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Polymer-Based Sensors for Dynamic Intravascular Shear Stress Analysis

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ABSTRACT

This paper describes a polymer-based shear stress sensor built on catheter for *in vivo* measurements and potential application in atherosclerosis diagnosis. MEMS shear stress sensor with backside wire bonding has been used to address *in vitro* applications for micro-scale hemodynamics with high temporal and spatial resolution. However, to assess shear stress in the tortuous and dynamic arterial circulation, we had to develop a new generation of polymer- and catheter-based sensors that are both flexible and deployable. The individual sensor was packaged near the tip of a catheter for intravascular shear stress analysis. The wire bonding and electrode leads were insulated by a film of Parylene C and were connected to the external circuit along the guide-wire. The sensor was deployed through the catheter into the aorta of New Zealand White (NZW) rabbits by the femoral cut-down procedure. Based on the heat transfer principle, the device was able to detect small temperature perturbation in response to the pulsatile flow at ~200 beats/minutes in the rabbits. The sensor was calibrated in the presence of rabbit blood flow at 37.8°C. We demonstrated the feasibility of translating a polymer-based device for dynamic intravascular measurement with a potential for clinical applications in detecting coronary artery disease and stroke.

INTRODUCTION

Acute coronary syndromes remain the leading cause of death in the industrialized nations [1]. Hemodynamic forces, specifically, fluid shear stress, play an important role in the development of coronary artery disease [2,3]. The development of micro electro mechanical systems (MEMS) sensors provides an entry point for precise assessment of spatial and temporal variations in shear stress for small-scaled hemodynamics otherwise difficult with the conventional technologies, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and laser Doppler velocimetry. The operational principle of thermal shear stress sensor is based on convective cooling of a heated sensing element as flow passes by its surface. The heat transfer from the heated surface to the fluid depends on the flow characteristics in the viscous region of the boundary layer [4]. The heat convection from the resistively heated element to the flowing fluid is measured in terms of the changes in voltage, from which shear stress can be inferred [5].

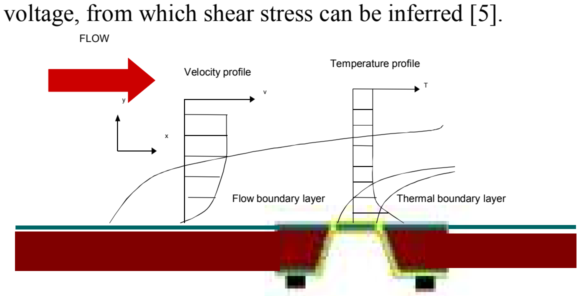

Fig.1 Principle of thermal shear stress sensors

The sensor was fabricated by surface micromachining technique utilizing Parylene C as microelectronic insulation; titanium (Ti) and platinum (Pt) as the sensing elements. The polymer-embedded sensor enables conformability to the arterial bifurcations and curvatures while retaining its mechanical strength and operational function. The resistance of the sensing element was measured approximately to be 1 kΩ, and the temperature coefficient of resistance was approximately 0.16%/°C, which was compatible for blood rheology. A flexible guide wire was cannulated through the catheter and connected to the sensing element for transmitting the signal from the vessel to the external circuitry.

METHODS AND RESULTS

Microfabrication

To dovetail to the arterial circulation, we have fabricated the sensors with (1) thermal growth of SiO_2 and deposition of a 1µm sacrificial silicon layer, (2) deposition and patterning Ti/Pt layers with thickness of 0.1µm for the sensing element; (3) deposition of Parylene C, (4) deposition and patterning of a metal layer of Cr/ Au for electrode leads (2µm), (5) deposition and patterning of a thick layer of Parylene C to form the device structure, and

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(6) etching the underneath silicon sacrificial layer leading to the final device. The resulting sensors were 4 cm in length, 320µm in width and 21µm in thickness. The Ti/Pt sensing elements (160µm in length by 80µm in width) were encapsulated with parylene which was in direct contact with the blood flow.

Packaging of the Sensors

The sensors were packaged to a catheter (**Fig. 2**). The Cr/Au electrode leads were connected to a guide wire with conductive epoxy (which were cured at 90^{o}C in about 3 hours) to carry the electric signals from the arterial circulation to the external circuitry. After that the sensor was mounted to the catheter with biocompatible epoxy leaving the sensing elements facing the blood flow. This step took one day for the epoxy to cure and complete the packaging process. The diameter of the packaged sensor was around 400µm.

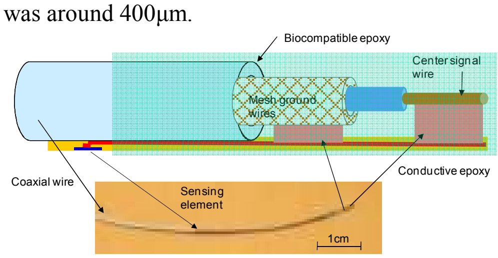


Fig.2 Packaging of the polymer shear stress sensor.

