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Permeability of subcutaneous tissues surrounding long-term implants to oxygen

Lucas S. Kumosa [a], Timothy L. Routh [b], Joe T. Lin [b], Joseph Y. Lucisano [b], David A. Gough [a, *]

[a] Department of Bioengineering, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0412, USA
[b] GlySens Incorporated, 6450 Lusk Blvd., Suite E-109, San Diego, CA 92121, USA

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ABSTRACT

Certain types of implanted medical devices depend on oxygen supplied from surrounding tissues for their function. However, there is a concern that the tissue associated with the foreign body response to implants may become impermeable to oxygen over the long term and render the implant nonfunctional. We report oxygen flux recordings from electrochemical oxygen sensor devices with wireless telemetry implanted in subcutaneous porcine tissues. The devices remained implanted for up to 13 weeks and were removed with adjacent tissues at specified times for histologic examination. There are four main observations: (1) In the first few weeks after implantation, the oxygen flux to the sensors, or current density, declined to a sustained mean value, having unsynchronized cyclic variations around the mean; (2) The oxygen mass transfer resistance of the sensor membrane was negligible compared to that of the tissue, allowing for a sensitive estimate of the tissue permeability; (3) The effective diffusion coefficient of oxygen in tissues was found to be approximately one order of magnitude lower than in water; and (4) Quantitative histologic analysis of the tissues showed a mild foreign body response to the PDMS sensor membrane material, with capillaries positioned close to the implant surface. Continuous recordings of oxygen flux indicate that the tissue permeability changes predictably with time, and suggest that oxygen delivery can be sustained over the long term.

1. Introduction

What is the rate of oxygen delivery to a medical device implanted in subcutaneous tissues over the long term? And, What is the permeability to oxygen of tissues that surround implants? These questions are central to the function of implanted devices that depend on the transport of oxygen from the subcutaneous tissues in which they are implanted, such as biosensors for oxygen and other analytes [1,2], polymer-encapsulated pancreatic islets for use in diabetes [3,4], tissue engineered devices containing metabolically active cells [5,6], and implantable electronic devices [7] or fuel cells that rely on the transport of oxygen and metabolic fuels from the tissue environment.

All implants elicit some degree of foreign body response in the surrounding tissues that may be expected to affect tissue permeability [8,9]. The characteristics and magnitude of this response can depend on many things, such as: the properties of the implant and the extent to which it releases even small amounts of irritants into the tissues, such as toxic organic and metallic species, residual sterilants, and ionic current; the type of tissue in which the device is implanted and the local mechanical stresses; the means of introduction of the implant into the tissue; and other factors. The resulting foreign body response may include some or all of the following features: a localized formation of dense and granular tissue, remodeling of the local microvasculature near the tissue-implant interface, the infiltration of granulocytes and macrophages, the development of chronic localized inflammation and tissue edema, and even the formation of a pocket of fluid transudate. Minimizing these affects by proper selection and preparation of implant materials, optimal design and placement of the implant, and the use of appropriate manufacturing and sterilization methods is a common goal.

* Corresponding author. Tel.: +1 858 822 3446.
E-mail address: dgough@ucsd.edu (D.A. Gough).

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Although the development of some degree of foreign body response seems unavoidable, little is known about the resulting permeability of the tissues adjacent to implants and how the tissue permeability changes with time. It is necessary to establish quantitative methods for measuring tissue permeability as a basis for the selection of biomaterials and for assessment of the effects of the tissue response on implant function.

Several approaches have been used previously to evaluate the effective permeability of foreign body tissues to oxygen. In one study, a perfusion chamber was implanted against the rat abdominal omentum, having a hydrogel membrane in contact with the tissue on one side and perfused with buffer on the other side [10]. After a 28-day period for stabilization of the tissue neovascularization, samples were collected from the buffer and the oxygen concentration was assayed. The overall permeability to oxygen was estimated to be 9.4×10^{-4} cm s^{-1}, observed by transport through both the tissues and membrane, and separately *in vitro* through the membrane alone, leading to the conclusion that the oxygen mass transfer resistance of the tissue is comparable to the resistance of the hydrogel membrane. The use of a membrane that is substantially more permeable than the tissue would have been advantageous to assess the limiting mass transfer resistance of the tissue, independent of membrane properties.

An alternative approach based on modeling has also been used to predict the oxygen distribution in tissues around implants. Models have been based the assumption that oxygen distributions can be inferred from tissue structural features seen by post-mortem histologic examination [11,12]. This approach is, however, limited by several factors, including: the lack of an unambiguous means of defining the local oxygen distribution; incorporating the heterogeneous properties of living tissues, such as intermittent microvascular blood flow, diffusion and metabolic consumption of oxygen; and including changes in these properties with time.

Microarchitectural features on the surface of implants have been used to encourage the development of microvascularization at the tissue-implant interface [13], and have enabled maintenance of neovascularization for over 330 days in one study [14]. For comparison, the effective diffusion coefficient of glucose in such fibrotic tissue capsules implanted subcutaneously in rats was estimated to be one to two orders of magnitude lower than the diffusion coefficient in water [15].

