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REVIEW

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Noninvasive monitoring of peripheral perfusion

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Abstract *Background:* 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. This review discusses noninvasive methods for monitoring perfusion in peripheral tissues based on clinical signs, body temperature gradient, optical monitoring, transcutaneous oximetry, and sublingual capnometry. *Discussion:* 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.

Keywords Body temperature gradient · Hemodynamic assessment · Noninvasive monitoring · Peripheral tissue perfusion · Sublingual capnometry · Transcutaneous oximetry

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, 2, 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, kidneys). Thus monitoring perfusion in these less vital tissues could be an early marker of vital tissue hypoperfusion. Second, the assess-

ment 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. Also, it can be performed directly (clinical evaluation and body temperature gradient) or by signal processing (optical monitoring; transcutaneous oximetry; sublingual capnometry). This review discusses several available noninvasive methods to monitor peripheral perfusion and oxygenation (Table 1).

Clinical assessment

During circulatory failure the 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. Skin temperature is measured 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 in capillary refill time. In particular, skin temperature and capillary refill time have been advocated as a measure of peripheral perfusion [6, 7, 8, 9, 10, 11].

Capillary refill time (CRT) has been introduced into the assessment of trauma, and a value less than 2 s is considered normal [12]. This 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 on a normal population reported that CRT varied with age and sex. It was found that a CRT of 2 s was a normal value for most young children and young adults, but the lowest CRT was substantially higher in healthy women (2.9 s) and in the elderly (4.5 s). Using these normal variations it was further shown that a prolonged CRT did not predict a 450-ml blood loss in adult blood donors or hypovolemic states in patients admitted to the emergency room [10]. Several clinical studies have reported a poor correlation between CRT, heart rate, blood pressure, and cardiac output [6, 7, 10]. However, prolonged CRT in pediatric

Table 1 Measurement methods to study peripheral perfusion (*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* oxygenated hemoglobin, *HbT* total hemoglobin, StO_2 tissue oxygen saturation, $Cytaa_3$ cytochrome aa_3, *OPS* orthogonal polarization spectroscopy, *FCD* functional capillary density, *LDF* Laser Doppler flowmetry, $PtcO_2$ oxygen partial pressure in the skin, $PtcCO_2$ carbon dioxide partial pressure in the skin, *Tc-index* transcutaneous oxygen index, $PslCO_2$ sublingual tissue PCO_2, *Psl-a*CO_2 gradient between $PslCO_2$ and arterial PCO_2)

Method	Variable	Advantage	Limitations
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_2, and HbT variations StO_2 $Cytaa_3$	Assessment of oxygenation in all vascular compartments; 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; semiquantitative 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	$PtcO_2/PtcCO_2$	Direct measurement of $PtcO_2/PtcCO_2$; early detection of peripheral hypoperfusion	Necessity to frequently change the sensor position; requires blood gas analysis
Sublingual capnometry	Tc-index $PslCO_2$ Psl-aCO_2	Direct measurement of tissue PCO_2 noninvasively	Requires blood gas analysis to obtain $PaCO_2$; normal and pathological values not yet defined

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 8 h 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. This study 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. This study reported the presence of a cold and clammy skin to be an independent predictor of 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction.

The findings of these studies show 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 Weil [15] and Ibsen [16] studied the toe temperature as an indicator of the circulatory shock, 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 (dTp-a) and central-to-peripheral (dTc-p) can better reflect cutaneous blood flow than the skin temperature itself. Considering a constant environment condition, dTp-a decreases and dTc-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 dTc-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, and therefore the central temperature rises and the dTc-p increases. A gradient of 3–7°C occurs in patients with stable hemodynamics [19]. Hypothermia, cold ambient temperature (<20°C) [20], and vasodilatory shock limits the use of dTc-p as an estimate of peripheral perfusion. Forearm-to-fingertip skin-temperature gradient (Tskin-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 Tskin-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, 22, 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 Tskin-diff increases. Experimental studies have suggested a Tskin-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 examined the correlation between body temperature gradient and global hemodynamic variables in hypovolemic, septic and cardiogenic shock, but these have produced conflicting results [15, 25, 26, 27, 28, 29, 30, 31]. Henning et al. [28] studied dTp-a in patients with circulatory failure associated with hypovolemia and low cardiac output. An increase in dTp-a to more than 4–6°C over 12 h was observed in survivors, and a good relationship between the lowest dTp-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 is associated with an increase in dTp-a of more than 2°C, and that dTp-a is correlated to increases in cardiac output and a reduction in blood lactate levels. In examining the value of dTp-a for assessing peripheral perfusion in cardiogenic shock Vincent et al. [27] found that a cardiac index below 1.8 l/min^{-1} m^{-2} is associated with a decrease in dTp-a below 5°C, and that the increase in dTp-a occurs earlier than the increase in skin oxygen partial pressure during recovery; this correlation was not found in septic shock. No relationship has been observed between dTc-p and cardiac output in adults with diverse causes of shock [31] or 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 an

