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MEASURING INTERSTITIAL FLUID PRESSURE WITH FIBEROPTIC PRESSURE TRANSDUCERS

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Abstract

In this report we describe a practical procedure for measuring interstitial fluid pressure (IFP) using fiberoptic pressure transducers based on optical interferometry. Eight mice were used for subcutaneous IFP measurements and four mice for intramuscular IFP measurements with a FOBPS-18 fiberoptic pressure transducer. We used four mice for subcutaneous IFP measurements with a SAMBA-420 MR fiberoptic pressure transducer. One measurement was made for each mouse simultaneously by using a fiberoptic system and an established approach, either transducer-tipped catheter or wick-in-needle technique.

The mean IFP values obtained in subcutaneous tissues were -3.00 mm Hg (SEM $-/+0.462$, $n=8$), -3.25 mmHg (SEM $-/+0.478$, $n=4$), -3.34 mm Hg (SEM $-/+0.312$, $n=6$), and -2.85 (SEM $-/+0.57$, $n=6$) for the FOBPS fiberoptic transducer, the SAMBA fiberoptic transducer, the transducer-tipped catheter, and the wick-in-needle technique, respectively. There was no difference between these techniques to measure IFP (Friedman test, $p=0.7997$). The subcutaneous IFP measurements showed strong linear correlation between fiberoptic transducer and transducer-tipped catheter ($R^2=0.9950$) and fiberoptic transducer and wick-in-needle technique ($R^2=0.9966$).

Fiberoptic pressure transducers measure the interstitial fluid pressure accurately, comparable to conventional techniques. The simplified IFP measurement procedures described in this report will allow investigators to easily measure IFP, and elucidate the unit pressure change per unit volume change (dP/dV) in normal or cancer tissues in the presence of strong electromagnetic fields encountered in MRI.

Keywords

fiberoptic; interstitial; fluid; pressure; Starling-Landis; volume; cancer; angiogenesis; pericyte; hypertension; MRI

INTRODUCTION

Interstitial fluid pressure is one of the components of the Starling-Landis equation which states that net convection through capillary membranes is proportional to the transmembrane hydrostatic pressure difference minus the transmembrane colloid osmotic pressure difference. The interstitial fluid pressure within any tissue is regulated through interactions between cells and extracellular-matrix molecules. In most tissues, with the exception of muscle and kidneys, the interstitial fluid pressure (IFP) is negative (Guyton et al., 1976) (Scholander et al., 1968).

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By contrast, IFP is often increased in tumor tissue and forms a barrier against efficient drug delivery into the tumor as shown by seminal work by Dr. Rakesh K. Jain (Jain, 1987).

Several techniques have been described for IFP measurements over the last four decades. They include: wick catheter (Scholander et al., 1968), wick-in-needle technique (Fadnes et al., 1977), glass micropipette/servonull transducer (Wiederhielm et al., 1964), semiconductor-tipped Millar transducer for acute studies of IFP (Ozerdem and Hargens, 2005) and subcutaneous capsule implantation for 4-6 weeks (Guyton, 1963) which permits prolonged testing of IFP. Some of the pressure transducers mentioned above are subject to artifacts when used in strong electromagnetic fields. Measurement artifacts may be important for the transducers that contain metallic components. Such transducers cannot be used in an MR scanner. Glass micropipettes and wick-in-needle techniques pose the additional risk of leaving a foreign body in human tissues and are therefore subject to limitations for measuring IFP safely in deep tissues.

MATERIALS AND METHODS

All experiments were performed in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals. We used 8 mice for subcutaneous IFP measurements and 4 mice for intramuscular IFP measurements with WPI-FOBPS-18 fiberoptic pressure transducer (Figure A). We used 4 mice for subcutaneous IFP measurements with SAMBA-420 MR fiberoptic pressure transducer (Figure B). One measurement was made for each mouse simultaneously by using a fiberoptic system and an established approach, either Millar transducer or wick-in-needle technique. We performed 8 subcutaneous IFP measurements with FOBPS, 4 subcutaneous IFP measurements with SAMBA transducers as matched pairs with 6 measurements with Millar transducer and 6 measurements with wick-in-needle technique. The correlation between fiberoptic transducers (FOBPS and SAMBA) and conventional IFP techniques (Millar catheter and wick-in-needle) was calculated with linear regression analysis by using Graphpad Prism 4.0 software. It was also necessary to test the fiberoptic transducers *in vivo* in supra-atmospheric pressure ranges. We chose to use subcutaneous tissue or muscle tissue in this investigation since healthy subcutaneous tissue has negative IFP while muscle tissue has supra-atmospheric (positive) IFP (Scholander et al., 1968). We further increased IFP in muscle by injecting 0.5ml (500mm³) saline solution intramuscularly in 4 mice where we applied WPI-FOBPS-18 transducer. This form of manipulation of IFP in a given tissue provides valuable biomechanical information about the unit pressure change per unit volume change (dP/dV). Since SAMBA-420 MR transducer was extremely fragile we did not expose it to such surgical manipulations in muscle tissue.

