A COMPARISON OF THROMBUS SUSCEPTIBILITY FOR TWO PULSATILE

50 CC LEFT VENTRICULAR ASSIST DEVICES

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by
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Abstract:

Left ventricular assist devices (LVADs) have proven successful as a bridge to transplant and more recently as a viable destination therapy. Despite increasing survival rates, destination therapy for pulsatile devices remains limited by adverse events including thrombus formation within the device. Thrombosis is correlated to the fluid dynamics within the device and has been shown to be a result of sustained wall shear rates below 500 s$^{-1}$ on polyurethane, a material similar to that used within the Penn State pulsatile LVAD. A rotating disk is used to assess platelet adhesion to the device specific polyurethane urea material used for the blood sac within the Penn State LVAD. The effects of altered shear exposure upon adhesion are quantified across a physiologically relevant shear range. Particle image velocimetry (PIV) is then used to compare flow within two 50 cc LVAD designs to measure flow patterns and quantify wall shear rates in regions known to be susceptible to thrombus formation, from previous in vivo studies, to determine which design limits platelet adhesion to the greatest extent. The two designs differ in their front face geometry while maintaining identical stroke volume and port orientations. The V1 model has an outward facing “dome” whereas the front face of the V2 model is flat.

A thrombus susceptibility metric, adapted from a computational study of the Penn State LVAD, is applied to objectively compare pump designs over the entire cardiac cycle. For each design, there are regions where wall shear rates remained below 500 s$^{-1}$ for the entire cardiac cycle resulting in high thrombus susceptibility potential. Results of this study indicate that V2 has an overall lower propensity for thrombus formation and is the
better design. Results of the study are correlated to findings of platelet and fibrin deposition on an implanted blood sac from a V2 device and are also compared to computations.
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Chapter 1
Introduction

1.1 Clinical Population

Approximately 5.7 million Americans are afflicted with heart failure (HF), with a reported 670,000 newly diagnosed patients each year (Lloyd-Jones 2009). Additionally, HF contributed to 300,000 deaths and 2.4-3.5 million hospitalizations per year. Those with advanced stage HF constitute between 1-10% of the afflicted population. Primary causes of HF include myocardial infarction, coronary artery disease, high blood pressure, and diabetes. While dietary changes and medicinal therapy may improve such a condition, a transplant may be necessary for advanced stage HF. Over the previous decade, the number of transplants in the United States has been approximately 2,000 per year. The number of donor organs does not meet the increasingly high demand, as approximately 3,100 Americans remain waitlisted, some for greater than 5 years (UNOS, 2009).

1.2 Ventricular Assist Device History

Due to a lack of organ availability, mechanical support systems have been under development for several decades. In 1963, the first human was supported for a short time on a ventricular assist device (VAD). Since that time, a great number of technological advances have been made in the field, culminating in the first FDA approved device in 1994 (Gray 2006). Ventricular assist devices are often used to support the left side of the heart, as this side must pump against the large systemic resistance. VADs differ from an artificial heart in that the patient’s native heart is left intact, not completely replaced. The
LVAD drains blood from the left ventricle and pumps into the aorta. LVADs are favorable for end stage HF patients for several reasons. First, if the LVAD should mechanically fail, the native heart remains in place for temporary support until a repair can be performed. Additionally, the LVAD can help strengthen the patient’s native heart as a means of bridge to recovery.

In 2001, the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) demonstrated the success of LVADs as a means of mechanical circulatory support (Lietz 2007). The collaborative study between Columbia University, the National Heart, Lung, and Blood Institute, and Thoratec Corporation concluded that LVADs can significantly extend and improve the lives of end stage HF patients who are ineligible for transplantation. The study randomly grouped 129 patients ineligible for transplant into either a LVAD supported group (HeartMate™ XVE) or a group receiving inotropic therapy. Those implanted with the LVAD reported 52% one year survival rates compared to 25% for patients in the control group. The current one year survival rate for clinically used LVADs is approximately 85% and is reaching a similar outcome as heart transplantation (Deng 2011).

1.3 LVAD Classifications

Ventricular assist devices are generally considered to fall into two broad categories, pulsatile and continuous flow. Pulsatile devices pump blood in a similar way as the native ventricle. A filling diastolic phase is followed by a systolic ejection phase to pump blood through the systemic circulation (Deutsch 2006). This characteristic is
favorable in that blood flow retains its native pulsatile characteristics. The largest obstacle for pulsatile devices is thrombus formation due to stagnant flow at points throughout the cardiac cycle. Additionally, mechanical valves used within pulsatile devices have been reported to activate platelets entering the device by high shear stresses (Bleustein 2004). The combination of these two factors can lead to thrombosis.

The second class of LVAD is continuous flow (or non-pulsatile) devices. These devices are typically much smaller than pulsatile devices and move blood by rotating an impeller at several thousand rotations per minute to move blood either axially or centrifugally from the inlet (Olsen 2000, Song 2003). These devices have become the choice for implant by surgeons due to their small size. However, continuous devices have several drawbacks that may contraindicate their favorable size. They are typically more difficult to control in order to meet the changing oxygen demands of the active human body (Ohuchi 2001). These devices also generate high shear stresses in the vicinity of the rotating blades and are thought to degrade the von Willebrand factor (vWF) molecule (John 2009). This blood glycoprotein is involved in hemostasis, and as a result, many patients supported by continuous devices experience gastrointestinal tract bleeding (Klovaite 2009). Additional concerns regarding the absence of pulsatile blood flow within the circulatory system remain unanswered. Therefore, there is a continuing need to study and develop pulsatile devices.
1.4 Thrombosis and Hemocompatibility

Thrombosis remains one of the largest obstacles to permanent pulsatile device use. The coagulation cascade is complex, involving numerous pathways, cellular material, glycoproteins, and interacting cofactors (Figure 1.4.1). Protein adsorption to a foreign material surface is well accepted as a primary event in this process. Fibrinogen is one of the most abundant blood proteins, present at a concentration of approximately 2-4.5 mg/ml. Additional adhesion proteins found in blood plasma are: fibronectin (0.3 mg/ml), vitronectin (0.3 mg/ml), and vWF (0.05 mg/ml). Upon adsorption, fibrinogen plays a key role in mediating platelet adhesion to the surface and polymerization to form fibrin (Colman 2001). Platelets are anuclear cell bodies approximately 2-4 microns in diameter and are derived from fragmentation of precursor megakaryocytes produced in the bone marrow. The average lifespan of these circulating cells is on the order of 5-9 days, and average platelet counts range between $150-450 \times 10^6$ platelets/ml in a healthy individual. Upon shear stress activation, platelets tend to clump together and adhere to an encountered surface primarily through fibrinogen and vWF mediation. Activated platelets release numerous cofactors of the coagulation cascade including adenosine diphosphate and calcium, which then further amplify the thrombolytic process by promoting additional platelet aggregation and adhesion through chemotaxis (Walsh 1994).
The thrombogenicity of a biomaterial is defined by its propensity to form thrombi (which are a combination of platelets, fibrin, and entrapped red blood cells) when coming into contact with blood. Biomaterials are extensively studied for their interactions with clotting proteins and platelets to help predict outcomes of implant and blood exposure along with inflammatory and immune responses (Gorbet 2004). The formation of thrombi within a LVAD is dangerous should embolization occur, as possible vessel occlusion, altered flow, stroke, and tissue necrosis might result. The current study is primarily concerned with the thrombogenicity of a polyurethane derivative known as polyurethane urea (PUU) (Biospan MS/0.4), as it is used for the blood contacting sac within the Penn State pulsatile LVAD. In addition to having a preferred biologic response, the PUU has desirable mechanical properties, including good fatigue resistance, high tensile strength, and the compliance necessary to perform optimally within the LVAD chamber.
The PUU material has been used for biomedical applications such as shunts, catheters, and LVADs since the 1960s (Yamanaka 2006). It has proven superior to other biomaterials in terms of the previously listed mechanical properties along with its hemocompatibility (Yamanaka 2006). The material is composed of a methylenediisocyanate hard segment, a polytetramethyene oxide soft segment, an ethylene diamine chain extender with an endcap of 2000 molecular weight poly-(dimethysiloxane) at 0.04% by weight, and a 0.4% silicone backbone (Milner 2005). The PUU has been previously shown to limit fibrinogen adsorption and platelet activation better than alternative materials such as silicone rubber, polytetrafluoroethylene, and polyvinylchloride (Elam 1992). The PUU surface has been shown to be further improved from a hemocompatibility standpoint through modifications to surface chemistry (Sefton 2001), addition of anticoagulants (Blezar 1997), and bulk modifications (Kim 1996). Sub micron texturing in the form of nano-pillars has also been shown to reduce platelet adhesion in comparison to a smooth surface under identical shearing conditions (Milner 2005).

1.5 History of the Artificial Heart Lab

The first Penn State LVAD implant occurred at Hershey Medical Center in 1976 (Gaines 1985). Since this time, a specific aim has been to reduce the original device from 100 cc to a smaller version more compatible with adult patients of limited chest cavity size. The device was first reduced to a 70 cc volume and was most suitable for patients weighing between 60-100 kg. Along with Arrow International, the LionHeart™ reached clinical trials by 2001 (Mehta 2001). The device incorporates a transcutaneous energy
system that allows for increased patient mobility and decreased risk of infection. During surgical implantation (Figure 1.5.1), the inlet cannula is connected to the apex of the left ventricle while the outlet cannula is joined to the descending aorta through an end-to-side anastomosis (Mehta 2001). The PUU blood sac is housed within the titanium chamber.

Figure 1.5.1 Depiction of LionHeart™ implant (Arrow International).

