

Monitoring Tissue Gas Tensions in Critical Illness

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ABSTRACT

Objective: To review the technology and the role of monitoring tissue oxygenation in critical illness.

Data Sources: Articles and published peer review abstracts on monitoring tissue oxygenation.

Summary of review: Miniaturised optodes and electrode systems are the commonly used technology for measurement of tissue gas tensions. Reductions in tissue perfusion frequently leads to a decrease in tissue PO_2 and an increase in tissue PCO_2 which has been confirmed in a number of animal and human trials in hypovolaemic shock. Monitoring tissue oxygenation has also enabled the delineation of cytopathic hypoxia, which is one of the important pathophysiological mechanisms of sepsis. Although these devices have improved our understanding of pathophysiological mechanisms of critical illness, at a clinical level titrating oxygen therapy to tissue oxygen tensions has only been shown to be useful in patients with impaired wound healing.

A number of questions remain unanswered in relation to the monitoring of tissue oxygenation in critical illness. These include establishing normal values of PO_2 and PCO_2 in humans at the various tissue beds, establishing dysoxic thresholds for the various tissues, identifying optimal sites for monitoring and improving measurement accuracy. Furthermore, the nature of microcirculatory blood flow and tissue gas exchange in critical illness is complex and incompletely understood, limiting our ability to interpret changes from the baseline. Knowing critical tissue PO_2 thresholds will provide the clinician with practical resuscitation endpoints in hypoxia and shock, and may even modify the practice of 'permissive hypoxia' in severe respiratory failure. These questions need answers in the years to come.

Conclusions: Monitoring of tissue oxygenation is largely a research tool. For its application in the critically ill patient there needs to be a greater understanding of normal values of PO_2 and PCO_2 at the various tissue beds, dysoxic thresholds for the various tissues and optimal sites for monitoring. (**Critical Care and Resuscitation 2002; 4: 291-300**)

Key words: Tissue oxygen tension, tissue carbon dioxide tension, critical illness, oxygen delivery, septic shock, monitoring

The ability to measure arterial blood gases and pH became a clinical reality in the 1950s. Whilst valuable information concerning gas exchange and acid-base homeostasis was gained through blood gas analysis, it soon became apparent that it did not provide a good index of tissue well being. Tissue carbon dioxide measurement did not come into prominence for a further 30 years. Routine measurement of tissue PO_2 became a possibility in the late 1980s.

Present day monitoring of tissue oxygenation incorporates many technological advances in electrode miniaturisation, fiberoptics and spectrophotometry.¹ Some milestones culminating in present day measuring systems are outlined in Table 1.²

We present an update on techniques of measurement of tissue gas tensions and consider their potential usefulness in critical care practice and research.

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Table 1. Milestones in tissue oxygen measurement

1909	Sorensen described the pH nomenclature
1916	Hasselbach's modification of Henderson's equation
1933	McInnes & Belcher adapted the glass electrode for blood pH measurements ³
1954	Richard Stow described the CO ₂ electrode ⁴
1956	Leland Clark described the O ₂ electrode ⁵
1957	Severinghaus & Bradley designed and built the first blood gas analyser
1959	Boda & Murayani described gastric tonometry as a means of determining PaCO ₂ ⁶
1969	Lubbers & Huch described transcutaneous oxygen measurement
1982	Fatt & Deutsch described conjunctival PO ₂ monitoring
1984	Gastric tonometry introduced by Fiddian-Green for measuring gastric mucosal PCO ₂ ⁷
1994	Clinical use of continuous intra-arterial blood gas monitoring systems ⁸
1990s	Widespread use of electrodes and optodes for measurement of tissue pH, PCO ₂ and PO ₂

Why measure tissue PO₂ and PCO₂?

