FLEXIBLE SHEAR STRESS SENSOR FOR IN VIVO CARDIOVASCULAR TESTING

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ABSTRACT

A catheter-based intravascular micro sensor was deployed into the aorta of New Zealand White (NZW) rabbits for real-time shear stress measurement. The sensor body was built on a biocompatible polymer Parylene C, and packaged with a flexible coaxial wire while the sensing element was composed of Titanium (Ti) and Platinum (Pt). With the newly developed sensor, we translated the MEMS sensors for real-time focal measurements in the arterial system of NZW rabbits for the first time. In the abdominal aorta, shear stress was measured to vary from 0 to 43 dynes/cm² in response to the heart beats at ~180 beats/min and the respiratory variations at ~30 breaths/min.

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]. The development of Micro Electro Mechanical Systems (MEMS) sensors provides an entry point to assess small-scaled hemodynamics with high spatial and temporal variations [3] that is difficult with Computed Tomography (CT), Magnetic Resonance Imaging (MRI), ultrasound, and laser Doppler velocimetry.

MEMS shear stress sensors have been developed for aerodynamics and fluid mechanics [4, 5]. A flexible shear-stress sensor skin containing a 1-D array of 36 shear-stress sensors has been designed to acquire shear stress measurement on the non-planar surfaces [6]. We have previously fabricated MEMS shear stress sensors with backside wire bonding to address micro-scale hemodynamics with high temporal and spatial resolution [3]. However, to assess shear stress in the complicated arterial geometry in the presence of time-varying component of blood flow, we hereby developed a new generation of polymer-based sensors that are flexible, biocompatible, and deployable into the arterial system.

Our sensor design addressed hemocompatibility of the sensor function in the rabbit blood, and integration of sensors with the catheter to transmit voltage signals to the external electronics. We demonstrated that the flexible and biocompatible polymer-based sensor allowed for direct real-time shear stress analysis in the abdominal aorta of NZW rabbits. The direct shear stress measurement agreed with that of the computational hemodynamics (CFD) code within an acceptable range of experimental differences. Thus, the polymer-based sensors provide a basis to investigate the interplay between hemodynamics and arterial plaque formation with a potential for clinical diagnostics.

THEORY

Fluid shear stress (τ) is a frictional force per unit area that is tangential to the surface of vascular endothelial cells (EC). For a Newtonian fluid at steady state, shear stress is defined as:

$$\tau = \mu \frac{du}{dy} \quad (1)$$

where μ and du/dy are viscosity and vertical velocity gradient along the y-axis perpendicular to the wall surface, respectively [7]. Our

device works as a thermal anemometer to measure the shear stress. The operation principle is based on convective cooling of a heated sensing element as fluid flows over its surface (Fig. 1). The heat transfer from the heated surface to the fluid depends on the flow characteristics in the viscous region of the boundary layer [5]. We measure the resistance change of the sensing element due to temperature perturbation, and convert it to the shear stress.

Fig. 1. Bulk micromachined Si-based hot anemometer for shear stress sensing.

Fig. 2. The fabrication process of intravascular shear stress sensor.

FABRICATION

The sensor was fabricated using surface micromachining with biocompatible materials including parylene C, Ti and Pt. To dovetail to the arterial circulation, we have fabricated the sensors with the steps illustrated in Fig. 2 that are consisted of (1) dry thermal growth of 0.3 μ m thick SiO₂ and deposition of a 1 μ m thick sacrificial amorphous silicon layer using E-beam evaporator, (2) deposition (and patterning) of Ti/Pt layers with thicknesses of 0.06 μ m/0.015 μ m for the sensing element with E-beam evaporator, (3) deposition of 9 μ m thick Parylene C with Parylene vacuum coating system (PDS2010, Specialty Coating System, Inc., IN), (4) deposition (and patterning) of a metal layer of Cr/Au (Au being 2 μ m thick) for electrode leads with E-beam evaporator, (5) deposition and patterning of another 12 μ m thick layer of Parylene C to form device structure, (6) etching the underneath silicon sacrificial layer with XeF₂ dry etching system to release the device.