The device is capable of monitoring changes in physiologic demand through a motor controller that adjusts the pusher plate timing as a function of end diastolic volume. The controller’s programmed algorithm ensures complete filling and ejection by altering systolic duration with changes in inlet pressure. A DC motor drives a roller screw, which is attached to the pusher plate that contacts the PUU diaphragm. A compliance chamber adjusts for changes in gas volume during the cyclic motion of the pusher plate (Mehta 2011).
In vitro laser Doppler anemometry flow measurements within the device chamber measured shear stresses in the range of 300-500 dynes/cm² (Baldwin 1994), well above previously suggested thresholds necessary to inhibit thrombus growth on polyurethane (20 dynes/cm²) (Hubbel and McIntire 1986). The LionHeart™ also showed little deposition during clinical trials; however, the size remained problematic for a large portion of the patient population. The 50 cc device, designated V0, was developed in 2000 and could benefit a larger patient population (Hochareon, 2004). During the following decade, extensive effort has been put forth to characterize thrombus development within this device. Although the 50 cc and 70 cc devices share many of the same features, lower Reynolds numbers within the 50 cc device lead to less mixing and greater risk of deposition of platelets and fibrin.

Hochareon et al. conducted particle image velocimetry (PIV) measurements throughout the device chamber to determine regions where wall shear rates remained below 500 s⁻¹ for the majority of the cardiac cycle (Hochareon 2004). At the same time, thirty day animal implants were used to test the performance of the device within bovines. Yamanaka examined PUU blood sacs for deposition from three such explants following animal termination (Yamanaka 2003). Deposition was found in regions where the measured wall shear rates remained below 500 s⁻¹ for a large portion of the cardiac cycle. Regions within the device chamber experiencing high blood residence times are susceptible to platelet adhesion.
Baldwin et al. noted the importance of a strong diastolic jet to promote a rotational flow capable of washing a large portion of the device chamber (Baldwin, 1994). Effects of altered mitral valve orientation were considered in a parametric study by Kreider et al. for valve angles of $0^\circ$, $15^\circ$, $30^\circ$, and $45^\circ$ within the V0 device for a Bjork-Shiley Monostrut mechanical heart valve (Figure 1.5.2). A rotation angle of $30^\circ$ toward the front fluid region increased the duration of wall washing in thrombus prone regions by approximately 50 ms and exhibited the strongest late diastolic rotation (PIV parallel planes 3, 5, and 8 mm from the front wall at 75 beats per minute (bpm)) (Kreider 2006). Alterations in mitral valve orientation improved flow penetration and washing. Changes to the port orientation have also been shown to exhibit a substantial influence on wall washing within the 50 cc device.

![Figure 1.5.2 Valve angles studied by Kreider for the 50 cc V0 device (Kreider 2006)](image)

Nanna et al. evaluated three design iterations designated V2, V3, and V4 in an in vitro setting. The V2 design has an outlet port parallel to the inlet, to preserve rotational flow. The V3 outlet port is rotated away from the inlet port to decrease the time blood remains in contact with the PUU surface, while the V4 outlet port is moved to the center of the pump with the intent of prolonging the rotational flow (Figure 1.5.3).
Incorporating the optimal mitral valve angle, PIV measurements were made at the 3, 5, and 8 mm parallel planes along with three normal planes spaced throughout the ports, while operating at 86 bpm. Altering the outlet port position led to the intended results; however, little wall washing was observed for V3 and little flow was measured between the ports for V4. The V2 design was designated the model of choice, as it combines the favorable aspects of the V3 and V4 designs (Nanna 2011).

![V-2 V-3 V-4](image)

**Figure 1.5.3** Front profile of 50 cc iterations illustrating alterations in outlet port orientation considered by Nanna *et al.* (Nanna 2011)

Most recently, Nanna *et al.* conducted an extensive shear rate study within the V2 device to determine the necessary PIV data collection frequency and resolve flow features along the lower device wall at 75, 115, and 150 bpm, using high magnification PIV measurements of 12 µm/pixel. Ten millisecond intervals showed significant variability in the shear near the wall locations, that 50 millisecond intervals missed. To compare beat rates, data was collected in 7% intervals of both diastole and systole to account for changes in systolic duration. Along a 6 mm wall section, shear magnitude was shown to scale with the kinematic viscosity over the square of the average inlet
velocity (Figure 1.5.4). The normalization is useful for predicting thrombus potential against varying operating conditions (Nanna 2011).

![Figure 1.5.4 Scaling of shear magnitude by kinematic viscosity over the square of the average inlet velocity across beat rates of 75, 115, and 150 bpm (Nanna, 2011).](image)

1.6 Present Study

We examined the effects of pulsatility and quantified levels of shear exposure on platelet adhesion to the PUU used for the Penn State 50 cc LVAD blood sac. A disk with a blood contacting PUU surface was rotated in platelet rich bovine plasma for two hours under both steady and pulsatile shearing conditions. The pulsatile conditions (which included the inflow waveform for the LVAD operating at 86 bpm and three sawtooth waveforms) maintained the same RMS angular velocity as the steady shearing condition, for comparison. Alterations in peak shear exposure were examined by comparing the
three sawtooth waveforms, which had peak angular velocities of 0, +25%, and -25% that of the peak angular velocity of the inflow waveform. Adhesion was quantified by examining immunofluorescently labeled platelets adhered to the PUU by confocal microscopy at specific locations on the disk surface where the shear rate was known.

Platelet adhesion levels are a primary indicator of thrombus formation on blood contacting surfaces such as PUU. Clotting events following adhesion were not considered within this study, as it would involve more complex whole blood modeling. Adherent platelets provide a connection point for fibrin and red cell entrapment leading to an eventual thrombus. Bovine platelets were utilized for this study because the Penn State LVAD is often tested first in bovines. This allowed for correlations between measured adhesion levels within this study and adherent platelets bound to explanted blood sacs.

Particle image velocimetry was used to compare flow within two 50 cc designs. The V2 design, which has been designated the standard based upon previous work, was compared to the V1 model. The two designs are identical in terms of stroke volume, port orientation, valve type, and valve orientation but differ in their front face geometry. The V1 model has an outward facing “dome” whereas the face of the V2 model is flat (Figure 1.6.1). The designs are compared at 75 bpm (38% systolic duration) which represents the lower end of the beat rate spectrum for bovine studies. PIV is taken in planes both normal and parallel to the front face of the LVAD with a focus on the lower front wall region where thrombus susceptibility is known to be high. The designs are objectively
compared by relating calculated wall shear rates across the cardiac cycle to shear rate values found to be thresholds for inhibition of platelet and thrombus deposition by the platelet adhesion studies and the cited literature.

Figure 1.6.1  Comparison of front face geometry between V1 and V2 designs. The V1 model has an outward facing dome (Nanna 2011).
Chapter 2

Methods: Platelet Adhesion Measurements

2.1 Smooth Polyurethane Urea Synthesis

PUU samples were prepared at Hershey Medical Center by successively spin casting and curing 18% Biospan MS/0.4 on a smooth PDMS mold three times. The first layer is spun at 1500 rpm for 60 s to create a very thin, smooth layer. The second layer was spun at 800 rpm for 60 s and the third layer was spun at 400 rpm for 60 s. The sample was cured overnight in a vacuum at room temperature following each casting. In this way, we increased the thickness of the material while maintaining smoothness and reducing bubble formation. A PUU material sample is shown in Figure 2.1.1 below.

![PUU material sample](image)

**Figure 2.1.1** PUU material sample prepared at Hershey Medical Center (courtesy of Dr. Siedlecki)
2.2  **Platelet Rich Plasma Preparation**

Whole bovine blood was drawn from the jugular vein of healthy bovines at the Penn State dairy barns according to IACUC #31641. Whole blood was anti-coagulated with citrate phosphate dextrose adenine-1 (CPDA-1) in a 500 ml donor bag for approximately 20 minutes during transportation from the dairy barn to the laboratory. Platelet function and viability are unaltered when stored at room temperatures and short periods with CPDA-1 (Scott 1980, and Kahn 2003). The blood bag was placed in an insulating cooler during transportation.

The blood was centrifuged at 600 g for 12 minutes, with 1% acceleration and deceleration. These slow acceleration periods were used to reduce mixing between the separated cells. Platelet rich plasma (PRP) was gently separated from the red cells and buffy coat (white cells) and transferred into a clean 50 ml centrifuge tube. Platelet concentration measurements were made using a hemacytometer (Reicher, Buffalo, NY) and bright-field microscope (Nikon, Melville, NY) with a 40x lens (Nikon, Melville, NY). A hemacytometer, shown in Figure 2.2.1a, is an etched glass chamber with raised sides that hold a cover-slip approximately 0.1 mm above the chamber floor. The surface has varying sizes of etched squares arranged in groups. For a given square size, the volume is calculated by the surface area times the surface height (0.1 mm). The cell concentration, in platelets/ml, is determined by the total cell count in five squares of the same size (Figure 2.2.1b), times the dilution factor, times the volumetric coefficient. The larger sized squares in Figure 2.2.1b are more appropriate for counting cells with larger diameters such as red blood cells.
Bulk platelet concentration ($C_\infty$) was adjusted to 350 x $10^6$ platelets/ml by the addition of either phosphate buffered solution or PRP of higher concentration. The plasma was measured to have an average kinematic viscosity of 1.55 cSt at 30° Celsius using a viscoelastic analyzer (Vilastic, Austin, TX). Plasma was then transferred to a 100 ml polytetrafluoroethylene (PTFE) beaker and maintained at 30° Celsius throughout the experiment by a hot plate (Figure 2.3.1).

