Tissue oxygen tension monitoring of organ perfusion: rationale, methodologies, and literature review

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Abstract

Tissue oxygen tension is the partial pressure of oxygen within the interstitial space of an organ bed. As it represents the balance between local oxygen delivery and consumption at any given time, it offers a ready monitoring capability to assess the adequacy of tissue perfusion relative to local demands. This review covers the various methodologies used to measure tissue oxygen tension, describes the underlying physiological and pathophysiological principles, and summarizes human and laboratory data published to date.

Key words: monitoring, intraoperative; monitoring, intensive care; monitoring, oxygen; oxygen, tissue

In vivo measurement methods

Tissue oxygen tension may be measured by polarographic or dynamic fluorescence quenching methods, or using electron paramagnetic resonance (EPR) oximetry.

The Clark polarographic technique (Fig. 2) consists of electrodes that generally contain a platinum cathode and a silver anode linked by a salt bridge. As oxygen is reduced at the cathode surface, more oxygen diffuses through the oxygen-permeable membrane to be reduced at the cathode surface. Upon doing so, the circuit is completed, and this generates a current proportional...
to the oxygen content at the measurement site. Such electrodes consume oxygen, and this may potentially be disadvantageous when $tP_O_2$ values are very low.

Electron paramagnetic resonance spectroscopy and imaging can provide structural and dynamic information on materials with unpaired electrons. Excitation of the material or tissue provides characteristic EPR spectra for different free radical species. Indeed, molecular oxygen is a naturally occurring triplet radical; however, there are no stable free radicals occurring naturally in vivo at either adequate concentration or biological half-life. Injection or tissue implantation of an external spin probe consisting of paramagnetic material in either particulate (solid) or soluble form will, however, enable tissue oxygen monitoring. The EPR spectrum width is broadened by an interaction between molecular oxygen and the spin probe, permitting quantification of local oxygen concentration (Fig. 3). Electron paramagnetic resonance oximetry can monitor for long periods of time with no loss of sensitivity, but this methodology is expensive, requires a high level of knowledge and user expertise, and is not applicable to human study.

In vivo studies have been performed in animal models using injection of gloxy, a paramagnetic component of certain coals, either i.v. or directly into the organ under study.
Newer techniques promise more flexible measurement capabilities. Oxygen molecules can quench the fluorescence and phosphorescence of certain luminophores. Fluorescence is the light emitted by a substance that has absorbed light (or other electromagnetic radiation) of a different wavelength. While phosphorescence is related to fluorescence, a phosphorescent material does not immediately re-emit the radiation it absorbs. Dynamic fluorescence quenching (Fig. 4) was first described by Kautsky in 1939. Collision of an oxygen molecule with a fluorophore in its excited state (stimulated by a pulse of light) leads to non-radiative energy transfer. This is emitted as fluorescence and phosphorescence over tens to hundreds of milliseconds. The degree of quenching relates to the frequency of collisions, and thus to the concentration, pressure, and temperature of the oxygen-containing media. This is described by the Stern-Vollmer equation, where luminescence decay is inversely proportional to the local $P_{O_2}$ within the tissue:

$$\frac{\tau_0}{\tau_1} = 1 + (\kappa q \times \tau_0 \times [O_2])$$

where $\tau_0$ is the decay time at zero oxygen, $\tau_1$ is the decay time at a specific oxygen concentration ($[O_2]$) and $\kappa q$ is a diffusion-controlled rate constant that denotes the probability of a single-state luminophor and ground-state oxygen molecule colliding.

Unlike Clark-type polarographic electrodes, no oxygen is consumed; indeed, because of the longer decay time with low $P_{O_2}$, measurement accuracy increases as the partial pressure of oxygen decreases.

