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Intra-breath arterial oxygen oscillations detected by a fast oxygen sensor in an animal model of acute respiratory distress syndrome

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Editor's key points

- A fibreoptic sensor was developed which can measure P_{O_2} continuously in blood.
- The sensor was tested in animal models over a range of Pa_{O_2} values.
- The sensor agreed with conventional blood gas analysis.
- In a model of cyclical atelectasis, the sensor detected arterial P_{O_2} oscillations.
- The sensor has clinical potential.

Background. There is considerable interest in oxygen partial pressure (P_{O_2}) monitoring in physiology, and in tracking P_{O_2} changes dynamically when it varies rapidly. For example, arterial P_{O_2} (Pa_{O_2}) can vary within the respiratory cycle in cyclical atelectasis (CA), where Pa_{O_2} is thought to increase and decrease during inspiration and expiration, respectively. A sensor that detects these Pa_{O_2} oscillations could become a useful diagnostic tool of CA during acute respiratory distress syndrome (ARDS).

Methods. We developed a fibreoptic P_{O_2} sensor (<200 μm diameter), suitable for human use, that has a fast response time, and can measure P_{O_2} continuously in blood. By altering the inspired fraction of oxygen ($F_{I_{O_2}}$) from 21 to 100% in four healthy animal models, we determined the linearity of the sensor's signal over a wide range of Pa_{O_2} values *in vivo*. We also hypothesized that the sensor could measure rapid intra-breath Pa_{O_2} oscillations in a large animal model of ARDS.

Results. In the healthy animal models, Pa_{O_2} responses to changes in $F_{I_{O_2}}$ were in agreement with conventional intermittent blood-gas analysis (n=39) for a wide range of Pa_{O_2} values, from 10 to 73 kPa. In the animal lavage model of CA, the sensor detected Pa_{O_2} oscillations, also at clinically relevant Pa_{O_2} levels close to 9 kPa.

Conclusions. We conclude that these fibreoptic Pa_{O_2} sensors have the potential to become a diagnostic tool for CA in ARDS.

Keywords: acute respiratory distress syndrome; arterial oxygen monitoring; cyclical atelectasis; fibreoptic sensor

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It is commonly accepted that arterial oxygenation remains essentially constant during the respiratory cycle in the healthy lung. Only minimal variations have been observed, with a period corresponding to the breathing period.[1–4] In contrast, in some conditions of lung injury, the arterial partial pressure of oxygen (Pa_{O_2}) is known to oscillate to a great extent.[5–7] It is thought that these Pa_{O_2} oscillations are caused by alveolar opening during inspiration, when Pa_{O_2} increases, and by alveolar collapse during expiration, when Pa_{O_2} decreases; this phenomenon is called cyclical atelectasis (CA). This understanding is supported in part by evidence from imaging studies using, for example, computed tomography and positron emission tomography scans (reviewed in[8] and[9]) and in part by studies using optical intravascular sensors, which showed Pa_{O_2} oscillations in animal models of lung injury.[6 7 10–13]

These insightful investigations have furthered our understanding of the relationship between Pa_{O_2} levels and lung mechanics, and have better informed the management of mechanical ventilation. However, investigations using fast Pa_{O_2} sensors have not yet been conducted in human patients because early embodiments of these sensors contained ruthenium, a toxic material,[14] which needs to be exposed in order for the sensors to achieve a sufficiently rapid response time.[15] The assessment of individual sensors is a critical step when using these prototype sensors for physiological or medical research.[15–17] Furthermore, the relevance of animal studies and their translation into medical practice remain unclear, due, for example, to anatomical and pathophysiological differences between species.

In order to avoid the requirement for a toxic component in these sensors, we produced a Pa_{O_2} sensor based on a platinum

complex, immobilized in a polymer matrix,[18 19] which has the potential to be safely used in humans, once its reliability is established in large animal models. We recently showed that this sensor can detect up to 60 P_{O_2} oscillations per minute *in vitro*, simulating the occurrence of CA at a high respiratory rate.[17] We also showed that, when exposed to non-heparinized blood, the sensor is resistant to blood clotting at least for a period of 24 h *in vivo*.[17]

This sensor has the potential to become a useful diagnostic tool for CA in the acute respiratory distress syndrome (ARDS), or in other clinical scenarios where Pa_{O_2} is thought to change rapidly. Moreover, the continuous real-time Pa_{O_2} signal would provide immediate feedback on the effect of changes in ventilatory settings, which could be tailored on an individual basis, possibly leading towards a more personalized form of ventilation therapy.

This study aimed at establishing the sensor's response time, exploring the Pa_{O_2} range over which the sensor can generate reliable results, using standard blood gas analysis as a control measurement, and assessing whether it could detect Pa_{O_2} oscillations in an ovine model of ARDS *in vivo*.

Methods

The methods for the assessment of sensor's response time *in vitro* are presented elsewhere,[18 20] and outlined in the Supplementary material.

