Monitoring Tissue Perfusion, Oxygenation, and Metabolism in Critically Ill Patients

Chest - Volume 143, Issue 6 (June 2013) - Copyright © 2013 The American College of Chest Physicians

MDC Extra Article: This additional article is not currently cited in MEDLINE®, but was found in MD Consult's full-text literature database.

Postgraduate Education Corner

Monitoring Tissue Perfusion, Oxygenation, and Metabolism in Critically Ill Patients

Nasirul J. Ekbal, MBBS
Alex Dyson, PhD
Claire Black, MSc
Mervyn Singer, MD

Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, London, England

* Correspondence to: Prof Mervyn Singer, MD, Bloomsbury Institute of
Intensive Care Medicine, University College London, Cruciform Bldg, Gower
St, London, WC1E 6BT, England

E-mail address: m.singer@ucl.ac.uk

Manuscript received July 23, 2012, accepted November 27, 2012

Funding/Support: The authors work at University College London Hospitals/University College London, which receives a proportion of its funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centre's funding scheme. Dr Ekbal is funded by the Medical Research Council and Claire Black by the UK National Institute for Health Research. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.
Alterations in oxygen transport and use are integral to the development of multiple organ failure; therefore, the ultimate goal of resuscitation is to restore effective tissue oxygenation and cellular metabolism. Hemodynamic monitoring is the cornerstone of management to promptly identify and appropriately manage (impending) organ dysfunction. Prospective randomized trials have confirmed outcome benefit when preemptive or early treatment is directed toward maintaining or restoring adequate tissue perfusion. However, treatment end points remain controversial, in large part because of current difficulties in determining what constitutes “optimal.” Information gained from global whole-body monitoring may not detect regional organ perfusion abnormalities until they are well advanced. Conversely, the ideal “canary” organ that is readily accessible for monitoring, yet offers an early and sensitive indicator of tissue “unwellness,” remains to be firmly identified. This review describes techniques available for real-time monitoring of tissue perfusion and metabolism and highlights novel developments that may complement or even supersede current tools.

Abbreviations

ATP
adenosine triphosphate

COX
cytochrome oxidase

LDF
laser Doppler flowmetry

MRS
magnetic resonance spectroscopy

NADH
reduced form of nicotinamide adenine dinucleotide

NIRS
near-infrared resonance spectroscopy

PCr
phosphocreatine

Pi
inorganic phosphate

SDF
sidestream dark field

StO₂
tissue oxygen saturation

tPO₂
tissue oxygen tension

The role of the circulation is to deliver adequate oxygen and nutrients to meet tissue metabolic demands. Circulatory shock represents inadequate cellular oxygen supply (hypoxia), and/or impaired oxygen use (dysoxia). This can, if not corrected promptly, progress to organ dysfunction and failure. Early resuscitation regimens targeted toward prespecified hemodynamic values improve outcomes in patients with severe sepsis or undergoing high-risk surgery. This strategy does not, however, benefit patients in established organ failure. Thus, a relatively narrow window of opportunity exists to provide tissues with sufficient oxygen to restore cellular metabolism and prevent/ameliorate further organ dysfunction.

Assessment of the adequacy of oxygen delivery and use is therefore key to early identification and intervention. Traditional markers such as urine output and BP remain in common use to evaluate tissue hypoperfusion yet are nonspecific and often change belatedly. Newer techniques, although superior, still have limitations. For example, mixed or central venous oxygen saturation reflects the global oxygen supply-demand balance yet may not recognize any local mismatch, particularly in “canary organs” whose perfusion may be compromised before others. Organs vary in their metabolic activity and the blood flow they receive. As exemplars, 70% to 75% of hepatic blood flow arises from the portal vein that carries blood already deoxygenated after passage through the gut. Renal blood flow accounts for 20% to 25% of cardiac output yet only consumes 7% to 8% of total oxygen consumption. The kidney regions also vary markedly in terms of oxygen delivery and metabolic rate, resulting in marked intrarenal differences in oxygen tension. Oxygen extraction by the resting heart exceeds 55%, so substantial increases in myocardial oxygen supply require significant (up to fivefold) increases in coronary blood flow. Hyperlactatemia, the product of an imbalance between lactate production and metabolism, is also frequently used as a marker of tissue hypoperfusion. Although sensitive, it too is a somewhat nonspecific marker of global tissue hypoxia.