Although not approved for human use, in vivo measurement of microvascular or tissue oxygenation can be achieved in animals by i.v. or interstitial injection of a phosphorescent metal-organic protein (an ‘oxyphor’). Oxyphors (e.g. palladium porphyrin) were formerly bound to albumin to enhance aqueous solubility and bring the quenching variables $\kappa q$ and $\tau_0$ into the physiological range. Newer polyglutamyl dendritic porphyrins, such as Oxyphor G2, have a much higher intrinsic aqueous solubility and do not require albumin prebinding. Once injected, these complex with endogenous albumin and serve predominantly as intravascular oxygen sensors, although some extravasation may occur into the perivascular space. PEGylated dendrimers, such as Oxyphor G4, have been used to image $P_{O_2}$ within tumours and surrounding tissues, with phosphorescence even detected externally in mice after whole-body transillumination by emission of excitation pulses. More recently, a microsensor containing Oxyphor G4 has been developed that can be sited into peripheral tissue. To our knowledge, this is not yet commercially available.

A more established technique for in vivo monitoring, commercially available from Oxford Optronix Ltd (Abingdon, Oxon, UK) and used extensively in our laboratory studies, uses a platinum-based luminophore sensor of 220 $\mu$M diameter. This can be inserted into tissues, with the excitation light and the resulting luminescence emitted from the sensing tip being transmitted along a thin fibre-optic cable connected to a monitor. With larger sensors, tissue areas of up to 8 mm$^2$ can be sampled. A further advantage is that the sensors are precalibrated before insertion, allowing ‘plug-and-play’ ease of use. This monitor is also highly responsive, so that complete and sudden occlusion of the nutrient vessel to an organ bed will result in a rapid reduction in tissue oxygen tension within 10–20 s as residual oxygen is consumed, whereas a partial albeit significant occlusion results in a more gradual reduction.

**Shock and tissue oxygen tension**

Shock is defined physiologically as an inadequate supply of oxygen relative to the body’s needs (hypoxia) or a failure to use the available oxygen adequately (dyoxia). More than 90% of total body oxygen consumption is used by mitochondria, predominantly for the production of ATP (by oxidative phosphorylation), but also for heat generation (through uncoupling) and reactive oxygen species production. As defined by Barcroft a century ago, failure of delivery of sufficient oxygen may be attributable to inadequate cardiac output (‘circulatory hypoxia’), insufficient haemoglobin (‘anaemic hypoxia’), or decreased arterial oxygen concentrations (‘hypoxic hypoxia’), alone or in combination. This insufficiency will impact upon the ability of the mitochondria to generate enough ATP to meet the metabolic requirements of the cells. The problem may be global (e.g. after severe haemorrhage or cardiac arrest) or regional, as seen after an acute interruption of vascular supply that results in local ischaemia, or an inability to meet increased metabolic demands, for example, angina occurring upon exercise. Additional pathological conditions not recognized by Barcroft include cellular hypoxia and an increased diffusion barrier related to tissue oedema. With dyoxia, oxygen is available to the cell, but the mitochondrial bioenergetic apparatus is dysfunctional, such as after sepsis, cyanide poisoning, or carbon monoxide intoxication that directly inhibit components of the electron transport chain. Tissue oedema after injury may prevent diffusion of oxygen from vessel to cell, as Fick’s law of diffusion states that diffusion is inversely proportional to tissue thickness.

Depending upon the underlying pathology, the local oxygen supply–demand balance will be distorted during shock states. Thus, an inadequate delivery—for whatever reason—relative to demand will decrease the $P_{O_2}$. This can be obviated to some degree by increasing glycolytic ATP production (anaerobic respiration) and by reducing metabolic demands through physiological adaptation or decreasing cellular metabolism, or through intravenous intervention, such as by cooling or anaesthesia. On the contrary, a primary reduction in metabolic demand or a pathological failure of oxidative phosphorylation will leave oxygen supply largely unaffected, and thus, the $P_{O_2}$ will increase. This is exemplified by the increase in mixed or central venous saturation frequently seen in patients with resuscitated sepsis. Indeed, physiological adaptation and protection often result in blood flow bypassing the affected region (shunting) to prevent excessive and potentially toxic concentrations of oxygen accumulating in the tissues. A perfect matching of oxygen supply and demand, be it an overall increase or decrease in turnover, will result in no net change in $P_{O_2}$. 
**Tissue oxygen tension monitoring in shock states and other related conditions**

