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Real-time Assessment of Flow Reversal in an Eccentric Arterial Stenotic Model

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Abstract

Plaque rupture is the leading cause of acute coronary syndromes and stroke. Plaque formation, or otherwise known as stenosis, preferentially occurs in the regions of arterial bifurcation or curvatures. To date, real-time assessment of stenosis-induced flow reversal remains a clinical challenge. By interfacing Micro-electro-mechanical Systems (MEMS) thermal sensors with the high frequency Pulsed Wave (PW) Doppler ultrasound, we proposed to assess flow reversal in the presence of an eccentric stenosis. We developed a 3-D stenotic model (inner diameter of 6 mm, an eccentric stenosis with a height of 2.75mm and width of 21 mm) simulating a superficial arterial vessel. We demonstrated that heat transfer from the sensing element ($2 \times 80 \mu\text{m}$) to the flow field peaked as a function of flow rates at the throat of the stenosis along the center/midline of arterial model, and dropped downstream from the stenosis where flow reversal was detected by the high frequency ultrasound device at 45 MHz. Computational fluid dynamics (CFD) codes were in agreement with the ultrasound-acquired flow profiles upstream, downstream, and at the throat of the stenosis. Hence, we characterized regions of eccentric stenosis in terms of changes in heat transfer along the midline of vessel and identified points of flow reversal with high spatial and temporal resolution.

Keywords

PW Doppler; atherosclerotic plaque; shear stress; CFD; MEMS sensors

Introduction

Hemodynamics, specifically, fluid shear stress, is intimately involved in vascular oxidative stress¹ and atherosclerotic lesions²⁻⁵. Rupture of the “vulnerable” plaque often results in stroke and acute coronary syndromes⁶. The plaque disruption tends to occur at the most vulnerable points on the plaque surface, coinciding with the points where stresses are concentrated⁷. Despite compensatory vessel remodeling in response to plaque, or stenosis,

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the arteries ultimately fail to maintain luminal patency and the atherosclerotic lesions start to occlude the lumen, affecting local micro-hemodynamics.

Plaque formation engenders dynamic changes in shear stress profiles. The upstream, shoulder and apical regions of the plaque are often exposed to high shear stress levels while the downstream regions are exposed to low shear stress and flow separation - a departure from axially aligned and unidirectional flow profiles⁸⁻¹⁰. Hence, the ability to characterize flow reversal in region of flow separation that modulates vascular oxidative stress and pro-inflammatory states holds a potential for the lesion-specific detection and treatment strategy for arteriosclerosis.

Recently, IVUS imaging technology has revolutionized diagnosis and treatment of individuals with non-obstructive, albeit extensive calcified atherosclerotic lesions¹¹. Color Doppler ultrasound provides real-time cross-sectional images of endovascular structure and quantitative details about the vessel wall with plaque distribution¹². PW Doppler ultrasound further allows for real-time assessment of blood flow at multiple depths along the sound beam axis; thereby, providing quantification of flow regurgitation and pressure gradients across the cardiac valves¹³. The conventional ultrasonic imaging systems operate at frequency range from 2 to 15 MHz, generating a resolution on the order of millimeters. In this study, high frequency ultrasound (45 MHz) enabled us to enhance both lateral and axial resolution linearly¹⁴ for interrogation of flow separation in superficial vessels such as carotid arteries.

The development of MEMS thermal sensors in our group has also provided a high spatial and temporal resolution to assess micro-hemodynamics in the arterial bifurcation model¹⁵ and abdominal aorta¹⁶. The operational principle of MEMS sensors is based on convective heat transfer principle^{17, 15, 16}. In this study, we proposed to assess flow reversal in a stenotic model simulating superficial vessels, such as carotid arteries. MEMS sensors was cannulated into the 3-D model to profile changes in convective heat transfer, and a high frequency PW Doppler ultrasound device was positioned on the surface of 3-D model to interrogate velocity profiles upstream, downstream, and at the throat of stenosis. We characterized regions of eccentric stenosis in terms of changes in voltage measurements along the midline of vessel and identified points of flow reversal in a 3-D stenotic model with high spatial and temporal resolution.

