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Monitoring oxygen partial pressure in tissue using microdialysis sampling and membrane coated oxygen sensors[1]

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Abstract

The use of microdialysis sampling coupled to oxygen sensors for monitoring oxygen tension in the tissue of animals was examined. The response time of the microdialysis sampling system was not different than oxygen sensors implanted directly in the tissue. The microdialysis system could be calibrated in vivo using the no-net-flux calibration method while directly implanted oxygen sensors had to rely on in vitro calibration. No difference was found in the oxygen tensions determined in vivo between microdialysis sampling and direct sensor implantation.

Keywords: Oxygen; Measurements; Partial pressure; Tissue; Sensors

1. Introduction

Oxygen measurement in biological systems has been intensively studied [1,2]. There are numerous reports on oxygen measurement, oxygen sensor fabrication, and new techniques for oxygen monitoring are spread throughout the scientific and engineering literature. Extensive reviews and books on this subject have been published [3–5].

Bare platinum wires or disks were prevalent as oxygen sensors until the development of the membrane-covered polarized oxygen sensor for biological measurement [6]. For the Clark-type sensor, the platinum working electrode and a reference electrode (silver wire) were put side-by-side in a single compartment which contains its own electrolyte. The communication between the electrodes and the testing matrices is through an oxygen permeable membrane. Although miniaturized Clark-type oxygen sensors or 'bipolar' sensors in needle form can be easily fabricated [7], 'monopolar' microsensors are still dominant in tissue oxygen partial pressure measurement [8–10]. For 'monopolar' microsensors, only the working electrode is covered with the oxygen permeable membrane and the current must pass through the measuring medium.

In recent years, continuous noninvasive or minimally invasive monitoring of biological species with ex vivo chemical sensing has become popular [11,12]. In this method, the chemical species of

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interest are carried to an analyzer which is located outside the tissue. The analyzer can sense the analyte of interest without direct contact with the tissue. Hunt suggested that an oxygen permeable tubular plastic tonometer (100-cm long Teflon tubing) could be implanted permanently in the tissue of interest (subcutaneous). An appropriate solution was perfused through the tubing with a constant flow rate. The perfusate in the implanted tubing equilibrated to the tissue oxygen partial pressure and then measured externally with a standard oxygen electrode [13]. A few years later, Smyth substantiated the feasibility of this method by implanting a 100-cm long Teflon tubing (250 μm I.D., 550 μm O.D.) into the amniotic cavity [14].

Much shorter tubing than the 100 cm lengths must be used in most tissues. In this study, the feasibility of combining microdialysis sampling with a membrane coated platinum oxygen sensor to monitor muscle oxygen partial pressure was examined. The main aim of this study was to examine the feasibility to add another analytical dimension to microdialysis sampling by simultaneously monitoring oxygen at the same time and location as other compounds.

The appropriate calibration procedure for oxygen sensors implanted in vivo has not been established [2]. In general practice, an in vitro two point calibration (air and N_2 saturated) in a buffer solution is recommended [15]. However mathematical models have indicated that the steady state diffusion current for an implanted membrane coated oxygen sensor is influenced by the properties of both the coating material and the surrounding tissue which exerts a source and sink effect on the implanted oxygen sensor by the capillary network and the cell mitochondria [16–18]. Therefore, it is questionable whether oxygen sensors can be calibrated in a buffer solution of known oxygen tension to predict the absolute values of oxygen tension in tissue [2]. With microdialysis sampling the electrodes are not in direct contact with the muscle tissue. The steady state oxygen reduction current is only a function of the electrode size, the diffusion properties of the coated membrane, and the oxygen partial pressure in muscle tissues. Therefore the electrode can be calibrated in vitro by varying the oxygen content in a buffer solution and the absolute muscle oxygen tension can then be estimated by using the zero-net-flux extrapolation with these calibrated electrodes.