**Haemorrhage**

Haemorrhagic shock represents inadequate perfusion of vital organ beds secondary to blood loss. Although its aetiology is multifactorial, decreases in circulating blood volume (affecting cardiac output) and reduction in haematocrit will both reduce oxygen delivery. Studies confirm decreased values of $P_{O_2}$ in both peripheral (e.g. s.c. tissue, conjunctiva) and deep sites (e.g. liver, kidney) after haemorrhage. Our group previously reported concurrent changes in $P_{O_2}$ in muscle, bladder, liver, and renal cortex during progressive exsanguination in an anaesthetized rat model. While bladder, liver, and muscle $P_{O_2}$ reduced in tandem, renal cortex $P_{O_2}$ was maintained until shortly before death, despite a marked reduction in renal blood flow. This is likely to indicate an adaptive reduction in glomerular filtration, thus reducing the need to reabsorb large volumes of filtrate, which represents the major oxygen-consuming role within the kidney.

Studies during haemorrhage in either pigs or rats report reductions in $P_{O_2}$ in liver, muscle, bladder, or, in combination of these, affected before standard haemodynamic variables, such as blood pressure and cardiac output. However, one group reported contrary findings in a pig model, where changes in systemic haemodynamic variables were more sensitive than tissue oxygen tension measured with Clark-type electrodes in the jejunal and colonic wall, liver, and s.c. tissue (using a tonometer) during haemorrhage. Here, the tissue oxygen tensions did not decrease until 20–40% of estimated blood volume had been withdrawn, which is a rather surprising finding. The reasons for this disparity are unclear but could be methodological.

**Sepsis**

Sepsis may lead directly to abnormalities in both cellular delivery and utilization of oxygen. Provided the patient is adequately fluid resuscitated, $P_{O_2}$ values in septic patients are generally reported to be elevated. Boekstegers and colleagues found that skeletal muscle $P_{O_2}$ was elevated in septic patients with multiple organ failure, within the normal range in patients with limited infection, and depressed in patients in cardiogenic shock. The $P_{O_2}$ normalized in septic patients who went on to survive.

Experimental studies of sepsis and endotoxaemia report a much wider variation in $P_{O_2}$, with increases in bladder, gut, and skeletal muscle $P_{O_2}$, no change in gut serosal $P_{O_2}$, and decrease in gut mucosal, skeletal muscle, liver, and kidney $P_{O_2}$ all being noted. This probably relates to both intra-organ differences and methodological issues, such as the severity and rapidity of the administered endotoxin insult, degree (if any) of fluid resuscitation, and short- vs long-duration model. Using a longer-term (24 h), fluid-resuscitated rat model of faecal peritonitis, we found an increase at 6 h in bladder epithelial $P_{O_2}$, major decreases in renal cortical and liver $P_{O_2}$, and an unchanged skeletal muscle $P_{O_2}$ implying marked early intra-organ differences in oxygen delivery and utilization. By 24 h, however, the values in all organs had returned to levels seen in sham-operated animals yet, at this point, the animals were clinically much more severely ill. The relevance of these findings is currently being explored further.

**Trauma**

The main focus of neurocritical care for traumatic brain injury relates to the prevention, detection, and management of secondary brain injury. This relies heavily upon monitoring of systemic and cerebral variables. In a study of 139 patients, using a micro-Clark electrode sited within the brain parenchyma, 65% of patients had an initially low $P_{O_2}$ after standard resuscitation. By using a protocol directed at elevating $P_{O_2}$, there was better control of intracranial pressure and maintenance of cerebral perfusion pressure. Mortality was significantly lower in patients receiving brain $P_{O_2}$-directed care (25.9%) compared with 41.5% in a historical cohort. In a similar comparison study, Spiotta and colleagues found that maintaining brain $P_{O_2}$ > 25 mm Hg was also associated with lower mortality rates (25% vs 44% in historical controls).

In a retrospective analysis of patients with severe traumatic brain injury, a combination of anaemia and brain $P_{O_2}$, but not anaemia alone, was a risk factor for unfavourable outcomes, irrespective of the severity of injury. Longhi and colleagues reported that brain $P_{O_2}$ was lower in pericontusional tissue than in normal-appearing tissue assessed by computed tomography and that multiple episodes of brain hypoxia occurred over the 5 day monitoring period. Brain $P_{O_2}$ monitoring may also facilitate early recognition of low oxygen-delivery situations, enabling appropriate therapeutic interventions. For example, brain-injured children with an eventual poor outcome had a greater $P_{O_2}$ response to an increase in inspired oxygen (an ‘oxygen challenge’ test).