2.3 The Rotating Disk System

The flow field near the surface of a rotating disk has been studied extensively (Benton 1966, and Dailyn 1960). The rotating disk system (RDS) developed by Pine Instruments (Pine Instruments, Grove City, PA) is shown in Figure 2.3.1. The motor rotates the shaft at a level of 1 rpm per applied mV, from a programmable voltage delivered by a function generator (Agilent, Santa Clara, CA). A 20 mm diameter metallic
disk is scribed with six radial lines spaced at 60° intervals and nine concentric circles, each separated by 1 mm. The PUU is pasted to the disk surface by double sided tape. Just prior to rotation, the disk with PUU is lowered approximately 3 mm into the PRP. During rotation, the shear rate along a radial line extending outward from the center is easily defined at the surface, as the velocity increases linearly with radial distance.

**Figure 2.3.1 Rotating disk system used for platelet adhesion studies** (adapted from Milner 2005).

All applied waveforms maintained the same root mean square (RMS) angular velocity of 29.63 rad/s and had the same period of 700 ms (Figure 2.3.2). A constant voltage was used to produce a baseline steady rotation of 29.63 rad/s for six experiments. A cardiac inflow waveform obtained from the Penn State 50 cc LVAD operating at 86 bpm was used to study the effects of pulsatility on platelet adhesion in another six experiments. The inflow waveform reached a peak angular velocity of 54.35 rad/s with an acceleration of 0.16 rad/s². The effects of peak shear exposure were tested by
applying three sawtooth ramp waveforms, six experiments each, at different peak angular velocities. The waveforms were programmed to have a 90% rise and 10% fall of the total cycle. The “baseline ramp” peaked at the same peak angular velocity as the cardiac pulse waveform (54.35 rad/s, acceleration = 0.09 rad/s²). The second (“-25% ramp”) reached a peak 25% lower (40.76 rad/s, acceleration = 0.04 rad/s²) than the baseline ramp waveform. The third (“+25% ramp”) reached a peak 25% higher than the baseline sawtooth waveform (67.93 rad/s, acceleration = 0.15 rad/s²).

Figure 2.3.2  Angular velocity (rad/s) for pulsatile waveforms over the course of one 700 ms period.

Following the rotation, platelets were removed from the PUU suspension by 6 aspirations of 35 ml phosphate buffered saline (PBS). PBS was then replaced with a 1% para-formaldehyde (PFA) solution for one hour to fix the platelets. PFA was then
replaced by PBS and allowed to equilibrate for 10 minutes. The disk, with adhered PUU, was then detached from the RDS.

2.4 Epi-Fluorescent Laser Scanning Microscopy

Platelets adhered to the PUU surface were immunofluorescently labeled by treatment with a primary CAPP2A mouse anti-bovine \( \alpha IIb\beta3 \) antibody (VMRD, Pullman, WA) (1.5 µl CAPP2A+1 ml 6% donkey serum (Sigma-Aldrich, St. Louis, MO)) within a 12 well tray. Following this, the sample was refrigerated overnight to allow for complete binding between the primary \( \alpha IIb\beta3 \) antibody and adherent platelets. The following day, the PUU surface was gently rinsed with five 3 ml PBS additions to remove non-specifically bound \( \alpha IIb\beta3 \) antibody. A secondary Alexa-Fluor 488 donkey anti-mouse IgG (Invitrogen, Eugene, OR) (1.25 µl +1 ml 6% donkey serum) was then added to the well containing the disk/PUU surface and allowed to incubate at room temperature in the dark for one hour. The same rinse procedure was then used to eliminate non-specifically bound secondary antibody.

Imaging was conducted using a FV-1000 confocal microscope (Olympus Microscopes, Shinjuku, Tokyo). Figure 2.4.1 shows a diagrammatic representation of the confocal light path. The laser light (with an excitation wavelength of 488 nm) emitted from the source passes through a pinhole aperture. The light is scanned across the specimen by an oscillating dichromatic mirror after passing through the objective to the focal plane. The secondary fluorescence, given off by the excited Alexa-Fluor, passes back through the dichromatic mirror and is focused through a pinhole at the
photomultiplier detector tube (PMT). The PMT increases the signal energy to detectable levels. Light from points above and below the focal plane have a very low emission signal and are not detected by the photomultiplier tube. The majority of background light is blocked from planes that are not confocal with the pinhole apertures of the light source and detector. As a result, confocal microscopy produces a much stronger signal compared to traditional wide-field epi-fluorescence microscopy.

![Diagram of confocal light path and optical components](Olympusmicro.com).

**Figure 2.4.1** Diagram of confocal light path and optical components (Olympusmicro.com).

A 10x objective (Olympus Microscopes, Shinjuku, Tokyo) was used for locating radial intersections of interest. A 100x dry objective (Olympus Microscopes, Shinjuku, Tokyo) was used for imaging the sample. The objective has a 1 mm working distance and numerical aperture of 0.95. While oil or water immersion lenses can produce a higher numerical aperture as a result of its higher refractive index, the PUU material could not be cover-slipped due to the risk of altering the arrangement of surface bound
platelets. The numerical aperture (\(NA\)) of a lens is a dimensionless number that characterizes the range of light acceptance angles. The \(NA\) is calculated by:

\[
NA = n \sin(\vartheta) \quad [1]
\]

where \(n\) is the index of refraction of the medium and \(\vartheta\) is the half-angle of the maximum cone of light that can enter the objective. The dry objective uses air as a medium which has a value of \(n=1.0\). The image area produced following scanning with the 100x objective was 120 \(\mu m^2\) and centered on the radial intersection of interest. For the RMS angular velocity of 29.63 rad/s, this image area results in a shear variation of 6.22 s\(^{-1}\) from image center to edge.

### 2.5 Quantification of Platelet Adhesion

The platelet count at the disk center, along with the average number of platelets for three randomly chosen radial intersections, constitutes one experiment. The adhesion coefficient (AC) is defined as:

\[
AC = \frac{N}{j * t} \quad [2]
\]

where \(N\) is the average number of platelets per unit area, \(j\) is the mass flux, and \(t\) is the rotation time \[15\]. The flux is defined as:

\[
j = 0.62D^{2/3}v^{-1/6} \omega^{1/2}C_\infty \quad [3]
\]

where \(\omega\) is the RMS angular velocity, \(C_\infty\) is the bulk concentration, \(v\) is the kinematic viscosity. The diffusivity (\(D\)) is defined as:

\[
D = \frac{K_b T}{6\pi \eta b} \quad [4]
\]
where $K_B$ is the Boltzmann constant, $T$ is the absolute temperature, $\eta$ is the dynamic viscosity of PRP, and $b$ is the average platelet radius (Wang 2003).
Chapter 3

Methods: Particle Image Velocimetry

3.1 Theory

A two-dimensional PIV system was used for the current study. The system provides a non-invasive fluid velocity measurement at planar locations within the LVAD flow field. By making multiple planar measurements throughout the flow field, in both normal and parallel planes, three dimensional reconstruction can be formed. A typical diagram of a PIV alignment is shown diagrammatically in Figure 3.1.1 below.

![Diagram of typical PIV experimental design](Raffel 1998)

Conceptually, PIV data is acquired by pulsing two light sheets over a user defined time delay, \( \Delta t \) apart to generate two image frames. In Figure 3.1.1 these frames are indicated by \( t \) and \( t' \). The fluid passing through the light sheet is seeded with 10 \( \mu \)m hollow glass spheres (Potters Industries, Inc., Valley Forge, PA). Upon illumination, the
particle position is captured for each frame by a charge-coupled device (CCD) camera. Post-processing divides the image frames into 32 $\mu \text{m}^2$ interrogation regions (IRs). Within each IR, cross-correlation between image frames determines particle displacement. The fluid velocity is then calculated by dividing the particle displacement by the $\Delta t$ used during image acquisition. By applying this technique to all IRs, a 2D velocity field is obtained for the entire illuminated plane (Raffel 1998). For this data, two hundred image pairs are averaged for each data acquisition time during the cardiac cycle for statistical accuracy.

Light Source

The PIV system incorporated a Nd: YAG laser, part of a Gemini PIV 15 system (New Wave Research, Inc., Fremont, CA), for the laser emission source (Figure 3.1.2). Two infrared laser beams ($\lambda = 1064$ nm) are directed by fold mirrors to the polarizer assembly where the output is combined. The lasers are polarized to a wavelength of 532 nm by the second-harmonic generator (labeled SHG in Figure 3.1.2). The energy source is then transmitted to the optical attenuator which is user-controlled to regulate energy emission from the laser head.
After exiting the laser head, the laser beam is passed through a light arm, with an internal mirror array, which allows the output to be easily moved and directed to the desired position. The beams are then directed through a negative 25 mm cylindrical lens and 500 mm spherical lens to produce a light sheet that is 300 µm thick at the focal length of 500 mm where the acrylic model is positioned (Figure 3.1.3). The lens arrangement is placed on a Newport 443 Series Low-Profile, Ball Bearing Linear Stage (Newport Corporation, Irvine, CA) to accurately align the light sheet to within a resolution of 10 µm.
Figure 3.1.3  Top and side view of cylindrical and spherical lens arrangement. The acrylic model is positioned at the spherical lens focal length (TSI, 1999).

Image Capture

A two megapixel CCD camera (TSI, Inc., Shoreview, MN) with a 50 mm F1.8 lens (Nikon Corporation, Tokyo, Japan) is used for image capture. The camera is positioned on a traverse system capable of three-dimensional movement to align the lens parallel to the light sheet. Laser pulsing and image capture are coordinated through a LaserPulse Synchronizer (TSI, Inc., Shoreview, MN). The synchronization of camera exposure and laser pulses for each set of images is controlled through Insight™ 3G software (TSI, Inc., Shoreview, MN).
3.2 *In Vitro* Modeling

*PIV Particles*

The 10 μm glass spheres effectively follow fluid motion within the device as the Stokes number is <<1 for all measurement conditions (Crowe, 1998). The non-dimensional Stokes number is defined as:

\[
St = \frac{d^2 \rho_{\text{particle}}}{18 \mu_{\text{fluid}} \Delta t}
\]  

[5]

Here, \(d\) represents the particle diameter, \(\rho\) is the particle density, \(\mu\) is the dynamic fluid viscosity, and \(\Delta t\) is the pulse separation for the particular PIV collection conditions. For these experiments, the Stokes number ranged from 0.00145-0.0145 for the range of pulse separations used. While particles must be small enough to satisfy the Stokes criterion, they must also be sufficiently large to scatter the light sheet generated by the pulsed laser. The 10 μm particles satisfy both criterion and are detectable by the CCD camera. Particle concentration is also important for statistical purposes; particle density was maintained at between 5-15 particles per 32 μm² interrogation region (Figure 3.2.1) (Raffel, 1998).
Figure 3.2.1  Particle density within four 32 $\mu$m$^2$ interrogation regions (highlighted in orange), brightest particles are most nearly “in-plane” with the laser sheet.

