Published in final edited form as:

Biomech Model Mechanobiol. 2012 January ; 11(0): 231–244. doi:10.1007/s10237-011-0306-2.

Experimental measurement of dynamic fluid shear stress on the ventricular surface of the aortic valve leaflet

Choon Hwai Yap, Neelakantan Saikrishnan, and Ajit P. Yoganathan

The Wallace H. Coulter Distinguished Faculty Chair in Biomedical Engineering and Regents, Wallace H. Coulter School of Biomedical Engineering, Georgia Institute of Technology and Emory University, Room 2119 U.A. Whitaker Building, 313 Ferst Drive, Atlanta, GA 30332-0535, USA

Ajit P. Yoganathan: ajit.yoganathan@bme.gatech.edu

Abstract

Aortic valve (AV) calcification is a highly prevalent disease with serious impact on mortality and morbidity. The exact causes and mechanisms of AV calcification are unclear, although previous studies suggest that mechanical forces play a role. It has been clinically demonstrated that calcification preferentially occurs on the aortic surface of the AV. This is hypothesized to be due to differences in the mechanical environments on the two sides of the valve. It is thus necessary to characterize fluid shear forces acting on both sides of the leaflet to test this hypothesis. The current study is one of two studies characterizing dynamic shear stress on both sides of the AV leaflets. In the current study, shear stresses on the ventricular surface of the AV leaflets were measured experimentally on two prosthetic AV models with transparent leaflets in an in vitro pulsatile flow loop using two-component Laser Doppler Velocimetry (LDV). Experimental measurements were utilized to validate a theoretical model of AV ventricular surface shear stress based on the Womersley profile in a straight tube, with corrections for the opening angle of the valve leaflets. This theoretical model was applied to in vivo data based on MRI-derived volumetric flow rates and valve dimension obtained from the literature. Experimental results showed that ventricular surface shear stress was dominated by the streamwise component. The systolic shear stress waveform resembled a half-sinusoid during systole and peaks at 64–71 dyn/cm², and reversed in direction at the end of systole for 15–25 ms, and reached a significant negative magnitude of 40–51 dyn/cm². Shear stresses from the theoretical model applied to in vivo data showed that shear stresses peaked at 77–92 dyn/cm² and reversed in direction for substantial period of time (108–110 ms) during late systole with peak negative shear stress of 35–38 dyn/cm².

Keywords

Aortic valve; Fluid shear stress Laser; Doppler Velocimetry; Ventricular surface; Aortic valve fluid mechanics

1 Introduction

Calcific aortic valve (AV) disease is a highly prevalent disease affecting up to 2% of the elderly population (Lindroos et al. 1993); however, the exact mechanism of the disease is unclear. *Ex vivo* studies have suggested that mechanical forces play an important role in mediating valve biology and could play a role in the development of this disease (Xing et al. 2004; Butcher et al. 2006; Balachandran et al. 2009; Sucosky et al. 2009; Smith et al. 2010). In particular, physiological fluid shear stress was found to be protective against pro-inflammatory and pro-oxidative expressions in cultures of valvular endothelial cells (Butcher et al. 2006). Simultaneously, adverse patterns of shear stress were found to up-regulate inflammatory markers in valve tissues (Sucosky et al. 2009). Consequently, it has been proposed that the phenomenon of calcium nodules developing exclusively on the aortic surface as opposed to the ventricular surface is due to the pathological shear stress magnitudes and disturbed patterns on the aortic surface, compared to the ventricular surface (Topper and Gimbrone 1999; Stevens et al. 2001). Additionally, it has been observed that the non-coronary leaflet of the AV is more susceptible to calcification, which is hypothesized to be due to low shear stresses compared to the other leaflets from the lack of diastolic coronary flow (Freeman and Otto 2005).

To prove the hypothesis that disturbed shear stress plays a role in causing aortic valve leaflet calcification, we need to first characterize the shear stress environments of both the aortic and the ventricular surfaces of the AV and contrast their characteristics. Subsequently, experiments must be performed to demonstrate the differential regulation of pathological biological responses on the AV endothelium due to differences in shear stress environments. Further, measuring the physiological shear stress regimen can provide important information for pre-conditioning of tissue engineered aortic valves, in which mechanical stimuli is penultimate for proper functioning of the valve cells populating the tissue engineered scaffolding (Sarraf et al. 2002; Sacks et al. 2009).

Computational fluid dynamics (CFD) and fluid–structure interaction (FSI) simulations are capable of providing the full mechanical environment of the AV (Makhijani et al. 1997; De Hart et al. 2003, 2004; Carmody et al. 2006; Morsi et al. 2007; Weinberg and Kaazempur Mofrad 2008; Ge and Sotiropoulos 2010). These studies have collectively demonstrated the complex dynamics of flow and shear stresses on the valve leaflets. However, the task of numerically modeling the AV remains difficult, with complications in meshing the fluid-solid boundaries, modeling the coupled fluid-solid interaction, modeling transitional flow and turbulence, and achieving Reynolds number of physiological peak flow rate. Simulations require validation of modeling assumptions, and experimental measurements are the only reliable means of providing this validation.

To our knowledge, only one previous study has attempted to experimentally measure fluid shear stresses on AV leaflets. Weston et al. (1999) performed Laser Doppler Velocimetry (LDV) measurements on a tri-leaflet polymeric valve to obtain fluid shear stresses on the valve leaflet. However, only steady flow conditions were employed and the time-varying characteristics of shear stress could not be measured. Noninvasive medical imaging modalities, such as magnetic resonance imaging (MRI) and cardiac ultrasound, can be used

to evaluate the native fluid mechanical environment of the AV; however, they have insufficient spatial and temporal resolution to accurately measure fluid shear stresses. Hence, experimental measurements of AV shear stresses must still be done in vitro by employing physiological valve models.

