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Best Practice Guideline article

Peripheral haemodynamics in newborns: Best practice guidelines

Michael Weindling *, Fauzia Paize

School of Reproductive and Developmental Medicine, University of Liverpool, Neonatal Unit, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, United Kingdom

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ABSTRACT

Peripheral haemodynamics refers to blood flow, which determines oxygen and nutrient delivery to the tissues. Peripheral blood flow is affected by vascular resistance and blood pressure, which in turn varies with cardiac function. Arterial oxygen content depends on the blood haemoglobin concentration (Hb) and arterial pO2; tissue oxygen delivery depends on the position of the oxygen-dissociation curve, which is determined by temperature and the amount of adult or fetal haemoglobin.

Methods available to study tissue perfusion include near-infrared spectroscopy, Doppler flowmetry, orthogonal polarisation spectral imaging and the peripheral perfusion index. Cardiac function, blood gases, Hb, and peripheral temperature all affect blood flow and oxygen extraction. Blood pressure appears to be less important. Other factors likely to play a role are the administration of vasoactive medications and ventilation strategies, which affect blood gases and cardiac output by changing the intrathoracic pressure.

Contents

1. Introduction: why monitor peripheral haemodynamics?

The term 'peripheral haemodynamics' is used in this paper to refer to blood flow, which determines oxygen and nutrient delivery to the tissues of a newborn infant. Tissue oxygen consumption (VO_2) is

* Corresponding author. Tel.: +44 151 702 4055.
E-mail address: a.m.weindling@liv.ac.uk (M. Weindling).

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usually independent of oxygen delivery (DO_2), but, particularly for infants who are sick, this is not always the case. Oxygen consumption is determined by its rate of delivery and depends on the microcirculation, the smallest component of the cardiovascular system, where cell function is maintained at the interface between blood and tissue. A healthy microcirculation is therefore vital for the maintenance of efficient tissue perfusion and thus oxygenation.

Blood flow is generally regulated to maintain a consistent internal tissue environment (the concept of homeostasis) and blood flow in major vessels is determined by vascular resistance and blood pressure. However, delivery of oxygen to the tissues is more complex and involves control of the microcirculation, viscosity and the position of the oxygen-dissociation curve and the proportion of fetal and adult haemoglobin. These are discussed in more detail below.

Tissue perfusion is difficult to measure directly and clinicians resort to biomarkers which are considered to represent tissue perfusion: changes in heart rate, blood pressure, skin perfusion, urine output and blood lactate concentration. These are not particularly sensitive as clinically relevant cellular hypoxia and poor tissue perfusion may be present before there are clinically apparent changes. Researchers have investigated other approaches. This paper considers the various methods that have been used and then the principle factors that affect the peripheral circulation and tissue oxygen delivery.

2. Methods available

2.1. Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) technology utilises light in the near-infrared range and has been used in newborn infants since 1985. Fibre-optic bundles or optodes are placed either on opposite sides of the tissue being interrogated (usually a limb or the head of a young baby) to measure transmitted light, or close together to measure reflected light. Light enters through one optode and a fraction of the photons is captured by a second optode and conveyed to the measuring device.

NIRS uses a frequency band between 650 nm and 1000 nm [2] and relies on three important phenomena: (1) human tissue is relatively transparent to light in the near-infrared region of the spectrum; (2) pigmented compounds known as chromophores absorb light as it passes through biological tissue; and (3) human tissues contain substances whose absorption spectra at near-infrared wavelengths are well defined and depend on their oxygenation status.

Three different methods of using near-infrared light for monitoring tissue oxygenation are currently used: (1) continuous wave [3–5]; (2) the time-of-flight method (also known as time-domain or time-resolved) [6]; and (3) the frequency domain method or phase modulation [3]. The *continuous wave method* has a very fast response but only registers relative change or trends and absolute measurements are not possible because of the lack of information available about pathlength. To address this problem, a modification, called *spatially resolved spectroscopy* (SRS) was developed. Multiple optodes operating simultaneously allow for a pathlength correction, but the tissue being interrogated is assumed to be homogeneous. Thus, a light detector measures an absolute value, tissue oxygenation index (TOI), with three sensors at different distances from the light source. Scatter and absorption attenuate light passing into tissue and, if the distance between the light source and the sensor is large enough, the isotropy of scatter distribution becomes so homogeneous that the loss due to scatter is the same at the three sensors. This distance may be greater than 3 cm, which limits the use of SRS for studying the very small limbs of premature infants. SRS has a reasonable signal to noise ratio and between 1 and 3 cm of tissue can be interrogated from the surface. SRS measures haemoglobin oxygen saturation and, in contrast to standard continuous wave near-infrared spectroscopy, gives absolute values. The *time-of-flight method* needs extensive data processing but provides more accurate measurements with the possibility of its becoming a valuable tool in research and clinical environments. The *frequency domain or phase modulation method* has a lower resolution than the time-of-flight method but has the potential to provide estimates of oxygen delivery sufficiently quickly for clinical purposes. This frequency domain or phase modulation technology is probably the best candidate for the neonatal intensive care setting and for bed-side usage. The principles used in the three methods are described in more detail elsewhere [7].

2.1.1. Peripheral venous oxygen saturation (svO_2)

Peripheral svO_2 can be measured by two methods using NIRS [8,9]. This was developed for preterm infants in Liverpool[9] by adapting a method described and validated by de Blasi et al.: the forearm blood flow in adults at rest was 1.9 ± 0.8 ml/100 ml min^{-1}, increasing after exercise to 8.2 ± 2.9 ml/100 ml min^{-1}. These values correlated well with those made using forearm plethysmography [10].