Viscoelastic Blood Analog

A shear thinning, Non-Newtonian blood analog composed of water (33.97%), glycerin (16.0%), xanthan gum (0.03%), and sodium iodide (50.0%) by weight was used to simulate 40% hematocrit human blood, as this represents an average red cell proportion within whole blood. This composition was developed by Long et al. to study the affects of viscoelasticity on inlet filling characteristics for pulsatile blood pumps (Long 2005). The glycerin and water components of the fluid were used to match the viscous properties of the fluid while the xanthan gum was responsible for providing the elasticity. Sodium iodide (NaI) was used to match the fluid to the refractive index of the acrylic model (1.49). Index matching between the fluid and acrylic is essential to prevent the laser sheet from bending when passing between acrylic and fluid media. Following the addition of NaI, the fluid must be maintained in an environment protected from sunlight due to the risk of photoionization. Should this occur, the fluid’s optical clarity degrades as a
function of exposure level. This degradation may be corrected to an extent by mixing the fluid with several milliliters of sodium thiosulfate.

The viscoelastic properties of the fluid (Figure 3.2.2) were measured over a physiologic shear range using a Vilastic-3 viscoelasticity analyzer (Vilastic, Austin, TX). Measurements below 10 s\(^{-1}\) are not accurate due to large oscillations during measurement. Kinematic blood viscosity reaches an asymptotic level for shear rates greater than several hundred inverse seconds. Due to the pulsatile nature of flow within the LVAD, the fluid must also be accurately modeled for low shear rates to account for low flow periods. Low shear rates may also be encountered for a continuous devices operating under low flow conditions or when modeling flow through the venous system.

![Figure 3.2.2 Viscoelastic properties matched between 40% hematocrit whole blood and blood analog](image)

**Figure 3.2.2** Viscoelastic properties matched between 40% hematocrit whole blood and blood analog (blood data taken from Long 2005)
Acrylic models

For both the V1 and V2 designs, acrylic models were machined from optically clear acrylic with a refractive index of 1.49 (Figure 3.2.3). Each model accurately represents the geometry of the device used clinically. The chamber has a radius of 33.5 mm, inlet port diameter of 19.5 mm, and outlet port diameter of 17.7 mm. The front face of the V1 device has an outward facing dome which extends approximately 8 mm at the apex. The V2 device has a flat front face. Clinically, the internal pusher plate contacts the PUU blood sac contained within the housing chamber. For the \textit{in vitro} modeling, the pusher plate contacts the PUU diaphragm used to seal the acrylic chamber.

![Acrylic model machined from optically clear acrylic](image)

\textbf{Figure 3.2.3} Acrylic model machined from optically clear acrylic (Nanna 2010).
Valve Selection

Bjork-Shiley Monostrut (BSM) tilting disk valves were placed at both the inlet and outlet ports to maintain unidirectional flow through the device (Figure 3.2.4). The inlet valve has an outer diameter of 23 mm while the outlet valve has an outer diameter of 21 mm. The valves have major and minor orifice areas with the combined area known as the effective orifice area (EOA). The inlet valve has an EOA of 2.5 cm$^2$. Suture rings were removed from the valve perimeter and the valves seated within a plastic casing to smoothly fit within each of the ports. Based upon previous studies by Kreider et al., the inlet valve was rotated 30° from the horizontal axis of the pump toward the front wall (Figure 1.5.2). The outlet valve was positioned parallel to the horizontal axis of the device.

Figure 3.2.4  BSM tilting disk valve. The suture ring is removed prior to placement within each port of the acrylic model.
Mock Circulatory Loop

Both models were independently incorporated into a mock circulatory loop shown diagrammatically in Figure 3.2.4. The system was developed by Rosenberg et al. and was designed to accurately duplicate conditions measured during in vivo animal trials (Rosenberg 1981). The flow loop elements, which included a venous reservoir, atrial and aortic compliance chambers, acrylic model, and a resistance plate, are connected in series by compliant Tygon tubing with a 3.2 mm wall thickness. The blood analog is introduced into the system through the venous reservoir and then covered to prevent spilling. The reservoir sits atop a magnetic stir plate to ensure that particles remain homogenously distributed throughout the fluid. All air is removed from the circulatory system prior to the experiment. During data acquisition, the entire loop is covered by black draping to reduce external light saturation on the CCD chip.

Figure 3.2.4  Mock circulatory loop used to maintain physiologic conditions within the LVAD (adapted from Roszelle 2010).
Each compliance chamber is designed to mimic the native compliance of vessels within the cardiovascular system. The chambers have variable volume cylinders with a flexible metallic rod and piston system which can be manually adjusted. For a given flow rate through the chambers, the internal pressures can be adjusted by either adjusting the fulcrum location or changing the thickness of the rod. The relation of compliance (C), change in pressure (\(\Delta P\)), and flow (\(\Delta V\)) is given by:

\[
\Delta P = \frac{\Delta V}{C} \quad [6]
\]

Pressures were monitored by pressure transducers (Argon Medical Devices, Athens, TX) at taps in each compliance chamber. A calibration curve was established for each transducer over a range of -30-120 mmHg by a pneumatic transducer (Model DPM 1B, Bio-Tek Instruments, Inc., Winooski, VT) and universal pressure meter (Model DPM-II, Bio-Tek Instruments, Inc., Winooski, VT). In the atrial chamber, located 254 mm upstream of the LVAD, we maintained systolic/diastolic pressures of 30/5 mmHg. The arterial chamber maintained pressures of 120/80 mmHg at a location 254 mm downstream of the LVAD. The atrial chamber location in relation to the LVAD was chosen to be 10 times the tubing diameter. The aortic chamber was then matched for symmetry.

The adjustable resistance plate was used for adjusting pressures to meet the desired conditions. Physiologically, this resistive element represents the blood vessels, which are capable of altering their diameter by relaxation or contraction of smooth
muscle. The primary source of resistance takes place at the arteriolar level. Mathematically, the resistance (R) through a tube can be quantified by the Poiseuille equation:

\[ R = \frac{8\mu L}{\pi r^4} \]  \[7\]

Based upon this relation, it is evident that resistance is primarily a factor of vessel radius (r) for a laminar flow.

Ultrasonic flow probes (Transonic Systems, Inc., Ithaca, NY) were located at the inlet and outlet ports of the LVAD (Figure 3.2.4). Each probe was calibrated for the NaI blood analog and connected to a flow meter (Model TS410, Transonic Systems, Inc., Ithaca, NY) where a digital readout displayed the instantaneous flow rate. At 75 bpm, each LVAD maintained an average outflow of 3.8 liters per minute, verifying complete ejection of the 50 cc stroke volume. All pressure and flow waveforms were monitored by a 1 MHz data acquisition board (IOtech, Inc., Norton, MA) connected to a PC.

Flow was driven by a positive displacement piston system (StarFish Medical, Victoria, B.C.). The motion of the piston was coordinated through a ViViGen Waveform Generator (StarFish Medical, Victoria, B.C.). At 75 bpm, the sinusoidal piston motion had a peak to peak amplitude of 23 mm to ensure that the pusher plate fully detached from the diaphragm at the end of diastole. This condition is maintained clinically to prevent material fatigue. Full detachment was verified by high speed video prior to data collection. In previous studies, diaphragm motion has been found to have substantial effects upon flow characteristics (Hochareon 2003). The pusher plate is composed of
dark PVC to reduce CCD pixel saturation when it moves into the flow field. All flow loop components are bolted to a breadboard to reduce vibration.

3.3 Data Collection

A trigger box was manufactured by the Penn State Applied Research Lab to coordinate data collection timing at user defined points throughout the cardiac cycle. Triggering was based upon the voltage rise in the inflow waveform (arrow in Figure 3.3.1). The trigger signal was measured through WaveView software (IOtech, Inc., Norton, MA) and measured on screen through the PC. Two hundred images were collected every 7% of diastole and systole for statistical averaging. For 75 bpm (38% systolic duration), diastole is 496 ms while systole is 304 ms. Prior to data collection at each time point, a $\Delta t$ for laser pulse separation was chosen to best fit the changing pulsatile flow field throughout the cardiac cycle. Pulse separation was optimized so that average particle motion between frames was half an IR to ensure peak locking (velocity gradients biased to 0 m/s) did not occur (Raffel, 1998). For this data set, the $\Delta t$ ranged from 100-1000 $\mu$s.
Figure 3.3.1 Inflow and outflow waveforms. The negative flow seen for the inflow waveform is a result of regurgitation through the mitral valve. Percentages of diastole and systole are referenced in the results section.

For both model geometries, data was collected in two imaging orientations. The box in Figure 3.3.2a contains the portion of the flow field imaged during normal plane analysis (30 µm/pixel) along with location of pusher plate for reference. The box in Figure 3.3.2b contains the region imaged at the 1 mm parallel plane (45 µm/pixel). The locations of the nine normal planes are shown if Figure 3.3.2b; all distances (mm) are measured from the outer edge of the inlet port. For reference: the plane labeled 34.25 mm is the center of the pump body, 9.75 mm corresponds to the center of the inlet port, and the 59.6 mm plane is the center of the outlet port.
Figure 3.3.2 Imaging regions for a) normal planes and b) 1 mm parallel plane. The location of the nine normal planes is shown in b) measured in mm from the outer edge of the inlet port.

