Published in final edited form as:

Ann Biomed Eng. 2015 September ; 43(9): 2231–2241. doi:10.1007/s10439-015-1260-4.

Coronary Flow Impacts Aortic Leaflet Mechanics and Aortic Sinus Hemodynamics

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Abstract

Mechanical stresses on aortic valve leaflets are well-known mediators for initiating processes leading to calcific aortic valve disease. Given that non-coronary leaflets calcify first, it may be hypothesized that coronary flow originating from the ostia significantly influences aortic leaflet mechanics and sinus hemodynamics. High resolution time-resolved particle image velocimetry (PIV) measurements were conducted to map the spatiotemporal characteristics of aortic sinus blood flow and leaflet motion with and without physiological coronary flow in a well-controlled *in vitro* setup. The *in vitro* setup consists of a porcine aortic valve mounted in a physiological aorta sinus chamber with dynamically controlled coronary resistance to emulate physiological coronary flow. Results were analyzed using qualitative streak plots illustrating the spatiotemporal complexity of blood flow patterns, and quantitative velocity vector and shear stress contour plots to show differences in the mechanical environments between the coronary and non-coronary sinuses. It is shown that the presence of coronary flow pulls the classical sinus vorticity deeper into the sinus and increases flow velocity near the leaflet base. This creates a beneficial increase in shear stress and washout near the leaflet that is not seen in the non-coronary sinus. Further, leaflet opens approximately 10% farther into the sinus with coronary flow case indicating superior valve opening area. The presence of coronary flow significantly improves leaflet mechanics and sinus hemodynamics in a manner that would reduce low wall shear stress conditions while improving washout at the base of the leaflet.

Keywords

Aortic valve; Coronary flow; Calcification; Sinus; Vortex

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ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (doi:10.1007/s10439-015-1260-4) contains supplementary material, which is available to authorized users.

DISCLOSURES

None.

INTRODUCTION

Heart disease is the leading cause of death in the US, and valvular diseases comprise a large subset of this disease. Aortic valve stenosis, in particular, is present in over 5% of the overall population in the United States.⁹ While specific causes of stenosis are not entirely known, much evidence suggests that hemodynamics regulate stenosis, specifically those in the aortic sinus since calcification preferentially develops on the aortic (rather than ventricular) side of the leaflet.²⁵ Results from multiple studies support this claim. For example, fluid shear stress patterns similar to those on the fibrosa side of the leaflet have been shown to generate cell responses strongly linked to stenosis.^{22,23} Additionally, it has been shown that bicuspid valves, which have significantly different sinus hemodynamics, typically calcify earlier and more often than “normal”, tricuspid counterparts.^{2,20}

Aside from calcification in particular, sinus hemodynamics is a crucial factor in overall valve function and health. Leonardo da Vinci was perhaps the first to notice this importance when he hypothesized and documented the now well-known sinus vortex.⁸ This flow feature has since been studied extensively, and Lee and Talbot hypothesized that one of its main functions is to aid in leaflet closure.¹⁴ Additionally, our recent work has demonstrated the complex spatiotemporal nature of the sinus vortex, which could be influenced by a number of factors.¹⁶

One such factor that could influence sinus vorticity dynamics, and therefore valve health, is the presence of coronary ostia. The non-coronary cusp often calcifies first, and it has been hypothesized that the reason for this is reduced shear stress from a lack of diastolic coronary flow.⁷ Some studies have focused on coronary flow in the context of aortic sinuses. For example, an experimental study by de Paulis *et al.* examined coronary flow as regulated by presence and/or shape of sinuses of Valsalva.⁵ Similarly, Nobari *et al.* aimed to include coronary arteries in computational models of the aortic valve.¹⁷ However, no studies to date have investigated in detail the impacts of coronary flow through the coronary ostia on sinus vortex dynamics throughout the cardiac cycle.

