Institution: City University London

Unit of Assessment: 15 General Engineering

Title of case study: New sensors for detecting oxygen levels in organs and tissues in critically ill patients

1. Summary of the impact

Research undertaken at City University London has led to the development of new blood oxygen optical and fibre optic sensors that advance clinical assessment in hospitals by monitoring a patient's arterial blood oxygen in specific organs or tissues. The applications of such sensors extend the boundaries of current state-of-the-art medical sensors in this field. They are capable of monitoring blood perfusion at times where the current commercial techniques fail to do so and have the advantage of providing organ-specific perfusion (oesophagus, bowel, liver, stomach, brain, etc.), enabling the effective monitoring of the wellbeing of specific parts of the body. These new sensors help clinicians monitor more reliably and provide the most appropriate treatment for very sick patients.

2. Underpinning research

Research in Biomedical Engineering is an area of significant growth around the world. Biomedical optics and biophotonics (optical techniques such as imaging to study molecules, cells and tissues) have played an important role in medicine and biology for many years for monitoring, diagnostic, prognostic or therapeutic purposes. In recent years, the study of optical sensors has been applied in medicine mainly for the detection of chemical and biochemical changes in the body. The development of optical sensors with applicability in healthcare represents a strength in research taking place in the UK. The high degree of miniaturisation of optical and fibre optic sensors and their considerable geometrical versatility make possible their use in medicine for continuous and in many cases non-invasive monitoring of many physiological and chemical changes.

Innovative Biomedical Engineering research at City University London, led by Professor P. Kyriacou (a member of academic staff since 2004), has involved the design, development and clinical evaluation of a series of optical and fibre optic sensors for monitoring the levels of oxygen and blood volume in arterial and venous blood in critically ill patients (adults, children and neonates). Earlier work was also undertaken at St Bartholomew's Medical School and Hospital as part of Professor Kyriacou's PhD studies prior to joining City. Key members of the City team include Dr J. Phillips (Senior Lecturer, at City since 2006), Dr M. Hickey (Research Fellow, at City since 2007), Dr J. May (Research Assistant, at City since 2010) and Ms T. Zaman (PhD student at City since 2011). The key clinical collaborators are Ms H. D. L. Patel (Consultant Plastic Surgeon, The Royal London Hospital); Professor R. M. Langford (Director of Anaesthetic Laboratory, St. Bartholomew's Hospital) Professor A. Petros (Director of Neonatal Intensive care, Great Ormond Street Hospital for Children); and Professor S. K. Pal (Director of Research & Development, St Andrew's Centre for Plastic Surgery & Burns).

The basis of this research is the current inability to continuously monitor organ blood oxygen saturation in specific locations (organs and tissues), which prevents the early detection of inadequate tissue oxygenation and so increases the risk of severe lack of oxygen in the blood, multiple organ failure and death. Current commercial devices require adequate oxygenated blood flow in the extremities to give accurate oxygen saturation results. Poor blood flow is common in decreased blood volume, hypothermia and constriction of the blood vessels, for example, after prolonged operations or in patients suffering with peripheral vascular disease or any other cardiovascular pathologies. Because conventional pulse oximeters must be attached only to peripheral parts of the body, where pulsating flow is most easily compromised, oxygen readings are unreliable or can cease entirely. Thus blood oxygen readings may be unavailable at the time when they would be most valuable. Current commercial pulse oximeters will only reveal information about the global perfusion of the body and not specific/regional perfusion.

The application of these new oesophageal, organ and free flap sensors has pushed the boundaries of current practices and clinical monitoring techniques. Normally, pulse oximeter sensors (used for measuring arterial blood oxygen saturation) are placed on peripheral parts of the body such as the finger, toe or ear lobe. The new sensors can be applied to specific parts of the body such as the oesophagus, bowel, liver, stomach, the 'soft spot' of a newborn baby's skull or the free flaps in plastic surgery. They enable direct monitoring of the viability (wellbeing) of certain organs, tissues or other parts of the body and provide doctors with knowledge of the condition and blood circulation in specific areas which will enhance their assessment, diagnosis and treatment of the patient.

3. References to the research

1. Kyriacou P.A. (2013). Direct pulse oximetry within the esophagus, on the surface of abdominal viscera, and on free flaps, *Anesthesia and Anelgesia*, 117(4), 824-833 10.1213/ANE.0b013e3182a1bef6
2. Kyriacou P.A. *et al.* (2002). Esophageal Pulse Oximetry Utilizing Reflectance Photoplethysmography. *IEEE Transactions of Biomedical Engineering*, 49(11), 1360-1368 10.1109/TBME.2002.804584
3. Hickey M. *et al.* (2010). Measurement of splanchnic photoplethysmographic signals using a new reflectance fibre-optic sensor, *Journal of Biomedical Optics*, 15(2), 027012 10.1117/1.3374355
4. Kyriacou P.A. *et al.* (2008). A pilot study in neonatal and pediatric esophageal pulse oximetry, *Anesthesia and Analgesia,* 107(3), 905-908 10.1213/ane.0b013e31817e67d1
5. Phillips J.P. *et al.* (2010). Cerebral Arterial Oxygen Saturation Measurements using a Fiber-optic Pulse Oximeter, *Neurocritical Care*, 13(2), 278-285 10.1007/s12028-010-9349-y
6. Kyriacou P.A. (2006). Pulse Oximetry in the oesophagus, *Physiological Measurement,* 27(1), R1-R35 10.1088/0967-3334/27/1/R01