A number of arguments can be proposed for measuring tissue gas tensions. Firstly, tissue PO₂ and PCO₂ reflect adequacy of tissue blood flow.⁹ Secondly, tissue gas tensions, coupled with global oxygenation indices (e.g. $\dot{D}O_2$ and $\dot{V}O_2$) should enhance the detection of tissue dysoxia, a pathophysiological process implicated in the genesis of multiple organ dysfunction syndrome.¹⁰

The fact that continuing tissue dysoxia can persist despite normal global indices of total body oxygenation underscores the need for monitoring at the level of the tissues.¹¹ As cellular sensitivity and response to ambient hypoxia play important roles in the pathogenesis of numerous disorders in critical care medicine, monitoring tissue PO₂ and PCO₂ would facilitate early recognition and treatment of tissue hypoxia and its attendant consequences.

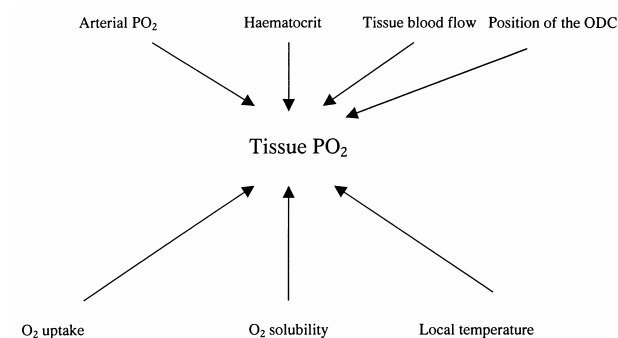
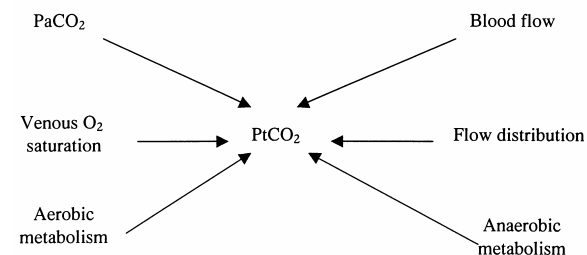
Which one to measure: tissue PCO₂ or PO₂ or both?

Paradoxically, it is tissue PCO₂ rather than PO₂ which has become an established index of tissue dysoxia, whether due to ischaemia or sepsis. Also, tissue PCO₂ is normally independent of F_IO₂, unlike PO₂. Therefore under conditions of high F_IO₂, tissue PCO₂ should be a more reliable index of flow. However, an elevated tissue PCO₂ on its own does not distinguish between ischaemic and septic aetiologies. As tissue PO₂ is reduced in ischaemia and often increased in sepsis,¹²

combining the two measurements may be sufficient to distinguish between these states.

Determinants of tissue gas tensions

Tissue PO₂ reflects a balance between oxygen delivery to and oxygen consumption by the tissue (Figure 1). Similarly, tissue PCO₂ is determined by the balance between arterial PCO₂, tissue blood flow and distribution, the mix of aerobic and anaerobic metabolism and venous oxygen saturation (Figure 2).

**Figure 1.** Determinants of tissue oxygen tension**Figure 2.** Determinants of tissue carbon dioxide tension

Elevations in tissue PCO₂ during circulatory failure are thought to arise from two processes: an initial rise in tissue PCO₂ due to flow stagnation, whereby the PCO₂ is not cleared by the circulation and a delayed rise due to anaerobic metabolism, if the circulatory failure is severe and persistent.

Methods of measurement of tissue gas tensions

Blood gas analyser

As all tissue cells are bathed in extracellular fluid (ECF), measurement of ECF gas tensions should provide a good index of tissue gas tensions. However, there are major problems in employing a blood gas analyser for this purpose. Firstly, sampling the ECF of a particular organ without significant tissue invasion or damage is not feasible. Secondly, the measurement of gas tensions on non-blood fluids, such as the ECF, by blood gas analysers are inaccurate.¹³⁻¹⁷

The quest for minimal invasiveness and accuracy of measurement provided the impetus for the development of miniaturised sensors, designed for relatively atraumatic insertion into various tissue spaces. While several methods of analyte detection have been tried in these devices, currently available systems employ two general configurations; namely the fiberoptic system and the electrochemical system.