The current study is one of two studies characterizing dynamic shear stress on both sides of the AV leaflets. This study focuses on characterizing shear stresses on the ventricular surface while the other focuses on characterizing shear stresses on the aortic surface (Yap et al. 2011). Polymeric valves with transparent leaflets were used as in vitro valve models instead of native valves, due to the lack of optical access to the ventricular surface in native valves through the aortic sinuses. Shear stresses were measured in two polymeric valves with slightly varying systolic geometry to ensure repeatability of observed shear stress characteristics and to understand the variation of shear stresses with geometry. Two-component Laser Doppler Velocimetry (LDV) was utilized to obtain high spatial and temporal resolution data in two orthogonal directions for full characterization of the fluid shear stresses on the ventricular surface. Further, bulk flow waveforms from the LDV experiments were used in theoretical modeling of pulsatile flow in straight tubes of matching dimensions, to show that such theoretical modeling can reasonably predict shear stresses. Finally, this theoretical modeling was then used on in vivo bulk flow waveforms to predict in vivo valve leaflet shear stresses.

2 Methods

2.1 Valve models

The tri-leaflet polymeric valve models (AorTech, Europe) employed in the study are shown in Fig. 1a, b. The valve leaflets were made of high silicone polyurethane copolymer (Elast-EonTM), and valve frames were machined from polyetheretherketone. Two valves of slightly different geometry were studied, and their characteristics are listed in Table 1. Valve 1 was slightly taller than valve 2 due to the extension of the polyurethane leaflets about 1.1mm above the stents. Valve 1 had a smaller valve orifice but was longer axially.

The polymeric valve was inserted into a clear acrylic aortic chamber with idealized tri-lobed sinuses so as to provide optical access for LDV measurements, and the valve and chamber collectively constituted the valve model. To mimic physiologic geometry, the acrylic aortic chamber was carefully designed to dimensionally match those noted earlier in rubber casts of human aortic roots (Thubrikar 1990). The valve chamber is shown in Fig. 1c.

2.2 Flow loop setup

The valve model was inserted into the Georgia Tech Left Heart Simulator, a pulsatile flow loop capable of generating physiologic pressure and flow waveforms. Details of this loop could be found in previous publications (Leo et al. 2006; Yap et al. 2010a). Thirty-six percentage glycerin solution was used as the working fluid to match the viscosity of blood (3.5 cSt). The slight difference in refractive index between this solution and the acrylic model resulted in optical distortions, but corrections were incorporated in all the results presented here. The valve model was tested under normal adult resting conditions: heart rate 70 beats/min, cardiac output 5 L/min and aortic pressure 80/120 mmHg. An ultrasonic flow

probe (T108, Transonic System, Ithaca, NY) was used to measure bulk flow rate directly upstream of the AV, and pressure gauges (Baxter Uniflow pressure transducer, Baxter Healthcare corp., Irvine, CA), connected to a Cardiomed CM 4008 system (Medi-Stim, Oslo, Norway) were used to measure pressures directly upstream and downstream of the AV. Pressures and flow were recorded at 500 Hz with a Data Acquisition system (DAQ, National Instruments, Austin, TX) controlled by a custom Labview program.

2.3 LDV measurement technique

A fiber optic, three-component, coincident LDV system (Aerometric System, TSI Inc., Shoreview, MN) was used to measure 2D velocities in the valve model. A 4W Argonion laser was coupled to a fiber drive unit, allowing color separation of the incoming primary beam. A two-component fiber optic transceiver probe with a 100-mm focal length lens was connected to the fiber drive. The resulting optics train produced an ellipsoidal probe volume, which, after accounting for the relative optical density between the flow loop fluid and air, had dimensions of $19\mu\text{m}$ by $126\mu\text{m}$. Doppler signals were processed with Fast Fourier Transform-based real-time signal analyzers (RSA-1000, TSI Inc., Shoreview, MN). All measurements were obtained in the backscatter mode in which a single probe acted as both the transmitter and the receiver for the Doppler signals, and all measurements were gated to the pulse programmer, to phase lock the measurements to the cardiac cycle. The LDV system was set to a 5 MHz sampling frequency, giving a velocity resolution of 1.8 cm/s.

Velocity measurements were performed at multiple points along a radial line between the sinus wall and the center of the valve, as shown in Fig. 2. Velocities were simultaneously measured in the streamwise (from AV annulus to sino-tubular junction) and the non-streamwise (from commissure to commissure of the AV) directions. The distance between consecutive measurement points was $88\mu\text{m}$ after accounting for flow loop fluid optical density. At least 30,000 data points were collected at each measurement location, distributed over the entire cardiac cycle. At each location, velocity measurements were binned into 86 phases of 10 ms each spanning the entire cardiac cycle. Thus, the velocity profile near the leaflet surface at 86 phases of the cardiac cycle was reconstructed. The velocity profile gradient at the surface was obtained by performing a parabolic least squares fit to the 10–15 velocity data points nearest to the leaflet surface and obtaining the gradient of the parabolic curve at the leaflet surface. The shear stress was then computed by scaling the wall-normal velocity gradient with the viscosity of the fluid.

Dynamic shear stresses were measured only on the ventricular surface of the polymeric valve, taking advantage of the transparency of the leaflets. Shear stress was only calculated during systole, since there was little flow near the ventricular surface during diastole.

2.4 Leaflet location and orientation

By definition, shear rate was always computed with the leaflet surface as the reference orientation. In the pulsatile system described in this work, the position of the leaflet was time-varying; hence, it was necessary to accurately characterize the leaflet location and orientation at all points in the cardiac cycle to calculate the shear rate experienced by the leaflet.

At peak systole, the valve leaflets were relatively stationary, so a reliable method to detect the leaflet location was by the peak of the second spatial derivative of velocity on the ventricular side of the leaflet. This second spatial derivative described the location where the velocity profile experiences a sharp change in gradient, and indicated the point where the LDV probe volume first moved from being inside the leaflet thickness into the fast moving fluid within the valve orifice during systole.

To obtain leaflet location over the remaining time periods of systole, a different method was utilized. The scattered LDV laser light intensity at each measurement location was recorded concurrently with LDV measurements, and the location of peak scattered LDV laser light intensity was noted. This peak-reflected light intensity location was expected to correspond to the location of the valve leaflet, since the presence of the leaflet in the probe volume (where both lasers are focused on) would lead to maximum amount of light reflected into the LDV probe.