Research Grants

The research has been and still being supported by key funding bodies. To date the work has attracted funding from EPSRC (£250,000), NIHR (£650,000) and the NHS (£400,000).

The selected work is published in peer reviewed journals which are highly regarded in their field and/or which have strong dissemination to clinicians.

4. Details of the impact

The technological innovations described above have the following benefits:

1) Improvement to the health and wellbeing of patients, along with greater peace of mind for parents in the case of babies and children undergoing treatment
2) Provision of target monitoring of organs
3) Enhanced accuracy of diagnosis, leading to the delivery of optimum treatment
4) Contribution to more cost-effective healthcare
5) Generation of new clinical knowledge of current unresolved chronic diseases.

All of the sensors and instrumentation were designed and fabricated in the Biomedical Research Laboratory at City University London, led by Professor Kyriacou. The optical sensors and instrumentation were all rigorously evaluated in clinical trials ongoing since 2008 in the collaborating hospitals which included Great Ormond Street Hospital for Children, St Bartholomew's Hospital, The Royal London Hospital, The Royal Brompton Hospital and St Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital. The sensors have already benefited more than 200 patients.

Clinical trials were carried out in different populations of patients (neonates, children, adults) with different clinical conditions and pathologies (intensive care patients, surgery patients, etc.). The sensors were customised for each situation and patient population, including suites of sensors as follows:

- Optical and fibre optic oesophageal sensors for adult patients undergoing cardiothoracic bypass graft surgery
- Optical and fibre optic oesophageal sensors for adult patients undergoing general surgery
- Optical oesophageal sensors for intensive care patients with severe burns
- Optical oesophageal sensors for intensive care neonates and children

- Optical and fibre optic sensors for abdominal organ monitoring during surgery
- Optical fontanelle sensor for monitoring brain oxygenation in neonates in intensive care
- Optical sensors for monitoring survivability of flaps in plastic reconstructive surgery.

The sensors are designed for minimal discomfort to the patient. In the majority of applications the placement of the sensors is completely non-invasive or semi-invasive: for example, in newborn babies the probe is placed on the skull. Some are semi-invasive, for example, where the sensor is placed in the oesophagus and where sensors to detect oxygen in organs and tissues are used during surgery in the unconscious patient. The sensors do not require extraction of blood to give readings.

Oesophageal and organ sensors
Oesophageal sensors were fabricated in the laboratory utilising miniaturised monochromatic light emitting diodes and photodetectors sensitive to specific absorbers (i.e. oxyhaemoglobin in blood) in blood or tissue. The sensor's geometry was custom-made for each anatomical placement. For example, the oesophageal sensors (adult, paediatric, neonatal) were designed and fabricated in the laboratory to be cylindrical and small enough to be placed in the human oesophagus with relative ease (e.g., the neonatal oesophageal sensors has a cross diameter of about 2mm). Encapsulation of the sensors was carefully designed to include biocompatible materials in order to ensure the safety of the patient during the clinical trials. The fibre optic oesophageal sensors used fibres of sizes down to 150 microns. These have pushed the limits of current design capabilities, as they have incorporated miniature prisms at the end of the probe to shine light at the wall of the oesophagus (reflectance pulse oximetry).

All custom-made oesophageal optical sensors were evaluated in clinical trials in over 100 healthy and critically ill patients at St Bartholomew's Hospital, The Royal London Hospital, Great Ormond Street Hospital for Children and St Andrew's Centre for Plastic Surgery and Burns.

The abdominal organ sensors were similarly custom-designed for specific application. Different probe geometries were utilised in the Biomedical Laboratory again using monochromatic light emitting diodes and photodetectors. A spatula-shaped optical reflectance probe developed on a flexible printed circuit board was used for placement on solid organs such as the liver and kidney. A pencil-shaped hand-held optical and fibre optic probe (with a footprint of approximately 1.5cm) was developed for spot measurements on top of solid and hollow organs during open laparotomy surgical operations.

The custom-made abdominal organ optical sensors were used in clinical trials in approximately 50 adult patients at St Bartholomew's and The Royal London Hospitals undergoing open laparotomy operations. During these measurements arterial oxygen saturation measurements for each organ were displayed continuously and in real time on a computer screen. For the first time surgeons and anaesthesiologists were able to observe direct oxygenation measurements from specific organs, revealing their state of health before and after the surgical procedure. The clinical trials showed that it is feasible to provide valuable information at the bedside regarding the adequacy of the blood supply to the gut and other vital organs.

