Studies of Stented Arteries and Left Ventricular Diastolic Dysfunction Using Experimental and Clinical Analysis with Data Augmentation

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Dissertation submitted to the faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
In
Biomedical Engineering

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April 1, 2009
Blacksburg, Virginia, USA

Keywords: Coronary Stents, Digital Particle Image Velocimetry, Wall Shear Stress, Oscillatory Shear Index, Left Ventricular Diastolic Dysfunction, Dilated Cardiomyopathy, phase contrast Magnetic Resonance Imaging
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ABSTRACT

Cardiovascular diseases are among the leading causes of deaths worldwide, but the fluid mechanics of many of these conditions and the devices used to treat them are only partially understood. This goal of this dissertation was to develop new experimental techniques that would enable translational research into two of these conditions. The first set of experiments examined \textit{in-vitro} the changes in Wall Shear Stress (WSS) and Oscillatory Shear Index (OSI) caused by the implantation of coronary stents into the arteries of the heart using Particle Image Velocimetry. These experiments featured one-to-one scaling, commercial stents, and realistic flow and pressure waveforms, and are believed to be the most physiologically accurate stent experiments to date. This work revealed distinct differences in WSS and OSI between the different stent designs tested, and showed that changes in implantation configuration also affected these hemodynamic parameters. Also, the production of vortices near the stent struts during flow reversal was noted, and an inverse correlation between WSS and OSI was described.

The second set of experiments investigated Left Ventricular Diastolic Dysfunction (LVDD) using phase contrast magnetic resonance imaging (pcMRI). Using this technique, ten patients with and without LVDD were scanned and a 2D portrait of blood flow through their heart was obtained. To augment this data, pressure fields were calculated from the velocity data using an omni-directional pressure integration scheme coupled with a proper-orthogonal decomposition-based smoothing. This technique was selected from a variety of methods from the literature based on an extensive error analysis and comparison. With this coupled information, it was observed that healthy patients exhibited different flow patterns than diseased patients, and had stronger pressure differences during early filling. In particular, the ratio of early filling pressure to late filling pressure was a statistically significant predictor of diastolic dysfunction. Based on these observations, a novel hypothesis was presented that related the motion of the heart walls to the observed flow patterns and pressure gradients, which may explain the differences observed clinically between healthy and diseased patients.
This work is dedicated to Bob Beve and the beautiful granddaughter he helped raise into the wonderful woman I am going to marry.
ACKNOWLEDGEMENTS

There are so many people that have in some way contributed to this work or have helped me get here that it is impossible to thank them all.

In particular, I would like to thank my parents and sister for their undying support and encouragement throughout my life. I would also like to thank my fiancé, Cami Johnson, for her love and for all her help keeping me sane! Without her pushing me to finish, who knows how many more years this work would have taken to finish?

In addition, my advisor and everyone in the AEThER lab deserve thanks for helping me out with advice, support, patience, and friends to talk to.

To all those named, and many more, my deepest thanks. Without you, this milestone in my life would not have been possible.
ATTRIBUTION

As mentioned in the acknowledgements, many people have contributed in some way to my dissertation. However, in particular, the following people have made specific scholarly contributions to this work, and deserve mention. All have contributed to proofreading or editing various portions of this document, as referenced on the first page of each chapter. A brief description of their background and additional contributions is included below.

**Asst. Prof. Pavlos P. Vlachos** – Ph.D. (Dept. of Engineering Science and Mechanics, Virginia Tech) is committee chair and provided insight and direction throughout this work.

**Satyaprakash Karri** – M.S. (Dept. of Mechanical Engineering, University of Texas at Arlington) is a fellow Ph.D. student in my group and designed the flow loop, and assisted with the experiment setup used throughout the stent work (Chapters 3-5). He also assisted me in performing portions of the experiments.

**Jaime M. Schmieg** – M.S. (Dept. of Biomedical Engineering, University of California, Irvine) is a fellow Ph.D. student in my group and assisted in performing the experiments detailed in Chapters 3-5. She also assisted with the post-processing of that data.

**Santosh Prabhu** – Ph.D. (Dept. of Mechanical Engineering, University of Delaware) is employed at Abbott Vascular. Together with Dr. Vlachos, he wrote the original proposal that led to the stent work detailed in Chapters 3-5. He also provided advice throughout the project.

**Rahul Kumar** – M.D. (Northwestern University) works at Wake Forest University Baptist Medical Center and was responsible for acquiring the MRI images used in the study of left ventricular diastolic dysfunction (Chapter 7). He also provided assistance in interpreting the results.

**William C. Little** – M.D. (Ohio State University) is section chief of cardiology at Wake Forest University Baptist Medical Center. He helped formulate the hypothesis that drove Chapter 7, and provided assistance in interpreting the results.
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Chapter 1: Dissertation Overview and Problem Background

INTRODUCTION

Motivation

One in five Americans has some form of Cardiovascular Disease (CVD), killing nearly one million people in 2006. CVD encompasses such diverse diseases as high blood pressure, coronary heart disease (CHD), and stroke, and heart failure. In order to achieve these improvements, it is necessary to understand the causes and development of these conditions, both biologically and mechanically. One factor that has been repeatedly implicated in the development of many cardiovascular diseases is alterations in the hemodynamic stresses created within the circulatory system.

Overall Objectives

The guiding principle of this investigation was the extension of state-of-the-art tools for fluid velocity measurement to allow the better understanding of the fluid mechanics of cardiovascular disease. Specifically, the application of recent methods for the enhancement of the dynamic range of Digital Particle Image Velocimetry (DPIV) measurements will allow a
more realistic in-vitro measurement of the WSS in stented arteries, and improved pressure
calculation schemes were applied to Phase Contrast Magnetic Resonance Imaging (pcMRI) data
in conjunction with fluid dynamics analysis to better understand Left Ventricular Diastolic
Dysfunction (LVDD). These goals were realized through the four Specific Aims detailed below.
The goal of these analyses was provide a framework for future biomechanical work to translate
interchangeably between engineering insights into physiological processes and clinical realities.

**Specific Aims**

The four specific aims of this dissertation were to:

- test an method for increased dynamic velocity range for DPIV measurements
- develop and compare schemes for calculating pressure data from experimental velocity fields
- conduct a physiologically-accurate high-resolution time-resolved DPIV study of stented
  arteries in-vitro
- study in-vivo the fluid dynamics of left ventricular diastolic dysfunction using pcMRI

**Scientific Contributions**

The contributions of this research included the following:

- provided the first comprehensive error analysis of the derivation of pressure fields from
  experimental planar velocity data (a technique quickly gaining in popularity) and identified
  the combination of smoothing approach and solver that provides the best accuracy
- developed a methodology for performing physiologically accurate DPIV studies in-vitro of
  one-to-one scale flow models of coronary circulation
- presented the first detailed experimental measurements of WSS in stented arteries and
  explored the fluid dynamics that give rise to them
• used pcMRI to quantify in-vivo the changes in fluid dynamics and pressure distribution in the left atrium and ventricle of patients with LVDD

It is expected that these developments (the improved tools and the individual experimental studies) will each produce one or more submissions to the archival literature.

BACKGROUND

One in five Americans suffers from Cardiovascular Disease (CVD). CVD is responsible for killing nearly one million people in 2006 and creating health-care costs of $430 billion per year [1]. CVD encompasses such diverse diseases as high blood pressure, coronary heart disease (CHD), and stroke, and heart failure. Deaths from CVD accounted for approximately 35.2% of all fatalities in 2005 [2], more than the next top 5 causes combined; similar statistics occur world-wide. Of CVD deaths the top three killers are CHD (52%), stroke (17%), and congestive heart failure (7%). It has been estimated that eliminating CVD would extend the lifespan of the average American by 7 years [2]. Clearly improvements in the prevention, diagnosis, and treatment of these diseases are one of the most acute and important health challenges we face today.

In order to achieve these improvements, it is necessary to understand the causes and development of these conditions, both biologically and mechanically. One factor that has been repeatedly implicated in the development of many cardiovascular diseases is alterations in the hemodynamic stresses created within the circulatory system. These can include both shearing stresses (as in coronary artery disease) and pressures (as in dysfunctions of cardiac function). Traditionally, direct measurement of these quantities has been difficult. This dissertation will develop extensions to existing state-of-the-art fluid velocimetry techniques in order to improve
the accuracy of existing measurements and to allow the extraction of additional information about the stresses that are caused by and drive fluid flows.

The objective is to improve our understanding of how these stresses are developed and altered, and how alteration in the normal flow patterns lead to decreased physiological efficiency or abnormal cellular environments. Because the field of cardiovascular biomechanics is so broad, this work concentrated on two specific cardiovascular conditions: coronary arteries following the implantation of intravascular stents (a treatment for CHD), and the left ventricle of the heart through various stages of diastolic dysfunction (a major player in CHF).

**Coronary Artery Disease**

Coronary artery disease has historically been among the leading causes of death in the USA, and the use of intravascular stents is a leading treatment for it. Traditional bare metal stents (BMS) are subject to high failure rates due to restenosis and thrombosis [3-10], which are believed to be influenced by abnormal wall stresses and disruption of the blood flow around the stent. Although the estimates of restenosis vary widely, rates of 10-30% over 6-12 months following the intervention are typical [11]. Drug-Eluting Stents (DES) were introduced as a remedy to these problems, and while initial trials were very promising [12], recent controversial results triggered extensive investigations to re-examine whether they are as safe and successful as first estimated [13-16]. In particular, DES have been implicated in higher rates of Late Stent Thrombosis (LST), which often manifests as excessive fibrin formation coupled with incomplete re-endothelialization. LST has been linked to increased risk of myocardial infarction and mortality [13].

One of the major hypotheses of this dissertation was, given the proven links between stent design, implantation strategy and patient outcome [5-8,9,17,18], and the proven links
between wall shear stress and neointimal formation, thrombosis, re-endothelialization, and restenosis [19-24], that a substantial part these two trends can be explained by altered WSS levels as a result of differing stent design and implantation configurations. Furthermore, despite the successes of DES in reducing restenosis rates, their tendency toward incomplete re-endothelialization means that stent-induced flow disturbances will play a role in the hemodynamics for a much longer period than would be expected in BMS.