Scattered laser light intensity was measured at all velocity measurement locations. Scattered laser light was transmitted by the receiver fiber of the LDV probe and was sent to the photomultiplier box (PMT) through optical fiber cables. Raw signal output from the PMT was then recorded at 500 Hz by the Data Acquisition System. At least 40 cardiac cycles were recorded from the PMT, and an ensemble-averaged reflected light intensity over 1 cardiac cycle was obtained. At each time phase, intensity of back-scattered light was plotted over approximately 200 spatial locations at approximately 11 points/mm. This was then interpolated using a Fourier transform to a resolution of 200 points/mm, before the point of highest intensity was noted.

To measure the orientation of the leaflet to the flow direction, leaflet location measurements were made at two additional locations: one slightly upstream and one slightly downstream of the primary measurement location. The computed shear stress was corrected using the square of the cosine of the angle between the leaflet and the probe direction. For the non-streamwise direction, a correction was not used because the probe was carefully positioned at the center of the chamber and at the center of the valve leaflet between the two adjacent commissures.

Streamwise and non-streamwise velocities measured about 90 μm from the leaflet location were taken as leaflet streamwise and non-streamwise velocities, respectively, using the assumption of the no-slip flow boundary condition of viscous flows. From the leaflet tracking, the out-of-plane velocities (toward and away from the probe) were obtained. Leaflet velocities were checked to ensure that velocity was low during the measurement time window to ensure that leaflet motion did not substantially affect velocity measurements.

2.5 Theoretical modeling of fluid shear stress

A theoretical model of pulsatile flow through the AV is also presented here. The AV from the base of the leaflet to the free edge could be viewed as a slightly converging axis-symmetric tube. As a first estimate, this could be approximated to pulsatile flow in a straight tube at the same volumetric flow rate, which could be described using the Womersley

solution (Bellhouse and Reid 1969) for oscillatory flow. Since the Womersley solution linearized the Navier-Stokes equation, we could decompose the volumetric flow curve into its Fourier components, find the corresponding Womersley solution wall shear stress for each component, and then superimpose the component shear stresses to obtain the resultant shear stress. Volumetric flow rate was decomposed as follows:

$$Q = Q_0 + \sum_{n=1}^N Q_n e^{in\omega_n t} \quad (1)$$

where Q was the volumetric flow rate, Q_0 was the temporal-mean flow rate, Q_n were the Fourier coefficients, n was the frequency number, ω_n was frequency, and t was time. The summation was performed to a frequency number of $N = 20$, since additional terms had negligible effects. From the Womersley solution, shear stresses on the walls of the tube could be expressed as a function of Q_0 and Q_n as follows:

$$\tau = Q_0 \left(\frac{4\mu}{\pi R^3} \right) + \sum_{n=1}^N Q_n \left(\frac{i\mu\alpha_n^2}{\pi R^3} \right) \left\{ \frac{J_1(i^{3/2}\alpha_n)}{i^{3/2}\alpha_n J_0(i^{3/2}\alpha_n) - 2J_1(i^{3/2}\alpha_n)} \right\} \quad (2)$$

where τ was shear stress, J_n was the Bessel function of the first kind to the n th order, α_n was the Womersley number corresponding to the frequency number of the term, and i was the square root of -1 .

The theoretical model was applied first to the bulk flow rate waveform obtained from the in vitro experiments with polymeric valves. Shear stresses obtained were analyzed under comparison with measured data. The model was then applied to two published in vivo ascending aorta bulk flow waveforms acquired with phase contrast MRI (Powell et al. 2000; Langerak et al. 2001). The diameter of the AV orifice was assumed to be 18 mm for data obtained from Powell et al., since subjects had a median age of 12.8 years, and 24 mm for data extracted from Langerak et al., since subjects were adults between ages of 24 and 31. Subjects in the Langerak et al. study were healthy volunteers, while those in the Powell et al. were patients with normal aortic flow. This sizing of the valves was performed according to BSA estimates and correlation between BSA and aorta size (Roman et al. 1989).

2.6 Evaluation of systolic valve geometry

Since the ventricular surface shear stress depended on valve geometry, it was important that the geometry was documented. One leaflet of the valves was colored with a marker, and the valves were mounted into clear acrylic chambers with an index-matching sodium iodide-glycerin solution and subjected to steady forward flow of 20 L/min. Images of the valves were taken with a conventional camera, and the valve taper angles were obtained with Matla®.

3 Results

3.1 Experimental hemodynamics

The flow and pressure waveforms from the experiments were presented in Fig. 3. Physiological flow conditions were maintained throughout the experiments (Aortic pressure: 80/120 mmHg, cardiac output: 4.5–5.0 L/min, heart rate 70 beats/min), and results from the two valves are shown in Table 2. The measured hemodynamics showed that valve 2 had a smaller forward flow pressure gradient than valve 1 for the same forward flow rate, indicating a larger flow orifice area. Oscillations in flow rate were recorded with both valves immediately after early diastolic valve closure, with relatively larger oscillations with valve 2. These oscillations were an artifact of using polymeric valves, which were less flexible during valve closure and might not be observed in native valves. Since the focus of the current study was on systolic shear stresses, these oscillations did not affect results presented here. Overall, the two valves displayed small differences in hemodynamics, consistent with minor design differences between the two valves.

3.2 Leaflet dynamics

The reflected light intensity technique provided signals with low noise and provided a description of the valve leaflet location along the scan line over the entire cardiac cycle. A sample of the reflected light intensity map is shown in Fig. 4a for valve 2 while the segmented leaflet location plot for both valves is shown in Fig. 4b. The gradient of the segmented leaflet location gave the out-of-plane velocity of the valve leaflet. Further, valve leaflet velocities in the stream-wise direction were estimated from LDV velocity measurements within 90 μm from the valve leaflet surface location, assuming that the no-slip boundary condition applied at the leaflet surface.

For valve 1, during systole, the valve leaflet remained almost stationary in the open position. Out-of-plane leaflet velocities were less than 0.02 m/s, and streamwise leaflet velocities did not exceed 0.03 m/s. For valve 2, systolic out-of-plane leaflet velocities were less than 0.05 m/s, and streamwise leaflet velocities were less than 0.01 m/s. In the non-streamwise direction, the average leaflet velocity was always zero, because measurements were performed along the line of symmetry. Overall, the velocities of the leaflets during the period of shear stress measurements were much smaller compared to the forward flow velocities (~ 1.5 m/s during peak systole). Hence, measurement errors due to in-plane and out of plane motions of the valve should be minimal.