unstable environment, as skin temperature depends also on ambient temperature, and the thermoregulatory response is suppressed in anesthetized 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 various states of these tissues [35]. At physiological concentrations the molecules that absorb most light are hemoglobin, myoglobin, cytochrome, melanins, carotenes, and bilirrubin. 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_2), deoxygenated hemoglobin (Hb) and cytochrome aa_3 ($cytaa_3$). 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 photoeletric plesthysmographic 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_2 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 infrared light (940 nm) absorbed. As other tissues also absorb light, such as connective tissue, bone, and venous blood, the pulse oximetry distinguishes the pulsatile component of arterial blood from the nonpulsatile component of other tissues. Using a two-wavelength system the nonpulsatile component is then 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, with a spectrum that resembles that of both Hb and HbO_2. 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 nonpulsatile component (other tissues) of the light reaching the detector of the pulse oximetry, and it is calculated independently of the patient's oxygen saturation (Fig. 1). A peripheral perfusion alteration is accompanied by variation in the pulsatile component, and because the nonpulsatile component does not change, the ratio changes. As a result the value displayed on the monitor reflects changes in peripheral perfusion.

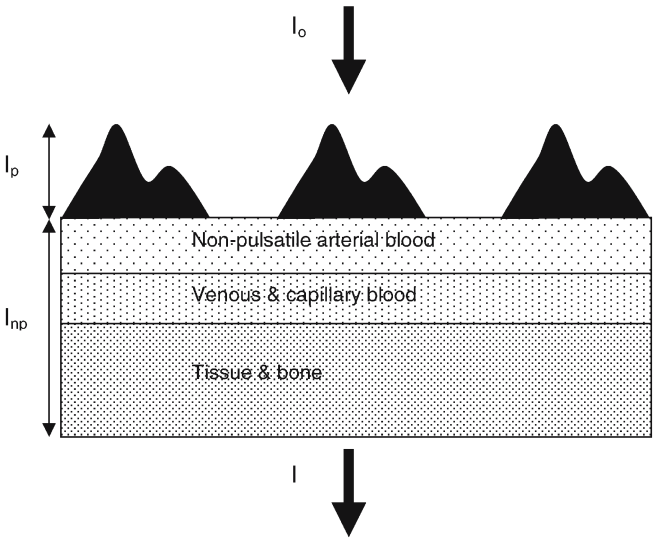

Fig. 1 The pulsation of arterial blood causes a pulsating volume variation. Peripheral perfusion index (*PFI*) is calculated as the ratio between the arterial pulsatile component (I_P) and the nonpulsatile component (I_{NP}). I_0 Source light intensity; I light intensity at the detector

Studies with body temperature gradient suggest that PFI can be a direct indicator of peripheral perfusion. A PFI of 1.4 has been found to be correlated best with hypoperfusion in critically ill patients using normal values in healthy adults [36]. A good relationship between Tskin-diff and PFI is observed in anesthetized patients to identify the initiation of thermoregulatory vasoconstriction [37]. The PFI reflects changes in dTc-p and Tskin-diff and therefore vascular reactivity in adult critically ill patients [36, 38]. Another study has shown that PFI can be used to predict severity of illness in neonates, with a cutoff value of1.24 [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.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) offers a technique for continuous, noninvasive, bedside monitoring of tissue

