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Review Article

CRITICAL CARE

Optimising organ perfusion in the high-risk surgical and critical care patient: a narrative review

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Summary

Maintenance or prompt restoration of an oxygen supply sufficient to facilitate adequate cellular metabolism is fundamental in maintaining organ function. This is particularly relevant when metabolic needs change markedly, for example in response to major surgery or critical illness. The consequences of inadequate tissue oxygenation include wound and anastomotic breakdown, organ dysfunction, and death. However, our ability to identify those at risk and to promptly recognise and correct tissue hypoperfusion is limited. Reliance is placed upon surrogate markers of tissue oxygenation such as arterial blood pressure and serum lactate that are insensitive to early organ compromise. Advances in oxygen sensing technology will facilitate monitoring in various organ beds and allow more precise titration of therapies to physiologically relevant endpoints. Clinical trials will be needed to evaluate any impact on outcomes, however accurate on-line monitoring of the adequacy of tissue oxygenation offers the promise of a paradigm shift in resuscitation and perioperative practice. This narrative review examines current evidence for goal-directed therapy in the optimisation of organ perfusion in high-risk surgical and critically ill patients, and offers arguments to support the potential utility of tissue oxygen monitoring.

Keywords: critical care; hypoxia; outcomes; perfusion; perioperative; tissue oxygenation

Editor's key points

- Tissue hypoxia is a major determinant of outcome in surgical and critical care patients.
- Current strategies including goal-directed fluid therapy aimed to detect and correct tissue hypoxia by resuscitating to predefined physiological targets, thought to imply adequate perfusion.
- Prompt recognition of tissue hypoxia presents a diagnostic challenge. Thus, an accurate tissue oxygenation monitor would prove invaluable.

Much has been written about haemodynamic optimisation of both the critically ill ICU patient and the high-risk surgical patient. Diverse strategies and monitoring approaches have been advocated and discarded, and no clear consensus has been reached despite decades of research.

While presenting different challenges, high-risk surgical and ICU patients share some commonalities that warrant joint consideration. High-risk surgery accounts for only 12.5% of surgical procedures, yet more than 80% of surgical deaths.[1] Alongside increased mortality, this cohort is at greater risk of postoperative complications including poor wound healing, anastomotic breakdown, surgical site and chest infections, prolonged ileus, and delayed discharge

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from hospital. Independent of preoperative risk, the occurrence of a complication within 30 days of surgery was associated with a 69% reduction in long-term patient survival.[2] Likewise, sepsis, as an example of critical illness, accounted for >50 000 ICU admissions in England in 2015 with a hospital mortality exceeding 30%.[3] There is also a considerable long-term morbidity and mortality risk; about one-third die in the year after sepsis, one-sixth experience severe persisting weakness, psychiatric or cognitive issues, and only half make a complete or near-complete recovery.[4]

Inadequate organ perfusion with resultant tissue hypoxia represents a common pathway to poor outcomes in both surgical and ICU patient groups. How best to identify and respond to such perfusion abnormalities and any associated oxygen supply/demand mismatch remains unresolved both in the operating theatre and on the ICU. This continues to generate considerable debate and controversy. The notable absence of actual perfusion targets within organ beds has hampered progress. Clinicians rely upon: (i) indicators suggesting circulatory stability such as arterial blood pressure (BP), heart rate (HR), and cardiac output, (ii) surrogates of blood volume status such as fluid responsiveness, respiration-induced variations in pulse pressure and stroke volume, and central venous pressure, and (iii) markers of the adequacy of organ perfusion such as urine output, serum lactate, and central venous saturation (SvO_2).

Such global measures do not account for between-organ variations; the perfusion of some tissue beds is compromised earlier than others (e.g. gut and skin as compared with brain). In the case of lactate, the measured blood concentration depends on the balance between production and utilisation; lactate is an important energy substrate, particularly at times of cellular and metabolic stress. Hyperlactataemia may not occur until significant perturbation has occurred.[5]

