarded. The special senses are rendered more or less unimpressible. Articulation is imperfect, and the voice feeble or altogether lost. Respiration is feeble; but it becomes quickened with the pulse, though not in any fixed ratio. Its chief peculiarity is irregularity. Most of the inspirations are shallow and of the most varying degrees of rapidity. Sighing inspirations are frequent, but with no regular order of succession. Respiration may be so feeble as to be with difficulty detected. Deglutition is mostly possible as to fluids, and to solids thrust within the reach of the constrictors. Nausea and vomiting may also be present, but rarely in the most marked periods of shock. If the rectum be loaded at the occurrence of the injury, the contents will be spontaneously evacuated. The contents of the bladder are retained.

In the slighter forms of shock, the surface is cold, and the recipient of the injury complains, often repeatedly, of feeling cold. Muscular action is much impaired, but not suspended; indeed, impaired muscular action and enfeebled circulation are the most apparent characteristic indications of the slighter forms of shock. The pulse is feeble, intermittent, fluttering, and irregular. Respiration is shallow, with irregular sighs; the sighs being every second or third inspiration at one time, at the fifth or seventh at another, at the ninth or tenth at another. The brain, unless the injury have been direct to the head, is comparatively active, especially if the position of the body be recumbent, but quite unequal to the higher efforts of the intelligence. Digestion, the intestinal peristaltic action, and gland-secretion, are all retarded. Nausea and vomiting often occur in this degree of shock.

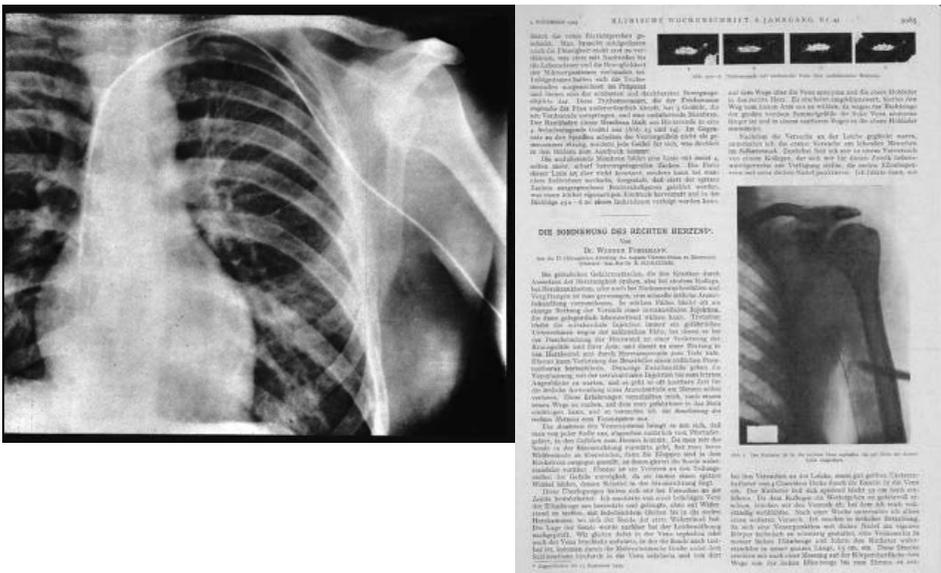
Shock is not always proportionate in its intensity to the severity of the wound. It may be severe when the injury is slight, or it may be slight when the injury is severe. Many circumstances contribute to this apparent inequality in the operation of given causes. But this remark applies chiefly to the varieties of shock other than the most severe. In the most intense form of shock which is compatible with the continuance of life, the nature of the injury,

\* Continued from page 76 of JOURNAL for Jan. 26th.

**Figure 1.** One of the first descriptions of abnormalities in peripheral perfusion during shock conditions done by Dr. Jordan Furneaux. He emphasized the cold, clammy and mottle skin associated with high heart rate (underlined)



**Figure 2.** The ability to measure blood pressure with the mercury sphygmomanometer was first developed by *Riva-Rocci S.*



**Figure 3.** Werner Forssmann (1904–1979), Berlin, introduced a ureteral catheter into his left basilic vein (1929). Thorax X-ray and his paper. His success culminated later on with the development of the thermodilution cardiac output measurements

pathophysiology of shock. Thus, the definition of shock and its alterations over decades correlated with advancements in technology used to assess the condition. In the 1940s, shock definition was based only on blood volume alterations (8). In 1950s, shock definition was expanded to the concept that shock condition could become irreversible (9). In 1960s, low cardiac output started to be used to define shock, and more recently with current knowledge, shock definition is extended to the cellular level (**Table 1**)(10;11).

### ***Systemic versus Local Regulation***

One important step in the understanding of the dynamics of shock was the recognition of the participation of peripheral circulation. In this context, one of the earliest references about dynamic component of peripheral vascular bed is the work of Danish scientist August Krogh in the 1920s. He addressed fundamental issues underlying the behavior of the microvasculature during physiological stimulus. In his line of work, he demonstrated adaptive microvascular adjustments in the muscle during exercise (12). His investigations suggested a selective increase in the delivery of oxygen to the tissue by mechanisms of recruitment or derecruitment of capillaries with an active blood flow. For this, he was awarded the Nobel Prize in 1920 and became an internationally well known biomedical scientist during the first decade of the 20th century.

**Table 1.** Definitions of shock over last decades. From *blood volume alterations* to *celular injury*.

**“shock is a peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid.”**

Alfred Blalock, 1940s (8)

**“shock is a syndrome that results from a depression of many functions, but in which reduction of the effective circulating blood volume is of basic importance, and in which impairment of the circulation steadily progresses until it eventuates in a state of irreversible circulatory failure.”**

Carl Wiggers, 1950s (9)

**“a clinical condition characterized by signs and symptoms, which arise when the cardiac output is insufficient to fill the arterial tree with blood, under sufficient pressure to provide organs and tissues with adequate blood flow.”**

Simeone, 1960s (10)

**“state in which profound and widespread reduction of effective tissue perfusion leads first to reversible, and then if prolonged, to irreversible cellular injury.”**

Kumar and Parrillo, 2001 (11)

August Krogh studies not only provided one of the fundamental principles of blood-tissue perfusion relationship, but also attracted a new generation of clinical investigators who ameliorate human studies in the circulatory function. From the 1930s and 1940s, physiology was beginning its growth as a science and investigations of the phenomena of shock and variations of local blood flow in the peripheral circulation became the focus of scientists' attention. During this period, many investigators have shown that the terminal network of microscopic-sized vessels represents an organic unit essential in the maintenance of tissue perfusion. But it was in 1950 that the American physiologist Carl John Wiggers, in his experimental studies of hemorrhagic shock, introduced the term 'peripheral circulation failure' by demonstrating the association between acute reduction of circulating blood volume and impairment of perfusion at the tissue level (13). His studies were followed by a broad spectrum of basic physiologic questions that was posed with respect to the participation of the peripheral circulation under circulatory shock conditions.

Although in the early 1900s the scientific community had already realized the existence of other origins of shock than trauma, it was only in the 1920s and 1940s that it became recognized that intravenous administration of endotoxins (e.g., typhoid toxin) could produce hypotension. Some doctors even suggested a therapeutic use for endotoxin derived from *P. aeruginosa* to treat malignant hypertension, fortunately a treatment further rejected by the medical establishment (14). The connection between hypotension and peripheral vasodilatation in the so-called vasodilatory shock was first published in a review by Gilbert in 1960 (15). It was clear from his review that local vascular changes and general cardiovascular alterations were both part for endotoxin challenge. He suggested that changes in systemic vascular resistance could not provide information about local vascular resistance changes and describe this phenomenon as "dilation in one (vascular) bed might be accompanied by constriction elsewhere", and he was one of the first to provide evidence of heterogeneous distribution of blood flow in sepsis. This phenomenon was later confirmed with the use of intravital microscopy in 1960s with experimental shock models, when it became apparent the different behavior between peripheral circulation within organs and systemic circulation during acute shock situations (16). This overlap "systemic versus local regulation" led a shift in thinking concerning separate sets of regulatory mechanisms for central and peripheral circulation during shock conditions. In this regard, the work of the physiologist Arthur Clifton Guyton was perhaps one of the most important scientific contributions in this field. Guyton is most famous for his experiments in the 1950s and 1960s, which studied the physiology of cardiac output and its relationship with the peripheral circulation. He elaborated the *Frank-Starling law of the heart* by showing that it is not only the function of the heart which controls cardiac output but instead that cardiac output is controlled by the various factors in the peripheral circulatory system which regulate the return of

blood to the heart. It was Guyton who formalised that the venous return is approximately proportional to the mean circulatory filling pressure minus the right atrial pressure, which pressure difference is called the “pressure gradient for venous return” (17). The clinical relevance of such studies became apparent in 1970s and 1980s when investigators recognized that resuscitation is based on knowledge of fundamental physiological variables not only of central but also of peripheral circulation.

### ***Monitoring of Peripheral Perfusion***

In 1958, Dr. Weil, in an attempt to perform real time measurements of vital signs and alarms in a four-bed unit called “shock Ward”, introduced continuous monitoring of electrocardiogram, blood pressure, pulse rate, respiratory rate, and other vital signs complemented by arterial and central venous pressures, urine output and by peripheral temperatures. With initial emphasis in myocardial infarction complicated with cardiogenic shock, it was the first prototype of an intensive care unit with continuous monitoring, that later became a 42-bed intensive care unit at the University of Southern California. His service pioneered routines of bedside monitoring and measuring devices, including the earliest use of arterial and central venous catheters (18). In 1960s, respiratory and hemodynamic measurements were complemented by laboratory measurements, including lactate and blood gases analysis. Critical care medicine has emerged as an independent multidisciplinary speciality with first organization created in 1967 by Drs. Safa, Shoemaker and Weil, which evolved into the ‘Society of Critical Care Medicine’. Over the years that followed, increasingly more sophisticated hemodynamic and respiratory methods of monitoring were introduced. Weil was one of the first investigators to study the relationship between peripheral circulation measured with skin temperature and prognosis of low flow shock. In 1969, in a cohort of 100 patients (44 nonsurvivors) admitted with diagnosis of cardiogenic or hypovolemic shock, he showed that the likelihood of death was high when skin temperature measured on great toe persisted low ( $<27^{\circ}\text{C}$ ) during the first three hours of admission (19). He also found a high correlation between skin temperature and cardiac output. Weil suggested that skin temperature measurements in low flow shock could be an alternative approach to overcome the technical difficulty of measuring cardiac output, which by that time was still problematic at the bedside.

New concepts have evolved which defined organ or systemic failures. Clinical reports of patients who developed multiple organ failure after trauma, shock or sepsis started to emerge describing the factors contributing to organ dysfunction. In the 1970s, systemic organ perfusion was assessed indirectly at the bedside by measuring the degree of derangement in global variables, such as cardiac output, lactic acidosis and base deficit, and resuscitation of the critically ill was based on normalization of these global hemodynamic values. In the 1980s, some studies proposed to increase cardiac output or oxygen

delivery to so-called 'supranormal' values, an alternative approach aiming at adequate organ utilization (20;21). In 1990s, it became clear that even though global hemodynamic variables may be normalized, there may be regions with inadequate oxygenation at the tissue level, suggesting the importance of assessment of regional oxygenation at the organ level. Of all the various tissue-specific vascular beds that could be monitored, the gut mucosa, more specifically, the gastric mucosa was more appropriated due to its easy assessment. Gastric tonometry was then effectively introduced in the clinical practice for the assessment of the adequacy of local gastrointestinal perfusion, and it represents an important landmark in the history of peripheral hemodynamic monitoring (22-25). Since the introduction of gastric tonometry has proved to be of prognostic value, the field of regional noninvasive monitoring gained wide interest, and studies started to address the importance of monitoring peripheral vascular beds more susceptible to hypoperfusion, such as skin, muscle, and gastrointestinal tract.

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## OUTLINE OF THESIS

The present thesis aims to address several aspects of monitoring peripheral perfusion in critically ill patients, from defining the basic concepts and methodological issues to clinical studies further exploring the potential prognostic value of noninvasive monitoring of peripheral perfusion in different patient groups.

**PART A** presents a brief introduction to the concepts of noninvasive monitoring of peripheral perfusion and summarizes current knowledge about available techniques to detect abnormalities of peripheral perfusion and oxygenation in critically ill patients (Chapter 1). Additionally, it provides relevant background information and discusses clinical applicability of such monitoring approach at the bedside (Chapter 2).

**PART B** presents and discusses some of the methodological aspects of peripheral perfusion monitoring focusing mainly on portable optical devices. Chapter 3 introduces and validates the *perfusion index* from the pulse oximetry signal to detect abnormal peripheral perfusion. First, it describes the variation of this variable in healthy individuals. Then, it shows its relationship with clinical indicators of poor peripheral perfusion in critically ill patients. Chapter 4 presents a comprehensive evaluation on the issue of best measurement site (Forearm vs. Thenar) and probe spacing (15 mm vs. 25 mm) to assess peripheral tissue oxygenation (StO<sub>2</sub>) using near-infrared spectroscopy (NIRS). Chapter 5 and 5a evaluates and discusses the potential contribution of variations in peripheral blood flow on NIRS-derived signal, induced either by peripheral cooling or head-up tilt test.

**PART C** reports a series of observational studies investigating the prognostic factor and potential clinical applications of monitoring peripheral perfusion noninvasively. Chapter 6 analyses the predictive value of clinical abnormalities in peripheral perfusion for organ and metabolic dysfunction in critically ill patients. Chapter 7 describes the prognostic value of continuous monitoring of StO<sub>2</sub> during early goal-directed therapy of critically ill patients. Chapter 8 and 8a discuss the relationship between the condition of peripheral circulation and NIRS-derived measurements of tissue oxygenation in critically ill patients. Additionally, it describes the predictive value of both parameters in identifying an unfavourable outcome for severe organ and metabolic dysfunction.

**PART D** discusses administration of nitroglycerin as vasodilator therapy to reverse peripheral hypoperfusion and presents the results of an intervention study with step-wise dose of intravenous infusion of nitroglycerin to improve clinical abnormalities of peripheral circulation in patients with circulatory shock (Chapter 9).

**PART F** presents general discussion, main findings, conclusion, summary of this thesis, and recommendations for future work.





## **PART A**

Available noninvasive methods to monitor peripheral perfusion and oxygenation



# Chapter 1

## Non-invasive monitoring of peripheral perfusion

*Intensive Care Med 2005; 3:1316-1326*

*Alexandre Lima, Jan Bakker*

**ABSTRACT**

Early hemodynamic assessment of global parameters in critically ill patients fails to provide adequate information on tissue perfusion. It requires invasive monitoring and may represent a late intervention initiated mainly in the intensive care unit. Noninvasive monitoring of peripheral perfusion can be a complementary approach that allows very early application throughout the hospital. In addition, as peripheral tissues are sensitive to alterations in perfusion, monitoring of the periphery could be an early marker of tissue hypoperfusion. In this review, we discuss noninvasive methods for monitoring perfusion in peripheral tissues based on clinical signs, body temperature gradient, optical monitoring, transcutaneous oximetry, and sublingual capnometry. Clinical signs of poor peripheral perfusion consist of a cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time. The temperature gradients peripheral-to-ambient, central-to-peripheral and forearm-to-fingertip skin are validated methods to estimate dynamic variations in skin blood flow. Commonly used optical methods for peripheral monitoring are perfusion index, near-infrared spectroscopy, laser Doppler flowmetry and orthogonal polarization spectroscopy. Continuous noninvasive transcutaneous measurement of oxygen and carbon dioxide tensions can be used to estimate cutaneous blood flow. Sublingual capnometry is a noninvasive alternative for gastric tonometry.

## INTRODUCTION

An important goal of hemodynamic monitoring is the early detection of inadequate tissue perfusion and oxygenation to institute prompt therapy and guide resuscitation, avoiding organ damage. In clinical practice, tissue oxygenation is frequently assessed by using conventional global measurements, such as blood pressure, oxygen derived variables and blood lactate levels. However, the assessment of global hemodynamic parameters fails to reflect increased blood lactate levels, the imbalance between oxygen demand and oxygen supply, or the status of the microcirculation [1-3]. In addition, it often requires invasive monitoring techniques that usually limit early initiation, typically after the patient has been admitted to the intensive care unit (ICU).

To address these limitations, there have been many attempts to perform measurements of blood flow and oxygenation in peripheral tissues [4, 5]. In circulatory failure, blood flow is diverted from the less important tissues (skin, subcutaneous, muscle, gastrointestinal tract) to vital organs (heart, brain and kidneys). Thus, monitoring perfusion in these less vital tissues could be an early marker of vital tissue hypoperfusion. Second, the assessment of perfusion in peripheral tissues is more easily obtainable using noninvasive monitoring techniques, thus facilitating earlier initiation.

Monitoring of peripheral perfusion and oxygenation does not need any intravascular catheter, transesophageal probe insertion, blood component analysis or penetration of the skin. It can be performed directly (clinical evaluation and body temperature gradient) or through signal processing (optical monitoring; transcutaneous oximetry; sublingual capnometry). In this review, we discuss several available noninvasive methods to monitor peripheral perfusion and oxygenation (table 1).

### Clinical Assessment

During circulatory failure, global decrease in oxygen supply and redistribution of blood flow caused by increased vasoconstriction results in decreased perfusion in organ systems. Some organs, including the brain, heart and kidney, have vasomotor autoregulation that maintains blood flow in low blood pressure states. However, the cutaneous circulation is deprived of autoregulation, and the sympathetic neurohumoral response predominates resulting in a decrease in skin perfusion and temperature in these conditions. The assessment of skin temperature is made using the dorsal surface of the examiner hands or fingers, because these areas are most sensitive to temperature perception. Patients are considered to have cool extremities if all examined extremities are cool to the examiner, or only the lower extremities are cool despite warm upper extremities, in the absence of peripheral vascular occlusive disease. Clinical signs of poor peripheral perfusion consist of a cold, pale, clammy, and mottled skin, associated with an increase

**Table 1.** Measurement methods to study peripheral perfusion

<i>Method</i>	<i>Variable</i>	<i>Advantage</i>	<i>Limitations</i>
Clinical Assessment	Warmth and Coolness skin CRT	Depends only on physical examination; Valuable adjunct for hemodynamic monitoring in circulatory shock	Difficult interpretation in distributive shock
Body Temperature Gradient	dTc-p dTp-a Tskin-diff	Validated method to estimate dynamic variations in skin blood flow	At least two temperature probes required; Does not reflect the variations in real time
Pulse Oximetry	PFI	Easily obtainable; Reflect real time changes in peripheral blood flow	Not accurate during patient motion
NIRS	Hb, HbO <sub>2</sub> and HbT variations StO <sub>2</sub> Cytaa <sub>3</sub>	Assessment of oxygenation in all vascular compartments; It can be applied to measure regional blood flow and oxygen consumption	Requires specific software to display the variables.
OPS	FCD	Direct visualization of the microcirculation	Observer-related bias; Semi-quantitative measure of perfusion
LDF	Microvascular blood flow	Useful method to evaluate endothelium-dependent vascular responses	Small sampling volume for cutaneous blood flow measurement; Does not reflect heterogeneity of blood flow
Transcutaneous Oximetry	PtcO <sub>2</sub> / PtcCO <sub>2</sub> Tc-index	Direct measurement of PtcO <sub>2</sub> / PtcCO <sub>2</sub> ; Early detection of peripheral hypoperfusion	Necessity to frequently change the sensor position; Requires blood gas analysis
Sublingual Capnometry	PslCO <sub>2</sub> Psl-aCO <sub>2</sub>	Direct measurement of tissue PCO <sub>2</sub> noninvasively	Requires blood gas analysis to obtain PaCO <sub>2</sub> ; Normal and pathological values not yet defined

**CRT:** capillary refill time; **dTc-p:** temperature gradient central-to-peripheral; **dTp-a:** temperature; gradient peripheral-to-ambient; **Tskin-diff:** forearm-to-fingertip skin-temperature gradient; **PFI:** peripheral perfusion index; **NIRS:** Near-infrared spectroscopy; **Hb:** deoxygenated hemoglobin ; **HbO<sub>2</sub>:** oxygenated hemoglobin ; **HbT:** total hemoglobin (HbO<sub>2</sub> + Hb); **StO<sub>2</sub>:** tissue oxygen saturation; **Cytaa<sub>3</sub>:** cytochrome aa<sub>3</sub>; **OPS:** Orthogonal polarization spectroscopy; **FCD:** functional capillary density; **LDF:** Laser Doppler flowmetry; **PtcO<sub>2</sub>:** oxygen partial pressure in the skin; **PtcCO<sub>2</sub>:** carbon dioxide partial pressure in the skin; **Tc-index:** transcutaneous oxygen index ( PtcO<sub>2</sub> / PaO<sub>2</sub> ); **PslCO<sub>2</sub>:** sublingual tissue PCO<sub>2</sub>; **Psl-aCO<sub>2</sub>:** gradient between PslCO<sub>2</sub> and arterial PCO<sub>2</sub>

in capillary refill time. In particular, skin temperature and capillary refill time have been advocated as a measure of peripheral perfusion [6-11].

Capillary refill time (CRT) was introduced into the assessment of trauma and a value of <2 seconds was considered normal [12]. It is based on the assumption that a delayed return of a normal color after emptying the capillary bed by compression is due to decreased peripheral perfusion. CRT has been validated as a measure of peripheral perfusion with significant variation in children and adults. Schriger and Baraff [8], in a study in the normal population, reported that CRT varied with age and sex. It was found that a CRT of 2 sec was a normal value for most young children and young adults, but the lowest CRT was substantially higher in healthy women (2,9 sec) and in elderly (4,5 sec). Using these normal variations, it was further shown that a prolonged CRT did not predict a 450 ml blood loss in adult blood donors nor hypovolemic states in patients admitted to the emergency room [10]. Clinically, several studies have reported a poor correlation between CRT, heart rate, blood pressure and cardiac output [6, 7, 10]. However, prolonged CRT in pediatric patients has been found to be a good predictor of dehydration, reduced stroke volume and increased blood lactate levels [6, 11]. In adult patients following cardiac surgery, no significant relationship between cardiac index and CRT was found during the first 8h following ICU admission [7].

Distal extremity skin temperature has also been related to the adequacy of the circulation. Kaplan et al. [9] compared distal extremity skin temperature (evaluated by subjective physical examination) with biochemical and hemodynamic markers of hypoperfusion in adult ICU patients. In this study, it was found that patients with cold periphery (including septic patients) had lower cardiac output and higher blood lactate levels as a marker of more severe tissue hypoxia. In another study, Hasdai et al. [13] showed the importance of the physical examination in determining the prognosis of patients with cardiogenic shock. In this study, the presence of a cold and clammy skin was an independent predictor of 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction.

From these studies it is clear that skin temperature together with CRT are a valuable adjunct in hemodynamic monitoring during circulatory shock, and should be the first approach to assess critically ill patient. Not much is known about the clinical applicability of these variables after the patient has been admitted to the intensive care unit [14].

### **Temperature Gradients**

Since Joly and Ibsen studied the toe temperature as an indicator of the circulatory shock [15, 16], body temperature gradients have been used as a parameter of peripheral perfusion. In the presence of a constant environmental temperature, a change in the skin temperature is the result of a change in skin blood flow [17]. The temperature gradients peripheral-to-ambient (dT<sub>p-a</sub>) and central-to-peripheral (dT<sub>c-p</sub>) can better reflect cuta-

neous blood flow than the skin temperature itself. Considering a constant environment condition,  $dT_{p-a}$  decreases and  $dT_{c-p}$  increases during vasoconstriction. The peripheral skin temperature is measured using a regular temperature probe attached to the ventral face of the great toe. This site is more convenient for peripheral temperature measurement because of the negligible local heat production and the distal location from other monitoring devices [18]. The concept of the  $dT_{c-p}$  is based on the transfer of heat from the body core to the skin. The heat conduction to the skin by the blood is also controlled by the degree of vasoconstriction of the arterioles and arteriovenous anastomoses. High blood flow causes heat to be conducted from the core to the skin, whereas reduction in blood flow decreases the heat conduction from the core. During vasoconstriction, the temperature of the skin falls and the heat conduction from the core decreases, so that the central temperature rises and the  $dT_{c-p}$  increases. A gradient of 3 to 7°C occurs in patients with stable hemodynamics [19]. Hypothermia, cold ambient temperature (<20°C) [20] and vasodilatory shock limits the use of  $dT_{c-p}$  as an estimate of peripheral perfusion. Forearm-to-fingertip skin-temperature gradient ( $T_{skin-diff}$ ) has also been used as an index of peripheral circulation to identify the initiation of thermoregulatory vasoconstriction in patients following surgery [21]. Fingertip temperature is measured with the temperature probe attached to the ventral face of the finger. The use of  $T_{skin-diff}$  is based on assumption that the reference temperature is a skin site exposed to the same ambient temperature as the fingertip. It has been applied in conditions where an ambient temperature is not stable, such as in patients undergoing surgery [21-23]. A change in ambient temperature, therefore, affects similarly forearm and fingertip temperature, producing little influence in the gradient. Basically, when vasoconstriction decreases fingertip blood flow, finger skin temperature decreases, and  $T_{skin-diff}$  increases. Experimental studies have suggested a  $T_{skin-diff}$  threshold of 0°C for the initiation of vasoconstriction, and a threshold of 4°C for severe vasoconstriction in anesthetized patients [22, 23].

The body temperature gradient was first applied to assess patients with circulatory shock and to differentiate central heat retention caused by fever from peripheral vasoconstriction [15, 16, 24]. A number of studies have attempted to correlate body temperature gradient to global hemodynamic variables in hypovolemic, septic and cardiogenic shock, with conflicting results [15, 25-31]. Henning et al. [28] studied  $dT_{p-a}$  in patients with circulatory failure associated with hypovolemia and low cardiac output. An increase in  $dT_{p-a}$  to more than 4 to 6°C over an interval of 12 hours was observed in survivors, and a good relationship between the lowest  $dT_{p-a}$  and the highest blood lactate levels was found in hypovolemic patients at time of admission. In assessing the potential value of dopamine as a therapeutic agent to treat circulatory shock, Ruiz et al. [25] showed that survival was associated with an increase in  $dT_{p-a}$  of more than 2°C, and that  $dT_{p-a}$  was correlated to increases in cardiac output and a reduction in blood lactate

levels. To determine the value of dTp-a to assess peripheral perfusion in cardiogenic shock, Vincent et al. [27] found that a cardiac index below 1.8 l/min.m<sup>2</sup> was associated with a decrease in dTp-a below 5°C, and that the increase in dTp-a occurred earlier than the increase in skin oxygen partial pressure during recovery; this correlation was not found in septic shock. No relationship was observed between dTc-p and cardiac output in adults with diverse causes of shock [31] and in children after open heart surgery [26, 29, 30]. One reason for the inaccurate relationship between body temperature gradient and global hemodynamic parameters could be related to unstable environment, as skin temperature depends also on ambient temperature, and the thermoregulatory response is suppressed in anesthetised patients [32]. In addition, global hemodynamic parameters may not be sensitive enough to reflect changes in peripheral blood flow in critically ill patients [33, 34]. Tskin-diff may be an alternative, but its use in these conditions has not yet been defined.

### Optical Monitoring

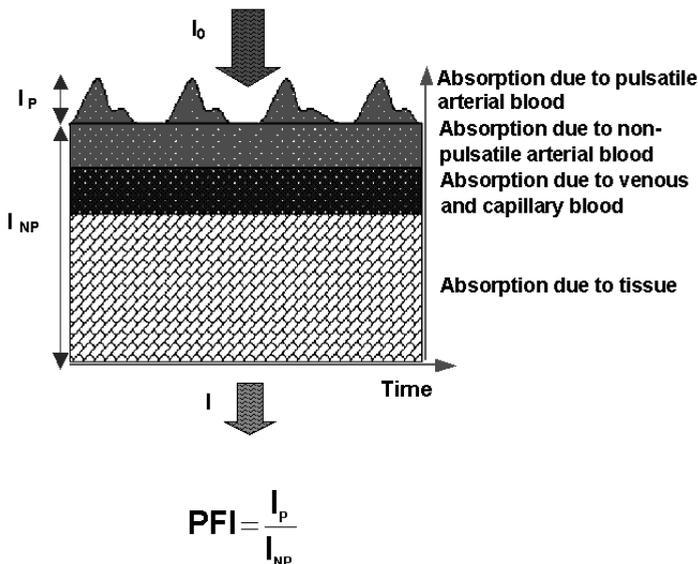
Optical methods apply light with different wave lengths directly to tissue components using the scattering characteristics of tissue to assess different states of these tissues [35]. At physiologic concentrations, the molecules that absorb most light are hemoglobin, myoglobin, cytochrome, melanins, carotenes and bilirubin. These substances can be quantified and measured in intact tissues using simple optical methods. The assessment of tissue oxygenation is based on the specific absorption spectrum of oxygenated hemoglobin (HbO<sub>2</sub>), deoxygenated hemoglobin (Hb) and cytochrome *aa*<sub>3</sub> (cytaa<sub>3</sub>). Commonly used optical methods for peripheral monitoring are perfusion index, near-infrared spectroscopy, laser-Doppler flowmetry and orthogonal polarization spectral.