In this study, we aim to elucidate specific sinus hemodynamics that occur in both coronary and non-coronary sinuses using time-resolved *in vitro* particle image velocimetry (PIV). PIV is well-suited for studies requiring higher spatiotemporal resolution than is possible with *in vivo* imaging techniques such as CT, Echocardiography, or MRI. Specifically, we show that (a) presence of coronary flow alters the shape and location of the systolic sinus vorticity, (b) diastolic fluid shear stress is higher within the coronary sinus, and (c) the coronary aortic valve leaflet(s) tend to open farther into the sinus than the non-coronary aortic leaflet. Therefore, new information gained from this work contributes to a better understanding of aortic hemodynamics and could help educate surgeons and clinicians on a proper course of treatment for patients with, or at risk for, calcific aortic stenosis or other diseases affecting the aortic valve or coronary arteries.

METHODS

A similar methodology was developed for our previous work on aortic sinus hemodynamics and is the basis for this study.¹⁶ However, numerous differences do exist so the full methodology for this work is detailed below.

Flow Loop Setup

Two-dimensional *in vitro* particle image velocimetry (PIV) experiments were conducted to visualize fine-scale aortic sinus hemodynamics. A 25 mm Medtronic Hancock II T505 (Medtronic, Minneapolis, MN, USA) porcine bioprosthetic aortic valve was “flush” mounted inside a clear, acrylic sinus chamber machined to mimic the outer walls of the aorta, based on Yap *et al.*²⁸ The flush mounting ensures that the stent-posts are within the wall of the aorta as is the case with the native valve. Dimensions of this chamber yielded a sinus radius of 13.5 mm, a sinus height of 16.5 mm, and an aortic radius of 9 mm. Detailed dimensions are given in Fig. 1. A 4 mm diameter hole was drilled through the chamber wall and into one sinus in order to mimic a coronary artery connected to the coronary ostia within the sinus. This hole intersected the sinus (i.e., the ostium) at the midpoint between the annulus and sinotubular junction, a location that was chosen based on a previous clinical study.¹³ The chamber was inserted into the aortic position of a left heart simulator which also included a coronary flow circuit (see Fig. 2). This coronary circuit was designed to yield physiological flow at all times during the cardiac cycle. In order to do so, a time-varying Windkessel chamber was fabricated. The purpose of this chamber was to add resistance to the coronary flow during systole, thereby mimicking the systolic coronary constriction that results from myocardial contraction. For the control case with no coronary flow, the coronary tube was clamped off just downstream of the ostium.

The working fluid used was a 60/40 water/glycerin mixture by volume (density $\rho = 1090$ kg/m³ and kinematic viscosity $\nu = 3.88$ cSt). An in-house Lab-VIEW program was used to control the motion of the piston pump. Aortic and coronary flow rate was measured with ultrasonic flow probes (Transonic Inc., Ithaca, NY), located just downstream of the aortic valve and ostium outlet (see Fig. 2). Pressures were measured just upstream and downstream of the valve using Validyne pressure sensors (Validyne Engineering Corp., Northridge, CA) to ensure physiological conditions. Flow measurements were recorded in Lab-VIEW at average resting conditions (HR ~ 60 bpm; BP ~ 120/80 mmHg) and ensemble averaged over 20 cycles. Experimental aortic and coronary flow waveforms are shown in Fig. 3.

PIV Parameters

For visualization purposes, the flow was seeded with PMMA-Rhodamine B seeding particles (microParticles GmbH, Berlin, Germany) with particle sizes ranging from 1 to 20 μm . These particles were illuminated by a laser sheet, which passed through the center plane of one sinus and bisected the coronary artery. The laser sheet was created with a Nd:YLF single-cavity diode-pumped solid-state, high-repetition-rate laser (Photonic Industries, Bohemia, NY) coupled with external spherical and cylindrical lenses. A high-speed CMOS camera (Photronix, Inc) was positioned at approximately a 60° angle to the laser sheet for

optimal viewing of flow within the sinus and coronary ostium, with limited obstruction from valve stent posts (Fig. 4).