While these flows can be simulated in CFD studies, a large number of confounding factors, including moving, compliant walls, complex stent geometries, and unsteady transitional flows make obtaining numerical solutions very challenging. Existing studies simplified stent strut geometry, idealized flow curves, ignored the phase offset between pressure and flow in the coronary circulation, or failed to consider compliant walls (one of the most common simplifications) [25-33].

In addition, high fidelity experimental investigations were non-existent until recently, for many of the same reasons that made computational studies difficult, and validation of the numerical models is difficult [26,30,34,35]. An additional difficulty for experimental studies is matching the physical scaling of the small coronary vessels, as it is often difficult to fully match dynamic similarity with a scaled-up model.

It was one of the goals of this work to measure these fluidic shearing stresses at the vessel walls, and understand the dynamics that give rise to variations in them for different stent designs and configurations. In a significant advancement from previous work, these tests featured commercially available stent designs implanted into compliant vessel models and subjected to realistic coronary waveforms, including offset pressure and flow curves. The setup and methodology needed to perform these experiments is detailed in Chapter 2 of this work. Flow
measurement was performed using digital particle image velocimetry (DPIV). Fulfilling this goal required the development of new experimental tools to accurately measure fluid velocities *in-vitro* over a much greater range of speeds than has previously been possible using traditional DPIV techniques. The techniques are described in detail in Chapter 3 of this dissertation, and the results of this investigation are presented in Chapters 4 and 5.

**Left Ventricular Diastolic Dysfunction**

The second condition of interest, Left Ventricular Diastolic Dysfunction (LVDD) is a disease in which the heart is unable to properly fill the chamber of the left ventricle before the systolic contraction pushes the blood out of the heart into the rest of the body [36]. It is frequently characterized by elevated filling pressures within the heart. Over 70 million people in the United States with high blood pressure are at risk for LVDD [1], and numerous studies have shown a link between LVDD and heart failure [37-40]. However, due to compensatory mechanisms early stage dysfunction can be difficult to diagnose. One survey of asymptomatic individuals in Olmsted County, Minnesota revealed that 21% have mild diastolic dysfunction and 7% have moderate or severe LVDD. Either condition was associated with increased risk for heart failure and was predictively correlated with death [2]. Despite numerous advances in clinical modalities the prognosis and diagnosis of LVDD has remained unchanged over the past 20 years; clearly, better tools and understanding of the disease are required. Correct diagnosis of the causes of heart failure is important to the proper treatment of the condition, and can be confounded by the presences of other factors such as heart disease and age-related changes that cause apparent filling abnormalities without actually reflecting an underlying ventricular dysfunction [36].
One hypothesis is that the development of this disease is linked to alterations in the pressure gradients between the left atrium and ventricle at different points during each heartbeat. It is believed that in normal hearts most of the work of filling the left ventricle during diastole (the relaxing or filling part of the heart cycle) is achieved by a suction effect created by the active relaxation of the myocardium and the consequent enlargement of the left ventricle [41]. In contrast, in unhealthy hearts this effect is diminished, and more of the work needs to be done by an active contraction of the left atrium during early systole [36], or an increased left atrial pressure during diastole [41]. This work attempted to validate this hypothesis and illuminate the dynamics that give rise to the observed gradients. Because technical and ethical problems exist with direct measurements of intra-cardiac pressures in-vivo, the pressure gradients were calculated from phase contrast Magnetic Resonance Imaging. A number of different algorithms have been proposed for such pressure calculations. To choose the most effective method for dealing with the experimental noise on the measured velocity fields, a detailed comparison and error analysis of these techniques was performed, as outlined in Chapter 6.

In-vivo, investigation of LVDD using quantitative velocity measurements has mostly been constrained to echocardiography, particularly color M-mode. Although the use of pcMRI is well established in the study of left ventricular flows, examination of the fluid mechanical concepts has been limited, especially in the context of LVDD. As of yet this quantitative tool has mostly been used to derive qualitative visualizations featuring vector fields, or blood element pathlines [42-48]. Additionally, available pathophysiological studies of the left ventricle using pcMRI appear to be limited to consideration of dilated cardiomyopathy [47, 49]. No previous pcMRI studies of LVDD appear to have been undertaken.
In response to this need, a study of eight total normal and diastolic dysfunction patients imaged at Wake Forest University Baptist Medical Center was performed. Clear differences were observed between the two groups of patients. Based on the calculated pressure fields and observed flow patterns, a hypothesis was formulated that attempts to explain these measurements in terms of known changes in the physiology and heart motions in patients with diastolic dysfunction. I believe this explanation to be a novel explanation of how the interaction of the heart muscle and the flow through the mitral valve interact to give rise to the changes commonly observed clinically in LVDD patients. These results are discussed in detail in Chapter 7 of this work.

APPENDICES

As the volume of data from the analysis of stented arteries was too great for convenient placement within the body of the work, a more extensive listing of many of the key measurements of WSS and OSI has been provided in an appendix.
REFERENCES


Chapter 2. Development of a System for High-Resolution Particle Image Velocimetry in Stented Compliant Vessels under Physiological Conditions.

John J. Charonko, Satya P. Karri, Jaime Schmieg, Santosh Prabhu, Pavlos P. Vlachos

ABSTRACT

A complete methodology for the testing of coronary stents in-vitro in compliant transparent vessels is developed and presented. The system is capable of creating physiologically-accurate pressure and flow waveforms featuring realistic phase offsets. The repeatability of these waveforms was tested, and the error on the desired Reynolds number was found to be around 5%. To successfully measure these flows using particle image velocimetry, the use of a light-intensified camera was required. Resolutions down to 1.74μm/pixel were achieved in the resulting tests. Wall shear stress and oscillatory shear index were calculated using a novel gradient estimation scheme using radial basis functions developed to minimize propagation of error from noisy flow fields. These methods were successfully applied to a set of nine different stent configurations, and sample results are presented.

Key Terms: Digital Particle Image Velocimetry, Coronary Flow Loop, Stents, Radial Basis Functions
INTRODUCTION

The goal of this effort was to quantify the hemodynamic behavior of the flow in coronary arterial models stented with different commercial stent designs. This was successfully accomplished through *in-vitro* measurements of the flow field within stented artery models. Physiologic flow conditions and arterial geometries were considered and the performance of the stents designs were compared using the well defined hemodynamic indices: Wall Shear Stress (WSS) and Oscillatory Stress Index (OSI) [1]. Previous research on stented arteries has shown that the effect of stent length and design are important to clinical outcome. Therefore, emphasis was placed on measuring their effects as well as on the effect of stent expansion diameter and stent overlap on the hemodynamics of stented arteries. We also considered the differences in hemodynamic performance between a coated and uncoated stent. The ultimate goal of this research was to develop correlations of the measured flow structures with clinically observed pathology using hemodynamic indices or provide the foundations for developing new parameters.

To accomplish these objectives Time-Resolved Digital Particle Image Velocimetry (TRDPIV) measurements within models of stented compliant arteries undergoing physiologically similar pulsatile flow were carried out. The goal was to correlate the resulting experimental data with clinically observed pathological response to the deployment of these stent designs. To fulfill these aims, it was necessary to develop several new techniques for estimating near-wall shear stress in experimental flows, and employ in novel fashion high-speed digital video cameras coupled with light-intensification hardware. The goal of this paper is to present in detail the methodology that was developed.
This work represents the first experiments to capture the spatiotemporal dynamics of coupled physiological flows of commercial stents, implanted in compliant vessels at a one-to-one scale, and successfully measure the resulting wall shear stresses in vitro.

METHODS

**Particle Image Velocimetry**

Digital Particle Image Velocimetry (DPIV) is a non-invasive method for optically quantifying the velocity field within a region of a given flow. It typically uses a high-power laser and digital video cameras to image the motion of reflective or fluorescent particles homogeneously seeded throughout the flow field of interest. For time-resolved measurements (TRDPIV) high-speed cameras (>1000 fps) and pulsing lasers are used. The basics of PIV have become well established, and review papers by Adrian [2] and Grant [3] provide an excellent background and introduction. The fundamentals of the digital implementation is established by the work of Willert and Gharib [4], Westerweel [5,6], and Huang et al. [7]. Another review, also by Adrian [8], summarizes some of the more recent advances in the field.

The particular implementation implemented in this project was developed in-house and employs specialized hardware and custom post-processing software that builds upon iterative, discrete window offset (DWO) methods developed to increase accuracy and spatial resolution [9, 10, 11, 12], along with adaptive central difference DWO algorithms [13] to further improve accuracy when performing TRDPIV on vortical, near-wall, and multi-phase flows. Further details of the system used have been previously presented elsewhere [14-16].

The method is capable of simultaneously providing excellent spatial and temporal resolution, with errors typically less than 5% on the measured velocities [17].
Several plots below show example flow fields from this study, specifically at the first strut on the proximal end of a Cordis Cypher™ stent for the Re=160 flow conditions. Complete details of the experimental conditions will be presented later. Features such as average flow profiles, the presence of vortical flow structures, and uneven reversal of the flow are visible in these figures. From this data can be extracted such quantities as vorticity (a measure of the rotation of the flow), fluid shear stress (a measure of frictional forces within the fluid), particle residence times, and many others.

**Wall Detection**

To obtain accurate measurements of fluid shear stress at the walls (WSS and OSI), it is important to know accurately the location of the wall in original images and relative to the calculated PIV vector field. Over the years, a variety of methods has been presented to works by extracting a region of an image and comparing it to some template containing a feature that the user wishes to locate. The two images are then cross-correlated, and the resulting field features a peak at the location of the best match.

For this experiment, the feature of interest is the boundary of the flow. Because the optical image filtering removed ambient background illumination and laser light, the images contained only the fluorescent tracers within the vessel lumen, and the target feature took the form of a step change in image intensity at the inner edge of the vessel wall. To increase the signal to noise ratio, the maximum intensity over a series of 20 images at each pixel location was used as the target image. A single sawtooth function with the step oriented the same direction as the vessel wall was selected as the best corresponding template. The more obvious choice of a top hat function was avoided because of the possibility that a rearward facing discontinuity elsewhere in the image would correlate more strongly with the backside of the top hat than the
Figure 2.1: PIV flow results for a Cypher™ stent. (Left): time averaged vector field, skipping every 2\textsuperscript{nd} vector vertically, and every 10\textsuperscript{th} along the x-direction. Color contours of vorticity are plotted in the background. (Right): Instantaneous streamtraces at $t/T_0=0.18$ (flow deceleration) colored with the longitudinal velocity magnitude at each point.