Fiberoptic systems

Fiberoptic systems can be either fluorescent or absorbent. In fluorescent systems, usually used for the measurement of PO_2 , the excitation wavelength of the incident light is absorbed by the dye, causing electrons to be briefly excited to a higher energy level. When the electrons return to a lower energy level, they emit energy in the form of light (i.e. fluorescence). The difference between the excitation wavelength and the emission wavelength is known as the Stoke's shift, which is proportional to the ambient PO_2 .

The relationship between the wavelength and the tissue PO_2 is mathematically described by the Stern - Volmer equation,¹⁸ forming the basis of most fiberoptic oxygen sensors which have generally become known as "optodes".^{19,20} In absorbance based systems used for pH and PCO_2 measurements, light is transmitted to an optical dye phase, the absorbance of specific wavelengths by the dye varies in an inverse relationship to the analyte of interest. The mathematical relationship is described by Beer-Lambert's law.

Polarographic systems

Electrochemical systems measure voltage (potentiometric), a characteristic of the pH and the PCO_2 electrodes,⁴ or current (amperometric), a characteristic of the PO_2 electrode.⁵ The PO_2 electrode has been successfully miniaturised in several commercial devices. The current generated by the reduction of oxygen is linearly related to the partial pressure of oxygen in the solution.

In theory the optodes are potentially more accurate at a lower PO_2 ,²¹ thus making them more attractive for measuring tissue oxygen tension. However, in practice this may not be true. One study comparing optodes and electrodes showed no difference in accuracy at low levels of ambient PO_2 .²²

An example of the optode system is the Paratrend 7 (Diametrics Medical, UK). This is a multiparameter optode system with a capacity to measure pH, PCO_2 and PO_2 .^{23,24} It is used widely in tissue oxygenation measurements and is also commercially marketed as the Neurotrend for the measurement of cerebral tissue oxygenation.²⁵⁻²⁷ The Licox (GMB Medical, Germany) is an example of miniaturised PO_2 electrode which has

found application in neurosurgical intensive care.²⁸

Phosphorescence quenching

The phosphorescence decay technique provides a way of measuring simultaneous microcirculatory intravascular and extravascular PO_2 .²⁹⁻³¹ The principle behind the technique utilises the fact that metallo-porphyrins bound to albumin, when injected intravenously into a subject and are excited by a pulsed light to their triplet state, emit phosphorescence. The associated energy release causing the phosphorescence is transmitted to oxygen present in the vicinity of the measuring site. The decay in phosphorescence is proportional to the local oxygen tension and the mathematical relationship is governed by Stern-Volmer equation as in the optodes. Although most of the injected porphyrin remains in the circulation, the normal exchange of albumin between blood and tissue causes this compound to be detectable in the tissue 30 minutes after injection and thus allows the measurement of tissue PO_2 . This technique combined with orthogonal polarisation spectroscopy microscopy³² provides valuable information on both microcirculatory blood flow and oxygenation.

The bulk of the data published on this technique have been in animal models. Human data are lacking. As this compound is bound to albumin, the impact of hypoalbuminaemia, a frequent finding in critically ill patients, on the accuracy of this measurement has not been determined.

Tissue PO_2 histogram

Data from tissue sensors located in a fixed position yield single site measurements and may not reflect true tissue PO_2 , given the heterogeneity and dynamic nature of the microcirculation, vasomotion, the potential for insertion trauma, and the limited scanning area of sensors.^{33,34} Hence it has been advocated that repeated PO_2 measurements be obtained after forward and backward motion of the probe, thus generating a series of measurements resulting in a histogram pattern of tissue PO_2 . Alternatively, a multiwire configuration of many microelectrodes packaged in a bundle is placed in contact with the tissue to generate the tissue histogram pattern.³⁵

Which site to measure?