In the venous occlusion method, optodes are positioned on the upper arm and the interoptode distance recorded (Fig. 1). A blood pressure cuff around the upper arm is inflated to 30 mm Hg for approximately 5–10 s. This brief venous occlusion results in a rise in the blood volume within the forearm, assumed to be due to an increase in the venous blood. The changes in HHB and O_2Hb concentration are used to calculate the saturation of venous blood within the forearm tissues [9]. Comparing svO_2 measurements using this venous occlusion technique with measurements by co-oximetry shows close agreement between the methods (mean difference 6%; limits of agreement −5.1% to 17.1%) but peripheral svO_2 measured by co-oximetry was generally slightly higher than that measured by NIRS, and this difference was more pronounced at higher levels of svO_2 [1,11].

2.1.2. Tissue oxygenation index (TOI)

Spatially resolved NIRS has been used to measure tissue oxygenation index (TOI) as an index of cerebral oxygenation and has been validated for studies of the brain [12]. It is likely to be useful for peripheral perfusion and criteria for its evaluation have been set out by Pichler et al. [13,14].

2.1.3. Peripheral blood flow

NIRS has also been used as a research tool for measuring cerebral and peripheral blood flow. From the measurements made using partial venous occlusion, haemoglobin flow (Hbflow) is calculated from the rate of increase of tHb within the forearm, and blood flow from the relationship Hbflow/cHb, where cHb is the venous haemoglobin concentration [7].

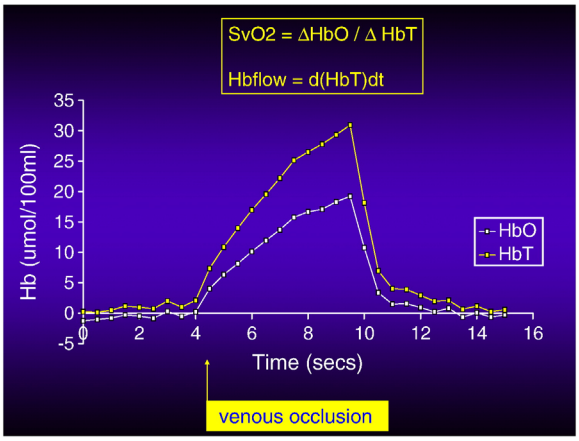

Fig. 1. NIRS with partial venous occlusion to measure venous oxygen saturation. Taken from Yoxall and Weindling [1].

2.1.4. Peripheral oxygen delivery

Oxygen delivery (DO_2) is the total amount of oxygen delivered to the tissue per minute and can be calculated from the formula [15]:

$$\begin{aligned} DO_2 &= \textit{Cardiac output} \times \textit{arterial oxygen content} \\ &= \textit{Cardiac output} \times (\textit{oxygen bound to haemoglobin} + \textit{dissolved oxygen}) \\ &= \textit{Cardiac output} \times [(\textit{cHb}\ (\mathrm{g/dl}) \times \textit{SaO2} \times 1.39) + (\textit{dissolved oxygen})], \end{aligned}$$

where 1.39 is the oxygen carrying capacity of haemoglobin.

As dissolved oxygen is negligible, oxygen delivery to the entire body = Cardiac output × (cHb (g/dl) × SaO_2 × 1.39). Oxygen delivery to the peripheral tissue = Peripheral blood flow × (cHb (g/dl) × SaO_2 × 1.39).

2.1.5. Fractional oxygen extraction (FOE)

FOE is the amount of oxygen consumed as a fraction of oxygen delivery [16]. It has also been called 'oxygen extraction ratio' [16], 'oxygen extraction' [17] and 'oxygen extraction fraction' [18]. It is calculated as [16,19]:

$$FOE = VO_2 / DO_2.$$

Since,

VO_2 = Cardiac output × [(Hb × 1.39) × ($SaO_2 - SvO_2$)], where 1.39 is the oxygen carrying capacity of haemoglobin,
and

$$DO_2 = \textit{Cardiac output} \times (Hb \times 1.39) \times SaO_2$$

the equation may be simplified:

$$FOE = (SaO_2 - SvO_2) / SaO_2$$

and FOE can be calculated if SaO_2 and SvO_2 are known. SvO_2 is measured using the methods described above and peripheral SaO_2 is measured by pulse oximetry. The amount of oxygen dissolved in blood is considered to be negligible.

FOE varies from organ to organ and with levels of activity [20]. Measurements of FOE for the whole body produce a range of approximately 0.15 to 0.33 [20]. That is, the body consumes 15% to 33% of oxygen transported. The heart and brain are likely to have consistently high values of FOE during active states [20].

2.2. Doppler

Laser Doppler uses a laser of a wavelength of 770–790 nm, which is directed onto the skin surface. It is a repeatable method of studying moving blood cells in the skin circulation, and obtaining a measurement of blood flow [21]. Light that is reflected off stationary tissue undergoes no shift whilst light that is reflected off cells with velocity such as red blood cells undergoes a Doppler shift. The degree of Doppler shift is then proportional to the velocity of the cells. This light is randomly reflected back out of the tissue and onto a photodetector which calculates the average velocity of cells within the tissue. Laser Doppler flowmetry has been used to study the peripheral microvasculature of the skin [22].

Stark et al. used the Periflux 5001 Laser Doppler (Perimed AB, Järfälla, Sweden) to characterise early neonatal microvascular function, in term neonates, following preeclamptic pregnancies. They studied peripheral microvascular blood flow from 6 to 72 h of age [23]. There was a surprising gender difference. Male infants of preeclamptic women had greater microvascular blood flow at 6 h with no change over time, whereas boys of normotensive women had blood flow that increased with time. By contrast, female infants of preeclamptic mothers exhibited similar blood flows at 6 h of age as females of normotensive mothers, but this was then also followed by increased blood flow by 72 h. It was concluded that altered fetal microvascular structure and function in response to maternal preeclampsia may result in sexually dimorphic patterns of fetal growth and account for alterations in neonatal microvascular adaptation after birth.

