BJA

British Journal of Anaesthesia, 2015, 357–65

doi: 10.1093/bja/aev162
Advance Access Publication Date: 21 July 2015
Review Article

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

V. De Santis and M. Singer*

Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, Cruciform Building, Gower Street, London WC1E 6BT, UK

*Corresponding author. E-mail m.singer@ucl.ac.uk

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

Editor's key points

- The authors explore the concept of tissue oxygen tension and describe the utility of its measurement and the methods available.

Tissue oxygen tension (tP_{O_2}) is the partial pressure of oxygen within the interstitial space of a particular tissue. It represents the balance between local oxygen delivery and consumption at any given time.[1] The tP_{O_2} varies between different organs in resting healthy subjects and animals, and this relates to both the organ's metabolic activity and its blood flow. Of note, the tP_{O_2} within an individual organ remains reasonably comparable across species, allowing for methodological variations (Fig. 1, Supplementary Table S1). Likewise, there may be intra-organ differences, depending on regional variations in organ flow and activity, of which the kidney is a prime exemplar. The tP_{O_2} increases if oxygen delivery increases in excess of consumption and decreases if local oxygen requirements cannot be met. Matched increases or decreases in local oxygen delivery and consumption will thus not impact upon the tP_{O_2}.

Tissue oxygen tension monitoring offers the capability of continuous assessment of the adequacy of regional perfusion. Apart from indicating the local situation in the organ bed being monitored, it may serve as a surrogate for perfusion adequacy in other organ beds, particularly if such an organ can be accessed readily and safely. Such a technology is not in routine clinical use at present but, if shown to be reliable, offers significant utility in the critically ill or in patients undergoing high-risk surgery. We are shortly to embark upon a clinical study exploring the clinical utility of bladder tP_{O_2} monitoring. It is thus timely to review the available methodologies, the underlying (patho)physiological principles, and the prior literature in both patients and laboratory models, and to address any implicit challenges.

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.[6] 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