Recognition of the limitations of global “whole body” monitoring techniques has stimulated efforts to develop devices that evaluate regional tissue perfusion and oxygenation. Characteristics of the ideal monitoring system are summarized in Table 1. For any monitor of a regional bed, an important consideration is whether it reflects changes occurring in other organs during a systemic insult. Preferably, this should occur concurrently or, ideally, beforehand to provide an early warning system enabling prompt intervention and correction of the problem. This is particularly pertinent when using an accessible site such as mouth (sublingual), bladder, muscle, or subcutaneous tissue as a surrogate for deeper “vital” organs such as liver, brain, and kidney. This is complicated by physiologic differences specific to certain organs, as described previously, and to pathophysiologic or compensatory mechanisms.

Table 1 -- Key Properties of an Ideal Monitor for Organ Hypoperfusion

| Provides accurate and reproducible results |
| High sensitivity and specificity delivered at an early point |
| Easy to use |
| Noninvasive or minimally invasive and causes no harm |
| Provides continuous and interpretable data |
| Not only reflects regional data but also useful as an early indicator of systemic hypoperfusion |
| Provides information to guide therapeutic interventions |

Techniques that monitor regional perfusion target different compartments (Fig 1). This review highlights key principles underlying these techniques and their current usefulness. Some are available as clinical tools, whereas others are still at the animal or early human testing stage. No commercial device has yet been enshrined as “standard of care” within (inter)national management protocols. This is often because of their relative lack of user friendliness as a bedside tool, and/or an inability to deliver quantitative data, and/or a paucity of multicenter trial outcomes data to make an overwhelming case for their incorporation as a routinely used bedside device.
Figure 1  Techniques for monitoring regional perfusion. LDF = laser Doppler flowmetry; MRS = magnetic resonance spectroscopy; NIRS = near-infrared resonance spectroscopy; \(O_2\) = oxygen; SDF = sidestream dark field; \(tPO_2\) = tissue oxygen tension.

Microcirculation Measurements

The microcirculation is defined as vessels with diameters <100 μm (ie, arterioles, capillaries, and venules).[10] Several techniques can monitor or visualize the microcirculation in situ and are available for patient use.

Microcirculatory Hemoglobin Oxygenation

Near-infrared resonance spectroscopy (NIRS) is a noninvasive optical technique based on passage of infrared light (680-800 nm) through biologic tissues. By the Beer-Lambert law, the NIRS signal is limited to interrogating small vessels (<1 mm diameter) only. The amount of light recovered after illumination depends on the degree of scattering within the tissue and by the three molecules known to affect near-infrared light absorption, namely hemoglobin, myoglobin, and mitochondrial cytochrome oxidase (COX). Differential absorption patterns depend on whether these chromophores are oxygen bound (Fig 2). Predefined algorithms generate concentrations; as the contributions of myoglobin and COX to light attenuation is relatively minor, NIRS predominantly assesses microvascular oxyhemoglobin and deoxyhemoglobin. Some specialized machines can generate a COX signal (see later).
**Figure 2** NIRS absorption spectra for HbO$_2$ and Hb, MbO$_2$, and Mb. The spectrum for COx represents the oxidized minus the reduced form. Line A and line B correspond to peak Hb and HbO$_2$ absorption wavelength, respectively. Line C corresponds to the isobestic point. COx = cytochrome oxidase; Hb = deoxyhemoglobin; HbO$_2$ = oxyhemoglobin; Mb = deoxymyoglobin; MbO$_2$ = oxymyoglobin. See Figure 1 legend for expansion of other abbreviation.

Tissue oxygen saturation (StO$_2$) is calculated from the fractions of oxyhemoglobin and deoxyhemoglobin. As 75% of blood within skeletal muscle is venous, the NIRS StO$_2$ value mostly represents local venous oxyhemoglobin saturation rather than that of tissue. It thus reflects both local supply-demand balance and any arteriovenous shunting present.