This has been the subject of debate for a number of years. The argument for performing site-specific measurements will depend on the clinical scenario e.g. brain PO_2 and PCO_2 in neurotrauma.³⁶ However, under conditions of global circulatory compromise, the ability to measure tissue gas tensions at one site most representative of whole body tissue oxygenation would

appear to be desirable. To this end, a number of sites have been examined including gastric,³⁷⁻³⁹ intestinal,^{40,41} subcutaneous,⁴²⁻⁴⁵ sublingual,⁴⁶ skeletal muscle⁴⁷ and urinary bladder.^{48,49}

Gastrointestinal

Fiddian-Green pioneered the technique of gastric tonometry for the measurement of intra-mucosal pH (pH_i) as an index of adequacy of splanchnic oxygenation.⁷ The heightened sensitivity of the gastrointestinal mucosa to a hypoxic and a hypotensive insult formed the basis of this technique. It was based on the principle that tissue PCO_2 rose and tissue pH dropped (both respiratory and metabolic acidosis) during circulatory failure.

Accurate measurement of gastric luminal PCO_2 was therefore essential for a reliable assessment of intramucosal pH. Initial problems with CO_2 measurement errors associated with the use of saline^{13,14} were overcome by the use of air as an equilibration medium.¹⁶ However, potential problems with the technique include the intermittent nature of the measurement, the potential for duodeno-gastric reflux of bicarbonate rich secretions,⁵⁰ the blunting of the sensitivity of the signal by luminal feeds⁵¹ and luminal blood,⁵² and doubts about the validity of using arterial bicarbonate for the calculation of pH_i .⁵³ After nearly 20 years of the availability of gastric tonometry, no convincing data exist to show that titrating therapy to pH_i improves outcome.⁵⁴

Changing the therapeutic endpoint from pH_i to the PCO_2 gap (tissue - arterial PCO_2) overcame the "bicarbonate limitation" of gastric tonometry.⁵⁵ This resulted in a spurt of enthusiasm for rapidly responsive fiberoptic PCO_2 sensors for real time tracking of gut ischaemia (Figure 3) in animal models.^{40,41} However, attempts to adapt these devices for clinical use have been largely unsuccessful. Besides, other factors such as the demonstration of large CO_2 gradients between the mucosal wall and the lumen during circulatory shock³⁸ and the finding of differential permeability of the basal and luminal membranes of the gastric mucosal cells to CO_2 ⁵⁶ raises doubt that the PCO_2 gap will be a significant improvement over pH_i in its ability to reflect mucosal well being.

Subcutaneous

The attraction of subcutaneous monitoring is its ready accessibility and its minimal oxygen consumption, thus making its PO_2 measurement a sensitive indicator of local blood flow. It shares a number of anatomical and physiological characteristics with the gut mucosa which result in its increased responsiveness to hypoxic and hypovolemic insults.⁵⁷ A large body of data

exists to support the usefulness of monitoring subcutaneous oxygen tension in covert shock states.^{42,43,45,58} We have demonstrated that subcutaneous oxygen tension is more rapidly responsive than gut luminal carbon dioxide tension and arterial lactate in an animal model of evolving haemorrhagic shock.⁴⁴ We have applied the technique of subcutaneous PO_2 monitoring to patients during burns shock and resuscitation, providing further insights into trends in tissue oxygenation in these patients.⁵⁹ Using the Paratrend 7 system and a gastric tonometer, we were able to demonstrate progressive tissue hypoxia and hypercarbia during fluid resuscitation to standard formulae, suggesting an oedema-induced increase in the diffusion barrier.