The commercial PIV software, DaVis (LaVision, Germany) was used for data acquisition and processing. Velocity vectors were calculated using an advanced PIV cross-correlation method with a 50% overlap multi-pass approach of two 32×32 pixel interrogation window passes. No pre-processing was done, but post-processing was performed using adaptive median filtering. The effective spatial resolution was 29 microns per pixel and the temporal resolution was 4000 Hz. Particle seeding density was approximately 0.02 particles per pixel²⁵ and the particle displacement was around 0–10 pixels per frame (average 5 pixels). The number of particles per interrogation window averaged 20.5 which are acceptable for high-quality PIV.¹⁵ Qualitative streak plots and quantitative vector plots were created for both non-coronary and coronary cases. Vectors and vorticity contours were ensemble averaged across 5 trials.

Leaflet Kinematics Tracking

Leaflet tip motion was tracked manually to within 56 μm accuracy (corresponding to ± 2 pixels) across five trials (repeats) for each case with and without coronary flow. Radial distance from the aorta centerline was recorded and averaged across the two sets of five trials from start of opening until end of closing.

Analysis of Refractive Errors

Imaging errors can be introduced due to differences in refractive index between the water/glycerin fluid that was used and the acrylic valve chamber. This can be further complicated by the curvature of the sinus as well as the 60 angle of the camera viewing window to the laser sheet. Therefore, error analysis has been done to quantify the deviations in apparent particle locations. In order to accomplish this, a 1 mm-resolution grid was inserted into the chamber along the centerline of the viewing sinus (Fig. 5a). A picture was taken from outside the sinus chamber and grid intersection points were picked manually (Fig. 5b). This array of points was then compared to an array of points representing a grid under no optical deformation, and relative displacements were calculated between these two sets of points (Figs. 5c, 5d). The maximum difference between apparent image location and actual location was approximately 0.7 mm. Bilinear interpolation was employed to compute the adjustment of any point within the sinus.¹⁶

RESULTS

Coronary Flow Profile

Since this is the first *in vitro* experimental study to include coronary flow in an aortic valve model, results for the coronary flow waveform are presented (Fig. 3). There is an increase in flow rate during early systole, with a subsequent decrease at mid systole. Coronary flow then increases again from mid systole to early diastole, before tapering off to around zero at end diastole. This yielded a maximum flow rate around 275 mL/min, with an average rate of about 125 mL/min.

Qualitative Sinus Flow Visualization

High resolution PIV was used to capture flow patterns within the sinus for coronary and non-coronary cases. A sliding average over ten frames was implemented to create “streak” images which help give a qualitative understanding of sinus hemodynamics. Videos of these particle streaks are included for one complete cardiac cycle for both non-coronary and coronary cases (see videos S1 and S2 respectively). Annotated snapshots of these videos are included in Fig. 6. Note that these snapshots include manually-drawn arrows, not computed vectors, as a means to better explain the flow patterns present in the videos.

For the non-coronary case, Fig. 6a shows the development of a sinus vortex during early systole. This vortex is positioned along the wall of the sinus and is relatively small compared to the overall size of the sinus. Additional streamwise flow is also present in the sinus, which is redirected toward the sinotubular junction by the curvature of the sinus wall. As systole progresses, the main vortex migrates slightly downstream (Fig. 6b), and toward the end of systole flow magnitude decreases significantly in the sinus (Fig. 6c). During diastole there is some initial counterclockwise fluid motion (Fig. 6d), which appears to decay by mid diastole (Fig. 6e).

Examination of hemodynamics in the presence of coronary flow yields some differences from the non-coronary case. While sinus flow patterns are similar for both cases during early systole (Fig. 6f), the sinus vortex—present in both cases—is positioned slightly more upstream in the coronary case during mid systole (Fig. 6g). Additionally there is clear fluid motion near the annulus that is absent when coronary flow is suppressed. During late systole (Fig. 6h), significant flow can be seen entering the coronary ostium and an area of clockwise rotation is evident just downstream of the ostium. Particle movement is still present near the base of the leaflet (i.e., at the annulus). These patterns are in contrast to those of the non-coronary case. Particle motion during diastole is mainly noticeable only near the ostium for the coronary case (Figs. 6i, 6j).