Calibration of the Polymer-based Sensors

Based on the heat transfer principle, the output voltage of the MEMS sensors is responsive to the fluctuation in ambient temperature (**Fig. 1**). The temperature overheat ratio governs the temperature variations of the sensor [6]. The relation between resistance and temperature overheat ratios is expressed as:

$$\alpha_R = \frac{(R - R_0)}{R} = \alpha(T - T_0)$$

where α is temperature coefficient of resistivity or TCR. For shear stress measurement, we applied a high overheat ratio by passing higher current and by generating a "hot" sensing element to stabilize the sensor. Calibration was conducted for individual sensors to establish a relationship between heat exchange (from the heated sensing element to the flow field) and shear stress over a range of steady flow rates (Q_n) in the presence of rabbit blood flow at 37.8^{o}C. The theoretical shear stress value corresponding to each flow rate was calculated using:

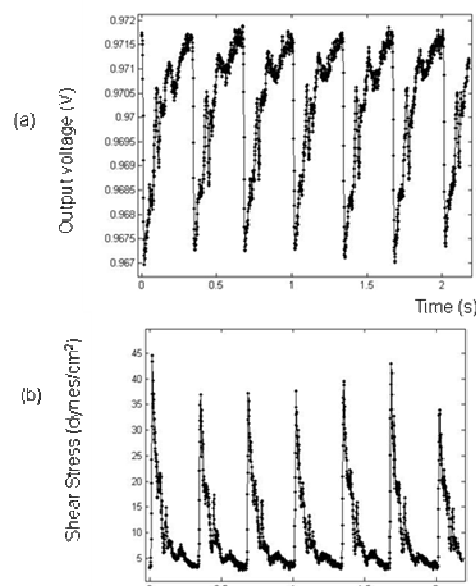
$$\tau_w = \frac{6Q_n\mu}{h^2 w}$$

where τ_w is the wall shear stress, µ is the blood viscosity, and h and w are the dimensions of the flow channel. The viscosity of the blood as a function of flow rate was measured using a viscometer. The individual calibrated sensors were then deployed into the NZW rabbit's aorta for real-time shear stress assessment.

In vivo assessment of intravascular shear stress

We tested the feasibility of acquiring real-time intravascular shear stress (ISS) measurements from the NZW rabbit's aorta; specifically, abdominal and aortic arch. Deployment of the polymer device into the rabbit's aorta was performed in compliance with the Institutional Animal Care and Use Committee in the Heart Institute of the Good Samaritan Hospital, Los Angeles. Six male NZW rabbits (10 to 12 weeks, mean body weight 2,105 ± 47 g) were acquired from a local breeder (Irish Farms, Norco, CA) and maintained by the USC vivaria in accordance with the National Institutes of Health guidelines. After a 7-day quarantine period, all rabbits were anesthetized for percutaneous access according to the institutional review committee. A 23 gauge hypodermic needle and a 26 gauge guide wire were introduced into the left femoral artery via a cut-down. A rabbit femoral catheter (0.023''ID x 0.038''OD) was passed through the left femoral artery. The animals were heparinized (100 U/kg) intra-arterially. All of the catheters and needles were rinsed with heparin at 1000units/mL prior to the procedure. Under the fluoroscopic guidance (Phillips BV-22HQ C-arm), the catheter integrated with the micro vascular device was advanced to aortic arch and ISS was recorded. The catheter was then withdrawn to the abdominal aorta above the renal arties for ISS measurements under fluoroscopy guidance.

The rabbits were maintained under normal conditions and undergo periodic blood pressure measurement using an automated tail cuff (IITC/Life Science Instruments). The ISS recording were synchronized with the rabbit's cardiac cycle via electrocardiogram (ECG) (The ECGenie$_{TM}$, Mouse Specifics). After 5 to 10 minutes' interval, the catheter was removed and the femoral artery was tied off. The output voltage measurement of the shear stress sensor was captured by a labview program with a data acquisition system. Figure 3 illustrates real-time voltage signals which were obtained from the abdominal aorta of NZW rabbits. Shear stress profile was converted from the measured output voltage profile. Shear stress tracing (in green in Fig.3c) in one cardiac cycle was compared with computational fluid dynamics (CFD) simulation. The color scale revealed the instantaneous wall shear stress at the maximal and minimal points.



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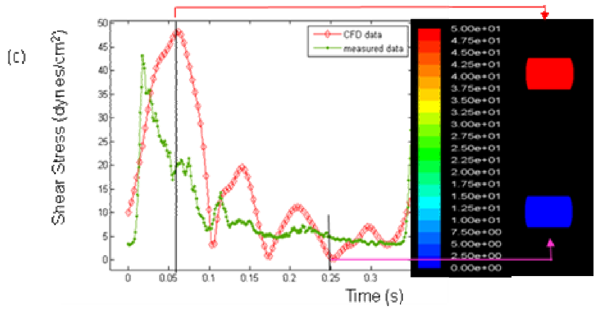

Fig.3. Shear stress data obtained from the abdominal aorta of NZW rabbits in comparison with CFD data

SUMMARY

We demonstrate that the polymer-based sensor was able to detect small but distinct temperature perturbation in response to the pulsatile blood flow in two specific regions of the arterial circulation; namely, abdominal aorta and aortic arch, in the NZW rabbits. We have also addressed several engineering challenges for *in vivo* investigation: (1) hemocompatibility and hemostasis of the sensor function in the rabbit blood, (2) signal-to-noise ratios and frequency responses under pulsatile arterial blood flow, and (3) novel packaging technique to transmit voltage signals to the external electronics. The overall Microfabrication process was succinct and compatible for both large and small scale hemodynamics with a potential to access atherosclerosis in the mid-size animal models.

ACKNOWLEDGMENT

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