Suiches et al. showed that the microcirculation of the neonate is subject to considerable changes in the first days of extra-uterine life by using laser Doppler flowmetry to show skin blood flow changes in the first week after birth [42]. It is also altered by the type of delivery [43] and hypoxia [44,45].

2.3. Temperature

A fall in central–peripheral temperature difference was observed in only half of sick preterm neonates treated by albumin infusion as intravascular volume expansion for hypovolaemia [24]. Although the report concluded that the inclusion of an assessment of central–peripheral temperature difference might improve the haemodynamic assessment of a preterm neonate [24], an investigation of the ability to detect low upper body blood flow in very premature infants using blood pressure (BP), capillary refill time (CRT), and central–peripheral temperature difference showed that central–peripheral temperature difference did not correlate with low SVC flow on the first day after birth and that BP and CRT were imperfect predictors of low SVC flow. The investigators concluded that future studies of cardiovascular interventions in very preterm infants should measure SVC blood flow [25].

2.4. Capillary refill time

Capillary refill time (CRT) is defined as "the time required for the return of colour after the application of a blanching pressure to a distal capillary bed." The upper normal has been accepted for some time as being 3 s in a neonate. A study of 469 preterm and term healthy neonates at 1 to 7 days of age demonstrated significant site and observer variations when CRT was measured on the chest, forehead, palm, and heel [26].

Raichur et al. reported that when two independent observers measured CRT at the forehead, chest, palm, and heel in 155 healthy term neonates [27], there was good intraobserver repeatability when CRT was measured on the chest but not the forehead, palm or heel. A prospective multicentre cohort study of 128 preterm neonates below 30 weeks gestation evaluated the sensitivity and specificity of CRT to predict low superior vena cava blood flow [25]. CRT was measured on the chest and palm after pressure was applied for 5 s. CRT>3 s had a sensitivity of 55% and a specificity of 81% for predicting low SVC flow. Thus there is a lack of evidence to support the use of CRT as a single indicator of a hypovolaemic state in a neonatal population.

2.5. Orthogonal polarisation spectral imaging (OPS) and Sidestream darkfield imaging (SDF)

Orthogonal polarisation spectral imaging (OPS) and Sidestream darkfield imaging (SDF) non-invasively visualise the microcirculation in real time at the bed-side. These are small, hand held devices emitting light at a wavelength of 548 nm. As this is within the haemoglobin absorption spectrum, red blood cells appear dark when visualised on a computer screen. An objective lens focuses the light onto a region of approximately 1 mm in diameter [28]. A thin layer of mucosal tissue is needed for image attainment in adults and children, the most convenient method being sublingual [28,29]. Although the SDF probe in commercial use (The Microscan™) is too large for neonatal mucosal visualisation, SDF imaging is the superior technique with higher quality images but has not yet been applied to neonatal research.

In premature babies, the transdermal application of OPS has provided quantitative data on the microcirculation [30]. OPS imaging has been applied to the upper arm of preterm anaemic neonates, mean gestational age 26 weeks, mean birth weight 730 g between 2 and 24 h after a blood transfusion. It showed a significant increase in capillary density at both time points indicating improved microvascular perfusion. There were no significant changes in clinical variables, such as blood pressure, heart rate, or body temperature. Conventional monitoring methods did not show any changes after transfusion, although quantitative analyses of OPS images indicated improved perfusion [31]. Increasing incubator temperature has also been shown to improve blood flow to the extremities in preterm infants with impaired microvascular perfusion [32]. In neonates with proven infection, capillary density has been shown to decrease one day prior to changes in laboratory parameters [33].

OPS and SDF imaging are potential approaches to the detection of sepsis and monitoring responses to therapies aimed at improving tissue perfusion. The main limitation is the lack of an ability to carry out continuous monitoring and changes in haemodynamics can be missed in the time periods where images are not obtained.

2.6. Peripheral perfusion index (PFI)

Pulse oximetry is widely used for monitoring arterial saturation. The signal comprises two components: one, which is arterial and pulsatile, and the other, which is non-pulsatile and originates from other light-absorbing tissues (connective tissue, bone, and venous blood). In deriving the signal for arterial saturation monitoring, only the pulsatile component is analysed. However, by computing the ratio between the pulsatile component and the non-pulsatile component of the light reaching the detector of the pulse oximetry, a peripheral perfusion index (PFI) can be calculated [34]. Proponents of the technique consider that peripheral perfusion alteration is accompanied by a variation in the pulsatile component, and, because the non-pulsatile component does not change, there is a change in the ratio, which is displayed by the monitor. Studies of body temperature gradients in critically ill adults suggest that PFI may indicate peripheral perfusion with a PFI of 1.4 correlating best with apparent hypoperfusion [35]. A study on neonates suggested a cutoff value of 1.24 [36]. However, reviewing this technology, Lima and Bakker concluded that more studies were needed to define its clinical utility [34].