We describe here the use of an oxygen sensor device having a wireless RF telemetry system that was implanted in the subcutaneous tissues of pigs to analyze, in conjunction with histology studies, the permeability of foreign body tissues to oxygen over the long term.

2. Methods

2.1. Implant description

The implant is shown in Fig. 1. The ceramic disc on the upper surface is composed of an imbedded sensor array of 300 μm diameter platinum disc sensing electrodes, Ag/AgCl potential reference electrodes, and platinum counter electrodes [2]. The electrodes and disc surface are covered by a thin electrolyte layer and a smooth, 25 μm thick membrane of medical grade polydimethylsiloxane (PDMS). A diffusion-limited reaction, $O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$, occurs quantitatively at the electrode surface at an applied cathodic potential of −500 mV *vs* the Ag/AgCl reference electrode [16]. The pore-free hydrophobic PDMS membrane is permeable to oxygen but not to polar molecules, and prevents current passage into the tissues.

The ceramic disc with the sensors is fused into a hermetically sealed titanium housing that contains individual potentiostats for each sensor and a wireless, battery powered telemetry system with a projected 2-year lifetime. The telemetry system samples the currents from individual sensors, converts the samples into multiplexed segments, and transmits the segments as a train of radio frequency signals at regular 2-min intervals to an external receiver where they are decoded and archived. Inactive implants having identical mass, shape and materials, but lacking internal sensing and telemetry electronics, were used for serial removal and collection of histology samples. Eleven devices with a total of 60 functional sensors and 20 inactive sensors were implanted at four dorsal subcutaneous tissue locations for thirteen weeks in four 20 kg adult female Yucatan minipigs. The PDMS membrane and titanium materials have been evaluated previously in standard cell culture tests [17]. Implants were sterilized using a validated chemical sterilization procedure [18]. The hermetic wireless telemetry system makes possible long-term recordings in animals without infection-prone percutaneous electrical leads.

Fig. 1. Oxygen sensor array with integrated wireless telemetry system at implantation. The electrodes are imbedded into a ceramic disc that is hermetically sealed into the titanium housing. The electrodes are covered by a PDMS membrane. The implant is 3.4 cm in diameter and 1.5 cm thick.

In related studies, analogous sensors for glucose based on immobilized glucose oxidase coupled to dual oxygen sensors have functioned as implants in subcutaneous tissues of pigs for periods as long as 520 days [2]. This sensor system and has also been implanted in humans for extended periods with similar results.

2.2. Implantation procedure

All procedures involving animals were consistent with AAALAC guidelines [19] and approved by the UCSD Animal Subjects Committee. The implantation procedure emphasized blunt dissection to avoid bleeding and minimize damage to the tissue and lymphatics. Implant locations were chosen on the dorsal skin of the pigs, offset on either side of the midline at a minimum of 15 cm from each other. A 5 cm long, 1–2 cm deep incision was made in each location, exposing the dermal layers. Using blunt dissection to ensure minimal damage to the fascia, a pocket was formed between the sub-dermal fat and underlying muscle. Implants were inserted into the pockets with the PDMS surface facing ventrally and the titanium surface facing dorsally. With the properly seated implant inside, the skin was sutured and a povidone-iodine topical antiseptic and sterile dressing were applied. A dual-lumen Hickman catheter (Bard Access Systems) for blood sampling and fluid infusion was placed into the central vena cava with access ports exposed at the midscapular region. The catheter was routinely flushed with a dilute heparin solution to maintain patency.

2.3. Explantation

The animals were given a combination of general and local anesthetics, and an incision was made in the skin, exposing the implant underneath. Tissue samples were excised from regions of the pocket adjacent to the PDMS and titanium surfaces and placed in histological fixative. The incision was sutured and wound site treated with antiseptic. No severe abnormalities, defects or injuries were seen in any of the procedures, indicating healthy tissue and implant pocket. Sterile technique was used in all procedures.

2.4. Model of oxygen flux

The observed oxygen flux (shown in Fig. 2) is described by the product of four terms given sequentially in the descriptive equation below: (1) a quasi-steady state term containing mass transfer parameters and the local oxygen concentration; (2) an exponential decay term; (3) an oscillatory term corresponding to observed cyclic oxygen fluctuations; and (4) a term for the bias or background current produced in the absence of oxygen. Summed over J sensors having K oscillations, the normalized oxygen flux, which is equivalent to the transient current density, is described by

$$\frac{I_o(\tau)}{n\,FA} = \sum_{j=1}^{J}\sum_{k=1}^{K}\frac{1}{j}\left[\left[\frac{c_o P_m}{1+Bi_j^{-1}}\right]\left[1 - M_j \times \exp\left[\frac{\tau}{\tau_{d_j}}\right]\right]\left[\cos\left[\frac{2\pi}{T_{j,k}}\left[\tau + \tau_{o_{j,k}}\right]\right]\right] + C_j\right] \quad (1)$$