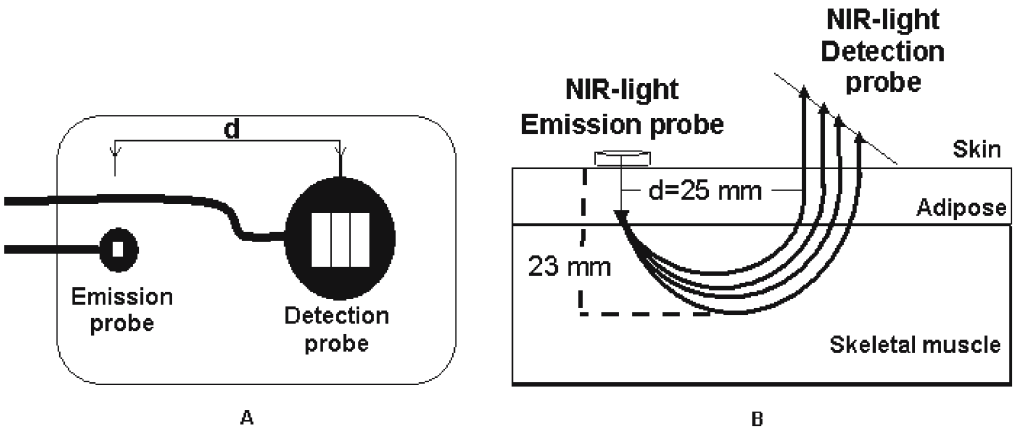

Fig. 2 **A** Diagram of a distal tip of the NIRS optical cable. **B** With 25 mm spacing (*d*) between emission and detection probes, approx. 95% of the detected optical signal is from 23 mm of tissue penetration

oxygenation. As with pulse oximetry, NIRS uses the principles of light transmission and absorption to measure the concentrations of hemoglobin, oxygen saturation (StO_2), and $cytaa_3$ 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). Tissue penetration is directly related to the spacing between illumination and detection fibers. At 25 mm spacing approx. 95% of the detected optical signal is from a depth of 0 to 23 mm (Fig. 2). NIRS has been used to assess forearm skeletal muscle oxygenation during induced reactive hyperemia in healthy adults and produces 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 HbO_2 and Hb changes [40, 41, 42]. In the venous occlusion method a pneumatic cuff is inflated to a pressure of approx. 50 mmHg. Such a pressure blocks venous occlusion but does not impede arterial inflow. As a result venous blood volume and pressure increase. NIRS can reflect this change by an increase in HbO_2, Hb, and total hemoglobin. In arterial occlusion method, the pneumatic cuff is inflated to a pressure of approx. 30 mmHg greater than systolic pressure. Such a pressure blocks both venous outflow and arterial inflow. Depletion of local available O_2 is monitored by NIRS as a decrease in HbO_2 and a simultaneous increase in Hb, whereas total Hb remains constant. After release of the occluding cuff a hyperemic response is observed (Fig. 3). Blood volume increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb. In addition to blood flow and evaluation of HbO_2 and Hb changes, NIRS can assess $cytaa_3$ redox state. $Cytaa_3$ is the final receptor in the oxygen transport chain that reacts with oxygen to form water, and approx. 90% of cellular energy is derived from this reaction. $Cytaa_3$ remains in a reduced state

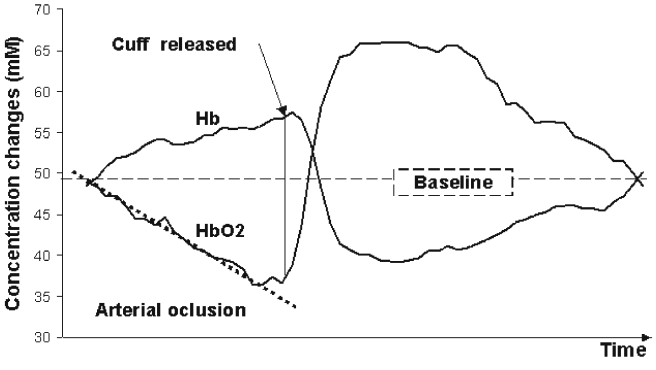

Fig. 3 Quantitative NIRS measurements during arterial occlusion. After release of the occluding cuff blood volume increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb, followed by a hyperemic response. Oxygen consumption is calculated as the rate of decrease in HbO_2 (*dotted line*)

during hypoxemia. The absorption spectrum of $cytaa_3$ 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 $cytaa_3$ 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 both small- and large-animal models of hemorrhagic shock and resuscitation NIRS has demonstrated sensitivity in detecting skeletal muscle and visceral ischemia [44, 45, 46, 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