The resulting sensor bodies were 4 cm in length, 320 μ m in

width and 21 μm in thickness (Fig. 3). The fabrication process illustrates the application of Ti and Pt as the heating and sensing element (Fig. 2f). The Ti/Pt sensing elements (Strip of 280 μm in length by 2 μm in width) were encapsulated with parylene which was in direct contact with the blood flow. The Ti/Pt sensing element offers low resistance drift, large range of thermal stability, low 1/f noise with absence of piezoresistive effect, and resistance to corrosion/oxidation.

Fig. 3. Flexible intravascular sensors. (a) The sensor was bended or folded in a zigzag fashion without structural or functional damage. (b) The sensor was measured at 4 cm in length, 320 μm in width and 21 μm in thickness; (c) The sensing element was positioned at the tip of the sensor, and the sensing element resistor was made of 2 μm wide Ti/Pt strip with a dimension of 280 μm .

The sensors then were integrated to an electrical coaxial wire as catheter's guide wire application for intravascular shear stress analysis (Fig. 4). The Cr/Au electrode leads were connected to an electrical coaxial wire (Precision Interconnect Portland, OR) using the biocompatible conductive epoxy (H20E, www.epotek.com) that was cured at 90°C over 3 hours. The electrical coaxial wire allowed for transmitting the electrical signals from the arterial circulation to the external circuitry. The sensor was mounted to the coaxial wire at 4 cm from the tip analogous to the entrance length required to deliver well-defined laminar flow field. This distance avoided flow disturbance at the tip of the coaxial wire. The biocompatible epoxy anchored the sensing elements on the coaxial wire surface. The coaxial wire was 0.4 mm in diameter, and the sensing element pad was 80 μm in width and 240 μm in length.

Using the fluoroscope in the animal angiographic lab, the operator was able to visualize and steer the sensor wire in the aorta of the New Zealand White rabbits to the anatomic regions of interest; namely, aortic arch and abdominal aorta (Fig. 5a). Contrast dye was injected to delineate the position of the wire in relation to the inner diameter of the aorta (Fig 5b).

Fig. 4. Packaging of the polymer shear stress sensor.

Fig. 5. Fluoroscope images of In vivo testing of the MEMS sensor.

CALIBRATION AND MEASUREMENT

Based on the heat transfer principle, the output voltage of the MEMS sensors under the constant current detection circuits was sensitive to the fluctuation in ambient temperature. The temperature overhear ratio (α_T) is defined as temperature variations of the sensor over the ambient temperature (T_0) [4]:

$$\alpha_T = \frac{(T - T_0)}{T_0} \quad (2)$$

where T denotes the temperature of the sensor. The relation between resistance and temperature overhear ratios is expressed as:

$$\alpha_R = \frac{(R - R_0)}{R} = \alpha(T - T_0) \quad (3)$$

where α is temperature coefficient of resistance (TCR). For shear stress measurement, we applied a high overhear ratio (~3%) by passing higher current and by generating a “hot” sensing element to stabilize the sensor. Calibration was performed in a 2-D flow channel 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°C (Fig. 6).

Fig. 6. The schematic diagram of 2-D micro PDMS channel for sensor calibration in the rabbit blood.

For a Newtonian fluid at steady state, the theoretical shear stress value in relation to the flow rate in the 2-D flow channel was established using the following formula based on the analysis of Truskey, et al. [26]:

$$\tau_w \Big|_{y=\frac{H}{2}, x=0} = \mu Q \cdot \frac{6 - \sum_{n=0}^{\infty} \frac{48}{(2n+1)^2 \pi^2 \cosh(\frac{(2n+1)\pi W}{2H})}}{WH^2 - \sum_{n=0}^{\infty} \frac{96H^3}{(2n+1)^5 \pi^5 \cosh(\frac{(2n+1)\pi W}{2H})} \cdot \exp(-\frac{(2n+1)\pi W}{2H})} \quad (4)$$

$$y \in (-\frac{H}{2}, \frac{H}{2}), \quad x \in (-\frac{W}{2}, \frac{W}{2})$$

where τ_w is the wall shear stress; μ is the blood viscosity; Q is ; and H and W are the height and width of the flow channel, respectively ($H/W = 0.433$). The viscosity used in the above equation was obtained from the published data for rabbit blood [7]. The individually calibrated sensors were then deployed to the NZW rabbit's aorta for real-time shear stress assessment.