Quantitative Flow Results

Figure 7 shows velocity vectors superimposed over vorticity contours in the sinus for multiple time points throughout the cardiac cycle both with and without coronary flow. These images provide a slightly less intuitive, yet more quantitative, picture of sinus hemodynamics than particle streak plots. However, many common flow patterns are apparent in each.

When viewing velocity fields, similarities to qualitative streak plots emerge. Recirculating flow is present in both sinus cases, however a complete vortex is only seen in the non-coronary case (Figs. 7a–7b). In the coronary sinus, much of the flow near the sinus wall is redirected into the coronary ostium rather than recirculating toward the freestream jet (Figs. 7f, 7g). Additionally, there is relatively stagnant fluid near the leaflet base throughout systole in the non-coronary case, in contrast to the same region with coronary flow. This trend is displayed quantitatively in Fig. 8, which shows time-varying velocity and vorticity magnitudes at different points within the sinus. The velocity magnitude at Position 1 in this figure is significantly higher for the coronary sinus throughout the cardiac cycle. It can also

be seen at all time points during systole that there is significant streamwise flow in portions of the sinus closer to the aortic axis. This flow seems to reach deeper into the sinus when coronary flow is present. In diastole, there is less stagnation near the annulus due to the presence of the coronary artery (Figs. 7d–7e and 7i–7j).

One of the more detailed trends that becomes apparent when viewing vorticity contours is the size and location of the high vorticity region during early and mid systole. This region is larger in the non-coronary sinus with higher peak vorticity values. Additionally, the core location of this vorticity is generally located closer to the annulus (i.e., upstream) in the coronary as opposed to the non-coronary sinus. These trends are reflected in Fig. 8 at Positions 2 and 3. Vorticity magnitude at Position 2, which is closer to the ostium as well as the leaflet, remains higher in the coronary sinus as systole progresses. Alternatively, vorticity is greater at these later systolic time points for the non-coronary case at Position 3. These two trends suggest a systolic vortex that migrates farther downstream in the non-coronary sinus. From late systole to end diastole, vorticity magnitude is much lower than during the earlier phases of systole. One of the only notable differences in vorticity between the two cases is the relatively weak sinus vortex that is still present in the non-coronary case but is hardly noticeable in the coronary case (Figs. 7c, 7h).

Shear Stress Distribution

Shear stress is often a useful parameter in valve studies since it is a known cause of blood damage and also strongly linked to leaflet calcification.^{1,4} While leaflet wall shear stress was not obtained in this study, fluid shear stress throughout the sinus was computed to give an order of magnitude of shear stresses in the vicinity of the leaflet. Shear stress contours are presented in Fig. 9.

One of the first notable differences in shear stress due to coronary flow arises during early systole (Figs. 9a, 9f). At this point, there is significant shear stress near the annulus between the leaflet and sinus wall in both cases, with magnitudes reaching slightly over 1 Pa. However, this peak shear region is near the sinus wall in the non-coronary case and along the leaflet in the coronary case. Direction of shear is also different for the two cases. Likewise, there is a region of shear on the sinus wall for the non-coronary case that is of opposite direction to the main sinus shear region. At mid systole, shear stress near the annulus is nearly unchanged for the coronary case but has switched direction and reduced in magnitude to around 0.4 Pa for the non-coronary case (Figs. 9b, 9g). Near the end of systole, there is greatly reduced shear in the base of the sinus for both cases (Figs 9c, 9h). At this same time point, there is a positive shear region near the inferior portion of the ostium which is not present at the corresponding location in the non-coronary case. While diastolic shear stress is generally much less, it is still present near the ostium (or where the ostium would be) in both cases during early diastole (Figs. 9d, 9i). Once mid diastole is reached the only shear stresses in the sinus are near the ostium in the coronary case, with magnitudes around 0.3 Pa (Figs. 9e, 9j).

