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Measurement of Oxygen in Biological and Medical Experiments

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ABSTRACT

Since the maintenance of the appropriate levels of oxygen is essential for ensuring the success of many of the specialized experiments in space missions, such as tissue culture experiments, the continuous monitoring of partial pressures of oxygen provides important data. We are developing optical methods of monitoring not only oxygen but also many dissolved constituents in blood and tissue culture solutions. The optical system uses tiny optical fibers, which easily fit inside a fine-gauged needle, for monitoring each specimen. Moreover, the beam can be split so that multiple specimens can be monitored simultaneously. The same optical technology can also be used for monitoring the blood chemistry of humans and animals; it is minimally invasive. It has a medical application for measuring tissue partial pressures of oxygen.

INTRODUCTION

The shuttle have been used for a variety of scientific experiments in the biological and medical sciences. Oxygen is essential for survival of aerobic (oxygen-utilizing) organisms. Low or elevated oxygen partial pressures can derange metabolism and cause cellular injury. For ground-based experiments, oxygen electrodes are available are available. Though they have limitations for continuous, long-term monitoring, they are accurate and widely used, for example, in medicine (operating rooms) and for environmental studies. Thus, maintaining oxygen partial pressures within a narrow optimal range is essential for conducting successful experiments. However, in spacecraft where size and weight are extremely limited and the time of the astronauts is divided among multiple experiments, it has not been feasible to monitor oxygen continuously with current methods. Instead, periodic measurements or estimates usually substitute for intermittent or continuous analyses. Thus, the development of reliable automated analyses would improve the environmental control of tissue culture and other experiments and also reduce the ambiguity that has plagued the interpretation of the results of many experiments.

Optical sensors offer an advantage for routine tests that are frequently performed for extended periods of time on space missions, such as monitoring oxygen partial pressures (pO_2).

BACKGROUND OF PROBLEM

Our interest in monitoring tissue oxygen partial pressures (pO_2) began when we started a project relating to the treatment of late radiation tissue injury (LRTI). LRTI, a form of radionecrosis, occurs in up to 5% of cancer patients treated with high dose curative intent radiation therapy. A frequent manifestation of LRTI is the occurrence of a hypoxic non-healing wound about 3 months later, for which hyperbaric oxygen therapy (HBOT) has become well established as the principal therapy (Mader, 1989). The primary benefit of HBOT in LRTI related wounds appears to be the establishment or a suitably steep gradient at the interface between normal tissue and LRTI, promoting angiogensis (formation of capillaries, veins, arteries) via macrophage mediated growth factors (Baffour et al., 1992; Knighton et al., 1981; Marx et al., 1990, 1995; Schweiki et al., 1992). For treatment of radionecrosis, Marx (1995) found that a 20 exposure therapy greatly enhanced the chances (90%) of complete wound healing.

Hyperbaric oxygen therapy has been employed for treating a number of different medical conditions besides wound healing. For example, surgery for certain forms of congenital heart disease is sometimes carried out in high-pressure tanks (Ganong, 1995; pg. 635). Hyperbaric oxygen has also been used to treat gas gangrene (pO_2 > 70 mm Hg stops the growth of clostridial organisms), carbon monoxide and cyanide poisoning (Guyton, 1991; pg. 475). However, because of the risk of oxygen toxicity, the patient's exposure to hyperbaric oxygen must be carefully monitored to conform to time and pressure schedules. These schedules are medically conservative and provide guidelines for exposure times to protect patients against developing overt symptoms of oxygen toxicity. Nonetheless, these methods are indirect and are based on behavioral or other manifestations rather than on direct real-time measurement of tissue pO_2.

Although an oxygen electrode can be inserted into the artery for periodic measurements during surgery, there is no device for hyperbaric conditions that provides continuous real-time monitoring of oxygen direct that is the counterpart to pulse oximetry and transcutaneous oximetry (see below). Moreover, there are no routine methods for the continuous monitoring of blood and tissue pO_2 during exposure to hyperbaric oxygen. Thus, our goal was to develop a method of measuring tissue pO_2 directly.