2. Materials and methods

2.1. Materials

Cellulose acetate was obtained from Aldrich Chemical Company (Milwaukee, WI). Medical grade polyurethane elastomer was purchased from Thermedics (Woburn, MA). Teflon-coated platinum (90%)/iridium (10%) wire was purchased from Medwire Sigmund Cohn Corp. (Mount Vernon, NY). The coated wire diameter was 0.007″ with a bare diameter of 0.005″. Teflon tubing, which was used as a gas exchanger, was purchased form Small Parts Inc. (Miami, FL). An IBM EC/522 voltammetric analyzer (IBM Instruments, Inc.) and a BAS LC-4A Amprometric Detector (Bioanalytical System, Inc.) were used as the detectors. The current was recorded on a dual channel Kipp and Zonen strip chart recorder. A gas flow meter was purchased from Aalborg Instruments and Controls Inc. (Monsey, NY). UV adhesive # 518 was bought from UVEXS (Sunnyvale, CA). Fused silica tubings were purchased from Polymicro Technologys Inc. (Phoenix, AZ). Polyetheretherketone tubing was obtained from Upchurch Scientific (Oak Harbor, WA).

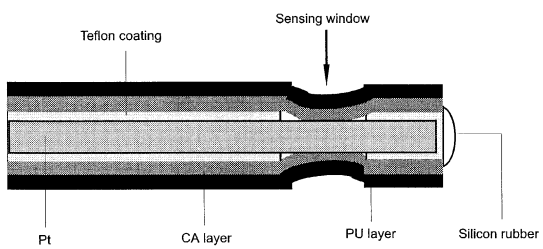

Fig. 1. Schematic diagram of the oxygen sensor.

2.2. Oxygen sensor fabrication

A typical oxygen sensor is shown in Fig. 1. The oxygen sensors were made of Teflon-coated Pt/Ir wire (90:10). A sensor length of 50 mm was used in the 'titration reservoir' and a 70-mm length sensor at the detection end. A 1.2-mm length Teflon-coating was removed at one end of the wire with a perpendicular cut to the wire's axis. The exposed portion was then coated with cellulose acetate and polyurethane.

A 6% CA solution was made by dissolving CA powder (6 g) into 100 ml of acetone/ethanol solution (1:1 v/v) and stirred overnight. The sensor was then dipped into this 6% CA solution to a depth of approximately 6 mm from the tip and pulled out smoothly. The CA coating was dried in the air for 1 min. A layer of smooth off-white CA coating can be seen under a microscope. This coating process was repeated two more times. This coated sensor was then immersed in a phosphate buffered saline, pH 7.4, for 10 h to stabilize the membrane.

A 4% PU solution was prepared by dissolving 4 g of polyurethane beads in 98 ml of tetrahydrofuran (THF) and 2 ml of *N*,*N*-dimethyl formamide (DMF). The solution was stirred for 48 h. A wire loop 4 mm in diameter was made at one end of a piece of plastic coated wire with a diameter of 1 mm. The loop was dipped into the PU solution and pulled out perpendicularly with a thin film across the loop. Immediately, the CA coated sensor was pushed through the loop starting from the sensing end until the cavity was fully covered with a layer of PU and the sensor was then pulled back out of the loop. Therefore, two thin layers of PU were deposited evenly over the CA coating. Under a microscope a transparent coating was observed over the sensing end. After air drying for 10–15 min, the coated sensor was left in a phosphate buffer solution overnight to stabilize the coating.

2.3. Preparation of buffer solution

The pH 7.4 phosphate buffered saline was prepared by dissolving 12.3 g of Na_2HPO_4, 2.2 g of KH_2PO_4, and 8.8 g of NaCl in distilled H_2O. The pH was adjusted to 7.4 and the solution then diluted to 1000 ml in a volumetric flask with distilled H_2O.

2.4. Microdialysis system

The microdialysis system for monitoring oxygen was composed of a microinfusion pump (CMA 200), a 5-ml Hamilton gas tight syringe filled with Ringer's solution, a 180-cm long coil of Teflon tubing (gas exchanger) in a 200-ml wide-mouth jar filled with phosphate buffered saline (titration reservoir), a linear microdialysis probe, and a detection reservoir filled with Ringer's solution (Fig. 2).

The titration reservoir was a 200-ml wide-mouth jar filled with phosphate buffered saline to 2/3 capacity and sealed with a rubber stopper. A piece of 'U-shaped' stainless steal wire (1.5 mm in diameter) was fixed onto the stopper in such a way that the Teflon tubing gas exchanger could be wrapped onto it and was immersed in the buffer solution when the jar was sealed. Additional holes through the rubber stopper were drilled for the Ag/AgCl reference electrode and the Pt wire auxiliary electrode. A medium pore size gas immersion was set to the bottom of the jar and the other end was connected to a gas flow meter through a piece of thick wall Tygon tubing of 15 cm length (508 μm I.D.; 1500 μm O.D.).

