Variants of the tissue-sensor array window chamber

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Makale, Milan T., Peter C. Chen, and David A. Gough. Variants of the tissue-sensor array window chamber. Am J Physiol Heart Circ Physiol 289: H57–H65, 2005. First published February 25, 2005; doi:10.1152/ajpheart.01001.2004.—Sensors are being developed that can be implanted in tissues for continuous monitoring of oxygen, glucose, and other metabolites. However, there have been difficulties in inferring metabolite concentrations in blood from the signals of tissue sensors due to the properties of tissues at the implant site and local physiological phenomena that can affect sensor responses. A multisensor array has been previously developed for implantation in a hamster skinfold window chamber preparation to study these effects. The preparation allows recording of concentration-dependent signals from multiple sensors while nondestructively visualizing the adjacent tissue and microvascular function. Variants of the tissue-sensor array window chamber described here have respective advantages over the original chamber design, including improved tissue visualization and reduced surgical intervention, and allow exposure of the sensor to different tissues. Results indicate that mass transfer within tissues is heterogeneous, and sensor signals are affected by variable perfusion of local microvasculature in addition to vascular metabolite concentration. These observations suggest new strategies for sensor design and operation. Window chamber variants are important tools for validation of implanted sensors.

implanted biosensors; tissue visualization; sensor validation

THERE IS CONSIDERABLE INTEREST in developing implantable electrochemical sensors to monitor glucose, oxygen, lactate, and certain other metabolites for applications in diabetes, pulmonary insufficiency, shock, extreme exertion, and other conditions. The sensors would be implanted in a tissue site for periods of weeks to years, continuously monitor the metabolite of interest, and transmit the information externally either via a wire connection or wireless telemetry link. The goal is to infer dynamic blood concentrations of the metabolite of interest from signals of the sensors implanted in tissues. Sensors would ideally function continuously to provide an automatic and timely indication of metabolic imbalances. One example is the potentiostatic oxygen sensor based on the direct electrochemical reaction of oxygen at a membrane-covered, polarized, noble metal electrode (15). This sensor produces a signal current that is proportional to both the concentration and rate of mass transfer of oxygen to the sensor (16). Other examples include implantable enzyme electrode-type sensors for monitoring glucose, lactate, and other metabolites, in which membranes containing immobilized enzymes are coupled to electrochemical oxygen sensors (3, 4). As these sensors are based on the oxygen sensor, many of the response characteristics are similar to those of oxygen sensors, and the simpler oxygen sensor can therefore serve as a model.

In validating the function of sensors when operated in tissues, difficulties have arisen in assuring that the signals provide an accurate representation of blood concentrations (9, 11, 13, 19, 20, 23). These difficulties have been of two types. In certain cases, the sensors themselves have been the problem as a result of not being selective for the metabolite of interest, adequately sensitive at physiological concentrations, or sufficiently stable over the long term, or for various other reasons that are best addressed before implantation. In other cases where the sensor per se has been acceptable, ambiguous and confusing signals have often resulted when the sensors were operated as implants in tissues. Examples of such unpredictable responses are the following: sensor signals that vary over the short term while blood concentrations remain constant; signals that do not respond to changes in blood concentration; signals that display lags or delays; and neighboring sensors in the same tissue that produce quite different responses. Unfortunately, there have been few detailed, systematic studies to determine the causes of these phenomena. Rather, most previous studies have been attempts to establish simple correlations between signals and substrate concentrations in the blood, with little consideration of the underlying physiological events.

New biological preparations are needed to address the reasons for ambiguous sensor response. These preparations must permit a nondestructive study of the tissue environment in the vicinity of sensors. For example, it is necessary to visualize the microvascular pattern and measure the distance for mass transfer between the nearest capillaries and the sensor. Furthermore, it is important to determine whether the capillary permeability is intact and whether local blood vessels are fully perfused and functional. Blood flow must be documented in microvessels in the immediate vicinity of individual sensors and in the regional vasculature affecting all sensors in the array. It is necessary to ascertain the composition, structure, and function of tissues in the vicinity of the sensor and whether these features change with implant time over the long term.