Methods

1. Three-Dimensional Eccentric Stenotic Model

A 3-D eccentric stenotic model was constructed to assess micro-hemodynamics. A range of steady flows from 50 to 150 ml/min was generated by a digital modular drive (Master Flex L/S 77300-80, Cole-Palmer Instrument Co., Vernon Hills, IL) and a pump drive (Master Flex L/S 7518-12). The pump setting was calibrated using an electromagnetic flow meter (MAGFLO®, Danfoss A/S, DK)¹⁶. An eccentric stenosis was created by depositing Araldite 5-Minute AB Epoxy Adhesive (Huntsman Advanced Materials, Basel, Switzerland) in the 3-D model (ID = 6mm) to mimic a 60% arterial stenosis (Fig. 1). A pulse dampener (EW-07596-20, Cole-Palmer Instrument Co.) was introduced in the flow loop to reduce the pulsation generated by the peristaltic pump. Dextran 40 (40,000 mol wt), dissolved in the saline at a concentration of 14%, wt/vol, was used to provide the working solution. The viscosity of the solution was measured by using a viscometer (Brookfield Engineering, Newhall, CA). The Dextran concentration was chosen to yield a viscosity ($0.00345 \text{ Kg/(m}\cdot\text{s)}$) at 37°C to match that of the rabbit blood at high shear rates ($>100 \text{ s}^{-1}$).

2. Doppler Ultrasound Assessment

2.1. Pulsed-wave Doppler system—The system incorporates the PW Doppler system described previously¹⁸. A flat tip PMN-PT (HC Materials Corp., Urbana, IL) single crystal needle transducer was used¹⁹. This transducer has a center frequency of 45 MHz and a bandwidth of 50%. The needle shape and the small aperture size of the transducer allowed for insertion into the tube for the assessment of flow profiles (Fig. 1a). The Doppler ultrasound system generated a burst, consisting of a fixed number of cycles of reference sinusoids, at intervals defined by the pulse-repetition frequency (PRF). In this study, seven cycles of pulses were used, corresponding to a length of approximately 115 μ m. The PRF was 44 kHz. The received echoes from the transducer were amplified by a low noise amplifier (Miteq-1114 Miteq Inc., Hauppauge, NY). The amplified signals were filtered by a customized band-pass filter FN-2181 (Filtronetics Inc., Kansas City, Missouri), and input into a 14-bit analog-to-digital converter (ADC) at a sampling frequency of 200 MHz (CS14200, Gage Applied Technologies, Inc., Lachine, QC, Canada). The digitized radio-frequency (RF) signals were processed off-line to extract flow information.

2.2. Flow profile estimation—The axial flow velocity at each depth along the sound beam was estimated using the 1-D autocorrelator²⁰⁻²¹, as described by Eqn. (1). This estimator uses an autocorrelation approach to calculate the mean Doppler frequency within the depth window of interest along the axial direction of the transducer.

$$v_a = \frac{c}{2} \frac{F_s \tan^{-1} \left\{ \frac{\sum_{n=0}^{N-2} \left[\sum_{m=0}^{M-1} Q(m,n) \sum_{m=0}^{M-1} I(m,n+1) - \sum_{m=0}^{M-1} I(m,n) \sum_{m=0}^{M-1} Q(m,n+1) \right]}{\sum_{n=0}^{N-2} \left[\sum_{m=0}^{M-1} I(m,n) \sum_{m=0}^{M-1} I(m,n+1) + \sum_{m=0}^{M-1} Q(m,n) \sum_{m=0}^{M-1} Q(m,n+1) \right]} \right\}}{2\pi f_0} \quad (1)$$

where v_a denotes the estimated axial blood velocity; c speed of sound in water; F_s pulse repetition frequency (PRF), and f_0 center frequency of transducer. I and Q represent the in-phase and quadrature sampled signals, respectively. M is the depth window length in samples and N is the number of pulses used for estimation. The value of M was set to 30, corresponding to 150ns (seven cycles of the transmitted signal). One thousand pulses were employed to improve the signal-to-noise ratio for velocity estimation. The flow velocity v is then obtained by Eqn. (2):

$$v = v_a / \cos\theta \quad (2)$$

where θ is the angle between the sound beam and the flow vector.

A conventional ultrasound transducer (Philips SONOS 5500 at 12 MHz) was also utilized to measure the flow field in the stenotic model. The geometrical information was used to estimate the flow angle offset (θ_d) (Fig. 1c). The transducer probe was positioned on the surface of 3-D model and swept over from upstream to downstream of the stenosis to acquire its geometrical information. The local changes in flow profiles upstream, at the throat, and downstream of the stenosis were interrogated under inlet flow rates ranging from 50mL/min to 150mL/min (Reynolds numbers ranging from 54 to 162).