In Vivo Assessment of Intravascular Shear Stress

Under the fluoroscopic guidance, the catheter integrated with the micro vascular device was deployed into the abdominal aorta above the renal arteries of the rabbit for shear stress measurements under fluoroscopy guidance (Fig. 5). Periodic blood pressure measurement was obtained with an automated tail cuff. The shear stress recordings were synchronized with the rabbit's cardiac cycle via ECG. After measurement, the catheter was removed and the femoral artery was tied off.

The position of the catheter in relation to the arterial wall was visualized via the contrast dye under fluoroscope. The output voltage of the sensor was high when the sensor was facing the blood whereas the signal was attenuated as we steered the sensor toward the arterial wall. Unlike our previously published wall shear stress measurement for an *in vitro* bifurcating model [8], the unique feature of our catheter-based approach allowed for intravascular shear stress analysis in response to pulsatile blood flow in the abdominal aorta of NZW rabbit.

Data Acquisition

The constant current circuit was used to measure the shear stress in Aorta. Electrical current of 0.9833mA was input from a Multimeter (HP34401A, Santa Clara, CA, USA), which was working at resistance measurement mode. When the current passed through the sensor, sensing element was heated up at an overhear ratio of $\sim 3\%$. The voltage across the sensing element was monitored by LabView data acquisition board (NI USB-6251, Austin, TX, USA) and BNC adaptor board (BNC-2110, Austin, TX, USA) which was connected to a laptop computer (Thinkpad T61, Lenovo, China). The main source of noise source was electrical magnetic interference from the environment at 60Hz. We analyzed the data to filter out 60Hz noise and improved the noise floor from 1.2mV to 0.5mV. The sampling rate for data acquisition was at 800 points/sec.

Development of Computational Fluid Dynamic Stimulation

Computational fluid dynamic (CFD) code was developed for non-Newtonian fluid to simulate real-time shear stress in the abdominal aorta and to compare with the experimental measurements. The luminal geometrical model of the rabbit abdominal aorta was constructed and meshed using a specialized pre-processing program GAMBIT (Fluent Inc., Gambit 2.3.16, Lebanon, NH, USA). The local effects of branching arteries were assumed to be negligible. The meshed models were then imported into the main CFD solver FLUENT (Fluent Inc., Fluent 6.2.16, Lebanon, NH, USA) for pulsatile flow simulation. The grid was generated by meshing the inlet surface using Pave scheme type to create unstructured mesh, followed by generating a volume mesh using Cooper scheme type to sweep the mesh node patterns that specified the inlet surface as the "source" faces. The model was composed of 174,510 cells which were primarily the wedge elements. For simulation of wall shear stress, boundary layers immediately adjacent to the wall were constructed to generate sufficient information for characterization of the large fluid velocity gradients near the wall. The diameter of the rabbit abdominal aorta, D , which was measured from angiography during sensor deployment, was set at 2.4 mm. The total length was set at 8.27 times of the diameter to provide sufficient entrance length for the flow to develop [9].

The pulsatile centerline flow velocity information was applied to compute a complex Fourier series approximation for the inlet flow rate pulse using Womersley solution [10]. The blood flow was simulated by applying the 3-D Navier-Stokes equations. The governing equations, including mass and momentum equations, were solved by the FLUENT software for laminar, incompressible,

and non-Newtonian flow. The arterial wall of rabbit abdominal aorta was assumed to be rigid and impermeable.