Current Clinical Methods

Table 1 summarizes the types of sensors for measuring oxygen. Details of the uses of oxygen electrodes, pulse oximetry, and transcutaneous oximetry are described below.

Table 1. Types of sensors for measuring oxygen partial pressures that are currently used clinically

Type	Operational Principle	Advantages	Disadvantages
Oxygen (Clark) electrodes	Blood is drawn at regular intervals to measure the O_2	Reliable. Has been used for decades. Large body of technical expertise available for its use in operating rooms.	Does not measure in real time. Time lag of withdrawal of blood and the O_2 measurement.. Costly. Requires calibration.
Pulse oximetry	Measures pulse-gated changes in optical density of tissue.	Fast, non-invasive.	Does not monitor organ tissue oxygenation. Gives poor results in some clinical settings.
Transcutane -ous oximetry	Measures cutaneous pO_2 as a surrogate for tissue pO_2	Fast, non-invasive, repeatable.	Cutaneous pO_2 often differs markedly from pO_2 of deeper tissues.

Oxygen Electrodes

The Clark electrode is the most commonly used (Clark, 1956) and established method for measuring concentrations of oxygen in arterial and venous blood. In critical care settings, intravascular sensors are inserted into a catheter for analyzing blood pH, pCO_2, pO_2. Intravasulcar sites pose the hazard of blood clot formation and infections. On the other hand, tissues do not provide representative monitoring sites, since concentrations vary between parts of the body (Alcock and Turner, 1994). Moreover, because it consumes oxygen, the oxygen electrode cannot be used for determining oxygen concentrations in poorly vascularized whole tissues or in cells.

Pulse Oximetry

Pulse oximeters are commonly used in surgery and in intensive care units for measuring (estimating) arterial hemoglobin-oxygen saturation continuously and non-invasively. Pulse oximeters determine the pulsatile variations in optical density of tissues in the red and infrared wavelengths to compute arterial oxygen saturation without calibration (Alcock and Tuner, 1994). Pulse oximetry instruments assume that the forward scattered plethymographic pulsatile signals are due to arterial blood. In fact, blood pressure and flow remain pulsatile in microcirculation, which allow the noninvasive measure of arterial saturation from the finger tip or the ear lobe (Takatani and Ling, 1994).

Pulse oximetry is limited in applications sites of transmission. This device, however, does not provide an accurate representation of organ tissue oxygenation, in particular, the brain (Li et al., 1990). There are marked regional differences because of flow patterns controlled because of dilation or constriction of vessels by the sympathetic nervous system.

Transcutaneous Oximetry

Transcutaneous oximetry uses a Clark-type electrically heated oxygen-sensing electrodes that are attached to the skin (Rooke, 1992). The electrode attaches to the skin with double-sided adhesive tape. An electric heating element, which is built into the electrode, controls local skin temperature. The heating element is warmed to 43-45C which minimizes local vasomotor tone and causes nearly maximal vasodilation of the underlying cutaneous vasculature. Transcutaneous oxygen tension serves as an index of the adequacy of skin blood flow, and therefore yields valuable “functional” information not provided by noninvasive “anatomical” testing modalities such as echo-doppler ultrasound imaging.

Transcutaneous oximetry measures cutaneous oxygen tensions ($TcPO_2$) from the outside of the skin. In brief, oxygen in the blood diffuses out of the cutaneous capillaries into the interstitial spaces and surrounding skin cells. Although some of this oxygen is used for skin cellular metabolism, the remainder diffuses throughout the skin, which in turn is responsible for cutaneous oxygen tension.

Transcutaneous oxygen measurements provide good reproducibility and detect relatively small changes in $TcPO_2$ produced by disease progression or therapeutic intervention, such as in people with longstanding diabetes because of the high incidence of vascular degeneration the extremities (Hauser et al., 1984).