#### *Peripheral Perfusion Index*

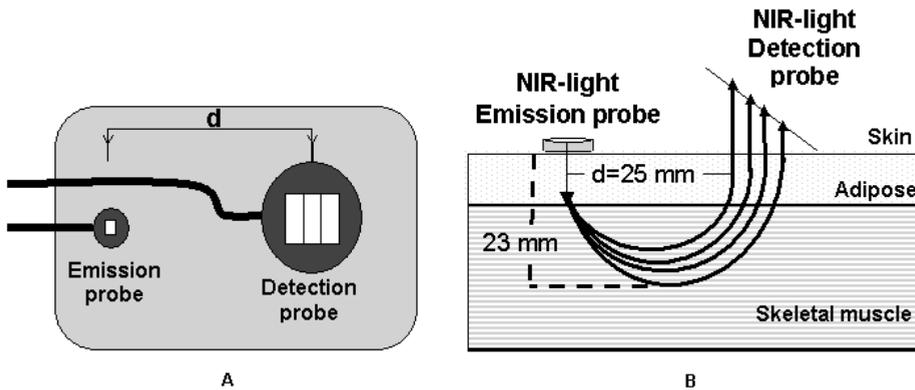
The peripheral perfusion index (PFI) is derived from the photoelectric plethysmographic signal of pulse oximetry and has been used as a noninvasive measure of peripheral perfusion in critically ill patients [36]. Pulse oximetry is a monitoring technique used in probably every trauma, critically ill and surgical patient. The principle of pulse oximetry is based on two light sources with different wavelengths (660 nm and 940 nm) emitted through the cutaneous vascular bed of a finger or earlobe. The Hb absorbs more light at 660 nm and HbO<sub>2</sub> absorbs more light at 940 nm. A detector at the far side measures the intensity of the transmitted light at each wavelength, and the oxygen saturation is derived by the ratio between the red light (660 nm) and the infra-red light (940 nm) absorbed. As other tissues also absorb light, such as connective, bone and venous blood, the pulse oximetry distinguishes the pulsatile component of arterial blood from the non-pulsatile component of other tissues. Thus, using a two-wavelength system, the non-pulsatile component can be discarded, and the pulsatile component is used to

calculate the arterial oxygen saturation. The overall hemoglobin concentration can be determined by a third wavelength at 800 nm, which resemble the spectrum for both Hb and HbO<sub>2</sub>. The resulting variation in intensity of this light can be used to determine the variation in arterial blood volume (pulsatile component). The PFI is calculated as the ratio between the pulsatile component (arterial compartment) and the non-pulsatile component (other tissues) of the light reaching the detector of the pulse oximetry and it is calculated independently from the patient oxygen saturation (Fig. 1). A peripheral perfusion alteration is accompanied by variation in the pulsatile component, and because the non-pulsatile component does not change, the ratio changes. As a result, the value displayed on the monitor reflects changes in peripheral perfusion.

Studies with body temperature gradient suggest that PFI can be a direct indicator of peripheral perfusion. A PFI of 1.4 was found to correlate best with hypoperfusion in critically ill patients using normal values in healthy adults [36]. A good relationship between T<sub>skin-diff</sub> and PFI was observed in anesthetised patients to identify the initiation of thermoregulatory vasoconstriction [37]. PFI could reflect changes in dTc-p and T<sub>skin-diff</sub> and therefore it could reflect vascular reactivity in adult critically ill patients [36, 38]. Another study showed that PFI could be used to predict severity of illness in neonates with a cutoff value  $\leq 1.24$  [39]. The inclusion of PFI into the pulse oximetry signal is a recent advance in clinical monitoring. However, more studies are needed to define its clinical utility.



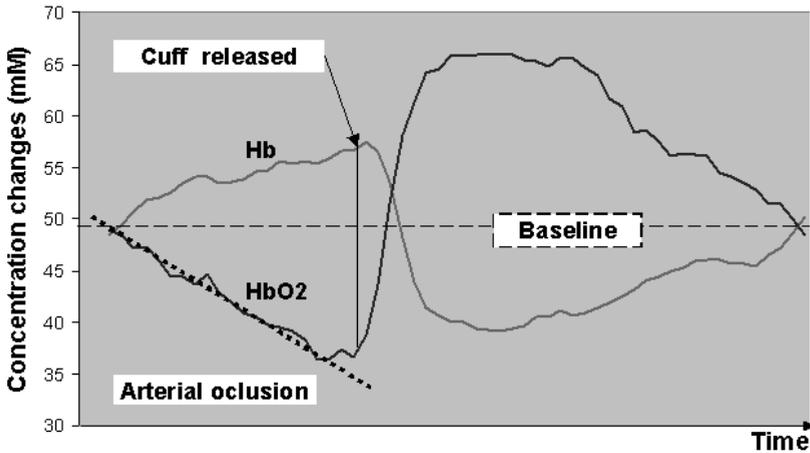
**Fig. 1** The pulsation of arterial blood causes a pulsating volume variation. Peripheral perfusion index (PFI) is calculated as the ratio between the arterial pulsatile component ( $I_P$ ) and the nonpulsatile component ( $I_{NP}$ ).  $I_0$  Source light intensity;  $I$  light intensity at the detector



**Fig. 2** A Diagram of a distal tip of the NIRS optical cable. B With 25 mm spacing ( $d$ ) between emission and detection probes, approx. 95% of the detected optical signal is from 23 mm of tissue penetration

### Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) offers a technique for continuous, noninvasive, bedside monitoring of tissue oxygenation. Like pulse oximetry, NIRS uses the principles of light transmission and absorption to measure the concentrations of hemoglobin, oxygen saturation ( $\text{StO}_2$ ), and cytaa<sub>3</sub> noninvasively in tissues. NIRS has a greater tissue penetration than pulse oximetry, and provides a global assessment of oxygenation in all vascular compartments (arterial, venous and capillary). The tissue penetration is directly related to the spacing between illumination and detection fibers. With 25 mm spacing, approximately 95% of the detected optical signal is from a depth of zero to 23 mm (Fig. 2). NIRS has been used to assess forearm skeletal muscle oxygenation during induced reactive hyperemia in healthy adults, and it produced reproducible measurements of tissue oxygenation during both arterial and venous occlusive events [40]. Using the venous and arterial occlusion methods, NIRS can be applied to measure regional blood flow and oxygen consumption by following the rate of  $\text{HbO}_2$  and Hb changes [40-42]. In the venous occlusion method, a pneumatic cuff is inflated to a pressure of approximately 50 mmHg. Such a pressure blocks venous outflow, but does not impede arterial inflow. As a result, venous blood volume and pressure increase. NIRS can reflect this change by an increase in  $\text{HbO}_2$ , Hb and total hemoglobin (tHb). In arterial occlusion method, the pneumatic cuff is inflated to a pressure of approximately 30 mmHg greater than systolic pressure. Such a pressure blocks both venous outflow and arterial inflow. Depletion of local available  $\text{O}_2$  is monitored by NIRS as a decrease in  $\text{HbO}_2$  and a simultaneous increase in Hb, whereas tHb remains constant. After release of the occluding cuff, a hyperaemic response is observed (Fig. 3). Blood volume increases rapidly, resulting in an increase in  $\text{HbO}_2$  and a quick washout of Hb. In addition to blood flow and evaluation of  $\text{HbO}_2$  and Hb changes, NIRS can assess cytaa<sub>3</sub> redox state. Cytaa<sub>3</sub> is the final receptor in the oxygen transport chain that reacts with oxygen to form water, and approximately 90%



**Fig. 3** Quantitative NIRS measurements during arterial occlusion. After release of the occluding cuff blood volume increases rapidly, resulting in an increase in HbO<sub>2</sub> and a quick washout of Hb, followed by a hyperemic response. Oxygen consumption is calculated as the rate of decrease in HbO<sub>2</sub> (dotted line)

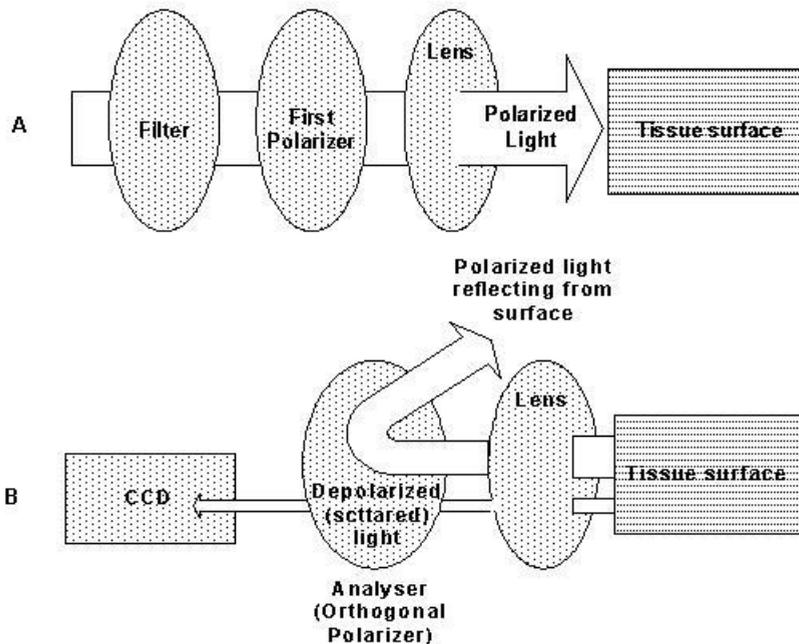
of cellular energy is derived from this reaction. Cytaa<sub>3</sub> remains in a reduced state during hypoxemia. The absorption spectrum of cytaa<sub>3</sub> in its reduced state shows a weak peak at 70 nm, whereas the oxygenated form does not. Therefore, monitoring changes in its redox state can provide a measure of the adequacy of oxidative metabolism. Despite the potential clinical applications of NIRS, some limitations still exist. The contribution of the cytaa<sub>3</sub> signal is small, and its interpretation remains controversial, requiring more rigorous development [43]. There is no a gold standard to which NIRS data can be directly compared and one of the reasons is that a variety of NIRS equipment is commercially available with different working systems.

In small and large-animal models of hemorrhagic shock and resuscitation, NIRS demonstrated sensitivity in detecting skeletal muscle and visceral ischemia [44-47]. As a noninvasive measure of peripheral perfusion, NIRS has been applied in superficial muscles (brachioradialis muscle, deltoid muscle, tibialis anterior) of trauma ICU patients to monitor the adequacy of tissue oxygenation and the detection of a compartment syndrome [48-52]. The use of NIRS in deltoid muscle during resuscitation of severe trauma patients has been reported recently [48, 49]. Cairns et al. [49] studied trauma ICU patients and reported a strong association between elevated serum lactate levels and elevated cytaa<sub>3</sub> redox state during 12 hours of shock resuscitation and development of multiple organ failure. More recently, Mckinley et al. [48] showed a good relationship between StO<sub>2</sub>, systemic oxygen delivery and lactate in severely trauma patients during and after resuscitation, over a period of 24 hours. In a recent study with septic and non-septic patients, NIRS has been used to measure both regional blood flow and oxygen consumption after venous occlusion [53]. In this study, septic patients had muscular

oxygen consumption two times greater than nonseptic patients, but oxygen extraction was similar in both groups, emphasizing oxygen extraction dysfunction in sepsis. In another study, no relationship was found between forearm blood flow, measured by NIRS, and systemic vascular resistance in septic shock patients [41]. These studies outline the ability of NIRS to reflect microcirculatory dysfunction in skeletal muscle in septic shock. The potential to monitor regional perfusion and oxygenation noninvasively at the bedside makes clinical application of NIRS technology of particular interest in intensive care.

#### *Orthogonal Polarization Spectral*

Orthogonal polarization spectral (OPS) is a noninvasive technique that uses reflected light to produce real-time images of the microcirculation. The technical characteristics of the device has been described elsewhere [54]. Light from a source passes through the first polarizer and it is directed towards the tissue by a set of lens. As the light reaches the tissue, the depolarized light is reflected back through the lenses to a second polarizer or analyzer and forms an image of the microcirculation on the CCD, which can be captured through a single videotape (Fig. 4). The technology has been incorporated into a small, hand-held video microscope, which can be used in both research and clinical settings. OPS can assess tissue perfusion using the functional capillary density (FCD),



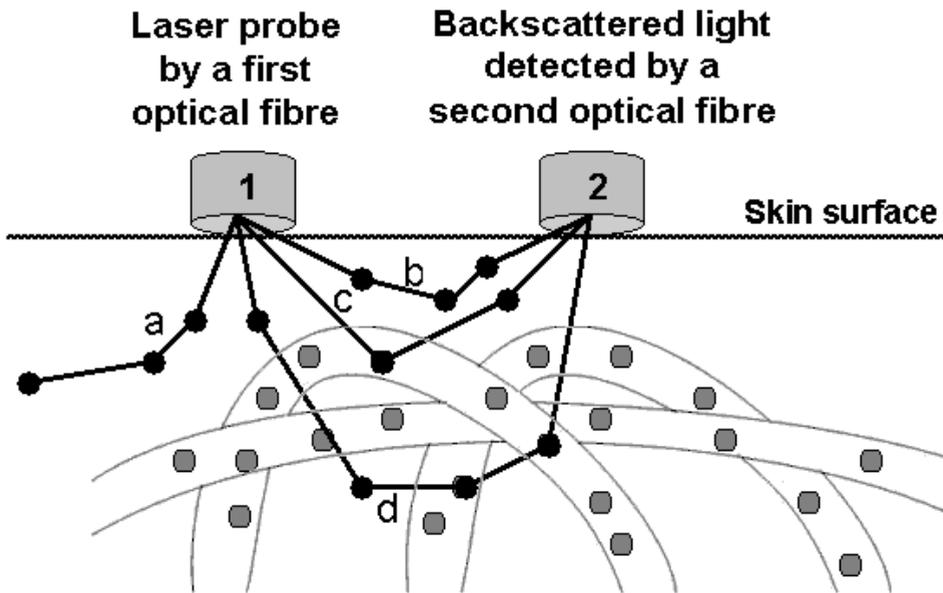
**Fig. 4** OPS optical schematic. (A) The light passes through the first polarizer and is reflected back through the lens. (B) The polarized light reflecting from the surface is eliminated, and the depolarized light forms an image of the microcirculation on a videocamera (charge-coupled device, CCD)

i.e., the length of perfused capillaries per observation area given as  $\text{cm}/\text{cm}^2$ . FCD is a very sensitive parameter for determining the status of nutritive perfusion to the tissue and it is an indirect measure of oxygen delivery. One of the most easily accessible sites in humans for peripheral perfusion monitoring is the mouth. OPS has been able to produce excellent images of the sublingual microcirculation by placing the probe under the tongue. Movement artifacts, semi-quantitative measure of perfusion, the presence of various secretions such as saliva and blood, observer-related bias and patients adequately sedated to prevent them from damaging the device are some of the limitations of the technique.

The use of sublingual tissues with OPS provides information about the dynamics of microcirculatory blood flow and, therefore, it can monitor the perfusion during clinical treatment of circulatory shock. It was used to monitor the effects of improvements in microcirculatory blood flow with dobutamine and nitroglycerin in volume resuscitated septic patients [55, 56]. OPS has been applied in the ICU to study the properties of sublingual microcirculation in both septic shock and cardiogenic shock [2, 56-58]. In septic patients, it was shown with OPS that microvascular alterations were more severe in patients with a worse outcome, and that these microvascular alterations could be reversed using vasodilators [2]. In patients with cardiac failure and cardiogenic shock, the number of small vessels and the density of perfused vessels were lower compared with control patients, and the proportion of perfused vessels was higher in patients who survived than in patients who did not survive [57]. Using OPS during the time course of treatment of patients with septic shock, Sakr et al. [58] demonstrated that the behaviour of the sublingual microcirculation differed between survivors and nonsurvivors. Although alterations in the sublingual microcirculation may not be representative of other microvascular beds, changes in the sublingual circulation evaluated by capnometry during hemorrhagic shock have been related to changes in perfusion of internal organs such as the liver and intestine [59]. Thus, OPS could be of use in the monitoring of tissue perfusion.

#### *Laser Doppler Flowmetry*

Laser Doppler flowmetry (LDF) is a non-invasive, continuous measure of microcirculatory blood flow, and it has been used to measure microcirculatory blood flow in many tissues including neural, muscle, skin, bone and intestine. The principle of this method is to measure the Doppler shift - the frequency change that light undergoes when reflected by moving objects, such as red blood cells. LDF works by illuminating the tissue under observation with a monochromatic laser from a probe. When the tissue is illuminated, only 3-7% is reflected. The remaining 93-96% of the light is either absorbed by various structures or undergoes scattering. Another optical fibre collects the backscattered light from the tissue and returns it to the monitor (Fig. 5). As a result, LDF produces an



**Fig. 5** Schematic diagram of laser Doppler flowmetry. When the tissue is illuminated by a laser source (1), 93–97% of the light is either absorbed by various structures or undergoes scattering (a, b). The remaining 3–7% is reflected by moving red blood cells (c, d) and returns to the second optical fiber (2). Microvascular perfusion is defined as the product of mean red blood cells (RBC) velocity and mean RBC concentration in the volume of tissue under illumination from the probe

output signal that is proportional to the microvascular perfusion [60]. Depending on the device and the degree of invasiveness, it can be used to assess blood flow in muscle, gastric, rectal and vagina mucosae. But as a non-invasive measure of peripheral blood flow, its use is limited to the skin [60]. LDF has been applied to obtain information on the functional state of the skin microcirculation during reactive hyperemia in several conditions, such as diabetes mellitus, essential hypertension, atherosclerosis and sepsis [61]. A major limitation of this technique is that LDF does not take into account the heterogeneity of blood flow as the velocity measurements represent the average of velocities in all vessels of the window studied. In addition, skin blood flow signal varies markedly depending on probe position. No current laser Doppler instrument can present absolute perfusion values (e.g. ml/min/100 gram tissue) and measurements are expressed as Perfusion Units, which are arbitrary.

LDF has been useful to evaluate endothelium-dependent vascular responses in the skin microcirculation during either reactive hyperemia [61, 62] or the noninvasive local application of acetylcholine or sodium nitroprusside [63–65]. This characteristic of LDF was used in critically ill patients to evaluate endothelial dysfunction in sepsis. Observational studies have shown that the hyperaemic response in septic patients is decreased, and a relationship between changes in vasculature tone and severity of sepsis has been

described [66-68]. In addition, restored vasomotion in patients with sepsis evaluated by LDF seems to be associated with a favourable prognosis [67]. The ability of LDF to assess abnormalities of skin blood flow control in sepsis could be of clinical use for early detection of microcirculatory derangements in high-risk patients.

### **PO<sub>2</sub> and PCO<sub>2</sub> Transcutaneous Measurements**

Continuous noninvasive measurement of oxygen (O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>) tensions is possible because both gases can diffuse through the skin and thus their partial pressures can be measured in transcutaneous tissue. Normally the skin is not very permeable to gases, but at higher temperatures, the ability of the skin to transport gases is improved. Oxygen sensors for transcutaneous electrochemical measurements are based on polarography: a typical amperometric transducer in which the rate of a chemical reaction is detected by the current drained through an electrode. The sensor heats the skin to 43-45°C. The skin surface oxygen tension is increased as a result of 3 effects: [69] heating the stratum corneum beyond 40°C changes its structure, which allows oxygen to diffuse faster; [70] the local oxygen tension is increased by shifting the oxygen dissociation curve in the heated dermal capillary blood; and [71] by dermal capillary hyperemia. These transcutaneous sensors enable us to directly estimate arterial oxygen pressure (PaO<sub>2</sub>) and arterial carbon dioxide pressure (PaCO<sub>2</sub>) and it has been successfully used for monitoring PaO<sub>2</sub> and PaCO<sub>2</sub> in both neonates and in adults [72-74]. Newborn infant is suitable because of its thin epidermal layer. However, in adults the skin is thicker and differences in the skin cause the PtcO<sub>2</sub> to be lower than PaO<sub>2</sub>. The correlation between PtcO<sub>2</sub> and PaO<sub>2</sub> also depends on the adequacy of blood flow. The low blood flow caused by vasoconstriction during shock overcomes the vasodilatory effect of PtcO<sub>2</sub> sensor. This causes a mild tissue hypoxia beneath the PtcO<sub>2</sub> sensor. The lack of the PtcO<sub>2</sub> ability to accurately reflect the PaO<sub>2</sub> in low flow shock enables us to estimate cutaneous blood flow through the relationship between the two variables. Some studies have suggested the use of a transcutaneous oxygen index (tc-index), i.e., the changes of PtcO<sub>2</sub> relative to changes of PaO<sub>2</sub> [72, 75-78]. When the blood flow is adequate, the PtcO<sub>2</sub> and PaO<sub>2</sub> values are almost equal and the tc-index is close to 1. During low flow shock the PtcO<sub>2</sub> will drop and becomes dependent to the PaO<sub>2</sub> value and tc-index decreases. A tc-index more than 0,7 has been associated with hemodynamic stability [72, 75, 77, 78]. Transcutaneous Carbon Dioxide Partial Pressure (PtcCO<sub>2</sub>) has been also used as an index of cutaneous blood flow. Differences between PaCO<sub>2</sub> and PtcCO<sub>2</sub> have been explained by local accumulation of CO<sub>2</sub> in the skin due to hypoperfusion. Because of the diffusion constant of CO<sub>2</sub> is about 20 times greater than O<sub>2</sub>, PtcCO<sub>2</sub> has been showed to be less sensitive to changes in hemodynamics than PtcO<sub>2</sub> [79]. One of the main limitations of this technique is the necessity of blood gas analysis to obtain the tc-index and PaCO<sub>2</sub>. In addition, the sensor position has to be changed every one to two hours to avoid burns.

After each repositioning, a period of 15 to 20 min is required for the next readings, which limits its use in emergency situations.

The ability of  $PtcO_2$  to reflect tissue perfusion in critically ill adult patients has been applied using the tc-index. Tremper and Shoemaker [75] found a good correlation ( $r=0.86$ ) between tc-index and cardiac index in patients with shock. In this study, the authors showed that when cardiac index was  $>2.2$  L/min.M<sup>2</sup>, tc-index averaged 0.79; when cardiac index was between 1.5 and 2.2 L/min.M<sup>2</sup>, tc-index was 0.48; and when cardiac index was  $<1.5$  L/min.M<sup>2</sup>, tc index was 0.12. However, the relationship between tc-index and cardiac index may not exist in hyperdynamic shock. Reed et al. [78] studied  $PtcO_2$  at different cardiac indices. In this study, 71 measurements were made in 19 patients, and a low tc-index was seen in 71% of the patients with a cardiac index  $>4.2$  L/min.m<sup>2</sup>.  $PtcO_2$  and  $PtcCO_2$  monitoring have been used as an early indicator of tissue hypoxia and subclinical hypovolemia in acutely ill patients [80, 81]. Tatevossian et al. [81] studied 48 severely injured patients during early resuscitation in the emergency department and operating room. The sequential patterns of  $PtcO_2$  and  $PtcCO_2$  were described throughout initial resuscitation. The nonsurvivors had lower  $PtcO_2$  values and higher  $PtcCO_2$  values compared with the survivors. These differences were already evident early after the patient's arrival. The authors reported a critical tissue perfusion threshold of a  $PtcO_2 <50$  mmHg for  $>60$  min and a  $PtcCO_2 >60$  mmHg for  $>30$  min. Patients who failed to avoid these critical thresholds had 89% to 100% mortality. This technology has not gained widespread acceptance in clinical practice, as the time needed for calibration limits its early use in the emergency department, and critical  $PtcO_2$  and  $PtcCO_2$  values have not been established.

### Sublingual Capnometry

The measurements of tissue-arterial  $CO_2$  tension gradient have been used to reflect the adequacy of tissue perfusion. The gastric and ileal mucosal  $CO_2$  clearance has been the primary reference for measurements of regional  $PCO_2$  gradient during circulatory shock [82]. The regional  $PCO_2$  gradient represents the balance between regional  $CO_2$  production and clearance. During tissue hypoxia,  $CO_2$  is produced by hydrogen anions buffered by tissue bicarbonate, which adds to the amount of  $CO_2$  produced by normal oxidative metabolism. The amount of  $CO_2$  produced, either aerobically or because of tissue hypoxia will be cleared if blood flow is maintained. In low flow states,  $CO_2$  increases as a result of stagnation phenomenon [83]. Gastric tonometry is a technique that can be used to assess the adequacy of gut mucosal blood flow to metabolism. The methodological limitations of gastric tonometry demanded a search for a tissue where  $PCO_2$  could be easily measured in a noninvasive approach. Comparable decreases in blood flow during circulatory shock have been also demonstrated in the sublingual tissue  $PCO_2$  ( $PsICO_2$ ) [84, 85]. The currently available system for measuring  $PsICO_2$  consists of a disposable

PCO<sub>2</sub> sensor and a battery powered handheld instrument. The instrument uses fibre optic technology to transmit light through the sensor placed between the tongue and the sublingual mucosa. Carbon dioxide diffuses across a semi-permeable membrane of the sensor and into a fluorescent dye solution. The dye emits light that is proportional to the amount of CO<sub>2</sub> present. This light intensity is analyzed by the instrument and displayed as a numeric PslCO<sub>2</sub> value.

Clinical studies have suggested that PslCO<sub>2</sub> is a reliable marker of tissue hypoperfusion [86-89]. Weil et al. [89] applied PslCO<sub>2</sub> in 46 patients with acutely life threatening illness or injuries admitted to the emergency department or ICU. In this study, 26 patients with physical signs of circulatory shock and high blood lactate levels had higher PslCO<sub>2</sub> values, and a PslCO<sub>2</sub> threshold value of 70 mmHg was predictive for the severity of the circulatory failure. Similarly as PCO<sub>2</sub> in the gut mucosal, PslCO<sub>2</sub> is also influenced by PaCO<sub>2</sub> [90]. Hence, the gradient between PslCO<sub>2</sub> and PaCO<sub>2</sub> (Psl-aCO<sub>2</sub>) is more specific for tissue hypoperfusion. This has been shown in the study of Marik and Bankov [88] who determined the prognostic value of sublingual capnometry in 54 hemodynamic unstable critically ill patients. In this study, Psl-aCO<sub>2</sub> was a sensitive marker for tissue perfusion and a useful end point for the titration of goal-directed therapy. In contrast to PslCO<sub>2</sub> alone, the Psl-aCO<sub>2</sub> better differentiated between survivors and nonsurvivors, and a difference of >25 mm Hg indicated a poor prognosis. One limitation of this technique includes the necessity of blood gas analysis to obtain PaCO<sub>2</sub>. In addition, established normal and pathological Psl-aCO<sub>2</sub> values are not well defined.

## CONCLUSION

The conventional systemic hemodynamic and oxygenation parameters are neither specific nor sensitive enough to detect regional hypoperfusion. In clinical practice, a more complete evaluation of tissue oxygenation can be achieved by adding noninvasive assessment of perfusion in peripheral tissues to global parameters. Noninvasive monitoring of peripheral perfusion could be a complementary approach that allows very early application throughout the hospital, including the emergency department, operating room, and hospital wards. Such approach can be applied using both simple physical examination and new current technologies, as discussed above. Although these methods may reflect variations in peripheral perfusion with certain accuracy, more studies are needed to define the precise role of such methods in the management of the critically ill patients. Finally, evidence for clinical and cost effectiveness of these methods is an important aspect that needs further investigations with a more formal technology assessment.

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# Chapter 2

## Monitoring peripheral perfusion in critically ill patients at the bedside

*Curr Opin Crit Care* 2012; 18(3): 273-9

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## **ABSTRACT**

### **Purpose of review**

The goal 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 normalisation 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 neurohumoural 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 hypo- 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.

**Table 1.** Different methods used to measure peripheral perfusion.

Method	Variable	Main advantage	Main limitation	Suggested cut-offs
<b>Clinical assessment</b>	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
<b>Body temperature gradient</b>	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
<b>Optical monitoring</b>	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

## 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, i.e., 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. in 1981 as a component of the international trauma severity score for the rapid and structured cardiopulmonary assessment of critically ill patients (8). 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, Bohnborst 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).