3. Factors affecting peripheral haemodynamics and tissue oxygen delivery in the neonate

3.1. Blood pressure, peripheral blood flow, oxygen consumption and oxygen delivery

The amount of oxygen required by a tissue depends on the functional state of the component cells. Some tissues like the brain, liver and renal cortex have persistently high oxygen demands, while the oxygen demands of tissues like the spleen are low. Other tissues like the skeletal muscle have variable oxygen demands [16]. The relationship between cerebral DO_2 and VO_2 has been described using a biphasic model (Fig. 2), which was first developed by Cain from animal work using dogs [37] and has subsequently been demonstrated in several other animal models [38] and in critically ill adults [39,40], but not in preterm babies. During phase 'a', as oxygen delivery decreases but demand remains constant, FOE (Fig. 2), indicated by line 'c', increases to maintain aerobic metabolism and consumption remains independent of delivery [16]. However at a critical point, the FOE (line 'b') is maximum and VO_2 becomes delivery dependent with any further decrease in oxygen leading to tissue hypoxia [16]. However, the situation in vivo is likely to be more complex. VO_2 regulates DO_2 under normal physiological conditions and DO_2 is likely to vary to ensure balance between delivery and consumption, at least till critical DO_2 is reached. At this time, further decreases in DO_2 result in falling VO_2 with diminished metabolism, although not initially hypoxic tissue damage.

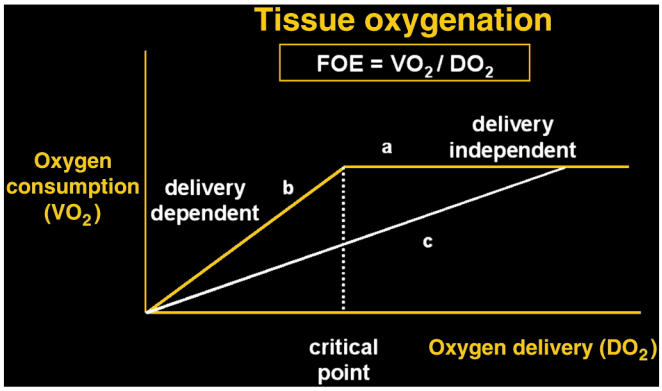

Fig. 2. Schematic representation of the biphasic relationship between oxygen delivery and oxygen consumption in tissue. (a) Indicates the normal situation when oxygen consumption (VO_2) is independent of oxygen delivery (DO_2). (b) As DO_2 decreases, VO_2 is dependent on DO_2. The slope of the line indicates the FOE, which in this case is about 0.50. (c) The slope of the line indicates the FOE in the normal situation where oxygenation is DO_2 independent, usually <0.35.

The clinical implication of this model is that decreases in DO_2 can occur without changes in function or critical damage unless DO_2 is severely diminished. As DO_2 decreases, there may be compensation (and therefore preserved VO_2) by increased FOE. The exact mechanism for this is unknown, but it has been suggested that, since oxygen diffusion to the cell is a passive process, increased oxygen extraction occurs through capillary dilatation and recruitment [18]. Studies examining this have demonstrated little or no capillary dilatation [41–43], although a theoretical model suggests that alterations in membrane diffusability may be responsible for increasing oxygen extraction [18]. Another possible mechanism is through changing oxygen–haemoglobin dissociation. As arterial oxygen tension decreases, the affinity of oxygen to haemoglobin decreases dramatically due to the sigmoid shaped relationship. The position of the oxygen–haemoglobin dissociation changes with changing pH, as may occur if there is local hypoxia and consequent acidosis.

3.2. The type of haemoglobin

Fetal haemoglobin (HBF) has a much greater affinity for oxygen than adult haemoglobin (HbA), accounting for the ability of the fetal circulation to attract oxygen from the maternal circulation (Fig. 3). The oxygen is then delivered to the fetal tissues because of the local decrease in pH in the fetal microcirculation. HbA has a lower affinity to oxygen, and this probably accounts for the rapid improvement when a premature baby is transfused with blood, which contains adult haemoglobin. The switch from fetal haemoglobin (HBF) to adult haemoglobin is progressive from about 30 weeks onwards [44]. However, even at 40 weeks, only about 20% of circulating haemoglobin is HbA.

In a study of hypotensive preterm infants between 26 and 29 weeks' gestation, there was a significant correlation between mean blood pressure and peripheral blood flow [7,9]. Preterm infants with a low mean arterial blood pressure of 25 mm Hg had a median peripheral blood flow of 4.6 ml/100 ml min^{-1}, which was significantly lower than the median peripheral blood flow (8.3 ml/100 ml min^{-1}) of infants with a higher mean arterial blood pressure of 39 mm Hg [9]. After treatment of hypotension, there were increases in the median forearm oxygen delivery from 38 to 64 μmol/100 ml min^{-1}, and in forearm oxygen consumption from 11 to 22 μmol/100 ml min^{-1} [9]. Several variables were similar in the normotensive and the hypotensive groups: FOE, forearm arterial resistance, blood lactate concentrations and

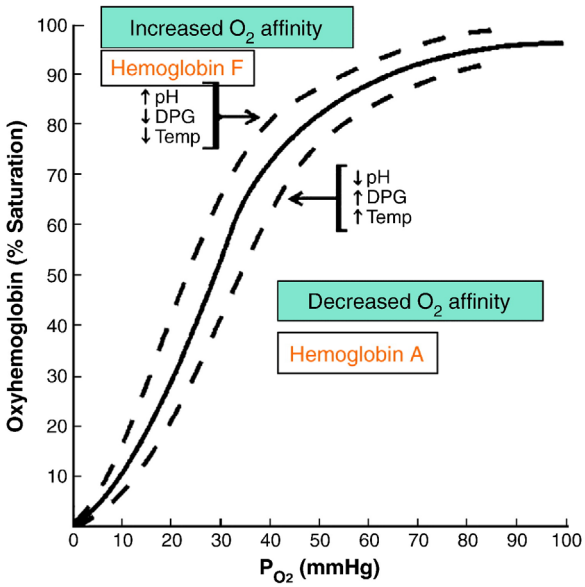

Fig. 3. The oxygen-dissociation curve.

central (core) temperatures. However, the median skin temperature of the hypotensive group was 0.3 °C lower ($p = 0.05$) than that of the normotensive group. After therapies (fluid and dopamine) intended to correct hypotension, there was a significant increase in median Hb flow from 10.2 to 16.6 μmol/100 ml min^{-1}. This study, like that of others [45], showed a weak relationship between systemic arterial blood pressure and peripheral blood flow. However, the effect may not have been primarily on blood flow because the treatment of hypotension consisted mainly of treatment with dopamine, which is known to stimulate metabolic activity particularly within muscle tissue, and it is possible that the increase in blood flow and increased DO_2 was a consequence of increased VO_2 because of increased metabolism [9].