Goal-directed therapy refers to the administration of fluids, vasoactive drugs, and other clinical interventions to achieve predefined physiological targets in an attempt to optimise global perfusion. Such an approach is physiologically coherent, though does not necessarily guarantee improved clinical outcomes. Some studies, mostly single-centre, have signalled improved survival and decreased complication rates across a range of surgical subspecialties,[6–9] and in critically ill patients with sepsis.[10] However, outcome improvements have not been consistently reproducible, especially in large, multicentre trials.[11–14] Does this lack of benefit represent an overall failure of the concept or reflect inadequacies in the monitoring technologies utilised, lack of user expertise, inappropriate study design (e.g. using fixed drug or fluid dosing), targeting the wrong goals, unsuitable patient selection, failure to adhere to the study protocol, or combinations thereof? Are these negative studies a victory of real-world pragmatism over theoretical purity, for example selecting sample sizes based on unrealistic treatment effects, or enrolling lower-risk patients to meet recruitment schedules? In this review we shall explore the current evidence base for goal-directed therapy in the optimisation of organ perfusion in high-risk surgical and critically ill patients, and offer a rationale supporting the potential utility of tissue oxygen monitoring.

Defining perioperative risk, predicting outcomes

Strategies aimed at improving perioperative perfusion and surgical outcomes, such as goal-directed fluid therapy, will most likely benefit those at greater risk. A predicted post-operative hospital mortality above 5% has become a widely accepted definition of high-risk surgery.[15] Patient factors such as frailty, nutritional status, cardio-respiratory and metabolic fitness, and pre-existing organ dysfunction, alongside surgical factors such as emergency or urgent surgery, the degree of surgical complexity, blood loss, and the extent of tissue trauma should all contribute to this risk prediction.

A variety of scoring tools have been developed, attempting to quantify surgical risk before operation.[16–18] Cardiopulmonary exercise testing is also used for the quantitative appraisal of surgical fitness and risk, generally based on dichotomised anaerobic threshold values above and below 11 ml O_2 kg^{-1} min^{-1}. Such an approach remains contentious; a recent large, multicentre study failed to demonstrate the utility of anaerobic threshold measurement at predicting poor surgical outcomes.[19] Nevertheless, a lack of cardiorespiratory reserve, characterised by an inability to increment oxygen delivery, consumption, or both in the face of increased metabolic stress, should plausibly identify the high-risk surgical patient who may benefit from perioperative haemodynamic optimisation.

Oxygen delivery and tissue hypoxia

Oxygen is essential to sustain cellular respiration in all eukaryotic life forms, including humans. More than 90% is consumed by mitochondria, predominantly for generation of adenosine triphosphate (ATP) by oxidative phosphorylation, but also for production of reactive oxygen species and heat production via ATP-uncoupled respiration. Importantly, the contribution of these latter processes may increase significantly under conditions of inflammation and critical illness, but are rarely considered within the general concept of whole-body oxygen delivery and consumption.

The oxygen cascade describes the progressive, step-wise diminution of oxygen partial pressure from inspired air to mitochondrion. Established dogma dictates it is this pressure gradient that drives tissue oxygenation, however, this neglects the centrality of cardiac output in maintaining oxygen delivery to meet cellular needs.

Tissue hypoxia is a major pathophysiological determinant of outcome in both high-risk surgical and sick ICU patients. An initial increase in oxygen consumption is characteristic of the stress response after a surgical insult. Failure to meet this increased demand, with consequent development of a conceptual tissue oxygen debt, is detrimental; an increased incidence of complications, organ failure, and death correlate with an increasing severity and duration of tissue hypoxia.[20] Likewise, early, non-resuscitated sepsis is often characterised by hypotension, hyperlactataemia, and reduced central or SvO_2. These abnormalities imply, but do not conclusively prove, compromised organ perfusion with increased anaerobic metabolism and tissue hypoxia. Failure to significantly improve circulatory status after seemingly adequate resuscitation prognosticates for poor outcome.[21]