3.3 Valve geometry

Images of the valves in the steady flow loop are shown in Fig. 5. The opening angle of the valves was defined as the angle made by the valve leaflet from the annular plane. Using this definition, a fully open valve with leaflet parallel to the aortic root has an opening angle of 90° . The opening angle of the valves in the open configuration under 20 L/min steady flow condition for both valves was quantified to be 72.1° in valve 1 and 77.4° in valve 2.

3.4 Flow fields

All velocity and shear stress results presented here correspond to ensemble-averaged flow and were not identical to the instantaneous flow. Ensemble averaging preserved the dominant features while filtering out the small scale instantaneous variations across cycles. Figure 6 shows the ensemble-averaged velocity measurements along the interrogation line from the sinus wall to the center of the valve for valve 1 and was representative of both valves. In this figure, horizontal scan lines represent an instant in the cardiac cycle with systolic duration occurring between 90 and 400 ms. In the sinus region, low velocities were observed, and velocities were lower during early systole compared to late systole. After valve closure, fluid motion gradually dissipated over the duration of diastole.

During systole, high streamwise velocities were observed within the valve orifice. Velocities increased from near zero on the ventricular surface of the leaflet to about 1.5m/s near the center of the valve. The ventricular surface displayed a time-varying boundary layer, which was uniform across different cycles, consistent with theoretical considerations at this Reynolds number. This profile could be accurately characterized using a parabolic profile. In Fig. 7, the ensemble-averaged velocities with the least square best-fit parabolic curve at two systolic time points for both valves are plotted. The R^2 value of the fit for all the time points on the leaflets for both valves were between 0.81 and 0.99, with an average of 0.98, demonstrating the goodness of the fit. Figure 7 also shows very low cycle-to-cycle variability in the measured velocities, as indicated by the small standard deviations of the ensemble-averaged velocities.

Figure 8 shows the ventricular velocity profiles at various systolic time points, as well as the flow profiles normalized by the free-stream velocity. The flow velocity was seen to attain a relatively constant value for distances greater than 1.5 mm from the surface, and this was used as the free-stream velocity. As shown in Fig. 8c, d, the normalized flow profiles were observed to have a gradually decreasing gradient in the boundary layer over time, indicating the slight increase in boundary layer thickness and the occurrence of flow development. During late systole, flow reversal was observed, which manifested first in the boundary layer.

3.5 Shear stress computation

In Fig. 9, the ventricular surface shear stresses measured for both valves are plotted. Concurrent streamwise and non-streamwise shear stresses were measured for both valves at only one location on the leaflet: point 2, which is at the center of the valve leaflet, approximately 9 mm radially away from the annulus. Streamwise shear stresses were also measured at a point 0.32 mm upstream of point 2 (point 1) for both valves and at a point 0.32 mm downstream of point 2 (point 3) for valve 2. In Fig. 9, shear stresses are shown for the systolic durations where the valve leaflets were sufficiently stationary. As described in Sect. 3.2, valve 1 had shorter closing and opening times; hence the shear stress measurement window is larger for valve 1.

Streamwise shear stress waveforms from all points for a given valve matched each other within experimental errors. The two different valves displayed similar streamwise shear

stress waveforms. The waveforms had a half-sinusoid shape, resembling the volumetric flow curve. The streamwise shear stress and flow curves matched identically during early systole, increasing toward their maximum values. However, the rate of increase in shear stress started trailing that of volumetric flow near peak systole (~ 200 ms). Peak shear stress was observed about 30–55 ms before peak volumetric flow rate. Peak shear stress at point 2 was 64 dyn/cm² for valve 1 and 71 dyn/cm² for valve 2. Beyond its peak, the shear stress initially decreased gently and finally decreased rapidly for the remaining duration of systole. For valve 1, the shear stress became negative 37 ms before the flow curve became negative, whereas this time was 27 ms for valve 2. Shear stresses remained negative during late systole for 15 ms for valve 1 and 25 ms for valve 2. The rate of decrease in shear stress was higher for valve 1 than valve 2. For both valves, the stream-wise shear stress was significant at end systole (–40 dyn/cm² for valve 1 and 51 dyn/cm² for valve 2). During early systole, the shear stress curve displayed a spike, which is most likely associated with disturbance in the flow at this instant in time.

Figure 9a, b also showed the non-streamwise shear stresses for the two valves. The overall magnitude of this component of shear stress was much smaller than the stream-wise component. Except for early systole, non-streamwise shear stress was near to zero. During early systole, valve 1 displayed a small duration of positive shear stress, before becoming negative for the entire systolic duration. The change in sign of shear stress corresponded to the spike in streamwise shear stress. Valve 2 displayed similar trends, but the positive portion of the shear stress was not recorded due to the smaller sampling window during systole. The peak non-streamwise shear stress magnitude was 8 dyn/cm² for valve 1 and 18 dyn/cm² for valve 2.

3.6 Theoretical modeling of shear stress on polymeric valve models

Figure 10 shows the non-normalized and normalized flow profiles generated using the theoretical model of shear stresses. In Fig. 10c, d, the profiles were normalized by the centerline velocities. The Womersley solution was applied to straight tubes with 10 mm radius, nominally similar to the radii of the valves. Overall, the theoretical profiles gradually developed through systole and reversed during late systole, similar to the experimental profiles. Differences could be observed, for example, during early systole (around 150 ms) the simulations showed a point of inflexion in the flow profile slightly medial from the boundary layer, but such a profile shape was more subtle in the experimental measurements. Further, the normalized flow profile shapes showed flow development more prominently than the experimental measurements. These differences could be accounted for by the taper angle of the polymeric valves.