3.4 Post-Processing

Following completion of data collection, images are masked to block background pixels unrelated to the flow field (Figure 3.4.1). The LVAD fluid boundary is manually identified by a fifth order polynomial regression to reconstruct the wall geometry (Hochareon 2004). Upon boundary identification, the masking algorithm identifies pixel intensity gradients orthogonal to the wall. Cooper et al. (2008) determined that the wall can be identified to within half a pixel. Following masking, all pixels outside the flow field are given a zero intensity thus reducing errors associated with cross correlation between image frames.
Following zero masking of all images, vector fields were created through an Insight\textsuperscript{TM}3G processing algorithm. Each image pair was divided into small IRs of 32 pixels\textsuperscript{2} (Figure 3.4.1). Particle displacement between frames for each IR was analyzed by cross-correlation to observe changes in particle location. Using a fast Fourier transform correlation engine, Gaussian peak detection algorithm, and recursive Nyquist grid, displacement vectors were determined. For the recursive Nyquist grid, the first processing pass computes the vector field at the starting IR dimension which is 64 pixels\textsuperscript{2}, at 50\% overlap grid spacing. Results of the first pass are used to optimize the spot offsets for the second processing pass. The offset is equal to the integer pixel displacement measured in the first processing pass so that subsequent processing passes have a peak location within a half pixel of the correlation center.
For each IR, displacement vectors were divided by the laser pulse separation time to produce velocity vectors for the entire flow field. An Insight™ 3G vector conditioning method was used to replace invalid vectors with the median of neighboring valid vectors. These invalid counts could result from a number of factors including out-of-plane flow, low particle displacement, or large flow gradients.

Wall Shear Rate Calculation

Following computation of the velocity field, vectors are averaged for all 200 image pairs to obtain a velocity flow field for each time step. The average flow field is then processed by a first-order wall shear rate algorithm developed by Hochareon et al. (Hochareon 2004). The near wall tangential component of velocity, applied at the IR centroid, is divided by the normal distance to the wall for each near wall IR. The no-slip boundary condition is applied at each point along the wall. Interrogation regions near the wall must contain greater than 10% fluid area to be considered for the wall shear calculation.

3.5 Error Analysis

PIV data was acquired at resolutions of 30 µm/pixel and 45 µm/pixel; the nearest point to the wall in which we can calculate wall shear rate is 96 µm and 144 µm, respectively (Nanna 2011). The wall shear rate calculation is resolution dependent, as velocities and wall location can be more accurately resolved at higher magnifications (Nanna 2011). For data that are not pixel locked, we can estimate the minimum velocity
resolution to 0.1-0.2 times the spatial resolution divided by the laser pulse delay (Raffel 1998). At a resolution of 30 µm/pixel, the maximum velocity resolution achievable is 0.003 m/s to 0.006 m/s. At a resolution of 45 µm/pixel, maximum velocity resolution is 0.0045 m/s to 0.009 m/s. Maximum velocity resolutions are calculated under the assumption of a low velocity, planar flow, where the maximum pulse separation of 1000 µs was used.

PIV error analysis has shown that measurements are sub pixel accurate up to 10-20% of the spatial resolution. As such, the bias error with the wall shear calculation is ±20% (Cooper 2008, Raffel 1998). The precision error was calculated to gain an estimate of repeatability. To calculate precision error, an array of velocity values corresponding to a distinct point within the flow field were extracted (one for each of the 200 images acquired for a given time step). This was done for 10 distinct points within three different time steps containing 200 images each. A student t-distribution at a 95% confidence interval was then performed to assess the difference in velocity between the 200 images in a given time step for each distinct point chosen. The average precision error was found to be 1.8%. Using the bias error (20%) along with the average precision error (1.8%), overall uncertainty was estimated to be approximately 20.1% (as the Euclidean norm). The ratio of precision error to bias error suggests that repeatability is not a dominant source of error in these measurements.

Data was also checked for sample loss which could occur due to strong three dimensional flow. This was done through Tecplot 360 by reviewing plots of vector
counts and looking for dropout in the 200 samples from each averaged velocity field. This was limited experimentally by altering the pulse separation until greater than 80 percent of valid vector counts were obtained prior to data collection at every temporal interval. Histograms of velocity magnitude counts were plotted using Tecplot 360 (Tecplot, Inc., Bellevue, WA) to verify that peak locking did not occur. Peak locking is evidenced by a high distribution of counts centered upon 0 m/s (Figure 3.5.1). Proper pulse separation ($\Delta t$), and particle displacement within IRs is necessary to prevent this.

![Histogram of velocity magnitude for a) peak locked data and b) data not peak-locked.](image)

Figure 3.5.1  Histogram of velocity magnitude for a) peak locked data and b) data not peak-locked.
Chapter 4
Results and Discussion

4.1 Platelet Adhesion

A characteristic image of platelets adhered to the PUU surface at the disk center following a two hour rotation in PRP can be seen in Figure 4.1.1. Scale bars in each image are 5 $\mu$m in length. A pseudopodia, exhibited by activated platelets, is indicated by the arrow in Figure 4.1.1. Bovine platelets lack the open canalicular system (OCS) exhibited by human platelets. Upon activation, the OCS contributes to an increased surface area during human blood hemostasis (Milner 2005).

![Figure 4.1.1 Characteristic image of platelets adhered at the disk center.](image)

Using Equation [2], average platelet adhesion was quantified for each of the waveforms displayed in Figure 2.3.2 by the AC as a function of shear rate (Figure 4.1.2). The error bars associated with each data point indicate plus or minus the standard error of the mean. The platelet flux, Equation [3] was defined using the RMS angular velocity...
shared by all waveforms. For each shearing pattern, the AC is highest at the center of the disk corresponding to a shear rate of 0 s\(^{-1}\). At this location ACs were 0.65 (steady), 0.30 (cardiac pulse), 0.74 (-25% ramp), 0.44 (baseline ramp), and 0.19 (+25% ramp). Unequal adhesion at the disk center is surprising because all waveforms theoretically share a shear rate of 0 s\(^{-1}\), irrespective of shearing pattern. Similarly large variations in adhesion levels were found by Milner \textit{et al.} when comparing different textured PUU surfaces (Milner, 2005). A shear rate of 0 s\(^{-1}\) only occurs at the infinitesimal center of the disk. As mentioned previously, a shear variation from image center to edge of 6.22 s\(^{-1}\) exists for the RMS speed of 29.16 rad/s. Adhesion coefficients decayed exponentially (trend lines in Figure 4.1.2), for all shearing patterns, with increasing shear rate. The correlation coefficient (\(R^2\)) was 0.89 (steady), 0.73 (cardiac inflow), 0.79 (-25% ramp), 0.90 (0% ramp), and 0.57 (+25% ramp). At the outer most radial location measured, corresponding to an RMS shear rate of 933 s\(^{-1}\), ACs had decayed to 0.01 (steady), 0.05 (cardiac pulse), 0.003 (-25% ramp), 0.03 (control ramp), and 0.02 (+ 25% ramp).
The three ramp waveforms are shown in Figure 4.1.3 to directly compare the significance of peak shear exposure on mean ACs at each radial location. Significance is characterized by the Analysis of Variance Test (ANOVA) at a 95% confidence interval (CI). The test measures whether two or more populations are equal under the assumption that the sampled populations follow a normal distribution. The test was performed with peak shear rate as the main variable. The test relates variance within groups to variance between groups for the measured sample size. Despite large variations in AC at the disk center, no statistical significance was found due to large standard error of the mean. The next four points measured, corresponding to shear rates of 103.6, 207.3, 310.9, and 414.5
s⁻¹, were found to be statistically different. This result indicates that platelet adhesion at or below 414.5 s⁻¹ is directly affected by the peak shear exposure. At the next radial location, corresponding to a shear rate of 518.15 s⁻¹, no significance was observed. No significant differences were found at any of the remaining (higher shear rate) points examined. This indicates that at or above RMS calculated shear rates of 518.15 s⁻¹, platelet adhesion is not affected by peak shear exposure. The RMS shear at the outer radial locations was sufficient to wash platelets from the PUU surface.

**Figure 4.1.3** Mean adhesion coefficients for the three ramp waveforms. *Four of the five points measured below 500 s⁻¹ show significant difference (95% CI) as a function of peak shear exposure.*

Previous findings by Hubbell and McIntire showed platelet adhesion to be markedly reduced when increasing a steadily applied shear rate from 100 s⁻¹ to 500 s⁻¹ (Hubbell and McIntire 1978). These studies were performed using epi-fluorescent video microscopy within a parallel-plate flow chamber lined with polyurethane. This study was
conceptually different, as real time analysis was performed in that study, compared to current studies examining adhesion levels following a two hour period of shearing.