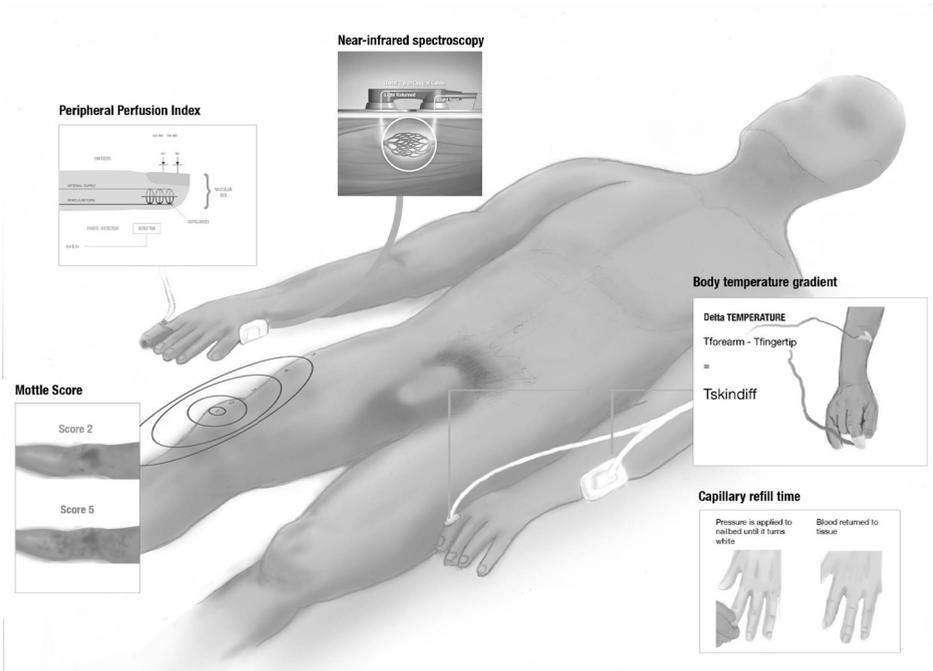
In a healthy adult population, Schriger et al. (12) reported that the upper limit of a normal CRT is 4.5 seconds. After applying this cutoff in critically ill patients, we demonstrated that a delayed return of normal colour (>4.5 seconds) can be regarded as decreased peripheral perfusion. Moreover, we found that following initial haemodynamic optimisation during the first 24 hours of intensive care unit (ICU) admission, the CRT could be used to discriminate patients with more severe organ dysfunction. In addition, a prolonged CRT (>4.5 seconds) was related to tissue hypoperfusion and a greater likelihood of worsening organ failure in the following days, compared to patients with a normal CRT (5;13). Although inter-observer variability remains a matter of debate, an upper normality limit of >4.5 seconds 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 (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 recognised 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



**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.

vasoconstriction and is thought to reflect abnormal skin perfusion. To analyse mottling objectively, Ait-Oufella et al. recently developed a clinical scoring system (from 0 to 5) based on the area of mottling from the knees to the periphery (Fig. 1) (18). This group reported that a higher mottling score within 6 hours 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 inter-observer 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 (Tskin-diff). Increased vasoconstriction during circulatory shock leads to decreased skin temperature and a diminished ability of the core 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 to 7°C occurs once the patient's haemodynamics have been optimised (22). Because the effect of the operating room environment on skin and body temperature changes during surgery, especially with the use of cardiopulmonary bypass, Tskin-diff may be a more reliable measurement for critically ill patients (23). The use of Tskin-diff is based on assumption that the reference temperature is a skin site exposed to the same ambient temperature as the fingertip. A different ambient temperature, therefore, affects similarly forearm and fingertip temperature, producing little change in the gradient (Fig. 1). Experimental studies have suggested Tskin-diff thresholds of 0°C for initiating vasoconstriction and 4°C for severe vasoconstriction (24;25). In critically ill adult patients, Tskin-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 post-resuscitation 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 elsewhere; (26)) that apply optical methods to visualize the microcirculation, assess oxygen availability, measure PCO<sub>2</sub>, 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 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 non-pulsatile 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 (27). Similarly, the PPI was shown to be rapidly reduced following sympathetic response-induced vasoconstriction after the introduction of a nociceptive skin stimulus (28) or an intravenous injection of epinephrine (29) or norepinephrine (30). 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 (31).

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;32). Therefore, this easily obtainable and non-invasive method can be used for monitoring peripheral perfusion in critically ill patients.

### **Near-infrared spectroscopy**

Near infrared spectroscopy (NIRS) is a noninvasive technique that enables the determination of tissue oxygenation based on the spectro-photometric quantitation of oxy- 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 (StO<sub>2</sub>) and the absolute tissue haemoglobin index (THI), an indicator of blood volume in the microvasculature tissue region, can be obtained (33). In addition, changes in StO<sub>2</sub> levels during a VOT have been used to represent microvascular reactivity (6;34-36). 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 (37-40). In a study by Shapiro et al., the dynamic NIRS variables collected during a VOT were strongly associated with the severity of organ dysfunction and mortality in patients with septic shock (41). In this study, the StO<sub>2</sub> recovery slope was most sensitive for the prediction of mortality. This is of special interest because there

is a lack of agreement on standardisation for the appropriate method for performing a VOT (42;43). When measured at the thenar eminence, NIRS-derived measurements are influenced by the peripheral circulation condition (Fig. 1) (9;20). Nevertheless, when used in conjunction with other peripheral perfusion methods, repeated StO<sub>2</sub> monitoring has the potential to assess the effect of therapeutic intervention on the peripheral microvascular circulation in various shock states. Similarly, Colin et al. (44) investigated the dynamic response of StO<sub>2</sub> at different sites during the first 6 hours of severe sepsis resuscitation, and argued that StO<sub>2</sub> 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 to 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 (32). Similar observations have been made during therapeutic hypothermia following cardiac arrest (45). 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 (23). 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 (46;47).

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. showed that the administration of nitroglycerine to septic patients following early resuscitation significantly improved peripheral perfusion, independently of systemic haemodynamics (48). Although there was a trend to increasing mortality, this was accompanied by reduced morbidity in

the nitroglycerine-treated patient group compared to 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. recently showed that the administration of a fluid challenge had positive effects on peripheral tissue oxygenation in patients undergoing major abdominal surgery (49).

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 intensive care unit.

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# **PART B**

Methodological aspects



# Chapter 3

Use of a peripheral perfusion index derived from the pulse oximetry signal as a non-invasive indicator of perfusion

*Crit Care Med 2002, 30:1210-1213*

*Alexandre Lima, Peter Beelen, Jan Bakker*

## ABSTRACT

**Objective:** Peripheral perfusion in critically ill patients frequently is assessed by use of clinical signs. Recently, the pulse oximetry signal has been suggested to reflect changes in peripheral perfusion. A peripheral perfusion index based on analysis of the pulse oximetry signal has been implemented in monitoring systems as an index of peripheral perfusion. No data on the variation of this index in the normal population are available, and clinical application of this variable in critically ill patients has not been reported. We therefore studied the variation of the peripheral perfusion index in healthy adults and related it to the central-to-toe temperature difference and capillary refill time in critically ill patients after changes in clinical signs of peripheral perfusion.

**Design:** Prospective study.

**Setting:** University-affiliated teaching hospital.

**Patients:** One hundred eight healthy adult volunteers and 37 adult critically ill patients.

**Interventions:** None.

**Measurements and Main Results:** Capillary refill time, peripheral perfusion index, and arterial oxygen saturation were measured in healthy adults (group 1). Capillary refill time, peripheral perfusion index, arterial oxygen saturation, central-to-toe temperature difference, and hemodynamic variables were measured in critically ill patients (group 2) during different peripheral perfusion profiles. Poor peripheral perfusion was defined as a capillary refill time  $>2$  secs and central-to-toe temperature difference  $\geq 7^{\circ}\text{C}$ . Peripheral perfusion index and arterial oxygen saturation were measured by using the Philips Medical Systems Viridia/56S monitor. In group 1, measurements were made before and after a meal. In group 2, two measurements were made, with the second measurement taken when the peripheral perfusion profile had changed. A total of 216 measurements were carried out in group 1. The distribution of the peripheral perfusion index was skewed and values ranged from 0.3 to 10.0, median 1.4 (inner quartile range, 0.7–3.0). Seventy-four measurements were carried out in group 2. A significant correlation between the peripheral perfusion index and the core-to-toe temperature difference was found ( $R^2 = .52$ ;  $p < 0.001$ ). A cutoff peripheral perfusion index value of 1.4 (calculated by constructing a receiver operating characteristic curve) best reflected the presence of poor peripheral perfusion in critically ill patients. Changes in peripheral perfusion index and changes in core-to-toe temperature difference correlated significantly ( $R = .52$ ,  $p < 0.001$ ).

**Conclusions:** The peripheral perfusion index distribution in the normal population is highly skewed. Changes in the peripheral perfusion index reflect changes in the core-to-toe temperature difference. Therefore, peripheral perfusion index measurements can be used to monitor peripheral perfusion in critically ill patients.

## INTRODUCTION

Early recognition of impaired organ perfusion is important to avoid tissue hypoxia that ultimately could lead to organ failure. During circulatory shock, skin blood flow decreases to preserve vital organ perfusion. This results in the clinical signs of poor peripheral perfusion, such as a cold, pale, clammy, and mottled skin (1). Indexes of peripheral perfusion thus have been used to identify inadequate perfusion in critically ill patients (2–4). Peripheral perfusion can be assessed from clinical signs (1), from the central-to-toe temperature difference (2, 3, 5), or with techniques such as laser Doppler and capillary microscopy (6). Recently, the pulse oximetry signal has been suggested to reflect changes in peripheral perfusion (7). In addition, the ratio between the pulsatile and nonpulsatile component of the pulse oximetry signal has been related to peripheral perfusion (8). Because a pulse oximeter is universally available in the operating room and intensive care unit, this ratio could be used to monitor perfusion in these circumstances.

Although the manufacturer reports the lower and upper limit of normal to be 0.3 and 10.0, respectively, the variation in normal subjects and the clinical application of this ratio as an index of peripheral perfusion in critically ill patients have not yet been studied. The objective of the current study, therefore, was to assess the variation of this perfusion index in healthy adults and study the relationship between the peripheral perfusion index (PFI) and clinical signs of poor peripheral perfusion in critically ill patients.

## METHODS

### Participants

The study was conducted at a university-affiliated teaching hospital. Group 1 consisted of 108 healthy adult volunteers (mean age,  $30 \pm 9$  yrs). Group 2 consisted of 37 critically ill patients (mean age,  $70 \pm 13$  yrs) admitted to the medical/surgical intensive care unit.

### Measurements

Group 1. The measurements included capillary refill time, PFI, and arterial oxygen saturation (Spo<sub>2</sub>). We measured capillary refill time by applying firm pressure to the distal phalanx of the index finger for 5 secs and recording the time for return of the normal color by using a conventional wristwatch. PFI and Spo<sub>2</sub> were measured by using the Viridia/56S monitor (Philips Medical Systems). The Viridia system calculates the PFI as the ratio between the pulsatile component and the nonpulsatile component of the light reaching the light-sensitive cell of the pulse oximetry probe.

Group 2. The measurements included PFI, Spo<sub>2</sub>, ambient temperature, central temperature, great toe temperature, finger temperature, capillary refill time, and hemodynamic

variables including heart rate and mean arterial pressure. The central temperature was measured by using either a pulmonary artery catheter or a rectal probe. The peripheral temperature was measured on the ventral face of the great toe with a temperature probe (Philips Medical Systems 21078A). The finger temperature was measured simultaneously with the PFI measurement on the same finger by using a similar probe. The central-to-toe temperature difference was calculated, and a difference up to 7°C was considered normal (9). The doses of vasoactive drugs were recorded. Poor peripheral perfusion was defined as a capillary refill time >2 secs or a central-to-toe temperature difference  $\geq 7^{\circ}\text{C}$ .

### **Protocol**

To evaluate the variation of the PFI in healthy volunteers (group 1), measurements were taken in the hospital restaurant before and after their normal lunch after a 5- to 10-min rest. Volunteers were seated and instructed to keep their hands still on the table to avoid motion artifacts and to have the hands at the level of the heart. A questionnaire was used to collect information about history of smoking and vascular disease (diabetes, hypertension). In group 2, two measurements were taken from each patient. The first measurement was taken when peripheral perfusion was abnormal; the second measurement was taken when the peripheral perfusion profile had normalized. Patients with central hypothermia (core temperature  $<36^{\circ}\text{C}$ ) and limb ischemia attributable to vascular occlusion were excluded.

### **Statistical Analysis**

Data are presented as mean  $\pm$  sd and medians with the 25th and 75th percentiles unless otherwise indicated. Differences between groups or within groups were assessed by using the Mann-Whitney test for nonparametric data. Pearson's correlation index was calculated where applicable. We considered  $p < .05$  to be statistically significant. Statistical analyses were conducted with Statistical Package for the Social Sciences version 9.0 (SPSS, Chicago, IL).

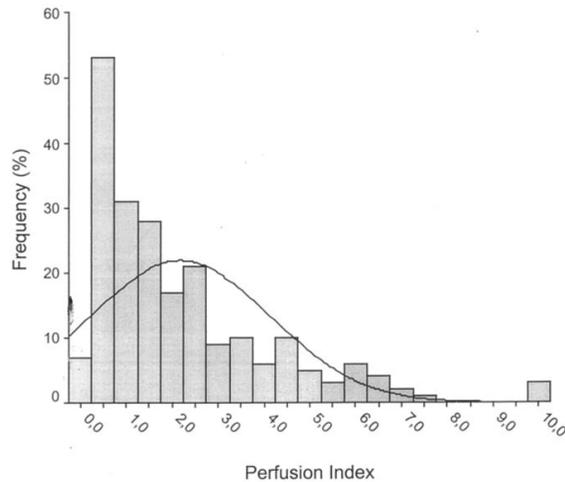
### **Informed Consent**

The Institutional Review Board waived the need for written informed consent from the healthy volunteers. Informed consent was obtained from the relatives of the patients.

## **RESULTS**

### **Group 1.**

One hundred and eight healthy volunteers were included, and a total of 216 measurements were made. The distribution of age in the healthy volunteers was normal: skew-



**Figure 1.** Frequency distribution of all 216 peripheral perfusion index values in the normal volunteers. Line represents normal distribution

**Table 1.** Descriptive statistics of peripheral perfusion index (PFI) measurements in healthy volunteers (group 1)

PFI	All Measurements (n = 216)	Before Meal (n = 108)	After Meal (n = 108)	p Value
Mean	2.2 ± 2.0	2.2 ± 2.0	2.2 ± 1.9	NS
Median (IQR)	1.4 (0.7–3.0)	1.4 (0.6–3.2)	1.5 (0.8–2.8)	NS
P5–95	0.3–6.0	0.3–6.0	0.4–6.3	
Skewness	1.61 ± 2.44	1.59 ± 2.42	1.64 ± 2.42	NS
Variance	3.84	4.12	3.59	NS

IQR, inner quartile range; P5–95, 5th and 95th percentiles; NS, not significant.

ness, 0.06; median, 36 yrs (inner quartile range, 30–45 yrs). The distribution of PFI was skewed (Fig. 1, Table 1). Descriptive analysis showed no significant difference between variance and skewness of the measurements before and after the meal (Table 1). Also, no significant differences were found between smokers (n = 26) and nonsmokers (n = 82), as well as between volunteers with (n = 11) or without (n = 97) vascular disease (diabetes, hypertension). All volunteers had a normal capillary refill time and arterial oxygen saturation (96% to 100%).

## Group 2.

A total of 74 measurements were carried out in the 37 patients studied. Descriptive statistics revealed a mean PFI of  $2.2 \pm 0.22$  with a median of 1.8 (inner quartile range, 0.5–3.2). Table 2 summarizes hemodynamic data during abnormal peripheral perfusion

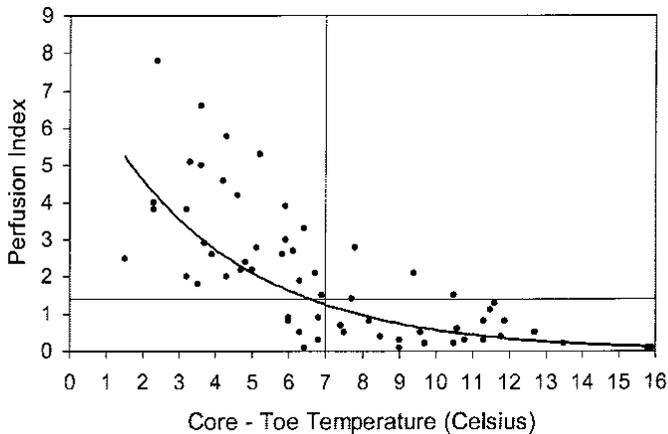
**Table 2.** Hemodynamics, variables of peripheral perfusion, and vasoactive medication during abnormal and normal peripheral perfusion in the 37 patients

	T1	T2	<i>p</i>
Core temperature, °C	37.5 ± 0.2	37.5 ± 0.1	NS
Heart rate, bpm	92 ± 3	91 ± 3	NS
Mean arterial pressure, mm Hg	81 ± 3	78 ± 2	NS
SpO <sub>2</sub> , %	97 ± 1	96 ± 0	NS
Core-to-toe temperature difference, °C	9.0 ± 0.45	4.9 ± 0.3	<.001
Perfusion index	0.7 ± 0.1	3.6 ± 0.3	<.001
Dopamine, µg/kg·min	2.5 ± 0.83	1.4 ± 0.44	NS
Dobutamine, µg/kg·min	2.9 ± 1.1	2.1 ± 0.5	NS
Noradrenaline, µg/kg·min	0.09 ± 0.03	0.05 ± 0.02	NS

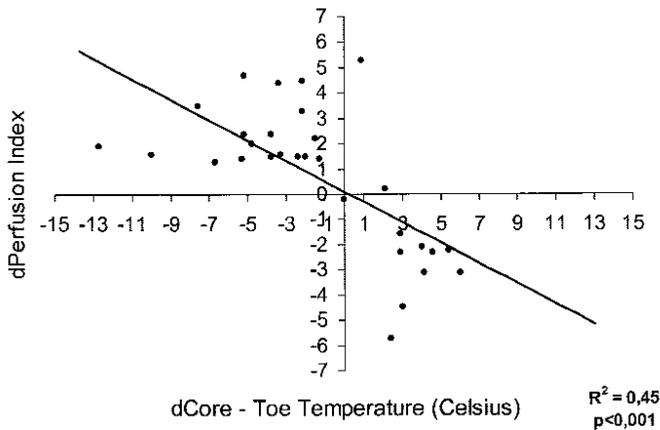
T1, condition of abnormal peripheral perfusion; T2, condition of normal peripheral perfusion; SpO<sub>2</sub>, arterial oxygen saturation; NS, not significant.

and normal peripheral perfusion, as well as the mean doses of vasoactive drugs. No significant relationship between core temperature and PFI or core-to-toe temperature difference was found. A significant exponential relationship between PFI and the core-to-toe temperature difference was found ( $R^2 = .52$ ,  $p < .001$ ; Fig. 2).

We found a significant linear correlation between changes in PFI and changes in the core-to-toe temperature difference ( $R^2 = .52$ ,  $p < .001$ ; Fig. 3). In all cases, a concordant change in PFI and core-to-toe temperature difference was found. No significant relationship was found between mean arterial pressures, dose of vasoactive agents, and PFI or between changes in these variables and changes in PFI.



**Figure 2.** Relationship between peripheral perfusion index (PFI) and core-to-toe temperature difference in all 74 measurements in the 37 patients studied. Displayed is the best fit curve (logarithmic)  $R^2 = .52$ ,  $p < .001$ . Reference lines are the median PFI of healthy volunteers and the reference for an abnormal core-to-toe temperature difference



**Figure 3.** Relationship between changes in peripheral perfusion index (PFI) and changes in core-to-toe temperature difference. Displayed are the linear regression and the correlation coefficient. dPerfusion index, PFI during abnormal perfusion - PFI during normal perfusion; dCore-Toe temperature, temperature difference during abnormal perfusion - temperature difference during normal perfusion

In 16 patients, cardiac output was measured. No significant relationship was found between changes in cardiac output and changes in either core-to-toe temperature difference or PFI.

We assessed the ability of the PFI to indicate an abnormal peripheral perfusion, as reflected by an abnormal core-to-toe temperature difference by constructing a receiver operating characteristic curve. A PFI of 1.4 discriminated best between a normal and abnormal core-to-toe temperature difference in these critically ill patients (area under the curve, 0.91; 95% confidence interval, 0.84–0.98). Table 3 reports the corresponding sensitivity, specificity, and likelihood ratios.

**Table 3.** Use of peripheral perfusion index (PFI) as a measure of abnormal core-to-toe (C-T) temperature difference, an abnormal capillary refill time, or either

	C-T	Refill	Either
Sensitivity, %	81	84	86
Specificity, %	86	88	100
Likelihood ratio after positive test	6.0	7.1	—
Likelihood ratio after negative test	0.19	0.18	0.14

Normal PFI was defined as a PFI  $\leq$  1.4. Definition of abnormal C-T temperature difference and abnormal capillary refill time: see text.

## DISCUSSION

We studied whether a perfusion index calculated from the pulse oximetry signal, and available on-line in some monitoring systems, can reflect clinical signs of decreased peripheral perfusion (capillary refill time and central-to-toe temperature difference) in critically ill patients. Because no data were available on normal values for this perfusion index, we also studied the variation of this variable in healthy individuals. We show that a PFI of 1.4 can be used to detect abnormal peripheral perfusion in critically ill patients, corresponding with the median value found in the healthy volunteers. In addition, changes in this perfusion index adequately reflect changes in clinical signs of peripheral perfusion and thus can be used to assess effect of therapeutic interventions on peripheral perfusion.

During circulatory failure associated with hypovolemia and low cardiac output, redistribution of blood flow caused by increased vasoconstriction results in decreased perfusion of the skin (1). Therefore, in critically ill patients, skin perfusion frequently is used to assess adequacy of global blood flow. Clinical signs of poor skin perfusion consist of a cold, pale, clammy, and mottled skin. Recently, techniques have become available to measure perfusion of the skin. Laser Doppler flow measurements and capillary microscopy (6) can adequately quantify changes in capillary blood flow but are not readily available in the emergency department or intensive care unit.

When blood supply to the skin decreases, the temperature of the skin also decreases. Therefore, measurements of skin temperature have been used to indicate decreases in skin blood flow as a marker of vasoconstriction and poor oxygen delivery (3, 2). Also, peripheral skin temperature has been advocated as a marker of the severity of shock (4). In addition, because vasoconstriction of the skin reduces body heat loss, the difference between the core temperature and skin temperature may increase. The central-to-toe temperature difference therefore has been used to diagnose and treat patients with global blood flow abnormalities (3, 5). To have this parameter of peripheral perfusion available online, at least two temperature probes are necessary, and the skin temperature probe should be carefully affixed. These requirements may limit the use of these variables in emergency situations and clinically unstable patients.

Pulse oximetry is a monitoring technique used in almost every trauma and critically ill patient. Monitoring of pulse oximetry during surgery is mandatory in many countries. The principle of the pulse oximetry is the difference in absorbance of light with different wavelengths (660 and 940 nm) by oxygenated hemoglobin. Other tissues, such as connective tissue, bone, and venous blood, also absorb light and thus affect the resulting signal. However, whereas the arterial component of the signal is pulsatile, the absorption of light by other tissues is fairly constant. So, to have a proper estimate of the arterial oxygen saturation of the hemoglobin, the pulse oximetry has to distinguish the

pulsatile component from the nonpulsatile component, where the pulsatile component is used subsequently to calculate the arterial oxygen saturation (10, 11). When the signal is weak, for example, during vasoconstriction, the pulse oximetry signal requires amplification up to  $\times 10^9$  (10). Although analysis of the pulse oximeter waveform has been used to assess the volume status of patients during major surgery (7), the amplification necessary during a low signal (vasoconstriction, hypovolemia) could limit its clinical application in critically ill patients. The perfusion index, used in this study, is calculated as the ratio between the pulsatile and the nonpulsatile component of the light reaching the detector of the pulse oximeter. When peripheral hypoperfusion exists, the pulsatile component decreases, and because the nonpulsatile component does not change, the ratio decreases. Because the amplification necessary during the low signal affects both the pulsatile and nonpulsatile component, the ratio between these components is not affected. Although this variable has been incorporated in some monitoring systems as a parameter of peripheral perfusion, no data are available on the variation in the normal population. Also, no studies have been published on the relationship between the index and clinically used variables of peripheral perfusion in critically ill patients.

In the current study, we found a skewed and wide range of PFI values in healthy volunteers. We found no significant differences in the distribution of PFI values before or after a meal in this group of volunteers. Also, no differences were found between volunteers with or without chronic disease associated with vascular (or microvascular) abnormalities (e.g., hypertension, diabetes) or between smokers and nonsmokers. The variation in PFI was not related to differences in capillary refill times because these were all normal in the volunteers. Unfortunately, it was impossible to measure other indexes of peripheral perfusion, for example, the central-to-toe temperature difference in these volunteers.

By constructing a receiver operating characteristic, we found the median value of the healthy volunteers to be the best discriminating cutoff value to detect an abnormal core-to-toe temperature difference. This cutoff value also resulted in adequate predictability to detect an abnormal capillary refill time. Although this cutoff value suggests that 50% of the healthy volunteers had an abnormal peripheral perfusion, the two groups probably do not compare. Most of the critically ill patients were treated with vasoactive agents and were likely to have a disturbed regulation of peripheral circulation. Probably the cutoff value to detect abnormal peripheral circulation in the healthy volunteers is closer to the lower limit of normal reported by the manufacturer (0.3) representing the 5th percentile in our study. In addition, changes in clinical indicators of peripheral perfusion were met by concordant changes of the PFI in all patients.

Although poor peripheral perfusion often accompanies circulatory failure, the practical application of these indexes and the relationship with central hemodynamics or tissue oxygenation are not well studied. Assessment of capillary refill time has been

found difficult in emergency situations, whereas the application of toe temperature measurements is often very limited in emergency medicine (12). In adult cardiac surgery patients and patients with cardiogenic shock, a crude correlation between the central-to-toe temperature difference and cardiac output has been reported (13, 2). In pediatric patients, both capillary refill time and the central-to-toe temperature difference was not related to global hemodynamics or blood lactate concentrations (14). However, in general pediatric patients, most of whom had septic shock, these indexes of peripheral perfusion correlated significantly with global hemodynamics and blood lactate concentrations (14). In contrast with this study, the central-to-toe temperature difference has been found of limited value in adult patients with septic shock (2). Also in our study, changes in cardiac output did not correlate with changes in clinical signs of poor peripheral perfusion or the PFI. These different findings could be related to the heterogeneity in skin blood flow regulation during changes in global blood flow and associated sympathetic nerve activity (15). Nevertheless, improvements in peripheral perfusion after treatment are associated with improved outcome in patients with circulatory shock (16). The PFI represents an easily obtainable measure of peripheral perfusion and thus could be used to monitor the effect of therapy on peripheral perfusion in critically ill patients.

## CONCLUSION

Our results show that the PFI in normal populations has a highly skewed distribution. The best discriminating value to detect an abnormal peripheral perfusion in critically ill patients equals the median value of normal volunteers but nevertheless can adequately reflect the presence of clinical indicators of poor peripheral perfusion in critically ill patients. Changes in these clinical indicators are reflected by changes in the PFI. Therefore, this easily obtainable and noninvasive method may have a role in monitoring peripheral perfusion in critically ill patients.

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## Chapter 4

Assessment of tissue oxygen saturation during a vascular occlusion test using near-infrared spectroscopy: the role of probe spacing and measurement site studied in healthy volunteers

*Crit Care 2009; 13 Suppl 5: S4*

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## ABSTRACT

**Introduction:** To assess potential metabolic and microcirculatory alterations in critically ill patients, near-infrared spectroscopy (NIRS) has been used, in combination with a vascular occlusion test (VOT), for the non-invasive measurement of tissue oxygen saturation (StO<sub>2</sub>), oxygen consumption, and microvascular reperfusion and reactivity. The methodologies for assessing StO<sub>2</sub> during a VOT, however, are very inconsistent in the literature and, consequently, results vary from study to study, making data comparison difficult and potentially inadequate. Two major aspects concerning the inconsistent methodology are measurement site and probe spacing. To address these issues, we investigated the effects of probe spacing and measurement site using 15 mm and 25 mm probe spacings on the thenar and the forearm in healthy volunteers and quantified baseline, ischemic, reperfusion, and hyperemic VOT-derived StO<sub>2</sub> variables.

**Methods:** StO<sub>2</sub> was non-invasively measured in the forearm and thenar in eight healthy volunteers during 3-minute VOTs using two InSpectra tissue spectrometers equipped with a 15 mm probe or a 25 mm probe. VOT-derived StO<sub>2</sub> traces were analyzed for baseline, ischemic, reperfusion, and hyperemic parameters. Data were categorized into four groups: 15 mm probe on the forearm (F15 mm), 25 mm probe on the forearm (F25 mm), 15 mm probe on the thenar (T15 mm), and 25 mm probe on the thenar (T25 mm).

**Results:** Although not apparent at baseline, probe spacing and measurement site significantly influenced VOT-derived StO<sub>2</sub> variables. For F15 mm, F25 mm, T15 mm, and T25 mm, StO<sub>2</sub> ownslope was  $-6.4 \pm 1.7\%/minute$ ,  $-10.0 \pm 3.2\%/minute$ ,  $-12.5 \pm 3.0\%/minute$ , and  $-36.7 \pm 4.6\%/minute$ , respectively. StO<sub>2</sub> upslope was  $105 \pm 34\%/minute$ ,  $158 \pm 55\%/minute$ ,  $226 \pm 41\%/minute$ , and  $713 \pm 101\%/minute$ , and the area under the hyperemic curve was  $7.4 \pm 3.8\%-minute$ ,  $10.1 \pm 4.9\%-minute$ ,  $12.6 \pm 4.4\%-minute$ , and  $21.2 \pm 2.7\%-minute$  in these groups, respectively. Furthermore, the StO<sub>2</sub> parameters of the hyperemic phase of the VOT, such as the area under the curve, significantly correlated to the minimum StO<sub>2</sub> during ischemia.

**Conclusions:** NIRS measurements in combination with a VOT are measurement site-dependent and probe-dependent. Whether this dependence is anatomy-, physiology-, or perhaps technology-related remains to be elucidated. Our study also indicated that reactive hyperemia depends on the extent of ischemic insult.