3.3. The transitional circulation: flow, pressure and vascular resistance

The combination of physiological changes involved in transition from intra- to extra-uterine life, and immaturity of the cardiopulmonary system complicates the process of neonatal tissue perfusion. In utero, 85% of the fetal circulation bypasses the lungs through the foramen ovale and the ductus arteriosus. Suprasystemic pulmonary vascular resistance maintains this flow pattern. When oxygen is inhaled with the first breath, pulmonary vascular resistance (and therefore pulmonary artery pressure) is reduced, allowing transition from the fetal to neonatal circulation with blood now flowing through the pulmonary circulation. The transition is completed when the ductus arteriosus and the foramen ovale closed. Pulmonary vascular resistance and artery pressures can remain elevated and the ductus arteriosus can remain open up to 6 weeks after birth or longer. The foramen ovale can remain patent for several years.

Tissue oxygen delivery is by the arterial blood and is mostly carried bound to haemoglobin. Tissue oxygen delivery therefore relies on the haemoglobin concentration of blood, the oxygenation of the arterial blood and the rate of flow of that blood through the tissues. Peripheral oxygen delivery is determined by peripheral blood flow (PBF) and arterial oxygen content. By analogy with Ohm's law,

$$\textit{Forearm blood flow} = (\textit{mean arterial blood pressure} - \textit{venous pressure}) \div \textit{Periph eral resistance}$$

Thus PBF is related to vascular resistance and blood pressure, which in turn depends on cardiac function; arterial oxygen content depends on the blood Hb concentration and arterial pO_2. As blood flow is related to vascular resistance and blood pressure, there are a number of other factors that may influence blood flow and thus oxygen delivery to the peripheral tissues. These include blood gases, peripheral temperature, arterial Hb concentration, and cardiac function. The first few hours after birth is a period of great instability for the critically ill preterm infant when blood pressure, left ventricular output and systemic blood flow are all low [45–47]. PBF and thus oxygen delivery may be inadequate. Peripheral fractional oxygen extraction (FOE), the ratio of oxygen consumption to oxygen delivery [15], gives information on the adequacy of tissue oxygen provision. An elevated FOE (usually below 0.30, indicating that about 1/3 of delivered oxygen is consumed in the course of tissue metabolism) most likely represents decreased oxygen delivery, which may be due to reduced blood flow (poor perfusion) or reduced arterial oxygen content (hypoxaemia).

3.4. Viscosity

Viscosity describes a fluid's internal resistance to flow and has an important role in peripheral haemodynamics. Red blood cells (and haematocrit) are not the only factors affecting blood viscosity, although red blood cells contribute significantly. Polycythaemia is a result of an increase in red cell mass, with a decreased, normal, or increased plasma volume. Neonatal polycythaemia is defined as a haematocrit above or equal to 65%. The haematocrit normally peaks at 4–6 h of life, then drops slowly over the next 12–18 h and at 24 h it is similar to the value at birth. After this point it remains relatively stable. Red blood cells are the most prominent particles suspended in the blood and in neonates have greater deformability than in adults. Additionally, acidosis leads to fluid entering red cells and thus altering their shape. Polycythaemia and hyperviscosity are associated with alterations in organ blood flow due to decreased organ blood flow as a result of changes in red cell mass. These changes are caused by the movement of fluid out of the intravascular space [48]. Linderkamp et al. showed a relationship between blood viscosity and haematocrit in the neonate and that peripheral blood flow, blood pressure and peripheral resistance of preterm neonates were all influenced by blood volume and blood viscosity [49]. Hb concentration has been shown to be one of the variables that influenced peripheral FOE but not peripheral blood flow [50].

3.5. Anaemia

The physiological effects of anaemia in the preterm infant are complex and indications for blood transfusions in preterm infants are controversial. Wardle et al. [51] hypothesised that a measure of the adequacy of tissue oxygenation may be a better guide to the need for transfusions than currently used criteria. They considered whole blood lactate concentration and peripheral FOE. Mean FOE was significantly higher in symptomatic (0.425 ± 0.06) but not asymptomatic (0.334 ± 0.05) compared to controls (0.352 ± 0.06). After transfusion there was a significant fall in FOE in symptomatic infants to 0.367 ± 0.06 but there was no change in infants who were asymptomatic. FOE correlated with other measures known to reflect the adequacy of oxygen availability during anaemia, suggesting that peripheral FOE may be suitable as a guide to the need for blood transfusions in preterm infants.[52] However, there was only a weak correlation between Hb and FOE. The explanation for this observation is likely to be that the total Hb concentration is a relatively poor indicator of the adequacy of the provision of oxygen to the tissues, discussed in detail by Holland et al. [53], and may not wholly reflect oxygen availability to the tissues. A better definition of anaemia is the inadequacy of Hb-determined oxygen availability to meet tissue requirements. FOE may be a clinically useful additional measurement because it was shown to be highest in babies who had symptoms attributable to anaemia.