Figure 2.2: Close up of the flow behind the first strut in a Cypher™ stent at $t/T_0=0.14$. Every 2\textsuperscript{nd} vector is plotted, colored by the velocity magnitude.
wall boundary does with the front edge. The gradual slope on the backside of the sawtooth avoids this problem.

It was assumed here that each column of pixels in the target image contained at a single wall location. This allowed vertical position of the wall to be calculated in a single operation. A portion of the image containing the wall was extracted from the flow images, and a sawtooth template the same size, shape, and orientation was constructed. These two images were then cross-correlated. The wall position at each horizontal position could then be identified by searching for the height of the peak intensity in each column of the image. An example of this operation can be seen in Figure 2.3. Using this method, the average positions for both the top and bottom walls were identified in each block of 20 images over the entire sequence of PIV data, creating a time history of the wall locations at each horizontal location. One such time instant is shown in Figure 2.4.

Figure 2.4 shows a raw image of the stented region with color-encoded intensity and the axis presenting the total pixel count in each direction. As can be seen in the figure, areas that are blocked by the stent struts yielded poor wall detection. However, this did not affect the analysis since these regions were manually identified and removed from consideration in the later WSS and OSI calculations.

For later tests (described in Chapter 5), this method was replaced by a CUMSUM test for change point analysis [18] based on the local value of the horizontal standard deviation of image intensity [19]. The assumption here is that the presence of the particles will increase the variance of the image signal, while smooth background illumination will not. The advantage of this strategy over the correlation-based approach is that it avoids false matches with areas of diffuse glow near the wall.
Once the time history of the wall locations is determined, a smoothing spline is fitted to the data in order to minimize the effect of small regions where the wall location was incorrectly determined. In addition, the spline fit yields an analytical expression for the wall location as a function of time. This function can be interpolated in time between the blocks of 20 images back to the individual image snapshots, and the direction of the wall normal at each point in space can be extracted. This wall normal is required to calculate the WSS component of the strain rate tensor, as described in a later section.

Finally, the vessel diameter can be calculated from these wall splines over the visible length at each time instant recorded. When plotted, this gives an image similar to that shown in Figure 2.5. In this example, the dataset corresponds to the proximal end of a stent, and
Figure 2.4: Trace of identified wall positions for one time instant. The top and bottom walls are marked in black, and the image is shown in false color for better contrast.
encompasses a single cycle of pulsatile flow. In the figure we observe that before the stent, the vessel is approximately the 3mm in diameter, and fluctuates noticeably with the incident pressure wave. The beginning of the stented region has a nearly constant diameter, about 3.2 mm wide. Between strut rings, some pulsatility is still apparent, but less compared to the unstented region. If desired, this information can be compared with synchronized measurements of intravascular pressure to back-calculate an effective modulus of elasticity for the vessel-stent system [20]. Performing such a calculation led to an estimate of 1 MPa for the vessel material, and an average value near the mid-point of 6.7 MPa, though local values varied between 3 and 100 MPa [21].

Figure 2.5: Time history of the vessel diameter vs length for a region near the proximal end of the stent.
Radial Basis Functions for Velocity Gradient Estimation

The next step in the calculation of wall shear stress is the estimation of the velocity gradients near the walls. There are many different schemes available to extract derivative estimates of discretely sampled fields, each with their own strength and weaknesses. However, the presence of noise in experimental data presents a special challenge, defeating many otherwise appealing methods designed for use with computational data. To overcome this difficult, Karri et al. developed a novel gradient estimation scheme based on radial basis functions. The complete details were published in reference [22].

In brief, using one of a variety of radial basis functions, a surface fit could be calculated for each velocity field and gradients are derived analytically from that surface at each point. The best methods were those which minimized the surface roughness estimator given in equation 1.

\[
E(f) = \int_{\Omega} \left[ \left( \frac{\partial^2 f}{\partial x^2} \right)^2 + 2 \left( \frac{\partial^2 f}{\partial x \partial y} \right)^2 + \left( \frac{\partial^2 f}{\partial y^2} \right)^2 \right] dxdy
\]  

(1)

Specifically, the two functions that satisfied this criterion were Thin Plate Splines (which satisfied equation 1 exactly), and the Generalized Multiquadric functions when paired with an interactive, discrete minimization of equation 1.

From the methods developed in that work, the generalized multiquadratic radial basis functions (GMQ-RBF) were selected for the wall-gradient estimation of the PIV data of the data presented in Chapter 4, and the Thin Plate Splines for the analysis in Chapter 5. At each wall location, a 5x5 vector grid with one of its edges centered on that point was used to derive a surface fit. The obtained function was then differentiated analytically to obtain the wall gradients. This method has been demonstrated to be more resistant to experimental error than
traditional finite differencing and polynomial interpolation schemes [22], both of which were tried here and yielded qualitatively poorer results.

**Velocity-Based Hemodynamic Parameters (WSS and OSI)**

**Estimation of Wall Shear Stress (WSS)**

Computation of wall shear stress (WSS) is straightforward in the case of straight walls, where the strain rate in equation 2 can be directly used to estimate WSS as given by equation 3.

\[
\dot{\varepsilon}_{ij} = \left[ \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right] \quad (2)
\]

\[
WSS = \mu \dot{\varepsilon}_{12} \quad (3)
\]

In the case of curved walls as shown in Figure 2.6, the location of wall is detected as described in the “Wall Detection” section above. Analytical surface fits using RBFs can be used to estimate strain rates at the wall locations, even in between sampled velocity nodal values. Estimation of WSS from these gradients involves transformation of these strain rates to a co-ordinate system oriented along and transverse to the wall, given by equation 4. For the current experiment, we used a 5x5 interpolation grid to prevent the corruption of the data from locations that were blocked by the stent and also to reduce the computational time.

\[
\dot{\varepsilon}_{mn} = a_m a_n \dot{\varepsilon}_{ij} \quad (4)
\]

\[
WSS = \mu \dot{\varepsilon}_{12} \quad (4)
\]

Where

\[
a_{ij} = \begin{bmatrix} \cos \theta & \sin \theta \\ -\sin \theta & \cos \theta \end{bmatrix} \quad (5)
\]
Figure 2.6: Curved wall given by solid line within the interrogation area, the blue points indicate discrete points where velocity is estimated using PIV. The green arrow is the wall normal vector, and its angle from the vertical is measured by $\Theta$.

**Oscillatory Shear Index (OSI)**

Oscillatory shear Index (OSI) is used to evaluate the oscillatory effects of flow which has been shown to correlate with atherosclerotic lesions [23]. OSI is defined by equation 6,

$$OSI = \frac{1}{2} \left( 1 - \frac{1}{T} \int_0^T \tau_w^+ dt \right) \frac{1}{T} \int_0^T |\tau_w^-| dt,$$

where $T$ is the period of the cycle, and $\tau_w$ is the instantaneous WSS vector. The equation calculates a “total mean” of the shear experienced at a particular location, regardless of direction, and compares it to the true mean value, including the directionality. OSI values range between 0 and 0.5, with zero indicating a region in which the instantaneous shear is in the direction of the average shear 100% of the time (0% reversal), and a value of 0.5 indicating that 50% of the total shearing exerted on the wall was in either direction (the mean shear will be zero because the forward and backward shears were perfectly balanced over a single cycle).
Propagation of Error on WSS and OSI Measurements

Based on the error analysis shown above for the MQ RBF functions for gradient measurements on a 5x5 grid, it was estimated that the average total error on each measurement will be approximately 15%, of which the dominant portion will be random (as opposed to bias) errors. While this level is certainly acceptable, it does make assessing small differences in the WSS between the various stent configurations and positions difficult. However, the large amount of variability in the WSS patterns over time and space makes direct comparison of individual measurements less useful. Accordingly, in many cases temporal and/or spatial averaging was used to condense this information into smaller data sets that are more amenable to comparison. This also had the advantage of reducing the effect of the random measurement errors.

To determine the error level of these averaged quantities, simplified WSS profiles as a function of time and space were assumed. As shown in Figure 2.7, the WSS was assumed to vary sinusoidally over each period, with the fixed amplitude and offset from zero defined in Table 2.1. The magnitudes were chosen to approximate representative WSS curves measured by this study (see the Results sections for further details). For simplicity, it was assumed that the WSS profile was not a function of position along the vessel wall, a condition that was often approximately satisfied by the actual data. The sample size used for the averaging operations was based on the typical spatial size of the inter-strut regions seen in the study, and the time samples reflect the actual period of measurements.

From these assumptions, it was possible to use standard error propagation formulas to determine the total RMS error remaining in the calculated averages. Here the following form was used (in index-summing notation)
\[
(\delta F)^2 = \left( \frac{\partial F}{\partial n_i} \right)^2 (\delta n_i)^2
\]  \hspace{1cm} (7)

This equation gives the dependence of the RMS error, \(\delta F\), on the RMS errors of the individual measurements, \(n_i\), that are used in the computation of \(F\). The sensitivity of the final result on each of these errors, \(\delta n_i\), is determined from the partial derivative of \(F\) with respect to variations in each of its component variables. It is clear that when using this form, if the computation can be written as an explicit function of its independent components, and an

![Assumed WSS profile over time for the Re=160 cases.](image)

**Figure 2.7:** Assumed WSS profile over time for the Re=160 cases. It was assumed that the true WSS values did not vary as a function of position.

<table>
<thead>
<tr>
<th>Reynolds number</th>
<th>WSS(_{\text{min}}) (dynes/cm(^2))</th>
<th>WSS(_{\text{max}}) (dynes/cm(^2))</th>
<th>Spatial sample size, Nx (points)</th>
<th>Time sample size, Nt (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>-10</td>
<td>40</td>
<td>30</td>
<td>257</td>
</tr>
<tr>
<td>300</td>
<td>-10</td>
<td>60</td>
<td>30</td>
<td>150</td>
</tr>
</tbody>
</table>

**Table 2.1:** Parameters chosen for error propagation study of WSS averages
estimate of the errors on each are known, a final error level can be easily computed without recourse to the Monte-Carlo type analysis that was needed for testing the gradient estimation schemes.