Leaflet Kinematics

Leaflet tip position was manually tracked and its distance from the aortic axis was subsequently calculated for coronary and non-coronary cases. As seen in Fig. 10, this distance was generally greater throughout systole for the coronary case. From the initial fully open time point (~10% systolic duration) to start of closure (~85% systolic duration), the coronary leaflet opened an average of 10% farther into the sinus than the non-coronary leaflet.

DISCUSSION

Validation of Simulated Coronary Waveform

The experimental coronary waveform from our model (see Fig. 3) compares both qualitatively and quantitatively to physiological coronary flow.^{12,18,21} These agreements with *in vivo* published data were considered sufficient validation since inherent patient variability prohibits a perfectly ideal coronary waveform.

Sinus Flow Patterns

One of the main flow patterns often cited when examining aortic hemodynamics is the sinus vortex.¹⁹ This vortex was indeed present in this study, however its shape, location, and strength were all affected by the introduction of coronary flow. Presence of a coronary artery prevented fluid from fully recirculating, so the classical vortex shape was not seen in the coronary sinus. Rather, fluid appeared to make a U-turn before being diverted into the ostium. Additionally, a “suction” effect from the coronary is likely responsible for pulling the vortex more toward the ostium, thus altering its location. Regarding rotational strength, peak vorticity was lower and the systolic vortex generally encompassed a smaller portion of the sinus in the coronary case.

Another hemodynamic difference aside from the sinus vortex is present near the annulus of the valve, along the base of the sinus and leaflet. In this region, there is significantly more flow for the coronary than non-coronary case during all times during the cardiac cycle. The reason for this appears to be the presence of an open coronary ostium and it could have implications for disease. For example, the “washout” effect gained by this increased flow eliminates the stagnant region of blood near the annulus, which is beneficial since stagnation is often associated with thrombosis.^{24,26} Similarly, low wall shear stress due to minimal flow often leads to less alignment of endothelial cells, which leaves the tissue more susceptible to inflammation.^{4,26}

Shear Stress

Shear stress contour maps are presented in Fig. 9. The main area of interest is near the base of the leaflet since wall shear stress on the fibrosa has been strongly linked to calcification. Generally, higher shear stress values are present in this region for the coronary case, with peak magnitudes around 1.2 Pa s vs. 0.4 Pa s for the non-coronary sinus. Additionally, direction of shear stress is constant when coronary flow is present as opposed to without, which demonstrates an oscillatory shear stress pattern. Both low and oscillatory shear stresses have been linked to calcification,³ so these findings could explain the trend of earlier

and more frequent calcification on the non-coronary cusp.⁷ These factors should be considered in other studies that involve examination of shear stresses along the aortic side of the valve leaflets. This work suggests that differing sinus hemodynamic environments should lead to differing shear stress patterns on the non-coronary and coronary cusps. Results yield a three-fold increase in systolic shear stress near the leaflet in the coronary sinus, which could likely have pathological impact for the non-coronary sinus. However, most studies have neglected coronary arteries when attempting to predict fibrosa shear stress patterns.^{3,27,28} Therefore, the results from many of these previous studies are largely applicable to the non-coronary sinus only.

Leaflet Kinematics

The coronary leaflet is shown to open farther into the sinus than the non-coronary leaflet. This is likely due to a lower sinus pressure, which could be caused by the coronary ostium providing an alternate path for high pressure fluid in the sinus during systole. Da Vinci first hypothesized that the sinus vortex helped aid in leaflet closure, and recent studies have demonstrated how lowered pressure in the sinus could aid in leaflet opening.^{8,10} The vortex core is positioned between the leaflet free edge and the sinus wall in the coronary case, rather than downstream of the free edge in the non-coronary case (see Fig. 8). This creates a low pressure at the center of the vortex that pulls more radially outward on the leaflet in the coronary sinus, which could help explain the greater valve opening in this case.