NEW DEVELOPMENTS AND THEIR USES: THERAPEUTIC AND SPACE MISSIONS

The use of fiber optics for measuring oxygen is not new (Wolthuis, 1994). We are proposing an improved methodology that is adaptable to more medical and research needs (Ham and Cohen, 1996). The sensor is based on the principle of reflection or backward scattered optical spectroscopy. The concept of the prototype pO_2 sensor (shown in Fig. 1) uses multi-mode optical fibers in a bundle to allow a *remote* scenario for the sensor. That is, all of the instrumentation electronics would be located external to the test chamber (i.e., remote processing), and the only portion of the sensor system that would be inside of the chamber are the optical fibers. Details of the needle sensor are shown in Fig. 2. Of importance in this type of pO_2 sensor is the wavelength dependent absorption properties of various species such as hemoglobin and cytochrome contained in tissue samples which will affect the measured transmittance and reflectance (Takatani and Ling, 1994). The optical fiber approach allows tremendous flexibility in carrying out experiments because it reduces limitations of the particular configuration of the samples to be tested. Also, an optical fiber approach would be necessary if this concept was taken to the level of use in a hyperbaric chamber. The main design criterion for this type of sensor would be nonflammability because of the oxygen levels in the hyperbaric chamber where the sensor would be used. Discrimination of the net tissue oxygen saturation levels will be carried out using a Partial Least-Squares (PLS) (Ham and Kostanic, 1996; Marten and Naes, 1989) statistical calibration modeling approach.

Therapeutic. There is currently no simple method to quantitate directly interstitial/cellular pO_2 for diagnostic or therapeutic purposes in an HBO environment. If such a method is developed, the therapeutic benefit of HBOT for LRTI could be more reliably predicted and documented. Since the O_2 metabolic effect on angiogenesis occurs within the interstitial compartment and lags the alveolar and arterial pO_2 (Well et al., 1977), the objective assessment of LRTI related wounds (Marx, 1995) requires a direct method of quantitating interstitial/cellular pO_2.

However, HBOT also poses health and safety hazards (Mader,1989; Sheffield and Dunn, 1997). For these reasons, the development of a method for monitoring of the O_2 gradient would significantly improve the therapeutic potential and safety of HBOT: 1) quickly and accurately establishing the appropriate O_2 gradient between the normal and the wounded hypoxic tissue and 2) maintaining the O_2 gradient for a therapeutically appropriate length of time.

Space Missions. Because of the shortage of space and limitations of energy consumption, a greater number biological and medical experiments are employing tissue culture in its various forms. In tissue culture, cells are maintained in an artificial medium that approximates body fluids or blood serum (blood without the cells and clotting factors). The maintenance conditions are critical for the success of the experiments. Although cells sometimes display a physiological latitude for survival under suboptimal conditions, they will often shutdown nonessential functions during conditions of stress or synthesize stress substances to help them survive. During the conditions of stress, the ability of the cells to respond normally to the test substances is compromised or eliminated. The inability to maintain optimal conditions is largely responsible for the ambiguous results and failed experiments that have plagued many biological and medical experiments. The small size of the fiber optics will allow continuous monitoring of multiple tissue culture systems (Fig. 2). The fiber optics can be connected to a feedback loop to increase/decrease oxygen partial pressures as needed or sound an alarm to alert the astronaut to correct the problem.