We previously described a modification of the hamster skinfold window chamber in which an array of identical oxygen sensors was implanted (17). This system has a number of useful features, including 1) the tissue environment around individual sensors can be visualized in a nondestructive manner over a period of weeks to months by using optical microscopy, without the need for anesthesia and its potentially depressive effects on microcirculatory function; 2) many identical sensors can be studied in the same animal and blood concentrations can be simultaneously sampled, reducing between-animal variation; 3) studies can be carried out repeatedly to determine the effects of implant time and aging; and 4) postmortem histological analysis of tissues can be per-
formed to analyze tissue structure and composition. These features have been advantageous in understanding the determinants of oxygen mass transfer to implanted oxygen sensors (16).

The previous tissue-sensor array window chamber is a modification of tissue-viewing chambers developed for use in the mouse, rat, hamster, and humans (6, 8, 18, 22, 25). Various types of tissue-viewing chambers have been used extensively for study of the microvasculature (12, 18), tumors (10, 22), cellular behavior (1), wound healing (7, 24), and imaging of internal organs (5). Versions of chambers have been adapted for visualization of rabbit ear tissues (2), mouse, rat, and hamster dorsal skinfold (8, 25), the body wall of the mouse (5), superficial tissues of the human arm (6), and tissues of the human leg (24).

We have found that the tissue-sensor array window chamber can be prepared in several ways with the array exposed to different tissue layers. The basic “tissuefold-sensor array” window chamber (17) has a window on one side of the debrided tissuefold and the sensor array on the opposite side, with the fold having either subcutaneous muscle or connective tissue exposed to the array. This preparation can be modified to become a “one-sided tissue-sensor array” window chamber variant, in which one side of the tissuefold is removed and the sensor array is placed in contact with inner layers of the opposing fold. The outer layers are left intact, and a window is not used. Another variant is the “single-layer tissue-sensor array” window chamber variant, in which all tissue layers are removed except a single layer of retractor muscle or connective tissue, with the array on one side and the window on the other. Another version is based on a novel sensor array, the “porthole sensor array,” which has transparent viewing ports in the plane of the disc between the individual sensors. The “one-sided tissue/porthole sensor array” window chamber variant allows direct visualization of tissue-array interface without intervening tissue or use of a separate window. These preparations differ in the type of tissue in contact with the array, the ability to visualize the tissue-array interface, the amounts of tissue removed and associated disruption of microvascular perfusion, and the viable lifetime.

In this communication, we describe these preparations and outline their use for addressing questions about the response of implanted sensors. Detailed analyses of implanted sensor response are given elsewhere.

METHODS AND MATERIALS

Animal subjects. Male Syrian golden hamsters (Charles River Laboratories, Cambridge, MA), weighing between 60 and 200 g, were housed in standard microisolator cages ventilated with filtered air. Male animals were used because they have less subcutaneous fat and a smaller range of normal variation in tissue composition. Animals were fed Purina Hamster Chow and water ad libitum. Animals were treated in accordance with National Institutes of Health guidelines for the care and use of laboratory animals. Protocols were approved by the University of California-San Diego Institutional Animal Care and Use Committee.

Tissue and array support apparatus. The support apparatus, shown in Fig. 1 and described in detail elsewhere (17), consisted of two titanium alloy frames, each having a 12-mm-diameter circular opening fitted with a ring for attachment of the window or sensor array. Each ring extended 0.95 mm toward the tissue and, in conjunction with appropriate spacers to separate the frames, produced sufficient separation to allow vigorous perfusion of the microvasculature in the thin sheet of tissue. One ring had three small pins that penetrate the tissue and mate with holes of the opposing ring to restrict tissue movement. A glass microscope coverslip was secured into the window of one frame, and the sensor array disc was secured into the other frame by using slotted retaining rings. In some experiments, an additional 100-μm-thick plastic disc was glued to the internal surface of the window to minimize any fluid layer between the tissue and array surfaces. The frames were held together with four M2-4 × 10-mm bolts and nuts.

Sensor arrays. The fabrication of oxygen sensor arrays has been described in detail elsewhere (16). The standard sensor array, shown in Fig. 2A, is a 12-mm-diameter ceramic disc with thick-film electrodes in specified patterns. The electrodes are composed of disc platinum working electrodes of 125 or 300 μm in diameter, four common Ag/AgCl disc reference electrodes ~875 μm in diameter, and a ribbon-like common platinum counter electrode. There are 18 working electrodes separated from each other by distances of 1–2 mm on each array. A 25-μm layer of conductive electrolyte (1.0 N NaCl, pH 7.3, in cross-linked polyhydroxyethylmethacrylate gel) is depos-

Fig. 1. Tissue support apparatus. A: window frame. B: sensor array support with sensor array. Sensor array disc is secured to the frame with connector strip. Electrical contacts at the tip are shown in black, extending vertically.
The injection of 100 mg/kg of ketamine and 250 mg/kg of medetomidine, is injected upon completion of surgery. When the animal was ready for study. At the conclusion of the experiment, the animal was euthanized with an overdose of pentobarbital (300 mg/kg) according to National Institutes of Health guidelines.