## INTRODUCTION

It is now well established that tissue oxygen utilization and regional microcirculatory oxygen transport properties are severely affected during sepsis and shock [1-9]. To assess and identify these metabolic and microcirculatory alterations non-invasively, near-infrared spectroscopy (NIRS) has recently been applied to measure the behavior of tissue oxygen saturation (StO<sub>2</sub>). Besides observation of steady-state values, a vascular occlusion test (VOT) has been introduced for the measurement of tissue oxygen consumption and of microvascular reperfusion and reactivity [9-14].

The VOT seems to be sensitive to the progress and outcome of sepsis in critical illness [9,12]. A large number of variables exist in the performance of this maneuver, however, yielding apparently conflicting results and uncertainty as to the significance of the various VOT-derived StO<sub>2</sub> parameters [11]. The analysis, interpretation, and understanding of VOT-derived StO<sub>2</sub> traces, although being widely employed in septic and trauma patients, is limited, especially for the post-occlusion phase of the VOT. Consequently, identification of which StO<sub>2</sub> parameters are most appropriate for scoring (micro)vascular reperfusion and reactivity remains to be determined. Proper characterization of VOT-derived StO<sub>2</sub> parameters in health is hence needed to allow translation of results obtained in patients to pathophysiological phenomena.

The main problem with the interpretation of StO<sub>2</sub> data in the literature is the diversity of methodologies used for assessing StO<sub>2</sub> during a VOT. Results vary from study to study, making data comparison and interpretation difficult and possibly inadequate. Two major aspects regarding the inconsistent methodology are the measurement site and probe spacing (that is, the spatial separation between the illumination and detection fibers of the NIRS probe). The measurement site is important because differences may exist in the sensitivity of muscle groups and/or other anatomical structures to the VOT during health and/or pathophysiological conditions. Probe spacing, on the other hand, will determine the depth of measurement within the respective muscle group. To study the roles of both variables, we performed 3-minute VOTs in healthy volunteers and measured using 15 mm and StO<sub>2</sub> 25 mm probe spacings on the thenar and the forearm. VOT-derived StO<sub>2</sub> traces were quantified for baseline, ischemic, reperfusion, and hyperemic StO<sub>2</sub> parameters. We expect these results to provide an essential frame of reference for conducting StO<sub>2</sub> measurements in future clinical studies.

## MATERIALS AND METHODS

### Subjects

The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam. Eight healthy volunteers (Table 1) who were not receiving any

**Table 1.** Demographic characteristics of the studied subjects

<b>Demographic characteristic Mean <math>\pm</math> standard deviation</b>	
Age (years)	28 $\pm$ 6
Gender (%)	
Female	25
Male	75
Dominant hand (%)	
Right	87.5
Left	12.5
Weight (kg)	78 $\pm$ 10
Height (cm)	178 $\pm$ 8
Tympanic temperature ( $^{\circ}$ C)	36.6 $\pm$ 0.5
Systolic blood pressure (mmHg)	112 $\pm$ 9
Diastolic blood pressure (mmHg)	73 $\pm$ 7
Mean arterial pressure (mmHg)	91 $\pm$ 8
Heart rate (beats/minute)	69 $\pm$ 8

vaso-active medication were requested to refrain from consuming caffeine-containing beverages prior to the experiments. The subjects were comfortably seated in the experimental room (mean  $\pm$  standard deviation room temperature was 21  $\pm$  1 $^{\circ}$ C) 1 hour before measurements and were requested not to perform any physical labor (for example, lifting and writing).

### **Near-infrared spectroscopy**

StO<sub>2</sub> was continuously and non-invasively measured using two InSpectra tissue spectrometers (Model 325; Hutchinson Technology, Hutchinson, MN, USA). The spectrometers use reflectance mode probes that have a 1.5 mm optical fiber to illuminate the tissue and a 0.4 mm optical fiber to collect the backscattered light from the tissue. Two types of probes were used for this study: one with 15 mm spacing between the illumination and the collecting optical fibers, and one with 25 mm spacing. Both probes have been used in various studies with varying results [9-12].

The relative optical attenuation of the backscattered light at four wavelengths (680 nm, 720 nm, 760 nm, and 800 nm) is measured to calculate two second-derivative attenuation values, one centered at 720 nm and the other at 760 nm [15]. The ratio of the 720 nm to 760 nm second-derivative values is directly extrapolated to StO<sub>2</sub>, defined as

$[\text{HbO}_2]/([\text{Hb}] + [\text{HbO}_2])$ , via a calibration table. The calibration table relating StO<sub>2</sub> to the second-derivative attenuation ratio is stored permanently within the NIRS device and is common to each device and probe used [15]. The NIRS devices were calibrated before the first measurement in each subject using a light-scatter calibrator.

### **Vascular occlusion test**

One NIRS probe was placed on the skin of the thenar eminence and another NIRS probe was placed on the lateral side of the anterior surface of the forearm for simultaneous measurement of thenar StO<sub>2</sub> and forearm StO<sub>2</sub> during the VOTs. Both the hand and the forearm were kept at heart level with the palms up. The subjects were instructed not to move their hand or arm, or to change their sitting position during measurements.

Baseline arterial pressure was measured using a manual sphygmomanometer. After a 3-minute stabilization period (baseline measurement), stagnant ischemia was induced for 3 minutes by rapidly inflating a pneumatic cuff (within 5 seconds), placed around the upper arm, to 50 mmHg above systolic blood pressure. The cuff was subsequently deflated (within 1 second) and StO<sub>2</sub> measurements were continued up to 5 minutes post ischemia.

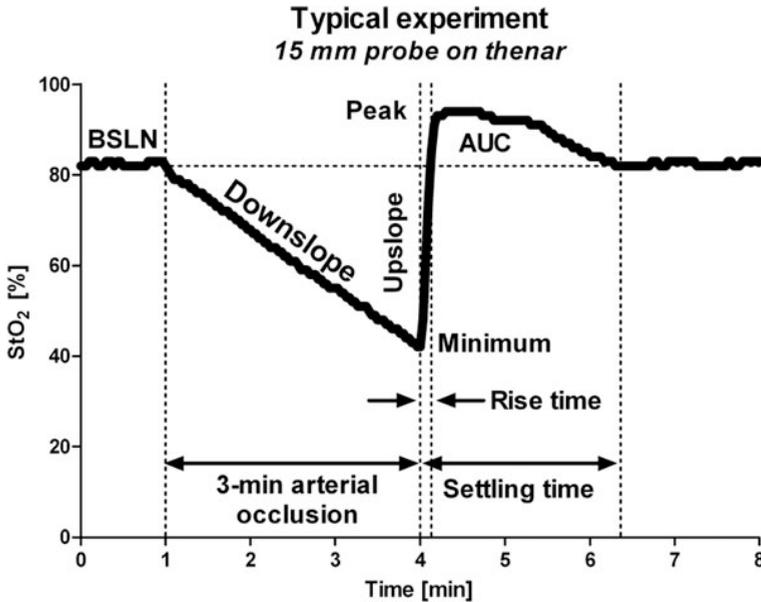
### **StO<sub>2</sub> curve characteristics**

StO<sub>2</sub> data from the two devices were continuously saved (one sample every 3.5 seconds) on two computers and were retrospectively analyzed using InSpectra Analysis V3.3 software (Hutchinson Technology). The VOT-derived StO<sub>2</sub> traces were divided into four phases: baseline, ischemia, reperfusion, and hyperemia (Figure 1).

The ischemic phase was analyzed for StO<sub>2</sub> downslope (%/minute), minimum StO<sub>2</sub> after 3 minutes of ischemia (%), and  $\Delta\text{StO}_2$  (%; that is, the difference between baseline and minimum StO<sub>2</sub>). The StO<sub>2</sub> downslope is generally considered to reflect muscle metabolism and the minimum StO<sub>2</sub> is considered to indicate the extent of ischemia.

The reperfusion phase was analyzed for two parameters: upslope (%/minute) and rise time (minutes), both StO<sub>2</sub> measured over the interval from minimum StO<sub>2</sub> to baseline (Figure 1). Although these parameters are directly StO<sub>2</sub> related ( $\text{StO}_2 \text{ upslope} = \Delta\text{StO}_2 / \text{Rise time}$ ), the StO<sub>2</sub> upslope is metabolism-dependent as it is based on  $\Delta\text{StO}_2$  after a fixed time of occlusion (that is, 3 minutes), while the rise time solely represents the time required to wash out the stagnantly deoxygenated blood by oxygenated arterial blood during reperfusion. These two parameters were therefore measured and analyzed separately.

The hyperemic phase of the VOT was analyzed for peak StO<sub>2</sub> during reperfusion (%), for StO<sub>2</sub> overshoot (that is, difference between peak StO<sub>2</sub> and baseline StO<sub>2</sub>), for the area under the hyperemic curve (AUC; %-minute), and for the settling time from release of the cuff to recovery to baseline StO<sub>2</sub> (minutes).



**Figure 1.** Vascular occlusion test-derived tissue oxygen saturation phases and parameters. The vascular occlusion test-derived tissue oxygen saturation (StO<sub>2</sub>) traces were divided into four phases (baseline, ischemia, reperfusion, and hyperemia) and were analyzed for baseline StO<sub>2</sub> (BSLN), StO<sub>2</sub> downslope, minimum StO<sub>2</sub>, StO<sub>2</sub> upslope, rise time, peak StO<sub>2</sub>, area under the hyperemic curve (AUC), and settling time.

### Measurement protocol

Three measurement variables were investigated and compared for the assessment of VOT-derived StO<sub>2</sub> parameters: dominant arm versus nondominant arm, forearm versus thenar, and superficial tissue versus deep tissue (as measured by the different probe spacings). For this purpose, four measurements were performed per subject: two on the dominant side and two on the nondominant side. Although good reproducibility of NIRS measurements during sequential VOTs has been demonstrated by Gómez and colleagues [11], the side and probes were switched after every VOT. Additionally, to avoid any effect of starting conditions, the first measurement in four subjects was performed on the dominant side with the 15 mm probe on the forearm and the 25 mm probe on the thenar, whereas in the other four subjects the first measurement was performed on the nondominant side with the 15 mm probe on the thenar and the 25 mm probe on the forearm.

#### Statistical analysis

First, differences between the dominant arm and the nondominant arm were analyzed and data were subsequently categorized into four groups: 15 mm probe on the forearm (F15 mm), 25 mm probe on the forearm (F25 mm), 15 mm probe on the thenar (T15 mm), and 25 mm probe on the thenar (T25 mm). Statistical analysis was performed in

GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Normal distribution of the data within all groups (dominant, nondominant, F15 mm, F25 mm, T15 mm, and T25 mm) was confirmed for each StO<sub>2</sub> parameter using the D'Agostino and Pearson omnibus normality test. Comparative analysis between groups was performed using analysis of variance with a Bonferroni post-hoc test. Correlation analysis was performed by Pearson's analysis for normally distributed datasets. All data are presented as the mean  $\pm$  standard deviation. Differences between groups with  $P < 0.05$  were considered statistically significant.

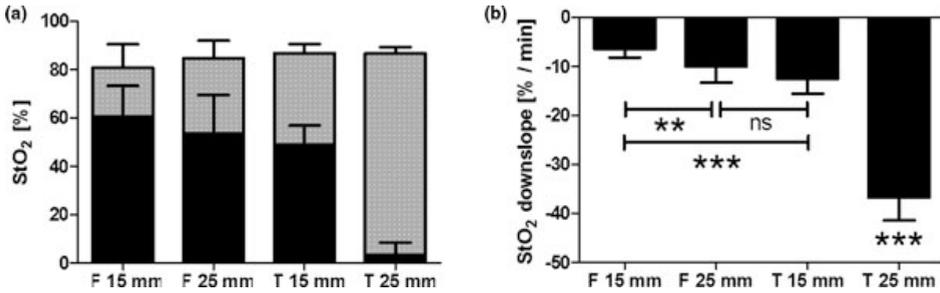
## RESULTS

No differences between the dominant and nondominant sides were found and data could therefore be categorized into four groups: F15 mm, F25 mm, T15 mm, and T25 mm. Baseline StO<sub>2</sub> was similar in all groups and independent of probe spacing and measurement site:  $81 \pm 10\%$  for F15 mm,  $85 \pm 7\%$  for F25 mm,  $87 \pm 4\%$  for T15 mm, and  $87 \pm 3\%$  for T25 mm. Occlusion of the upper arm by a pneumatic cuff resulted in an immediate decrease in StO<sub>2</sub>. Release of the occlusion after 3 minutes was followed by a rapid increase in StO<sub>2</sub> and a StO<sub>2</sub> overshoot relative to baseline. Less than 3 minutes post-ischemia, StO<sub>2</sub> values were restored to baseline level.

### Ischemic phase

The downslopes during ischemia were measured using linear regression analysis over the linear part (that is,  $R^2 > 0.95$ ) of the StO<sub>2</sub> curve. For the first three groups (F15 mm, F25 mm, and T15 mm), the downslopes were linear over the entire 3-minute period of ischemia. The downslopes measured in the T25 mm group, in contrast, were linear over a time interval of  $2.34 \pm 0.38$  minutes. For F15 mm, F25 mm, T15 mm, and T25 mm, StO<sub>2</sub> down-slopes were  $-6.4 \pm 1.7\%/minute$ ,  $-10.0 \pm 3.2\%/minute$ ,  $-12.5 \pm 3.0\%/minute$ , and  $-36.7 \pm 4.6\%/minute$ , respectively (Figure 2). Hence, during 3 minutes of ischemia, StO<sub>2</sub> decreased significantly ( $P < 0.001$ ) by  $20 \pm 5\%$ ,  $31 \pm 11\%$ ,  $38 \pm 9\%$ , and  $84 \pm 6\%$  for F15 mm, F25 mm, T15 mm, and T25 mm, respectively, which resulted in a minimum StO<sub>2</sub> of  $60 \pm 13\%$ ,  $54 \pm 16\%$ ,  $49 \pm 8\%$ , and  $3 \pm 5\%$  in these groups (Figure 2).

For all groups, minimum StO<sub>2</sub> values were significantly lower than baseline values ( $P < 0.001$ ). For the downslopes and  $\Delta$ StO<sub>2</sub> during ischemia, values for F15 mm differed significantly from values for F25 mm ( $P < 0.01$ ), for T15 mm ( $P < 0.001$ ), and for T25 mm ( $P < 0.001$ ). The minimum StO<sub>2</sub> was significantly higher in the F15 mm group with respect to T15 mm ( $P < 0.05$ ) and to T25 mm ( $P < 0.001$ ). No significant differences between F25 mm and T15 mm were found for these parameters. Downslopes,  $\Delta$ StO<sub>2</sub>, measured in the



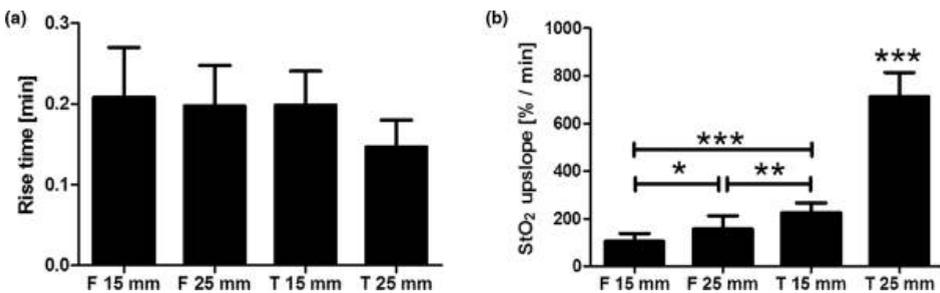
**Figure 2.** Tissue oxygen saturation at baseline and after ischemia, and the corresponding downslopes. **(a)** Measured tissue oxygen saturation (StO<sub>2</sub>) baseline values and minima after 3 minutes of ischemia. **(b)** Corresponding StO<sub>2</sub> downslopes (right). ns = not significant ( $P > 0.05$ ),  $**P < 0.01$ ,  $***P < 0.001$ . F, forearm; T, thenar.

and minimum StO<sub>2</sub> T25 mm group were significantly different from those measured in the other groups ( $P < 0.001$ ).

### Reperfusion phase

After release of the cuff pressure, StO<sub>2</sub> rapidly increased to (and above) baseline StO<sub>2</sub>. In F15 mm, F25 mm, T15 mm, and T25 mm, StO<sub>2</sub> rise times (that is, time from minimum StO<sub>2</sub> to baseline StO<sub>2</sub>) were  $0.208 \pm 0.062$  minutes,  $0.198 \pm 0.050$  minutes,  $0.198 \pm 0.042$  minutes, and  $0.147 \pm 0.033$  minutes, respectively. None of these results were significantly different between groups (Figure 3).

In contrast to the rise times, differences between the StO<sub>2</sub> upslopes (calculated over the same interval as the rise time) were found between groups due to differences in baselines and minima (StO<sub>2</sub> upslope = (StO<sub>2</sub> baseline - StO<sub>2</sub> minimum)/Rise time). Upslopes were  $105 \pm 34\%$ /minute,  $158 \pm 55\%$ /minute,  $226 \pm 41\%$ /minute, and  $713 \pm 101\%$ /minute for F15 mm, F25 mm, T15 mm, and T25 mm, respectively. The upslopes in the thenar were significantly higher than the upslopes in the forearm, and the upslopes



**Figure 3.** Measured rise times and the corresponding tissue oxygen saturation upslopes. **(a)** Measured rise times. **(b)** Corresponding tissue oxygen saturation (StO<sub>2</sub>) upslopes.  $*P < 0.05$ ,  $**P < 0.01$ ,  $***P < 0.001$ . F, forearm; T, thenar.

measured with the 25 mm probe were significantly higher than those measured with the 15 mm probe (Figure 3).

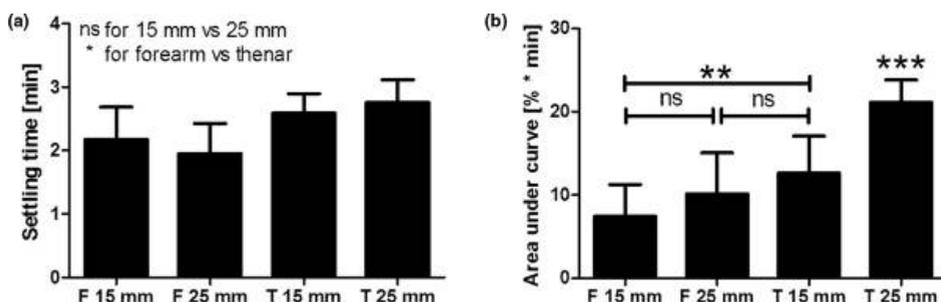
Although the rise time and StO<sub>2</sub> upslope both describe (micro)vascular reperfusion following ischemia, apparently these parameters are sensitive to different variables. Hence, where the rise time is similar for the forearm and the thenar and is independent of the applied probe, the StO<sub>2</sub> upslope depends significantly on both the muscle and the probe type.

### Hyperemic phase

Peak StO<sub>2</sub> following release of the upper arm occlusion was  $88 \pm 7\%$ ,  $93 \pm 5\%$ ,  $95 \pm 3\%$ , and  $98 \pm 0\%$  for F15 mm, F25 mm, T15 mm, and T25 mm, respectively. Only the peak in the F15 mm group differed significantly from the thenar ( $P < 0.001$  with respect to T15 mm and T25 mm). No significant differences were found for the StO<sub>2</sub> overshoot (that is, peak StO<sub>2</sub> - Baseline StO<sub>2</sub>):  $6.9 \pm 3.8\%$ ,  $8.6 \pm 3.7\%$ ,  $8.7 \pm 3.2\%$ , and  $11.3 \pm 2.7\%$  for F15 mm, F25 mm, T15 mm, and T25 mm, respectively.

The settling time, defined as the time required for the StO<sub>2</sub> to completely restore to baseline (Figure 4), was  $2.170 \pm 0.511$  minutes,  $1.950 \pm 0.475$  minutes,  $2.588 \pm 0.306$  minutes, and  $2.755 \pm 0.360$  minutes for F15 mm, F25 mm, T15 mm, and T25 mm, respectively. No significant differences were found with respect to the probe spacing (that is, F15 mm versus F25 mm ( $P > 0.05$ ) and T15 mm versus T25 mm ( $P > 0.05$ )), but significant differences existed between measurement sites (that is, F15 mm versus T15 mm and T25 mm ( $P < 0.05$ ), and F25 mm versus T15 mm and T25 mm ( $P < 0.01$ )).

The AUC was  $7.4 \pm 3.8\%$ -minute,  $10.1 \pm 4.9\%$ -minute,  $12.6 \pm 4.4\%$ -minute, and  $21.2 \pm 2.7\%$ -minute for F15 mm, F25 mm, T15 mm, and T25 mm, respectively (Figure 4). No significant differences were found between the 15 mm probe and the 25 mm probe on the forearm. Using the 15 mm probe, the AUC in the thenar was significantly higher ( $P < 0.01$ ) than in the forearm. AUCs measured in the T25 mm group were significantly higher than those measured in the other groups ( $P < 0.001$ ).



**Figure 4.** Measured settling times and the corresponding areas under the hyperemic curves. (a) Measured settling times. (b) Corresponding areas under the curves. ns = not significant ( $P > 0.05$ ), \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . F, forearm; T, thenar.

### Correlation analysis

To investigate the relationship between the extent of ischemia and the parameters of reperfusion and hyperemia, StO<sub>2</sub> correlation analysis (Pearson's analysis) was performed for minimum StO<sub>2</sub> versus reperfusion parameters (StO<sub>2</sub> upslope and rise time) and hyperemic parameters (peak StO<sub>2</sub>, StO<sub>2</sub> overshoot, AUC, and settling time) from combined data of F15 mm, F25 mm, and T15 mm. T25 mm data were excluded from the analysis because StO<sub>2</sub> downslopes were not linear over the entire 3-minute period of ischemia, which would affect the consistency in the correlation analysis.

StO<sub>2</sub> upslope correlated significantly with minimum StO<sub>2</sub> ( $r = 0.81, P < 0.001$ ), while the rise time did not ( $r = 0.12, P > 0.05$ ). The peak StO<sub>2</sub> ( $r = 0.3, P < 0.05$ ), StO<sub>2</sub> overshoot ( $r = 0.44, P < 0.001$ ), and AUC ( $r = 0.45, P < 0.01$ ) exhibited a weak positive correlation with minimum StO<sub>2</sub>, whereas a correlation was absent with respect to settling time ( $r = 0.16, P > 0.05$ ).

To illustrate why the rise time and StO<sub>2</sub> upslope behave differently in relation to the measurement site and probe spacing, two individual measurements are described in detail. One measurement was performed with the 15 mm probe on the forearm and the other with the 15 mm probe on the thenar, both with a baseline StO<sub>2</sub> of 88%. The StO<sub>2</sub> downslope during ischemia was -8%/minute in the forearm and -16%/minute in the thenar. This resulted in different StO<sub>2</sub> minima for the two curves: 64% in the forearm and 40% in the thenar. After release of the occlusion, both curves restored back to their baseline level in 0.233 minutes. The rise times, and thus the reperfusion dynamics, for both curves were therefore equal. The StO<sub>2</sub> upslopes, in contrast, were very different: 103%/minute in the forearm and 206%/minute in the thenar. This suggests that the StO<sub>2</sub> upslope does not solely reflect post-ischemia reperfusion dynamics, but is also strongly influenced by the extent of StO<sub>2</sub> decrease during ischemia.

## DISCUSSION

The primary finding of this study was that, although not apparent at baseline, the probe spacing and measurement site significantly influenced VOT-derived StO<sub>2</sub> variables. The upslope in the reperfusion phase of the VOT was StO<sub>2</sub> shown to depend on the minimum StO<sub>2</sub> after 3 minutes of ischemia, while the rise time was not. Furthermore, the StO<sub>2</sub> parameters of the hyperemic phase of the VOT were shown to significantly correlate to the minimum StO<sub>2</sub> value after 3 minutes of ischemia.

Among the investigations employing a NIRS device identical to the ones used in the present study, some studies have used 15 mm probe spacing [10,11,14] while others have used 25 mm probe spacing [9,12,16-18]. In healthy volunteers, all of these studies - including ours - have shown that baseline StO<sub>2</sub> values were similar, independent of the applied probe. The VOT-derived StO<sub>2</sub> variables as reported in the literature, however,

varied widely between the studies using a 15 mm probe and the studies using a 25 mm probe [9-12,14,16-18]. The values obtained in the present study are comparable to those obtained in the above-referenced studies. In the present study we quantitatively compared the VOT-derived StO<sub>2</sub> variables obtained using both probes and confirmed the hypothesis that this difference in StO<sub>2</sub> downslopes is indeed caused by the use of different probe spacings. In the thenar, the 15 mm probe provided a longer time interval of linear StO<sub>2</sub> decay during ischemia than the 25 mm probe, which could make the estimation of the ischemic insult and muscle metabolism inaccurate and possibly inadequate when using the 25 mm probe.

The potential mechanisms by which the VOT-derived StO<sub>2</sub> traces might be different when measured by the 15 mm or 25 mm probes could be anatomy-related, physiology-related, or even technology-related. It is well established that muscle cells consume much more oxygen per unit time compared with skin and adipose tissue. Additionally, if the ischemic stimulus is more extensive in the muscle compared to the more superficial layer of (sub)dermal tissue, the reactive hyperemia is probably also of a larger extent in the deeper, muscular, layer. In this light, the probe dependence, and thus the measurement depth dependence, of the StO<sub>2</sub> downslope and hyperemic parameters could therefore be explained by variable relative contributions of (sub)dermal tissue and muscular tissue to the NIRS signal for the different probing depths. Another option that might explain the probe dependence of the StO<sub>2</sub> traces, however, is that the number of photons that reach the detection fiber of the NIRS probe decreases with increasing probe spacing, which, in turn, could decrease the accuracy of the StO<sub>2</sub> calculation. This could be especially true at low microcirculatory oxygenation, as occurs during ischemia, where the optical absorbance of blood is much higher compared to at high oxygenation. This, however, is purely suggestive and no evidential data are present to support this speculation.

In the present article we provide a frame of reference for comparison of data measured in the thenar and forearm using the 15 mm probe and the 25 mm probe for a very broad spectrum of VOT-derived StO<sub>2</sub> parameters; that is, baseline parameters, ischemic parameters, reperfusion parameters, and hyperemic parameters.

An important conceptual issue that is addressed in the present study is the difference between StO<sub>2</sub> upslope and the rise time in the reperfusion phase of the VOT. First, it was shown that StO<sub>2</sub> upslopes were different between the experimental groups while rise times were similar in these groups. Second, the correlation analysis performed on the minimum StO<sub>2</sub> values after 3 minutes of ischemia versus the StO<sub>2</sub> upslopes and rise times showed that the StO<sub>2</sub> upslope correlated significantly with the minimum StO<sub>2</sub> while the rise time did not. From a physiological point of view, the rise time represents the time it takes to wash out (or replace) the stagnantly deoxygenated blood in the measurement volume of the NIRS probe by oxygenated arterial blood. The StO<sub>2</sub> upslope, on the other

hand, has no single physiological meaning as it is the product of multiple variables, such as the baseline StO<sub>2</sub>, minimum StO<sub>2</sub>, and rise time. Hence, the use of rise time seems to be a more representative measure of (micro)vascular reperfusion than StO<sub>2</sub> upslope.

Another pertinent result from the correlation analysis was the significant positive correlation between the hyperemic parameters and the minimum StO<sub>2</sub>, indicating that the extent of hyperemia is related to the extent of ischemia. This suggests that the use of a target or threshold StO<sub>2</sub> might be more appropriate for standardization of the hyperemic phase of the VOT. After 3 minutes of ischemia, however, StO<sub>2</sub> decreased to a minimum of 60% in the forearm and 49% in the thenar when one uses the 15 mm probe and to 54% in the forearm and 1% in the thenar if one uses the 25 mm probe. The probe type should therefore be taken into account when one uses a defined StO<sub>2</sub> threshold value of 30 or 40%. Moreover, the occlusion time might exceed 3 minutes when using the 15 mm probe, which could be uncomfortable for the studied subject.

Conclusively, the data from this study support the hypothesis that the NIRS measurements in combination with a VOT are measurement site-dependent and probe-dependent. The present study showed that the use of upslope is StO<sub>2</sub> sensitive to the minimum StO<sub>2</sub> after 3 minutes of ischemia and does not solely reflect the (micro)vascular reperfusion rate. Although the rise time seems a better measure for (micro)vascular reperfusion following ischemia, this study could not determine whether the use of the rise time can distinguish healthy (micro)vasculature from nonhealthy (micro)vasculature. Our study also indicated that reactive hyperemia depends on the extent of ischemic insult and supports the use of a target StO<sub>2</sub> over the use of a fixed time of occlusion for a metabolism-independent analysis of (micro)vascular reactivity, whereby the type of probe should be taken into account. Whether the observed measurement site dependence and probe dependence is anatomy-related, physiology-related, or perhaps technology-related remains to be elucidated.

### **Abbreviations**

NIRS: near-infrared spectroscopy; StO<sub>2</sub>: tissue oxygen saturation; VOT: vascular occlusion test.

### **Competing interests**

The NIRS devices were provided by Hutchinson Technologies.