Applying this method to this problem, the averaging operations in space and time were defined, respectively, as

\[
WSS_x = \frac{1}{N} \sum_{i=1}^{N_x} WSS(x_i) \quad (8)
\]

and

\[
WSS_t = \frac{1}{N_t} \sum_{i=1}^{N_t} WSS(t_i) \quad (9)
\]

From these equations, it can be seen that the sensitivity of the calculated averages to the errors on the individual measurements, \( WSS(x_i) \) or \( WSS(t_i) \) depends only on the number of points used in the average, and is obtained by the partial differentials

\[
\frac{\partial WSS_x}{\partial WSS(x_i)} = \frac{1}{N_x} \quad (10)
\]

and

\[
\frac{\partial WSS_t}{\partial WSS(t_i)} = \frac{1}{N_t} \quad (11)
\]

Finally, substituting equations 8-11 into equation 7, and simplifying, the following expressions were obtained.

\[
\left( \delta WSS_x \right)^2 = \sum_{i=1}^{N_x} \left( \frac{\partial WSS_x}{\partial WSS(x_i)} \right)^2 \left( \delta WSS(x_i) \right)^2 = \frac{1}{N} \left( \delta WSS(x_i) \right)^2 \quad (12)
\]

\[
\left( \delta WSS_t \right)^2 = \sum_{i=1}^{N_t} \left( \frac{\partial WSS_t}{\partial WSS(t_i)} \right)^2 \left( \delta WSS(t_i) \right)^2 = \frac{1}{N_t^2} \sum_{i=1}^{N_t} \left( \delta WSS(t_i) \right)^2 \quad (13)
\]
To obtain relative error levels using these equations, it was assumed that conservatively the relative RMS error on each of the WSS measurement profiles, as defined by Table 2.1 and Figure 2.7, was 20% (slightly higher than is believed to be true for this project). The resulting profiles and absolute error levels could then be substituted into equations 12 and 13. The procedure was then repeated for simultaneous spatial and temporal averaging (the order of these operations is interchangeable for the purposes of this calculation). The results of these analyses are reported in Table 2.2, normalized by the time-averaged WSS level for each Reynolds number (25 and 35 dynes/cm²).

<table>
<thead>
<tr>
<th>Reynolds number</th>
<th>$\delta WSS_x$</th>
<th>$\delta WSS_t$</th>
<th>$\delta WSS_{x,t}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>1.93%</td>
<td>0.19%</td>
<td>0.02%</td>
</tr>
<tr>
<td>300</td>
<td>2.40%</td>
<td>0.38%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

As can be seen from the table, the initial per-measurement random error of 20% has been reduced to negligible levels. This means that any remaining error in the reported average WSS values will be primarily systematic in nature. Because the multi-quadratic gradient methods have very low bias errors, this leaves the PIV displacement measurement as the primary source of errors. Bias errors for 2nd-order central difference DWO methods as were used here are typically on the order of 5% of the true displacement. Consequently, total errors on the averaged WSS measurements reported hereafter should be on the same order. A similar analysis holds for the oscillatory shear indices (OSI) reported below, as those values are also calculated by averaging the individual WSS measurements over time.
EXPERIMENTAL DESIGN

Flow Loop Layout and Monitoring

Testing was conducted in an artificial flow loop designed to simulate a wide range of coronary and peripheral arterial conditions. The initial setup, design, and construction of this flow loop was conducted by Satya Karri, while the customization of this apparatus for the specific conditions of this test was performed jointly. Similar designs have been used in previous work conducted by our group [24-29], but for this project a greater control of the conditions was required to insure repeatedly between the large number of different cases (over 70 individual runs were required in order to acquire the complete test matrix).

A schematic of the flow loop design is shown in Figure 2.8. The setup consisted of a computer controlled variable speed gear pump IsmaTec MV-Z/DDZ, a reservoir chamber, a compliance / pressurization chamber, a test section mount, a computer-actuated solenoidal clamp valve, and a pressure wave damping chamber. The loop is a sealed to allow it to be pressurized to physiological levels. The compliance chamber is partially filled with the working fluid, and serves two roles within this setup. The first is to allow adjustment of the pressure within the loop; the second is simulate the capacitance of the systemic circulation, absorbing pressure fluctuations and storing excess fluid until the clamp valve opens. The chamber is connected to a pressurized air supply via a relief valve. By varying the inlet pressure, the relief valve setting, and the fluid level within the cylinder, the maximum and minimum pressure levels within the test chamber over one simulated heartbeat can be adjusted to any desired level. As the pump is activated, fluid is drawn from the reservoir, which has a small amount of air remaining. This air expands, creating a partial vacuum. Because the clamp valve is closed when the pump is running, the chamber stores the fluid and the air inside the compliance region is compressed,
raising the pressure in the test section. When the valve opens, the combination of the low pressure in the reservoir and high pressure in the compliance chamber drives the fluid through the test section even as the pressure drops. The offset between the pressure and the flow rate is one of the main characteristics that distinguish coronary blood flow from that in the systemic circulation.

In order to duplicate blood flow in the large coronary arteries, the level of fluid in the two chambers, the flow pattern and rate of the gear pump, and the duration and offset of the clamping valve action relative to the pump are adjusted. These levels were determined empirically at the beginning of the project, and maintained throughout testing to help insure consistency of the flow patterns between the different trials. Further details of the exact conditions used in this project are given below.

Figure 2.8: Schematic of flow loop design
Figure 2.9: Images of setup.

(Top left): Photo of entire setup before installation of motorized traverses for alignment of vessel
(Top right): Data acquisition and control computers (laser controls not shown)
(Bottom left): 2 axis motorized traverse for alignment, with 2 axis micro-traverse for focusing
(Bottom right): Standard DPIV camera is replaced by IDT X5i light-intensified camera
The coronary stents being tested were inflated into simulated vessels constructed of silicone (Sylgard 184, DOW Corning). The vessels have been previously tested to have similar compliance as arteries [21]. The Sylgard was mixed in a ratio of 14:1 by mass of elastomer base to the curing agent to yield a modulus of elasticity of about 1 MPa, and were constructed via a casting process to have radius and diameter matching the larger coronary arteries (see Table 2.3). The test section consisted of an optically clear acrylic box with adjustable mounting points for these vessels to account for different lengths. To simulate the axial tension found in physiological arteries, each vessel was stretched to 5% strain when mounted, based on their original length. The mounting points were interchangeable so that their inner diameter matched the inner diameter of the vessel currently in use.

<table>
<thead>
<tr>
<th>Nominal Size</th>
<th>Inner Diameter</th>
<th>Outer Diameter</th>
<th>Wall Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 mm</td>
<td>2.9845 mm</td>
<td>3.8100 mm</td>
<td>0.413 mm</td>
</tr>
<tr>
<td>4.0 mm</td>
<td>3.9878 mm</td>
<td>4.7625 mm</td>
<td>0.387 mm</td>
</tr>
</tbody>
</table>

The working fluid within the flow loop was a mixture of 60% glycerin and 40% water maintained at room temperature. Use of this mixture had two purposes. The first and most important was that it approximately matches the kinematic viscosity ($\nu = 3.77 \text{ m}^2/\text{s}$) and density ($\rho = 1100 \text{ kg/m}^3$) of human blood. The non-Newtonian properties of blood were not considered. Secondly, the curvature of the vessel walls can introduce significant optical distortion due to the mismatched indices of refraction of the various materials in the optical path between the camera and the focal plane. Since the test section walls are perpendicular to the path, they do not contribute to the problem; instead, the main source of distortion is the interface between the test section interior and the vessel, and between the vessel and the working fluid in the lumen. By
convenient coincidence, the index of refraction of the glycerine solution nearly matches the index of refraction of the Sylgard vessels. By filling the test section outside the vessel with the same working fluid as inside, distortions are nearly eliminated. The exact glycerin to water ratio of the external fluid was further tuned to remove as much remaining refraction as possible. Without proper index matching, light is bent while traveling through the vessel, and accurate measurements are impossible. In fact, near the top and bottom of the vessel, the interior of the vessel may not be visible at all, and these are precisely the regions we are most interested in. However, this procedure removed almost all visible distortion from the images, and allowed clear imaging of features up to the inner wall of the vessel.

In addition to Particle Image Velocimetry, the test loop was instrumented with an ultrasonic flowmeter and two pressure sensors. The flowmeter (Transonic Systems, T110 Lab Tubing Flowmeter) was installed between the test section and the compliance chamber, and was used to calibrate the average flow rate for each trial. The exact instantaneous flow rate within the vessel was calculated from the PIV data during post processing. The pressure sensors were attached via fine gauge flexible tubing to the vessel mounting points within the test section to obtain readings as close to that within the vessel as possible. The upstream sensor (Omega PX302-15GV) measured the fluid pressure over a range of 0-15 psi. The downstream sensor (Setra 0-2 psi differential, part# 2301002PD2F2DB) was intended to measure the relative pressure between the upstream and downstream ports, but began malfunctioning near the beginning of testing. Existing data from the second sensor was deemed unreliable, and no further measurements were made.
Particle Image Velocimetry Setup

To perform DPIV, the flow was seeded with 7µm fluorescent polymer particles provided by Duke Scientific (Catalog #36-2D). These particles were selected to fluoresce in the red wavelengths under excitations from green light such as that provided by our laser. The region of interest was illuminated by 532 nm light from a high intensity, high frequency pulsing laser purchased from Dantec Dynamics (Lee Laser LDP-100MQG). This laser is capable of operation at speeds above 10kHz, with pulse energy above 10 mJ/pulse at lower speeds, and average power of around 45 W at optimum firing conditions. For this experiment, the light intensity was approximately 5 mJ/pulse, and the laser was fired in pairs of equal intensity at a rate of 300Hz to match the camera frame rate. The intra-pair delay time was adjustable to match the flow conditions (see Table 2.4).