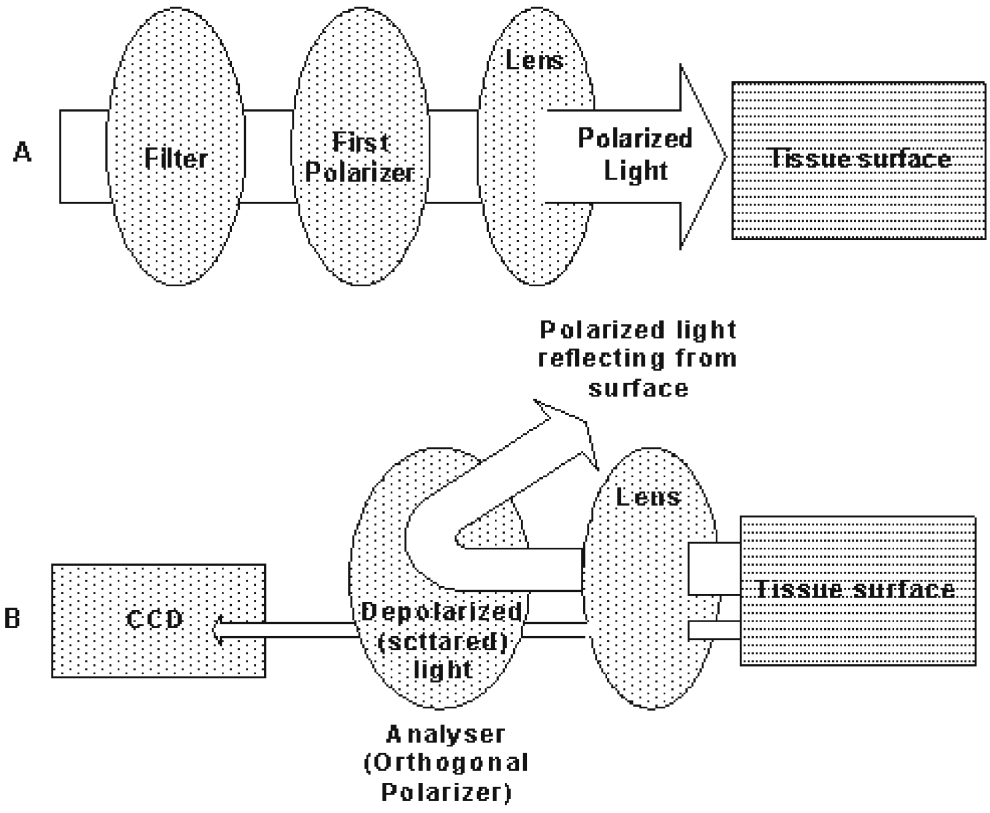

Fig. 4 OPS optical schematic. **A** The light passes through the first polarizer and is reflected back through the lens. **B** The polarized light reflecting from the surface is eliminated, and the depolarized light forms an image of the microcirculation on a videocamera (charge-coupled device, *CCD*)

oxygenation and detect a compartment syndrome [48, 49, 50, 51, 52]. The use of NIRS in deltoid muscle during resuscitation of severe trauma patients has recently been reported [48, 49]. Cairns et al. [49] studied trauma ICU patients and reported a strong association between elevated serum lactate levels and elevated cytaa$_3$ redox state during 12 h of shock resuscitation and development of multiple organ failure. More recently Mckinley et al. [48] showed a good relationship between StO_2, systemic oxygen delivery and lactate in severely trauma patients during and after resuscitation over a period of 24 h. A recent study with septic and nonseptic patients used NIRS to measure both regional blood flow and oxygen consumption after venous occlusion [53]. In this study septic patients had muscular oxygen consumption twice that of nonseptic patients, but oxygen extraction was similar in both groups, emphasizing oxygen extraction dysfunction in sepsis. Another study observed no relationship between forearm blood flow, measured by NIRS, and systemic vascular resistance in septic shock patients [41]. These findings demonstrate 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 have 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 charge-coupled device, 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), i.e., the length of perfused capillaries per observation area (measured as cm/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 produces excellent images of the sublingual microcirculation by placing the probe under the tongue. Movement artifacts, semiquantitative measure of perfusion, the presence of various secretions such as saliva and blood, observer-related bias, and inadequacy of sedation