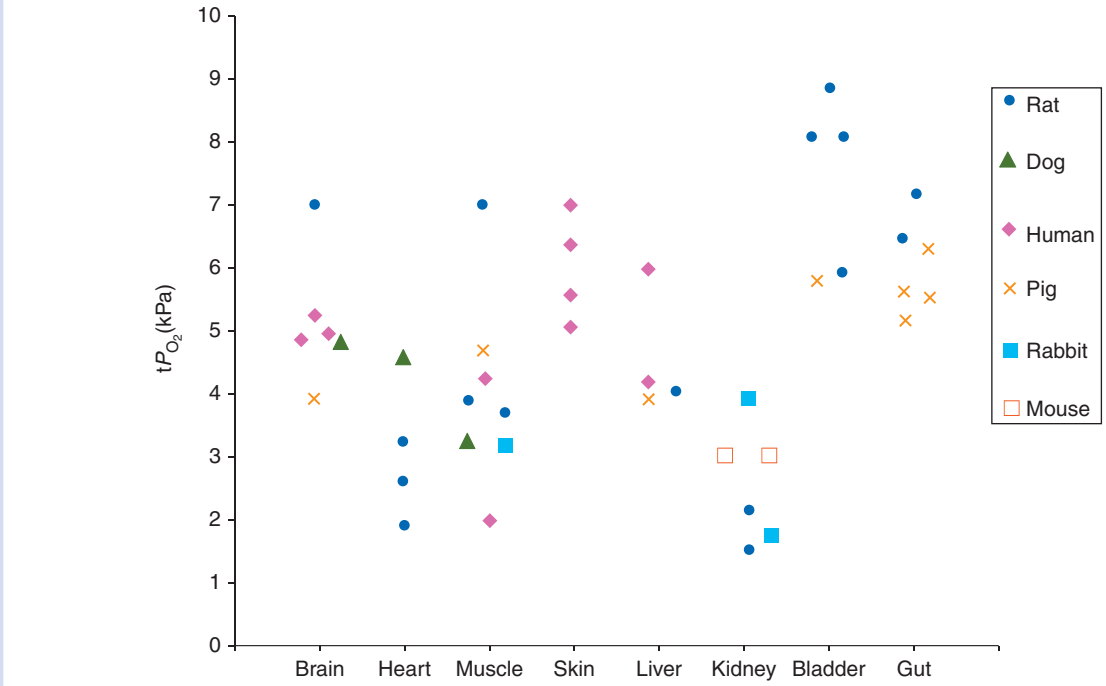

Fig 1 Tissue oxygen tension (tP_{O_2}) values measured in different organs in different species. Only studies in which the inspired O_2 fraction was reported to be 0.21 are included. Ranges for human brain P_{O_2} are reported as 3.4 (SD 0.2) kPa,[2] for muscle 3.8 (0.8) kPa,[3] for skin 7.2 (3.3) kPa, and for liver either 6.1 (5.8)[4] or 4.1 (range 2.6–5.4) kPa.[5]

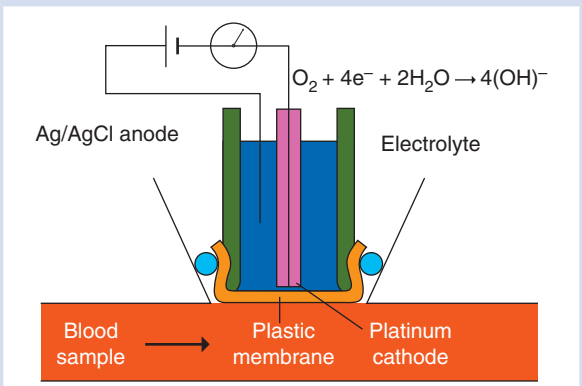

Fig 2 The Clark polarographic technique.

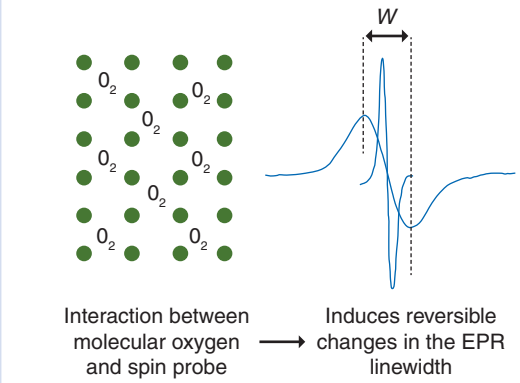

Fig 3 Principle of electron paramagnetic resonance (EPR) spectroscopy. W, linewidth.

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.[7] 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.[8 9]

Newer techniques promise more flexible measurement capabilities. Oxygen molecules can quench the fluorescence and phosphorescence of certain luminophores.[1] 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.[10] 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.[11] This is described by the Stern-Vollmer equation, where luminescence decay is inversely proportional to the local P_{O_2} within the tissue:

$$\left(\frac{\tau_0}{\tau_1}\right) = 1 + (\kappa_q \times \tau_0 \times [O_2])$$

where τ_0 is the decay time at zero oxygen, τ_1 is the decay time at a specific oxygen concentration ($[O_2]$) and κ_q is a diffusion-controlled rate constant that denotes the probability of a singlet-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 tP_{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 metallo-organic protein (an 'oxyphor').[12] Oxyphors (e.g. palladium porphyrin) were formerly bound to albumin to enhance aqueous solubility and bring the quenching variables κ_q and τ_0 into the physiological range. Newer polyglutamic 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 tP_{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.[13] 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 μM 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.

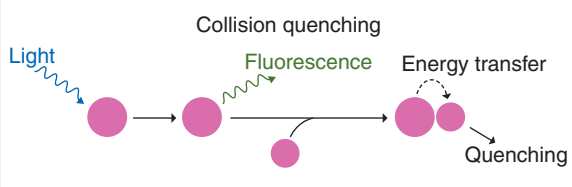

Fig 4 Dynamic fluorescence quenching.