In some cases, it was necessary to anesthetize the animal with 75 mg/kg of ketamine and 2.5 mg xylazine/100 mg body wt during imaging so that acceptable images could be obtained without movement artifact. This anesthetic regimen (14) resulted in a ~20% reduction in mean arterial blood pressure and ~35% reduction in heart rate in other species. These perturbations were considered tolerable to produce acceptable images.

Sensor calibration. Although individual sensors were similar in their manufacture and in vitro response to oxygen concentration, there was no intention in this study to achieve identical sensitivity and performance. Rather, the sensitivity of each sensor was determined individually by using a method described previously (16), in which measurements are made in the gas phase where boundary layers are absent. This method allows repeatable measurement of sensor signals without error due to the effects of variable mass transfer boundary layers found in the stirred liquid phase. The sensitivity of each sensor was archived respectively and used in calculation of oxygen concentrations. The measurement of oxygen sensitivity was repeated at the end of the study to verify individual sensor stability.

Sterilization. The window chamber plates, bolts, glass coverslips, and sensor arrays were sterilized by soaking for 24 h in a solution of 6% glutaraldehyde in phosphate-buffered isotonic saline (PBS), pH 7.4. The sensors were removed from the solution, rinsed with sterile PBS, and then soaked in sterile PBS with several changes over 48 h. All surgical instruments and gauze were sterilized before use, and a bead sterilizer was used to resterilize instruments during surgery.

Animal care. The animals were anesthetized by intraperitoneal injection of 100 mg/kg of ketamine and 250 μg/kg of medetomidine using a 1-ml syringe fitted with a 30-gauge needle. In our experience, this anesthetic combination offers a higher margin of safety than pentobarbital sodium, with a smoother induction, longer duration, and more rapid recovery, especially when atipamezole, the antide of medetomidine, is injected upon completion of surgery. When the animals attained a surgical plane of anesthesia, as determined by toe pinch, the fur was shaved from the dorsum. Fine residual hair was removed with a depilatory, and both skin areas were swabbed with Betadine and washed with sterile PBS.

The anesthetized animal was placed prone on a heated pad, and the dorsal skin was gently suspended as a longitudinal fold using 4-0 silk secured to vertical metal rods. After tissues were dissected and the respective tissue-sensor chamber was installed as described below, the animal was injected subcutaneously with 25–75 μg of atipamezole and allowed to recover in a heated enclosure. After a 24-h recovery period, the animal was ready for study. At the conclusion of the experiment, the animal was euthanized with an overdose of pentobarbital (300 mg/kg) according to National Institutes of Health guidelines.

Single-layer variant. The skin and subcutaneous fat and fascia were removed as a disc on one side, and the sensor array was placed against an unfolded, single layer of retractor muscle or fascia, with the...
retractor muscle, subcutaneous tissue and skin removed from the opposite side. The result was a single thin layer of retractor muscle or fascia sandwiched between the sensor array and the coverslip window. This preparation differed from the skin variant in that more tissue was removed at implantation reducing the viable lifetime of the preparation, but visualization through the single muscle layer was improved. Otherwise, the preparation involved procedures described above.

Porthole variant. For the tissue-porthole sensor array preparation, the disc of skin, subcutaneous fat, and fascia was removed from the anterior region of one side of the skinfold opposite to the frame. Both layers of the retractor muscle were also removed. Several drops of sterile PBS containing broad-spectrum antibiotic were applied to subcutaneous fat, and topical antibiotic was spread on the skin surrounding the surgical site. The array frame was secured in place so that the array surface contacted either the vascularized fascia or the skin.