It was theorized that altered levels of platelet adhesion between shearing conditions was caused by different peak platelet flux for each of the waveforms considered in Figure 2.3.2. To test this hypothesis, Equation [3] was calculated based upon the peak angular velocity of each waveform. Equation [2] was then calculated based upon peak platelet flux. The results of this analysis, for the same platelet counts used to calculate the data presented in Figure 4.1.2, are shown in Figure 4.1.4. The ACs calculated for peak platelet flux are plotted as a function of peak shear rate experienced at each radial location. This was done to maintain consistency of peak angular velocity for both ordinates. Results of this analysis validate the theory of peak platelet flux and shear rate being the primary indicators of platelet adhesion at each radial location. Peak platelet flux collapsed the data set to a greater degree than RMS platelet flux. A second interesting observation from Figure 4.1.4 is the asymptotic, low adhesion levels past a shear rate of approximately 1000 s\(^{-1}\). Aside from one singularity (cardiac inflow, 1544 s\(^{-1}\)), all AC measurements remain below 0.1 for all higher peak shear rates (>1000 s\(^{-1}\)). A shear rate of 1000 s\(^{-1}\) was found to be sufficiently high to inhibit platelet deposition on polyurethane by Balasubramanian et al. (Balasubramanian 2002).
In summary, these results indicate that below a shear rate of 500 s\(^{-1}\), platelet adhesion is directly influenced by peak shear exposure. For higher shear rates, adhesion is reduced and dependent solely upon RMS levels of shearing. At peak shear rates greater than \(~1000\) s\(^{-1}\), platelet adhesion reaches an asymptotically low level. These findings are incorporated within the thrombus susceptibility potential metric discussed later in section 4.2.
4.2 Fluid Mechanic Comparison of Devices

Flow Visualization

To compare the thrombus susceptibility between the V1 and V2 designs, near wall velocity measurements were made for planes both normal and parallel to the diaphragm (Figure 3.3.2) at 75 bpm using PIV. Flow visualization at the 1 mm parallel plane was used to compare near wall flow patterns at a resolution of 45 µm/pixel. This plane encompassed the region where shear measurements were calculated across the nine normal planes (Figure 3.3.2). Data was acquired for 7% increments of diastole and systole (Figure 3.3.1). Four percentages of diastole are compared in Figure 4.2.1 for a) V1 and b) V2. Percentages are, from left, 7, 35, 64, and 92% of diastole. The remaining percentages of diastole are shown in Appendix A.

Baldwin et al. noted that a strong diastolic jet is necessary to promote rotational flow patterns leading to washing across the device (Baldwin, 1994). The inlet jet for each device reached peak velocities of 1.44 m/s (V1) and 1.35 m/s (V2), both at 42% diastole. The inlet jet for both designs is blocked from reaching the base of the device by a secondary jet moving perpendicular (right to left) to the downward inlet flow. The secondary jet, thought to be caused by the 30° rotation of the inlet valve, reached a maximum velocity of 0.85 m/s (for V1) and 1.08 m/s (for V2), both at 50% of diastole.
While inlet velocity magnitudes are relatively similar, morphological changes during diastole are more noticeable. At 35% diastole (Figure 4.2.1), the inlet jet for the V1 device is tapered toward the edge of the inlet port in relation to the V2 inlet profile. This limits the degree of washing near the inner edge of the inlet port and is most likely caused by stagnant flow residing within the outward facing dome. Additionally, the flat face of the V2 design causes the center of rotation to remain tighter and more centrally located in comparison to the center of rotation for V1. This tighter flow may be the result of the faster moving secondary jet within V2. These differences result in improved washing conditions for the V2 design through diastole.

A comparison of four percentages of systole (Figure 3.3.1) are shown in Figure 4.2.2. In comparison to diastole, strong flow is primarily contained on the outlet side during systole. Flow intensifies within this region as the pusher plate forces the
diaphragm into the fluid region, increasing the LVAD pressure above the aortic pressure, subsequently opening the aortic valve. Outflow peaks at 0.73 m/s (V1) and 0.74 m/s (V2), both at 50% of systole. There are less noticeable differences in flow patterns during systole in comparison to the distinct differences observed during diastole (inlet jet formation and center of rotation). The data for remaining percentages of systole can be found in Appendix B.

![Flow visualization for four time points during the systolic cycle for a) V1 and b) V2.](image)

**Figure 4.2.2** Flow visualization for four time points during the systolic cycle for a) V1 and b) V2.

*Calculated Wall Shear Rates*

Contour plots were created to gain a perspective of wall shear rates for both diastole and systole. Wall shear rates are normalized by 500 s$^{-1}$, that is, a value of 1 corresponds to 500 s$^{-1}$. Wall shear rates calculated along the perimeter of the 1 mm parallel plane are shown in Figure 4.2.3 for a) V1 and b) V2 for the entire cardiac cycle.
Yellow to red hues indicate shear resulting from clockwise flow while blue hues indicate counterclockwise flow. The location 0 mm corresponds to the upper right edge of the inlet port within the interrogation region shown for the 1 mm parallel plane in Figure 3.3.2 b. The location 110 mm corresponds to the upper left edge of the outlet port in the same figure. The end of diastole is indicated by the time 496 ms.

Figure 4.2.3 Wall shear rates for a) V1 and b) V2 calculated along the 1 mm parallel plane for the entire cardiac cycle.

The V2 model shows much stronger washing during diastole along the outer edge of the inlet port at the 1 mm parallel plane. Stronger shearing along the edge of the inlet port and through the center of the pump continues through early systole for the V2 device. Both devices show very low shear over the cardiac cycle, indicative of flow separation, in the region near the 50.8 mm normal plane (circled). The V2 device shows significantly stronger shear along the edge of the outlet port from mid-diastole through
mid-systole in comparison to V1. Overall patterns of shearing are similar between devices with higher magnitudes for V2.

Nine planes normal to the diaphragm were used to compare wall shear rates along the front face of each design (Figure 3.3.2). These planes were imaged at a PIV resolution of 30 µm/pixel. Three planes were located within the inlet port, three within the mid-body, and three within the outlet port for each device. Contour plots for these planes are normalized in the same fashion as the plots for the 1 mm parallel plane. For the normal planes, blue hues indicate shear resulting from a downward moving flow while yellow to red hues indicate flow moving up the face of the device. Here, the location 0 mm corresponds to the base of the pump at a plane 10.16 mm from the front face. This point marks the location where the acrylic model is sealed by the PUU diaphragm.

A comparison of the inlet port region for both designs is shown in Figure 4.2.4 for diastole. In Figure 4.2.4 a, the 9.75 mm plane is exposed to visualize the location where wall shear measurements are made; similarly for the 4.87 and 19.5 mm planes. The majority of washing within the inlet port occurs during the first 496 ms of the cardiac cycle. For both models, there is strong shearing over the upper two thirds of the wall examined, through the middle of diastole at the 4.87 and 9.75 mm planes. This is the result of the inlet jet. Wall shear rates are lower for the bottom third of these sections due to the blockage of the inlet jet by the secondary jet. The component of flow caused by the secondary jet (Figure 4.2.1) moves up the face of the device, beginning near the base,
giving positive shear. Significant differences can be observed at the 19.5 mm plane between devices. The upper third of the wall for V2 is washed for a longer time in relation to V1. For both devices, the inlet jet only penetrates down the upper third of the wall, examined at the 19.5 mm plane.

![Image](image-url)

**Figure 4.2.4** a) Cross sectional view (lightened region) and wall location (black line) where shear rates were calculated for the 9.75 mm plane. b) Diastolic wall shear rates within the inlet port for each device.

Wall shear rates calculated for the mid-body of each device are compared in Figure 4.2.5. Flow is moving primarily up the face of each device in this region of the pump. Prolonged exposure to wall shear rates greater than 500 s⁻¹ exists for both systole and diastole in this region and so the entirety of the cardiac cycle is displayed. At the 26.9 mm plane, washing patterns are nearly identical between V1 and V2. Strongest
washing occurs during mid-diastole for each device at the center of the pump (34.25 mm). V1 exhibits stronger washing towards the base of the wall whereas V2 shows higher wall shear rates in the middle of the wall. There are significant differences between designs at the 42.5 mm plane. The V2 design exhibits stronger washing during diastole, with wall shear rates above 500 s\(^{-1}\) persisting through systole.

![Contour plots](image)

**Figure 4.2.5** Wall shear rates calculated within the mid-body for both devices.

Contour plots within the outlet port are shown below in Figure 4.2.6. Here, flow is moving up the face of the pump over the entire cardiac cycle. The wall along the 50.8 mm normal plane exhibits the lowest degree of washing for either device in comparison to the 59.6 and 64 mm planes. The base of the 50.8 mm plane is exposed to weak washing over the entire cardiac cycle. The pattern of shearing is highly similar within the outlet port for each pump design. The V2 design does however experience greater peak shears within the outlet port for the three planes compared in Figure 4.2.6.
Thrombus Susceptibility Potential

The wall shear rate contour plots displayed in Figures 4.2.4-4.2.6 are useful for identifying regions of high or low shear rates. The thrombus susceptibility of a given point within the LVAD is influenced by strength and duration of washing. The combination of these factors can make objective comparisons between the two models difficult. A more objective method for quantifying thrombus susceptibility (TSP) was developed by Medvitz through a computational study of the Penn State LVAD (Medvitz 2008). This method was used more recently by Roszelle to quantify weaning and valve orientation thrombosis potential in parametric studies involving the Penn State pediatric ventricular assist device (Roszelle 2010). The TSP relates calculated wall shear rates
over the cardiac cycle to shear rate values for peak platelet adhesion and inhibition on PUU. The TSP is given by the equation:

\[
TSP = 1 - \sum_{0}^{N} \frac{\Delta t \gamma_w \cdot e^{\left(\frac{\gamma_w - \gamma_{peak}}{\gamma_{cutoff} - \gamma_{peak}}\right)}}{\gamma_{cutoff} t_{crit} e^{1} - 1} - 1
\]  

For application to PIV measurements, N is the number of time steps taken through the cardiac cycle and \( \Delta t \) is the amount of time between acquisitions. The calculated wall shear rate is indicated by \( \gamma_w \). The \( \gamma_{peak} \) was set to 500 s\(^{-1}\), as this has been established as a threshold value for thrombus deposition on materials similar to that used in the Penn State LVAD (Hubbell and McIntire 1986). Results of the platelet adhesion experiments also indicated that within the range of 414.5 s\(^{-1}\)-518.15 s\(^{-1}\), adhesion was no longer influenced by peak shear exposure. Root mean square shear rates within or above this range were shown to reduce adhesion, independent of peak shear exposure. The exponential function is used to reduce \( \gamma_w \) in the vicinity of \( \gamma_{peak} \) from significantly lowering the TSP.

