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Development of a fibre optic oxygen sensor for respiratory monitoring in the intensive care unit

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Abstract. Arterial oxygen tension is commonly measured by means of intermittent arterial gas sampling. This technique is unable to detect within-breath oxygen tension changes that may be observed in mechanically ventilated patients, especially in the presence of lung injury. Moreover, it may not afford sufficient time resolution to detect potentially injurious settings of the mechanical ventilation itself. Continuous and rapid arterial oxygen tension measurement could detect within-breath changes in pulmonary gas exchange and offer clinically important feedback for the management of mechanical ventilation therapy in real time. We developed a novel fibre optic intravascular oxygen tension sensor, measured its fast response time *in vitro*, tested its blood clotting resistance over a period of 24 hours, and its capacity to measure arterial oxygen tension *in vivo* in a pig model of uninjured lung. This short communication will review the main steps of this collaborative project's progress to date, highlighting the technology's strengths, together with future potential for translation to a clinical scenario.

1. Introduction: the clinical need

The Acute Respiratory Distress Syndrome (ARDS) is a high-mortality, hypoxic condition where critically ill patients receive respiratory support with mechanical ventilation[1].

A risk of the life-saving mechanical ventilation therapy is that some regions of ARDS patients' lungs may cyclically open up during inspiration and collapse during expiration, causing lung injury[2]. This cyclical opening and closing of lung regions could affect pulmonary gas exchange, and could be detected as partial pressure of arterial oxygen (PaO_2) oscillations at the respiratory rate (RR)[3].

Figure 1 shows PaO_2 respiratory oscillations recorded with a ruthenium-based fibre optic sensor in a rabbit model of ARDS[4], and how they are affected by an increase in RR from 10 to 30 breaths per minute, while maintaining positive end-expiratory pressure (PEEP) at 10 cmH_2O and driving pressure (Δ) at 30 cmH_2O .



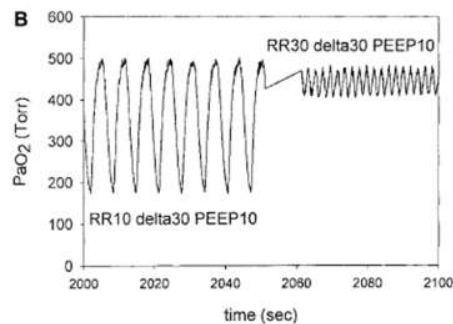


Figure 1. Example of respiratory PaO_2 oscillations, and how they can be affected by an increase in RR from 10 to 30 breaths per minute. PaO_2 data were collected in an anaesthetized, mechanically ventilated rabbit following induction of lung injury (surfactant depletion) via saline lavage. Figure is from Baumgardner *et al.*[4]. RR: respiratory rate; PEEP: positive end-expiratory pressure; delta: driving pressure.

The sensor used by Baumgardner *et al.*[4] was made with ruthenium, a toxic material that prevents the sensor being used in clinical settings[5]. We are developing and testing a medical-grade fibre-optic oxygen sensor to measure PaO_2 continuously. This sensor could be used to personalize mechanical ventilation therapy in ARDS patients, for example for the setting of RR, PEEP and driving pressure in order to avoid or at least reduce injurious cyclical lung opening and collapse.

2. A role for continuous arterial oxygen sensing in the management of mechanical ventilation

Figure 2 illustrates the different input variables that could be used by a computational model for personalized ventilation management in real time[6]. Together with measurements of airway pressure, pulmonary aeration and compliance, PaO_2 continuous monitoring by means of a fast-response sensor could afford a greater degree of personalization in the management of mechanical ventilation in ARDS patients.