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 (dysoxia). 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,[14] failure of delivery of sufficient oxygen may be attributable to inadequate cardiac output ('circulatory hypoxia'), insufficent 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 dysoxia and an increased diffusion barrier related to tissue oedema.[14] With dysoxia, 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.[15] Tissue oedema after injury may prevent diffusion of oxygen from vessel to cell,[16] 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 tP_{O_2}.[14] 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,[17] or through iatrogenic 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 tP_{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 tP_{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 tP_{O_2} in both peripheral (e.g. s.c. tissue, conjunctiva) and deep sites (e.g. liver, kidney) after haemorrhage,[18–20] and these are in line with the severity of haemorrhage and the adequacy (or otherwise) of resuscitation.[21–27] Our group previously reported concurrent changes in tP_{O_2} in muscle, bladder, liver, and renal cortex during progressive exsanguination in an anaesthetized rat model.[28 29] While bladder, liver, and muscle tP_{O_2} reduced in tandem, renal cortex tP_{O_2} was mantained 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.[30]

Studies during haemorrhage in either pigs[31] or rats[28] report reductions in tP_{O_2} in liver, muscle, and bladder, or a combination of these are 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.[32] 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.[33 34] Provided the patient is adequately fluid resuscitated, tP_{O_2} values in septic patients are generally reported to be elevated.[3 34 35] Boekstegers and colleagues[34] found that skeletal muscle tP_{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 tP_{O_2} normalized in septic patients who went on to survive.[34]

Experimental studies of sepsis and endotoxaemia report a much wider variation in tP_{O_2}, with increases in bladder,[36 37] gut,[38] and skeletal muscle tP_{O_2},[39] no change in gut serosal tP_{O_2},[39] and decreases in gut mucosal,[40] skeletal muscle,[40] liver,[8] and kidney[41] tP_{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 endoxin 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 tP_{O_2}, major decreases in renal cortical and liver tP_{O_2}, and an unchanged skeletal muscle tP_{O_2},[42] 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 microClark electrode sited within the brain parenchyma, 65% of patients had an initially low tP_{O_2} after standard resuscitation.[2] By using a protocol directed at elevating tP_{O_2}, there was better control of intracranial pressure and maintenance of cerebral perfusion pressure. Mortality was significantly lower in patients receiving brain tP_{O_2}-directed care (25.9%) compared with 41.5% in a historical cohort. In a similar comparison study, Spiotta and colleagues[43] found that maintaining brain tP_{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 tP_{O_2}, but not anaemia alone, was a risk factor for unfavourable outcomes, irrespective of the severity of injury.[44] Longhi and colleagues[45] reported that brain tP_{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 tP_{O_2} monitoring may also facilitate early recognition of low oxygen-delivery situations, enabling appropriate therapeutic interventions.[46 47] For example, brain-injured children with an eventual poor outcome had a greater tP_{O_2} response to an increase in inspired oxygen (an 'oxygen challenge' test).[48]

In critically injured adults, Ikossi and colleagues[49] found that deltoid muscle tP_{O_2} was a responsive, reliable, and continuous monitor of changes in base deficit. Initial low values were associated with postinjury complications. Monitoring tP_{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 tP_{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}.[50] The ratio of transcutaneous tP_{O_2} to arterial oxygen tension fell progressively with increasing shock.

Subarachnoid haemorrhage

Bohman and colleagues[51] found that the response to brain tP_{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[52] failed to demonstrate the value of brain tP_{O_2} as an early predictor of non-survival. Likewise, Kett-White and colleagues[53] only managed to show weak associations between episodes of low brain tP_{O_2}, abnormal microdialysis, and outcome.