Before each use, all fiberoptic transducers (WPI-FOBPS-18 fiberoptic, SAMBA-420 MR fiberoptic) were calibrated by using a distilled water column at 37° C to which was added detergent (Tween 20, Sigma-Aldrich, St. Louis, MO) at a ratio of 10,000:1. Adding detergent to the water column reduces the surface tension and drag as the water column is adjusted. A syringe attached to the short end of a 200 cm-high, J-shaped hard tubing with a T-shaped adapter is used to adjust and monitor the pressure around the transducer within the +100 cm-H₂O to -100cm-H₂O range. The change in the specific gravity of water in the presence of minute amounts of detergent was not significant. This calibration procedure is essential before any interstitial tissue fluid pressure measurement experiment is undertaken. After calibration, prior to advancing into the live tissue, the fiberoptic transducers were rinsed with distilled water to remove any detergent residue.

Application of WPI-FOBPS-18 fiberoptic transducer

This transducer had a tip diameter of 0.59 mm (1.8 F) and optical fiber diameter of 0.17 mm (0.51 F) (Figure A). The distal end of transducer tip was not sensitive to pressure while the

side of the transducer tip was. The volume of the transducer tip which was sensitive to pressure was 1.36 mm^3 in WPI-FOBPS-18 transducer as calculated from its dimensions. Following anesthesia, the transducer was introduced to the mouse tissue interstitium by using a needle guide (Figure C). Briefly, the transducer was passed through the lumen of a Becton-Dickinson 18 gauge, 1.5-inch precision glide needle (Franklin Lakes, NJ). The tip of the transducer was kept in the lumen of the needle during penetration into the tissue. The transducer was introduced into the tissue as the needle guide was withdrawn from the skin surface. The interstitial fluid pressure (IFP) was read by means of WPI-FOMS optic interferometry monitor after 15 seconds. We also explored the technical feasibility of using this transducer to investigate the interstitial fluid pressure-volume relationship (dP/dV) while isotonic saline is infused into the muscle interstitium on the opposite side of the tissue with a butterfly needle (Becton Dickinson cat# 367251).

Application of SAMBA-420 MR fiberoptic transducer

This transducer had a tip diameter of 0.42 mm (1.27 F) and optical fiber diameter of 0.25 mm (0.75 F), and was extremely fragile (Figure B). Its shape was similar to a piston which causes temporary pressure spikes and troughs when it was moved within the cylindrical space of the needle guide. The volume of the transducer tip which was sensitive to pressure was 0.072 mm^3 in SAMBA-420 MR transducer as calculated from its dimensions. As opposed to WPI-FOBPS-18 transducer, the distal end of the SAMBA 40-MR transducer tip was sensitive to pressure while the side of the transducer tip was not. To circumvent the fragility and pressure artifacts, a $\frac{1}{2}$ inch piece of a 23 gauge (0.66mm) polyurethane catheter was perforated using a 29 gauge insulin needle to create sixteen through-through holes (every $\frac{1}{32}$ inch) and then filled with isotonic sterile lubricant eye drop (Allergan, Irvine, CA) (Figure D). Following anesthesia the entire perforated polyurethane tube was inserted very slowly into the interstitium of subcutaneous tissue through a small (0.5 mm) skin incision (Figure E). Next the SAMBA-420 MR transducer was slowly and gently inserted halfway into the perforated polyurethane catheter. The interstitial fluid pressure (IFP) was read after 15 seconds via the SAMBA 3200 optic interferometry monitor.