Table 2.4: Laser pulse separation for the different flow rates and vessel diameters

<table>
<thead>
<tr>
<th></th>
<th>D = 3.0mm</th>
<th>D = 4.0mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re = 160</td>
<td>50 µs</td>
<td>70 µs</td>
</tr>
<tr>
<td>Re = 300</td>
<td>25 µs</td>
<td>45 µs</td>
</tr>
</tbody>
</table>

The beam was conducted to the test section by a series of high-intensity laser mirrors and lenses. The beam was opened into a fan via a cylindrical lens, and refocused in the out-of-plane direction using a spherical lens set before the cylindrical lens to achieve the smallest out-of-plane thickness for laser sheet possible over the entire ROI. These optics can be seen in the upper left image in Figure 2.9, and the regions of interest chosen for this experiment will be discussed later in more detail.

The flow was imaged using an IDT (Integrated Design Tools) X5i light-intensified camera (Figure 2.9, lower right). The full-frame sensor size was approximately 4 megapixels,
and the camera had a frame buffer of 4 GB. Using a real-time image compression feature provided by the camera hardware and a slightly smaller resolution (1708x2048), the camera was set to acquire images at a rate of 300 image pairs per second. With the camera’s built-in dual pulsing mode, the intra-pair delay time is on the order of 10 ns, much less than the separation time of the two laser pulses within each pair. Exposure times for the two frames were set sufficiently long to insure capture of the laser light pulses. Given the size of the frame buffer, 2570 images, or 1285 pairs, could be acquired per test case, allowing multiple periods of the pulsatile flow conditions to be recorded.

The intensifier also needed to be separately gated (turned on) only for the short period surrounding each laser pulse. This gating period was set to several microseconds in duration to insure that each pulse was correctly captured in each frame. With the gating signal on, the intensifier hardware captures and amplifies the incident light. After the gating signal is switched off, the light produced by phosphor coating of the intensifier rapidly dies out with a decay constant around 1 µs, but no new information is passed to the camera sensor. The camera sensor is never exposed directly to the light gathered by the camera’s lenses, and only records the light produced while the intensifier is active or during the brief decay following. In fact, the exposure time of the camera was set to significantly longer than the intensifier gating time to capture the most possible residual radiation from the phosphors; since the intensifier is off, this does not result in streaking, but does increase the signal to noise ratio of the final images.

The firing of the laser, digital shuttering of the camera, and gating of the intensifier were controlled and synchronized by a single computer with an installed high speed timed digital signal generator board from National Instruments (PCI-6251). Control signals were generated simultaneously and sent to all devices, and could be individually adjusted to account for the
different activation delays of each component. For example, the camera and intensifier activate almost immediately after triggering, while the laser takes approximately 4 µs to generate a laser pulse after receiving each control signal. The camera also emits a timing synchronization pulse that can be used to determine when the camera acquires each image. This signal was recorded simultaneously by the same hardware responsible for recording the pressure and flow rate measurements so that they could be synchronized after the experiment with the PIV velocity fields. Additionally, the beginning of each data acquisition was synchronized to and triggered by the solenoid clamp’s drive signal so that each data set began at an identical point within the flow cycle.

In order to achieve the required magnification, a series of extension tubes was mounted between the camera body and the camera lens, which was mounted using a reversing ring to further boost magnification (normally a camera lens shrinks large objects to fit on the sensor or film; flipping the lens reverses this effect). These had the effect of reducing the field of view without introducing optical distortion, but also substantially reduced the incident illumination falling on the sensor. For larger fields of view, this is not usually an issue, but for this experiment the magnification required was very high, so the light gathered by the lens system is much smaller. This is one of the reasons a light intensified camera was necessary.

A dichroic filter was used in front of the camera optics to improve the signal to noise ratio of the acquired images. The filter choice was optimized with a cutoff frequency midway between the green laser light and the red light from the particle fluorescence. Reflected light from the setup, stent struts, and image background was rejected, while the light emitted from the illuminated particles was allowed to travel to the intensifier. This was also very important to avoid damage to the intensifier, since the wall reflections are much brighter than the
fluorescence. Without the filter, adjusting the gain to optimally view the particles will cause these reflections to burn out those portions of the intensifier, but reducing the gain to prevent this leaves the particles too dim to image. Use of the filter allows the particles to be viewed without the risk of damage to the camera. Figure 2.10 shows an example of the dramatic improvement in image quality that results from using the filter. A complete outline of the camera optics can be seen in Figure 2.11.

![Figure 2.10: Example raw camera images. (Left) Without filtering, reflections from the laser wash out the particle images and obscure large portions of the flow. (Right) With the filter in place, particles are clearly visible, and the struts and vessel wall do not affect the PIV results. Photos by John Charonko (2007).](image)

![Figure 2.11: Schematic of camera setup used for experiment. The laser light is removed by the filter, while the light from the fluorescent particles travels to the intensifier and is captured by the digital sensor.](image)
To focus the optics, and align the field of view with the region of interest, the camera was mounted on a 2-D micro-traverse system. This apparatus was further attached to a large-scale computer-controlled 2-D traverse system to make gross adjustments to the camera alignment relative to the test section and stent locations. This system can be seen in the two lower images in Figure 2.9.

Image pairs were processed into velocity vectors with an aggressive multi-pass 2nd order central difference discrete window offset algorithm [9-13]. Cross-correlations were computed by use of an FFT-based algorithm for speed. The flow was sampled on a grid with 8x8 pixel spacing, yielding a field of 255x175 vectors (44625 in total) per image. To capture the initial displacement of the flow tracers, for each grid point an initial window size of 128x32 pixels was used (stretched in the primary flow direction. Subsequent passes iteratively reduced the window size in the pattern 64x32, 32x16, and finally 16x16 pixels. For each new pass, the displacement was checked against the previous iterations results for consistency. If the check failed, the window was enlarged to capture more particle images at the current window offset, and the iterative process resumed from that point. If no agreement could be achieved, the process stopped on the current window size, meaning the final vector field consisted of the optimum window size for the given flow field and seeding conditions. Poorly seeded regions tended to stop on larger window sizes, while slow flow or higher shear regions with good seeding terminated at the 16x16 pixel windows. This process was repeated at each grid point in the final vector field, and each measurement was independent of the results of all other vector calculations.

Following computation of each vector field, the resulting fields were validated to remove outliers using a multi-pass mean-based validation algorithm. For each vector in the flow field,
the mean of the surrounding 7x7 block of vectors was computed, and if the displacement of center vector fell outside of a prescribed number of standard deviations of the mean, it was replaced by that mean. The cutoff began at five standard deviations, and was decreased iteratively by 75% at each following pass for 6 total passes, or until the variation fell below a single standard deviation. This method was judged to provide the optimum balance between the correct detection and removal of outliers, and the preservation of correct measurements.

For the analysis in Chapter 5, this processing regime was replaced by a robust phase correlation [30], and paired with a multi-frame correlation strategy, as will be described in Chapter 3.

**Selection of Stent Configurations**

Nine different stent configurations were selected for testing the effect of several different design parameters commonly encountered in practice, including size, shape, and manufacturer. All but one of the stents tested were drug-coated. Table 2.5 outlines these selections.

Abbott’s XIENCE™ drug-eluting stent was selected as the base reference configuration to which the others would be compared. The nominal size for this stent was 3mm in diameter by 18 mm long. This stent size will be referred to as 3x18 in the remainder of this report; the other stents will be designated similarly. The stents were deployed via their attached catheters from a port upstream of the test section, and were guided into place at the midpoint of a fresh vessel for each new configuration. Each stent was inflated according to manufacturer’s recommendations for usage to a diameter 10% greater than the nominal vessel size (3.3mm for the 3mm stents, and 4.4 mm for the 4mm stent), unless noted otherwise, in order to more closely match clinical practice. This inflation was performed using water and an Abbott Vascular endeflator. The vessels were each constructed to have an inner diameter equal to the nominal diameter of the
stent under consideration (see above), but no effort was made to model the influence of atherosclerotic plaque deposits as it was deemed outside the scope of this investigation.

The first parameter examined was the effect of strut layout and design. To test this, in addition to the Abbott XIENCE™ stent, three other stents of similar size from different manufacturers were selected. These were Boston Scientific’s TAXUS® Liberte™, Medtronic’s Endeavor™, and Cordis’s Cypher® Stent. The size of each stent was selected to match the XIENCE™ 3x18 stent as closely as possible, as indicated by Table 2.5.

The second parameter examined was the effect of stent length. For this test, the flow measurements from the XIENCE™ 3x18 stent in section 1 were compared to the flow observed in the same XIENCE™ in a 3x28 configuration.

Table 2.5: List of the 10 different stent configurations tested, along with design features under examination

<table>
<thead>
<tr>
<th>Section</th>
<th>Stent tested</th>
<th>Stent size (diameter x length)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1</td>
<td>XIENCE™</td>
<td>3 mm x 18 mm</td>
</tr>
<tr>
<td>Effect of Stent Design</td>
<td>TAXUS® Liberte™</td>
<td>3 mm x 20 mm</td>
</tr>
<tr>
<td></td>
<td>Endeavor™</td>
<td>3 mm x 18 mm</td>
</tr>
<tr>
<td></td>
<td>Cypher®</td>
<td>3 mm x 18 mm</td>
</tr>
<tr>
<td>Section 2</td>
<td>XIENCE™</td>
<td>3 mm x 28 mm</td>
</tr>
<tr>
<td>Effect of Stent Length</td>
<td>XIENCE™</td>
<td>3 mm x 18 mm (3.75mm expansion)</td>
</tr>
<tr>
<td>Section 3</td>
<td>XIENCE™</td>
<td>4 mm x 18 mm</td>
</tr>
<tr>
<td>Effect of Stent Diameter</td>
<td>XIENCE™</td>
<td>3 mm x 18 mm (two stents, 4mm overlap)</td>
</tr>
<tr>
<td>Section 4</td>
<td>XIENCE™</td>
<td>3 mm x 18 mm</td>
</tr>
<tr>
<td>Effect of Stent Overlap</td>
<td>VISION™</td>
<td>3 mm x 18 mm</td>
</tr>
<tr>
<td>Section 5</td>
<td>VISION™</td>
<td>3 mm x 18 mm</td>
</tr>
</tbody>
</table>
To test the effect of the third parameter, stent diameter, two configurations were compared to the baseline case. The first examined the effect of an extreme overexpansion of the 3mm stent to a diameter of 3.75 mm. This will sometimes occur in practice to ensure re-opening of the target vessel. This configuration will be referred to as XIENCE™ 3.75x18 case. The second configuration examined the difference between flow in a 3 mm stented vessel, and a larger 4 mm vessel. Both conditions were compared to the XIENCE™ 3x18 results.