In critically injured adults, Ickossi and colleagues found that dodecyl muscle $P_{O_2}$ was a responsive, reliable, and continuous monitor of changes in base deficit. Initial low values were associated with postinjury complications. Monitoring $P_{O_2}$ may thus be useful for identifying patients with occult under-resuscitation who remain at risk of developing infection and multiple organ failure.

Transcutaneous $P_{O_2}$ was monitored in 106 critically ill surgical patients with different values of cardiac index, namely >2.2, 1.5–2.2 and <1.5 litre min$^{-1}$ m$^{-2}$. The ratio of transcutaneous $P_{O_2}$ to arterial oxygen tension fell progressively with increasing shock.

**Subarachnoid haemorrhage**

Bohman and colleagues found that the response to brain $P_{O_2}$-directed intervention was associated with improved long-term outcome (Glasgow Outcome Score-Extended and modified Rankin Scale) in patients with poor-grade aneurysmal subarachnoid haemorrhage. However, Meixensberger and colleagues failed to demonstrate the value of brain $P_{O_2}$ as an early predictor of non-survival. Likewise, Kett-White and colleagues only managed to show weak associations between episodes of low brain $P_{O_2}$, abnormal microdialysis, and outcome.

Brain $P_{O_2}$ has also been used to assess the impact of putative therapies and management strategies for subarachnoid haemorrhage. Oddo and colleagues found that a haemoglobin concentration < 9 g dl$^{-1}$ was associated with a lower brain $P_{O_2}$, while Helbok and colleagues reported that high-dose erythropoetin significantly increased brain $P_{O_2}$. The same group, however, reported a detrimental effect with diclofenac.

**Brain tumours**

The compressive effect of brain tumours on surrounding brain $P_{O_2}$ was investigated in the perioperative period.
increased significantly on dural opening and after tumour resection, implying the presence of local ischaemia.58

Cardiac pathology

Reported survival rates for victims of out-of-hospital cardiac arrest range from 0 to 30%, with ~20% of survivors having severe neurological complications. The mechanisms responsible for poor outcomes, despite relatively prompt resuscitation, are likely to include inadequate tissue oxygen delivery to critical organs, especially the heart and brain, during and after cardiopulmonary resuscitation. The ultimate goal of cardiopulmonary resuscitation is to provide critical organs with oxygen, so a direct measure of $\text{pO}_2$ may be a valid method for evaluation.

Brain $\text{pO}_2$ has been measured during cardiopulmonary resuscitation in animal studies19,59,60 and in a case report of a monitored patient with traumatic brain injury who suffered cardiac arrest.61 Yu and colleagues13 measured both brain and skeletal muscle $\text{pO}_2$ in a porcine model of arrest and resuscitation; while muscle $\text{pO}_2$ followed a similar trend to brain $\text{pO}_2$, the response times were slower.

Myocardial ischaemia induces an acute inflammatory response, decreased myocardial efficiency, further dysfunction, and heart failure. Stem cell therapy is being pursued as a potential treatment to replace lost cardiomyocytes, thereby revascularizing the ischaemic tissue. An impediment to successful treatment has been the inability to determine the optimal oxygen concentration necessary for the survival and engraftment of transplanted cells before they can provide functional benefits. Two studies established the ability of both electron paramagnetic resonance and oxygen-dependent phosphorescence quenching to measure and correlate changes in myocardial $\text{pO}_2$, with cardiac function in infarcted rat hearts treated with mesenchymal stem cells62 or endothelial progenitor cells,63 respectively.

Reperfusion after global cardiac ischaemia restores oxygen delivery to ischaemic tissue. The reintroduction of oxygen, however, results in an increased production of reactive oxygen species, which is considered to be the mechanism primarily responsible for postischaemic myocardial contractile dysfunction.64 This occurs on resuscitation from various clinical syndromes, including both regional (acute myocardial infarction) and global myocardial ischaemia (cardiac arrest). Lee and colleagues65 monitored myocardial $\text{pO}_2$ during ischaemia–reperfusion injury in rats and found poor recovery with prolonged ischaemia.