The flow meter had inlets for argon and compressed air and a single outlet leading to the gas immersion. The gas exchange element was a 90-cm of length Teflon tubing (300 μm I.D., 150 μm wall thickness), which was stretched to 180 cm length by applying force at both ends. This process generated a thinner wall Teflon tubing which facilitates the gas exchange rate. A 20-cm length of polyethylene tubing (PE-50; Clay Adams, Parsippany, NJ) was glued onto the stretched Teflon tubing and the other end of the PE-50 tubing was connected to the syringe which was then filled with air saturated Ringer's solution. The other end of the stretched Teflon tubing was sleeved onto a 10-cm long fused silica capillary (350 μm O.D., 247 μm I.D.). The overlapping portion was about 1 cm and was glued in place. This portion was also in the titration reservoir so that no

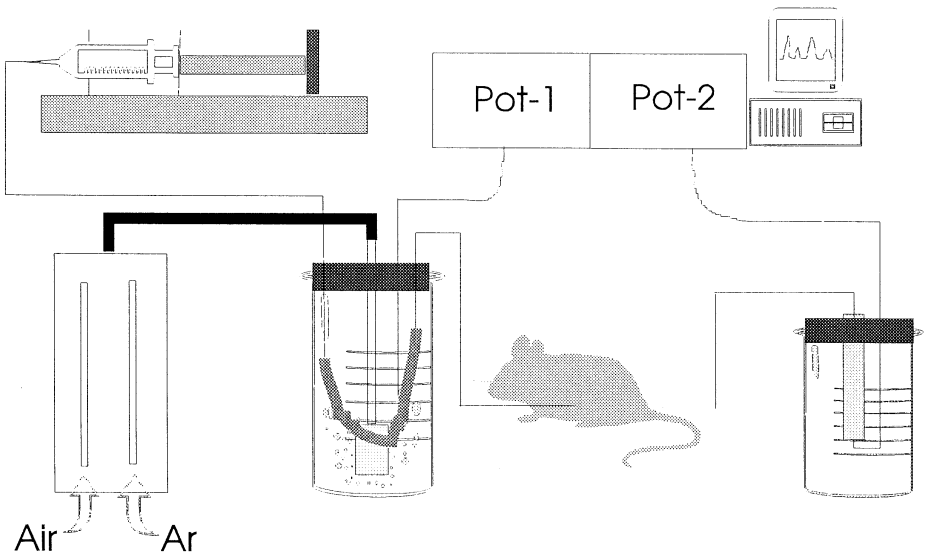

Fig. 2. Microdialysis system for monitoring oxygen tension in tissues.

Teflon tubing was exposed to the air. Finally the gas exchange tubing was wrapped onto the stainless steel wire and immersed in the buffer solution. An oxygen sensor with auxiliary and reference electrodes was placed in the buffer solution. This oxygen sensor was used as the reference sensor.

A rubber stopper-sealed 50 ml wide-mouth jar filled with Ringer's solution was used as the detection reservoir. Holes were drilled for the Ag/AgCl reference electrode and the platinum auxiliary electrode. An oxygen sensor was housed in a piece of polyetheretherketone tubing (PEEK) of 5 cm length (3175 μm O.D., 508 μm I.D.), which was sleeved onto a 10-cm length of fused silica tubing (75 μm I.D., 144 μm O.D.). The overlapping portion was about 0.5 mm and was glued in place with epoxy. About 4.5 cm of the oxygen sensor was inserted into the PEEK tubing and the open end of the PEEK tubing was immersed in the Ringer's solution to complete the circuit. The reference and auxiliary electrodes were placed in the Ringer's solution. This oxygen sensor was used as the detection sensor.

A constant potential of -550 mV versus Ag/AgCl was applied to both oxygen electrodes using two potentiostats. The current outputs were recorded with a dual channel Kipp and Zonen strip chart recorder which had a chart speed of 1 mm min^{-1} unless otherwise specified.