Figure 9 also shows wall shear stresses calculated from the Womersley solution. The wall shear stress results showed similar trends as those observed in the valves. During early systole, the theoretical results matched the experimental values very well, and the spike in shear stress at 150 ms was also observed in the simulations. The maximum shear stress during the peak flow phase occurred about 50 ms before peak volumetric flow occurred. During the deceleration phase, the shear stress steadily decreased and became negative during the mid-deceleration phase, about 60 ms before the volumetric flow curve became

negative. Shear stress reached a high negative value at end systole, before moving back to zero. The peak negative shear stress during end systole was 74 dyn/cm² for the valve 1 simulation, and the corresponding value for the valve 2 was 89 dyn/cm². Compared to the shear stresses in the valves, the simulated straight pipe shear stresses had smaller magnitudes in the forward direction, but higher magnitudes in the reverse direction, and the shear stress became negative earlier during late systole.

The shear stress magnitude deviation between the LDV measurements and the theoretical simulations are plotted in Fig. 11. In valve 1, this deviation was initially slightly negative, but increased over the duration of systole in a fairly linear fashion to about 39 dyn/cm². In valve 2, this deviation had a similar behavior to valve 1, except that during mid-to-late systole, deviations were slightly lower in magnitude than in valve 1.

3.7 Theoretical modeling of shear stress on in vivo flow rates

Figure 12 shows the ascending aortic volumetric flow rates acquired through PC-MRI obtained from the literature. These volumetric flow rates were used as inputs in the theoretical modeling to obtain shear stresses, which were shown in same figure. Modeling results showed that the peak ventricular surface shear stresses were approximately 92 dyn/cm² and 77 dyn/cm² for data from Powell et al. and Langerak et. al., respectively. The shear stress rose rapidly to its peak during early systole, and then gradually reduced to a negative value over the remaining systolic time. In both in vivo data sets, shear stress reversed in direction during late systole for a substantial amount of time (110 ms for Powell et al., and 108 ms for Langerak et.al.). Peak negative shear stresses were calculated to be 35dyn/cm² and 38dyn/cm² for data from Powell et al. and Langerak et. al., respectively.

The flow profiles computed from the theoretical modeling are shown in Fig. 13. Results showed similar characteristics as the in vitro measurements in the following aspects: (1) throughout the systolic duration, flow continuously develops, leading to redistribution of velocity profile; (2) reverse flow were observed first in the fluid closest to the leaflet during late systole.

Compared to in vivo flow curves, flow curves obtained from the in vitro LDV work had similar accelerating phase. However, the in vitro flow curve peaked later than the in vivo flow curve and had a steeper deceleration phase than the in vivo flow curve. As opposed to the in vitro shear stress results, in vivo data showed only one single shear stress peak, which occurred during an earlier time point in systole. Further, in vivo data showed longer duration of negative shear stresses, but smaller magnitudes of negative shear stresses. Differences in shear stress between the in vitro and in vivo cases can be explained by differences in the flow waveforms.

4 Discussion

The current study demonstrated that flow on the ventricular surface of the AV leaflet was constantly developing, since the out-of-plane gradient of the normalized streamwise velocity profile decreased and the boundary layer thickness increased over systole. In the present study, the instantaneous shear stress (τ) through systole was dictated by two opposing

forces. On the one hand, an increase in Q results in increased τ due to an increase in velocity gradient at the wall. Conversely, flow development reduced the velocity gradient at the wall and thus reduced τ . It is noted that the fully developed parabolic flow profile was never observed, indicating that forward flow was never fully developed within the short systolic duration. Thus, steady flow experiments (Weston et al. 1999) or fully developed numerical models could not capture these unsteady changes in flow and were incapable of accurately predicting instantaneous shear stresses τ .

The observed shear stress was a combination of these two effects and was clearly demonstrated in the experimental and numerical results. This was particularly demonstrated in two situations: (1) during early systole, the rate of change of shear stress ($d\tau/dt$) matched the rate of change of volumetric flow rate (dQ/dt). At peak systole, ($d\tau/dt$) lagged (dQ/dt) due to flow development. Since flow development occurred over time, it led to the accumulation of shear stress deficit over time, ensuring that shear stress gradually became less responsive to bulk flow rate increases; (2) peak shear stress occurred 30–55 ms before peak flow rate, which could be explained by flow development causing more shear stress reduction than increasing bulk flow could cause shear stress elevation within the 30–55 ms interval.

A comparison of the experimentally measured shear stresses to results from the numerical simulations showed the effect of opening angle of the valve. The two polymeric valves used in the current study had slightly convergent opening angles, whereas the numerical simulations were conducted in straight tubes. A more convergent leaflet opening angle provided a more favorable pressure gradient, which led to thinner boundary layers and reduced flow development. The time lag between peak shear stress and peak volumetric flow rate was shorter in the experimental results than simulation results, indicating that the taper of the leaflet opening angle in the experiments reduced flow development. Further, during late systole, favorable pressure gradient due to the taper in the valves resulted in delayed flow reversal near the leaflet surface, leading to delayed reversal of shear stress. This could also explain the lower magnitude of negative shear stresses found in the experimental results than simulations based on in vitro flow curves.

The effects of a convergent opening angle on shear stress are more clearly presented in Fig. 11, which showed the differences in shear stresses between the experiments (tapered valves) and the corresponding simulations (straight tube). During early systole, this difference was near zero, and it gradually increased to the end systolic value of approximately 40 dyn/cm². The curves for the two valves look similar to each other. Native valves have natural variations in valve opening angles ranging from 75° (convergent) to 110° (divergent) (Thubrikar et al. 1981). The polymeric valves used in the current study were on the convergent extreme of this spectrum, having opening angles of 72.1° and 77.4°. The small difference in opening angle between the two valves most likely explained the difficulty in discerning a difference in the two curves in Fig. 11. However, these results illustrated the effect of opening angle on the actual shear stresses and could be used to provide a correction to Womersley solutions calculated using in vivo flow rates. Shear stresses obtained from in vivo flow rates would be underestimated if the valves have opening angle less than 90°, and overestimated if the valves have opening angle greater than 90°. Most valves, however, were

reported to be parallel or close to parallel, thus the Womersley solutions were likely close to the true shear stresses and need minimal correction.