Gut and liver ischaemia

In many critically ill patients, poor tissue oxygenation may be attributable to disordered regional distribution of blood flow, despite an adequate global blood flow and oxygen delivery. Ischaemia of the gut may lead to cellular hypoxia and necrosis, and this may contribute to the development of multiple organ failure.66 Changes in intestinal $\text{pO}_2$ may allow early identification and implementation of pharmacological and nutritional treatments to prevent, limit, or modify disease progression.

In a rat model of chronic mesenteric ischaemia, $\text{pO}_2$ was monitored by electron paramagnetic resonance oximetry over a 7 day period;67 there was a marked initial reduction in $\text{pO}_2$ after superior mesenteric artery banding, followed by a progressive decline to a final $\text{pO}_2$ of 20.9 (SD 4.5) mm Hg, compared with 54.5 (0.9) mm Hg in control animals.

The effects of vasopressors on jejunal mucosal $\text{pO}_2$ have been assessed during experimental endotoxaemia. In one study, noradrenaline and phenylephrine improved jejunal mucosal $\text{pO}_2$, but the effect was blunted by simultaneous administration of vasopressin.68 However, in another study vasopressin alone did not compromise either mucosal $\text{pO}_2$ or oxygen supply in the acute phase of endotoxaemia.69 These studies highlight the variable and still poorly understood effects of vasoactive drugs on regional blood flow and tissue oxygenation and the ongoing debate about their utility in high-risk surgical patients.

Normovolaemic haemodilution can be used to delay or omit the need for blood transfusion during anaesthesia and in the critically ill. Although oxygen content is reduced, whole-body oxygen consumption is maintained by increases in cardiac output and oxygen extraction ratio. However, there is a limit to this process; when oxygen delivery decreases below a critical point, compensatory mechanisms will be insufficient. The critical level of haemodilution for intestinal oxygen consumption was studied in animal models using Pd-porphyrin phosphorescence.70–72 Critical values of haematocrit ranged from 10 to 16% yet, despite a decrease in intestinal oxygen delivery, microvascular $\text{pO}_2$ and oxygen consumption were well preserved, with an increase in $\text{O}_2$ extraction ratio.

Perioperative fluid management remains contentious. Some argue for maintenance or prompt recognition and early correction of tissue perfusion by fluid loading,73 whereas others argue for a more conservative, restricted approach.74 In reality, this is likely to depend on baseline fluid-loading practices. Hypotension not attributable to hypovolaemia may benefit from vasopressors, but this must be balanced against potentially detrimental effects on nutritive organ blood flow and the risk of organ ischaemia. In an abdominal surgery pig model, Hiltbrand and colleagues75 reversed intraoperative hypotension with norepinephrine to target mean blood pressures of 65 and 75 mm Hg and found no adverse effects on systemic blood flow, intestinal tissue $\text{pO}_2$, or local blood flow in the small and large intestines.

Liver dysfunction can also accompany critical illness and may be a significant cause of co-morbidity. Regional hypoxia, causing a reduction in tissue oxygenation, followed by resuscitation may cause significant tissue damage though ischaemia–reperfusion injury. This may be an important risk factor underlying the success of liver transplantation. Liver damage may potentially be prevented by avoidance or minimization of regional hypoxia. Monitoring $\text{pO}_2$ has been used in liver transplantation and during partial hepatectomy.76–78 The $\text{pO}_2$ changed predictably with changes in arterial and expired gas tensions, and with decreases in liver blood flow. In liver-transplanted patients, $\text{pO}_2$ values decreased over the first 24 h but subsequently recovered; this was associated with decreasing acidosis.4