Limitations and Future Work

A few major limitations were present in this study. First of all, the use of a rigid sinus chamber is not physiologically accurate. However, this simplification is not expected to significantly skew results. Additionally, there is three dimensional flow in the sinus, but we were only able to capture a two dimensional slice. Computational simulations are planned to help capture this out of plane motion. One other limitation was the inability to calculate wall shear stress on the leaflets. This was addressed by computing fluid shear stress throughout the sinus to still give a basic picture of leaflet wall shear stress patterns. Future computational modeling should also help address this issue. Last of all, there was a small amount of signal loss due to blockage of the laser sheet by the coronary tubing adapter, but this was limited to a small sliver in the base of the sinus. Additional testing using this setup is planned to examine the hemodynamic effects of transcatheter aortic valve implantations on both non-coronary and coronary sinuses, which could add value to similar transcatheter studies that haven't modeled coronary flow.^{6,11}

CONCLUSION

In conclusion, this study constitutes the first detailed look at aortic sinus hemodynamics with the inclusion of coronary flow. Novel methodology to simulate this coronary flow *in vitro* was developed and validated. Results show a systolic coronary sinus vortex that is located deeper in the sinus relative to its non-coronary counterpart. There is also a stagnant region of fluid in the non-coronary sinus that is not present in the coronary case. This coronary washout effect could help prevent thrombosis and possibly damage to the leaflet endothelium. Additionally, fluid shear stress contours suggest higher magnitude and less

oscillatory stresses on the coronary leaflet, which supports the claim that the non-coronary leaflet calcifies earlier. Finally, leaflet kinematics tracking shows that the coronary leaflet moves farther into the sinus than the non-coronary leaflet. These novel findings could have implications for past and future studies regarding the aortic valve's mechanical environment, since hemodynamics and shear stresses are significantly different for the non-coronary vs. coronary sinuses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge funding from National Institutes of Health (NIH) under Award Number R01HL119824, and the American Heart Association under award 11SDG5170011. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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FIGURE 1.

Detailed valve chamber dimensions (in mm) from (a) cross-sectional view and (b) side view. Notice the grooves for stent-posts which exactly match the prosthetic-valve to generate a flush-mounted stent, in order to mimic the native valve commissural region.

FIGURE 2.

Schematic of left heart flow loop with coronary circuit, used to impose physiological pressures and flow rates across the aortic valve.

FIGURE 3.
Aortic and coronary flow waveforms over one cardiac cycle.

FIGURE 4.

Image of (a) transparent acrylic valve chamber with depiction of laser sheet and camera viewing plane. Camera orientation is normal to this viewing window, which is at a 60° angle to the laser sheet. The coronary sinus that was studied is outlined in red. (b) Raw camera image of sinus used for PIV calculations with representative leaflet and stent post positions superimposed (masked area represents shadow).

FIGURE 5.

Visualization of distortion due to refractive differences was conducted by inserting a calibration grid into the sinus (a). Grid intersection points were picked manually (b) and deformation vectors were computed between these camera points and locations where the points should lie without image distortion (c) and (d).

FIGURE 6.

Annotated snapshots from particle streak plot videos. Manually-created vectors show major flow patterns from the videos. The coronary tube was clamped just downstream of the ostia to create the non-coronary case. Masked regions do not contain signal.

FIGURE 7.
Velocity vectors and vorticity contours at selected time points throughout the cardiac cycle.

FIGURE 8.

Time-varying velocity and vorticity magnitude are shown at three different points throughout the sinus model, with and without coronary flow.

FIGURE 9.

Fluid shear stress contours at selected time points throughout the cardiac cycle.

FIGURE 10.

Leaflet tip position is plotted, as a function of distance from the aortic axis, from beginning to end of systole for both coronary and non-coronary cases. Error bars represent standard deviation of 5 experimental trials.