In practice, doctors often use two or more overlapped stents to treat a single large lesion or multiple closely spaced lesions. To test the effect of this procedure, two XIENCE™ 3x18 stents were implanted in a new artificial vessel with a desired overlap of approximately 4 mm. In accordance with clinical practice, the distal stent was inflated first, and then its catheter was deflated and withdrawn. The proximal stent was then inserted as close to the target overlap position as possible, and inflated to create in effect a single stented region of approximately 32 mm in length. The actual overlapped region was measured post-deployment to be approximately 2.75mm long, or two periods of the strut-link-strut pattern. The struts for the overlapped upstream stent fell just distal to each matching strut on the downstream stent. Additionally, the XIENCE™ and VISION™ stent designs have threefold circumferential symmetry, with 3 links joining each strut ring, and this each set of three links is rotated 60 degrees relative to the previous set as you traverse downstream. For the overlapping section, the gaps in this three link pattern for the downstream stent aligned nearly exactly with the links in the matching section of the overlapped stent. The relative orientation of the struts and links in this overlapped region is depicted schematically in Figure 2.12 below, though the figure only depicts a single overlapped period, instead of two. This configuration was compared to the XIENCE™ 3x18 and XIENCE™ 3x28 cases, and will be referred to as 2-XIENCE™ 3x18.
The final parameter tested was the effect of the drug coating. To examine this, an Abbott VISION™ 3x18 stent was selected to compare to the previously tested XIENCE™ 3x18 stent. Both stents share an identical strut design and layout; the only difference is the presence of an additional 10 um drug-impregnated polymer coating on the XIENCE™ stent. The VISION™ stent has bare metal struts.

Figure 2.12: Diagram of the relative positions of the various ROI along the stent lengths.

**Regions of Interest**

For each of the 20 combinations of stent configuration and flow rate, the PIV was used to measure the velocities just inside the stent inlet at the proximal end, near the center of the stent, and just beyond the final strut at distal exit. These three locations will be referred to as the upstream, midstent, and downstream positions, or US, MS, and DS, respectively. Additionally, the two longer stent configurations, the XIENCE™ 3x28 and the 2-XIENCE™ 3x18, were also tested at a fourth location along the stent length, and consequently the midstent locations are referred to as midstent 1 and 2, or MS1 and MS2. Figure 2.12 shows cartoons of the relative
locations of these positions. For the XIENCE™ and VISION™ stent configurations the MS and MS1 positions were selected to be the same distance from the proximal end of the stent in each case. Additionally, for the XIENCE™ 3x28 stent, the MS2 position is very nearly the same distance from the inlet as the DS positions are for the 3x18 configurations. For the 2-XIENCE™ 3x18 case, the MS2 position was selected to be distal to the final strut in the overlap region, and is very near the MS2 position for the 3x28 configuration. For the other manufacturers’ stents, the MS position was selected as near to the center of the stent as possible given the constraints of the strut layout, and should be comparable to the MS positions for the XIENCE™ stents.

At each of the positions, the camera was oriented to image a region 2.44x3.56 mm in size (for the 3mm vessels), spanning the entire diameter of the vessel. Given an image size of 2048x1408 pixels, this required a resolution of 1.74 µm/pixel (4.02× magnification). To image the 4 mm diameter vessels, less magnification was used (2.31 µm/pixel or 3.03×) imaging a larger region of interest (ROI) 3.25x4.75mm in size. This ROI is shown schematically for the upstream 3mm case in Figure 2.13, outlined in green. The figure also shows in blue for comparison some of the ROI suggested in the original proposal for this project using older cameras. These cameras had a smaller sensor size (1024x1280), consequently allowing only smaller ROIs, and lacked the light intensifier possessed by the camera that was actually used, resulting in poorer image quality. As can be clearly seen, the light-intensified camera allowed imaging of a much larger ROI with improved image quality.

For each ROI, the camera and laser sheet were adjusted to insure visibility of a region immediately downstream of one of the stent’s struts. Because of the layout of the struts, it was generally possible to image only one such position for a particular ROI, and due to obstruction
by adjacent struts, only the upstream or downstream position could be chosen. For consistency, the downstream position was chosen in each ROI.

Figure 2.13: Schematic of relative size of ROI versus a 3.0 mm diameter vessel
Additionally, the laser beam was aligned with the stent struts in such a way as to achieve as much similarity between configurations as possible. These positions are diagrammed in Figure 2.14, with the laser beam marked in green, and the region where WSS was measured circled in red. The camera imaging plane was perpendicular to the view show in the figure. For the XIENCE™ and VISION™ stents, the ROI was selected so that a strut crossed the imaging plane aligned with a link to the previous ring of struts. On the TAXUS® Liberte™, the imaging plane crossed a corner of the strut pattern in such a way as to have a section of strut nearly perpendicular to the flow lie directly upstream from that corner. For the remaining stents, no comparable features existed, and because of imaging constraints it was only possible to view behind a strut midway between two bends, aligned so the strut was angled away from camera as you traverse downstream.

**Figure 2.14:** Location of the ROI for each manufacturer’s stent relative to the design features of that stent. A representative segment of each stent is shown, with the location of the laser plane marked in green, and the region where WSS was measured marked by a red circle. The direction of flow is from left to right.
**Experimental Flow Conditions**

Each of these 10 configurations was tested at two different flow conditions selected to correspond to resting and exercise conditions, as defined by a Reynolds number (computed based on average flow rate and original vessel diameter), beat frequency, and pressure range. The Reynolds number, $Re$, is computed as

$$Re = \frac{U_{avg} D}{\nu}$$  \hspace{1cm} (14)

with $\nu$ defined as the kinematic viscosity, $D$ as the vessel diameter, and $U_{avg}$ as the velocity average across the cross section over one period.

Matching the Reynolds number between the 3 and 4 mm vessels required in an increased flow rate for the larger vessel, but as the physical frequency was held constant, the non-dimensional frequency (Womersley parameter) increased as well. Here, the Womersley parameter, usually referred to by $\alpha$, is defined as

$$\alpha = D \sqrt{\frac{\omega}{\nu}}$$  \hspace{1cm} (15)

with $D$ and $\nu$ defined as before, and $\omega$ being the heart rate in radians.

The simulated heart rate would have had to be decreased to hold the Womersely parameter constant, and it was decided that it was more physiologically relevant to leave the rate fixed instead. Table 2.6 outlines the chosen Reynolds numbers, frequencies, and pressure ranges for the two conditions, as well as the corresponding average flow rate and velocity calculated for each of the two vessel sizes at their nominal diameters. The resting conditions will typically be referred to as the Re=160 or Re160 case, while the exercise conditions will be given as Re=300 or Re300.
The exact flow waveform chosen was qualitatively based on a RCA waveform provided by Abbott Vascular, as shown in Figure 2.15. This waveform was scaled to the desired flowrate, and served as a target for the experimentally generated flow patterns. Features of note include the flow reversal and the brief period of forward flow followed by a much larger pulse. By adjusting the timing of the flow clamping and its duration (simulating the effect of the heart muscle contraction), the magnitude and duration of the pump activation (simulating the ejection of blood from the heart), their phase offset, and the water level and pressure within the compliance chamber (simulating the effect of the systemic circulation), the shape and magnitude of the flow waveform generated within the test section was adjusted to match this target as closely as possible. Representative flow and pressure curves are shown in Figure 2.16. The match for the resting (Re=160) case was good, but it was not possible to recreate the initial small forward peak for the high flow, exercise condition (Re=300).

### Table 2.6: List of flow conditions tested for each stent configuration

**Diameter = 3 mm**

<table>
<thead>
<tr>
<th>Re#</th>
<th>Heart rate (bpm)</th>
<th>Womersley parameter</th>
<th>Flow Rate (mL/min)</th>
<th>Average Velocity (m/s)</th>
<th>Pressure Range (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>70</td>
<td>2.09</td>
<td>85</td>
<td>0.201</td>
<td>80 – 140</td>
</tr>
<tr>
<td>300</td>
<td>120</td>
<td>2.73</td>
<td>160</td>
<td>0.377</td>
<td>80 – 190</td>
</tr>
</tbody>
</table>

**Diameter = 4 mm**

<table>
<thead>
<tr>
<th>Re#</th>
<th>Heart rate (bpm)</th>
<th>Womersley parameter</th>
<th>Flow Rate (mL/min)</th>
<th>Average Velocity (m/s)</th>
<th>Pressure Range (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>70</td>
<td>2.78</td>
<td>114</td>
<td>0.15</td>
<td>80 – 140</td>
</tr>
<tr>
<td>300</td>
<td>120</td>
<td>3.64</td>
<td>213</td>
<td>0.28</td>
<td>80 – 190</td>
</tr>
</tbody>
</table>
Once the appropriate conditions were achieved, the same settings were used for all subsequent tests to insure consistency. Mean, minimum, and maximum flow rates were all tracked continuously during the experiment, as was the shape of the waveform, to verify that the desired conditions were achieved for every test.

Figure 2.15: Example RCA flow waveform provided by Abbott Vascular

Figure 2.16: Example experimental flow rate and pressure curves for Re=160 (left) and Re=300 (right)
**Repeatability of Flow Conditions:**

Given the large number of individual trials in this project, it was important to insure that the flow conditions for each case were consistent to allow valid comparison of derived flow parameters between them. If the flow rate peaked higher or lower in certain cases than others, or followed a different pattern, then the derived WSS would be similarly affected. The exact propagation of error will be nonlinear of course, but the dominant mode should be linear.

Figure 2.17 shows the flow rates as calculated from PIV data for one of the stent configurations tested (VISION™ 3x18) over a single period. While there are slight differences in the shape and temporal alignment, for the most part the agreement is very good, similar to the variation observed cycle-to-cycle within a given case. The remaining cases had similar agreement.