The linear microdialysis probes used in this experiment were constructed of 5 mm length polyacrylonitrile membrane connected to fused silica tubing. Fused silica tubing (75 μm I.D.; 144 μm O.D.) was used to make all connections between the titration reservoir and the microdialysis probe and the connections between the microdialysis probe and the detection reservoir.

2.5. In vitro oxygen sensor calibration

All oxygen sensors were calibrated in vitro prior to in vivo measurement. For calibration, the microdialysis probe was removed from the system and the outlet of the titration reservoir connected directly to the inlet of the detection reservoir. The microinfusion pump was set to a flow of 2.5 μl min^{-1}. Argon and air were introduced from cylinders into the titration reservoir through a dual-gas flow meter with a combined flow rate of 223 ml min^{-1}, which had a scale reading of 100 with glass float. By adjusting the ratio of compressed air to argon without changing the total flow rate, both could be calibrated at the same time.

2.6. In vivo oxygen partial pressure measurement

ACI male rats (3–4 month old) were used in this study. Linear probes were implanted into the hind leg muscle. The implantation procedure has been described previously [19]. One end of the implanted probe was inserted into the titration reservoir fused silica capillary and was glued in place. The other end of the probe was connected to the detection fused silica capillary by sliding a 1.5-cm length fused silica capillary (350 μm O.D., 247 μm I.D.) over the joint. The connection was secured by applying epoxy at both ends. The titration reservoir was purged with argon and a steady-state current at the detection end was obtained within 1 h. By varying the ratio of argon to compressed air, new steady-states were obtained and recorded. The change in perfusate oxygen tension was achieved by changing the titration reservoir oxygen tension. Therefore, 100% gas exchange efficiency was required which was achieved by stretching a 90-cm length Teflon tubing to 180 cm length. The least square linear regression analyses were based upon a minimum of four perfusate concentrations in which two points were higher and two points were lower than the expected tissue oxygen partial pressure. At the end of the experiment the titration reservoir was again purged with argon. The steady-state current at the detection reservoir at the beginning and the end were compared. If the two values were within 5%, the tissue oxygen partial pressure was considered to be constant throughout the experiment. The data was then used to estimate the zero-net-flux point. At the end of the experiment the rat was sacrificed by breathing argon and the baseline of the electrode at the detection end was established.

3. Results and discussion

3.1. In vitro calibration

As described in the experimental section, both sensors were calibrated prior to the in vivo measurements. Most of the oxygen sensors had a linear response between 100% argon and 100% compressed air as shown in Fig. 3. However, some electrodes' response was linear only up to 80%. The explanations for this phenomenon are not completely clear. The reproducibility of fabrication of this type of sensor is still not easily controllable, even though exact procedures were followed strictly. Therefore, all oxygen sensors were calibrated in vitro prior to use. The traditional two point calibration (100% argon and 100% air) was not used because of the possibility of nonlinear response. In this study, at least five calibration points were used in order to provide a reliable measurement.

3.2. Electrode stability

Until the advent of Clark-type oxygen sensors, the majority of oxygen electrodes were bare platinum wires or disks. Signal drift with these bare electrodes had been the major problem for their use in biological matrices [20]. This poisoning effect was mainly due to the absorption of biological materials on the electrode surface. It was found that this poisoning effect could be largely reduced or eliminated by applying a thin layer of collodion onto the electrode surface [21]. Other oxygen and small ion permeable membranes, such as, cellophane, dialysis membrane, latex rubber, polyethylene, and Teflon were also tested [22]. Recently, a dual coating of polyurethane coupled with cellulose acetate has been used in fabrication of glucose sensors for in vivo measurement to

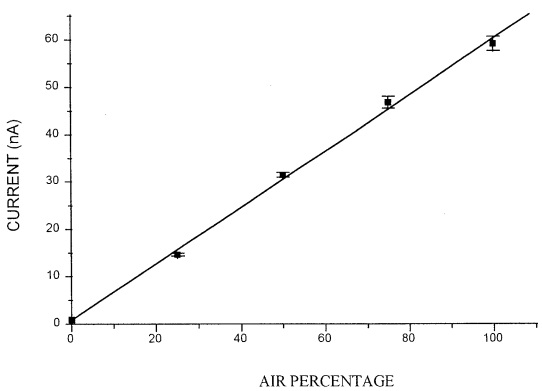

Fig. 3. Linear response of the oxygen sensor.