The thenar eminence, a superficial muscle with little interference from overlying fat and subcutaneous tissue, is the main site used for StO$_2$ monitoring. Edema may result in artifact and be problematic, with venous congestion, hypoalbuminemia, and/or increased endothelial leak. Brain StO$_2$ monitoring has been successfully applied in neonates [11] and animal models [12] but is more challenging in adults because of interference from scalp blood flow. [13] An issue with thenar muscle NIRS monitoring is the wide range (52%-98%) found in healthy subjects. [14] NIRS values are also affected by age, BMI, sex, race, and smoking.

As changes in StO$_2$ reflect changes in flow and/or metabolism, a proportional change may leave StO$_2$ unaltered. This may explain why absolute values fell outside the normal range in severely shocked trauma patients [14] and in septic shock only when oxygen delivery fell markedly. [15] , [16]

More utility can be derived from a dynamic vascular occlusion test to evaluate the StO$_2$ response to a sudden loss of oxygen supply. [17] , [18] The rate of fall of StO$_2$ following arterial and/or venous occlusion is decreased in shocked compared with nonshocked septic patients or healthy volunteers The StO$_2$ recovery slope seen on reperfusion evaluates both the limb's oxygen content and the capacity to recruit arterioles and venules (microvascular reserve). The slope may be altered by different pathologies or therapeutic interventions (Fig 3). In sepsis, the alterations seen suggest both microcirculatory dysfunction and impaired use of oxygen (mitochondrial dysfunction ± reduced metabolism). [17] , [18]
Figure 3  NIRS derived changes in thenar StO\textsubscript{2} following arterial and venous occlusion in septic patients. a = baseline measurements; b = SI; c = reperfusion; d = reactive hyperemia; e = return to baseline. SI = stagnant ischemia; StO\textsubscript{2} = tissue oxygen saturation. See Figure 1 legend for expansion of other abbreviation.

**Laser Doppler Flowmetry**

Laser Doppler flowmetry (LDF) uses wavelengths of visible and infrared light to measure tissue perfusion by exploiting changes in wavelength frequency (Doppler shifts) that moving erythrocytes impart to light. The chosen wavelength is usually 780 nm, as this is near the isobestic point (800 nm) where the absorption spectra of oxyhemoglobin and deoxyhemoglobin intersect (Fig 2); changes in blood oxygenation have little effect on measurement. Laser light is delivered fiberoptically and diffusely scattered by stationary tissue, with some being reflected back with no change in wavelength. However, photons that encounter moving RBCs experience a Doppler shift, which is also detected. This signal is proportional to perfusion (or flux) and represents microvascular blood cell transport.\[19\]

In porcine hemorrhagic shock, changes in skin LDF flux occurred earlier than heart rate, BP, arterial lactate, or base deficit.\[20\] After abdominal surgery or endotoxin administration, no effect was seen in intestinal microcirculation despite fluid resuscitation and norepinephrine to restore BP and regional blood flow to baseline levels or above. \[21,\] , \[22,\] By contrast, titrating norepinephrine to obtain a mean arterial pressure of 90 mm Hg in patients with established septic shock significantly increased red cell flux to deltoid muscle.\[23\]

LDF monitoring has several drawbacks. Outputs are obtained as arbitrary perfusion units and not absolute blood flow; thus, only trends can be assessed. The result is a net vector flow in line with the direction of the incoming Doppler-shifted signal. As this signal may contain components from blood flowing through multiple vessels at varying angles to the probe, results may vary considerably. This may also be seen in tissues with a heterogeneous microcirculation. It is thus important to fix the probe in position or to use a multifiber array to increase the surface area being captured.