### **Acknowledgements**

This article is part of Critical Care Volume 13 Supplement 5: Tissue oxygenation (StO<sub>2</sub>) in healthy volunteers and critically-ill patients. The full contents of the supplement are available online at <http://ccforum.com/supplements/13/S5>. Publication of the supplement has been supported with funding from Hutchinson Technology Inc.

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# Chapter 5

Peripheral vasoconstriction influences  
thenar oxygen saturation measured  
by nearinfrared spectroscopy

*Intensive Care Med 2012, 38(4): 606-11*

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# Chapter 5a

## Letter to the editor: Near infrared spectroscopy

*Crit Care Med* 2009 Jan; 37(1): 384-385

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## ABSTRACT

### Purpose

Near-infrared spectroscopy has been used as a noninvasive monitoring tool for tissue oxygen saturation (StO<sub>2</sub>) in acutely ill patients. This study aimed to investigate whether local vasoconstriction induced by body surface cooling significantly influences the thenar StO<sub>2</sub> as measured by InSpectra model 650.

### Methods

Eight healthy individuals (age  $26 \pm 6$  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<sub>2</sub> 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<sub>2</sub> values, rate of StO<sub>2</sub> desaturation (RdecStO<sub>2</sub>, %/min), and rate of StO<sub>2</sub> recovery (RincStO<sub>2</sub>, %/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<sub>skin-diff</sub>), 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<sub>2</sub> from 82% (80–87) to 72% (70–77) ( $P < 0.05$ ) and in RincStO<sub>2</sub> from 3.0%/s (2.8–3.3) to 1.7%/s (1.1–2.0) ( $P < 0.05$ ). Similar changes in CRT, T<sub>skin-diff</sub>, 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<sub>2</sub> 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 (StO<sub>2</sub>) 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 StO<sub>2</sub> 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 StO<sub>2</sub> 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 StO<sub>2</sub>-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 StO<sub>2</sub>? To answer this question, we performed StO<sub>2</sub>-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 StO<sub>2</sub> 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

*StO<sub>2</sub>-derived tissue oxygenation.* StO<sub>2</sub>-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 fore-

arm 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 StO<sub>2</sub> parameters were divided into three components: resting StO<sub>2</sub> values, rate of StO<sub>2</sub> desaturation (RdecStO<sub>2</sub>, expressed as %/min), and rate of StO<sub>2</sub> recovery (RincStO<sub>2</sub>, 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<sub>skin-diff</sub>), 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<sub>skin-diff</sub> 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<sub>skin-diff</sub> can better reflect changes in cutaneous blood flow than skin temperature itself. When being evaluated under constant environmental conditions, T<sub>skin-diff</sub> 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 StO<sub>2</sub> 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 ( $T = 22^{\circ}\text{C}$ ). Skin vasoconstriction was defined as a minimal 50% decrease either in the  $T_{\text{skin-diff}}$  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.

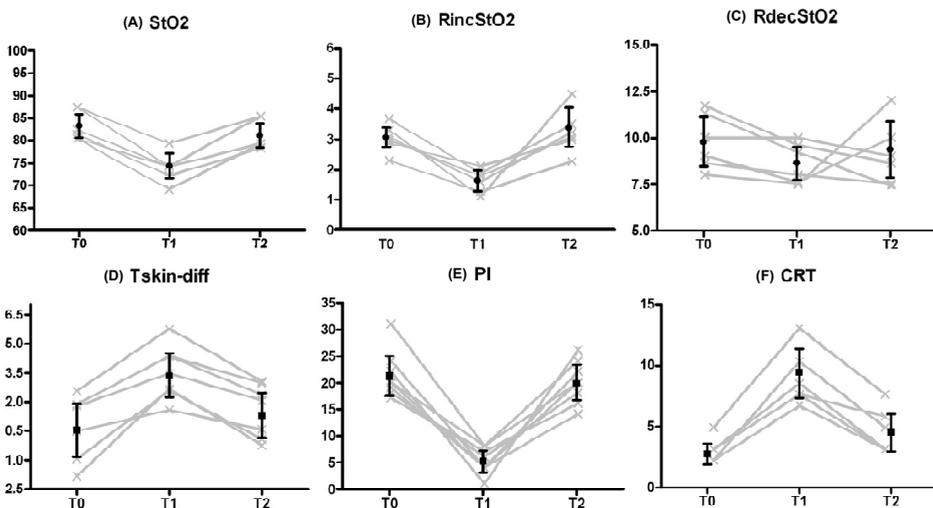
**Table 1.** Descriptive analysis of the physiological variables in all 8 healthy volunteers stratified by the time points T0 (baseline), T1 (during peripheral cooling) and T2 (after stop cooling and re-warming process). Data presented as median [25<sup>th</sup>;75<sup>th</sup>]

	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]

## RESULTS

Eight healthy individuals (4 male, 4 female) participated in the study. The mean age, height, and weight were  $26 \pm 6$  years,  $172 \pm 5$  cm, and  $74.1 \pm 6.2$  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 cooling resulted in skin vasoconstriction in all volunteers with a significant decrease in the T<sub>skin-diff</sub> temperature and in the PI signal: 55% (40–175) and 77% (62–83) compared with baseline, respectively. Concomitantly, we observed a significant decrease in StO<sub>2</sub> and RincStO<sub>2</sub> values but not in RdecStO<sub>2</sub>. The rewarming process increased StO<sub>2</sub> and RincStO<sub>2</sub> values towards baseline levels. Similar changes in CRT, T<sub>skin-diff</sub>, and PI were also observed. The THI values did not change significantly during the entire experiment.



**Figure 1.** Evolution of NIRS-derived variables and peripheral perfusion before peripheral cooling (T0), during peripheral cooling (T1) and after re-warming (T2). Abbreviation: (A) StO<sub>2</sub>=peripheral tissue oxygenation (%); (B) RincStO<sub>2</sub>=rate of StO<sub>2</sub> recovery after arterial occlusion (%/sec); (C) RdecStO<sub>2</sub>=rate of StO<sub>2</sub> desaturation during arterial occlusion (%/min); (D) T<sub>skin-diff</sub>=forearm-to-fingertip skin-temperature gradient (°C); (E) PI=perfusion index (%); (F) CRT=capillary refill time (sec). Lines represent individual values for each healthy volunteer. Bars are mean±95%CI

**Table 2.** Descriptive analysis of NIRS-derived variables and peripheral perfusion parameters stratified by the time points T0 (baseline), T1 (during peripheral cooling) and T2 (after stop cooling and re-warming process). Data presented as median [25th;75th]

	Time point		
	T0	T1	T2
StO <sub>2</sub> (%)	82 [80;87]	72* [70;77]	80 [79;85]
RincStO <sub>2</sub> (%/sec)	3.0 [2.8;3.3]	1.7* [1.1;2.0]	3.2 [3.0;4.2]
RdecStO <sub>2</sub> (%/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]
Tskin-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]

RincStO<sub>2</sub>= rate of StO<sub>2</sub> increase after arterial occlusion; RdecStO<sub>2</sub>=rate of StO<sub>2</sub> deoxygenation during arterial occlusion; THI=tissue hemoglobine index; Tskin-diff= forearm-to-fingertip skin-temperature gradient; CRT=capillary refill time; PI=Perfusion Index

\*  $P < 0.05$  vs. baseline 1 and baseline 2 (one-way repeated-measures ANOVA with Bonferroni post hoc test)

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 RincStO<sub>2</sub> than StO<sub>2</sub> and that RincStO<sub>2</sub> is more sensitive to changes in peripheral perfusion than StO<sub>2</sub> itself. When compared with baseline values, the magnitude of the RincStO<sub>2</sub> decreases was larger than that observed for StO<sub>2</sub> [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 StO<sub>2</sub>-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 StO<sub>2</sub> resting values and in the StO<sub>2</sub> recovery rate. 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 StO<sub>2</sub> measured. It is likely that the decreasing StO<sub>2</sub> 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 StO<sub>2</sub>-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 StO<sub>2</sub> 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 StO<sub>2</sub> 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 StO<sub>2</sub> 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 StO<sub>2</sub> 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 StO<sub>2</sub> and StO<sub>2</sub> recovery rate in our model provide evidence that peripheral vasoconstriction markedly influences the NIRS measurements of thenar tissue oxygenation and may confound interpretation of StO<sub>2</sub>-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 StO<sub>2</sub>-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 StO<sub>2</sub>-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 StO<sub>2</sub> as measured on the thenar [18]. These findings strongly suggest that StO<sub>2</sub>-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 StO<sub>2</sub>-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 StO<sub>2</sub> 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 StO<sub>2</sub>-derived measurements, particularly StO<sub>2</sub> and StO<sub>2</sub> 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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**LETTER TO THE EDITOR:****Critical Care Medicine 37(1), January 2009, pp 384-385****NEAR INFRARED SPECTROSCOPY**

Over the last years, tissue microcirculatory and regional perfusion and oxygenation have made an important entry into the functional hemodynamic monitoring of critically ill patients (1). Clinical assessment of these parameters has become possible by the introduction of optical spectroscopic technologies such as near-infrared spectroscopy. This technique is based on the oxygen-dependent optical absorption of blood in the near-infrared spectrum. There are three prime factors which distinguish the currently available devices: 1) the algorithm used to calculate regional/microcirculatory hemoglobin saturation; 2) the spatial separation of the illumination and detection fiber, which determines the measurement depth; and 3) the location of the probe.

In a recent issue of *Critical Care Medicine*, Soller et al (2) presented a study in volunteers where a decrease in venous return (as a model of hypovolemia) was induced by lower limb negative pressure. In the model, they compared a self-developed near-infrared spectroscopy device, which measures a parameter called muscle oxygen tension, to a commercially available device from Hutchinson Technology (HT), which measures a parameter called tissue oxygen saturation and has been studied clinically (3–5). The authors concluded that their device has “superior sensitivity” to detect acute hypovolemia when compared with the HT device. However, in their study design, two of the above-mentioned factors were not under experimental control resulting in a faulty conclusion. This may lead to confusion in the field of those using the near-infrared spectroscopy technique and needs to be addressed.

The first shortcoming concerns the probe distance. Their device has a 30-mm probe distance and they compared it with the HT device using a 15-mm probe distance. Second, a more serious shortcoming in their study design is of a physiologic nature. The authors put their probe on the forearm, whereas they put the HT probe on the thenar. However, the effect of the measurement site, i.e., forearm vs. thenar, was not validated. Surprisingly, the authors neglected to add a simple experiment by switching the probes around and repeating the experiment. To investigate the influence of the measurement site, we performed a similar experiment in two volunteers twice ( $n = 4$ ) using a tilt table to that by simulate hypovolemia. We used two HT devices applying a 15-mm probe, similar to Soller et al, on the thenar and on the forearm. We found that the forearm was more sensitive to acute changes in venous return than is the thenar, where thenar tissue oxygen saturation decreased from  $90 \pm 5\%$  to  $88 \pm 7\%$  and forearm tissue oxygen saturation decreased from  $83 \pm 5\%$  to  $75 \pm 4\%$ . This simple experiment demonstrated that the conclusion of Soller et al is incorrect and was based on an inadequate study design.

In conclusion, validation studies such as those presented by Soller et al should be performed with more methodologic rigor and a clear sense of objective where basic physiologic considerations should form the core component.

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## **PART C**

Prognostic value of monitoring  
peripheral perfusion



# Chapter 6

The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients

*Crit Care Med 2009 Mar; 37(3):934-8*

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## ABSTRACT

**Objective:** The physical examination of peripheral perfusion based on touching the skin or measuring capillary refill time has been related to the prognosis of patients with circulatory shock. It is unclear, however, whether monitoring peripheral perfusion after initial resuscitation still provides information on morbidity in critically ill patients. Therefore, we investigated whether subjective assessment of peripheral perfusion could help identify critically ill patients with a more severe organ or metabolic dysfunction using the Sequential Organ Failure Assessment (SOFA) score and lactate levels.

**Designed:** Prospective observational study.

**Setting:** Multidisciplinary Intensive Care Unit in a University Hospital.

**Patients:** Fifty consecutive adult patients admitted to the intensive care unit.

**Interventions:** None.

**Measurements and main Results:** Patients were considered to have abnormal peripheral perfusion if the examined extremity had an increase in capillary refill time ( $>4.5$  sec) or it was cool to the examiner hands. To address reliability of subjective inspection and palpation of peripheral perfusion, we also measured forearm-to-fingertip skin-temperature gradient (T<sub>skin-diff</sub>), central-to-toe temperature difference (T<sub>c-toe</sub>) and peripheral flow index (PFI). The measurements were taken within 24 hours of admission to the intensive care after hemodynamic stability was obtained (mean arterial pressure  $>65$  mmHg). Changes in SOFA score during the first 48 hours were analyzed ( $\Delta$ -SOFA). Individual SOFA score was significantly higher in patients with abnormal peripheral perfusion than in those with normal peripheral perfusion ( $9\pm 3$  vs.  $7\pm 2$ ,  $P<0.05$ ). T<sub>skin-diff</sub>, T<sub>c-toe</sub> and PFI were congruent with the subjective assessment of peripheral perfusion. The proportion of patients with  $\Delta$ -SOFA score  $>0$  was significantly higher in patients with abnormal peripheral perfusion (77% vs. 23%,  $P<0.05$ ). The logistic regression analysis showed that the odds of unfavourable evolution are 7.4 (95%CI 2-19;  $P<0.05$ ) times higher for a patient with abnormal peripheral perfusion. The proportion of hyperlactatemia was significantly different between patients with abnormal and normal peripheral perfusion (67% vs. 33%,  $P<0.05$ ). The odds of hyperlactatemia by logistic regression analysis are 4.6 (95%CI 1.4-15;  $P<0.05$ ) times higher for a patient with abnormal peripheral perfusion.

**Conclusions:** Subjective assessment of peripheral perfusion with physical examination following initial hemodynamic resuscitation in the first 24h of admission could identify hemodynamically stable patients with a more severe organ dysfunction and higher lactate levels. Patients with abnormal peripheral perfusion had significantly higher odds of worsening organ failure than did patients with normal peripheral perfusion following initial resuscitation.

## INTRODUCTION

Clinical signs of poor peripheral perfusion have been shown to be an early marker of inadequate tissue perfusion in acute circulatory shock (1-3). The rationale of monitoring peripheral perfusion is based on the concept that during hypotension the sympathetic neurohumoral response predominates on peripheral tissues resulting in a decreased skin perfusion and temperature (4, 5). Thus, monitoring of peripheral perfusion can assess the effect of the neurohumoral compensatory mechanism induced by low flow shock states in an acute stage of the disease.

Studies have showed that the subjective assessment of peripheral perfusion, in particular, the physical examination by touching the skin or measuring capillary refill time, can identify patients at high risk of complications from acute circulatory shock (6-9). Hasdai et al. (7) showed the importance of the physical examination of peripheral perfusion in determining the prognosis of patients with cardiogenic shock. In their study, the presence of a cold and clammy skin was an independent predictor of 30-day mortality. Although septic shock is associated with peripheral vasodilation, cool extremities may be present in the early stage of sepsis. In another recent study, Thompson et al. (8) studied the time course of the clinical features of meningococcal disease in children and adolescents before the admission to the hospital, and they identified cold hands and feet together with abnormal skin colour as the main important clinical signs within the first 12 h of the onset of illness. From these studies it is clear that subjective assessment of peripheral perfusion is a valuable adjunct in hemodynamic monitoring during circulatory shock, and should be the first approach to assess critically ill patient.

However, most studies on clinical assessment of peripheral perfusion have focused on specific populations of patients or have been performed during resuscitation in an acute stage of the disease (3, 8-10). It is unclear whether monitoring peripheral perfusion with physical examination in a general population of intensive care unit (ICU) after initial resuscitation still provides information about organ derangements and whether it predicts outcome in terms of organ dysfunction.

In view of these observations, we carried out a prospective study to evaluate whether subjective assessment of peripheral perfusion in the post-resuscitation phase of patients admitted to a general ICU could predict organ dysfunction. In particular, we wished to investigate if clinical monitoring of peripheral perfusion could help identify patients with a more severe organ dysfunction or metabolic dysfunction, as expressed by high Sequential Organ Failure Assessment (SOFA) score and lactate levels.

## MATERIALS AND METHODS

### *Study design and patients*

This prospective observational study was conducted in the intensive care of a university hospital, admitting all patients except those following cardiac surgery. We enrolled consecutive critically ill patients who had undergone initial resuscitation and stabilization within 24h of ICU admission. Patients were excluded if they had severe peripheral vascular disease (with a history of vascular surgery). The institutional review board approved the study. Each patient or relative provided written informed consent.

### **Measurements**

The assessment of peripheral perfusion was based on the subjective evaluation of the examiner, and patients were considered to have abnormal peripheral perfusion if the examined extremity had an increase in capillary refill time or it was cool to the examiner hands. Capillary refill time was measured by applying firm pressure to the distal phalanx of the index finger for 15 seconds. A chronometer recorded the time for return of the normal colour and 4.5 seconds was defined as the upper limit of normality (11). To address the reliability of the subjective assessment of peripheral perfusion by the examiner, we also measured forearm-to-fingertip skin-temperature gradient (T<sub>skin-diff</sub>), central-to-toe temperature difference (T<sub>c-toe</sub>) and peripheral flow index (PFI) simultaneously with clinical observation. The T<sub>skin-diff</sub> was obtained from two skin probes (Hewlett Packard 21078A) attached to the index finger and on the radial side of the forearm, mid-way between the elbow and the wrist. The T<sub>c-toe</sub> was calculated from central temperature, with an infrared tympanic thermometer (First Temp Genius Thermometer – 3000A), and great toe temperature measured on the ventral face with a skin probe (Hewlett Packard 21078A). The temperature gradients T<sub>skin-diff</sub> and T<sub>c-toe</sub> can better reflect cutaneous blood flow than the skin temperature itself. Considering a constant environment condition, T<sub>skin-diff</sub> and T<sub>c-toe</sub> increases during vasoconstriction (12, 13). PFI provides a noninvasive method to evaluate peripheral perfusion and it has been shown to reflect changes in peripheral perfusion (14, 15). PFI is derived from the pulse oximetry signal and it was measured using the Nellcor-OxiMax pulse oximetry and the Hewlett Packard monitor (Viridia/56S). To confirm the subjective assessment of abnormal peripheral perfusion condition, this study used the following definition of vasoconstriction: T<sub>skin-diff</sub> >0°C (12), T<sub>c-toe</sub> >7°C (13) and PFI <1,4 (14). Although the ambient temperature at each patient's bedside was not directly measured, the ICU has one-person closed rooms and the ambient temperature in each patient room was individually and actively controlled at 22°C. Thereafter, routine global hemodynamic variables such as heart rate, mean arterial pressure, central venous pressure and urine output were obtained.

Basic demographic characteristics and all the variables of SOFA score were collected for each patient. The investigator registered the measurements within 24 hours of admission to the intensive care after hemodynamic stability was obtained (mean arterial pressure >65 mmHg and no change in vasopressor infusion rate for 2 h). Changes in SOFA score during the first 48 hours ( $\Delta$ -SOFA) were also analyzed and was calculated as the difference between the 48-hour SOFA score and the admission score (16). Arterial blood samples were withdrawn for the determination of blood gases and lactate levels. Hyperlactatemia was defined as a blood lactate level >2mmol/L. We were interested in evaluating whether subjective assessment of peripheral perfusion could help identify patients with unfavorable evolution defined as  $\Delta$ -SOFA score >0 and hyperlactatemia.

### Statistics

The results are presented as mean  $\pm$ SD, unless otherwise specified. Differences between group means were tested by Student's t-tests, and for variables that were not normally distributed, by Mann-Whitney U test. The Chi-square test was used to compare frequencies. To estimate the association between abnormal peripheral perfusion and both  $\Delta$ -SOFA score and hyperlactatemia, logistic regression analysis was performed. *P* values  $\leq$ 0.05 were considered statistically significant.

## RESULTS

Of 50 patients included in the study, 39 had circulatory shock on admission of ICU, of whom 21 had septic shock and 18 had no septic shock. Table 1 summarizes the clinical data of the patients. During the first 24h of ICU admission, 23 (46%) patients had abnormal peripheral perfusion following resuscitation and stabilization. Individual SOFA score was significantly higher in patients with abnormal peripheral perfusion than in those with normal peripheral perfusion ( $9\pm 3$  vs.  $7\pm 2$ ,  $P<0.05$ ). Tskin-diff, Tc-toe and PFI measurements were congruent with the subjective assessment of peripheral perfusion (Table 2). Hemodynamic variables were similar in patients with abnormal and normal peripheral perfusion (Table 3). In patients who received vasopressor therapy (N=33), the dose of vasopressor did not differ between normal (N=17) and abnormal (N=16) peripheral perfusion condition ( $0.19\pm 0.11$  vs.  $0.17\pm 0.10$ ;  $P=0.80$ ).

The proportion of patients with unfavourable evolution was significantly higher in patients with abnormal peripheral perfusion (Table 4). Logistic regression analysis showed that the odds of unfavorable evolution are 7.4 (95%CI 2-19;  $P<0.05$ ) times higher for a patient with abnormal peripheral perfusion than for a patient with normal peripheral perfusion. Differences in global hemodynamic variables, such as heart rate, mean arterial pressure, central venous pressure and urine output were not statistically significant

**Table 1.**

Demographic data of the patients	
Number of patients	50
Age (years)	51 (17-80)
Male/Female	39/11
SOFA admission	8 (2-15)
APACHE II	23 (13-35)
Admission category	
Pneumonia	9
Trauma	8
Abdominal sepsis	7
Postoperative	5
COPD	3
Cardiogenic shock	2
Hepatic encephalopathy	2
Hypovolemic/Hemorrhagic shock	2
Mediastinitis	2
Meningitis	2
Pancreatitis	2
Post cardiac arrest	2
Cerebrovascular accident	1
Lung cancer	1
Systemic lupus erythematosus	1
Urosepsis	1
Survivor/Non-survivor	35/15

Values are given as mean (range) where appropriate

**Table 2.** Objective parameters of peripheral circulation according to the subjective evaluation of peripheral perfusion

Objective Parameters	Subjective Evaluation		
	Normal (N=27)	Abnormal (N=23)	P Value
Tskin-diff (°C)	-0.2±2.8	4.6±2.8	<0.01
Tc-toe (°C)	6.5±3.4	10±4.1	<0.01
PFI	2.3±1.6	0.7±0.8	<0.01

Tskin-diff=forearm-to-fingertip skin-temperature gradient; Tc-toe=central-to-toe temperature difference; PFI=peripheral flow index

**Table 3.** Global hemodynamics variables in abnormal and normal peripheral perfusion

	Peripheral Perfusion		P Value
	Normal (N=27)	Abnormal (N=23)	
HR (bpm)	90±22	94±20	0.53
MAP (mmHg)	80±14	81±18	0.87
CVP (mmHg)	14±6	13±7	0.84
Urine output (ml/h)	111±83	72±30	0.14

HR=heart rate; MAP=mean arterial blood pressure; CVP=central venous pressure

**Table 4.** Proportion of patients with unfavourable evolution ( $\Delta$ -SOFA>0) and favourable evolution ( $\Delta$ -SOFA score $\leq$ 0) stratified by normal and abnormal peripheral perfusion <sup>a</sup>

	Peripheral Perfusion	
	Normal (N=27)	Abnormal (N=23)
$\Delta$ -SOFA $\leq$ 0 (N=33), % of patients	70	30
$\Delta$ -SOFA > 0 (N=17), % of patients	23	77

<sup>a</sup>  $P < 0.05$ , by Chi-square test

**Table 5.** Proportion of hyperlactatemia and normal blood lactate levels between patients with abnormal and normal peripheral perfusion <sup>a</sup>

	Peripheral Perfusion	
	Normal (N=27)	Abnormal (N=23)
Normal lactate levels (N=29), % of patients	69	31
Hyperlactatemia (N=21), % of patients	33	67

<sup>a</sup>  $P < 0.05$ , by Chi-square test

between patients with and without unfavourable evolution (data not shown). The proportion of patients with hyperlactatemia was significantly higher in patients with abnormal peripheral perfusion (Table 5). Logistic regression analysis showed that the odds of hyperlactatemia in a patient with abnormal peripheral perfusion are 4.6 (95%CI 1.4-15;  $P < 0.05$ ) times higher than in a patient with normal peripheral perfusion.

## DISCUSSION

This prospective observational study shows that the subjective assessment of peripheral perfusion could discriminate patients with a more severe organ dysfunction, as expressed by high SOFA score and lactate levels in patients with abnormal peripheral perfusion. One may argue that high SOFA score in the abnormal peripheral perfusion group may be related to the level of mean arterial pressure or to the use of vasopressor support. However, our patients were all resuscitated and stabilized at the moment

that data were collected, and global hemodynamic variables or dose of vasopressor were similar between patients with normal and abnormal peripheral perfusion. This finding suggests that abnormal peripheral perfusion is not related to hypotension or vasoconstriction from a pharmacologic intervention. This lack of association between abnormal peripheral perfusion and global hemodynamic variables is not unexpected, since some studies have reported a poor correlation between clinical examination of peripheral perfusion and heart rate, blood pressure or cardiac output (3, 10, 17). In addition, recent observations suggest that microcirculatory alterations in circulatory shock are independent of systemic variables (18, 19) and that systemic variables may not be sensitive enough to reflect changes in peripheral blood flow in critically ill patients (20).

Delta-SOFA score has been suggested to monitor the evolution of organ failure (16). In our study, we investigated whether the condition of peripheral perfusion in resuscitated patients could predict an increase in severity of organ dysfunction. Our results show that patients who persist with abnormal peripheral perfusion after initial resuscitation have a significantly higher probability of unfavourable evolution, as indicated by an increase in the  $\Delta$ -SOFA score. Thus, monitoring peripheral perfusion could identify these patients who do not improve despite initial resuscitation and stabilization. Similarly, the logistic regression analysis showed that patients who have an abnormal peripheral perfusion following resuscitation are more likely to remain hyperlactatemic. The interpretation of hyperlactatemia in critically ill patients is complex, and factors other than hypoperfusion may be involved (21). Nevertheless, our findings are in agreement with those of Kaplan et al. (6) showing that patients with cold extremity are associated with higher blood lactate levels. The correlation between abnormal peripheral perfusion and high blood lactate levels in our patients is not surprising as hyperlactatemia in most cases takes place in the presence of organ dysfunction (22-24). This prospective study does not show a causal relation between poor peripheral perfusion and organ dysfunction or tissue hypoperfusion, but some reports indicate this relation (1, 25-27). Studies on measurements of blood flow and oxygenation in peripheral tissues suggest that compensatory vasoconstriction results in maldistribution of microcirculatory flow, which has been associated with organ dysfunction and multiple organ failure (1, 25-27).

In a recent consensus conference on hemodynamic monitoring in shock it was now recognized that the definition of shock requires evidence of circulatory and cellular dysfunction, manifested by markers of hypoperfusion such as elevated blood lactate levels, regardless of the presence of hypotension (20). Because data were collected in the post-resuscitation period, our patients exhibited no other clinical signs of circulatory shock apart from hyperlactatemia and abnormal peripheral perfusion. Normotension with persisting hyperlactatemia following initial resuscitation have been associated with a high incidence of organ failure (28, 29). Our study is in agreement with these findings, demonstrating that abnormal peripheral perfusion in patients with no other clinical

signs of shock is predictive of progressing organ dysfunction. Thus, if the clinician stops the resuscitation after the traditional end points have been normalized, a majority of patients will remain in a state of compensated shock. The absence of abnormal peripheral perfusion after initial resuscitation identifies patients with a more favourable outcome. Therefore clinical assessment of peripheral perfusion during resuscitation has potential to optimize resuscitation procedures. However, this was not the topic of this study. The subjective inspection and palpation of peripheral perfusion is safe, non-invasive and very easy to perform at the bedside and enables physicians to identify those patients with tissue hypoperfusion before continuing to invasive procedures. The subsequent potential of subjective assessment of peripheral perfusion in a general ICU population applied by multiple clinicians must be investigated further to address whether aiming at normalization of peripheral perfusion will have an impact on outcome.

As the focus of our study was to address the relationship between abnormal peripheral perfusion and organ failure, we minimized the variability of the subjective assessment of peripheral perfusion by having only one investigator collecting the data. In addition, we compared this subjective assessment of peripheral perfusion with 3 objective measurements: Tskin-diff, Tc-toe and PFI. These parameters are independent indicators of peripheral blood flow (30). We found that the subjective clinical assessment of peripheral perfusion was in agreement with the objective measurements of Tskin-diff, Tc-toe and PFI (Table 2).