to prevent patients 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 has been 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, 57, 58]. In septic patients it has been shown with OPS that microvascular alterations are more severe in patients with a worse outcome, and that these microvascular alterations can be reversed using vasodilators [2]. In patients with cardiac failure and cardiogenic shock the number of small vessels and the density of perfused vessels are lower than in controls, and the proportion of perfused vessels is 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 behavior of the sublingual microcirculation differs 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 noninvasive, 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 93–97% of the light is either absorbed by various structures or undergoes scattering. Another optical fiber collects the backscattered light from the tissue and returns it to the monitor (Fig. 5). As a result LDF produces an 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. As a noninvasive measure of peripheral blood flow, however, 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,

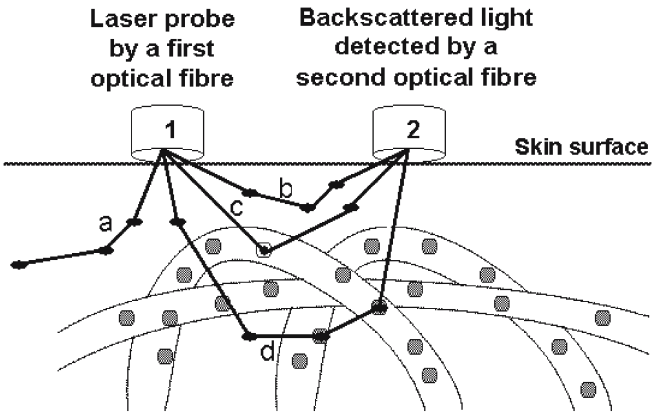

Fig. 5 Schematic diagram of laser Doppler flowmetry. When the tissue is illuminated by a laser source (*1*), 93–97% of the light is either absorbed by various structures or undergoes scattering (*a*, *b*). The remaining 3–7% is reflected by moving red blood cells (*c*, *d*) and returns to the second 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

such as diabetes mellitus, essential hypertension, atherosclerosis, and sepsis [61]. A major limitation of this technique is that it 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 per 100 g tissue) and measurements are expressed as perfusion units, which are arbitrary.

LDF is useful in evaluating 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, 64, 65]. This characteristic of LDF was used in critically ill patients to evaluate endothelial dysfunction in sepsis. Observational studies have shown that the hyperemic response in septic patients is decreased, and a relationship between changes in vasculature tone and severity of sepsis has been described [66, 67, 68]. In addition, restored vasomotion in patients with sepsis evaluated by LDF seems to be associated with a favorable 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_2 and PCO_2 transcutaneous measurements

Continuous noninvasive measurement of oxygen and carbon dioxide tensions is possible because both gases can diffuse through the skin, and thus their partial pres-