Catheterization. Catheters were implanted in the jugular vein and carotid artery of certain animals to facilitate blood sampling and infusion of solutions, fluorescent dye, and pharmacological agents. Catheterization was performed at the time of chamber implantation in some animals and 24–48 h after chamber implantation in others. The animal was anesthetized with 100 mg/kg ketamine and 250 μg/kg medetomidine injected intraperitoneally. The ventral aspect of the neck was shaved, swabbed with Betadine, and washed with saline. A 2-cm midline incision was made, and the right external jugular was exposed using blunt dissection. A sterile, 2-Fr cannula made of polyurethane tubing with a polished tip containing 100% glycerol USP with 50 U/ml of heparin was introduced into the vein and drawn under the skin to exit dorsally between the shoulder blades. The ventral and dorsal incisions were closed with tissue cement, and the catheter was coiled and secured to the dorsal skinfold chamber frames. The left carotid artery was similarly cannulated in certain animals. A schematic of the complete tissue-sensor array preparation and catheters mounted on a hamster is shown in Fig. 3.

Microscopy. The unanesthetized animal was introduced into a clear, perforated Plexiglas tube, and the chamber plates were secured to a block of Plexiglas to minimize movement of the chamber. The apparatus was placed on the microscope stage, and the chamber vasculature was imaged at ×4 and ×10. Approximately 12.5 mg FITC-dextran (2,000,000 mol wt) was injected via the jugular vein catheter. A CCD video camera (model 8215-1000, Cohu) attached to the microscope with a ×10 objective was used to visualize the vasculature in the vicinity of a working oxygen sensor electrode. Still images were obtained with a digital camera attached to the microscope. The video captured blood flow through the vasculature in the vicinity of the working electrode. Both still images and videos were obtained and transferred to a computer for storage and analysis.

Oxygen challenges. Step challenges in inspired oxygen were created by allowing the animal to breathe room air (20.9% oxygen) for typically 30 min, followed by 15% oxygen for 10 min, and a return to room air. Challenges produced no apparent discomfort.

RESULTS AND DISCUSSION

Tissue structure. The hamster intact dermal tissue is composed of several tissue layers with respective vascular supplies (21). A single tissue layer is shown in histological cross section...
in Fig. 4A, and a tissuefold is shown schematically in Fig. 4B. The components are epidermis or skin, which is typically 15–50 μm thick and minimally vascularized; the dermis and hypodermis, referred to here as fat and fascia, contains adipose cells and is typically 350–750 μm thick; and the retractor muscle, which is typically 25–200 μm thick and well vascularized.

Underlying the muscle is loose connective tissue that can be readily separated by dissection. The dimensions above are specific to the hamster and depend on body mass and the region from which the dorsum is sampled. Typical patterns of large feeder vessels in the plane of the skin are shown in Fig. 4C.

Summary of window chamber variants. Considerations in design of window chamber variants are the ability to 1) provide direct contact or exposure of the sensor array to different types of tissue, such as muscle, fascia, or dermis; 2) visualize the tissue-sensor interface with minimal interference from tissue layers; 3) employ nonsensor materials implants for biocompatibility studies; 4) minimize surgical intervention to the tissue, including interruption and redirection of the vascular structure and perfusion patterns; and 5) apply the preparation to other rodent species. The different preparations address these considerations to various degrees. The design variants are represented schematically in Fig. 5, A–C, and are summarized in Table 1.

Features of the variants. The tissuefold-sensor array window chamber (17) consists of a fold of dorsal skin retractor muscle with the skin layer removed, with the sensor array held adjacent to one side of the tissue and the window adjacent to the other side, as shown schematically in Fig. 5A. Visualization of the tissue-sensor array interface is through two layers of folded retractor muscle using either reflected light or illumination through the opaque ceramic disc. An advantage of the preparation is that there is relatively little modification of natural perfusion patterns in the muscle tissue, because only the dermal layer or the dermal layer and subcutaneous muscle layer are removed. Depending on the membrane material and its surface roughness, the tissue either becomes attached to the membrane surface or approximates the surface with a very small fluid-filled gap (1–5 μm). The impermeable glass window can serve as a control for the effects of tissue contact with the membrane and for potential effects on the tissue of oxygen consumption by the sensors.

The one-sided tissue-sensor array preparation (Fig. 5B) has intact, depilated skin on one side (a window is not used), and dermal tissue in contact with the sensor array or biomaterial on the opposite side. This preparation can accommodate a window, a sensor array, or a porthole sensor.