The lack of satisfactory techniques to measure ventricular surface shear stresses dictated the need for theoretical or empirical solutions for these quantities. The present study describes a theoretical framework based on the Womersley solution for pulsatile flow and validated this theory using LDV measurements in an optically clear polymeric valve. This theoretical framework allowed one to reasonably estimate ventricular surface shear stresses based on volumetric flow rates, allowing its application to clinical scenario, where volumetric flow rates could be obtained by non-invasive scans. We demonstrated this based on two clinical datasets obtained from the literature in the current manuscript.

AV opening angles can be easily obtained with echocardiography, which is routinely performed as standard of care. Information on the systolic AV orifice dimension can also be obtained through the same means, or from MRI scans. Bulk flow rates through the valve can be obtained through PC-MRI evaluation of the ascending aorta or through echocardiographic evaluation of ventricular volumes. Thus, the method of calculating ventricular surface shear stress using the Womersley solution is highly feasible on human subjects. This method holds the advantage of being much less computationally intensive than full fluid–structure interaction simulations, and shear stresses can be calculated with relative ease.

For the method to be feasible, valve leaflets must be sufficiently stable in the open position during systole. In the experimental work presented above, leaflet dynamics data indicated that the polymeric valve leaflets remained reasonably stationary during majority of systole (~ 100–380 ms). The high velocities of the leaflet during the closing and openings phases prevented the measurement of shear stress during these phases of the cardiac cycle. For in vivo data, Leyh et al. (Leyh et al. 1999) provided echocardiographic evidence that the AV leaflets behaved similarly to the polymeric valves, with rapid opening and closing motions but remained immobile during most of systole.

Furthermore, the current theoretical model can be improved to include effects of valve taper angle. Theories of pulsatile flow in a converging or diverging tube are available in literature, such as those by Cerny and Walawender (1966), Renjing and Chan (1993) and Rao and Devanathan (1973). Both studies were intended to model blood flow in blood vessels, but can be adapted for blood flow in the AV. Incorporation of these theories will allow closer approximation of ventricular surface shear stresses. However, at present, the explicit form of the solution in the tapered tube, which is directly applicable to valves, has not been developed and warrants further study.

In both measured and simulated results, reversal in shear stresses was observed during late systole, even before volumetric flow rate decreased to zero. Measured flow profiles showed that this is caused by reversal of flow within the immediate vicinity of the leaflet surface while overall forward flow was still positive. This observation was consistent with the Womersley solution of pulsatile pipe flow Hale et al. (1955). Thus, we could conclude that ventricular shear stress waveforms were most likely oscillatory instead of a conventionally

accepted half-sinusoid shape. The implications of this observation on valvular endothelium biology are currently unclear. For vascular endothelium, oscillatory shear stress patterns have been shown to be inflammatory and related to sclerosis. Since the ventricular surface of the AV almost never experience sclerosis, this may imply that valvular endothelium has different biological responses to shear stress as vascular endothelium, or this may imply that the high shear stresses on the ventricular surface counter the effects of shear stress oscillation, since low shear stress was also related to sclerosis for vascular endothelium. These ideas warrant further studies for complete understanding of the mechanisms of calcification.

In contrast, the aortic surface shear stresses was found to be mostly unidirectional Yap et al. (2011). When reversed shear stress on the aortic surface occurred, it was small in magnitude and was much smaller than shear stress magnitude in the original direction. Thus, contrary to conventional beliefs, the ventricular surface shear stress, instead of the aortic surface shear stress, was the oscillatory waveform. Other differences between shear stresses on the two surfaces were as follows: compared to the aortic surface shear stress, the ventricular surface shear stress was approximately 3–4 times higher in magnitude. Peak ventricular surface shear stress was 64–91 dyn/cm² as measured in the current study, while the peak aortic surface shear stress was 19 dyn/cm² (Yap et al. 2011). Further, ventricular shear stress was more sinusoidal in shape, while the aortic surface shear stress was skewed toward late systole. The ventricular surface shear stress was elevated earlier in systole than aortic surface shear stress, being driven directly by forward flow, while the aortic surface shear stress was elevated only after a delay from the onset of systole, because it was driven by the sinus vortex, which was a secondary flow driven by the forward flow jet.

A detailed description of the unsteady shear stress waveforms on the AV leaflets is crucial to the complete characterization of the mechanical environment of the AV. On top of being useful for shear stress mechanobiology experiments, data on fluid shear stresses experienced by the AV leaflet can be used to support mass transport studies, such as lipid transport on native valve leaflets (Zeng et al. 2007) or calcium transport in prosthetic valve leaflets. The fluid shear stress environment further allows a deeper understanding of the systolic deformation characteristics of the aortic valve leaflet, for example, the ventricular shear stresses allow the estimation of systolic radial stretch of the aortic valve leaflet (Yap et al. 2010b), and systolic stretch characteristics may hold mechanobiology implications.

5 Limitations

The key limitation of this paper is the in vitro nature of the study with valve models. Consequently, it suffers from the limitations of any in vitro model—it cannot completely replicate exact in vivo conditions, such as in vivo volumetric flow waveforms, compliance of the native aortic root, and person-specific AV and aortic root geometry. For example, in vivo flow waveforms peaked during early systole, while the in vitro flow waveforms peaked during mid-systole, and the in vivo flow waveforms had a smaller gradient than in vitro flow waveforms during the deceleration phase. Shear stress results from the in vitro studies consequently differed slightly from in vivo : in vitro results demonstrated an additional shear

stress peak during early systole due to flow disturbances related to snapping motion of leaflet opening, and in vitro results show shorter periods of reversed shear stresses.

Geometric differences exist between these polymeric valves and the native valves. The polymeric valves used were stented valves, which might slightly alter the dynamics of motion of the leaflets. However, transparency and optical access dictated the use of these valves, but the limitations in this aspect are acknowledged.

The LDV technique was unable to obtain shear stress measurements during the time periods when valve leaflets were rapidly opening or closing. A more advanced surface mounted measurement technique might be needed to achieve this. However, these rapid motions were restricted to a small portion of the cardiac cycle, and it was expected that a linear trend in shear stress exists between the points where measurements had been made.