**Microvideoscopic Techniques**

Historically, intravital microscopy was considered the gold standard for microcirculation imaging. However, this is restricted to transilluminable tissues, such as the nailfold bed, or requires specific dyes not licensed for human use. Videomicroscopic imaging devices such as sidestream dark field (SDF) imaging have supplanted intravital microscopy as a clinical tool to visualize the microcirculation. \[24,\] , \[25,\] Light is reflected by superficial tissue layers but absorbed by hemoglobin contained within erythrocytes. A 530-nm wavelength is usually chosen, as this corresponds to the other isobestic point in the absorption spectra of deoxyhemoglobin and oxyhemoglobin. Absorbed light is reflected back, allowing erythrocytes to be viewed as gray/black bodies moving against a white background (Fig 4). Tissue perfusion can be characterized in individual vessels or averaged over an area within the device's field of vision. Studies have mainly focused upon the sublingual circulation, although brain, eye, and digestive tract have also been assessed in patient studies. \[26,\] , \[27,\]
The microcirculation cannot be monitored continuously with SDF, although repeated images are generally obtainable and reproducible. Recorded video clips are measured offline using software that provides a semiquantitative analysis. SDF is operator dependent, so adequate training is needed to ensure that image acquisition is satisfactory and video clips objectively analyzed. A recent study found one-third of recordings by a trained investigator were technically excellent, whereas a further one-third showed pressure artifact from the probe on the tissue surface.[28] Recent design improvements may overcome such issues.[29]

Notwithstanding these caveats, interesting data have been generated during surgery in shocked patients and animal models. The sickest septic patients presenting to an ED had the greatest sublingual microcirculatory abnormalities, and this prognosticated for eventual outcome.[30] In a follow-up study investigating early goal-directed therapy resuscitation, an association was seen between microcirculatory improvement and better outcomes.[31] This may have been confounded by greater norepinephrine use in patients with poor outcome. In other human septic shock studies, no change in preexisting sublingual microvascular flow abnormalities was seen with norepinephrine, although considerable interindividual variation was reported.[23],[32]

Hypoperfusion and increased flow heterogeneity (rather than the expected hyperdynamic flow pattern) are the main characteristics of the sublingual microcirculation in patients with established septic shock.[33] Similar changes were seen in a cardiogenic shock model, although the cerebral microcirculation remained unaffected.[34] Differences were also seen between sublingual and intestinal microcirculations in septic patients.[35] Nitroglycerin in septic patients[36] and fluid loading plus dopexamine in high-risk surgical patients[37] improved microcirculatory flow, yet no outcome benefit was forthcoming. The precise role of microcirculatory manipulations in affecting mortality and morbidity thus remains to be elucidated.

**Monitoring the Extracellular (Interstitial) Compartment**
**Tissue Oxygen Tension**

Tissue oxygen tension (tPO$_2$) measures the partial pressure of oxygen within the interstitial (extravascular) space. It represents the balance between local oxygen delivery (from both microcirculation and microcirculation) and consumption. Thus, matched increases or decreases in local oxygen delivery and consumption will not impact on tPO$_2$. Depending upon an individual organ's metabolic activity and blood flow, the tPO$_2$ level varies markedly between organs. [38]

Traditional probes used Clark electrodes, which generally contain a platinum cathode and silver anode linked by a salt bridge. Oxygen diffusing through the electrode membrane is reduced at the cathode surface, completing an electrical circuit that generates a current proportional to the oxygen content. Such electrodes consume oxygen, which may be disadvantageous when tPO$_2$ is low. Newer techniques use dynamic luminescence quenching, involving transfer of absorbed energy to oxygen from a light-excited luminophore (eg, ruthenium, platinum) encased within a silicone matrix at the tip of a fiberoptic cable. [38] No oxygen is consumed by this process, and the decay half-life (“quenching”) is inversely proportional to local PO$_2$. These optodes thus reliably determine low tPO$_2$ values. Sensors can be precalibrated before insertion, facilitating their use. We use a platinum-complex fluorophore sensor with an active surface area of 8 mm$^2$ to broaden spatial tPO$_2$ averaging. This sensor is now being developed for patient use.

tPO$_2$ monitoring has been studied widely in animal models in multiple organs, including brain, gut, kidney, liver, muscle, and bladder. [39], [40], [41] In small-scale patient studies, brain, conjunctiva, subcutaneous tissue, muscle, and liver have been monitored during resuscitation from hemorrhagic shock and trauma, during sepsis and cardiogenic shock, and perioperatively. [42], [43], [44], [45], [46], [47], [48] Outcome improvements have been reported following the use of brain tPO$_2$ monitoring after traumatic brain injury [43], [44]; however, this requires confirmation in larger studies.