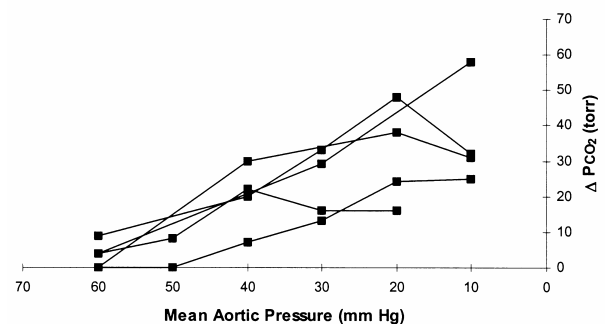


Figure 3. Relationship between severity of transient aortic hypotension and corresponding increases in luminal PCO_2 (expressed as ΔPCO_2 - difference between baseline and peak hypercapnic response following ischaemia) in individual rats. (Reproduced with permission from Williams & Wilkins, Morgan *et al.*⁴¹)

Bladder, urethra and urine

Monitoring of PO_2 in the urinary tract was based on the premise that renal perfusion falls early in shock states. Initial data suggested that PO_2 changes in the urinary tract could be an early warning signal of covert shock.^{48,60-62} Increases in bladder epithelial PO_2 were recorded in an animal model of endotoxic shock.¹² However, these findings are at variance with the data of Wong *et al* who showed that urine PO_2 was not a sensitive indicator of systemic hypoxia.⁶³ In fact, in 1958, Rennie *et al* showed that bladder urinary PO_2 measurements were relatively insensitive to renal ischaemia, compared with PO_2 measured in the renal pelvis.⁶⁴ These authors theorised that there was loss of oxygen across the ureteric and bladder wall. These objections combined with considerable technical difficulties have resulted in a waning of enthusiasm for using this route of monitoring.

Skeletal muscle

Skeletal muscle tissue gas tensions respond rapidly and reproducibly and on a similar time scale to that of

the gastrointestinal tract to haemorrhagic shock and resuscitation.^{47,65-68} However, the presence of myoglobin, an oxygen carrier, may potentially reduce the sensitivity of response to hypoperfusion and hypoxia. In animal models, evolving haemorrhagic shock causes greater reductions in blood flow to other tissues such as cutaneous and adipose tissue, thus reducing the value of skeletal muscle tissue gas tensions as a rapid early warning system.⁶⁹ Muscle twitches and injury currents may also lead to an unstable signal and may interfere with accuracy of data from skeletal muscle microelectrodes.⁷⁰

Oesophageal

Whilst changes in oesophageal PCO₂ have been reported to correlate with increases in gastric PCO₂ during haemorrhagic shock,⁷¹ the possibility of signal imprecision due to the segmental blood supply to the oesophagus and peristaltic activity has limited its application.

Sublingual PCO₂

Weil *et al* were instrumental in developing the sublingual PCO₂ measurement technique. In both animal and human studies,^{46,72,73} sublingual blood flow and sublingual PCO₂ were demonstrated to closely track gastric mucosal blood flow and PCO₂ respectively. Whilst the simplicity and the non invasiveness of this technique are appealing, sensor stability during the many medical and nursing procedures performed in intensive care needs further evaluation. Furthermore, the presence of large stores of myoglobin in the tongue⁷⁴ may allow tolerance of longer periods of dysoxia than in the intestine, thus limiting its usefulness as an early warning signal of covert under-resuscitation.

Other organs

Brain tissue pH, PCO₂ and PO₂ have been measured successfully in critically ill neurosurgical patients during anaesthesia and in critical illness.^{25-27,36,75,76} Alterations to cerebrospinal fluid⁷⁷ and brain tissue gas tensions in a variety of pathophysiological states are now better understood. Gas tensions in other organs such as the kidney, liver and myocardial tissue have also been studied.^{42,43,78,79} However, these sites are not readily accessible and thus not suitable for routine clinical monitoring.