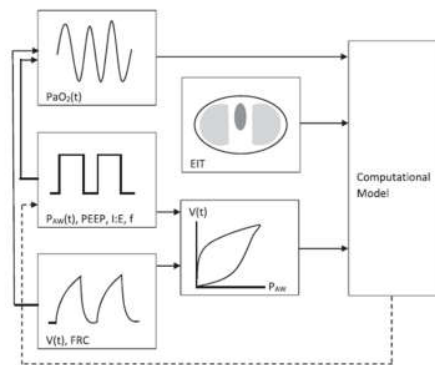


Figure 2. Flowchart illustrating the rationale for the integration of continuous PaO_2 monitoring as one of the input variables (continuous lines) for a computational model that could adjust and personalize mechanical ventilation settings in real time (dashed line). Figure is from Formenti and Farmery[6]. Abbreviations: PaO_2 : partial pressure of arterial oxygen; EIT: electric impedance tomography; PAW: airway pressure; PEEP: positive end-expiratory pressure; I:E: inspired-to-expired ratio; f: frequency; FRC: functional residual capacity; $V(t)$: tidal volume.

This short communication summarizes the *in vitro* and *in vivo* stages of this new technology's development to date. It briefly highlights how this technology is improving our understanding of the physiological response to mechanical ventilation.

3. *In vitro* development

The fibre optic PaO_2 sensor technique is based on the luminescence quenching by oxygen of a luminophore embedded in the matrix material[7]. Its initial development involved testing different polymer matrices to optimize the sensor's response time. The first experiments were performed in the gas phase in order to identify the best candidate polymer matrices for testing in the liquid phase, a more expensive and time-consuming stage of the development.

3.1. Gas phase

Figure 3 (left) shows the molecular structure of three different acrylate type polymer matrices used during the sensor's development: PMMA (poly-methyl methacrylate), PEMA (poly-ethyl methacrylate) and PPMA (poly-propyl methacrylate)[8]. Polymers with longer pendant groups (e. g. PPMA) tend to have greater oxygen solubility and diffusion coefficients than polymers with shorter pendant groups (e. g. PMMA), hence could have faster response time.

Figure 3 (right) shows the associated rapid response time recorded by the three polymer matrices used in a gas chamber[9]. This study of response time in the gas phase has implications for the monitoring of human breathing[10] and preceded the sensor's development in the liquid phase.

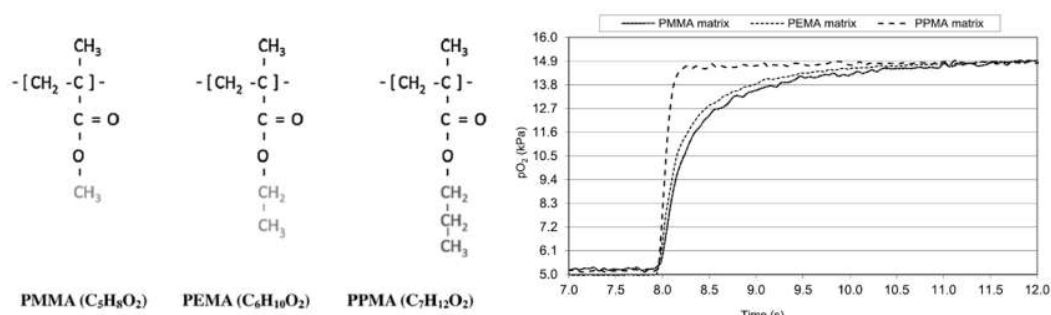


Figure 3. Illustration of (left) the molecular structure of polymer matrices and (right) their response time measured for a step-change in the partial pressure of oxygen (PO_2) in a gas chamber. Figures are from Chen *et al.*[8, 9]. PMMA: poly-methyl methacrylate; PEMA: poly-ethyl methacrylate; PPMA: poly-propyl methacrylate.

3.2. Liquid phase

A flowing liquid test system where the PO_2 could be altered rapidly and frequently was used to test the sensor's performance *in vitro*, simulating as much as possible the environment in which the sensor would be exposed to *in vivo*. Two extracorporeal oxygenators were arranged in parallel to provide PO_2 levels of 5 and 30 kPa, peristaltic pumps maintained the flow through the system and solenoid valves allowed computer-controlled rapid switching between the two parallel circuits. Figure 4 shows that in water at room temperature a PO_2 step-change between 5 and 30 kPa was recorded within ~100 ms[9].