To quantify the level of error on the actual flow rate compared to the desired rate, the average flow rate for each case was calculated. These results are tabulated in Table 2.7 for the VISION™ 3x18 configuration shown above, and the relative error of the measured Reynolds number versus the desired is reported. The calculated flow rate, $Q$, average velocity, and observed vessel radius, $r$, at the point of measurement were also reported. Because none of the other parameters in the calculation of $Re$ varied between cases, the error on it can also be interpreted as the variation of the average velocity, $U_{avg}$. The error on the flow rate averaged around 5% for all cases tested in this manner, and would be expected to transfer nearly linearly to the calculation of wall shear stress, as compared to some ideal condition.
Figure 2.17: Repeatability of flow rate curves for VISION\textsuperscript{TM} 3x18 stent, Re=180 (left), Re=300 (right)

Table 2.7: Comparison of actual flow rates for the 6 tests of the VISION\textsuperscript{TM} 3x18 stent

<table>
<thead>
<tr>
<th>Case</th>
<th>Re#</th>
<th>$Q$ (mL/min)</th>
<th>$U_{avg}$ (m/s)</th>
<th>$r$ (mm)</th>
<th>Re error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>160_DS</td>
<td>168.0</td>
<td>91.4</td>
<td>0.2068</td>
<td>1.531</td>
<td>+5.0</td>
</tr>
<tr>
<td>160_MS</td>
<td>167.2</td>
<td>89.3</td>
<td>0.2097</td>
<td>1.503</td>
<td>+4.5</td>
</tr>
<tr>
<td>160_US</td>
<td>152.2</td>
<td>81.3</td>
<td>0.1909</td>
<td>1.503</td>
<td>-4.9</td>
</tr>
<tr>
<td>300_DS</td>
<td>331.9</td>
<td>183.8</td>
<td>0.4013</td>
<td>1.559</td>
<td>+10.6</td>
</tr>
<tr>
<td>300_MS</td>
<td>304.2</td>
<td>162.5</td>
<td>0.3814</td>
<td>1.503</td>
<td>+1.4</td>
</tr>
<tr>
<td>300_US</td>
<td>306.7</td>
<td>163.8</td>
<td>0.3845</td>
<td>1.503</td>
<td>+2.2</td>
</tr>
</tbody>
</table>
CONCLUSIONS

A method and setup for measuring WSS (wall shear stress) and OSI (oscillatory shear index) in vitro in stented models of compliant coronary arteries has been described. As will be discussed fully in the following chapters, WSS was measured downstream of the struts, and ranges for the values fell within those reported previously in-vivo, in vitro, and through computer simulations. The measurements utilized a high-speed light-intensified digital camera to perform time-resolved PIV. WSS was computed via a new method for deriving velocity gradients using radial basis functions. This method was shown via Monte-Carlo simulation to have accuracy equivalent to or superior to existing methodologies when applied to noisy experimental flows similar to those found in the human circulation.

In total, nine different stent configurations were tested using this methodology, utilizing commercial stent designs, each at three or more positions per configuration and under two different flow conditions (Re=160 and Re=300). The complete results of these tests are described in Appendix A, while a shorter summary of this methodology and discussion of the meaning of the differences observed is given in Chapters 3 and 4. It is believed that the methodology detailed in this chapter represents a significant contribution to the study of vascular flows in-vitro.
REFERENCES


Chapter 3: A pair-straddling PIV method for increased dynamic range in velocity measurements

John J. Charonko and Pavlos P. Vlachos

ABSTRACT

The accurate measurement of velocity fields containing large dynamic ranges is important because many problems of interest feature regions of both very high and low velocity. Examples include mixing tanks, jets injected into quiescent chambers, and stagnation regions behind bodies in high speed flow. However, accurate calculation of the velocity is currently limited to displacements greater than the total error of the scheme used (typically in the range of 0.01 to 0.05 pixels) and less than one-quarter of the window size. Two new methods for improving the dynamic range of DPIV calculations have been developed. The first can be used with any double-pulsed time-resolved DPIV system where closely spaced frame pairs are captured at kilohertz rates. Displacement measurements can be made both within each frame pair (resolving high velocity regions), and between successive pairs (resolving low velocity regions). The two displacement fields are then reconciled, resulting in a single flow field measurement. This method has been applied to synthetic and experimental data and its performance has been characterized through error analysis. Results indicate that the method can increase the dynamic range by one to two orders of magnitude as compared to traditional techniques, while retaining similar total error and spatial resolution characteristics.

Key Terms: Digital Particle Image Velocimetry, Error Analysis, Improved Dynamic Range
INTRODUCTION

Over the past decade, Digital Particle Image Velocimetry (DPIV) has become well established as a method for the optical, non-invasive measurement of two- and three-dimensional velocity fields in an extremely wide variety of applications. Numerous papers have been published offering a large variety of improvements to nearly every part of the method. Review articles by Adrian [1] and Grant [2] provide comprehensive summaries of the principles of the method and its various applications. The work of Willert and Gharib [3], Westerweel [4,5], and Huang et al. [6] established the digital implementation of PIV. Further developments resulted in super-resolution, iterative, and hybrid DPIV algorithms that increased accuracy and spatial resolution [7-10]. For iterative DPIV methods the use of a discrete-window offset (DWO) was introduced [11]. The combination of iterative DPIV with DWO significantly reduces the spatial averaging effects, improves resolution and accuracy, and renders the uncertainty independent of the total measured displacement. The accuracy is further improved by the use of an adaptive Central Difference (CDI) second order DWO [12]. This is especially important for vortical flows and systems with large pulse separation such as µDPIV and TRDPIV systems.

Several methods for using DPIV to calculate acceleration as well as velocity information have also been proposed. Dong et al. [13] described the use of double pulsed, dual-image DPIV using both auto- and cross-correlations to obtain both velocity and acceleration from a single pair of images. More recently, Liu and Katz [14] suggested correlating every other frame in a set of 4 single-pulsed images in order to obtain an estimate of the material acceleration to be used in the calculation of pressure distributions.

One area that has seen little work, however, is improvements to the dynamic range of the velocity measurements themselves. Larger dynamic ranges are important because many
important problems of interest feature regions of both very high and low velocity. Examples include mixing tanks, jets injected into quiescent chambers, boundary layer flows, and stagnation regions behind bodies in high speed flow.

Adrian [15] studied the interaction of dynamic velocity range (DVR) and the dynamic spatial range (DSR) in PIV. He found that for a given PIV method the DVR is fixed by the minimum resolvable displacement of the method, and could be improved slightly by matching the particle image diameter to the resolution of the medium. With 64 pixel windows and a minimum displacement of about 0.11 pixels, this resulted in a DVR of about 143.

For a given DWO PIV measurement, the peak magnitude of the absolute error tends to remain fairly constant across the entire range of velocities for which the measurement is valid. Values of 0.01 - 0.05 pixels are typical. The majority of the variation observed is attributable to the peak locking effect, which causes displacement measurements to be biased toward the nearest integer value. This causes both the random and bias errors to reach a maximum midway between each integer value for displacement, but drop to nearly 0 at the integer values, with a linear variation in-between. However, as the measured displacement decreases, the relative error rapidly increases, typically reaching a maximum at 0.5 pixels of displacement. Below this point, the expected error will hold constant at 10% or more of the true displacement, assuming that the error decreases linearly as predicted in artificial image simulations. If instead for very low velocities in real, noisy images, the error decreases from its peak slower than this, relative errors will increase dramatically. In the worst case, in which the expected absolute error is constant for all measured displacements, the relative error quickly goes to infinity as the displacement drops towards zero. If accuracy for low velocity regions in a given flow field is of equal importance to the regions of highest velocities, using traditional methods it may not be possible to pick a single
magnification and pulse separation that will yield enough dynamic range to capture both regimes.

To counteract this difficulty, a method for improving the dynamic range of DPIV calculations has been developed and can be used with any double-pulsed time-resolved DPIV system where closely spaced frame pairs are captured at kilohertz rates. Displacement measurements can be made both within each frame pair (resolving high velocity regions), and between successive pairs (resolving low velocity regions). The two displacement fields are then reconciled, resulting in a single flow field measurement. This method is similar to those described previously in the literature [16-18]. In this work a detailed error analysis of the pair straddling method is presented for uniform, shearing, and vortical flows, and an example implementation with experimental data will be given. In addition, some theoretical considerations for the proper selection of the velocity cutoff between successive correlation have been developed and explained.

METHODOLOGY

**Artificial image generation**

Monte-Carlo style testing of the new DPIV methods discussed in this paper was conducted using artificially generated images. The images generated contained a uniformly random distribution of particle images. The intensity distribution for each particle was a Gaussian curve with diameter of 3 pixels. Intensities were stored as 8 bit integers. A laser plane was simulated by a Gaussian distribution of intensities in the out-of-plane direction, ranging from a maximum intensity of 255 to a uniform background illumination of 5. Particles were assigned a random z position using a uniform distribution within this illuminated plane, and allowed to translate in the x and y directions only (no out-of-plane motion). A variety of flow
fields were imposed, as described below, causing the particles to translate from one image to the next. Arbitrary timing sequences of illumination in and between each successive frame could be created, resulting in one or more particle field image per artificially created “camera exposure.”

**DPIV methodology**

DPIV was performed using in-house developed software based upon the work of Willert and Gharib [3], Westerweel [4,5], and Huang et al. [6]. It takes advantage of super-resolution, and iterative algorithms to increase accuracy and spatial resolution [7-10]. Accuracy is further improved by the use of DWO [11] and an adaptive Central Difference (CDI) second order DWO [12]. This system formed the “kernel” that was leveraged in the analysis performed in this paper, and has been successfully used in a number of Time-Resolved DPIV experiments [19-25].

**Error analysis**

Artificial images were generated for each flow field and method examined, and were processed using DPIV to obtain velocity measurements. No validation or outlier removal was performed. Because the flow fields are known exactly, the measurements, $U_i$, can be compared to the true velocities, $U_e$, to yield statistical estimates of error. Bias error was defined as

$$
\varepsilon_{bias} = \bar{U} - U_e,
$$

where $\bar{U}$ is the mean velocity; the random, or root-mean-square error as

$$
\varepsilon_{rms} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (U_i - U_e)^2},
$$

with $N$ being the number of samples; and the total error as

$$
\varepsilon_{total} = \sqrt{\varepsilon_{bias}^2 + \varepsilon_{rms}^2}.
$$

Relative total error was also examined, and defined as $\varepsilon_{total}/U_e$. 
The errors for the new proposed methods could then be compared directly to an analysis of the same flow field using the same DPIV kernel in a more traditional algorithm.