Difficulties in interpreting tissue gas tensions

a) Heterogeneity of tissue gas tensions

The mode of oxygen transfer from capillaries to tissues has been the subject of intense investigation. According to the Krogh model, tissue oxygen supply

was thought to arise solely from a homogeneously distributed pattern of capillaries.⁸⁰ Radial diffusion of oxygen from the capillary in the centre to the surrounding tissues, was thought to be the principal mode of oxygen transfer from the vasculature to the cells. Based on these principles, the existence of a microvascular lethal corner was proposed (i.e. the tissue site most distant from any capillary and therefore most vulnerable to impairment of capillary blood flow).²⁹ However, the architecture of the capillary network is far more complex than previously believed.^{81,82} Using phosphorescence quenching, it has been demonstrated that significant amounts of oxygen exit the arteriolar network prior to the capillary phase.⁸¹ Countercurrent circulations have been demonstrated in some tissues, with diffusive shunting of gases between arterioles and adjacent venules.⁸³ Features such as these may lead to fluctuating levels of carbon dioxide and oxygen tensions in different regions of the same tissue.⁸⁴ In reality, sensor measurements are profoundly influenced by its proximity to the investing vasculature, with the final signal likely to be an integration of arteriolar, venular, capillary and tissue values. Variations in tissue metabolism may also contribute to a wide range of gas tensions from tissue to tissue and within the same tissue. Finally, CO₂ and O₂ have different diffusion characteristics and tissue stores,⁸⁵ and for this reason alone their respective tensions are likely to respond differently during sudden perturbations in diffusion barriers and blood flow.

b) Direction of change in tissue gas tensions

The traditional thinking was that tissue PO₂ declined and PCO₂ rose during dysoxia. However, the direction of change is by no means consistent. For example, during endotoxaemia, elevations of ileal and urinary bladder PO₂ following endotoxin infusions have been demonstrated, suggesting a cytopathic hypoxia, thus shedding light on one of the important pathophysiological mechanisms of tissue dysoxia during sepsis.^{12,86} Similarly, an elevation in tissue PCO₂ during dysoxia is not a uniform finding. In an isolated hindlimb model, Vallet *et al* demonstrated differing tissue PCO₂ responses in hypoxic dysoxia versus ischaemic dysoxia.⁸⁷ Significant elevations in tissue PCO₂ were reported only in ischaemic dysoxia. They attributed the lack of significant elevation in tissue PCO₂ during hypoxic hypoxia to preservation of blood flow, which facilitated CO₂ clearance from the tissues.

c) Difficulties involved in interpreting a change in tissue gas tension from baseline

To examine this issue, one needs to be aware of the number of factors which influence tissue PO₂ and PCO₂

(Figures 1 and 2). Consequently, to decipher the contribution of a single perturbation on tissue PO₂ from a host of variables is difficult.

To illustrate this point, a few examples can be considered. Using Siggard-Andersen's algorithm, assuming a constant oxygen extraction by the tissues, it is possible to determine the end capillary venous oxygen tension, which is a close approximation of tissue PO₂. By manipulating some of the variables of the oxygen delivery equation, one can calculate the changes in the end capillary venous oxygen tension (a surrogate for tissue oxygen tension. Table 2). From this table, it can be appreciated that perturbations in oxygen delivery even of small magnitude can result in alteration of end capillary venous oxygen tension.

The above modeling is based on a number of assumptions: e.g. that there is a single discrete perturbation and oxygen extraction remains constant. This does not reflect the true clinical situation, nevertheless, it still highlights the difficulties involved in interpreting a change in tissue gas tensions and it must be borne in mind that the final tissue value may represent an additive, multiplicative or an opposing effect of a number of perturbations.