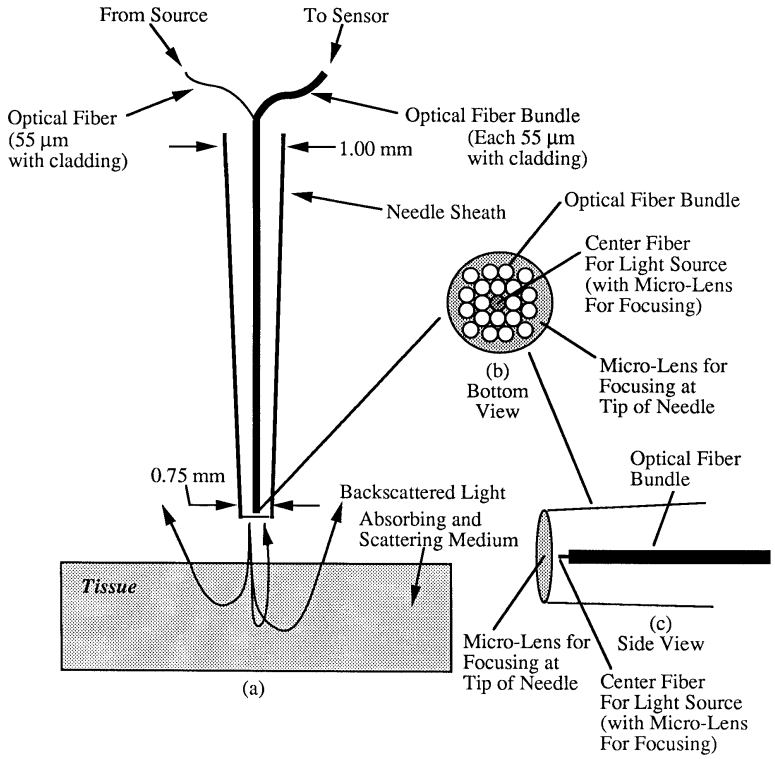

Figure 1. (a) Concept of the prototype pO_2 sensor for interstitial measurements in hyperbaric oxygen therapy. The sensor is based on the principle of reflection or backward scattered optic spectroscopy. (b) Bottom view of the needle sensor tip showing the optical fiber bundle with the center fiber (and micro-lens for focusing) for the light source. The other optical fibers in the bundle, along with the larger micro-lens, are used to collect the backscattered light. (c) Side view of the ne

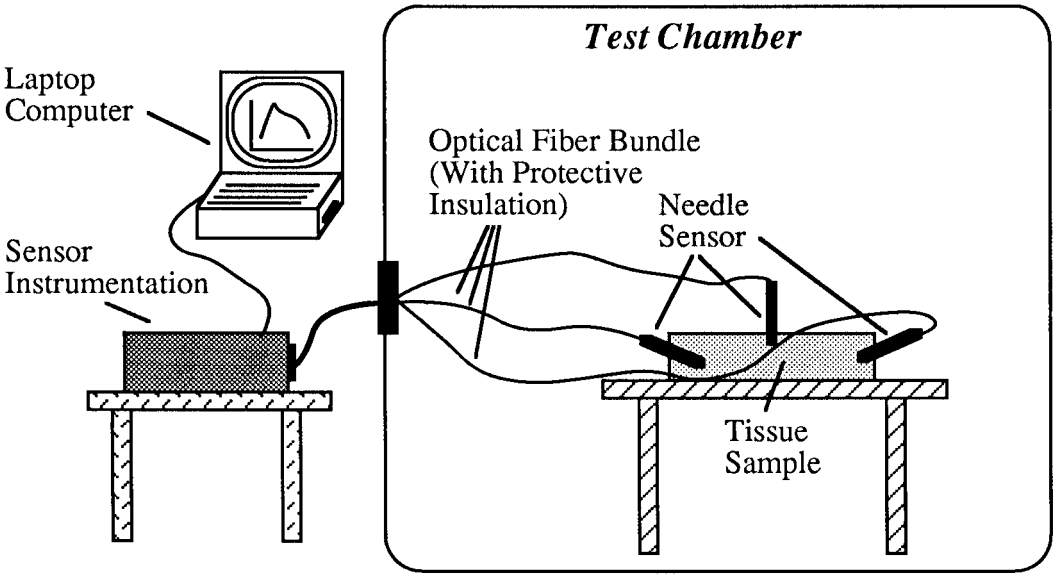

Figure 2. Optical fiber bundles can be inserted into multiple tissue culture specimens for monitoring oxygen partial pressures. The multiple monitoring of oxygen will automate this process.

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