Single-layer tissue-sensor array. Debrided dermal, fascia, fat or muscle

Table 1. Summary of window chamber variants

<table>
<thead>
<tr>
<th>Preparation Type</th>
<th>Tissue Type Adjacent to Array</th>
<th>Opposite Side</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Viability</th>
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<tr>
<td>Tissuefold-sensor array (17)</td>
<td>Folded muscle or connective tissue layer; skin removed</td>
<td>Window</td>
<td>Muscle vasculature left intact; good blood flow</td>
<td>Potential gap at tissue-implant interface; imaging through folded tissue layers</td>
<td>2–4 wk</td>
</tr>
<tr>
<td>One-sided tissue-sensor array</td>
<td>Dermal, fascia, fat or muscle</td>
<td>Intact skin</td>
<td>Good vascularity; no gap at interface; biocompatibility testing</td>
<td>Imaging through intact skin</td>
<td>&gt;4 wk</td>
</tr>
<tr>
<td>Single-layer tissue-sensor array</td>
<td>Debrided dermal, fascia, fat or muscle</td>
<td>Window</td>
<td>Single sheet of tissue; precise imaging</td>
<td>Substantial tissue removal; limited viability</td>
<td>Several days</td>
</tr>
<tr>
<td>One-sided tissue-porthole sensor array</td>
<td>Dermal, fascia, fat or muscle</td>
<td>Intact skin</td>
<td>Direct imaging of vessels at interface; removal of single skin layer</td>
<td>Limited window area adjacent to sensors</td>
<td>Several days</td>
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the opposite side. Visualization is through the single-thickness skin layer, and clarity can be comparable to the above tissue-fold-sensor array preparation. This preparation provides direct contact between the tissue and sensor array surface, without stretching the tissue to adhere to a glass window on the opposing side. The preparation can be maintained viable for several weeks, because there is less damage due to tissue removal and rearrangement of perfusion. This preparation is particularly useful to display the effects of blood flow and vascular density on sensor function. A different type of sensor
array used with this tissue configuration is the one-sided tissue-porthole sensor array, which has transparent holes in the plane of the ceramic disc between certain working electrodes and is implanted against the muscle, fascia, or subcutaneous fat. This variant allows direct imaging of the vascularity at the tissue-array interface adjacent to the working electrodes.

In the single-layer tissue-sensor array preparation (Fig. 5C), the tissue on both sides of the fold is removed leaving a single sheet of retractor muscle sandwiched between the array and window glass. Although visualization of the tissue is improved, the viable lifetime of the preparation is reduced due to the substantial amount of tissue removed.

Examples of tissue imaging. Figure 6, A–D, shows images taken from each of the preparations. The microvasculature was readily visualized by trans- or epi-illumination in all preparations. In some cases, the presence of intervening tissue precluded optical imaging of discrete capillaries, but the general level of perfusion on various regions of the chamber could nevertheless be readily identified using intravenously injected fluorescent dye. The tissue-sensor array preparations showing the retractor muscle and the feeding layer allowed still- and video-based imaging of the microvasculature, as performed with epi-illumination at ×1.25, ×4, and ×10 objective magnification. The best visualization of the microvasculature adjacent to the working electrodes was achieved with the single-layer tissue-sensor array (Fig. 6C) and the tissue/porthole sensor array preparations (Fig. 6D) at ×10. This created a limited field of view but provided a high degree of detail in terms of capillaries and the flow of blood through the microvessels. The porthole array preparation is advantageous in that it was relatively less traumatic, and blood flow appears relatively undisturbed, even though windows were not directly over individual sensors.

Optical parameters obtained with the preparations are summarized in Table 2. Estimates of working distance, depth of field, and resolution were made with three optical objectives used here.

Advantages of direct imaging. There are several advantages to direct tissue visualization provided by the preparations. First, the ability to see the vascular pattern adjacent to individual sensors can help explain different steady-state signals of neighboring sensors. Sensors in regions of higher capillary density can be expected to sustain higher substrate fluxes and produce higher currents. However, an important additional variable is the distance orthogonal to the tissue plane from the microvascular plexus and the sensor surface, which can be

![Fig. 7. A–D: examples of sensor recordings from each preparation. Simultaneous signal recordings (in nA) as a function of time in minutes during an inspired oxygen challenge are shown. Recordings were low-pass filtered, and some tracings have been removed for clarity. Inspired oxygen challenges (15% oxygen) caused a linear drop in all signals to a minimum, followed by a return to atmospheric inspired oxygen (21%) and a rise in signals. A detailed analysis of signals is given elsewhere (16).](http://ajpheart.physiology.org/)