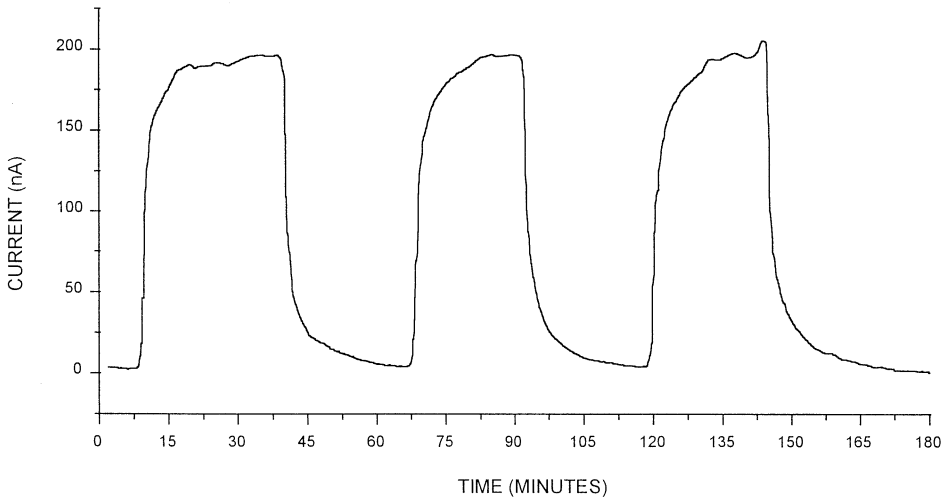

Fig. 4. Response time in vitro of an oxygen sensor through a microdialysis probe.

greatly minimize biological interferences [23]. In this study, polyurethane and cellulose acetate were combined as the coating material. The oxygen sensor stability was evaluated by applying a constant potential to an oxygen sensor which was immersed in an air saturated Ringer's solution. The electrodes were stable for more than 10 h which is sufficient to conduct a zero-net-flux experiment. This stability is due mainly to the membrane coating which allows oxygen to pass through but not larger biological molecules which could deposit onto the electrode surface.

3.3. Response time

The in vitro response time of the microdialysis method was tested by moving the probe rapidly between an air saturated Ringer's solution and an argon saturated Ringer's solution (Fig. 4). The response reached 90% of the steady state in 6.8 ± 0.8 min when the probe moved from an argon saturated solution to an air saturated solution and 7.3 ± 0.6 min when moved from an air saturated to an argon saturated Ringer's solution.

The response time comparison between a directly implanted oxygen sensor and through a microdialysis fiber was performed by manipulation the oxygen content of the air breathed by the rat. The results indicate that the response time is comparable between a directly implanted oxygen sensor and the microdialysis probe as shown in Fig. 5. Therefore, microdialysis sampling can be used to measure muscle oxygen partial pressure without sacrificing the response time compared with direct implantation of oxygen sensors.

3.4. Flow rate effects on oxygen monitoring

The diffusion current at the polarized oxygen electrode is controlled by the mass transport rate of oxygen from the bulk solution to the electrode surface. The diffusion rate is given by the diffusion equation

$$F = -D \times \frac{dC}{dX} \quad (2)$$

where F is the O_2 influx; D is the diffusion coefficient; dC/dX is the concentration gradient at the cathode.

In a quiescent solution, the concentration gradient is directly related to the oxygen concentration in the bulk solution. Whereas, in a stirred solution the stir rate also influences the observed reduction current. Therefore a constant stir rate is required between the calibration and the measurement since for a given condition of a solution, stationary or stirred, the dC/dX term is dependent linearly on the oxygen concentration in a solution.