This study has several limitations that should be acknowledged. First, measurements of global blood flow (cardiac output) were not made in this study. The main focus was to assess the relationship between the presence of abnormal peripheral perfusion following our standard hemodynamic optimization protocol and organ dysfunction. Second, we did not include other methods of peripheral perfusion monitoring, such as cutaneous laser Doppler flowmetry, transcutaneous oximetry or sublingual capnometry as we emphasized the subjective assessment of peripheral perfusion. In addition, we speculate that these noninvasive methods could have shown the same association with Tskin-diff, Tc-toe and PFI. Third, although Tc-toe is a well-validated method to estimate peripheral blood flow, central temperature in our study was obtained using a tympanic thermometer, which may not be a reliable representation of core temperature. However, the impact of central temperature in Tc-toe calculation is small compared to the skin temperature of the great toe, as abnormalities in Tc-toe are a result mainly of changes in peripheral vasoconstriction (30). Fourth, changes in ambient temperature may have influenced the subjective assessment of the skin temperature. Differences in ambient temperature at each patient's bedside were not directly measured. However, the ICU consists of one-person closed rooms and the ambient temperature in each patient room was individually controlled at 22°C. Moreover, the differences in subjective skin temperature were in agreement with differences in Tskin-diff in our study. As a change

in ambient temperature similarly affects forearm and fingertip temperature producing little influence in the gradient between forearm and fingertip (30) we think the effect of ambient temperature was small. Last, peripheral perfusion is not static; it alters over time in a constant dynamic situation, and our measurements were made within 24h of ICU admission.

## **CONCLUSION**

In conclusion, we found that a clinical assessment of peripheral perfusion by physical examination following initial hemodynamic optimization during the first 24h of admission could discriminate hemodynamically stable patients with more severe organ dysfunction. In addition, patients with abnormal peripheral perfusion following this initial resuscitation had significantly higher odds of worsening organ failure and higher lactate levels compared to patients with normal peripheral perfusion at this time point. The easy application of this clinical assessment of peripheral perfusion at the bedside has a potential as a simple and inexpensive tool for early detection of worsening organ dysfunction and possibly the adequacy of treatment in critically ill patients.

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# Chapter 7

Low tissue oxygen saturation at the end of early goal- directed therapy is associated with worse outcome in critically ill patients

*Crit Care 2009; 13 Suppl 5:S13*

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## ABSTRACT

### Introduction

The prognostic value of continuous monitoring of tissue oxygen saturation (StO<sub>2</sub>) during early goal-directed therapy of critically ill patients has not been investigated. We conducted this prospective study to test the hypothesis that the persistence of low StO<sub>2</sub> levels following intensive care admission is related to adverse outcome.

### Methods

We followed 22 critically ill patients admitted with increased lactate levels (>3 mmol/l). Near-infrared spectroscopy (NIRS) was used to measure the thenar eminence StO<sub>2</sub> and the rate of StO<sub>2</sub> increase (RincStO<sub>2</sub>) after a vascular occlusion test. NIRS dynamic measurements were recorded at intensive care admission and each 2-hour interval during 8 hours of resuscitation. All repeated StO<sub>2</sub> measurements were further compared with Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II and hemodynamic physiological variables: heart rate (HR), mean arterial pressure (MAP), central venous oxygen saturation (ScvO<sub>2</sub>) and parameters of peripheral circulation (physical examination and peripheral flow index (PFI)).

### Results

Twelve patients were admitted with low StO<sub>2</sub> levels (StO<sub>2</sub> <70%). The mean scores for SOFA and APACHE II scores were significantly higher in patients who persisted with low StO<sub>2</sub> levels (n = 10) than in those who exhibited normal StO<sub>2</sub> levels (n = 12) at 8 hours after the resuscitation period (P < 0.05; median (interquartile range): SOFA, 8 (7 to 11) vs. 5 (3 to 8); APACHE II, 32(24 to 33) vs. 19 (15 to 25)). There was no significant relationship between StO<sub>2</sub> and mean global hemodynamic variables (HR, P = 0.26; MAP, P = 0.51; ScvO<sub>2</sub>, P = 0.11). However, there was a strong association between StO<sub>2</sub> with clinical abnormalities of peripheral perfusion (P = 0.004), PFI (P = 0.005) and RincStO<sub>2</sub> (P = 0.002). The persistence of low StO<sub>2</sub> values was associated with a low percentage of lactate decrease (P < 0.05; median (interquartile range): 33% (12 to 43%) vs. 43% (30 to 54%)).

### Conclusions

We found that patients who consistently exhibited low StO<sub>2</sub> levels following an initial resuscitation had significantly worse organ failure than did patients with normal StO<sub>2</sub> values, and found that StO<sub>2</sub> changes had no relationship with global hemodynamic variables.

## INTRODUCTION

A more complete evaluation of tissue perfusion can be achieved by adding non-invasive assessment of peripheral perfusion to global parameters [1]. Non-invasive monitoring of peripheral perfusion is an alternative approach that allows very early application throughout the hospital, including the emergency department, operating room, and hospital wards. The rationale of monitoring peripheral perfusion is based on the concept that peripheral tissues are the first to reflect hypoperfusion in shock and the last to reperfuse during resuscitation [1,2]. Poor peripheral perfusion may therefore be considered an early predictor of tissue hypoperfusion and a warning signal of ongoing shock.

In the clinical practice, non-invasive monitoring of peripheral perfusion can be performed easily using current new technologies, such as near-infrared spectroscopy (NIRS) [3]. NIRS technology has been used as a tool to monitor tissue oxygen saturation (StO<sub>2</sub>) in acutely ill patients [4]. In addition, the analysis of changes in StO<sub>2</sub> during a vascular occlusion test, such as a brief episode of forearm ischemia, has been used as a marker of integrity of the microvasculature - in particular, the StO<sub>2</sub> recovery after the vascular occlusion test [5-7]. These reports, however, have studied the correlation of intermittent StO<sub>2</sub> measurements and outcome where there are only limited data describing whether continuous monitoring of StO<sub>2</sub> during the early resuscitation phase is related to morbidity or to mortality.

We therefore conducted the present prospective observational study to investigate the association between continuous StO<sub>2</sub> measurements during early resuscitation of high-risk patients and subsequent adverse outcomes. The primary study objective was to investigate whether persistence of low StO<sub>2</sub> values during early goal-directed therapy could help to identify patients with more severe organ dysfunction and severity of disease as expressed by Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Because the value of StO<sub>2</sub> as a parameter of peripheral perfusion is not quite clear, we also investigated the relation of low StO<sub>2</sub> values with global hemodynamic and peripheral circulation parameters.

## MATERIAL AND METHODS

### Study population

The current prospective observational study was conducted in the intensive care unit (ICU) of a university hospital. We enrolled 22 consecutive critically ill patients with increased lactate levels (>3 mmol/l) who had no history of severe peripheral vascular disease. The institutional review board approved the study. Each patient or relative provided written informed consent.

## Measurements

Global hemodynamic variables included the heart rate (HR), central venous pressure, mean arterial pressure (MAP) and central venous oxygen saturation (ScvO<sub>2</sub>). All measurements were obtained using standard equipment. ScvO<sub>2</sub> was measured continuously with a fiber-optic probe (CeVOX®; Pulsion Medical Systems AG, Munich, Germany). Thenar StO<sub>2</sub> was continuously monitored using an InSpectra Tissue Spectrometer Model 650 (Hutchinson Technology Inc., Hutchinson, MN, USA) with a 15 mm probe over the thenar eminence. Based on the variability of StO<sub>2</sub> values in previous studies, we used a cut-off value of 70% to define the StO<sub>2</sub> level as low [5-11].

We measured the StO<sub>2</sub> response to the vascular occlusion test to investigate peripheral perfusion reactivity. The vascular occlusion test was performed using a sphygmomanometer cuff wrapped around the arm over the brachial artery. After a 1-minute period to stabilize the NIRS signal, the cuff was rapidly inflated until 30 mmHg above the systolic arterial pressure. After 3 minutes of ischemia, the sphygmomanometer was rapidly deflated and the StO<sub>2</sub> was recorded until the StO<sub>2</sub> level returned to baseline values. The vascular occlusion test-derived StO<sub>2</sub> traces were analyzed for the rate StO<sub>2</sub> of increase (RincStO<sub>2</sub>) during the release. We calculated the RincStO<sub>2</sub> slope obtained by the regression line between the lowest StO<sub>2</sub> value and the StO<sub>2</sub> correspondent to the baseline value following the ischemic period (slope, expressed as percent per second). One individual who was blinded from all treatment and clinical data performed the NIRS measurements.

Peripheral circulation parameters included physical examination of peripheral perfusion and the peripheral flow index (PFI). Based on physical examination of peripheral perfusion, patients were considered to have abnormal peripheral perfusion if the examined extremities (both hands) had an increase in capillary refill time or were cool to the examiner's hands. The capillary refill time was measured by applying firm pressure to the distal phalanx of the index finger for 15 seconds. A chronometer recorded the time for the return of the normal color and 4.5 seconds was defined as the upper limit of normality [12]. The PFI provides a non-invasive method for evaluating perfusion and has been shown to reflect changes in peripheral perfusion [13,14]. The PFI is derived from the pulse oximetry signal, which was obtained from a Nellcor-OxiMax pulse oximeter and Hewlett Packard monitor (Viridia 56S, Philips Medical Systems, Boblingen, Germany). The ICU contains single-person closed rooms, and the ambient temperature in each patient's room was individually and actively set at 22°C.

## Study protocol

All patients were followed during the first 8 hours after ICU admission. Hemodynamic support in all patients - including vasopressor (noradrenaline) and, if needed, addition of dobutamine - was aimed at standard resuscitation endpoints adapted from the Surviving Sepsis Campaign Guidelines to maintain HR <100/minute, MAP ≥60 mmHg, central

venous pressure of 8 to 12 mmHg, urinary output  $\geq 0.5$  ml/kg/hour and  $ScvO_2 \geq 70\%$  [15]. Measurements, obtained continuously between admission and the 8-hour period of resuscitation, included temperature, all global hemodynamic variables,  $StO_2$ , the PFI and physical examination of peripheral perfusion. Arterial blood samples were withdrawn simultaneously for lactate measurement. The vascular occlusion test was performed at two time points: immediately upon admission to the ICU and again after 8 hours of resuscitation. Basic demographic characteristics, APACHE II and SOFA scores were collected for each patient. Clinical and laboratory data needed to calculate the SOFA and APACHE II scores were reported as the worst value within 24 hours after ICU admission.

Hyperlactatemia was defined as a blood lactate level  $>3$  mmol/l. We calculated the percentage of lactate decrease over the first 8-hour period of ICU admission. All patients were mechanically ventilated and sedation with midazolam and analgesia was provided according to individual needs.

### Statistical analysis

Unless otherwise specified, the results are presented as the median (interquartile range). Differences between group means were tested by Student t-tests; for variables that were not normally distributed, differences were tested by a nonparametric test. For clinical characteristics of the study groups, differences between groups were assessed using Fisher's exact test. The multiple regression analysis adjusted for global hemodynamic variables (HR, MAP and central venous pressure) was used to analyze the impact of the persistence of  $StO_2 < 70\%$  on the SOFA and APACHE II scores. We used the linear mixed-model analysis to assess the magnitude of contribution from each systemic and peripheral physiological variable on all repeated  $StO_2$  measurements during the 8-hour period of resuscitation.  $P \leq 0.05$  was considered statistically significant.

## RESULTS

Patients' demographic data are summarized in table 1. All data used in the analysis were obtained at 2, 4, 6 and 8 hrs after admission.

To explore the relationship between changes of  $StO_2$  and the severity of organ dysfunction, we stratified patients according to the evolution of  $StO_2$  levels within the 8-hour period of ICU resuscitation. Upon ICU admission, 12 (54%) patients had low  $StO_2$  levels. From these twelve patients, two patients showed normalization of the  $StO_2$  levels. All patients admitted with normal  $StO_2$  still had a normal  $StO_2$  at T8. Thus, after the 8 hrs of ICU resuscitation, a total of ten patients persisted with low  $StO_2$  and twelve patients with normal  $StO_2$  levels (Figure 1). Figure 2 shows the SOFA and APACHE II scores stratified by the groups at T8.

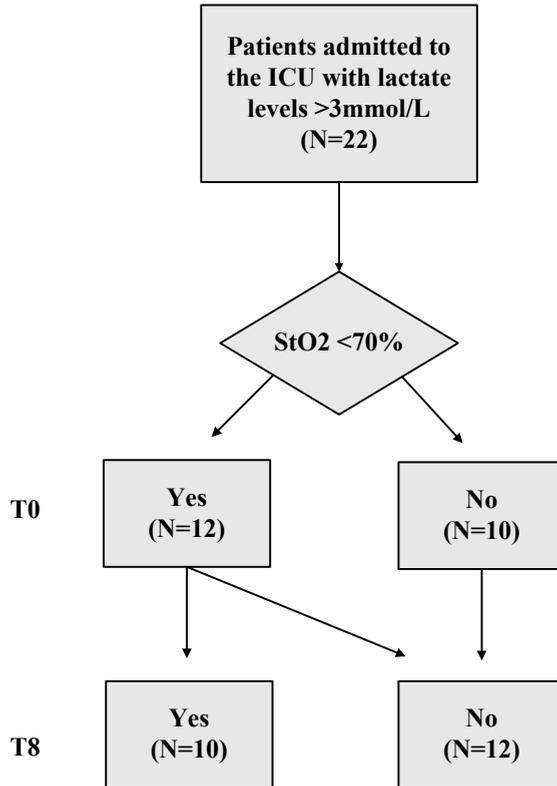
**Table 1.**

<b>Patient demographic data</b>	
Number of patients	22
Age (years)	62 [57-71]
Male/Female	16/6
SOFA	7 [5-9]
APACHE II	23 [16-30]
Admission category:	
	3 pneumonia
<i>Septic shock</i>	3 abdominal sepsis
	1 meningitis
	3 hypovolemic/hemorrhagic
<i>Circulatory failure not associated with sepsis</i>	3 cardiogenic
	4 postoperative
	2 trauma
	1 cerebrovascular accident
<i>Without circulatory failure or sepsis</i>	2 postoperative
Noradrenaline use, N (%)	16 (72%)
Noradrenaline dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	0.16 [0.07-0.24]
Dobutamine use, N (%)	8 (36%)
Dobutamine dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	4.3 [3.6-6.3]
Mechanical ventilation, N (%)	15 (68%)
Survivor/Non-survivor	17/5

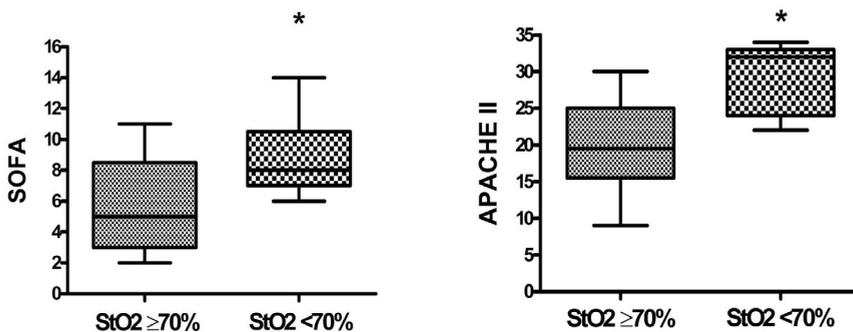
Values are expressed as medians [25<sup>th</sup>-75<sup>th</sup>]

The mean scores for both SOFA and APACHE II scores were significantly higher in patients who persisted with low StO<sub>2</sub> levels than those who exhibited normal StO<sub>2</sub> levels at 8 hrs after the resuscitation period ( $P < 0.05$ ; median [IQR]; APACHE II: 32 [24-33] vs. 19 [15-25], SOFA: 8 [7-11] vs. 5 [3-8]) (Figure 2). Multiple regression analysis on low StO<sub>2</sub> levels adjusted for global hemodynamic variables (HR, MAP and CVP) showed that low StO<sub>2</sub> levels had a significant contribution for the prediction of SOFA (regression coefficient =3.0, 95% CI 2.2-5.7;  $P=0.04$ ) and APACHE II (regression coefficient =9.1, 95% CI 3.3-13;  $P=0.026$ ).

The relationship between all repeated StO<sub>2</sub> measurements during the 8-hr period of resuscitation with standard hemodynamic variables and with peripheral circulation parameters was assessed using the mixed-model analysis to further explore the contribution from each of these variables on the StO<sub>2</sub> level. Table 2 shows the estimation coefficient from each variable. There was no significant relationship between StO<sub>2</sub> and global hemodynamic variables. However, there was a strong association between StO<sub>2</sub> and clinical abnormalities of peripheral perfusion, PFI and RincStO<sub>2</sub>. Table 3 shows the descriptive analysis of global hemodynamic variables and peripheral circulation parameters stratified by the level of StO<sub>2</sub> at admission and after 8 hours. In patients who received vasopressor



**Figure 1.** Evolution of StO2 levels in our patient population stratified by low (StO2 <70%) and normal (StO2 ≥70%) values upon admission (T0) and 8 h after resuscitation (T8). Patients were divided into two categories according to the StO2 evolution: patients who persisted with low StO2 at T8 and patients who exhibited normal StO2 levels at T8.



**Figure 2.** Box plotting demonstrating the outcome score values stratified by the StO2 levels after 8 hrs of resuscitation. SOFA and APACHE II scores were significantly higher in patients who persisted with StO2 <70% (N=10) than those who exhibited normal StO2 levels (N=12) at 8 hrs after the resuscitation period. \*P<0.05.

**Table 2.** Using the linear mixed models analysis, we assessed the magnitude of contribution from each systemic and peripheral physiological variables on all repeated StO<sub>2</sub> measurements during the 8-hr period of resuscitation.

	StO <sub>2</sub> (Estimate, 95%CI)	P value	Number of observations
Systemic Hemodynamic:			
Heart rate	-0.08 (-0.23-0.63)	0.26	88
MAP	-0.05 (-0.22-0.11)	0.51	88
ScvO <sub>2</sub>	0.11 (-0.13-0.36)	0.36	88
Peripheral circulation:			
Clinical abnormalities	5.7 (2.0-9.6)	0.004	88
PFI	8.1 (2.3-13.1)	0.005	88
RincStO <sub>2</sub>	3.9 (2.1-6.0)	0.002	44

MAP=mean arterial blood pressure; ScvO<sub>2</sub>=central venous oxygen saturation; PFI=peripheral flow index; RincStO<sub>2</sub>= rate of StO<sub>2</sub> increase after the vascular occlusion test.

**Table 3.** Global hemodynamic variables and peripheral circulation parameters in patients with low StO<sub>2</sub> (<70%) and normal StO<sub>2</sub> (>70%) at admission (T0) and after 8 hours (T8)

	T0			T8		
	Low StO <sub>2</sub> (N=12)	Normal StO <sub>2</sub> (N=10)	P value	Low StO <sub>2</sub> (N=10)	Normal StO <sub>2</sub> (N=12)	P value
<b>HR (bpm)</b>	94 [79-122]	91 [82-106]	0.90	95 [79-113]	98 [74-122]	0.90
<b>MAP (mmHg)</b>	77 [64-94]	79 [72-85]	0.87	67 [60-75]	72 [68-85]	0.14
<b>CVP mmHg)</b>	15 [11-18]	12 [9-14]	0.20	19 [6-20]	15 [7-15]	0.34
<b>SvO<sub>2</sub> (%)</b>	75 [63-79]	73 [68-84]	0.38	77 [68-85]	70 [65-80]	0.46
<b>PFI (%)</b>	0.2 [0.2-0.7]	1.8 [0.8-3.7]	0.001	0.9 [0.4-1.1]	2.1 [1.2-3.0]	0.004
<b>Clinical APP, N (%)</b>	11 [92%]	3 (30%)	0.006*	9 (90%)	1 (8%)	0.001*
<b>RincStO<sub>2</sub> (%/s)</b>	1.8 [1.4-2.0]	4.0 [2.6-4.7]	0.001	1.7 [1.2-2.5]	4.4 [2.9-4.7]	0.003

Values are expressed as median [25th-75th].

HR=heart rate; MAP=mean arterial blood pressure; CVP=central venous pressure; ScvO<sub>2</sub>=central venous oxygen saturation; PFI=peripheral flow index; Clinical APP=clinical abnormalities of peripheral perfusion; RincStO<sub>2</sub>= rate of StO<sub>2</sub> increase after the vascular occlusion test. \* Fisher's Exact Test.

therapy during resuscitation (N of patients=16; N of StO<sub>2</sub> measurements=64), the dose of vasopressor (noradrenaline) did not differ between low (N=35) and normal (N=29) StO<sub>2</sub> levels (P=0.13; median [IQR], in mcg/kg/min; 0.19 [0.10-0.33] vs. 0.13 [0.06-0.25]).

Although there was no difference in admission lactate levels between patients with low and normal StO<sub>2</sub> levels (P=0.34; median [IQR]; 3.6 [2.2-6.0] vs. 3.4 [3.0-5.0]), the percentage of lactate decrease between T0 and T8 was significantly lower in patients who persisted with low StO<sub>2</sub> levels (P<0.05; median [IQR]; 33% [12-43%] vs. 43% [30-54%]). A persistently low StO<sub>2</sub> level was associated with increased mortality. Among the non-survivors, 4/5 (80%) had persistently low StO<sub>2</sub> levels at T8 compared to 6/17 (35%) in the survivor group.

## DISCUSSION

In this prospective observational study, we performed repeated StO<sub>2</sub> measurements in critically ill patients to test the hypothesis that the persistence of low StO<sub>2</sub> levels during the early resuscitation phase of therapy is associated with a more severe organ dysfunction. The most important finding in our study is that patients who failed to normalize StO<sub>2</sub> during early treatment in the ICU had more severe organ dysfunction and disease severity, as assessed by SOFA and APACHE II scores. The higher SOFA score in our patients with low StO<sub>2</sub> levels could have been related to therapeutic interventions applied guided by global hemodynamic measurements. However, the association between low StO<sub>2</sub> levels and organ failure in our patients was not accompanied by any major differences in either global hemodynamic or doses of vasopressor therapy between patients with low and normal StO<sub>2</sub>. In addition, we also found that the APACHE II score was significantly higher in patients with low StO<sub>2</sub> levels. The APACHE II score differs from the SOFA score since the former is not adjusted for the use of vasoactive drugs. Therefore, these findings suggest that the presence of low StO<sub>2</sub> levels does not reflect global hemodynamic effects or vasoconstriction from a pharmacologic intervention.

The association between low StO<sub>2</sub> levels and organ failure in our patients were accompanied by alterations in clinical abnormalities of peripheral perfusion. Current observations have shown a significant association between clinical abnormal peripheral perfusion and severity of organ dysfunction in patients suffering from either septic or non-septic shock [16-19]. This relationship is supported by our study. The association of low StO<sub>2</sub> levels with clinical abnormalities of peripheral perfusion in our patients may partly explain the relationship between abnormal peripheral perfusion and a worse outcome. Additionally, low StO<sub>2</sub> levels were also associated with a slow rise in StO<sub>2</sub> following a vascular occlusion test. Abnormal RincStO<sub>2</sub> levels have been shown to reflect a variety of dynamic variables linked to local metabolic demand and vascular reactivity that have been associated with outcome in critically ill patients [5-7]. A causal relationship between low StO<sub>2</sub> and abnormal RincStO<sub>2</sub> in our patients is not clear, as it was not the topic of this study. Furthermore, the association between an abnormal RincStO<sub>2</sub> and low StO<sub>2</sub> levels is not always present, as previous reports have shown a decreased RincStO<sub>2</sub> in the presence of normal StO<sub>2</sub> values [5, 6]. However, in our patients abnormal RincStO<sub>2</sub> and low StO<sub>2</sub> values were associated with a low PFI, indicating either peripheral vasoconstriction and/or impairment of microcirculatory flow as indicated by the slowed reperfusion during ischemic recovery [20].

Although there was no difference in admission lactate levels, the percentage of lactate decrease during the study was significantly lower in patients who consistently exhibited low StO<sub>2</sub> values. The interpretation of hyperlactatemia in critically ill patients is complex, and factors other than hypoperfusion may be involved [21]. Both hyperlactatemia

at admission and the lack of its reduction during ICU treatment have been related to increased mortality [22-24]. The correlation between hyperlactatemia and low StO<sub>2</sub> in our patients could be related to the presence of tissue hypoperfusion [22, 25, 26]. Nevertheless, our findings support previous reports, including our own, showing that patients with clinical abnormal peripheral perfusion following resuscitation are more likely to remain hyperlactatemic [19, 27].

Regardless of the cause of peripheral tissue hypoperfusion, our data provide evidence that the persistence of low StO<sub>2</sub> values could have implications for the treatment of critically ill patients. Restoration of global hemodynamic parameters without an associated normalization of StO<sub>2</sub> may warrant further or intensified resuscitation efforts. As the thenar muscle StO<sub>2</sub> monitoring is safe, non-invasive, easily obtained at the bedside enabling the physicians to identify patients with peripheral tissue hypoperfusion it may represent a valuable addition to our monitoring tools and end-points of goal-directed therapy. However, the clinical value of repeated StO<sub>2</sub> measurements must be investigated further to assess whether a resuscitation goal of normalizing StO<sub>2</sub> levels will improve patient outcome.

This study has some limitations that should be acknowledged. First, previous studies have suggested that resting StO<sub>2</sub> values are insensitive indicators of tissue perfusion [5-7]. These studies noted that both patients and healthy controls had similar StO<sub>2</sub> levels despite evidence of impaired systemic oxygenation in patients. However, in these studies a StO<sub>2</sub> threshold as well as time factor was not taken into account. In our study, the repeated measurements of StO<sub>2</sub> during early resuscitation were the prognostic factor and the persistence of StO<sub>2</sub> levels below the threshold of 70% was associated with the development of a more severe organ injury. Although the optimal StO<sub>2</sub> threshold has not been fully investigated and not yet determined in critically ill patients, we arbitrarily chose 70% based on previous studies done in healthy volunteers, emergency and intensive care patients [5-11]. Second, the number of patients included in the study was limited. Only two patients changed their StO<sub>2</sub> level from low to normal; therefore, the prognostic value in this particular group could not be studied. However, it is clear from our findings that patients who consistently showed low StO<sub>2</sub> values within the first 8 hrs of ICU treatment had a significantly higher rate of unfavourable outcome. Additionally, the absence of low StO<sub>2</sub> levels identified patients with a more favourable outcome. Finally, measurements of global blood flow (cardiac output) were not made in this study. Our main focus, however, was to assess the relationship between the presence of low StO<sub>2</sub> level following our standard hemodynamic optimization protocol and organ dysfunction.

In conclusion, we established the usefulness of the continuous monitoring of StO<sub>2</sub> during the early resuscitation of critically ill patients. We found that patients who remained having low StO<sub>2</sub> levels following an initial resuscitation had significantly worse

organ failure than did patients with normal StO<sub>2</sub> values. In addition, low StO<sub>2</sub> levels were only accompanied by alterations in the peripheral circulation indicating that StO<sub>2</sub> abnormalities are closely related to regional hemodynamics rather than macrohemodynamics.

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# Chapter 8

The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients

*Crit Care Med 2011 Jul; 39(7):1649-5*

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## **Chapter 8a**

Letter to the editor: Noninvasive does not mean simple or accurate!

*Crit Care Med 2012, 40(2):713-4*

*Alexandre Lima, Jan Bakker*

## ABSTRACT

**Objective:** We conducted this observational study to investigate tissue O<sub>2</sub> saturation (StO<sub>2</sub>) during a vascular occlusion test (VOT) in relationship with the condition of peripheral circulation and outcome in critically ill patients.

**Design:** Prospective observational study

**Setting:** Multidisciplinary Intensive Care Unit in a University Hospital.

**Patients:** Seventy three critically ill adult patients admitted to the intensive care unit.

**Interventions:** None.

**Measurements and main Results:** Patients were followed every 24 h until day 3 after intensive care admission. Near-infrared spectroscopy (NIRS) was used to measure thenar StO<sub>2</sub>, StO<sub>2</sub> deoxygenation rate (RdecStO<sub>2</sub>) and StO<sub>2</sub> recovery rate (RincStO<sub>2</sub>) after VOT. Measurements included heart rate (HR), mean arterial pressure (MAP), forearm-to-fingertip skin-temperature gradient (T<sub>skin-diff</sub>) and physical examination of peripheral perfusion with capillary refill time (CRT). Patients were stratified according to the condition of peripheral circulation (abnormal: T<sub>skin-diff</sub> ≥4 and CRT >4.5 sec). The outcome was defined based on daily SOFA score and blood lactate levels. Upon ICU admission, 35 (47.9%) patients had abnormal peripheral perfusion (T<sub>skin-diff</sub> >4 or CRT >4.5s). With the exception of RdecStO<sub>2</sub>, StO<sub>2</sub> baseline and RincStO<sub>2</sub> were statistically lower in patients who exhibited abnormal than in those with normal peripheral perfusion: 72±9 vs. 81±9; P=0.001 and 1.9±0.7 vs. 3.2±0.9; P=0.001, respectively. When a mixed-model analysis was performed over time for estimate (s) calculation, adjusted to the condition of disease, we did not find a significant clinical effect between VOT-derived StO<sub>2</sub> measurements (as response variables) and mean systemic hemodynamic variables (as independent variables): StO<sub>2</sub> vs. HR: s (95% CI)= 0.007 (-0.08; 0.09); StO<sub>2</sub> vs. MAP: s (95% CI)= -0.02 (-0.12 ; 0.08); RdecStO<sub>2</sub> vs. HR: s (95% CI)=0.002 (-0.0004; 0.006); RdecStO<sub>2</sub> vs. MAP: s (95% CI)=0.0007 (-0.003; 0.004); RincStO<sub>2</sub> vs. HR: s (95% CI)=-0.009 (-0.02; -0.0015); RincStO<sub>2</sub> vs. MAP: s (95% CI)=0.01 (0.002 ; 0.018). However, there was a strong association between StO<sub>2</sub> baseline and RincStO<sub>2</sub> with abnormal peripheral perfusion (APP): StO<sub>2</sub> vs. APP: s (95% CI)=-10.1 (-13.9; -6.2); RincStO<sub>2</sub> vs. APP: s (95% CI)=-1.1 (-1.4; -0.81). Poor outcome was more closely related to abnormalities in peripheral perfusion than to StO<sub>2</sub>-derived parameters.