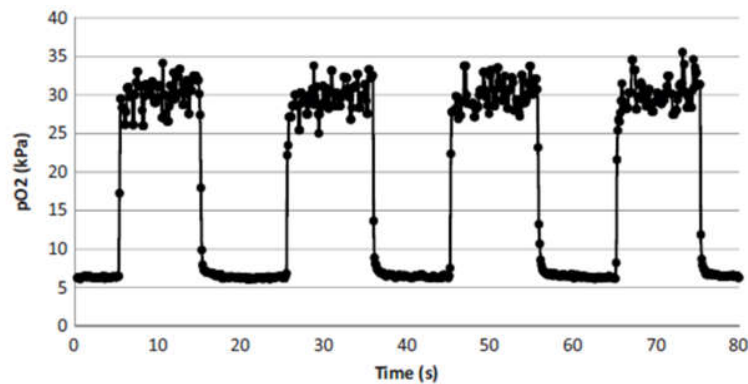


Figure 4. Illustration of the sensor's response time to PO_2 changes between 5 and 30 kPa in water at room temperature. Sampling rate was 10 Hz. Figure is from Chen *et al.*[9].

The final set of *in vitro* experiments involved experiments where the liquid test system was filled with heparinized lamb's blood, obtained from a local abattoir, and maintained at physiological temperature of $\sim 39^\circ\text{C}$. These measurements demonstrated the sensor's capacity to detect rapid PO_2 oscillations at frequencies between 10 and 60 breaths per minute[11], covering a large range used for mechanical ventilation in adult and pediatric intensive care.

4. *In vivo* development

All animal experiments were approved by the relevant ethics committees, conformed to the National Institutes of Health Guidelines for the Use of Laboratory Animals, and adhered to Animal Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines.

4.1. Blood clotting resistance

Blood clotting on the surface of the fibre optic oxygen sensor could reduce the sensor's response time. Sensors were tested for 24 hours in non-heparinised animal (pig) studies, representing a realistic challenge for the sensor's blood clotting resistance[11]. Following immersion in non-heparinised blood for 24 hours, sensors were examined by means of scanning electron microscopy (SEM). SEM did not detect clots on the sensors' surface (figure 5).

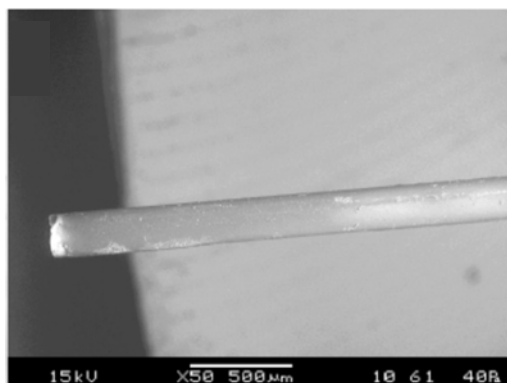


Figure 5. SEM image (small scale) of a sensor after 24 hours immersion in pig arterial non-heparinized flowing blood. Spectral analysis (data not shown) did not detect different materials on the sensor's surface before and after immersion in blood. Figure is from Formenti *et al.*[11].

4.2. Agreement with standard blood gas analysis

PaO₂ recorded with the fibre optic oxygen sensor was compared with standard blood gas analysis in 4 anaesthetised, mechanically ventilated pigs. Figure 6 shows the agreement between the two methods: the bias ratio value was small (0.98) with limits of agreement of 0.73 and 1.24 (n = 39)[12].