Goal-directed therapy in sepsis

Based on such observational findings, early correction of organ hypoperfusion using protocolised 'early goal-directed therapy' was advocated by Rivers and colleagues.[10] Their strategy utilised aggressive fluid resuscitation, with or without blood transfusion, with or without dobutamine, and specifically targeted central venous oxygen saturation ($ScvO_2$) alongside other physiological variables over a 6-h period. A prospective, randomised controlled trial (PRCT) in patients with presumed sepsis presenting to their emergency department demonstrated significant improvements in survival rates.[10] This study, however, generated multiple questions, for example why mortality reduction was seen only in patients dying acutely from sudden cardiovascular collapse rather than multi-organ failure. Nonetheless, this concept was enshrined within the early resuscitation bundle of the Surviving Sepsis Campaign guidelines[22 23] until three multicentre PRCTs (ProCESS, ARISE, ProMISe) failed to replicate morbidity or mortality benefit over the standard-of-care limbs.[11–13] To provide balance to the debate, the patients in these three trials were much less sick despite using the same entry criteria; baseline $ScvO_2$ values were much higher with the UK study reporting that a third of the enrolled patients would not normally have been admitted to a critical care unit.[11] The large majority of patients did not have any cardiac output monitoring to more accurately titrate fluid and drug therapy. It is reasonable to assume that the general quality of patient care (including resuscitation) has improved over the intervening 15–20 yr. Indeed, little between-group differences were seen in therapeutic interventions in the latter studies. This may also be, in part, related to a considerable proportion (>25–30%) of the protocol groups not achieving the targeted physiological endpoints. This is problematic for studies in which a treatment goal is the intervention under scrutiny.

Whether improved compliance to the protocol would have made a difference to outcomes remains moot. Nonetheless, it remains a generally accepted maxim that early recognition of a septic (or any other critically ill) patient followed by prompt and appropriate cardiorespiratory intervention is beneficial. Important questions remain as to what intervention is optimal and what physiological endpoint(s) should be targeted.

Perioperative goal-directed therapy

Resuscitation to predefined physiological targets has long been standard practice in ICUs. This is increasingly widespread, though not universal, in the perioperative setting, even though outcome studies predate those undertaken in the critically ill. In a landmark PRCT, targeting supra-normal perioperative oxygen delivery (>600 ml min^{-1} m^{-2}) in a high-risk surgical cohort using fluid and dobutamine, initiated before operation, halved complication rates and reduced mortality by 75%.[20] Comparable findings have been replicated in a number of other studies using fluid and dopexamine or epinephrine to achieve similar oxygen delivery targets.[6 7]

The fall from grace of the pulmonary artery flotation catheter after the negative UK multicentre PAC-MAN study[24] and other similar trials led investigators to seek new and less invasive ways of both monitoring and augmenting oxygen delivery, and to seek different endpoints. Some studies have targeted a stroke volume at the top of the Starling curve either intraoperatively or after operation. Utilising oesophageal Doppler, our group and others demonstrated reductions in postoperative complications and hospital length of stay in abdominal, cardiac, and orthopaedic surgical populations.[9 25–28] While not all oesophageal Doppler-guided optimisation studies have demonstrated outcome improvement, a recent systematic review found that postoperative complications were reduced in patients undergoing colorectal and high-risk surgery, but not in those undergoing intermediate-risk surgery.[29] Similar studies with other technologies have yielded more variable outcomes. This may reflect the risk status of the patients studied, but also methodological issues relating to the technology,[30 31] the intervention, or the choice of targeted endpoint. For example multiple perioperative studies using a regimen including a fixed dose infusion of dopexamine have all failed to show benefit, so the underlying rationale behind this approach needs to be questioned.[14 32 33]

Summarising the above, general improvements in perioperative practice and haemodynamic management mean than lower-risk patients are likely to do well regardless of optimisation, unless some untoward catastrophe occurs, as adequate tissue perfusion is likely to be maintained throughout. Even in higher-risk patients, 30-day mortality rates are now relatively low in developed countries.[19] The focus should perhaps be on a reduction in postoperative complications rather than mortality. Limitations in the monitoring technology being utilised must be fully appreciated by the user. For example changes in arterial compliance related to use of vasopressors, rapid major blood loss, or large volume fluid administration will invalidate trends in cardiac output assessed by non-calibrated pulse contour or bio-reactance devices.[34 35]

Finally, selection of appropriate treatment endpoints and safe interventions to achieve perfusion targets appear key. The use of a fixed rate vasoactive infusion can hardly be described as haemodynamic *optimisation*. The ongoing debate surrounding liberal *vs* restrictive perioperative fluid regimens fails to consider individual patient needs. From a physiological standpoint, the patient needs the right amount of an intervention to ensure adequate tissue perfusion. Too little or too much may both prove to be deleterious. These issues will be discussed in more detail below.