The flow angle offset (θ_d) obtained from the conventional ultrasound transducer was used to determine the Doppler angle (θ) of the flow vector at the individual data points along the trajectory of the Doppler ultrasound probe (Fig. 1c). For the velocity profile measured at 3mm downstream from the stenosis (along line B), the velocity vector at the center was

assumed to follow the direction of a line connecting the mid- points between lines A and B (line A is at the throat) (Fig. 1c). The offset angle of the flow velocity at this specific position was defined as θ_{d0} . Next, a parabolic function was applied to approximate the offset angles at the points along the entire trajectory as follows:

$$\theta_d(y) = ay^2 + \theta_{d0} \quad (3)$$

where at $y = 3\text{mm}$, $\theta_d = 0$. Given that $\theta_d(3) = 0$ and $\theta_d(0) = \theta_{d0}$, the coefficient a in Eqn. (3) was calculated to be -0.56 .

The needle transducer was inserted through the 3-D model along the symmetrical plane (Fig. 1). The probe of the transducer was positioned above the tube so that the velocity profile along the entire depth could be obtained. The steady velocity profile measured upstream from the stenosis was measured at a sufficient distance to minimize the effect of the stenosis. Velocity profiles were interrogated at various positions around the stenosis. The transducer was also placed above the center of the stenosis and at 3mm downstream from the stenosis at an angle of 80° and 70° , respectively. In the flow regions downstream from the stenosis, the streamlines were redirected asymmetrically following the geometry of the stenosis. Around the stenosis, the changes in flow direction were incorporated in Eqn. (2); that is, the values of θ in Eqn. (2) were varying in the presence of stenosis.

3. MEMS thermal sensors

3.1. Calibration of MEMS Sensors—The designed and development of sensors were based on surface micromachining as previously reported 16–22. The operational principle of the MEMS sensor is based on the convective cooling of the heated sensing element 22.

When an electric current passed through the heated element, the heat loss from a resistively-heated element to the flowing fluid was measured as the change in voltage across the element 23. Using the constant temperature (CT) mode driving circuit 24–25. The calibrated sensors were deployed into the stenotic model for real-time convective heat transfer assessment in terms of changes in voltages. The Wheatstone bridge circuit in the CT mode provided a feedback loop to balance to voltage across the sensing element 16, generating a high frequency response and sensitivity 26. The voltage signals were recorded when the sensing element was positioned downstream, upstream and at the throat of the eccentric stenosis.

3.2. In Vitro Deployment and Data Acquisition—The MEMS sensor was introduced into the stenotic model through a catheter at 3mm upstream, 3mm downstream and at the throat of and of the stenosis (Fig. 3a). We biased the voltage inputs between $+15\text{ V}$ and -15 V with DC Power Supply (Protek 3006B, Tempe, AZ) and a SourceMeter (Keithley 2400, Cleveland, OH) to heat up the sensing element to an overheat ratio of $\sim 3\%$. The changes in voltage were monitored by a LabVIEW-based data acquisition system 16. The average signal-to-noise ratio (SNR) was estimated to be 4 in the laminar flow region and increased significantly in response to an increase in Reynolds numbers. Wavelet decomposition and low-pass filters were applied to further optimize SNR 16–27.

4. Computational Fluid Dynamics (CFD)

4.1. Generation of 3-D Geometries and Meshes—The flow field in the 3-D model was solved in the absence of the eccentric stenosis. The geometry of the stenosis with respect to the latex tube diameter ($ID = 6.0\text{ mm}$) was illustrated in both a symmetric plane and a cross-sectional view at the throat (Fig. 2). By introducing the aforementioned pulse dampener to the flow loop, we assumed that the flow was steady. In the CFD model, the

tube was set to be 216 mm in length (L), and the center of the stenosis was at 4.0 cm downstream from the inlet to allow for fully developed flow 28· 29. The stenosis with a radius of 10.5 mm was in the middle of the tube (Fig. 2). The MEMS sensor was assumed to be positioned along the centerline. The 3-D luminal volumes were reconstructed in ProE Wildfire V.3.0 (Parametric Technology, Needham, MA) based on the measured dimensions. The entire luminal geometrical models were imported into Gambit for mesh generation (Fluent Inc., Gambit 2.3.16, Lebanon, NH, USA). The meshed models were imported into the main CFD solver (Fluent Inc., Fluent 6.2.16, Lebanon, NH, USA) for further flow simulation. For WSS assessment, fine mesh sizes immediately adjacent to the tube wall and stenosis surface were constructed to generate sufficient information for characterizing the large fluid velocity gradients near the wall.

4.2. Simulation of Flow and Boundary Conditions—The flow field was modeled by applying the 3-D Navier-Stokes equations. The governing equations, including mass and momentum equations, were solved for laminar, incompressible, and Newtonian flow.