**Microdialysis**

Microdialysis enables monitoring of energy-related metabolites within the interstitial space. A solution of known solute concentration (eg, Hartmann solution) is slowly pumped through a thin catheter with a semipermeable membrane sited in interstitial tissue. This is designed to mimic a capillary. Soluble small molecules up to 30,000 Da (eg, glucose, lactate, pyruvate [reflecting carbohydrate metabolism] and glycerol [reflecting lipid breakdown]) equilibrate across the membrane between extracellular space and perfusion fluid that can be collected and analyzed. Other small molecules such as adenosine, urea, amino acids such as glutamate, hormones, and cytokines can be measured to enable evaluation of drug delivery, pharmacokinetics/dynamics, bioavailability, and bioequivalence.

Animal studies of sepsis [49] and hemorrhage [50] show an increased tissue lactate and, more usefully, lactate:pyruvate ratios. This has been reproduced in studies of patients in septic shock. [51], [52] Changes in glucose, glycerol, glutamate levels, and lactate:pyruvate ratios denote the severity of brain injury and ischemia following trauma and can independently prognosticate. [53] Tissue cortisol and antibiotic concentrations can also be measured in patients. [54], [55] Before introduction into routine clinical practice its use as a monitoring tool needs to be validated.

**CO$_2$ Tonometry**

Tissue CO$_2$ represents the balance between local production and removal. A rising value likely reflects a decrease in local blood flow rather than increased local production of CO$_2$ related to buffering of lactic acid by tissue bicarbonate. [56]

Tissue CO$_2$ has been measured in various tissues, including subcutaneous, sublingual, small and large bowel and, most notably, the stomach. Gastric tonometry was in vogue as a research tool 15 to 20 years ago, prompted by the identification that an increasing gastric-arterial or gastric-end-tidal PCO$_2$ gap or a falling gastric intramucosal pH (placing the values into a Henderson-Hasselbalch equation) were predictive of complications and mortality in patients admitted to intensive care or undergoing major surgery. [57], [58] The original technique involved inserting saline into a semipermeable gastric luminal balloon, allowing PCO$_2$ equilibration with the gastric mucosa over 30 min, and then aspirating the saline and measuring the PCO$_2$ level in a blood gas analyzer. Gastric feed had to be interrupted premeasurement, and gastric acid suppressants were required. This proved too cumbersome for regular use. An automated, semicontinuous air tonometric technique using infrared spectrophotometry to measure gastric CO$_2$ levels offered faster equilibration times and ease of use. However, a multicenter study failed to confirm adequate prognostic capability, [59] so the product was commercially abandoned. Despite this checkered history, utility in early identification of tissue hypoperfusion has been demonstrated in animal shock models using alternative locations, such as subcutaneous tissue and bladder. [50], [60] Potentially, with newer technology offering user friendliness and increased accuracy, this concept could be gainfully revitalized.
Mitochondrial Monitoring

Most of the body's oxygen consumption is used by mitochondria towards production of adenosine triphosphate (ATP) and heat. Cell death pathways are triggered by a rapid fall in ATP levels or via specific mitochondrial mechanisms. Mitochondrial dysfunction also appears to be integral to the development of multiorgan failure in sepsis. Therefore, assessing mitochondrial function represents the holy grail of monitoring the adequacy of organ perfusion. Early identification of mitochondrial stress during major surgery or critical illness from reactive species and oxygen lack would enable prompt treatment and, potentially, improved outcomes.

Mitochondrial Redox State

The mitochondrial electron transport chain accepts electrons donated from the Krebs cycle via nicotinamide adenine dinucleotide (NADH) (to complex I) and flavin adenine dinucleotide H$_2$ (to complex II). These electrons are passed down the chain, which consists of a series of redox reactions, with oxygen being the terminal electron acceptor at complex IV (COX). The passage of electrons allows proton movement across the inner mitochondrial membrane; the generated membrane potential drives ATP synthase (complex V) to generate ATP from ADP and inorganic phosphate (Pi) (Fig 5).