6 Conclusions

In vitro measurements of systolic shear stresses on the ventricular surface of the aortic valve leaflet demonstrated that AV ventricular shear stress is the result of developing flow, with significant reversed shear stress during late systole. A framework for estimating ventricular surface shear stresses of aortic valves has been developed and in vivo shear stresses using bulk flow rates have been estimated.

Acknowledgments

The authors would like to thank Gowthami Tamilselvan for her assistance in the studies. This work is supported by the National Heart, Lung and Blood Institute grant number HL-070262, and by Tom and Shirley Gurley.

References

- Balachandran K, Sucosky P, Jo H, Yoganathan AP. Elevated cyclic stretch alters matrix remodeling in aortic valve cusps: implications for degenerative aortic valve disease. *Am J Physiol Heart Circ Physiol*. 2009; 296(3):H756–H764. [PubMed: 19151254]
- Bellhouse BJ, Reid KG. Fluid mechanics of the aortic valve. *Br Heart J*. 1969; 31(3):391.
- Butcher JT, Tressel S, Johnson T, Turner D, Sorescu G, Jo H, Nerem RM. Transcriptional profiles of valvular and vascular endothelial cells reveal phenotypic differences: influence of shear stress. *Arterioscler Thromb Vasc Biol*. 2006; 26(1):69–77. [PubMed: 16293796]
- Carmody CJ, Burriesci G, Howard IC, Patterson EA. An approach to the simulation of fluid-structure interaction in the aortic valve. *J Biomech*. 2006; 39(1):158–169. [PubMed: 16271600]
- Cerny L, Walawender W. The flow of a viscous liquid in a converging tube. *Bull Math Biol*. 1966; 28(1):11–24.
- De Hart J, Peters GW, Schreurs PJ, Baaijens FP. A three-dimensional computational analysis of fluid-structure interaction in the aortic valve. *J Biomech*. 2003; 36(1):103–112. [PubMed: 12485644]
- De Hart J, Peters GW, Schreurs PJ, Baaijens FP. Collagen fibers reduce stresses and stabilize motion of aortic valve leaflets during systole. *J Biomech*. 2004; 37(3):303–311. [PubMed: 14757449]
- Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005; 111(24):3316–3326. [PubMed: 15967862]
- Ge L, Sotiropoulos F. Direction and magnitude of blood flow shear stresses on the leaflets of aortic valves: is there a link with valve calcification? *J Biomech Eng*. 2010; 132(1):014505. [PubMed: 20524753]

- Hale JF, Mc DD, Womersley JR. Velocity profiles of oscillating arterial flow, with some calculations of viscous drag and the Reynolds numbers. *J Physiol.* 1955; 128(3):629–640. [PubMed: 13243354]
- Langerak SE, Kunz P, Vliegen HW, Lamb HJ, Jukema JW, van Der Wall EE, de Roos A. Improved MR flow mapping in coronary artery bypass grafts during adenosine-induced stress. *Radiology.* 2001; 218(2):540–547. [PubMed: 11161176]
- Leo HL, Dasi LP, Carberry J, Simon HA, Yoganathan AP. Fluid dynamic assessment of three polymeric heart valves using particle image velocimetry. *Ann Biomed Eng.* 2006; 34(6):936–952. [PubMed: 16783650]
- Leyh RG, Schmidtke C, Sievers HH, Yacoub MH. Opening and closing characteristics of the aortic valve after different types of valve-preserving surgery. *Circulation.* 1999; 100(21):2153–2160. [PubMed: 10571974]
- Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993; 21(5):1220–1225. [PubMed: 8459080]
- Makhijani VB, Yang HQ, Dionne PJ, Thubrikar MJ. Three-dimensional coupled fluid-structure simulation of pericardial bio-prosthetic aortic valve function. *ASAIO J.* 1997; 43(5):M387–M392. [PubMed: 9360067]
- Morsi YS, Yang WW, Wong CS, Das S. Transient fluid-structure coupling for simulation of a trileaflet heart valve using weak coupling. *J Artif Organs.* 2007; 10(2):96–103. [PubMed: 17574512]
- Powell AJ, Maier SE, Chung T, Geva T. Phase-velocity cine magnetic resonance imaging measurement of pulsatile blood flow in children and young adults: in vitro and in vivo validation. *Pediatr Cardiol.* 2000; 21(2):104–110. [PubMed: 10754076]
- Rao AR, Devanathan R. Pulsatile flow in tubes of varying cross-sections. *Zeitschrift für Angewandte Mathematik und Physik (ZAMP).* 1973; 24(2):203–213.
- Renjing C, Chan Q. Boundary layer development of pulsatile blood flow in a tapered vessel. *Appl Math Mech.* 1993; 14(4):319–326.
- Roman MJ, Devereux RB, Kramer-Fox R, O’Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol.* 1989; 64(8):507–512. [PubMed: 2773795]
- Sacks MS, Schoen FJ, Mayer JE. Bioengineering challenges for heart valve tissue engineering. *Ann Rev Biomed Eng.* 2009; 11:289–313. [PubMed: 19413511]
- Sarraf CE, Harris AB, McCulloch AD, Eastwood M. Tissue engineering of biological cardiovascular system surrogates. *Heart Lung Circ.* 2002; 11(3):142–150. (Discussion 151). [PubMed: 16352087]
- Smith KE, Metzler SA, Warnock JN. Cyclic strain inhibits acute pro-inflammatory gene expression in aortic valve interstitial cells. *Biomech Model Mechanobiol.* 2010; 9(1):117–125. [PubMed: 19636599]
- Stevens T, Rosenberg R, Aird W, Quertermous T, Johnson FL, Garcia JG, Hebbel RP, Tudor RM, Garfinkel S. NHLBI workshop report: endothelial cell phenotypes in heart, lung, and blood diseases. *Am J Physiol Cell Physiol.* 2001; 281(5):C1422–C1433. [PubMed: 11600404]
- Sucosky P, Balachandran K, Elhammali A, Jo H, Yoganathan AP. Altered shear stress stimulates upregulation of endothelial VCAM-1 and ICAM-1 in a BMP-4- and TGF-beta1-dependent pathway. *Arterioscler Thromb Vasc Biol.* 2009; 29(2):254–260. [PubMed: 19023092]
- Thubrikar, M. The aortic valve. CRC Press; Boca Raton: 1990.
- Thubrikar M, Piepgrass WC, Shaner TW, Nolan SP. The design of the normal aortic valve. *Am J Physiol.* 1981; 241(6):H795–H801. [PubMed: 7325246]
- Topper JN, Gimbrone MA Jr. Blood flow and vascular gene expression: fluid shear stress as a modulator of endothelial phenotype. *Mol Med Today.* 1999; 5(1):40–46. [PubMed: 10088131]
- Weinberg EJ, Kaazempur Mofrad MR. A multiscale computational comparison of the bicuspid and tricuspid aortic valves in relation to calcific aortic stenosis. *J Biomech.* 2008; 41(16):3482–3487. [PubMed: 18996528]
- Weston MW, LaBorde DV, Yoganathan AP. Estimation of the shear stress on the surface of an aortic valve leaflet. *Ann Biomed Eng.* 1999; 27(4):572–579. [PubMed: 10468241]