sures 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 three effects: (a) heating the stratum corneum beyond 40°C changes its structure, which allows oxygen to diffuse faster; (b) the local oxygen tension is increased by shifting the oxygen dissociation curve in the heated dermal capillary blood; and (c) by dermal capillary hyperemia. These transcutaneous sensors enable us directly to estimate arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure ($PaCO_2$), and it has been successfully used for monitoring PaO_2 and $PaCO_2$ in both neonates and in adults [69, 70, 71]. Newborn infant is suitable because of its thin epidermal layer. However, in adults the skin is thicker, and differences in the skin cause the transcutaneous oxygen partial pressure ($PtcO_2$) to be lower than PaO_2. The correlation between $PtcO_2$ and PaO_2 also depends on the adequacy of blood flow. The low blood flow caused by vasoconstriction during shock overcomes the vasodilatory effect of $PtcO_2$ sensor. This causes a mild tissue hypoxia beneath the $PtcO_2$ sensor. The lack of the $PtcO_2$ ability to accurately reflect the PaO_2 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 in $PtcO_2$ relative to changes in PaO_2 [69, 72, 73, 74, 75]. When blood flow is adequate, $PtcO_2$ and PaO_2 values are almost equal, and the tc-index is close to 1. During low flow shock the $PtcO_2$ drops and becomes dependent on the PaO_2 value, and tc-index decreases. A tc-index greater than 0.7 has been reported to be associated with hemodynamic stability [69, 72, 74, 75]. Transcutaneous carbon dioxide partial pressure ($PtcCO_2$) has been also used as an index of cutaneous blood flow. Differences between $PaCO_2$ and $PtcCO_2$ have been explained by local accumulation of CO_2 in the skin due to hypoperfusion. Because of the diffusion constant of CO_2 is about 20 times greater than O_2, $PtcCO_2$ has been showed to be less sensitive to changes in hemodynamics than $PtcO_2$ [76]. One of the main limitations of this technique is the necessity of blood gas analysis to obtain the tc-index and $PaCO_2$. In addition, the sensor position must be changed every 1–2 h to avoid burns. After each repositioning a period of 15–20 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 [72] found a good correlation (r=0.86) between tc-index and cardiac index in patients with shock. These authors reported that at cardiac index values higher than 2.2 l min^{-1} m^{-2} the tc-index averages 0.79, at 1.5–2.2 l min^{-1} m^{-2} it is 0.48, and at values lower than 1.5 l min^{-1} m^{-2} it is 0.12. However, the relationship between tc-index and cardiac index may not exist in hyperdynamic shock. Reed et al. [75] 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 higher than 4.2l min^{-1} m^{-2}. $PtcO_2$ and $PtcCO_2$ monitoring has been used as an early indicator of tissue hypoxia and subclinical hypovolemia in acutely ill patients [77, 78]. Tatevossian et al. [78] 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. Nonsurvivors had lower $PtcO_2$ values and higher $PtcCO_2$ values than survivors. These differences were evident even early after the patient's arrival. The authors reported a critical tissue perfusion threshold of $PtcO_2$ 50 mmHg for more than 60 min and $PtcCO_2$ 60 mmHg for more than 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

Measurement of the tissue-arterial CO_2 tension gradient has been used to reflect the adequacy of tissue perfusion. The gastric and ileal mucosal CO_2 clearance is been the primary reference for measurements of regional PCO_2 gradient during circulatory shock [79]. 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 [80]. 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 required a search for a tissue in which PCO_2 can be measured easily in a noninvasive approach. Comparable decreases in blood flow during circulatory shock have been also demonstrated in the sublingual tissue PCO_2 ($PslCO_2$) [81, 82]. The currently available system for measuring $PslCO_2$ consists of a disposable PCO_2 sensor and a battery powered handheld instrument. The instrument uses fiberoptic technology to transmit light through the sensor placed between the tongue and the

sublingual mucosa. Carbon dioxide diffuses across a semipermeable membrane of the sensor and into a fluorescent dye solution. The dye emits light that is proportional to the amount of CO_2 present. This light intensity is analyzed by the instrument and displayed as a numeric $PslCO_2$ value.

Clinical studies have suggested that $PslCO_2$ is a reliable marker of tissue hypoperfusion [83, 84, 85, 86]. Weil et al. [86] applied $PslCO_2$ 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 $PslCO_2$ values, and a $PslCO_2$ threshold value of 70 mmHg was predictive for the severity of the circulatory failure. Similarly as PCO_2 in the gut mucosal, $PslCO_2$ is also influenced by $PaCO_2$ [87]. Hence the gradient between $PslCO_2$ and $PaCO_2$ (Psl-aCO_2) is more specific for tissue hypoperfusion. This was shown in the study by Marik and Bankov [85] who determined the prognostic value of sublingual capnometry in 54 hemodynamic unstable critically ill patients. In this study Psl-aCO_2 was a sensitive marker for tissue perfusion and a useful endpoint for the titration of goal-directed therapy. Psl-aCO_2 differentiated better than $PslCO_2$ alone between survivors and nonsurvivors, and a difference of more than 25 mmHg indicated a poor prognosis. One limitation of this technique includes the necessity of blood gas analysis to obtain $PaCO_2$. In addition, normal vs. pathological Psl-aCO_2 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 a formal technology assessment.

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