Table 2. Impact of altering some of the oxygen delivery variables on tissue gas tensions

Event	Hb g/L	P ₅₀ mmHg	PaO ₂ mmHg	ECV PO ₂ mmHg
Normal	150	26.5	85	37.5
Red'n in Hb	100	26.5	85	30.8
Red'n in PaO ₂	150	26.5	60	33.8
Increase in PaCO ₂ (from 40 - 80 mmHg)	150	35.1	85	46.2

Hb = haemoglobin, PaO₂ = arterial blood oxygen tension, PaCO₂ = arterial blood carbon dioxide tension, P₅₀ = partial pressure of oxygen of a whole blood sample at which haemoglobin is 50% saturated, ECV PO₂ = end capillary venous PO₂, Red'n = reduction.

d) Limitations of tissue sensors

Sensor insertion may result in an "insertion haematoma". Blood acts as a CO₂ and O₂ 'sink', thus impacting on both the absolute values and dampening response times of the sensor (Figure 4).⁵² The presence of clot and devitalised tissue in the vicinity of the sensor can also interfere with its measurements.⁸⁸ Another problem is that once deployed, *in vivo* calibration of sensors is impossible, as the "true" tissue gas tension is unknown. This minimises the ability to correct for sensor drift. Also the sampling area for tissue sensors is small, limiting detection of adjacent areas of ischaemia.

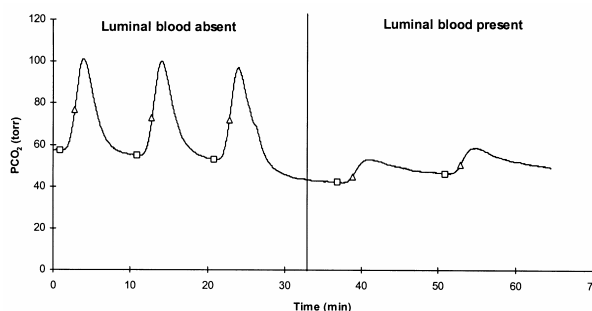


Figure 4. A representative trace of jejunal CO₂ from a rat illustrating the effect of blood on the luminal hypercapnic response to gastrointestinal ischaemia. Open squares denote the onset of subdiaphragmatic hypotension, and open triangles mark the time of offset. (Reproduced with permission from Springer-Verlag Venkatesh *et al.*⁵²)

Clinical outcome studies²

Results to date have been disappointing. At a clinical level, titrating oxygen therapy to tissue oxygen tensions has only been shown to be useful in patients with impaired wound healing.⁸⁹ Although a number of trials have demonstrated evidence of impaired tissue oxygenation (manifested as a low pH_i) in a variety of disease states,⁹⁰⁻⁹³ no convincing data exist to suggest that titrating therapy to pH_i improves outcome.⁵⁴ Similarly, although trials in neurosurgical patients have shown a correlation between impaired brain gas tensions and poor neurological outcome,^{25-27,36,75,76} there are no data yet showing that improvement in gas tensions translates into clinical benefit.

Tissue gas tensions –the future?

Whilst we now have the ability to monitor tissue PO₂ and PCO₂, either intermittently or continuously in many tissues, a number of questions remain unanswered. What are the normal values of PO₂ and PCO₂ in humans at the various tissue beds? Consequently, the dysoxic threshold (oxygen limited cytochrome turnover) in any given tissue is unclear. Is it fixed or does it vary depending upon the metabolic adaptation? Should we be monitoring one tissue bed or multiple sites in critical illness?

It would appear from published data that monitoring gases in the subcutaneous tissue, gastrointestinal tract or skeletal muscle might provide early warning of covert shock. However, the nature of microcirculatory blood flow and tissue gas exchange in critical illness is complex and incompletely understood, limiting our ability to interpret changes from baseline. The ability to identify the so called "microvascular lethal corner" in a large body of tissue is challenging. Knowing critical tissue PO₂ thresholds will provide the clinician with

practical resuscitation endpoints in hypoxia and shock, and may even modify the practice of 'permissive hypoxia' in severe respiratory failure.⁹⁴ These questions need answers in the years to come.

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