**Conclusions:** We found that the condition of peripheral circulation in critically ill patients strongly influences StO<sub>2</sub> resting values and StO<sub>2</sub> reoxygenation rate, but not StO<sub>2</sub> deoxygenation rate. In addition, changes in NIRS-derived variables were independent of condition of disease and were not accompanied by any major differences in systemic hemodynamic.

## INTRODUCTION

Near-infrared spectroscopy (NIRS) has been used as a tool to monitor tissue oxygen saturation (StO<sub>2</sub>) in critically ill patient (1). In addition, changes in StO<sub>2</sub> during a vascular occlusion test (VOT) have been used as a marker of microvascular reactivity, in particular the StO<sub>2</sub> recovery after the VOT (2- 5). During a VOT (upper arm arterial occlusion with a pneumatic cuff), depletion of local available oxygen is monitored by NIRS as a decrease in StO<sub>2</sub>; after the cuff release, the arterial inflow is monitored as the rate of StO<sub>2</sub> increase during the reperfusion phase. The former can be used to calculate the muscle oxygen consumption and metabolic rate, whereas the latter can be used to quantify the intensity of the reactive hyperemia during the reperfusion period.

The utility of NIRS in the management of critically ill patients is still a matter of debate. Increasing publications using NIRS have described profound alterations in microvascular function in patients suffering from different pathophysiologic conditions such as sepsis and traumatic shock (6, 2- 4). However, most of these studies have concentrated on correlating NIRS-dynamic variables with the condition of disease or with the patient's hemodynamic variables, and failed to show any consistent relationship with these parameters. For example, De Blasi et al (6) demonstrated that StO<sub>2</sub> recovery rate after a VOT was similar between septic and postsurgical patients. Similarly, Gomez et al. (3) using the same variable reported no differences between hemodynamically stable and unstable trauma patients.

Considering that hemoglobin levels and arterial oxygen saturation remain unchanged, local vasomotor tone is one of the main determinants of peripheral blood flow and thus tissue oxygen delivery. This suggests that NIRS measurements may be more correctly interpreted if measured in association with parameters that reflect the condition of peripheral circulation. Bedside assessment of peripheral blood flow is difficult and it has not yet been incorporated into routine clinical practice. An alternative method to estimate peripheral blood flow variations at the bedside is using forearm-to-fingertip skin-temperature gradient (T<sub>skin-diff</sub>) together with physical examination. Considering a constant environment condition, a T<sub>skin-diff</sub> threshold of 4°C has been showed to reflect vasoconstriction in critically ill patients (7, 8). Other data recently reported by our group showed that clinical abnormalities of peripheral perfusion assessed by physical examination were associated to an unfavourable outcome in critically ill patients (9). The objective of this study was, therefore, to propose a different approach for the interpretation of StO<sub>2</sub>-derived parameters by adding temperature measurements and physical examination of peripheral perfusion during StO<sub>2</sub> monitoring and to characterize the pattern of StO<sub>2</sub> dynamic in patients with peripheral vasoconstriction and vasodilation. Additionally, we investigated the relation of both parameters in identifying an unfavourable outcome for severe organ and metabolic dysfunction.

## MATERIAL AND METHODS

### *Study population*

This prospective observational study was conducted in the intensive care of a university hospital. We enrolled consecutive critically ill patients within 24h of ICU admission who had undergone initial resuscitation and stabilization. Patients were excluded if they had severe peripheral vascular disease (with a history of vascular surgery). The institutional review board approved the study. Each patient or relative provided written informed consent.

### **Measurements**

Peripheral circulation parameters included physical examination of peripheral perfusion with capillary refill time (CRT) and forearm-to-fingertip skin-temperature gradient (T<sub>skin-diff</sub>). Capillary refill time was measured by applying firm pressure to the distal phalanx of the index finger for 15 seconds. A chronometer recorded the time for the return of the normal colour and 4.5 seconds was defined as the upper limit of normality (10). The T<sub>skin-diff</sub> was obtained from two skin probes (Hewlett Packard 21078A) attached to the index finger and on the radial side of the forearm, mid-way between the elbow and the wrist. The temperature gradient T<sub>skin-diff</sub> can better reflect cutaneous blood flow than the skin temperature itself. Considering a constant environment condition, T<sub>skin-diff</sub> increases during vasoconstriction and a threshold of 4°C has been showed to reflect vasoconstriction in critically ill patients (7, 8). Patients were considered to have abnormal peripheral circulation if the examined extremities (both hands) had an increase in capillary refill time >4.5 seconds or when a T<sub>skin-diff</sub> >4 °C was present. The ICU has single-person closed rooms and the ambient temperature in each patient's room was individually and actively set at 22°C.

Systemic hemodynamic variables included heart rate (HR) and mean arterial pressure (MAP). All measurements were obtained using standard equipments. Thenar StO<sub>2</sub> was continuously monitored using an InSpectra Tissue Spectrometer Model 650 (Hutchinson Technology Inc., Hutchinson, MN, USA) with a 15 mm probe over the thenar eminence. The 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 systolic pressure for 3 minutes. On the completion of the ischemic period, the occluding cuff was rapidly deflated to 0 mmHg. VOT-derived StO<sub>2</sub> parameters were divided into three components: resting StO<sub>2</sub> values, rate of StO<sub>2</sub> desaturation (R<sub>dec</sub>StO<sub>2</sub>, expressed as %/min) and rate of StO<sub>2</sub> recovery (R<sub>inc</sub>StO<sub>2</sub>, expressed as %/s). One individual who was blinded from all treatment and clinical data performed the NIRS measurements.

The first measurement was performed within 24 hours of intensive care admission after hemodynamic stability was obtained (MAP >65 mmHg, and no change in vasopressor use for 2h) every 24 h thereafter until day 3. Information collected at enrolment included demographic characteristics, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and type of diagnose admission. Because our study was not powered to investigate the association with mortality, we replaced this endpoint by SOFA and blood lactate levels, based on their high relationship with poor outcome (11, 12). The outcome of interest in this study was therefore defined as a SOFA score above 8 points plus hyperlactatemia, defined as a blood lactate level >2mmol/L. Clinical and laboratory data needed for SOFA and lactate were collected at the moment of measurement.

### *Statistics*

Unless otherwise specified, results are presented as mean (SD). Differences between groups means were tested by Student's t-tests; for variables that were not normally distributed, differences were tested by Mann-Whitney U test. The linear mixed model analysis was used to assess the magnitude of contribution from central temperature, mean arterial pressure, heart rate, dose of vasopressor therapy and abnormal peripheral perfusion ( $T_{\text{skin-diff}} > 4$  or delayed capillary refill time) on all repeated  $\text{StO}_2$ -derived parameters measured during the 3 days study (13). We used generalized mixed-model analysis to estimate slope coefficient prediction for poor outcome (SOFA > 8 and lactate > 2mmol/L) at each combination of days with abnormal peripheral perfusion and NIRS-derived variables (14). A  $P$ -value < 0.05 was considered statistically significant. No correction for multiple testing has been performed. Statistical analysis was performed using SPSS (version 15.0, SPSS, Chicago, IL) for t-test and nonparametric test and Statistical Analysis Software 9.2 (SAS Institute Inc. Cary, NC, USA) for mixed model analysis.

## **RESULTS**

Of 73 patients included in the study, 79% had circulatory shock on admission to ICU, of whom 57% had septic shock and 43% had no septic shock. All patients were under analgesia or sedation and tolerated well the 3 min of occlusion test in the arm. Table 1 summarizes the clinical data of the patients.

All data used in the analysis were obtained at 24, 48 and 72 hrs after admission. Six patients had one set of data collected on admission only and another six patients had their data collected on 24 and 48 hrs only. Upon ICU admission, 35 (47.9%) patients had abnormal peripheral perfusion following resuscitation and stabilization. Table 2 shows NIRS-dynamic variables stratified by the condition of peripheral perfusion upon

**Table 1.**

Patient demographic data	
Number of patients	15
Age (years)	63 [48-71]
Male/Female	9/6
SOFA	10 [5-11]
APACHE II	22 [16-27]
Admission category:	6 abdominal sepsis 5 pneumonia
	2 postoperative 1 hemorrhagic shock 1 meningitis
Noradrenaline use, N (%)	14 (93%)
Noradrenaline dose ( $\mu\text{g}/\text{kg}/\text{min}$ )	0.13 [0.03-0.40]
Mechanical ventilation, N (%)	15 (100%)
Survivor/Non-survivor	10/5

**Table 2.** Global hemodynamic variables recorded in the three different time points during execution of the study protocol (n = 15). Time points are defined as before nitroglycerin infusion (T<sub>BL1</sub>), at the maximum dose of nitroglycerin (T<sub>MX</sub>) and 30 min after cessation of nitroglycerin (T<sub>BL2</sub>). Cardiac index and stroke volume were measured in 6 patients. Data are mean (SE)

	T <sub>BL1</sub>	T <sub>MX</sub>	T <sub>BL2</sub>
HR (bpm)	95 (4.3)	97 (4.4)	98 (4.4)
SBP (mmHg)	113 (4.6)	94 (4.0)*	111 (3.8)*
DBP (mmHg)	52 (4.9)	49 (4.8)*	57 (4.9)*
MAP (mmHg)	75 (3.0)	61 (2.9)*	71 (2.3)*
CI, n=6 (L/min/m <sup>2</sup> )	4.1 (0.4)	3,8 (0.5)	3,9 (0.4)
SV, n=6 (ml)	78 (15)	66 (14)	77 (12)

HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial blood pressure; CI=cardiac index; SV=stroke volume. \*  $P < 0.05$  vs. previous time point (linear model for repeated measurements)

ICU admission. There was a statistically significant difference in StO<sub>2</sub> and StO<sub>2</sub> recovery between patients with normal and abnormal peripheral perfusion condition (Table 2).

The relationship of NIRS-dynamic variables to the standard hemodynamic, central temperature and peripheral circulation parameters was assessed using the mixed-model analysis to further explore the contribution from each of these variables on the StO<sub>2</sub> derived parameters. After adjusting for hemodynamic variables (mean arterial pressure and heart rate) and for the diagnostic category (septic shock; circulatory shock not associated with sepsis; without shock and sepsis), the condition of peripheral circulation was found to have a major effect on StO<sub>2</sub> and StO<sub>2</sub> reoxygenation rate levels. Table 3 shows the esti-

**Table 3.** Peripheral perfusion parameters recorded in the three different time points during execution of the study protocol (n = 15). Time points are defined as before nitroglycerin infusion (TBL1), at the maximum dose of nitroglycerin (TMX) and 30 min after cessation of nitroglycerin (TBL2). RincStO<sub>2</sub> and RdecStO<sub>2</sub> were collected from 13 patients. Data are mean (SE).

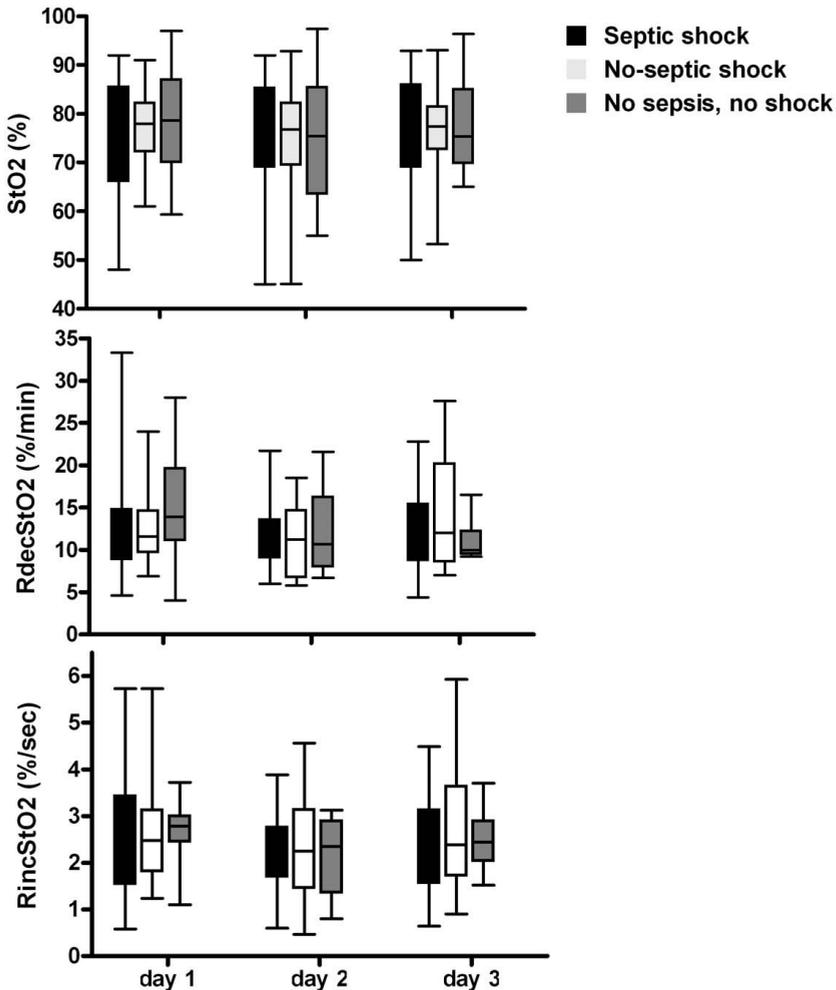
	T <sub>BL1</sub>	T <sub>MX</sub>	T <sub>BL2</sub>
CRT (sec)	9.4 (0.6)	4.8 (0.3)*	7.1 (0.8)*
Tskin-diff (°C)	3.3 (0.7)	0.7 (0.6)*	1.8 (0.6)*
PI.log (%)	-0.5 (0.2)	0.7 (0.1)*	0.2 (0.1)*
StO <sub>2</sub> (%)	75 (3.4)	84 (2.7)*	79 (2.8)
THI (a.u.)	11.1 (1.3)	13.2 (1.4)*	11.6 (1.2)*
RincStO <sub>2</sub> , n=13 (%/sec)	1.9 (0.08)	2.8 (0.05)*	2.4 (0.09)*
RdecStO <sub>2</sub> , n=13 (%/min)	8.6 (0.5)	9.2 (0.6)	9.14 (0.7)

CRT=capillary refill time Tskin-diff= forearm-to-fingertip skin-temperature gradient; PI=Perfusion Index; THI=tissue hemoglobine index; RincStO<sub>2</sub>= rate of StO<sub>2</sub> increase after arterial occlusion; RdecStO<sub>2</sub>=rate of StO<sub>2</sub> deoxygenation during arterial occlusion. \*P<0.05: previous time point (linear model for repeated measurements)

mation coefficient from each variable. The clinical importance of systemic hemodynamic variables was not significant or had no clinical impact on StO<sub>2</sub>-derived variables. However, there was a statistically significant association between StO<sub>2</sub> and StO<sub>2</sub> recovery with changes in the clinical condition of peripheral perfusion over time. Because the influence of abnormal peripheral perfusion on StO<sub>2</sub> was different in each day, a separate estimation was calculated for the three days apart and is shown on table 3.

We also were interested to investigate whether StO<sub>2</sub>-derived variables were related to the pathophysiologic condition of disease. Accordingly, our patients were stratified by the presence of sepsis and/or shock condition. The linear mixed model analysis showed that the presence of sepsis or shock had no influence on the repeated StO<sub>2</sub>-derived parameters measured over time (StO<sub>2</sub>: P=0.72; RdecStO<sub>2</sub>: P=0.45; RincStO<sub>2</sub>: P=0.39), and were similar among patients with and without sepsis or shock (Figure 1). In patients who received vasopressor therapy (N=49), the dose of vasopressor did not differ between peripheral vasoconstriction and vasodilation (N=25: 0.24±0.2 vs. N=24: 0.22±0.2; P=0.70). In addition, the estimation coefficient showed that the dose of vasopressor did not have any effect on StO<sub>2</sub> (-2±3; P=0.44), RdecStO<sub>2</sub> (1.12±1.15; P=0.42), and RincStO<sub>2</sub> (-0.62±0.41; P=0.14). We found no relationship between StO<sub>2</sub>, RdecStO<sub>2</sub>, RincStO<sub>2</sub> and mortality.

The coefficient prediction for poor outcome (SOFA>8 and lactate >2mmol/L) at each combination of days with abnormal peripheral perfusion and StO<sub>2</sub>-derived variables calculated with mixed-model showed that poor outcome was more closely related to abnormalities in peripheral perfusion than to StO<sub>2</sub>-derived parameters (Table 4).



**Figure 1.** Box plots demonstrating the time course of resting StO<sub>2</sub>, rate of StO<sub>2</sub> desaturation (RdecStO<sub>2</sub>) and rate of StO<sub>2</sub> recovery (RincStO<sub>2</sub>) in the different study groups (septic shock, no-septic shock and without sepsis and shock) during the 3 days of measurements

**Table 4.** Estimation of the effect of nitroglycerin dose on all parameters of peripheral perfusion

	Estimate	95% CI	P-value
Constant	8.9	[4.60, 13.10]	0.001
CRT (sec)	-0.91	[-1.10, -0.50]	0.001
Tskin-diff (°C)	0.35	[0.09, 0.61]	0.008
PI (%)	1.2	[0.55, 1.85]	0.001
StO <sub>2</sub> (%)	-0.02	[-0.07, 0.03]	0.42
StO <sub>2</sub> (%), corrected for baseline StO <sub>2</sub>	0.30	[0.14, 0.47]	0.001

CRT=capillary refill time Tskin-diff= forearm-to-fingertip skin-temperature gradient; PI=Perfusion Index

## DISCUSSION

The major new finding from this prospective observational study is that the condition of peripheral perfusion contributes significantly to NIRS-derived measurements of tissue oxygenation in critically ill patients. Using two distinct methods to evaluate peripheral perfusion (i.e., subjective assessment and skin temperature), we found that changes in peripheral circulation caused parallel changes in the  $\text{StO}_2$  resting values and in the  $\text{StO}_2$  reoxygenation rate, but not in the  $\text{StO}_2$  desaturation rate. In addition, changes in  $\text{StO}_2$ -derived variables were independent of pathophysiologic condition of disease as well as hemodynamic status of the patient. Possible explanation of our findings is that  $\text{StO}_2$  measurement is an estimation of hemoglobine oxygen saturation in the small vessels and, therefore, is widely influenced by volume of the underlined vascular bed (arterioles, capillaries and small veins), which is decreased in peripheral vasoconstriction. The  $\text{StO}_2$  baseline represents the resting intravascular hemoglobine saturation levels and the  $\text{StO}_2$  recovery after the vascular occlusion represents the sudden increase of arterial inflow during the hyperaemic response. Unlike the  $\text{StO}_2$  deoxygenation rate during arterial occlusion in which venous outflow and arterial inflow are blocked,  $\text{StO}_2$  and  $\text{StO}_2$  recovery rate are influenced by local blood volume and vasomotor tone. The data from this study support this hypothesis. Patients who presented daily changes in the skin peripheral temperature significantly changed  $\text{StO}_2$  values independently of changes in heart rate and arterial blood pressure (Table 3). The effect of peripheral blood flow variations in the  $\text{StO}_2$  measurements has been described in previous reports. In the study by Davis et al. (15), increases in skin blood flow during local heating in healthy volunteers significantly increased fourfold the  $\text{StO}_2$ -derived tissue oxygenation. In addition, NIRS response to an ischemic challenge during the vascular occlusion test has been shown to correlate to that observed with gauge plethysmography and with laser Doppler fluximetry (16, 17).

Among the investigations employing a NIRS device identical to the ones used in the present study, some have compared healthy volunteers with septic patients (18, 1, 4) while others have compared healthy volunteers with trauma patients (19, 20). To our knowledge, there are no studies comparing NIRS variables between septic and no-septic shock patients. Our study expands these observations with the demonstration that  $\text{StO}_2$ -derived variables measured over time in a mixed ICU population were independent of disease condition. These findings are consistent with previous reports showing that peripheral blood flow is altered in different experimental and clinical shock conditions (21- 25). From an etiologic perspective, both septic and no septic shock shares a combination of pathological derangements present in the peripheral circulation. These alterations include impaired arteriolar vasoregulation and capillary perfusion that are observed mainly in peripheral vascular beds, including skin, muscle, sublingual and gut (26- 29). This may explain the mechanism for the decrease of  $\text{StO}_2$  and  $\text{StO}_2$  recovery in

critically ill patients. For the analysis of changes in the  $\text{StO}_2$  during VOT, the NIRS probe is usually placed over the thenar eminence, which represents a peripheral vascular bed and is widely influenced by local vasoregulation. This relationship is supported by our study. Considering that hemoglobin levels and arterial oxygen saturation remained unchanged in our patients, the association of  $\text{StO}_2$ -derived variables with cold extremities partly explain the relationship between local vasomotor tone and peripheral tissue oxygenation.

In clinical practice, one of the first strategies to treat circulatory failure is targeting blood pressure as traditional end-point of resuscitation as well as to guide hemodynamic therapy. Some evidence indicates that MAP should be kept above a minimum value of 60 mmHg. This level of MAP represents the point at which autoregulatory control of blood flow to the heart, kidneys, and brain ceases, resulting in pressure-dependent organ blood flow. When MAP falls below this range, organ blood flow also decreases in a linear fashion (30). Therefore, a MAP of 65–90 mmHg is a widely accepted and recommended blood pressure range for critically ill patients. Vasoconstrictive agent such as noradrenaline is usually the initial vasopressor to increase MAP. Noradrenaline acts on both alpha-1 and beta-1 adrenergic receptors, thus producing potent vasoconstriction as well as a less pronounced increase in cardiac output. The association between low  $\text{StO}_2$ -derived variables and abnormal peripheral perfusion in our patients was not accompanied by any major differences in either systemic hemodynamic or dose of vasopressor therapy. These findings suggest that the presence of abnormal  $\text{StO}_2$  levels does not reflect systemic hemodynamic effects or vasoconstriction from a pharmacologic intervention. This lack of association between  $\text{StO}_2$  measurements and systemic hemodynamic variables is not unexpected, since some studies have reported a degree of disconnection between the macrocirculation and the microcirculation, indicating that strategies to target arterial blood pressure in circulatory shock will not necessarily ensure adequate regional perfusion (31- 33). In a study by LeDoux and colleagues (33), 10 patients with septic shock received increasing doses of norepinephrine to drive the MAP from 65 to 85 mmHg, with no changes in indices of regional perfusion (as measured by skin capillary blood flow, red blood cell velocity, urine output, and gastric mucosal partial pressure of  $\text{CO}_2$ ). The authors concluded that the use of a vasopressor to elevate the arterial blood pressure to above 65 mmHg in septic shock did not affect regional blood flow. This was recently supported by data from Dubin et al. (32) who reported the effects of titrating noradrenaline infusion to increase MAP level (65 to 85 mmHg) on sublingual microcirculation. Our results expand this knowledge by addressing the variation of peripheral tissue oxygenation according to condition of peripheral circulation, and not to MAP or heart rate. In particular, the change in the  $\text{StO}_2$  and  $\text{StO}_2$  reoxygenation rate was strongly dependent on skin temperature. In this way, our data support the hypothesis that  $\text{StO}_2$  measurements may be more correctly interpreted if measured in association

with skin temperature, and strategies to improve peripheral tissue oxygenation should be investigated in association with the condition of peripheral circulation.

Although our study was not powered to investigate the association with mortality, we replaced this endpoint by SOFA and lactate. The rationale of using SOFA and lactate is based on recent reports showing that the level and duration of blood lactate levels is associated with the magnitude of organ dysfunction as well as their high relationship with poor outcome (11, 12). Other data recently reported by our group showed that clinical abnormalities of peripheral perfusion assessed by physical examination were associated to an unfavourable outcome in critically ill patients (9). These findings are in agreement with the present study, in which clinical abnormalities of peripheral perfusion were correlated with SOFA and lactate, but not with  $\text{StO}_2$ -derived variables (Table 4). Altered  $\text{StO}_2$ -derived variables have also been associated with outcome in patients with either septic or non-septic shock (1). Taken together, our findings support the hypothesis that the outcome prediction of  $\text{StO}_2$ -derived variables reported in previous studies is partially explained by the relationship between altered  $\text{StO}_2$ -derived values and abnormalities of peripheral perfusion in critically ill patients.

This study has some limitations that should be acknowledged. First, measurements of global blood flow (cardiac output) were not made in this study. Our main focus, however, was to assess the relationship between  $\text{StO}_2$ -derived variables and the condition of peripheral perfusion. Second, we did not include other methods of peripheral blood flow monitoring, such as cutaneous laser Doppler flowmetry. Nevertheless, we speculate that any other noninvasive methods of peripheral flow could have shown the same association, as  $T_{\text{skin-diff}}$  is a well-validated method to estimate cutaneous blood flow. Third, changes in ambient temperature may have influenced skin temperature. Differences in ambient temperature at each patient's bedside were not directly measured. However, the ICU consists of one-person closed rooms and the ambient temperature in each patient room was individually controlled at 22°C. Moreover, changes in ambient temperature similarly affect forearm and fingertip temperature producing little influence in the gradient between forearm and fingertip (34). Last, we performed the VOT using a constant time interval of 3 min for the duration of occlusion time. Some studies, however, have used different occlusion times needed to reach a  $\text{StO}_2$  level of 40%. The former approach is based on the concept that the magnitude of the hyperemic response is dependent upon the duration of arterial occlusion, and the later method is based more on the level of  $\text{StO}_2$  after ischemia than the duration of ischemia. However, no supporting evidence in the literature show which of the methods is superior and more reliable to assess  $\text{RincStO}_2$  slope. Therefore, the results of our study can only be extended to studies that specifically use the methodology of 3 min occlusion time.

In conclusion, in this prospective observational study we found that the condition of peripheral perfusion contributes significantly to  $\text{StO}_2$ -derived measurements of tissue

oxygenation in critically ill patients. Of all  $\text{StO}_2$ -derived parameters,  $\text{StO}_2$  resting values and  $\text{StO}_2$  reoxygenation rate were most strongly associated with abnormal peripheral perfusion. In addition, changes in  $\text{StO}_2$ -derived variables were independent of the diagnosis and were not associated with significant differences in systemic hemodynamic.

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**LETTER TO THE EDITOR (AUTHOR REPLY):****Critical Care Medicine 40(2), Feb 2012, pp 713-4****THENAR TISSUE OXYGEN SATURATION MONITORING: NONINVASIVE DOES NOT MEAN SIMPLE OR ACCURATE!**

We thank Dr Podbregar for the interest and comments about our paper. We did not use the probe spacing of 25 mm because this probe size is no longer available and has been replaced by the 650 model with probe spacing of 15 mm. However, we share same concerns of Dr Podbregar regarding probe size. The question that remains is whether the effect of clinical abnormalities on StO<sub>2</sub> signal that we observed in our patients would be any different if using a 25 mm probe, which has deeper tissue penetration than the 15 mm probe. As nicely point out by Dr. Podbregar, probe spacing has been shown to provide different values mainly for VOT-derived StO<sub>2</sub> measurements. Since probes detect mean StO<sub>2</sub> across sampling measurement area, the relative proportion of muscle to skin that is sampled with 25 mm probe is greater than the 15 mm probe. Therefore, the 15 mm probe reports relatively more skin and subcutaneous tissue than muscle and is therefore under more influence of skin blood flow variations. We have emphasized this important point in our discussion and it is likely that the decreasing StO<sub>2</sub> signal effect in our patients with clinical abnormalities in peripheral perfusion is mainly due to the upper layers compromised perfusion as result of alterations in the cutaneous circulation, reflected by cold skin or delayed capillary refill time. The comments of Dr Podbregar shed a light in our study and bring to the discussion whether 15 mm probe has the appropriate spacing sensor to detect oxygenation mainly from muscle tissue. Therefore, regarding probe size we share the opinion that wider sensor spacing with greater tissue depth would be an alternative to decrease the relative contribution of skin blood flow to the total NIRS signal. However, before jumping to this conclusion, further investigation is required to compare the effect of changes in cutaneous circulation on StO<sub>2</sub> signal measured with 25 mm probe spacing.