In contrast to the effect of treating hypotension, anaemia has no apparent effect on forearm tissue oxygenation of preterm infants: forearm blood flow and oxygen consumption does not change after transfusion, regardless of whether babies have symptoms attributable to anaemia [54]. However, a significant positive correlation exists between forearm blood flow and postnatal age, which fits with observations made in animals, e.g. the fetal horse where there is a marked increase in systemic blood pressure and metatarsal blood flow with increasing gestation, associated with a fall in vascular resistance [55]. In a study to investigate factors determining peripheral blood flow and oxygen extraction in sick, newborn very low birth weight infants shortly after birth, the Hb concentration was found to influence peripheral FOE but not PBF. However, none of the babies in this study were extremely anaemic [47].

Using SRS NIRS to study peripheral oxygenation in term neonates, Pichler et al. [56] found no change in DO_2 with increasing age, but VO_2 and FOE increased and the tissue oxygenation index (TOI) decreased, in a similar manner to SvO_2 [11].

On the first day after delivery, peripheral TOI was significantly lower and peripheral FOE was significantly higher in babies of mothers who had smoked compared to those of non-smokers. DO_2 also tended to be lower and VO_2 tended to be higher in the babies of smokers, suggesting that smoking influences peripheral oxygenation on the first day. All differences had disappeared by the following day [57]. There is also evidence of oxygenation favouring central organs. In term infants, cerebral (c-) TOI (70.4%) was found to be higher than peripheral (p-) TOI measured at the calf (62.1%) with a c-TOI/p-TOI ratio of 1.14 ± 0.14 [58].

3.6. Vascular tone

Studies in an acute haemorrhagic rat model demonstrated that the administration of oxygen increased peripheral vascular resistance, without influencing renal or splanchnic perfusion and improved blood pressure [59,60].

These findings suggest that oxygen has a marked effect on vascular tone even in the sick, immature, ventilated human infant. The mechanism by which oxygen induces these changes is not clear. It is possible that the perfusion of capillaries is modulated by precapillary metarterioles, which are sensitive to changes in arterial paO_2. It has been suggested that these vessels respond to an increase in paO_2 by decreasing functional capillary density by redistribution of capillary blood flow, possibly through high-flow capillaries [61]. Thus, high values for paO_2 could be associated with reduced tissue blood flow at the microvascular level and a corresponding increase in peripheral oxygen extraction. This hypothesis does not explain the exact mechanism. One plausible mechanism for oxygen-induced vasoconstriction involves reactive oxygen species neutralising nitric oxide, a potent endogenous vasodilator [60]. Some evidence for this hypothesis comes from studies that demonstrated reduced vascular tone when levels of reactive oxygen species are reduced [61].

4. Key guidelines

Clinicians should take account of the complexity of peripheral tissue oxygen delivery. Cardiac function, blood gases, Hb, and peripheral temperature all play a part in determining blood flow and oxygen extraction in the sick, preterm infant. Blood pressure appears to be less important. Other factors are likely also to play a role, such as the administration of vasoactive medications and ventilation strategies, which affect blood gases and cardiac output by changing the intrathoracic pressure. Central blood pressure is a poor surrogate measurement for the adequacy of oxygen delivery to the periphery. Direct measurement of PBF or tissue metabolism using near-infrared spectroscopy or other means would probably give more useful information.

5. Research directions

Considerable information about the response of the peripheral circulation has been obtained using NIRS with venous occlusion [1,9,11,19,20,50]. Although these measurements were validated against blood co-oximetry in human adults [1] and infants [11], they can only be made intermittently by a trained operator and are thus not appropriate for general clinical use. Further research is needed to find other better measures of peripheral perfusion and oxygenation which may be easily and continuously monitored, and which could be useful in a clinical setting.