At the inlet of the abdominal aorta, a physiological flow waveform was introduced. The transient flow rate information was used to compute a complex Fourier series approximation for the pressure gradient pulse using Womersley solution. This profile was implemented by the user defined C++ code. The flow outlet was far downstream where traction-free condition was prescribed. This approach allowed the velocity profile to become a solution to the 3-D Navier-Stokes equations, and the velocity profile was propagated downstream along the aorta. No-slip boundary condition was implemented along the inner walls.

The flow field was initialized by propagating the constant time-averaged inlet velocity profile downstream into the computational domain. The initial pressure was set to zero in the entire domain as were the two cross-stream velocity components. An iterative scheme that marched toward a converged solution was employed by FLUENT. The second order implicit formulation of the solver was applied for the unsteady simulations. Second order-upwind discretization was applied for the governing equations. The pressure-velocity coupling was based on the SIMPLEC technique.

RESULTS

The resistance of the sensing element was ~ 1.0 kOhm, and the temperature coefficient of resistance was measured to be approximately $0.16\%/^{\circ}\text{C}$ (Fig. 7). These properties were compatible for *in vivo* analysis. The relation between the resistance and temperature was linear, suggesting that the thermal coefficient of resistance (TCR) over this temperature range remained constant.

Fig. 7. Measured data of the sensing element (Ti/Pt) resistance versus temperature.

To account for the non-Newtonian properties of the blood flow, we collected 10ml blood from the NZW rabbits and calibrated the sensor at 37.8°C in a 2-D flow channel (Fig. 6). The sensing element ($240 \times 80 \times 0.1 \mu\text{m}^3$) was positioned in a PDMS flow channel (1.32mm high and 3.0mm wide) for sensor calibration in the presence of rabbit blood flow at 37.8°C . We obtained a non-linear relation between changes in the sensor output voltage (due to heat dissipation from the sensing element) and the blood flow (converted to the shear stress) (Fig. 8).

Fig. 8. Calibration curve for changes in the sensor output voltage and shear stress in response to the rabbit blood flow.

Using the calibration curve, we obtained the intravascular

shear stress in the abdominal aorta from the real-time voltage measurement (Fig. 9a), and show it in Fig. 9b. The real-time voltage output was recorded in response to pulsatile flow at a heart rate of approximately 180 beats/min. The noise floor was 0.5 mV, giving signal-to-noise ratio of at least 4.8. Shown in Fig. 9a is a representative output voltage tracing over six cardiac cycles with an interval of 0.33 seconds per heart beat in the abdominal aorta, which is shown in the dashed line enveloping the signal. Fig. 9b is the corresponding intravascular shear stress profile.

The experimental shear stress value (green) is compared with the CFD solution (red) in Fig. 10. The measured shear stress peaked at 44 dynes/cm² during systole and bottomed at 5 dynes/cm² during diastole. The noise floor was approximately 1 dynes/cm². The CFD solution revealed a peak wall shear stress value at 48 dynes/cm². Despite the distinct waveforms between the intravascular shear stress (experimental) and the wall shear stress (CFD simulation), the two peak values vary by 9%, and the waveform profiles overlap within the range of acceptable experimental errors for wall shear stress measurement.

Fig. 9. (a) Measured real-time voltage signals that were obtained from the abdominal aorta of NZW rabbits. (b) Shear stress obtained from the measured voltage signals and the calibration curve.

Fig. 10. Shear stress tracing (in green) in one cardiac cycle was compared with CFD simulation.

CONCLUSIONS

In this paper, we describe the first flexible polymer sensors to acquire real-time shear stress measurement *in vivo* with a potential for clinical applications. The feasibility to translate a micro-device to *in vivo* real-time analysis represents an advance in the field of MEMS technology, and the *in vivo* measurements contribute to the understanding of hemodynamics and vascular disease. Our sensor design successfully addressed hemocompatibility of the sensor function in the rabbit blood and challenging fabrication issues of integrating a sensor with a catheter to transmit voltage signal to external electronics.

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