![Figure 5](image)

The redox reaction at complex I involves conversion of the reduced form (NADH) to the oxidized NAD$^+$. At complex IV, oxidized COX is converted to the reduced form. A lack of oxygen or a downstream block in the chain (eg, carbon monoxide or cyanide poisoning causing COX inhibition) will increase both the NADH/NAD$^+$ and the reduced/oxidized COX ratios. Specific absorbance of light by reduced NADH or oxidized COX enables ratiometric changes to be followed, assuming total NAD and COX pools remain unaltered. These properties can be used for clinical monitoring to provide a reflection of oxygen availability within the mitochondrion.

NADH Fluorometry

Conveniently, NADH (but not NAD$^+$) autofluoresces in response to 340 nm excitation light. The emitted light (450 nm) relates to the concentration of the fluorescent compound and represents changes in mitochondrial NADH, assuming no change in the total NADH/NAD$^+$ pool. Studies in animals subjected to a range of physiologic and pharmacologic insults have assessed NADH fluorescence in various organ beds including brain, liver, kidney, heart, spinal cord, and bladder. Clinical studies are still limited. Mayevsky et al reported a case series of responses of bladder wall NADH fluorescence in patients in intensive care or undergoing surgery. Falls in tissue oxygenation seen during aortic cross-clamping or cessation of spontaneous breathing led to rises in NADH. In a sequential hemorrhage rat model, there were progressive rises in NADH fluorescence intensity to greater peaks, which then normalized through hemodynamic/metabolic compensation. This continued until hemorrhage became so severe that compensation was no longer possible and the NADH intensity remained elevated (Fig 6).
Figure 6  Changes in skeletal tPO$_2$, LDF, and surface NADH fluorescence intensity following incremental hemorrhage. Due to physiologic compensation, the NADH:NAD$^+$ ratio recovers after each 10% hemorrhage until 50% of blood volume has been removed. See [Figure 1], [Figure 5] legends for expansion of other abbreviations.

Several challenges remain with this technique; absolute values cannot be obtained, so changes in fluorescence are calculated as percentage values (or arbitrary units) relative to calibrated signals made at the beginning of measurement. Only surface probes are used at present, and movement can result in changes in fluorescence. This limits the technique at present to short-term use. Data interpretation is also complicated by distortion from tissue scattering and absorption (eg, due to changes in blood volume), requiring the need for correction techniques, which also have limitations.[69] More development is needed to improve fixation to or within tissue before it can become a commonplace clinical tool.

COX Redox State

COX contains two heme iron (cytochrome a and a$_3$) and two copper centers (Cu$_A$, Cu$_B$) whose redox state changes during electron transfer (Fig 7). The Cu$_A$ center in the oxidized form strongly absorbs in the near-infrared spectrum with a characteristic shape and broad peak at 830 nm. When oxygen availability falls, the Cu$_A$ center becomes more reduced. This is detectable using near-infrared spectroscopy[70] and was shown in brain and skeletal muscle to correlate well with oxygen use in animal models of hypoxemia, hemorrhage, endotoxemia, and ischemia-reperfusion.[71, 72, 73, 74] By contrast, oxygen delivery and COX reduction were decoupled in trauma patients with multiple organ failure compared with those without multiple organ failure.[75]

Figure 7  NIRS interrogation of cytochrome oxidase redox state. c = cytochrome c; Cu$_A$ and Cu$_B$ = copper centers; Ha and Ha$_3$ = heme iron centers. See Figure 1 legend for expansion of other abbreviation.

Advantages of this technique include the steady state of the total COX concentration (unlike deoxyhemoglobin/oxyhemoglobin). However, the Cu$_A$ concentration is <10% that of hemoglobin, making optical detection
difficult. Since the absolute concentration of Cu\textsubscript{A} is unknown, as with oxyhemoglobin and NADH, all measurements are expressed as absolute changes from an arbitrary zero at the start of measurement.

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) may be readily combined with MRI. MRI uses signals from protons to form anatomic images, whereas MRS uses radiolabeled molecules to determine metabolite concentrations and quantify tissue enzyme kinetics. Although not a monitor as such, MRS offers useful diagnostic capacity so will be briefly described.