Another important point raised by Dr. Podbregar is related to the 3 min method of vascular occlusion test (VOT) used in our study. In others studies, the VOT has been made till the 40% threshold was reached (1,2). There is no standardization of arterial occlusion test, and no supporting evidence in the literature show which of the methods is superior and more reliable to assess the VOT-derived StO<sub>2</sub> slopes. It is the opinion of this study's authors that resaturation slope does not depend on StO<sub>2</sub> level achieved, and that 3 min of occlusion time is more adequate to perform a VOT. Defining the StO<sub>2</sub> 40% maximal desaturation threshold for stopping the VOT is based on concept that ReOx depends on

the level of StO<sub>2</sub> achieved during ischemia and thus it reflects same stimulus for reactive hyperemia for all patients. This argument, however, is in contrast with the physiological concepts of reactive hyperemia. This method of flow-mediated dilation induction of reactive hyperemia is a well understood method that has filled cardiovascular literature for over a decade. The guidelines for flow-mediated dilation testing recommend occluding arterial inflow for a standardized fixed length of time (3). The rationale of using a fixed occlusion time is based on the fact that reactive hyperaemia depends on endothelium, myogenic and tissue-derived metabolic factors, such as for example intravascular partial pressure of O<sub>2</sub> (main hypoxic stimulus). Since StO<sub>2</sub> is far to reflect any of these factors, let alone intravascular partial pressure of O<sub>2</sub>, and the duration of vascular occlusion test is known to influence the hyperaemic response, StO<sub>2</sub> cannot be used as a threshold marker for hypoxic stimulus. Thus, time of ischemia has more important influence on VOT-derived values than level of StO<sub>2</sub> itself. The recent study from Dr. Mayeur group (2) also supported the use of a fixed minimal muscle StO<sub>2</sub> target (40%) over the use of 3 min. Dr Mayeur's study, however, raised same issues as we have discussed above, some of them well addressed by Dr. Damoiseil and Dr. Payen (4) in the editorial of Dr. Mayeur's article. Regarding the deoxygenation rate, an arbitrary threshold of 40 % has been no logic for this parameter since it seems there is no difference in deoxygenation rate among different deflation thresholds (30%, 40%, and 50%) (5).

To conclude, our study aimed to extend our understanding of the effect of peripheral perfusion variations in critically ill patients to the NIRS signal. We found that peripheral perfusion condition contributes significantly to StO<sub>2</sub>-derived signal measured with a 15 mm probe on thenar. Therefore, the results of our study can only be extended to investigations that specifically use the InSpectra 650 model with a probe spacing of 15 mm and that employ the methodology of 3 min occlusion time.

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## **PART D**

Improving peripheral circulation



## Chapter 9

# Nitroglycerin Improves Abnormal Peripheral Perfusion And Tissue Oxygenation In Patients With Circulatory Shock

*NTG study, submitted*

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# **PART E**

General discussion and main findings



## GENERAL DISCUSSION

Clinically, the major causes of poor tissue perfusion in critically ill patients can be divided into systemic and regional causes. Inadequate systemic function of circulation may be directly measured. However, regional causes of altered tissue perfusion are more difficult to measure and more tenuous in appearance. From an etiologic perspective, the most common cause of regional hypoperfusion in critically ill patients is alterations in the peripheral vascular function. A variety of factors contribute to these derangements in peripheral circulation, and most of these alterations are shared by both septic and nonseptic shock. They are currently attributed to a combination of pathological derangements including impaired arteriolar vasoregulation and capillary perfusion. These are mainly observed in the peripheral vascular beds, such as skin, muscle, and gastrointestinal tract. Although these are functionally and metabolically different organs, at a circulatory functional level they are remarkably similar. Blood flow in these organs is moderately to strongly influenced by sympathetic vasoconstrictor mechanisms. In this regard, coronary, cerebral, and renal circulations show a high degree of autoregulation with poor sympathetic control, whereas skeletal muscle, gastrointestinal and cutaneous circulations show a predominant sympathetic control with a poor degree of autoregulation (1). Observations on the behaviour of the peripheral circulation permit the recognition of two broad phases during the development of shock, irrespective of initiating factors. There is an initial period during which compensatory mechanism predominate, when the neurohumoral response-induced vasoconstriction preserves the perfusion of the vital organs at expense of decreased perfusion in the peripheral tissues. Blood flow variations, therefore, follow a similar response pattern in the skin, muscle and gastrointestinal vascular beds, which makes these tissues highly sensitive for detecting occult tissue disoxia during acute circulatory shock. With the progression of circulatory shock and after initiation of appropriate therapy, the active participation of the peripheral circulation in supporting tissue perfusion becomes less striking and ultimately disappears. Some patients enter a phase of stability, and peripheral circulation alterations may no longer reflect the acute compensatory mechanisms. Others factors, such as mechanical ventilation, vasopressor, vasodilators, sedatives and opiates use overcome the neurohumoral physiologic response. Nevertheless, these may explain why abnormalities in peripheral circulation still persist despite the patient systemic hemodynamic stability has been reached. Although the metabolic functional disturbances that occur in cutaneous, muscle or gastrointestinal tissues following circulatory shock have been studied in detail, most of these studies are limited in comparing one vascular bed to another. To what extent each peripheral vascular bed contributes most to tissue hypoperfusion in shock remains to be studied.

## MAIN FINDINGS

In this thesis, we investigated the feasibility and relevance of monitoring peripheral perfusion in critically ill patients. We showed that noninvasive monitoring of peripheral perfusion is a complementary approach that allows very early application throughout the hospital, including the emergency department, operating room, and hospital wards (**Chapter 1**). Such approach can be easily applied using both simple clinical examination and new current technologies, particularly the pulse oximetry signal and near-infrared spectroscopy (**Chapter 2**).

### Clinical examination of peripheral circulation

Clinical examination of peripheral circulation allows for rapid and repeated assessment of critically ill patients at the bedside. Peripheral circulation can be easily assessed performing a careful physical examination by touching the skin or measuring capillary refill time (CRT). Clinical signs of abnormal skin circulation consist of a cold, pale, clammy, and mottled skin, associated to an increase in CRT. Pressure is applied to the distal phalanx of the index finger for 15 seconds, squeezing the blood from the cutaneous tissue. A delayed return of normal colour indicates decreased skin perfusion and it is usually related to decreased skin blood flow or cutaneous microcirculation derangement. Assessing the skin temperature will assist in evaluating the cause of sluggish capillary refill. Assuming normal core temperature, decreased skin blood flow as cause of delayed CRT can be estimated by measuring skin temperature, since cold extremities reflect constriction of cutaneous vessels that ultimately decreases the amount of blood volume within peripheral vasculature. Warm extremities indicate adequate cutaneous blood flow and a delayed CRT in this condition suggests cutaneous microcirculation derangement (**Chapter 8**). Over the past 30 years, the definition of a delayed CRT has been debated in the literature. Based on the clinical observations, the upper normal limit for CRT is often considered 2 seconds (2). However, a delayed return of more than 2 seconds seems to be of limited value in adult critically ill patients, since the upper limit of normality in a healthy population has been shown to be <4.5 seconds (3). Applying this upper limit of normality, we have been able to demonstrate that CRT >5 seconds at physical exam in patients following initial hemodynamic optimization in the intensive care unit was of great value to discriminate hemodynamically stable patients with more severe organ dysfunction, other than circulatory (**chapter 6**). In addition, patients with a prolonged CRT had significantly higher odds of worsening organ failure than patients with normal CRT. A CRT that is below or above 5 seconds seems to be a better clinical discriminator than the original 2 seconds.

Although skin temperature has been shown to be an easily accessible parameter for circulatory shock severity, body temperature gradients can better reflect changes in cuta-

neous blood flow than the absolute skin temperature itself. 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<sub>skin-diff</sub>). Increased vasoconstriction during circulatory shock leads to decreased skin temperature and a diminished ability of the core 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 to 7°C occurs once the patient's haemodynamics have been optimised (**Chapter 2**). Because the effect of the operating room environment on skin and body temperature changes during surgery, especially with the use of cardiopulmonary bypass, T<sub>skin-diff</sub> may be a more reliable measurement, as the two skin temperatures are exposed to the same ambient temperature as the fingertip. In critically ill adult patients, T<sub>skin-diff</sub> 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 post-resuscitation period (**Chapter 2; Chapter 6**).

### **Noninvasive Optical Monitoring**

Optical methods apply light with different wave lengths directly to tissue components using the scattering characteristics of tissue to assess different states of these tissues (4). The assessment of tissue oxygenation is based on the specific absorption spectrum of oxygenated hemoglobin and deoxygenated hemoglobin. Commonly used optical methods for peripheral perfusion monitoring that can be clinically applied at the bedside are pulse oximeter signal (peripheral perfusion index) and near-infrared spectroscopy (**Chapter 2**).

#### *Peripheral perfusion index*

The peripheral perfusion index (PPI) is derived from the photoelectric plethysmographic signal of pulse oximetry and has been used as a noninvasive measure of peripheral circulation in critically ill patients (**Chapter 1**). PPI is calculated as the ratio between the pulsatile component (arterial compartment) and the non-pulsatile component (other tissues) of the light reaching the detector of the pulse oximetry. Because the size of the pulsatile portion increases with vasodilation and decreases with vasoconstriction, changes in the PPI reflect changes in peripheral vasomotor tone. In our large population of healthy volunteers, the median PPI value was 1.4% (**Chapter 3**). 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. The inclusion of PFI into the pulse oximetry signal is a recent advance in clinical monitoring and its easily obtainable and noninvasive method can be used for monitoring peripheral circulation in critically ill patients.

### *Near-Infrared Spectroscopy*

Near-infrared spectroscopy (NIRS) offers a technique for continuous, noninvasive, bedside monitoring of tissue oxygenation. Like pulse oximetry, NIRS use the principles of light transmission and absorption to measure the concentrations of haemoglobin and oxygen saturation noninvasively in tissues. NIRS has a greater tissue penetration, which is directly related to the spacing between illumination and detection fibers. With 25 mm spacing, approximately 95% of the detected optical signal is from a depth of zero to 23 mm. The variables that are analysed using NIRS can either be directly calculated or derived from physiological interventions, such as a vascular occlusion test (VOT). Peripheral tissue oxygenation ( $StO_2$ ) measurements reported in the literature varied widely among studies using different probe spacing. Some have used the 15 mm probe spacing, while others have used the 25 mm probe spacing. Since probe spacing has been shown to provide different values mainly for VOT-derived  $StO_2$  measurements, we have investigated the influence of measurement sites (forearm and thenar) and probe spacing (15 mm and 25 mm) in the resting  $StO_2$  signal as well as in the VOT parameters (**Chapter 4**). We found that resting  $StO_2$  values were unrelated to probe spacing or measurement site. In the other hand, probe spacing and measurement site significantly influenced both deoxygenation and  $StO_2$ -recovery rate. Based in our findings, we therefore suggested using the 15 mm probe spacing on the thenar, as it provides reliable and more reproducible results.

Another important technical issue of NIRS-probe is related the potential impact of superficial tissues on NIRS light absorption and scattering. We have described an experiment study performed in healthy volunteers showing that the presence of peripheral vasoconstriction due to body surface cooling significantly affect  $StO_2$ -derived measurements, particularly  $StO_2$  and  $StO_2$ -recovery rate, which are exclusively dependent on local vasodilation capacity (**Chapter 5 and 5a**). We proposed that interpretation of peripheral tissue oxygenation should be performed in association with the condition of peripheral circulation. This finding has been supported by one study we performed to investigate the effect of peripheral perfusion variations in critically ill patients to the NIRS signal (**Chapter 8**). We found that peripheral perfusion condition contributes significantly to  $StO_2$ -derived signal measured with a 15 mm probe on thenar. Additionally, we showed that the presence of sepsis or shock in our patients had no influence on the repeated  $StO_2$ -derived parameters measured during consecutive three days. Variations in thenar  $StO_2$ -derived variables were independent of the pathophysiologic condition

of disease, and  $\text{StO}_2$ -derived variables were similar among patients with and without sepsis or shock.

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 (**Chapter 2**). In a study by Shapiro et al., for instance (5), the dynamic NIRS variables collected during a VOT were strongly associated with the severity of organ dysfunction and mortality in patients with septic shock. This is of special interest because there is a lack of agreement on standardisation for the appropriate method for performing a VOT (**Chapter 8a**). Nevertheless, when used in conjunction with other peripheral perfusion methods, repeated  $\text{StO}_2$  monitoring has the potential to assess the effect of therapeutic intervention on the peripheral microvascular circulation in various shock states. In our prospective observational study,  $\text{StO}_2$  and  $\text{StO}_2$ -recovery rate after VOT were measured in 22 critically ill patients admitted with increased lactate levels (**Chapter 7**). We found that patients who consistently exhibited low  $\text{StO}_2$  levels following an initial resuscitation had significantly worse organ failure than did patients with normal  $\text{StO}_2$  values. 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.

### **Clinical Applications in Patient Management**

From the above we can conclude that clinical and hemodynamic parameters must be combined with measures of peripheral circulation to continually monitor the critically ill patient as an attempt to maintain an adequate tissue perfusion. Although the mechanisms involved in shock resuscitation are not yet fully understood, it is clear that the persistence of abnormal peripheral circulation, measured in skin, muscle, sublingual or intestinal mucosa is associated with worse patient outcomes. It is likely that interventions specifically aimed at the peripheral vascular bed would have a greater effect on regional perfusion. This concept originated in the 1990's with clinical trials of different types of vasodilators (prostacyclin, N-acetylcysteine) targeting splanchnic perfusion as assessed by gastric tonometry (6). These studies demonstrated an improvement in gastric perfusion with drug administration suggesting that successful microcirculatory recruitment had occurred. More recently, some studies have evaluated short-term infusions of nitroglycerine in septic or non-septic shock and demonstrated significant improvements in capillary perfusion (7-9). In an effort to address whether nitroglycerin could correct abnormalities in peripheral perfusion in patients following initial resuscitation after admission in the intensive care unit, we demonstrated that stepwise dose of intravenous infusion of nitroglycerin reverses clinical abnormalities of peripheral circulation in patients with circulatory shock (**Chapter 9**). In addition, we showed that

the easy and reliable clinical parameters of peripheral perfusion can be an effective monitoring approach at the bedside to titrate the beneficial effects of nitroglycerin on microcirculation in individual patient with circulatory shock following initial resuscitation. Whether this intervention is capable of resuscitating different peripheral vascular beds remains to be determined. Current studies are ongoing to determine the effects of these interventions on peripheral circulation in critically ill patients.

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## SUMMARY AND CONCLUSIONS

Resuscitation of circulatory shock is aimed at reestablishing adequate tissue perfusion through optimization of traditional endpoints, such as mean arterial pressure, cardiac output and its determinants. Monitoring critically ill patients in the early hours of shock is therefore essential to recognize alterations in these predefined end points and to assess whether patient needs active intervention. Although the initial objective of hemodynamic monitoring is the restoration of these global macrocirculatory variables, abnormalities in peripheral circulation may still persist and are related to the development of organ failure and when unrecognized may worsen prognosis among critically ill patients. This scenario has led to growing interest in non-invasive methods designed to evaluate regional perfusion in peripheral tissues as a valuable adjunct to standard global parameters to predict or diagnosis ongoing tissue hypoperfusion. We propose to complement global parameters of oxygen transport with monitoring parameters of peripheral circulation. Real-time assessment of peripheral circulation at the bedside is easily obtainable using noninvasive monitoring techniques. Moreover, it is a simple approach that can be rapidly applied throughout the hospital, including the emergency department, operating room, wards and intensive care unit.



## SAMENVATTING EN CONCLUSIE

Tijdens acute circulatoire shock, een fase waarin verschillende weefsels niet goed doorbloed worden, is het herstellen van de doorbloeding van deze weefsels vooral gericht op conventionele hemodynamische parameters zoals bloeddruk, hartfrequentie en cardiac output. In deze ernstig zieke patiënten is goede hemodynamische monitoring en het zorgen voor herstel van de doorbloeding essentieel. Na de start van de juiste behandeling en herstel van de conventionele hemodynamische parameters zal bij de meeste patiënten de activiteit van compensatiemechanismen afnemen. Echter bij sommige patiënten blijven, ondanks succesvol behandelde conventionele hemodynamische parameters, compensatiemechanismen actief en kan lokale weefsel hypoperfusie voortbestaan. Hoewel de relatie met conventionele hemodynamische parameters afhankelijk is van het ziektebeeld, lijkt verstoring van de perifere circulatie hoe dan ook gerelateerd aan een slechter klinisch beloop (meer orgaanfalen) in verschillende patiënten groepen. De beoordeling van de perifere circulatie biedt niet alleen een ander referentiepunt voor de beoordeling van de circulatie, maar kan tevens onder alle omstandigheden en op verschillende manieren worden gebruikt en daarmee dienen als een potentiële rode vlag in kritisch zieke patiënten. Met de huidige methoden is beoordeling van de perifere circulatie bij ernstig zieke patiënten makkelijk uit te voeren, goedkoop en eenvoudig toe te passen aan het bed.



## ACKNOWLEDGEMENTS

Being new to a country brings challenges for everyone. Moving to the Netherlands was more than just changing location and signing papers; it was a complete life change. It's not as if the culture was a lot different from my Brazilian background, but there were enough little things here and there that caught me by surprised. Even so, I won't remember the bad moments nearly as much as I remember the good ones. The direct and friendly nature of the Dutch, the harsh sound of the language, the Dutch *dropjes*, *harings*, and water, water everywhere! Then there is the cycling. Before I came to the Netherlands I had not climbed on a bicycle over a decade. It became part of my daily life decision-making, such as the supermarket list; I used to buy only things that fit in my bike. It turns out that my experience in this tiny little country has been amazing, educational, cultural, beautiful and real. And yet, after eight years of living in the Netherlands, experiences I gained and time spent in the land of windmills, channels and tulips will always be memorable. *Heel erg bedankt lieverds.*

Continuing a fine tradition, I would here like to express my thanks to the people who have been very helpful to me during the time it took me to write this thesis. During my long travels from Brazil to Holland through these years, with laugh and tears, there is not enough space to thank all my family, friends and colleagues. Many people have contributed in numerous ways, to only some of whom it is possible to give particular mention. I do not have room to name everyone here, but be certain that your kindness will be always printed in my heart and reminded in this book.

First and foremost, I would like to start by thanking my promoter and friend **Prof.Dr. Jan Bakker**, a great teacher and guide, who played an instrumental role in shaping me as a medical researcher. **Dear Jan**, since we first met in the Sírío Libanes Hospital in São Paulo (I think it was in 2000!) you have been not only a good teacher and leader, but also a great person for making me feel so welcome with your encouragement and hospitality. Thank you for welcoming me in Apeldoorn (my first per-review paper!), in Zwolle (my first Dutch bike!), and finally in Rotterdam. I want to thank you not only as my formal promotor, but because you made this possible by accepting me in your department, giving me an opportunity to learn how to be a scientist and how to survive from it. Thanks for your time, energy, enthusiasm and advices, for teaching me to be independent in my research. Thanks to guide me through the scientific thinking process and for your patient during the long period of my study and career. Also, thank you for your friendship and support through my difficult moments during the thesis period. You are and will always be my source of inspiration and motivation on both academic and personal level.

I would like to express my deepest gratitude to the members of my inner PhD committee **Prof.Dr. A.H. van den Meiracker, Prof.dr. A.B.J. Groeneveld, and Prof.dr. D. De Backer** for accepting the invitation, for the time and for the energy you invested to read and approve my thesis. It is a great honour and privilege to have you in this committee. I also would like to express my sincere gratitude to the plenary committee members **Prof. dr. Can Ince, Prof.dr. Jukka Takala, Prof.dr. Peter Pikkers, Prof.dr. Eliezer Silva, and Prof.dr. M.H.J. Verhofstad**. It was a great honour to have such remarkable scientists in my reading committee. My sincere gratitude to **Dr. Peter Pikkers, Dr. De Backer, Dr. Jukka Takala and Dr. Eliezer Silva** for their enthusiasm to take part in my thesis defense and for their willingness to travel all the way to Rotterdam.

A very special thank goes to **Dr. Groeneveld, Dear Johan**, your support and guidance throughout my research projects as well as your help in proof reading my manuscript drafts are greatly appreciated. Also, enormous gratitude to **Prof.Dr. Can Ince** for his scientific expertise and encouragement, **Dear Can**, thank you for the in-depth conversations that stimulate my brain (not always about work!), your timely suggestions, and insightful discussions about microcirculation in the rooms and hallways of Erasmus (sometimes in the AMC) that certainly have much improved the quality of my work.

Endless gratitude goes to **Dr. Jasper van Bommel**, my co-promotor who did much more than a supervisor. **Dear Jasper**, you are a very good teacher, always giving me good advices, pushing me a lot for ideas. Your critical remarks and suggestions have always been very helpful in improving my skills and for strengthening our manuscripts. Thank you for never having any doubts I would manage to get my PhD... I know the beginning was not easy. Really thanks for being patient, tolerant, and above all wonderful company.

For this research, I collected *a lot* of data. Many people helped with this, for which I would like to particularly thank all the medical assistants of our department, some of whom already left, who cooperated greatly during the process of data collection, inform consent, technical support and bedside discussions. Special thanks to the vice chair of our department **Dr. Diederick Gommers, Dear Diederick**, thank you for welcoming me and watching me through the end of my work with continuous and constructive support, which was extremely valuable. Many thanks to, **Dr. Mathieu van der Jagt, Dr. Jelle Epker, Dr. Bart van den Berg, Dr. Marianne Zijnen, Dr. Johan van der Akker, Dr. Dinis dos Reis Miranda, Dr. Erwin Kompagne, Dr. Joachim Weigel, Dr. Patricia Geritsen, Dr. Ben van der Hovern, Dr. Willy Thijsse, Dr. Christine Groeninx, Dr. Hilde de Geus, Dr. Jubi de Haan, Dr. Nuray Kusadasi, and others** (my unreliable memory does not allow me to remember all names!), **dear all**, thanks for all support and to provide an excellent atmosphere for doing research.

Special thanks are also extended to all the **nurses, secretaries, stock supply workers, cleaners, and catering workers** from our department, all of whom through their enthusiasm contributed in the data collection process.

I would like to express my appreciation to **all patients and family members** who agreed to provide consent to participate in the studies, and without whom the clinical medical studies from this thesis would not be possible.

A warm thank to **Els Forman, Dear Els**, I have to thank you for helping me out with all the little problems I had (have) once in a while, not only with boring bureaucratic administrative issues, but also in a personal level. Thanks for always having a warm smile and always ready to help.

I thank **Michel and Eva** for being very good friends and brilliant collaborators, and without their practical help it would not be possible to develop some of the projects in this thesis. Both of them have agreed to become my paranymphs, and that certainly makes me feel confident during my defence. I'm glad I had the chance to work with you both for a while and following your advices, which helped me to accomplish important things in my career. **Dear Eva**, it was great to discuss research projects together and to learn from you things like 'how to get more acquainted with typical Dutch way to be' .... thanks for your friendship and all your support. I wish all the best for you and for your plus one! **Michel**, my dear Dutch Surinamese dude, it was a pleasure working side-by-side with you. I am very grateful for your help, your enthusiasm with research, and for the unique collaboration we have developed over last steps of my PhD. Thanks for those coffee breaks 'in your office' (great ideas were born there!), for the things we did together and for the ones we will do, for sure. And of course, I wish you success in your internship carrier. All the best for you thesis!

It is a great pleasure to thank all **Co-authors** who helped me write my manuscripts successfully. Especial thanks to **Dr. Tim Jansen** who I had the pleasure to work with and share the office during my first years in Erasmus. **Dear Tim**, thanks for your contribution, suggestions, scientific discussions, and for those COEUR lectures we attended together that have much improved the quality of my work. Also, many thanks to **Rick Bezemer** from the AMC to help me to concretise some of the NIRS projects we started to develop together, and for the constructive discussion from the technological point of view in the optical monitoring field. I also extended my thanks to my colleagues from the Department of Translational Physiology of AMC and especially to **Dan Milstein, Koray Yuruk, Peter Goedhart†** and **Bas Bartels** to provide a great collaboration and feedback to my work. Also, thanks to my Irish colleague **Dr. Eilish M. Galvin** from the department of

Anesthesiology in the Erasmus MC, who provided great support during our regional anaesthesia blocks studies.

A special thank to my officemates and current fellows PhD, the veterans and the novices, whom I have very much enjoyed working with, especially **Ditty, Patricia, Paul, Martijn, Helmi, Eva, Patrick, Egal, Rimom, Mats, Zoram, Herma, Yorick, Ido**, thanks all for the friendship, good humour, coffee, chocolates (Lekker!), coffee, science talks, coffee, cakes, coffee, dropjes (no thanks!), and much more, but more importantly to provide such welcoming academic and friendly atmosphere... and coffee! Thank you all!

Special thanks also to the graduate students **Amber** (thanks for your excel skills with NTG data!), **Thijs** (your student discount card is always welcome!), **Noel, Jordan, and Tanne** for their time and energy in being fully engaged in a variety of data collection that contributed to the development of this thesis.

I have been fortunate to come across many funny & good friends from inside and outside Erasmus. A huge thank goes therefore to my friends from Erasmus MC University for their friendship, who always bring joy, laughter and keep me young (not that I'm too old!). The list is far from complete, but I would like to especially mention my 'pub mates' **Rachel** (thanks for the fun moments; I wish success and a great time in New York!), **Katharina and Stefan, Nese, Heidi, Ivana, Marek, Minghui, Annemarie, Lisette, Mariana, Sten and Joris** ... thank you all for the great time! Special thanks to my polish friend **Karolina**, since we first met in 2010 for a statistical consult, I own you a lot to help me with my dummy statistical questions; even if you did not know the solution, you always tried to find a way to help, and for that I'm really grateful! I wish you success in your thesis! *Dziękuję bardzo!*

I have also had the chance to deepen some friendships as well as to build new ones inside and outside the Erasmus. To my portuguese friend **Marcia**, who shared with me the up's and down's of getting a PhD, *obrigado pelo convívio, amizade e apoio quando necessário e pelos bons momentos de distração na hora do almoço*. I have been fortunate to come across some Brazilians friends who through their friendship have kept me inspired and motivated. **Ricardo e Cintia**, *apesar de nos conhecermos há pouco tempo, muito obrigado pelo incentivo acadêmico, pela hospitalidade e pelo carinho de vocês!* Outside the Erasmus circle, my sincere thanks to **Catherine Transler**, a thoughtful friend who has recently published her book "Turning International" that shed a light into the challenges of living in a new country. Also, thanks to my Brazilian friend **Rachel** and her husband **Danny**, who friendly welcomed us in their lives, and have been of great support for providing exotics moments on the beach during the summer.

My family and friends from Brazil deserve special thanks for supporting me throughout the years in various ways. A loving thought is addressed to my parents, my father **Norberto**† and my mother **Aparecida**, *obrigado mãe pelo carinho incondicional, pelas orações e por sempre acreditar em mim!* To my brothers **Duarte** and **Henrique** and their respective wives **Renata** and **Mônica**, who made me an uncle of three nieces and two nephews: **Leila**, **Lilian**, **Falvio**, **Dudu**, and **Ana Carolina**, *obrigado pela força, atenção, carinho e ajuda ... amo vocês! Para 'seu' Fausto e toda família Arrais e de Oliveira, com especial agradecimento à minha querida sogrinha Dalci e também para as tias Izinha, Jesus e Lúcia pelo carinho, orações e amor. Agradeço de coração à toda minha família Lima no Brasil e em Portugal, tios, tias, primos e primas, não há espaço para todos nessa página, mas há para todos em meu coração.*

My big thanks to all my friends from Brazil, especially to my best friend, **Demian**, *meu caro amigo, irmão e compadre Demian, meu muito obrigado de coração!* **Maria Vitoria**, **Dani**, **João Pedro**, *obrigado pelo carinho, adoro vocês!* **Fernando e Helene**, *o apoio de vocês no Brasil foi e está sendo vital, agradeço de coração toda a juda de vocês!* To **Carlos Eduardo**, dear friend **Cazé**, thanks for caring and always cheer me up! (by the way, I have a Gouda cheese for you!)

Finally, I must thank my wonderful wife **Teresa Cristina**, as without her love, professional and motivational support, probably I may never have completed this thesis. **Tete**, you are the person who sacrificed the most during my PhD trajectory. We went through a lot and did a lot. I would have given up long ago without your steady support, wisdom and endless patient. *Ik hou van je!*



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**ABSTRACTS****24<sup>th</sup> Annual ISICEM Brussels, Belgium, 30 March – 2 April 2004:**

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## CURRICULUM VITAE

Alexandre Augusto Pinto Lima was born on June 25<sup>th</sup> 1969 in São Paulo, Brazil. He earned his medical degree from *Faculdade de Ciências Médicas de Santos*, São Paulo in 1996. He completed his internship and residency in tropical infectious diseases and HIV medicine at *Instituto de Infectologia Hospital Emilio Ribas, Universidade de São Paulo* in 1999. The first two years of fellowship were dedicated to clinical infectious diseases with special programme for research and training in Tropical Diseases. The third year was dedicated to severe infectious diseases in the Division of Intensive Care Unit, with main focus on leptospirosis, meningitis, dengue fever, malaria, and HIV opportunistic infections, in which triggered his interest in intensive care medicine. He decided to follow his career as an intensivist and continued his specialization in an intensive care fellowship at the department of intensive care of *Hospital Sírio Libanês*, São Paulo from 1999 to 2001. Subsequently, he was employed as Assistant Medical Doctor at *Department of Infectious Diseases and Critical Care Medicine of Universidade de São Paulo*, and Assistant Medical Doctor at *Department of Intensive Care Medicine at Hospital do Servidor Público Estadual*, São Paulo. He started his PhD journey in 2004 under the supervision of Prof. dr. J. Bakker at the adult *Intensive Care of the Erasmus University Medical Center Rotterdam*. He will continue his research in the Erasmus MC in the field of peripheral hemodynamic circulation, with the emphasis in optical methods for measuring tissue oxygenation.