We compared and validated the IFP measured with both fiberoptic pressure transducers to well-established methods; the wick-in-needle method (Fadnes et al., 1977), and the ultraminiature transducer-tipped catheter (Millar transducer) method (Ozerdem and Hargens, 2005). As a reference, we used the Spectramed P23XL transducer (wick-in-needle) and the Millar SPC320 ultraminiature transducer-tipped catheter (SPC320, 2F size i.e. 0.66 mm in diameter, Millar Instruments, Houston, TX). The fiberoptic pressure transducers were placed side-by-side with either the wick-in-needle probe or Millar ultraminiature transducer-tipped catheter probe in interstitial tissues of previously shaved C57BL/6 mice for simultaneous IFP comparisons. For wick-in-needle technique, a 0.6 mm needle was provided with a 2 mm-long side hole 2 mm from the tip. The edges of the side hole were polished with a sharpening stone. Strands of nylon fibers were pulled into the needle. The needle was connected to a P23XL pressure transducer (serial number 10153923, Spectramed, Oxnard, CA) by means of a polyethylene tube. The P23XL transducer was connected to a Windograf Model 40-8474 amplifier (serial number 1463, Gould Inc., Valley View, OH). The polyethylene tube and needle were filled with 0.9% saline through another port on the side of the plexiglass dome of the transducer (Ozerdem and Hargens, 2005). Care was taken to prevent air bubbles within the entire system. Zero reference pressure was obtained after accurately placing the wick-in-needle at the level of the plexiglass dome by using a slit beam of a laser level (Black and Decker, DL220S, Towson, MD).

RESULTS

All pressure transducers performed well and produced a linear pressure-output relationship with $R^2 = 0.99$ or higher goodness-of-fit in linear regression analysis during calibration in water columns (data not shown). The entire procedure, including calibration of the sensor, introduction into the tissue interstitium, and IFP reading takes less than 10 minutes, and can be performed with ease by anyone who can perform a subcutaneous or intramuscular injection. The SAMBA 420 MR system requires an additional 15 minutes for the optic interferometry monitor to warm up. The mean IFP values obtained in subcutaneous tissues were -3 mm Hg (SEM ± 0.462 , $n=8$), -3.25 mmHg (SEM ± 0.478 , $n=4$), -3.34 mm Hg (SEM ± 0.312 , $n=6$), and -2.85 (SEM ± 0.57 , $n=6$) for FOBPS fiberoptic transducer, SAMBA fiberoptic transducer, Millar catheter, and wick-in-needle technique, respectively. There was no statistically significant difference between these four techniques to measure IFP (Friedman test, $p=0.7997$) (Fig F). The subcutaneous IFP measurements showed strong linear correlation between FOBPS and Millar catheter ($R^2=0.9950$) and FOBPS and wick-in-needle techniques ($R^2=0.9966$) (Figure G-H). The rise of mean IFP to $+18.75$ mmHg (SEM ± 0.629) from baseline $+5$ mmHg (SEM ± 0.707) in tibialis anterior muscle in mice ($n=4$) resulting from injecting 0.5 ml saline slowly over the course of 1 minute was easily documented with WPI-FOBPS-18 transducer.

DISCUSSION

Pressure measurement with fiberoptic pressure transducers is based on Fabry-Perot optical interferometry principle. Two parallel, partially reflecting surfaces are spaced less than a coherence length apart, thereby forming an optical reflecting cavity. Since one of the partial reflecting surfaces is a pressure-sensitive diaphragm, changes in external pressure will alter optical cavity depth. A change in optical cavity depth will cause a change in optical cavity reflectance. The transducer comprises a sensor element mounted on the tip of an optical fiber. The light passes through the fiber and is reflected in a cavity inside the sensor element. When the pressure surrounding the sensor element is changing, the reflected light signal will change. The reflected light signal is then transformed to a readable pressure value. The sensor element is produced in silicon. The optical fiber is made of glass and has special coatings. The sensing light is transmitted to and reflected back from the detecting diaphragm and cavity of the sensor tip via a multimode fiberoptic cable without passing a metal conductor circuit through the tissues (Figure I).