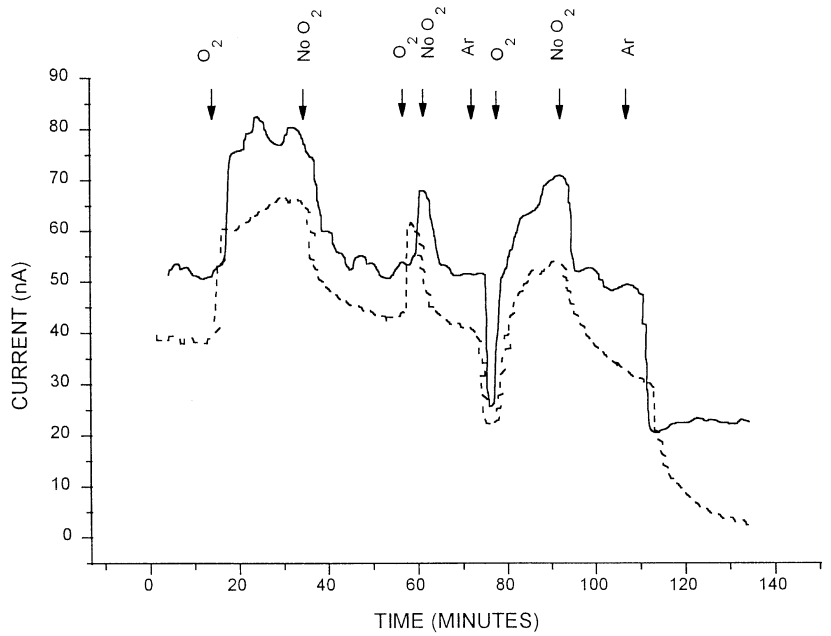

Fig. 5. Response time comparison between a directly implanted oxygen sensor (——) and through a microdialysis probe (- - -).

The constant stir rate was easily controlled at the titration reservoir by controlling the combined flow rate of argon and compressed air. However, the detection end could not be stirred easily since the electrode was housed in a 5-cm length PEEK tubing with an internal diameter of 508 μm. The thickness of the oxygen diffusion layer was then controlled by changing the microinfusion pump flow rate. As expected, higher flow rates provide higher sensitivity as shown in Fig. 6A. This is because faster flow rates produce a thinner diffusion layer and provide greater mass transport of oxygen. However, higher flow rates also result in lower recovery for microdialysis sampling [24]. A compromise between sensor sensitivity and microdialysis recovery must be made.

For a polarized oxygen sensor, the electric current occurs by the reduction of dissolved oxygen to hydroxide ion at the surface of the electrode. Theoretically no current should be seen in an argon purged solution. Because of impurities in the solution as well as in the membrane, residual current was observed even when the solution was completely deoxygenated. Furthermore, tubing leakage of oxygen and the back diffusion of oxygen into the PEEK tubing at the detection end also contributed to the background current. The minimum residual current at the detection end was obtained when the flow rate was greater than 10 μl min^{-1} as shown in Fig. 6B. Again, compromise has to be made since the oxygen recovery through the microdialysis probe also needs to be considered. By considering the sensitivity, background current, and the recovery of microdialysis sampling a flow rate of 2.5 μl min^{-1} was used throughout unless otherwise specified.

3.5. In vivo measurement of oxygen partial pressure by the zero-net-flux method

When an oxygen sensor is implanted directly into the muscle tissue, oxygen diffuses through the coated membrane to the Pt/Ir surface and is reduced. Therefore the observed current is a direct reflection of the tissue oxygen level. With the microdialysis sampling method, oxygen diffuses through the implanted microdialysis membrane and is subsequently brought to the electrode at the detection end by the perfusate. Since microdialysis is a non-equilibrium process, only a fraction