The \( \gamma_{cutoff} \) value was set to 1000 s\(^{-1}\), as this is an established experimental value for inhibition of platelet deposition by Balasubramanian (Balasubramanian 2002). Results of the platelet adhesion experiments upon PUU also indicated that at approximately 1000 s\(^{-1}\) of peak shear exposure, adhesion was reduced to a very low level. The critical
exposure ($t_{ex}$) was chosen to be twice the length of the PIV $\Delta t$ to reduce the effect of a high shear value at a single time-step (Roszelle 2010).

Application of the TSP results in a value between 0 and 1 for each measured location along the LVAD wall. A value of 0 corresponds to a very low potential for thrombus formation while 1 indicates a very high potential. The TSP decreases non-linearly with increasing shear rate. There is presently no specific value TSP known that will guarantee the absence of thrombus. Equation 8 was applied to the wall locations where PIV measurements were made for both pumps. The TSP at each location is summed over the entire cardiac cycle and then plotted to determine which areas along the surface have high thrombus susceptibility. Assumptions of the TSP are that platelet activation occurs upon entry into the device through the mitral valve, as shown in previous studies (Bluestein 2004); and low shear regions within the device are accumulating zones for deposition. The latter assumption was validated by the rotating disk experiments performed in this study. Greatest deposition was also found in regions of lowest shear for pulsatile flow conditions in previous correlative studies (Hochareon 2004).

The TSP comparison for V1 and V2 within the inlet port is shown in Figure 4.2.7. Along the 4.87 and 9.75 mm planes, both designs show a very high potential along the first 10 mm section of wall, beginning at the base (0 mm). Further up the wall the TSP declines to 0 very rapidly, in the region strongly sheared during diastole by the inlet jet, (Figure 4.2.4) and remains at this level along the remainder of the wall examined. The
inner edge of the inlet port, corresponding to the 19.5 mm plane, shows susceptibility for both devices over the majority of the wall examined. The V2 design has a potential near 0 at approximately 11 mm from the base; a location experiencing strong shearing from the secondary jet during diastole. At locations ~15-25 mm from the base, V1 has a lower potential, however; it is still generally greater than 0.4.

Figure 4.2.7  TSP calculated within the inlet port for a) 4.87, b) 9.75, and c) 19.5 mm planes for V1 (blue) and V2 (red).
As shown in Figure 4.2.5, wall shear rate patterns are generally similar within the mid-body of the pump between designs. The TSP calculated for these planes is shown in Figure 4.2.8 and illustrates the importance of the strength of the shear. Aside from two short instances (~3-7 mm along the 34.25 and 42.5 mm planes) V2 maintains a lower thrombus potential due to stronger washing, despite similar flow patterns. Both designs are highly susceptible along the 26.9 mm plane. V1 shows a potential near 1.0 along the entire wall measured. Thrombus potential for V2 is lower in comparison from ~13-30 mm however the TSP generally remains above 0.5. At the mid-body of the device (34.25 mm), V1 shows a potential near 0 along the base of the device while V2 shows 0 TSP ~14-20 mm from the base. All other locations along this plane showed higher susceptibility, with V1 showing higher susceptibility than V2.

Significant differences between calculated TSPs are present for the 42.5 mm plane between designs. Both devices have highest potentials near the base of the pump. Approximately 10 mm from the base, the potential for V2 drops to levels near 0 over the remainder of the wall examined whereas V1 shows a potential near 1 for this same line. The root of this difference can be seen in Figure 4.2.5 where V2 shows stronger, more sustained washing throughout the cardiac cycle. V1 is only washed over diastole at this plane (with wall shear rates approximately 500 s⁻¹). The 42.5 mm plane showed the greatest difference between calculated thrombus potentials between devices in the portion of the LVAD examined by this study.
Figure 4.2.8  Comparison of TSP calculated within the mid-body of the pump for a) 26.9, b) 34.25, and c) 42.5 mm planes for V1 (blue) and V2 (red).
The thrombus potential within the outlet port is shown in Figure 4.2.9. At the 50.8 mm plane, both devices show high susceptibility near the base (~0-7 mm). Further up the wall, TSPs are lower for both devices (with V2 lower than V1). V1 had TSPs ranging from 0.2-0.9 over the remainder of the wall while V2 had TSPs ranging from 0-0.5. Figure 4.2.9b gives the TSP calculated for the center of the outlet port (59.6 mm). Here the TSP is near 0 for the vast majority of the wall examined. Only the region corresponding to the pump base (~0-2 mm) had TSP>0; with V1 greater than V2. These low potentials are the result of strong washing throughout the cardiac cycle for each device, as seen in Figure 4.2.6.

The 64 mm plane, representing the location halfway between the middle of the outlet port and the outer edge of the outlet port, is shown in Figure 4.2.9c. The V2 design shows potentials near 0 along the entire wall examined. Over the first 10 mm of wall past the base, the V1 design shows much higher potentials intermittently mixed with very low potentials. Beyond 10 mm, V1 also shows potentials near 0 over the remainder of the wall examined. As a whole, the outlet port shows the lowest potentials for each device, with V2 having lower potentials than V1.
Figure 4.2.9  Comparison of TSP calculated within the outlet port for a) 50.8, b) 59.6, and c) 64 mm planes for V1 (blue) and V2 (red).

The TSP corresponding to the perimeter of the flow field measured by PIV at the 1 mm parallel plane is shown in Figure 4.2.10. The origin begins at the upper right
corner of the interrogation region as shown by the black curve in Figure 3.3.2b. The calculation progresses clockwise around the wall, ending at the upper left corner of the outlet side. Along this wall, the V1 model has a much higher TSP. This can be attributed to flow separation caused by the “dome-like” front wall. Both pumps exhibit elevated TSP near the upper corner of the inlet port where the diastolic jet does not maintain close contact with the wall (Figure 4.2.1). Flow reattaches past this region for each pump.

For V1, flow detaches once again approximately 40 mm circumferentially from the origin and remains detached resulting in a high TSP across the mid-body and outlet. Upon reattachment, the V2 model maintains strong washing until approximately 80 mm circumferentially from the origin. Here, there is a second separation persisting for nearly 10 mm until reattaching once again. The remainder of the outlet wall is sufficiently washed. The TSP of nearly 1 (for V2) seen at the 80-90 mm location corresponds to the same detachment region near the base of the 50.8 mm normal plane (Figure 4.2.9a). This indicates a highly susceptible region for V2, as the wall is minimally washed for both measured components of flow.
Figure 4.2.10  Thrombus susceptibility potential calculated for the perimeter of the 1 mm parallel plane for V1 (blue) and V2 (red).

The TSP was also applied to the rotating disk model. The calculated wall shear rates for all measured temporal points during the rotation period were incorporated in [8] for each radial intersection. The results, displayed in Appendix C, were plotted against both radial location and peak shear rate. When plotted against radial location, the results can be useful for correlating the TSP to in vitro platelet deposition. The calculated TSP between shearing patterns collapsed when plotted against peak shear rate; once again demonstrating the importance of peak shear exposure.
4.3 Correlations to *In Vivo* Explant

With metric values for thrombus susceptibility now calculated for a large number of locations within the device, correlations could be made to deposition found on a PUU blood sac from a device which had been operated *in vivo*. This work was performed by Stephen R. Topper (Topper 2012) at specifically indicated locations where planar PIV measurements had been made. The blood sac examined was obtained from the Hershey Medical Center, from a V2 LVAD which had been implanted in a bovine for 30 days, with the beat rate held at 75. Immediately following explant, the blood sac was flushed with saline and a 1% paraformaldehyde fixative solution was added to preserve surface formations. The sac was stored in 0.9% saline solution until evaluation.

At the designated locations, the blood sac was examined using both scanning electron microscopy (SEM) and confocal microscopy. A 4 mm by 8 mm portion of the sac was removed, centered upon the location of interest, and subdivided into four rectangular regions (Figure 4.3.1). Two diagonals were examined using SEM while the remaining diagonals were fluorescently labeled for platelets and fibrin and examined by confocal microscopy. The fluorescent labeling procedure for confocal imaging and SEM preparation can be found in Topper, 2012 (Topper, 2012).
Particular attention was given to susceptible regions predicted by the TSP calculated from wall shear rates measured by PIV. The base of the 50.8 normal plane was shown to be the most susceptible region within the V2 design due to low potentials calculated for both normal and parallel plane analysis. The TSP from the 50.8 normal plane, along with correlation images from the *in vivo* blood sac are shown below in Figure 4.3.2 for a) confocal and b) SEM. For confocal images, fibrin is stained red and platelets stained green. In regions along this plane (0, 17, 35 mm) showing elevated TSP values (>0.5), there is strong evidence of deposition. At a location (25 mm) predicted to have a very low potential (<0.1), little deposition was found in comparison.
Figure 4.3.2  Correlation of TSP with a) confocal and b) SEM images along the 50.8 normal plane for the V2 design from an \textit{in vivo} explant.

Confocal images correlating to locations along the perimeter of the 1 mm parallel plane are shown in Figure 4.3.3. Here 0 mm represents the upper right corner of the inlet point, 55 mm is the center of the device, and 110 mm the upper left corner of the outlet port within the interrogation region identified in Figure 4.3.3. Greatest deposition was predicted to be found approximately 80-100 mm circumferentially from the upper right corner of the wall examined. Prior to 80 mm, the TSP was found to be 0 past the 20 mm
wall location. The correlation study found little deposition over 36.69-63.33 mm. A large fibrin strand was observed at 72.35 mm, a location prior to the increasing TSP-predicted region. High fibrin deposition was also found within the region expected to show significant deposition (90 mm).