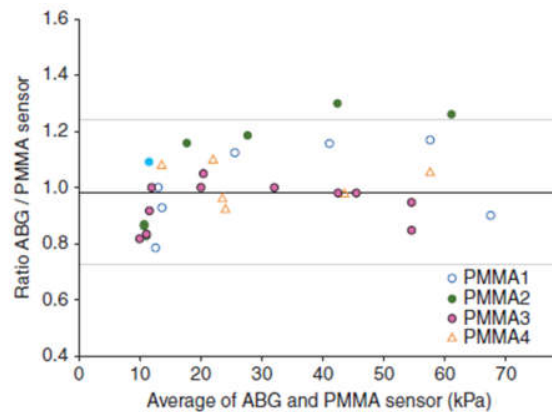


Figure 6. Arterial oxygen tension values measured using standard blood gas analysis and the fibre optic oxygen sensor (n = 39) compared by the Bland–Altman plot [13]. Figure is from Formenti *et al.*[12]. The horizontal axis is the paired average, and the vertical axis is the paired ratio (standard blood gas value / fibre optic oxygen sensor value). PMMA1-4 indicate the results from the four animal studies. The middle solid line represents the bias, and top and bottom grey lines represent the 95% limits of agreement [mean ratio (2 SD); SD was 0.13].

4.3. Arterial oxygen during breath holds and tidal breathing

Having collected evidence for the sensor's rapid response time and clotting resistance, we tested its performance in animal studies. Sensors were inserted in main arteries of eight anaesthetised, mechanically ventilated pigs and PaO₂ data were collected continuously alongside respiratory and cardiovascular parameters. These animals were studied as they presented to the laboratory, i. e. without induction of lung injury. The experimental protocol included a series of breath holding manoeuvres and tidal breathing with different mechanical ventilation settings.

Figure 7 illustrates that the fibre optic sensor detected rapid PaO₂ changes associated (a) with a breath hold manoeuvre performed at the end of an inspiration and (b) with tidal breathing, in an anaesthetised, mechanically ventilated pig[14]. Similar responses were observed in the other animals studied.

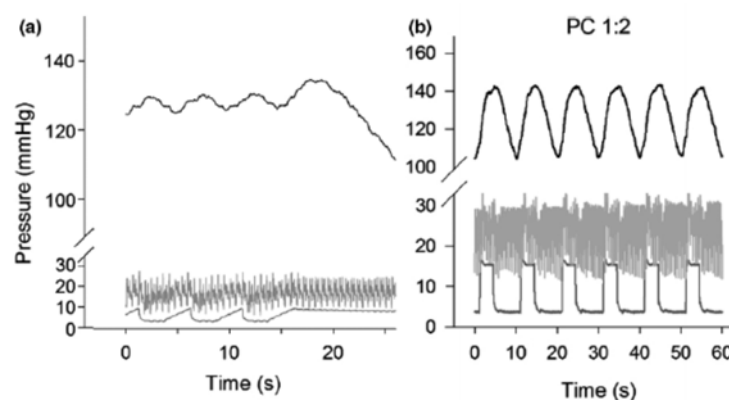


Figure 7. Representative continuous measurements of PaO₂ (top, black), pulmonary artery pressure (middle, light grey) and airway pressure (bottom, dark grey) are presented as a function of time during mechanical ventilation at a RR of 6 breaths per minute with PEEP of 5 cmH₂O. Figure is from Formenti *et al.*[14]. PC 1:2 indicates pressure control mechanical ventilation with a 1-to-2 ratio between inspiration (shorter, 2 s) and expiration (longer, 8 s).

This study provided experimental evidence in support of theoretical models that elegantly and accurately estimated alveolar gas concentration changes within a single breath[15], well before this fibre optic technology was available.

5. Ongoing research and future perspectives

The first animal studies in which the sensor was used demonstrated that PaO₂ respiratory oscillations can be observed in the absence of lung injury. The amplitude of these oscillations was smaller than that reported in the presence of lung injury[4], but was similar to that calculated from mathematical models[15].

Having demonstrated the sensor's performance in detecting respiratory PaO₂ oscillations in the uninjured porcine lung, we are now at the exciting and challenging pre-clinical stage of studying a pig ARDS model and progress to first-in-man study. Overall, this new technology is generating new data that are shedding light on the cardiopulmonary physiological responses to mechanical ventilation in anaesthetized animals [14], with implications that may be of interest in clinical settings.

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