Enhanced recovery after surgery, critical illness, and fluid regimens

A healthy debate has raged over the past two decades over the volume of fluid needed by a patient, both perioperatively and during critical illness. An association between a positive sodium and water balance and increased mortality and rates of complications has been reported perioperatively[36 37] and in patients with sepsis.[38] This study by Boyd and colleagues is instructive; they reported a median positive fluid balance after 4 days ranging from 1.5 L in the 'driest' quartile to 20.5 L in the 'wettest'. A quarter of patients in this 'wet' quartile received more than 36 L of fluid. At just 12 h, the median net fluid balance varied from 710 ml to 8150 ml in the two extreme quartiles. Mortality was twice as high in the wet quartile. While acknowledging that sicker patients are more likely to require, or at least be given, more fluid, a marked difference in outcomes remained even after adjustment for illness severity.

Baseline practices in the reporting institution, or even country, are generally overlooked. In the three Early Goal-

Directed therapy trials in septic shock,[11–13] fluid volumes were greater in the US study compared with both Australia and the UK. Traditional users of low volume fluid replacement have reported outcome benefit from additional (titrated) fluid administration, whereas the opposite appears true in places where fluid use has been traditionally more liberal. For example, Venn and colleagues[39] reported improved outcomes when more fluid was given intraoperatively to patients undergoing hip fracture repair, from a median 1392 ml–2051 ml titrated to an optimised stroke volume. Conversely, Brandstrup and colleagues[40] reported a reduced rate of postoperative complications with fluid *restriction*; a median fluid volume of 2740 ml was administered on the day of colorectal resection compared with 5388 ml in the 'liberal' fluid cohort.

Despite a paucity of high-quality evidence, recent consensus statements have advocated fluid restriction for patients undergoing abdominal surgery as part of 'enhanced recovery' protocols.[41–43] However, the story becomes more confusing with the recent publication of the RELIEF trial, a large PRCT of 3000 high-risk patients undergoing major abdominal surgery.[44] Outcomes, notably acute kidney injury, were *improved* in the liberal fluid group who received a median 6.1 L in the first 24 h after commencement of surgery compared with those receiving 3.7 L in the fluid restriction group.

Surrounded by such conflicting findings, to couch questions pertaining to optimisation of tissue perfusion simply in terms of '*wet vs dry*' is arguably reductionist thinking *par excellence*. Notably, few of the recent large perioperative trials have utilised more sophisticated monitoring. For example, in the RELIEF study, only one in seven of the enrolled patients received any form of intraoperative cardiac output monitoring. Intraoperative measurement of lactate and $ScvO_2$ was not reported, while only 30% had a postoperative lactate measurement performed. It is thus conceivable that some 'dry' patients may have been seriously under-perfused while some 'wet' patients may also have been under-perfused or overloaded with excessive fluid. Likewise, pursuit of arbitrary physiological surrogates of organ perfusion, or targeting of pre-specified values of oxygen delivery may not necessarily achieve the unmeasured goal of adequate tissue oxygenation, and may even prove deleterious if excessive volumes of fluid or inotrope are used.[45]

The wet-dry debate in the early resuscitation of septic patients has recently entered the public arena with forceful criticism of the ongoing Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (US CLOVERS) trial by Public Citizen, a consumer advocacy organisation. In this study, patients are being randomised to receive predominantly fluid or vasopressors for initial resuscitation; Public Citizen argue the need for a third group receiving standard of care rather than either extreme.[46]

A more nuanced approach acknowledges the enormous heterogeneity among these patients and abandons the concept of a rigid one-size-fits-all protocol. Comorbidities and variable cardiorespiratory reserve coupled with widely differing metabolic derangements and fluid shifts, alongside often unpredictable circulatory responses to sedative agents and anaesthetic interventions, dictate the need for a more bespoke management with appropriate targeted monitoring. Such an approach reframes the debate in terms of cellular wellbeing with haemodynamic optimisation of the high-risk surgical and sick ICU patient guided by verified, objective markers of tissue oxygenation.