All the animal experiments conformed to the National Institutes of Health Guidelines for the Use of Laboratory Animals. The protocols for the linearity experiments at the Charles University, Czech Republic, were approved by the local University Animal Care Committee. The protocols for the ovine lavage model studies were approved by the UK Home Office. At the end of each study, the animals were killed under anaesthesia with an overdose of pentobarbital ($\sim$100 mg kg^{-1}). Relevant sections of the ARRIVE guidelines were adhered to.

Assessment of sensor linearity

The *in vivo* linearity of the polymethyl methacrylate (PMMA) sensor was first assessed in experiments at the Faculty of Medicine, Charles University, Plzen, Czech Republic. One female domestic pig (weight 38 kg, age 3 months) was studied during the 8 h recovery and stabilization period from surgery, before the beginning of a separate experiment on the same animal.

Anaesthesia was induced with i.v. propofol (1–2 mg kg^{-1}) and ketamine (2 mg kg^{-1}). The trachea was intubated and the lungs were mechanically ventilated with tidal volumes of 8 ml kg^{-1}, with a PEEP of 6 cm H_2O, and $F_{I_{O_2}}$ of 35%. The respiratory rate was adjusted to maintain normocapnia. Anaesthesia was maintained with continuous infusions of propofol (1–4 mg kg^{-1} h^{-1}) plus fentanyl (10–15 μg kg^{-1} h^{-1}). After preparation, the infusion of fentanyl was decreased to 5 μg kg^{-1} h^{-1}, and maintained until the end of the experiment. Adequacy of anaesthesia was determined by end tidal agent monitoring, the absence of movement, haemodynamic monitoring (heart rate and arterial pressure), and absence of reflexes. Continuous infusion of Ringerfundin™ solution (Braun Melsungen Ag, Melsungen, Germany) was used as a fluid replacement in doses of 10 ml kg^{-1} h^{-1} during the preparation and reduced to 7 ml kg^{-1} h^{-1} thereafter.

The PMMA sensor was connected to the phase measurement system,[17] and inserted in the femoral artery through a standard catheter (length 10 cm, diameter 1.2 mm) to monitor Pa_{O_2} responses to changes in $F_{I_{O_2}}$. This was temporarily decreased to 21%, and then increased to 60%, 80%, and 100%, interspersed with recovery periods where $F_{I_{O_2}}$ was returned to baseline (i.e. 35%); each condition lasted for about 4 min. The sensor was calibrated *a posteriori*, on the basis of the smallest and greatest Pa_{O_2} values, as recorded with standard analysis of arterial blood gas (ABG, ABL710, Radiometer, Copenhagen, Denmark). Arterial blood samples were obtained once $F_{I_{O_2}}$ had been maintained at 21%, 35%, 60%, 80%, 100%, and 35% for $\sim$3 min, just before $F_{I_{O_2}}$ was changed to a different concentration; ABG results were used as a means of comparison with data continuously recorded through the sensor. The sampling rate was set at 10 Hz.

In a second set of experiments, the linearity of the sensor was assessed at the University of Bristol, School of Veterinary Sciences, where a series of $F_{I_{O_2}}$ changes (similar to those presented above) were applied before induction of lung injury in three ovine models. Female sheep [weight 69 (2) kg; age $\sim$18 months] were obtained from a local commercial farm source. For these studies, the sensor was calibrated *in vivo*, on the basis of standard ABG analysis at baseline (i.e. $F_{I_{O_2}}$=21%), and at $F_{I_{O_2}}$ of 35%; this range of values was chosen because it was associated with Pa_{O_2} values of about 11–20 kPa, where ABG analysis is frequently used. One PMMA sensor was used in each *in vivo* study (i.e. one for the porcine model, and three for the ovine models, such that a total of four sensors was used).

Detection of within-breath oscillations

To determine whether the sensor was capable of detecting within-breath Pa_{O_2} oscillations, one sheep with lavage-induced lung injury was studied at the School of Veterinary Sciences, University of Bristol, UK. An 18 G catheter was placed in the right cephalic vein and anaesthesia was induced with i.v. midazolam (0.4 mg kg^{-1}) and propofol to effect ($\sim$2 mg kg^{-1}). The trachea was intubated and anaesthesia maintained with isoflurane ($\sim$1% end-tidal) with the Anaconda system (Sedana Medical AB, Stockholm, Sweden). The sheep was positioned in sternal recumbency, morphine (0.15 mg kg^{-1} i.v.) was administered together with remifentanil or alfentanil infusion. Hartmann's solution was infused i.v. at $\sim$10 ml kg^{-1} h^{-1}. Adequacy of anaesthesia was determined by end tidal agent monitoring, the absence of movement, haemodynamic monitoring (heart rate and arterial pressure), and absence of reflexes. A catheter was placed in an auricular artery for arterial pressure measurement. The ECG, direct arterial pressure, Sp_{O_2}, and end-tidal carbon dioxide were monitored throughout. The PMMA sensor was positioned in the carotid artery via a standard arterial catheter (length 8 cm, diameter 0.9 mm), the insertion of which was guided with ultrasound imaging. Ventilation was achieved with a Siemens Servo 900C mechanical ventilator in