References

[1] Yoxall CW, Weindling AM. Measurement of venous oxyhaemoglobin saturation in the adult human forearm by near infrared spectroscopy with venous occlusion. Med Biol Eng Comput 1997 Jul;35(4):331–6.
[2] Irwin MS, Thorniley MS, Dore CJ, Green CJ. Near infra-red spectroscopy: a non-invasive monitor of perfusion and oxygenation within the microcirculation of limbs and flaps. Br J Plast Surg 1995 Jan;48(1):14–22.
[3] Fantini S, Hueber D, Franceschini MA, Gratton E, Rosenfeld W, Stubblefield PG, et al. Non-invasive optical monitoring of the newborn piglet brain using continuous-wave and frequency-domain spectroscopy. Phys Med Biol 1999 Jun;44(6):1543–63.
[4] Stankovic MR, Maulik D, Rosenfeld W, Stubblefield PG, Kofinas AD, Gratton E, et al. Role of frequency domain optical spectroscopy in the detection of neonatal brain hemorrhage—a newborn piglet study. J Matern Fetal Med 2000 Mar-Apr;9(2):142–9.
[5] Tsuji M, duPlessis A, Taylor G, Crocker R, Volpe JJ. Near infrared spectroscopy detects cerebral ischemia during hypotension in piglets. Pediatr Res 1998 Oct;44(4):591–5.
[6] Alfano RR, Demos SG, Galland P, Gayen SK, Guo Y, Ho PP, et al. Time-resolved and nonlinear optical imaging for medical applications. Ann N Y Acad Sci 1998 Feb 9;838:14–28.
[7] Victor S, Weindling AM. Near-infrared spectroscopy and its use for the assessment of tissue perfusion in the neonate. In: Kleinman CSSI, editor. Haemodynamics and Cardiology: Neonatology Questions and Controversy. Elsevier; 2008.
[8] Edwards AD, Richardson C, van der Zee P, Elwell C, Wyatt JS, Cope M, et al. Measurement of hemoglobin flow and blood flow by near-infrared spectroscopy. J Appl Physiol 1993 Oct;75(4):1884–9.
[9] Wardle SP, Yoxall CW, Weindling AM. Peripheral oxygenation in hypotensive preterm babies. Pediatr Res 1999 Mar;45(3):343–9.
[10] De Blasi RA, Ferrari M, Natali A, Conti G, Mega A, Gasparetto A. Noninvasive measurement of forearm blood flow and oxygen consumption by near-infrared spectroscopy. J Appl Physiol 1994 Mar;76(3):1388–93.
[11] Yoxall CW, Weindling AM. The measurement of peripheral venous oxyhemoglobin saturation in newborn infants by near infrared spectroscopy with venous occlusion. Pediatr Res 1996 Jun;39(6):1103–6.
[12] Naulaers G, Meyns B, Miserez M, Leunens V, Van Huffel S, Casaer P, et al. Use of tissue oxygenation index and fractional tissue oxygen extraction as non-invasive parameters for cerebral oxygenation. A validation study in piglets. Neonatology 2007;92(2):120–6.
[13] Pichler G, Grossauer K, Peichl E, Gaster A, Berghold A, Schwantzer G, et al. Combination of different noninvasive measuring techniques: a new approach to increase accuracy of peripheral near infrared spectroscopy. J Biomed Opt 2009 Jan-Feb;14(1):014014.
[14] Pichler G, Wolf M, Roll C, Weindling MA, Greisen G, Wardle SP, et al. Recommendations to increase the validity and comparability of peripheral measurements by near infrared spectroscopy in neonates. 'Round table', section of haematology, oxygen transport and microcirculation, 48th annual meeting of ESPR, Prague 2007. Neonatology 2008;94(4):320–2.
[15] Yoxall CW, Weindling AM. Measurement of cerebral oxygen consumption in the human neonate using near infrared spectroscopy: cerebral oxygen consumption increases with advancing gestational age. Pediatr Res 1998 Sep;44(3):283–90.
[16] Leach RM, Treacher DF. The pulmonary physician in critical care * 2: oxygen delivery and consumption in the critically ill. Thorax 2002 Feb;57(2):170–7.
[17] Greisen G. Cerebral blood flow and energy metabolism in the newborn. Clin Perinatol 1997 Sep;24(3):531–46.
[18] Hayashi T, Watabe H, Kudomi N, Kim KM, Enmi J, Hayashida K, et al. A theoretical model of oxygen delivery and metabolism for physiologic interpretation of quantitative cerebral blood flow and metabolic rate of oxygen. J Cereb Blood Flow Metab 2003 Nov;23(11):1314–23.
[19] Wardle SP, Yoxall CW, Weindling AM. Determinants of cerebral fractional oxygen extraction using near infrared spectroscopy in preterm neonates. J Cereb Blood Flow Metab 2000 Feb;20(2):272–9.
[20] Wardle SP, Yoxall CW, Weindling AM. Cerebral oxygenation during cardiopulmonary bypass. Arch Dis Child 1998 Jan;78(1):26–32.
[21] Yvonne-Tee GB, Rasool AH, Halim AS, Rahman AR. Reproducibility of different laser Doppler fluximetry parameters of postocclusive reactive hyperemia in human forearm skin. J Pharmacol Toxicol Methods 2005 Sep-Oct;52(2):286–92.
[22] Kubli S, Feihl F, Waeber B. Beta-blockade with nebivolol enhances the acetylcholine-induced cutaneous vasodilation. Clin Pharmacol Ther 2001 Apr;69(4):238–44.
[23] Stark MJ, Clifton VL, Wright IM. Neonates born to mothers with preeclampsia exhibit sex-specific alterations in microvascular function. Pediatr Res 2009 Mar;65(3):292–5.