Ultimately the oesophageal and organ sensors can be used to reduce stays in intensive care or death from sepsis and Multiple Organ Dysfunction Syndrome. They have provided clinical and physiological knowledge of how different organs perfused in different diseased states or conditions. They have demonstrated that monitoring specific organs can be superior to and more specific than global monitoring, which is currently the gold standard in measuring oxygen in the blood. This specific monitoring leads to more targeted therapy and better treatment. The new sensors proved that the oesophagus is a better place to monitor oxygenation when the patients are very ill. The results of the oesophageal sensor minimised the use of invasive blood sampling, which is much better for critically ill patients and more economical for the healthcare provider. The oesophageal sensor is also a more reliable monitor than the current state-of-the-art pulse oximeters (devices that measure oxygen levels in the blood), especially when patients are critically ill. The oesophageal technology helped the clinicians using it to optimise the management and therapy of the patients. This will have a direct effect on the time spent in intensive care for patients.

Free flap sensors for reconstructive surgery
Pilot clinical investigations involving 20 patients, in collaboration with St Andrew's Centre for Plastic Surgery and Burns, allowed the continuous and non-invasive measurement of the oxygenation in the free flap in reconstructive surgery for the first time.

This optical sensor was also custom built in the Biomedical Engineering laboratory at City, where academic staff worked in partnership with clinicians. It was designed as a reflectance circular optical sensor with a very small size and thickness in order to comfortably be placed and secured on the free flap during measurements. Plastic surgeons used the sensor from the beginning of the operation before the harvesting of a suitable flap. The sensor was used to confirm the suitability (good vasculature) of the flap, as it was capable of indicating good blood flow and blood oxygenation of the tissue on the donor site. After the completion of the reconstructive surgery the probe was placed and secured (taped) on the free flap in order to monitor the viability of the flap continuously and in real time. It is critical to ensure that the flap receives adequate oxygenated blood at the initial stages following surgical procedure.

Results from these clinical trials enable surgeons to understand the behaviour of free flaps during and after operations, thereby accurately assessing the survivability of the flap. This technology will be established as a gold standard in monitoring free flaps in plastic surgery as there is clearly a gap in monitoring technology for such applications. The continuous monitoring and non-invasive nature of the sensors enables surgeons to optimise their surgical procedures. The sensor is capable of detecting early complication in the flaps, allowing surgeons to reinvestigate the flap in good time and maximise their survivability. The development of the free flap sensor provides security and confidence to patients, knowing that they can be monitored accurately and effectively

All sensors are still in use within the NHS (St Bartholomew's Hospital, Great Ormond Street Hospital for Children and St Andrew's Centre for Plastic Surgery and Burns) as research tools in further clinical trials. Clinicians have confirmed that the trials have demonstrated the suitability of the opto-electronic sensors for use in patients where commercial medical devices do not yet exist or where they fail to provide an accurate measurement of arterial oxygen saturation; and of the optical free flap pulse oximeter as an alternative technique for monitoring perfusion in various types of flaps at all operative periods. There is no medical device currently available with the capability of monitoring splanchnic perfusion continuously; this important application is addressed by the development of the splanchnic optical sensor. Completion of clinical trials will led to the commercialisation of the sensors.

The sensor technologies have now attracted the attention of companies in the medical devices industry, such as GE Healthcare, Samsung, Philips, Masimo, Covidien and Intelligent Fabric Technologies plc. Following an expression of interest by these companies, discussions are underway with their research groups and non-disclosure agreements are in place.

5. Sources to corroborate the impact
Corroborating statements have been provided by senior clinicians at St Bartholomew's Hospital, The Royal London Hospital, Great Ormond Street Hospital for Children and St Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital, Essex.

Patents:

1. WO2005060825: Optical Fibre Catheter Pulse Oximeter. Inventors: Phillips Justin P (GB); Langford Richard M (GB); Jones Deric P (GB); Kyriacou Panicos A (GB)
2. WO2007060428: System and method for estimating substance concentrations in bodily fluids. Inventors: Kyriacou Panicos (GB), Rybynok Victor (GB)
3. P003017GB: An intelligent Artificial Intervertibral Disc Prosthesis (filed April 03 2009)
4. Inventors: Kyriacou Panayiotis (GB), Mehul Pancholi (GB)
5. GB1001436.3 – Non-Invasive Monitor; Inventors: Kyriacou Panayiotis, Rybynok Victor
6. GB1000532.0 – Method for monitoring blood components; Inventors: Justin Phillips, Panayiotis Kyriacou
7. GB1300611.9 –Lithium Analyser; Inventors: Panayiotis Kyriacou, Michelle Hickey, Iasonas Triantis