Table 2. Optical parameters

<table>
<thead>
<tr>
<th>Objective</th>
<th>Working Distance, mm</th>
<th>Depth of Field, μm</th>
<th>Resolution, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>×4</td>
<td>17.0</td>
<td>9.2</td>
<td>1.0</td>
</tr>
<tr>
<td>×10</td>
<td>16.0</td>
<td>5.9</td>
<td>0.5</td>
</tr>
<tr>
<td>×20</td>
<td>2.1</td>
<td>3.7</td>
<td>0.4</td>
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A cordings from implanted sensor arrays are shown in Fig. 7, sensor signals would not be possible. Without the ability to visualize the tissue, a full explanation of visualization is advantageous to document any changes in tissue or microvasculature adjacent to individual sensors. Finally, visualization of perfusion of the tissue as a whole as well as of the local microvasculature is advantageous to determine the degree of tissue phenomena that modify the response to local tissues. However, this response is not necessarily proportional to the inspired oxygen concentration, suggesting that local physiological mechanisms protective against hypoxia may be important.

These features were observed in all preparations. These observations suggest that new sensor designs or new operating procedures may be needed to reduce or adequately account for the effects of tissue phenomena that modify the response to intravascular substrate concentration. Detailed analysis of sensor design is presented elsewhere.

Examples of sensor recordings. Typical simultaneous recordings from implanted sensors arrays are shown in Fig. 7, A–D. The results are shown for oxygen because the interpretation is relatively straightforward, but results having similar characteristics have been obtained for sensors for glucose. Individual oxygen sensor signals are reported in nanoamperes as a function of time in minutes during challenges in inspired oxygen.

There are several interesting observations. After an initial decline in sensitivity immediately after implantation, the sensitivity to substrate concentration typically remains stable for the lifetime of the window chamber. After this stabilization period, the steady-state signal magnitude of the implanted sensor is substantially smaller than when tested in vitro for the same oxygen exposure. This difference is attributed to differences in mass transfer resistance, which have been quantitatively analyzed (16). There is also a certain variance in steady-state signal magnitude among sensors within a given array when tested in vitro in homogeneous mass transfer conditions, reflecting small irregularities in fabrication. The effect of this variance is compensated by individual sensor calibration and confirmation of the sensitivity to oxygen by the same method (16) after the study. However, when sensors are used in the window chamber, there is an additional, relatively large steady-state variance among sensors due to tissue heterogeneity, which is prominent in Fig. 7, A–D. Specific values of mass transfer parameters corresponding to individual implanted sensors have been reported (16).

Signals also show two types of transients during steady-state recording sessions. Rapid, small-amplitude fluctuations in signals may represent electronic noise or the effects spatially heterogeneous vasomotion in the vicinity of individual sensors. Slower, large-amplitude variations in signal that are often correlated among multiple sensors are also observed, which may reflect variations in regional perfusion. Interpretation of these phenomena is made feasible by the ability to visualize tissues afforded by the window chamber preparations. Extensive analysis of the relationship between signals and variations in perfusion local microvasculature and regional blood vessels is described in detail elsewhere. Furthermore, sensors respond rapidly and substantially to changes in inspired oxygen, indicating a relatively rapid overall mass transfer from the airways to local tissues. However, this response is not necessarily proportional to the inspired oxygen concentration, suggesting that local physiological mechanisms protective against hypoxia may be important.

In conclusion, sensors implanted in tissues for continuous monitoring of metabolites have promise for clinical applications, but there is a need to understand the effects of the tissue on the concentration-dependent signals. Variants of the tissue-sensor array window chamber described here are powerful tools for visualization of tissues and recording sensor signals while administering physiological challenges. The experimental system permits real-time, nondestructive observation of tissues, eliminates between-subject variance in the signals, and allows repeated studies with implant time. The respective window chamber variants have advantages for improved visualization, minimization of perturbations of normal vascular function, and extension of window chamber lifetime. The observations made possible here may suggest improved designs of implantable sensors to compensate for tissue phenomena.

Limitations of the window chamber methodology. Although the window chamber preparations have major advantages, several limitations are recognized. It is often necessary to perform extensive blood sampling to record blood substrate dynamics in certain experiments, which is not feasible in the hamster due to the limited blood volume. The respective window preparations have a maximal lifetime of several days to months, which can limit long-term testing. The sustained immobilization of the tissue may lead to unnatural perfusion and tissue growth. The surgical preparation represents a substantial tissue modification and prolonged tissue exposure, which likely leads to an unnatural wound healing response. With these reservations in mind, the disadvantages are mitigated in certain experimental situations by the unusual advantage of being able to observe tissues in a relatively natural, unanesthetized state while sensor recordings are being made.

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REFERENCES