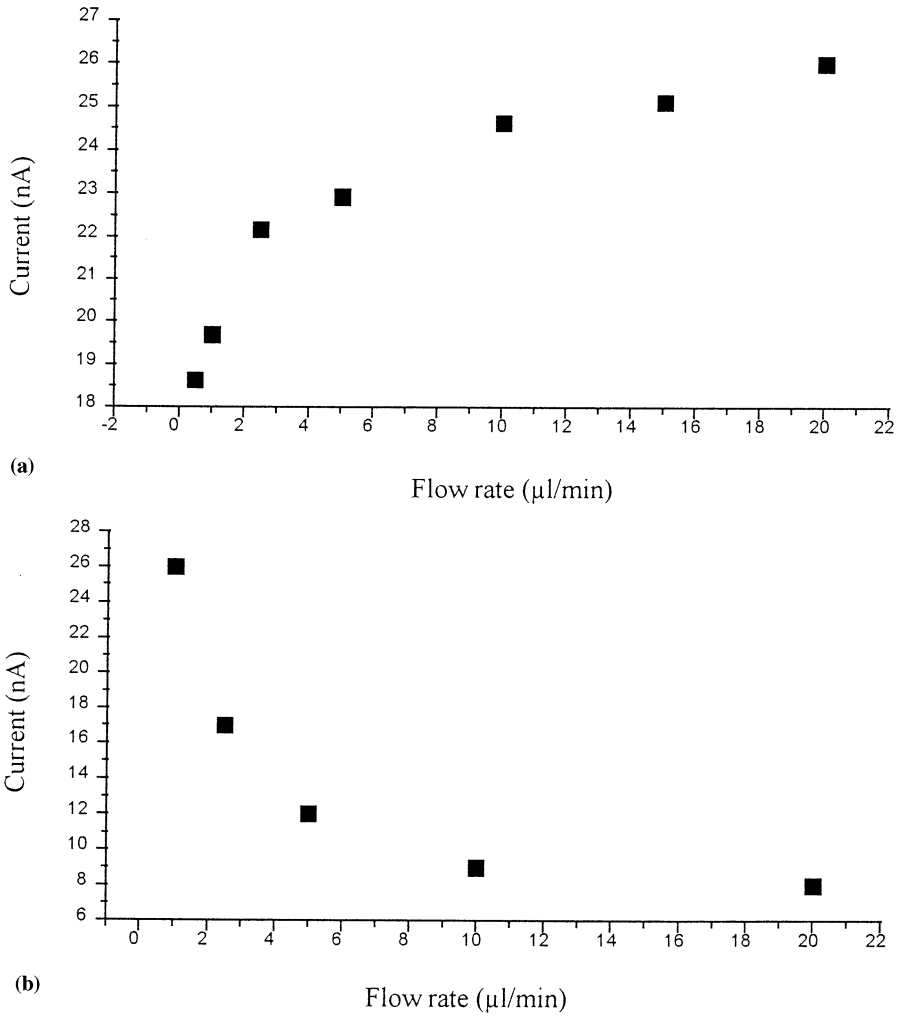

Fig. 6. Effect of microinfusion pump flow rate on the oxygen sensor response (A) and the residual current (B).

of the tissue oxygen can be collected [25]. In this case tissue oxygen partial pressure can be estimated using the zero-net-flux method, in which the microdialysis probe is perfused with a Ringer's solution with various oxygen concentrations [26]. A linear relation exists between the net oxygen change in the dialysate and that in the initial perfusate, which can be derived mathematically as the follows:

let pO_d = dialysate O_2 tension
pO_p = perfusate O_2 tension
$pO_{2,tissue}$ = constant tissue O_2 tension surrounding the probe
R = dialysis probe recovery which equals $pO_d/pO_{2,tissue}$
D = dialysis probe delivery which equals $(pO_p - pO_d)/pO_p$

the amount of oxygen in the dialysate equals the sum of the fraction recovered from the tissue and the fraction left in the perfusate after some fraction has defused out of the probe, then:

$$pO_d = R \times pO_{2,tissue} + (1 - D) \times pO_p \quad (3)$$

$$pO_d - pO_p = R \times pO_{2,tissue} - D \times pO_p \quad (4)$$

If $pO_{2,tissue}$ is constant throughout the experiment, which can be determined by comparing the steady state oxygen tension at the beginning and the end of the experiment, a linear relation exists between the net change in oxygen tension and the initial perfusate oxygen tension:

$$pO_d - pO_p = -D \times pO_p + A \quad (5)$$

where $A = R \times pO_{2,tissue}$, which is constant. The slop of the linear regression plot is $-D$. When the oxygen tension of the perfusate equals that of the surrounding tissue, this is the point of zero-net-flux which can also be estimated from the linear regression plot. The response of the oxygen electrodes in the titration reservoir and the detection reservoir during an in vivo zero-net-flux experiment are shown Fig. 7A. The resulting zero-net-flux plot is shown in Fig. 7B.