[24] Lambert HJ, Baylis PH, Coulthard MG. Central–peripheral temperature difference, blood pressure, and arginine vasopressin in preterm neonates undergoing volume expansion. Arch Dis Child Fetal Neonatal Ed 1998 Jan;78(1):F43–5.
[25] Osborn DA, Evans N, Kluckow M. Clinical detection of low upper body blood flow in very premature infants using blood pressure, capillary refill time, and central–peripheral temperature difference. Arch Dis Child Fetal Neonatal Ed 2004 Mar;89(2): F168–73.
[26] Strozik KS, Pieper CH, Roller J. Capillary refilling time in newborn babies: normal values. Arch Dis Child Fetal Neonatal Ed 1997 May;76(3):F193–6.
[27] Raju NV, Maisels MJ, Kring E, Schwarz-Warner L. Capillary refill time in the hands and feet of normal newborn infants. Clin Pediatr (Phila) 1999 Mar;38(3):139–44.
[28] Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ, Messmer K, et al. Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 1999 Oct;5(10):1209–12.
[29] Nadeau RGW. Orthogonal polarization spectral imaging: state of the art. In: Messmer K, editor. Orthogonal polarization spectral imaging. Basel: Karger; 2000. p. 9–20. 24.
[30] Genzel-Boroviczeny O, Strotgen J, Harris AG, Messmer K, Christ F. Orthogonal polarization spectral imaging (OPS): a novel method to measure the microcirculation in term and preterm infants transcutaneously. Pediatr Res 2002 Mar;51(3): 386–91.
[31] Genzel-Boroviczeny O, Christ F, Glas V. Blood transfusion increases functional capillary density in the skin of anemic preterm infants. Pediatr Res 2004 Nov;56(5): 751–5.
[32] Genzel-Boroviczeny O, Seidl T, Rieger-Fackeldey E, Abicht J, Christ F. Impaired microvascular perfusion improves with increased incubator temperature in preterm infants. Pediatr Res 2007 Feb;61(2):239–42.
[33] Weidlich K, Kroth J, Hiedl CN, Bauer A, Christ F, Genzel-Boroviczeny O. Changes in microcirculation as early markers for infection in preterm infants — an observational prospective study. Pediatr Res 2009 Jul 1.
[34] Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med 2005;31:1316–26.
[35] Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 2002;30:1210–3.
[36] De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002;161:561–2.
[37] Cain SM. Oxygen supply dependency in the critically ill — a continuing conundrum. Adv Exp Med Biol 1992;317:35–45.
[38] Adams RP, Dieleman LA, Cain SM. A critical value for O_2 transport in the rat. J Appl Physiol 1982 Sep;53(3):660–4.
[39] Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH. Oxygen delivery and consumption in patients with hyperdynamic septic shock. Crit Care Med 1987 Jan;15(1):26–8.
[40] Mohsenifar Z, Goldbach P, Tashkin DP, Campisi DJ. Relationship between O_2 delivery and O_2 consumption in the adult respiratory distress syndrome. Chest 1983 Sep;84(3):267–71.
[41] Bereczki D, Wei L, Otsuka T, Acuff V, Pettigrew K, Patlak C, et al. Hypoxia increases velocity of blood flow through parenchymal microvascular systems in rat brain. J Cereb Blood Flow Metab 1993 May;13(3):475–86.
[42] Pinard E, Engrand N, Seylaz J. Dynamic cerebral microcirculatory changes in transient forebrain ischemia in rats: involvement of type I nitric oxide synthase. J Cereb Blood Flow Metab 2000 Dec;20(12):1648–58.
[43] Seylaz J, Charbonne R, Nanri K, Von Euw D, Borredon J, Kacem K, et al. Dynamic in vivo measurement of erythrocyte velocity and flow in capillaries and of microvessel diameter in the rat brain by confocal laser microscopy. J Cereb Blood Flow Metab 1999 Aug;19(8):863–70.
[44] Bard H, Widness JA. The life span of erythrocytes transfused to preterm infants. Pediatr Res 1997 Jul;42(1):9–11.
[45] Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. J Pediatr 1996 Oct;129(4): 506–12.
[46] Earley A, Fayers P, Ng S, Shinebourne EA, de Swiet M. Blood pressure in the first 6 weeks of life. Arch Dis Child 1980 Oct;55(10):755–7.
[47] Evans N, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. Arch Dis Child Fetal Neonatal Ed 1996 Mar;74(2): F88–94.
[48] Linderkamp O, Versmold HT, Riegel KP, Betke K. Contributions of red cells and plasma to blood viscosity in preterm and full-term infants and adults. Pediatrics 1984 Jul;74(1):45–51.
[49] Linderkamp O, Strohhacker I, Versmold HT, Klose H, Riegel KP, Betke K. Peripheral circulation in the newborn: interaction of peripheral blood flow, blood pressure, blood volume, and blood viscosity. Eur J Pediatr 1978 Sep 8;129(2):73–81.
[50] Kissack CM, Weindling AM. Peripheral blood flow and oxygen extraction in the sick, newborn very low birth weight infant shortly after birth. Pediatr Res 2009 Apr;65(4):462–7.
[51] Wardle SP, Garr R, Yoxall CW, Weindling AM. A pilot randomised controlled trial of peripheral fractional oxygen extraction to guide blood transfusions in preterm infants. Arch Dis Child Fetal Neonatal Ed 2002 Jan;86(1):F22–7.
[52] Wardle SP, Weindling AM. Peripheral fractional oxygen extraction and other measures of tissue oxygenation to guide blood transfusions in preterm infants. Semin Perinatol 2001 Apr;25(2):60–4.
[53] Holland RA, van Hezewikj W, Zubzanda J. Velocity of oxygen uptake by partly saturated adult and fetal human red cells. Respir Physiol 1977 May;29(3):303–14.
[54] Wardle SP, Yoxall CW, Crawley E, Weindling AM. Peripheral oxygenation and anemia in preterm babies. Pediatr Res 1998 Jul;44(1):125–31.
[55] Giussani DA, Forhead AJ, Fowden AL. Development of cardiovascular function in the horse fetus. J Physiol 2005 Jun 15;565(Pt 3):1019–30.
[56] Pichler G, Grossauer K, Klaritsch P, Kutschera J, Zotter H, Muller W, et al. Peripheral oxygenation in term neonates. Arch Dis Child Fetal Neonatal Ed 2007 Jan;92(1): F51–2.
[57] Pichler G, Heinzinger J, Klaritsch P, Zotter H, Muller W, Urlesberger B. Impact of smoking during pregnancy on peripheral tissue oxygenation in term neonates. Neonatology 2008;93(2):132–7.
[58] Grossauer K, Pichler G, Schmolzer G, Zotter H, Mueller W, Urlesberger B. Comparison of peripheral and cerebral tissue oxygenation index in neonates. Arch Dis Child Fetal Neonatal Ed 2009 Mar;94(2):F156.
[59] Adir Y, Bitterman N, Katz E, Melamed Y, Bitterman H. Salutary consequences of oxygen therapy on the long-term outcome of hemorrhagic shock in awake, unrestrained rats. Undersea Hyperb Med 1995 Mar;22(1):23–30.
[60] Bitterman H, Brod V, Weisz G, Kushnir D, Bitterman N. Effects of oxygen on regional hemodynamics in hemorrhagic shock. Am J Physiol 1996 Jul;271(1 Pt 2): H203–11.
[61] Granger HJ, Goodman AH, Cook BH. Metabolic models of microcirculatory regulation. Fed Proc 1975 Oct;34(11):2025–30.