The mass flux calculated based on the steady flow rates was applied as the inlet boundary condition and implemented in FLUENT. The inlet Reynolds number, Re , calculated from the velocity was given by:

$$Re = \rho U_{mean} D_{vessel} / \mu \quad (4)$$

where U_{mean} is the mean flow velocity at the inlet which is half of the centerline velocity, U_c , under the assumption of parabolic velocity profile.

Results

MEMS Sensor Assessment of Convective Heat Transfer

The real-time voltage signals from upstream, at the throat of and downstream from the stenosis were obtained in response to three distinct steady flow rates, namely, 50, 100, and 150 ml/min. The mean voltage measurements showed a consistent trend pattern (Fig. 3). The voltage values increased significantly in response to the increased flow rates at the throat of stenosis. In the downstream region of the stenosis, the voltage values measured were slightly higher than those upstream from the stenosis.

CFD simulations were constructed to analyze both velocity profiles and wall shear stress distribution in the stenotic model in the absence of the MEMS thermal sensors (Fig. 4). The velocity profiles were elevated at the throat, followed by secondary flow patterns or the flow separation downstream from the stenosis (Fig. 4a). As a corollary, the shear stress level was also significantly elevated in the vicinity of the throat and gradually decreased downstream (Fig. 4b). Hence, CFD findings established a framework to predict and validate the ensuing findings by using the high frequency PW Doppler ultrasound 16· 30.

Comparing Doppler Ultrasound Assessment with the CFD Results

First, conventional ultrasound transducer was applied to interrogate the centerline velocity upstream, downstream, and at the throat of the stenosis (Fig. 5). In response to pulsatile flow at 800mL/min (Fig. 5a), the flow waveforms were captured by the ultrasound transducer, providing the basis for obtaining the boundary conditions for CFD modeling. The color Doppler further revealed the position and contour of the stenosis (Fig. 5b). Flow reversal was also virtualized downstream from the stenosis (Fig. 5c). More importantly, the geometric information obtained by the conventional ultrasound transducer provided

important information for determining the correction angle for the high frequency ultrasound probe.

Three steady flow rates ranging from 50 ml/min to 150 ml/min were generated into the 3-D stenotic model to assess flow reversal by the high frequency PW Doppler transducer. In parallel, algorithm for estimating velocities in the absence of eccentric stenosis was verified. The PW Doppler acquired velocity profiles upstream, downstream, and at the throat of the stenosis overlapped with the CFD results, and converged at the points of flow reversal downstream from the stenosis (Fig. 6). Upstream from the stenosis, the velocity profiles obtained by Doppler ultrasound measurements (blue) and CFD results (red) were in good agreement. At the throat, the flow disturbance introduced by the ultrasound probe tip resulted in a blunt velocity profiles which were not completely captured by the Doppler ultrasound probe; however, the magnitudes were in agreement (Fig. 6a, b and c). Downstream from the stenosis, the flow reversal was detected by the high frequency PW Doppler as predicted by the CFD results (red arrows).

Discussion

The novelty of our study was to assess flow reversal in real-time with high spatial and temporal resolution. By integrating MEMS sensor and high frequency Doppler ultrasound device, we demonstrated that convective heat transfer peaked at the throat of a stenotic model, and decreased downstream where flow reversal developed. CFD further predicted and validated the experimental findings. In this context, the ability to localize regions of arterial flow reversal has important clinical implication in assessing vascular oxidative stress and pro-inflammatory state in the high risk patients.

Despite advent of imaging modalities, it remains a clinical need to predict plaque rupture. One of the reasons lies in the difficulty to measure flow separation and WSS in the atherogenic prone regions in real-time. Experimental WSS measurements often entailed 20–50% of errors.³¹ Although IVUS and MRI have provided anatomic and hemodynamic information, the detection of WSS and flow reversal remain a challenge. Our *in vitro* model provided new insights into detecting points of flow separation where low shear stress and oscillatory shear stress modulate genotypic and phenotypic expression of vascular endothelial cells^{32, 33}.

We introduced the concept of convective heat transfer principle in the stenotic regions of our 3-D model³⁴. The increased velocity profiles at the throat engendered a rise in heat loss from the sensing element to the flow field. Under the constant temperature driving circuit²⁵, the rise in heat loss required a higher power input (voltage) to maintain the temperature. As a result, an elevated voltage across the sensing element was generated by the negative feedback circuit to compensate for the increased heat loss.