In a magnetic field, nuclear magnetic resonance-active nuclei absorb electromagnetic radiation at a frequency specific to the isotope. Although various nuclei may be used, only phosphorus and hydrogen exist in concentrations high enough in vivo to be used for routine clinical evaluation.\textsuperscript{[76,] [77]} For bioenergetic studies, \textsuperscript{31}P-nuclear magnetic resonance is primarily used, as it measures changes in phosphocreatine (PCr), ATP, Pi, and intracellular pH during stress conditions (eg, administration of dobutamine, transient hypoxia).\textsuperscript{[78,] [79]} Values of ATP, PCr, and Pi are obtained from characteristic peaks in the resonance spectrum. Intracellular pH is calculated from the shift in distance between Pi and PCr peaks, as the Pi signal is pH-sensitive (Fig 8).

![Figure 8](https://mdconsult.com/das/article/body/414310184-2/jorg%3Djournal%26source%3D...) Spectral peaks of ATP, PCr, and Pi obtained by nuclear magnetic spectroscopy. ATP = adenine triphosphate; PCr = phosphocreatine; Pi = inorganic phosphate.

PCr forms the primary ATP buffer in heart and muscle cells, transferring its phosphate to ADP.\textsuperscript{[79]} During ischemia, PCr decreases while Pi increases to maintain ATP homeostasis. Only when PCr is depleted do ATP levels fall. A decrease in PCr/ATP ratio indicates the level of stress to which myocardium or skeletal muscle is subject. This ratio remains constant under mild to moderate stress but rapidly falls with tissue ischemia. The rate of change in PCr/ATP ratio during or on recovery from ischemia provides an index of flux. Using saturation transfer techniques, ATP flux can be measured. This flux is reduced in heart failure.\textsuperscript{[79]}

Hydrogen MRS can measure molecules and metabolites involved in (patho)physiologic processes (eg, N-acetyl-aspartate [decreased in brain injury], creatine and phosphocreatine [involved in energy metabolism], lactate [marker of anaerobic metabolism], alanine, glucose, and choline compounds [markers of synthesis and breakdown of cell membranes]). It is used clinically for various conditions, particularly within the brain, including oncology, demyelinating inflammatory pathologies, infectious diseases, and metabolic pathologies such as hepatic encephalopathy and diffuse cerebral distress. In traumatic brain injury it can delineate the degree of injury and prognosis, as the detected metabolites are sensitive to hypoxia, energy dysfunction, neuronal injury, membrane turnover, and inflammation.\textsuperscript{[80]}
Conclusions

The goals of resuscitation in critically ill patients are to ensure adequate tissue perfusion and cellular metabolism. Current clinical tools are, however, lacking in the sensitivity and specificity needed to guide optimal management. Advances in technology are providing promising noninvasive or minimally invasive techniques. These, however, require initial validation to ensure reliability and to gain the necessary confidence that they can be used as surrogates reflecting or, better still, preceding changes in deeper, more vital organs. On satisfactory demonstration of the above, randomized controlled trials can assess their impact upon outcomes, and this must occur before potential implementation into management guidelines.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Ekbal holds a UK Medical Research Council Studentship to investigate NADH fluoroscopy. Dr Dyson participated in a study funded as above to develop tissue PO2 technology. University College London has an Intellectual Property agreement with Oxford Optronix Ltd to develop a clinical tissue PO2 monitor. Dr Black holds a fellowship grant from UK National Institutes of Health Research assessing means of individualizing rehabilitation of critically ill patients. This partly involves study of metabolic monitoring, a device for which was purchased under the grant. Dr Singer holds UK government/charitable grants to develop tissue PO2 and NADH fluorometry technologies and to study metabolic monitoring.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

REFERENCES:

17. Pare?nik R, Knezevic R, Voga G, Podbregar M: Changes in muscle tissue oxygenation during stagnant ischemia in septic


58. Mythen MG, Webb AR: The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. Intensive Care Med. 20. (3): 203-209.1994; Citation


Copyright © 2013 Elsevier Inc. All rights reserved. - www.mdconsult.com