Brain tP_{O_2} has also been used to assess the impact of putative therapies and management strategies for subarachnoid haemorrhage. Oddo and colleagues[54] found that a haemoglobin concentration <9 g dl^{-1} was associated with a lower brain tP_{O_2}, while Helbok and colleagues reported that high-dose erythropoietin significantly increased brain tP_{O_2}.[55] The same group, however, reported a detrimental effect with diclofenac.[56]

Brain tumours

The compressive effect of brain tumours on surrounding brain tP_{O_2} was investigated in the perioperative period.[57] Brain tP_{O_2}

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 tP_{O_2} may be a valid method for evaluation.

Brain tP_{O_2} has been measured during cardiopulmonary resuscitation in animal studies[13 59 60] and in a case report of a monitored patient with traumatic brain injury who suffered cardiac arrest.[61] Yu and colleagues[13] measured both brain and skeletal muscle tP_{O_2} in a porcine model of arrest and resuscitation; while muscle tP_{O_2} followed a similar trend to brain tP_{O_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 tP_{O_2} with cardiac function in infarcted rat hearts treated with mesenchymal stem cells[62] 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 colleagues[65] monitored myocardial tP_{O_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 tP_{O_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, tP_{O_2} was monitored by electron paramagnetic resonance oximetry over a 7 day period;[67] there was a marked initial reduction in tP_{O_2} after superior mesenteric artery banding, followed by a progressive decline to a final tP_{O_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 tP_{O_2} have been assessed during experimental endotoxaemia. In one study, norepinephrine and phenylephrine improved jejunal mucosal tP_{O_2}, but the effect was blunted by simultaneous administration of vasopressin.[68] However, in another study vasopressin alone did not compromise either mucosal tP_{O_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 tP_{O_2} and oxygen consumption were well preserved, with an increase in 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, Hiltebrand and colleagues[75] 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 P_{O_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 tP_{O_2} has been used in liver transplantation and during partial hepatectomy.[4 5] The tP_{O_2} changed predictably with changes in arterial and expired gas tensions, and with decreases in liver blood flow. In liver-transplanted patients, tP_{O_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 tP_{O_2} in various regions of the kidney in rat models of endotoxaemia, peritonitis, and haemorrhage–reperfusion.[26 78–80] Four hours after administration of endotoxin, total renal O_2 consumption and the gradient between microvascular P_{O_2} and tP_{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, tP_{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.[26] 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 tP_{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%.[81] While renal microvascular oxygenation and renal function were significantly impaired with crystalloid, less tissue oedema formation and an unchanged renal tP_{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.[83]

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 tP_{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. tP_{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 tP_{O_2} was seen in the arm and colon during elective colon resection.[87] The s.c. tP_{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[88] and in obese patients,[89] with an increased risk of infection. Postoperative pain may influence tissue perfusion and oxygenation, and hence, postoperative wound infection. The s.c. tP_{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.[90]

In the field of reconstructive surgery, tP_{O_2} measurement enabled assessment of free-flap viability.[91] Here, tP_{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} (Pa_{O_2}) and tP_{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:

$$\dot{V}O_2 = KO_2 \times (Pmicro_{O_2} - Pmit_{O_2})$$

where $\dot{V}O_2$ is oxygen consumption, KO_2 is a parameter dependent upon the diffusing capacity for oxygen from the microvascular network (vessel surface area and path length to the mitochondria), while $Pmicro_{O_2}$ and $Pmit_{O_2}$ 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 tP_{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 tP_{O_2}, while frequently reported, remains uncertain. Certainly, hyperoxaemia increases tissue oxygen tensions, albeit to 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 tP_{O_2} after an increase in Pa_{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 tP_{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 Pa_{O_2}. 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.[15 16 96]

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

V.D.S. is funded from a grant from the Health Innovation Challenge Fund (NIHR/Wellcome Trust) to assess the role of bladder tissue oxygen monitoring in man. This device is manufactured by Oxford Optronix Ltd (Abingdon, Oxfordshire, UK), which has an IP agreement with University College London, which employs M.S.

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Handling editor: J. G. Hardman