Figure 4.3.3 Correlation of TSP with confocal microscopy imaging along the 1 mm parallel plane perimeter for the V2 design from an in vivo explant.

For reference, animal experiments are typically characterized by beat rates ranging from 75-150 bpm (systolic durations 38-50%). The TSP values within this work were generated based upon wall shear rates calculated from flow conditions within the V2 device operating steadily at 75 bpm. The TSP found within this study should be viewed as a “worse case” for the LVAD operating at low flow conditions. As discussed
in the Introduction, wall shear rates have previously been found to scale by the square of the average inlet velocity divided by the kinematic viscosity within the V2 device. Therefore, TSPs would be lowered for LVAD operation at higher beat rates while maintaining the same flow patterns.

4.4 Computational Simulations

Dr. Richard Medvitz (Penn State Applied Research Laboratories) performed computational fluid dynamic (CFD) simulations for the V2 design operating at 75 bpm using the finite element solver AcuSolve™. Moving mesh geometry was used to represent the pusher plate/diaphragm motion. Valve selection and orientation were matched to those used for the in vitro PIV studies. Valve motion was not modeled dynamically. Valve closure was modeled by increasing the viscosity (between 5,000 and 50,000) in the ports to alter the fluid velocity at appropriate time points in the cardiac cycle for both the mitral and aortic valve. Viscosities were chosen to retain solution stability and minimize regurgitant flow through the mitral valve. The fluid was modeled as Newtonian for these simulations as a simplification. Fluid viscoelastic properties may be substantially different within low flow regions where the Non-Newtonian effects of the blood analog model would result in increased viscosity. Inflow and outflow boundary conditions were matched to those measured experimentally (Medvitz, 2009)

Computational simulations can be useful for predicting three dimensional flow characteristics throughout the entire device and across a wide range of beat rates much more rapidly than can PIV. The three dimensional capabilities of CFD simulations are
also more suitable for quantifying the complex flow field within the LVAD. The CFD model must first be validated by comparison with results obtained by PIV, prior to using the computational results in a predictive manner.

Flow at the 1 mm parallel plane for the same percentages of diastole displayed in Figure 4.2.1b are shown once again in comparison to CFD results in Figure 4.4.1. Results for the lower portion of the LVAD body acquired by PIV are shown in Figure 4.4.1a while CFD results for the entire device at the 1 mm plane are shown in Figure 4.4.1b. Flow patterns are qualitatively similar, however, they differ in velocity magnitude. The peak inlet velocity calculated by computational simulations is significantly lower than values measured by PIV. Additionally, the secondary jet has not yet entered the 1 mm plane at 35% diastole for CFD, as was the case for PIV. Valve motion simplifications, for CFD, could be in part responsible for this difference.
Figure 4.4.1  Flow maps for a) PIV and b) CFD for four percentages of diastole. The stationary position of the valve can be observed within the ports for the CFD flow maps.

Comparisons between PIV and CFD at the 1 mm parallel plane are shown for the same percentages of systole shown in Figure 4.2.2b. Within the region examined by PIV, flow patterns remain similar between the two methodologies throughout systole. Similar to diastole, the greatest disparities in velocity magnitude occur in the vicinity of the ports.
As discussed in section 3.5, PIV wall shear measurements are resolution dependent. For the PIV normal planes, wall shear rates were calculated 96 $\mu m$ from the wall. Computational simulations have the advantage of extracting data for fluid velocity at any distance from the wall. Therefore, wall shear rates may be quantified at various locations from the wall for the computational simulations. Figure 4.4.3 shows a comparison of wall shear rates between PIV and CFD at locations along the 50.8 mm normal plane where TSP correlations were made with the blood sac explant (Figure 4.3.2). Wall shear rates calculated from velocity measurements at CFD grid spacing’s of 25 $\mu m$ and 96 $\mu m$ are shown. For the PIV results, error bars representing $\pm 90$ s$^{-1}$ are shown and are indicative of the error associated with data collection at a PIV resolution of 30 $\mu m$/pixel (Nanna 2011). Along this plane, PIV and CFD measurements correlate reasonably well. A time lag can be seen when comparing CFD shear rates at grid
spacing’s of 25 \( \mu m \) and 96 \( \mu m \). There is no discernable trend for one modality (CFD or PIV) consistently calculating higher or lower shear rates, but rather the shear varies by location within the LVAD. At the base of the 50.8 mm plane, corresponding to the location 0 mm, wall shear rates never surpass 300 s\(^{-1}\).

Figure 4.4.3  Wall shear rates measured for PIV and CFD at a) 0 mm, b) 17 mm, and c) 25 mm along the 50.8 mm normal plane.
Chapter 5

Conclusions

5.1 Summary of Findings

Particle image velocimetry was used to study two LVAD designs not previously compared. A wall shear rate calculation and thrombus susceptibility metric were applied for two measured components of flow along the base and lower front wall of each model. This region was chosen for study based upon previous findings of sustained wall shear rates below $500 \text{ s}^{-1}$ within the V2 device. Overall, V2 showed improved washing characteristics when compared to the V1 model. The effects of altered geometry were most noticeable during diastole where V2 exhibited a tighter center of rotational flow. Systolic flow patterns and velocity magnitudes were similar on the whole between both designs.

The TSP calculation provided a means to objectively compare both models. Although the V2 model showed improved characteristics, susceptible areas were identified; specifically along the base between the 42.5 and 50.8 mm planes. This region was found to be susceptible based upon both parallel and normal plane analysis. The body region, between the ports, was proven to be the most susceptible to thrombosis. The base of the pump experiences the majority of its washing from the component of flow parallel to the front face of the device. This parallel component of washing was markedly reduced for the V1 design at the 1 mm parallel plane. The base of each device within the inlet port was found to be highly susceptible (TSP generally greater than 0.5) below the furthest penetration of the diastolic inlet jet. Passed the base of the pump, both
designs were shown to be least susceptible within the outlet port due to sustained washing throughout the cardiac cycle.

Based upon Virchow’s triad, risk factors for thrombosis include: the local fluid mechanics, blood properties, and properties of the blood contacting surface. The TSP is a reasonable means of analysis as the blood contacting sac material is the same for all Penn State LVADs. Additionally, patients are typically administered similar anti-coagulants. The local fluid mechanics are the variable differentiating the V1 and V2 devices. The calculated TSP for the V2 device was compared to deposition found upon an in vivo explant from a 30 day bovine study held at a constant 75 bpm. There were strong correlations between locations predicted to be susceptible by the TSP and locations where adherent platelets and fibrin were found. In some instances however, deposition was found in regions predicted to have a very low TSP (<0.1).

Variables used for the TSP calculation, such as $\gamma_{\text{peak}}$, $\gamma_{\text{cutoff}}$ were studied through platelet adhesion experiments to more accurately define them for use with the sac material. Platelet adhesion to PUU was found to decay exponentially with increasing shear rate and to scale by peak platelet flux. Below RMS shear rates of 500 s\(^{-1}\), adhesion levels were found to significantly decrease with increasing peak shear exposure. Past peak shear rates of 1000 s\(^{-1}\), adhesion was found to reach a very low level. As the V2 model has been shown to be less susceptible to thrombi and platelet adhesion, this model should continue to move forward.
5.2 Future Work

The V2 design was shown to have superior flow characteristics; however, a number of susceptible regions were identified. Alternative designs incorporating the favorable characteristics of V2 should continue to be tested in the effort of reducing thrombus susceptibility to the lowest possible levels. To this point, modifications in valve orientation, port orientation, and altered chamber geometry have been considered. The Penn State 50 cc LVAD is approaching optimal design in its general physical form from a fluid mechanic standpoint. The greatest advancements in thrombosis reduction and therefore improvement will likely come through future materials research. Previous studies have shown that a submicron textured PUU surface resulted in less platelet adhesion as compared to the smooth surface used here (Milner 2005). The blood sac material (PUU) has been shown to be one of the best currently available options for use as a biomaterial surface in comparison to alternatives. Due to the pulsatile nature of blood pumps, such as the Penn State 50 cc LVAD, long blood residence times will be difficult to prevent. Results of this work showed highest adhesion on PUU at points where RMS shear rates were low over the cycle.

More complete thrombosis models, with stronger theoretical grounding, are being developed to strengthen the TSP. The $t_{crit}$ parameter should be further studied through platelet adhesion experiments to best quantify its use with the TSP. Roszelle found that alterations to this parameter could have substantial effects on the predicted TSP value in regions where wall shear rates remained between 500-1000 s$^{-1}$ (Roszelle, 2010). Without an accurate understanding of the specific relationship between exposure time and platelet
adhesion, it is not yet possible to give a quantitative correlation between the TSP and *in vivo* deposition.

Computational simulations show strong correlations to flow profiles measured by PIV, however they differ in velocity magnitude by varying degrees depending upon the location. The port regions, where viscosity is manipulated computationally to model valve motion, showed the largest differences. The viscosity should be adjusted so that the flow matches PIV measurements in these locations to more accurately model flow through the device. Refined computational simulations will allow for much more rapid prediction of thrombus susceptibility within the V2 device and other future design geometries.
References:


Appendix A: Diastolic Flow Visualization: 1 mm Parallel Plane

V1:
V2:
Appendix B  Systolic Flow Visualization: 1 mm Parallel Plane

V1:
Appendix C  Thrombus Susceptibility Potential Applied to the Rotating Disk Model

![Graph showing radial distance (mm) vs. TSP for different shear rates.]

- **RDS TSP**
  - Steady
  - Cardiac Pulse
  - Baseline Ramp
  - -25% Ramp
  - +25% Ramp

![Graph showing peak shear rate (s^-1) vs. TSP for different shear rates.]

- **RDS TSP**
  - Steady
  - Cardiac Pulse
  - Baseline Ramp
  - -25% Ramp
  - +25% Ramp