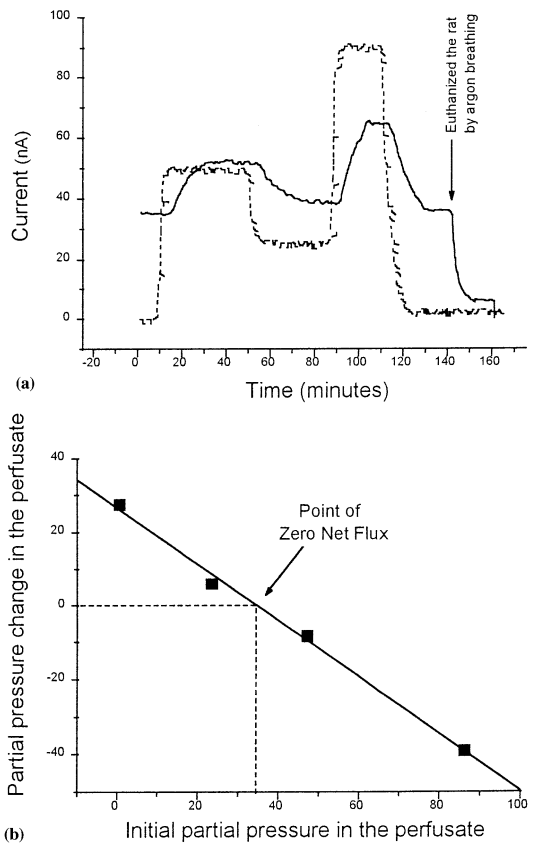

Fig. 7. Zero-net-flux experiment (A) and resulting calibration plot (B). Response of oxygen sensor in the titration reservoir (- - -) and of the oxygen electrode in the detection reservoir (——).

The oxygen partial pressure in the hind leg muscle of four healthy ACI was determined by microdialysis sampling using the zero-net-flux method. The muscle oxygen partial pressure obtained were in a range from 33 ± 3 to 37 ± 6 mmHg which is consistent with the literature [27].

3.6. Comparison between direct implantation and the zero-net-flux estimation

Traditionally, the polarized oxygen sensor is directly implanted in the tissue of interest for oxygen partial pressure measurement. The tissue oxygen then diffuses through the electrode membrane to the working electrode surface. The reduction current is recorded as a direct reflection of the oxygen partial pressure. However, the calibration of the oxygen sensor is performed in a buffer solution but not in the tissue. Therefore it is questionable whether the in vitro calibrated electrode can be used to measure the absolute oxygen partial pressure in tissues [2]. In this study, a calibrated (in vitro) oxygen sensor was implanted parallel to the microdialysis fiber which was used for the zero-net-flux measurement. The distance between the oxygen sensor and the microdialysis fiber was about 1 cm. Then the zero-net-flux estimation and the direct measurement of tissue oxygen partial pressure were performed simultaneously.

The results shown in Table 1 indicate that the oxygen partial pressure measured by the zero-net-flux estimation was not significantly different from that measured by direct implantation. These results further indicate that these oxygen sensors can be used to predict the absolute values of oxygen partial pressure in rat muscle by an in vitro.

4. Conclusions

In this report the possibility of measuring tissue oxygen partial pressure using a microdialysis fiber in conjunction with membrane coated platinum electrodes was examined. No difference in re-

Table 1
Tissue pO_2 determined using a directly implanted sensor and using microdialysis sampling

	Rat 1	Rat 2	Rat 3
Implanted sensor	32.0 ± 3.1	33.8 ± 7.1	33.5 ± 3.6
Microdialysis sampling	36.8 ± 6.2	28.9 ± 4.7	34.9 ± 3.3
Variance-ratio test (95% probability level)	Same	Same	Same
Student's t-test (95% confidence level)	Same	Same	Same

sponse time and oxygen tension determinations were found between directly implanted oxygen sensors and the microdialysis sampling approach. The use of microdialysis sampling provided an in vivo calibration method not possible with a directly implanted oxygen sensor. Comparison of the two approaches demonstrated that in vitro calibration of oxygen sensors is likely acceptable. While the use of directly implanted oxygen sensors is generally more practical if only oxygen is to be monitored, the use of microdialysis sampling with incorporated oxygen sensors provides the ability to simultaneously monitor several analytes at the same physiological site.

Acknowledgements

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