The SAMBA 420 MR has an extremely fragile tip rendering it difficult to use in tissues with a hard consistency (bone, cartilage, fascia) or contractile tissues (myocardium, skeletal muscle, intestinal or vascular smooth muscle layers) to measure IFP. Unlike WPI-FOBPS-18 system which provides only relative pressure readings, the SAMBA 420 MR system provides absolute and relative pressure readings both in liquid or air interface. This feature of SAMBA 420 MR system can potentially be useful when IFP measurement of tumors is needed during endoscopic procedures where the ambient pressure in the organ lumen is a confounding variable; it can be subtracted without using a second transducer (manometer) to monitor the luminal pressure during the endoscopy procedure. Both SAMBA 420 MR and WPI-FOBPS-18 transducers can be used for IFP measurements even in the presence of a strong electromagnetic field in the vicinity of organ of interest. However, the fragility of the tip of SAMBA420 MR transducer that requires a perforated membrane implantation coupled with piston-artifact leaves substantial room for improvement of materials and design to make the transducer tip more suitable for IFP procedures. In terms of accuracy both fiberoptic systems match the performance of the gold standard reference transducers (Spectramed P23XL and Millar SPC320 catheter) both in negative and positive pressure ranges.

Fiberoptic pressure transducers, recognized for impeccable accuracy in the pressure range between $-100\text{cm-H}_2\text{O}$ and $+100\text{cm-H}_2\text{O}$, provide a simple, accurate and thromboresistant method of measuring the interstitial fluid pressure at the source. The simplified IFP measurement procedures described in this report will allow basic researchers and clinicians to easily measure IFP, and investigate the relationship between IFP and interstitial fluid volume when they use the fiberoptic transducers in the presence of strong electromagnetic fields such as encountered in magnetic resonance imaging.

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Figure.

Interstitial fluid pressure measurement with fiberoptic pressure transducers. A. The distal end of the WPI-FOBPS-18 fiberoptic transducer tip is not sensitive to pressure while the side of the transducer (arrow) is sensitive to the same. This feature of WPI-FOBPS-18 prevents piston effect and consequent pressure artifact. Millar SPC 320, a non-fiberoptic transducer tipped catheter, is shown with an asterisk for comparison Scale bar indicates 590 μm . B. The distal end of the SAMBA 420 MR fiberoptic transducer (arrow) is sensitive to pressure while the side of the transducer is not. This feature of SAMBA 420MR causes piston effects and temporary pressure artifacts when the transducer is placed (introduced) into the tissue interstitium for IFP measurement. Scale bar indicates 250 μm .

C. The WPI-FOBPS-18 fiberoptic transducer is easily introduced through the interstitial space of tissues in a protective metal guide (18 gauge needle) (asterisk). The needle guide is withdrawn slowly while the sensor is introduced into the interstitial space in subcutaneous tissue. D. Implantation of a perforated polyurethane tube is necessary to prevent the SAMBA-420 MR fiberoptic transducer from breaking. E. Through a small (0.5 mm) skin incision the perforated tube can be inserted in its entirety to the subcutaneous tissue easily (arrow). F. The mean IFP values obtained in subcutaneous tissues were -3 mm Hg (SEM $-/+0.462$, $n=8$), -3.25 mmHg (SEM $-/+0.478$, $n=4$), -3.34 mm Hg (SEM $-/+0.312$, $n=6$), and -2.85 (SEM $-/+0.57$, $n=6$) for FOBPS fiberoptic transducer, SAMBA fiberoptic transducer, Millar catheter, and wick-in-needle technique, respectively. There was no statistically significant difference between these four techniques to measure IFP (Friedman test, $p=0.7997$). G. The subcutaneous IFP measurements showed strong linear correlation between FOBPS and Millar catheter ($R^2=0.9950$). H. The subcutaneous IFP measurements showed strong linear correlation between FOBPS and wick-in-needle technique ($R^2=0.9966$). I. Pressure

measurement with fiberoptic pressure transducers is based on Fabry-Perot optical interferometry principle. Two parallel, partially reflecting surfaces are spaced less than a coherence length apart, thereby forming an optical reflecting cavity. If one of the partial reflecting surfaces is a pressure-sensitive diaphragm, changes in external pressure will alter optical cavity depth. A change in optical cavity depth will cause a change in optical cavity reflectance. The transducer comprises a sensor element mounted on the tip of an optical fiber. When the pressure surrounding the sensor element is changing, the reflected light signal will change.