Acute kidney injury

Acute kidney injury (AKI) is a common problem in hospital patients, especially the critically ill. Sepsis, major surgery (in particular, open heart surgery), and acute decompensated heart failure are the most common triggers of AKI. Renal hypoxia makes a major contribution to the pathogenesis of both AKI and long-term chronic kidney disease arising from multiple causes.76,77 Oxygen regulation within the kidney is uniquely complex because oxygen consumption is dominated by the energy requirements needed for sodium reabsorption. Both renal tissue perfusion and the oxygen requirements of the tubular elements are heterogeneous. Countercurrent diffusion of oxygen and carbon dioxide within the renal vasculature also has a major impact on oxygen delivery within the kidney. As a result of this complexity, current understanding of the precise factors that affect kidney oxygenation in both physiological and pathophysiological conditions remains poor.
We and others have reported variable changes in renal \( P_{O_2} \) in various regions of the kidney in rat models of endotoxaemia, peritonitis, and haemorrhage–reperfusion.\(^{76–80}\) Four hours after administration of endotoxin, total renal \( O_2 \) consumption and the gradient between microvascular \( P_{O_2} \) and \( P_{O_2} \) remained unaltered, despite reductions in renal perfusion, oxygen delivery, and urine output.\(^{80}\) Taken in conjunction with the reduction in urine output, these results could represent either a functional renal impairment or even an adaptive response. During exsanguination, \( P_{O_2} \) was maintained in all intrarenal regions, despite significant reductions in blood pressure and total renal blood flow, indicative of a proportional reduction in oxygen consumption.\(^{76}\) Of note, intrarenal flow was redistributed, with reduced cortical, unchanged corticomedullary, and increased medullary blood flow. After resuscitation, significant increases above baseline were seen in blood pressure and \( P_{O_2} \) across all regions. As a more restrictive transfusion practice is being promulgated, the impact of haemodilution on AKI assumes increasing importance. Intrarenal hypoxia is one likely factor that will contribute to AKI during the perioperative period. A pig model was used to compare acute normovolaemic haemodilution achieved by either crystalloid or hydroxyethylstarch, targeting a haematocrit of 15%.\(^{51}\) While renal microvascular oxygenation and renal function were significantly impaired with crystalloid, less tissue oedema formation and an unchanged renal \( P_{O_2} \) were noted with colloid, with better preservation of renal function. Cardiopulmonary bypass is a major contributor to AKI after cardiac surgery,\(^{82}\) attempts to date to ameliorate this injury pharmacologically have been unsuccessful. However, in a pig model, endothelin A receptor antagonism reversed endothelial dysfunction, inflammation, tubular changes, and outer medullary hypoxia measured using a tissue \( O_2 \) sensor.\(^{53}\)

### Skin and soft tissue injury

Successful surgical wound healing requires resistance to infection, and this depends mainly upon oxidative killing of organisms by neutrophils. Tissue oxygen tension is an especially important determinant of postoperative wound healing, because neutrophil bactericidal ability is directly related to \( P_{O_2} \).

Several randomized trials have investigated the effects of supplemental perioperative oxygen administration on the incidence of surgical wound infection, with conflicting results.\(^{84–86}\) In one positive outcome study,\(^{84}\) s.c. \( P_{O_2} \) was significantly higher in the higher inspired oxygen concentration group, with a lower incidence of surgical wound infections. An additive effect of mild hypercapnia on \( P_{O_2} \) was seen in the arm and colon during elective colon resection.\(^{87}\) The s.c. \( P_{O_2} \) has also been measured in patients undergoing laparoscopic surgery\(^{88}\) and in obese patients undergoing major abdominal surgery.\(^{89}\) Tissue \( P_{O_2} \) decreased in the perioperative period both during laparoscopy\(^{55}\) and in obese patients,\(^{56}\) with an increased risk of infection. Postoperative pain may influence tissue perfusion and oxygenation, and hence, postoperative wound infection. The s.c. \( P_{O_2} \) was higher in patients undergoing knee surgery with superior postoperative pain relief, implying that poorly controlled surgical pain reduces tissue oxygen concentrations sufficiently to increase the risk of surgical wound infection significantly.\(^{50}\)

In the field of reconstructive surgery, \( P_{O_2} \) measurement enabled assessment of free-flap viability.\(^{91}\) Here, \( P_{O_2} \) monitoring could detect changes in skin oxygenation both during hyperbaric oxygen therapy and after neural block and extended normovolaemic haemodilution. Neural block did not improve tissue oxygenation, whereas haemodilution augmented oxygenation in a rodent ischaemic flap model.\(^{92}\)