While the MEMS sensors provided the spatial resolution to localize regions of eccentric stenosis, ultrasound device complemented the assessment of micro-hemodynamics in the superficial vessels such as carotid arteries. The conventional ultrasound transducer can be applied to interrogate the centerline velocities in the vicinity of stenosis, as well as to reveal the position and contour of the stenosis. The use of high frequency PW Doppler ultrasound, which provides better spatial resolution than conventional ultrasound transducer, further enabled the assessment of the detailed flow profile along the axial direction of the ultrasound beam so that the flow reversal downstream from the stenosis can be detected. Hence, the potential to interrogate arterial regions of flow separation would allow for *in situ* analysis of biochemical profiles on arterial walls for oxidative substrates, such as oxidized low density lipoprotein and macrophage infiltrates^{35–37}.

Fluid flows through a stenosis have been widely studied both experimentally and numerically 38-42, 43. Flow separation represents a fixed recirculation region (e.g. a stagnation area) in which low wall shear stress and flow recirculation are conducive to recruit inflammatory cells and low density lipoprotein (LDL) particles relevant for the initiation of atherosclerosis⁴⁴. In this stagnation region, a combination of low and oscillating shear stress values induce an increase in arterial intimal thickening⁴⁵. In parallel, the high wall shear stress occurring at the throat (Fig. 4) activates the platelets, resulting in a cascade of coagulation pathways towards acute occlusion of arterial lumen³¹.

In summary, we interfaced MEMS thermal sensors and high frequency ultrasound to interrogate post-stenotic flow separation with high spatial and temporal resolution. CFD results supported ultrasound-acquired flow velocity profiles upstream, downstream, and at the throat of the stenosis. This study addressed the unmet clinical need to identify regions of flow reversal in the superficial vessels such as carotid arteries with implication for preventing cerebral vascular events.

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Fig. 1.

Position of an ultrasound probe in relation to the 3-dimensional eccentric stenosis. (a) Photograph of a 60% eccentric luminal stenosis. An adhesive (Araldite 5-Minute AB Epoxy Adhesive) was deposited onto the inner lumen of Tygon® tubing. (b) Schematic diagram of the 3-D eccentric stenosis. A high frequency PW Doppler ultrasound probe (45 MHz) was positioned downstream from the stenosis at an angle to the y-axis. The transducer was oriented at an angle of $\sim 80^\circ$ with respect to the axial direction of the 3-D model and the transducer tip was located proximal to the tube wall without disturbing flow field. (c) Offset angle. The velocity vector (blue) along the trajectory of the ultrasound probe was assumed to have a large offset angle, defined as θ_d from the midpoint between points of A and B.

Fig. 2.

Geometry for reconstructing computational fluid dynamics (CFD) model. **(a)** Symmetric plane. The luminal stenosis was defined by x_{st} , denoting the displacement between proximal (upstream) and the throat, x_0 the displacement from the shoulder to the throat, the height of the stenosis, and D_0 the inner diameter. A catheter-based sensor was positioned along the centerline (red). **(b)** Cross-sectional view. The eccentricity of the stenosis was defined by the differential height between the centerline and circumferential border.

Fig. 3.

Mean voltage values along the midline (Fig. 2a) from upstream, the throat, and downstream of the eccentric stenosis. As the MEMS sensors were advanced along the midline, heat transfer from the sensing elements to the flow field increased as a function of flow rates and peaked at the throat. Downstream from the stenosis, heat transfer decreased. The extent of heat transfer from the sensing elements to the flow field was obtained by using the constant temperature circuit mode in which the Wheatstone bridge balanced the voltage drop across the sensing element.

Fig. 4. Representative CFD simulations for the eccentric stenosis at a steady flow rate of 150 ml/min. **(a)** The velocity profiles in the symmetric plane revealed the zone of flow separation. **(b)** The wall shear stress profiles revealed the highest magnitude along the throat corresponding to region of highest mean velocity magnitude.

Fig. 5. Conventional PW Doppler ultrasound probe (12MHz) to interrogate the centerline velocities in the vicinity of stenosis at a mean flow rate of 800mL/min. **(a)** Pulsatile flow profile was detected upstream from the stenosis. **(b)** The color Doppler revealed the position and contour of the stenosis. The color spectrum indicated the flow field. **(c)** Flow reversal was detected by the ultrasound transducer downstream from the stenosis as indicated by the arrow.

Fig. 6.

Angle correction for the PW Doppler ultrasound measurements. **(a)** Comparison for the axial velocity profiles was performed at 50ml/min. The results obtained from the ultrasound measurements were in agreement with the CFD results. Points of flow reversal were observed (arrow). **(b)** Comparison was performed at 100ml/min. **(c)** Comparison was performed at 150ml/min.