Tissue oxygen monitoring

Our current ability to detect evolving shock and tissue hypoxia at an early stage is limited. Physiological adaptation to blood loss, heart failure, and other low output states can effectively camouflage deterioration, especially in young, fit people who have considerable cardiorespiratory reserve. Animal and clinical studies confirm conventional haemodynamic measures such as HR and BP are poor markers of early tissue hypoperfusion, as is serum lactate.[5 47–49] While global blood flow monitoring gives some indication of the adequacy of tissue perfusion, it does not offer detail at the tissue level, the impact of any microcirculatory perturbations nor, as mentioned earlier, variability in blood flow between organ beds or the susceptibility of particular organs to tissue hypoxia.

In recognition of these limitations, investigators have turned to regional and tissue oxygenation monitoring in patients including gastric tonometry,[50] near-infra-red spectroscopy,[51] side-stream dark field imaging of the microcirculation,[52] and tissue oxygen tension monitoring of subcutaneous tissue[53] and conjunctiva,[54] albeit with limited success. None of these modalities have become established in routine clinical practice because of technical and reliability issues, and complexities of measurement.

We have worked with Oxford Optronix (Milton Park, Oxon, UK) to develop a bedside tissue oxygen (PtO_2) monitor inserted into the bladder via a modified 14 Fr Foley catheter. The sensing probe is advanced until resistance is encountered, indicating implantation into the bladder wall, analogous to a temporary pacing wire within the ventricular septum. The drained bladder contracts around the probe, such that it remains enveloped, and continuous contact with the urothelium is maintained. The sensor diameter is less than 1 mm, whilst the sensing area is 14 mm^2. This device is shortly to undergo clinical trials.

PtO_2 represents the partial pressure of oxygen of the interstitial space of a given tissue and varies between different organ beds.[55] As PtO_2 is a measure of the local oxygen supply/demand equilibrium to that tissue bed, the normal range in healthy humans and animals reflects the balance between blood flow to that organ and its aerobic metabolic activity. Thus resting muscle PtO_2 (averaging approximately 5.3 kPa) will be much higher than liver PtO_2 (averaging 2.7 kPa), as the liver is more metabolically active and its blood supply mainly constitutes a portal circulation containing deoxygenated haemoglobin after its earlier passage through the gut.[56] Of note, across different species (human, rat, dog, pig, rabbit, and mouse) values for each organ bed measured were largely consistent.[55]

PtO_2 decreases when tissue oxygen delivery cannot meet the metabolic requirements of predominantly mitochondrial respiration and increases in situations of relative metabolic inactivity, such as during the established organ failure of sepsis.[57] In rodent models of haemorrhage-reperfusion and hypoxaemia-reoxygenation,[58 59] PtO_2 fell progressively in line with the insult severity across a variety of organ beds ranging from superficial, accessible tissues, such as bladder and muscle, to deeper, more vital organs (liver and renal cortex). Prompt improvements in PtO_2 were seen during resuscitation, with normal values regained after sufficient treatment had been given. Similarly, upon translation to a 55–60 kg porcine model of progressive haemorrhage,[5] the decrease in bladder PtO_2 also *preceded* conventional clinical markers of shock such

as BP and lactate. These data offer further encouragement for its utility in human patients by raising the prospect that bladder PtO_2 monitoring may offer an 'early warning system', detecting incipient shock before current modalities used in routine clinical practice.

As noted earlier, a static PtO_2 value represents the balance between local oxygen supply and demand. Additional information regarding this balance and any occult perfusion abnormalities can be obtained with an 'oxygen challenge test' (OCT). The OCT represents a dynamic assessment of circulatory sufficiency analogous to a fluid challenge. It uses the expectant, incremental increase in PtO_2 in response to a short period of hyperoxia to assess the adequacy of tissue perfusion (Fig 1). The predictable increase in PtO_2 in different organ beds after hyperoxia in healthy animals was blunted during various shock states including hypovolaemia and resuscitated sepsis.[60] While this response was expected in hypovolaemia, the blunted tissue response that persisted despite resuscitation in sepsis implies local microcirculatory dysfunction or shunting. Notably, the degree of blunting was in line with illness severity and prognosis. A similar blunted response was prognostic in septic patients.[61] A small, single-centre study which used goal-directed therapy in septic patients to target a positive oxygen challenge response above a certain threshold, reported improved survival.[62] While concerns regarding hyperoxia and oxygen toxicity are increasingly aired,[63] given the brief nature of the exposure, comparable to preoxygenation before induction of anaesthesia, we consider this is unlikely to cause harm.