### The oxygen challenge test

Apart from changes in inspired oxygen concentration there is, in general, a poor relationship between arterial \( P_{O_2} \) (\( P_{A,O_2} \)) and \( P_{O_2} \). This disparity emphasizes the important physiological and clinical lesson that normal arterial values should not be used as a surrogate for satisfactory oxygenation at the tissue level. Other factors, such as macrocirculatory and microcirculatory delivery and local cellular metabolism, also impact significantly. Oxygen is delivered by convective flow, driven by blood flow, and transported predominantly by haemoglobin to the microcirculation. Thereafter, the driving force for oxygen diffusion into the tissues is determined by the pressure gradient between the microcirculation and the mitochondria, where most of the oxygen is used. This is related to Fick’s Law of Diffusion, which states that the rate of transfer of a gas through a sheet of tissue is proportional to both the tissue area and the difference in gas partial pressure between the two sides, and inversely proportional to the tissue thickness. For oxygen diffusion, this can be stated as follows:

\[
V_O = K_O \times (P_{microO_2} - P_{mitO_2})
\]

where \( V_O \) is oxygen consumption, \( K_O \) is a parameter dependent upon the diffusing capacity for oxygen from the microvascular network (vessel surface area and path length to the mitochondria), while \( P_{microO_2} \) and \( P_{mitO_2} \) are the mean microvascular and mitochondrial \( P_{O_2} \), respectively. Thus, the greater the pressure gradient and the microvascular surface area, the higher the total number of oxygen molecules that will diffuse.

Although it is this \( P_{O_2} \), gradient rather than the blood content of oxygen that drives diffusion, it is the haemoglobin-bound oxygen that acts as the main reservoir for oxygen. As oxygen diffuses from the plasma, plasma and red cell cytoplasmic \( P_{O_2} \) decrease, leading to greater amounts of oxygen dissociating from the haemoglobin and entering the dissolved plasma pool of oxygen, from where it diffuses into the surrounding tissues.

While traditional teaching has rightly emphasized the role of convective oxygen delivery, the potential contribution of a high \( P_{O_2} \) remains controversial. Hyperbaric oxygen therapy is clearly recognized to be beneficial in carbon monoxide poisoning, where the higher mitochondrial \( P_{O_2} \) achieved is able to displace carbon monoxide from cytochrome oxidase, the last component of the electron transport chain, thereby enabling improved oxidative phosphorylation. The relevance of normobaric hyperoxaemia to increasing \( P_{O_2} \), while frequently reported, remains uncertain. Certainly, hyperoxaemia increases tissue oxygen tensions, albeit by differing extents in different organ beds. The magnitude of this increase during mild hypovolaemia is similar to that observed during normovolaemia. However, this increment diminishes rapidly with continued blood loss, decreasing to the same (or even lower) concentrations as those seen in animals managed in room air. Measuring the downstream increase in \( P_{O_2} \) after an increase in \( P_{A,O_2} \) has been coined the ‘oxygen challenge test’.\(^{93}\) This was demonstrated to be a useful marker for the early detection of shock and an early prognosticator in septic patients.\(^{94}\) While the increment in peripheral \( P_{O_2} \) in normal physiological conditions was correlated with the fraction of inspired oxygen, this is compromised during low-flow states.\(^{27 29 95}\)

This relates to oxygen supply dependence, where the reduction in oxygen delivery exceeds the increased oxygen gradient.
generated by a high PaO₂. Hyperoxaemia (and its impact on diffusive oxygen delivery) may thus be beneficial, but only in the presence of an adequate blood flow (convective oxygen delivery), suggesting a potential utility for supplemental oxygen only after correction of hypovolaemia. However, injured tissue may not be able to extract any additional oxygen because of either increased diffusion barriers, mitochondrial dysfunction, or both.\textsuperscript{15,16,166}

**Conclusion**

Maintaining adequate tissue oxygenation remains one of the most significant tasks for anaesthetists and intensivists. Current clinical tools have advantages and significant limitations. However, newer minimally invasive devices are promising, but still require initial validation before assessing their impact upon clinical outcomes.

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Authors’ contributions**

V.D.S. and M.S. co-wrote the manuscript.

**Declaration of interest**

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