- Xing Y, Warnock JN, He Z, Hilbert SL, Yoganathan AP. Cyclic pressure affects the biological properties of porcine aortic valve leaflets in a magnitude and frequency dependent manner. *Ann Bio-med Eng.* 2004; 32(11):1461–1470.
- Yap CH, Dasi LP, Yoganathan AP. Dynamic hemodynamic energy loss in normal and stenosed aortic valves. *J Biomech Eng.* 2010; 132(2):021005. [PubMed: 20370242]
- Yap CH, Kim HS, Balachandran K, Weiler M, Haj-Ali R, Yoganathan AP. Dynamic deformation characteristics of porcine aortic valve leaflet under normal and hypertensive conditions. *Am J Physiol Heart Circ Physiol.* 2010; 298(2):H395–H405. [PubMed: 19915178]
- Yap CH, Saikrishnan N, Tamilselvan G, Yoganathan AP. Experimental measurement of dynamic fluid shear stress on the aortic surface of the aortic valve leaflet. *Biomech Model Mechanobiol.* 2011 [Accepted 4 March 2011].
- Zeng Z, Yin Y, Jan KM, Rumschitzki DS. Macromolecular transport in heart valves. II. Theoretical models. *Am J Physiol Heart Circ Physiol.* 2007; 292(6):H2671–H2686. [PubMed: 17220189]

Fig. 1. Polymeric valve models used for the study: (a) Valve 1, and (b) Valve 2; and (c) the acrylic chamber with idealized sinus geometry used to house the valves

Fig. 2.

a Definition of directions of velocity and shear stress measurements. The streamwise direction is defined as the direction pointing downstream, while the non-streamwise direction is defined as the direction from one commissure to the next. **b** Schematic of LDV velocity measurement scheme. Velocities in both streamwise and non-streamwise directions are measured at intervals of 88microns along a straight line at the center of the valve leaflet

Fig. 3.
Simulated pressure and flow conditions for (a) valve 1 and (b) valve 2

Fig. 4.

a Reflected light intensity map: ensemble-averaged reflected light intensity at various measurement points along the line of measurement at the center of the valve over time. **b** Valves leaflet position over the cardiac cycle, segmented from the reflected light intensity maps, represented by the distance of the leaflets from its position when valve is closed

Fig. 5. Images of (a) valve 1 and (b) valve 2 with one leaflet colored with marker, subjected to steady flow rates of 20L/min. Valve opening angles were found to be 72.1° in valve 1 and 77.4° in valve 2

Fig. 6.

Representative LDV measured velocity map: phase-locked ensemble-averaged velocity at all measurement points along the line of measurement at the center of the valve over time. Velocity map is shown for (a) the streamwise velocity, and (b) the non-streamwise velocity

Fig. 7.

Representative sample plot of the ensemble-averaged velocities and standard deviation of these velocities versus distance from the leaflet surface, and the best-fit least square parabolic curve (at 260 and 320 ms for valve 1), demonstrating that the parabolic profile fits well with the measured velocity

Fig. 8.

Flow profiles for various time points for (a) valve 1 and (b) valve 2. Flow reversal was observed during late systole, where velocities reversed in the boundary layer first. Flow profiles normalized by peak velocity, distinguished between early systole and late systole, excluding all flow profiles during flow reversals for (c) valve 1 and (d) valve 2. Flow development was observable in the normalized profiles

Fig. 9.

Plots of fluid shear stresses on the ventricular surface of the valves computed from measured velocities for (a) Valve 1 and (b) Valve 2. Point 2 is at the middle of the leaflet, Point 1 is 0.32 mm upstream of point 2, while Point 3 is 0.32 mm downstream of Point 2

Fig. 10.

Flow profiles at various time points for the volumetric flow waveform of (a) Valve 1 and (b) Valve 2; and flow profiles at various time points normalized by the tube centerline velocity for the flow waveform of (c) Valve 1 and (d) Valve 2, calculated from the Womersley solution for the straight tube using the same flow rate as those used in the experiments

Fig. 11.

Shear stresses measured in the polymeric valves in vitro less the shear stresses calculated with the simulation assuming the same volumetric flow rates and the same channel dimension. This deviation between the two datasets can be explained by the taper angle in the actual valves leaflets during systole, which contrasts with the lack of taper angle in the simulations

Fig. 12.

In vivo flow curve acquired with PC-MRI, obtained from **a** Powell et al. (2000), and **b** Langerak et al. (2001), and the ventricular surface shear stress on the aortic valve, calculated with theoretical simulations

Fig. 13.

Flow profiles near the ventricular surface of the aortic valve for in vivo flow curves from **a** Powell et al. **b** Langerak et al. Flow profiles normalized by centerline velocities for **c** Powell et al. **d** Powell et al. (2000), Langerak et al. (2001)

Table 1

Geometric characteristics of polymeric valve models

	Valve 1	Valve 2
Annulus inner diameter (in mm)	24.0	24.8
Height (in mm)	17.1	16.0
Leaflet thickness (in μm)	120	150

Table 2

Flow characteristics of polymeric valve models

	Valve 1	Valve 2
Peak pressure gradient (in mmHg)	38	22
Mean pressure gradient (in mmHg)	24	7.2
Peak flow rate (in L/min)	20.2	21.6