Tissue oxygen monitoring thus has a strong foundation in both basic science and clinical research. Animal models have allowed testing over diverse tissue beds, from brain and kidney to conjunctiva and muscle. Some studies have assessed responses to cardiorespiratory insults in different anatomical compartments of the same organ bed.[64] Superiority has been demonstrated in early detection of inadequate tissue perfusion compared with conventional monitoring modalities. The OCT further enhances this diagnostic capability, allowing early recognition of complex perfusion abnormalities such as those observed in sepsis.[61] Findings in these pre-clinical models suggest the bladder, an easily accessible, superficial organ, can act as a 'canary' tissue bed that accurately reflects changes in deeper, more vital organs.

Prior technologies have failed to become established in routine clinical practice, so resolution of practical, technical, and reliability issues is paramount. Monitoring of tissue oxygenation has evolved from polarographic Clark electrodes to modern devices based on photoluminescence quenching. Disadvantages of the Clark electrode technique are the need to calibrate *in vivo*, and the consumption of oxygen by the electrode itself that makes it less accurate at lower values of PtO_2. Modern photoluminescence technology uses a small, transition-metal containing optode sensor. After luminescence with incident light, this signal is quenched by oxygen. With partial pressures of oxygen inversely proportional to the decay half-life of the luminescent signal, lower oxygen tensions will result in a longer half-life. This basic physical concept offers three advantages. It can be incorporated into the Stern-Volmer equation to calculate PtO_2 in real-time, *in vivo* calibration is not needed, and detection of tissue hypoxia is increasingly accurate with longer half-lives at lower values of PtO_2.

Potentially, photoluminescence-based oxygen sensing may prove invaluable in optimising organ perfusion in patients undergoing high-risk surgery and in the critically ill. Urinary hypoxia measured using this technology has recently been shown to predict acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass,[65] though urine PO_2 values will be less responsive to cardiorespiratory alterations than tissue tension and more prone to contamination by room air.

Failure to maintain adequate organ perfusion and tissue oxygenation is a major determinant of outcome in these patients, yet trials targeting supraphysiological values of oxygen delivery have often proved disappointing. Arguably, the choice of targeted endpoint, the monitoring technology, and the patient population are responsible for the conflicting findings. PtO_2 may thus offer an early diagnostic capability of local oxygen supply/demand imbalance, and a theranostic role by guiding the choice of intervention and titrating the dose (of fluid, drug, ventilator setting) to an acceptable but not excessive level. Early mortality after elective surgery is low in developed countries, yet morbidity, delaying hospital discharge, or requiring readmission, is still problematic and impacts both on the patient and the efficiency of the healthcare system. This morbidity may be severe, necessitating intensive care (re-)admission, but even relatively minor morbidity can have a significant impact. An accurate, continuous means of measuring the adequacy of tissue perfusion is the ultimate goal of haemodynamic monitoring. Whether PtO_2 monitoring, or another novel technology, fulfils this dream remains to be seen. However, there is a definite and urgent need to progress from the current status quo.

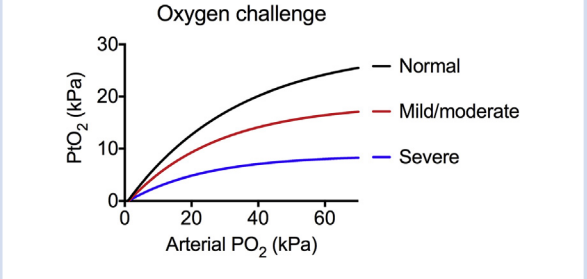

Fig. 1. Tissue PO_2 (PtO_2) response to an oxygen challenge. The incremental increase in PtO_2 in response to increased PaO_2 diminishes with increasing illness severity and perfusion deficit.

Authors' contributions

All authors contributed to the conception, writing, editing and finall approval of the final manuscript.

Declaration of interest

A tissue oxygen sensing device has been co-developed by Oxford Optronix and the Singer lab (University College London [UCL], London, UK). An intellectual property agreement exists between UCL and Oxford Optronix in the event of any commercial development.

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