**Pair-straddling algorithm**

The first method proposed takes advantage of the fact double-pulsed TRDPIV measurements are often taken at high enough frequencies that the time delay between successive measurements (frame pairs) is short enough that it is also possible to cross-correlate between pairs in addition to within each individual pair. For example, for a typical TRDPIV experiment, Δ\(t_1\) might be set at 62.5 μs to capture the maximum expected velocities, with a pair repetition rate of 1 kHz, resulting in a Δ\(t_2\) of 1000 μs. Figure 3.1 illustrates a typical timing sequence for this method.

![Figure 3.1: Schematic of laser pulse and camera exposure timing for pair straddling method.](image)

To implement pair straddling, then, one simply needs to correlate frames 1 and 3 to get CC\(_{1,3}\), in addition to CC\(_{1,2}\). From each cross correlation, a displacement can be measured, \(D_{1,3}\) and \(D_{1,2}\), respectively. Dividing by the appropriate time step for each, a velocity measurement can then be obtained. The advantage to this is that you are now free to optimize the window sizes and Δ\(t_1\) to best capture regions of high flow, independently of the measurement of CC\(_{1,3}\), which will capture much slower velocities over the period Δ\(t_2\). No special analysis needs to be
performed to obtain these two measurements; whatever DPIV algorithms best suit the data may be used.

The question then becomes how to integrate the two velocity measurements. The first difficulty is how to decide for a given interrogation region within the flow, which correlation to use. The highest resolvable displacement for a given DPIV measurement is usually considered to be $\frac{1}{4}$ of the window size used. Above this point, errors are typically assumed to make measurements untrustworthy, and so when the displacements are combined with the appropriate time step, an upper bound for the velocities measurable by each correlation is obtained. These are represented in Figure 3.2 by $L/4$.

The lower bound is less well defined, but depends on the DPIV method chosen and the characteristics of the flow (shear gradients, image noise, etc.). It should be set at the point below which the researcher feels the relative error has grown too great to make the velocity estimate trustworthy. It is important to note that unlike the $L/4$ criterion, below this point an estimate of velocity can still be made, the relative error will just be very high, and velocities may not be

![Figure 3.2: Upper and lower bounds for velocity measurements using CC1-3 (left) and CC1-2 (right). Cross-hatched regions indicate where errors may be too high for accurate velocity measurement. $U^*$ is a normalized velocity (see below).](image)

$U^* = \frac{\varepsilon_{\text{threshold}}}{(L/4)}$  
$U^* = \frac{\varepsilon_{\text{threshold}}}{(L/4)} \frac{\Delta t_2}{\Delta t_1}$  
$U^* = 1$  
$U^* = \frac{\Delta t_2}{\Delta t_1}$
distinguishable from a zero flow condition. This means that CC1-2 can be used as a predictor of the velocity at a given point, and then, if the measured displacement falls below some critical displacement, \( D_c \), CC1-3 can be calculated to refine the measurement of low speed regions. Figure 3.3 outlines how this would work.

![Flow chart of the pair straddling algorithm.](image)

It should be clear from Figure 3.2 that changing \( \Delta t_1 \) and \( \Delta t_2 \) will change the relative positions on a number line of the useful measurement regime of CC1-2 and CC1-3. To make pair straddling work, \( \Delta t_1 \) and \( \Delta t_2 \) must be chosen so that the lower limit on velocities for CC1-2 must meet or cross the upper limit for CC1-3. \( D_c \) should then be chosen to fall between these two limits. Assuming the same window size is used for both measurements, and that the lower error bound in pixels is also the same, when \( D_c \) should be defined in pixels on CC1-2 as

\[
\varepsilon_{\text{threshold}} \leq D_c \leq \frac{L}{4} \cdot \frac{\Delta t_1}{\Delta t_2}. \tag{4}
\]

The upper limit on \( D_c \) is set by the \( \frac{1}{4} \) rule for CC1-3, and the lower limit by the accuracy at low displacements for CC1-2. As an example, if the window size is 32 pixels, and the ratio \( \Delta t_1/\Delta t_2 \) is 1/16, then \( D_c \) should be less than 0.5 pixels. If the expected total error for a given displacement
measurement is about 0.05 pixels, to keep the relative error below 10%, $\varepsilon_{\text{threshold}}$ should be set at 0.5 pixels also. $D_c$ is therefore required to be set at a displacement of half a pixel when measured in CC1-2.

The second challenge is the localization of each measurement in time. As can be seen in Figure 3.1, the two correlations periods are not centered in time on the same instant, and therefore the velocity estimate cannot be strictly considered as a second order central difference in time. Instead, they both start at the same instant, and the velocity estimate should instead be considered a forward difference.

Defining the dynamic velocity range as the ratio of the maximum resolvable velocity to the minimum resolvable, for this method the $DVR$ is

$$DVR = \frac{U_{[L/4]}^*}{U_{[\varepsilon_{\text{threshold}}]}^*} = \frac{L/4}{\varepsilon_{\text{threshold}}} \frac{\Delta t_2}{\Delta t_1}. \tag{5}$$

As can be seen from equation (5), the use of pair straddling increases the $DVR$ over DWO alone by a factor of $\Delta t_2/\Delta t_1$, typically $10\times$ to $100\times$, or one to two orders of magnitude.

**RESULTS AND DISCUSSION**

**Error analysis**

To analyze the performance of this method, 1024x1024 pixel artificial images were generated as described above, and processed with 32x32 pixel windows using our DPIV algorithm. The images had an average of 20 particle images per interrogation window. The ratio of $\Delta t_2$ to $\Delta t_1$ was chosen to be 16:1, which for a 1kHz TRDPIV system would correspond to a $\Delta t_1$ of 62.5 $\mu$s. $D_c$ was chosen as $L/4 \cdot \Delta t_1/\Delta t_2$, or 0.5 pixels in CC1-2. For $\varepsilon_{\text{threshold}}=0.05$ pixels, the $DVR$ should be 160 for conventional DWO, and 2560 for pair straddling.
It is usually the convention when showing PIV error analysis to present errors in terms of pixels, to allow scaling of the results to any flow velocities, independent of magnification and timing. However, because this method depends heavily on the choice of \( \Delta t \)'s and makes measurements in two very different flow regimes, and two different correlation windows, it would be confusing to attempt to present both displacements on a single scale in terms of pixels. Instead, a non-dimensional velocity scale, \( U^* \), has been introduced:

\[
U^* = \frac{U}{L/(4 \cdot \Delta t_2)}
\]  

(6)

Because of the choice of \( D_c \), this normalization has the nice feature that the velocity corresponding to \( D_c \) is represented as \( U^* = 1 \). The maximum resolvable velocity is then \( U^* = L/4 \), and the velocity corresponding to \( \varepsilon_{\text{threshold}} \) is \( U^* = (\varepsilon_{\text{threshold}})/(L/4) \). Figure 3.2 above illustrates graphically how this scale relates to pixel displacements of each correlation.

Because of space limitations, bias and random errors will not be presented separately here, and only total errors will be reported. They follow the same trends as the total error, and match previously reported analyses of the bias and random errors. Additionally, for the uniform and shear flows only errors on the velocity measurement parallel to the translation are reported. The error on the measurement of the perpendicular velocity, which had a mean of 0, followed the same pattern as the tangential velocities.

The first flow field analyzed was uniform displacement in the x direction. Vectors were sampled on a grid spaced at 16 pixels. For each displacement, a total of 3969 vectors were averaged to calculate the error statistics for that displacement.

Figure 3.4 shows the total error for a portion of the entire dynamic range of the pair straddling method. For comparison, the errors for velocity estimate based solely on cross correlating frames 1 to 2 and frames 1 to 3 are also shown. These can be thought of as the errors
that would result if you could exactly repeat your experiment twice, the first time optimized for high velocities, and the second for regions of low velocity. While for time averaged data these two results could be compared in this way, for time-resolved DPIV it is not generally valid to combine the evolution of the flow as recorded at two separate times. This is an obvious advantage of the pair straddling method then, since it allows the extraction of measurements for both regimes from a single test.

The expected sawtooth pattern for the errors as described in the introduction, attributable to peak locking, is clearly observable for all three measurements. The error peaks for CC1-2 and CC1-3 are both at about 0.05 pixels in magnitude. Because of the different $\Delta t$’s the same pixel error corresponds to very different physical velocities though. As the velocity increases past $U^*=1$, CC1-3 is no longer able to track the particles, and the errors rapidly become enormous. In

![Figure 3.4: Total errors for the pair straddling method in uniform flow as compared to measurements of CC1-2 and CC1-3 alone.](image-url)
contrast, the pair straddling method matches the lower errors of CC1-3 measurement for the low velocity regions, but also is able to match the accuracy of the CC1-2 measurements in the high velocity region.

Examining Figure 3.5, the advantage of adding data from CC1-3 to CC1-2 becomes even clearer. For clarity, $U^*$ has been plotted on a logarithmic scale. While for most of their ranges, both CC1-2 and CC1-3 have a peak relative error of only about 2-5%, near and below $\varepsilon_{\text{threshold}}$ the relative errors climb dramatically to 13% or greater. However, the pair straddling method has errors equal to the component measurements across its range, with only a small spike of about 6% between $U^* = 1$ and 2. Average errors are also lower than either CC1-2 or CC1-3, and are detailed in Table 3.1.

![Figure 3.5: Percent total error for the pair straddling method in uniform flow](image)

<table>
<thead>
<tr>
<th>Velocity, $U^*=\frac{UL}{(4\Delta t)^2}$</th>
<th>Total relative error on $U^*$, $\varepsilon_{\text{total}}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWO, CC1-2</td>
<td>$\varepsilon_{\text{total}}$</td>
</tr>
<tr>
<td>DWO, CC1-3</td>
<td>$\varepsilon_{\text{total}}$</td>
</tr>
<tr>
<td>Pair straddling</td>
<td>$\varepsilon_{\text{total}}$</td>
</tr>
</tbody>
</table>
Table 3.1: Comparison of average percent total error for pair straddling and standard DWO methods in uniform flow

<table>
<thead>
<tr>
<th>$U^*$</th>
<th>CC1-3</th>
<th>CC1-2</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>1.95</td>
<td>12.2</td>
<td>1.95</td>
</tr>
<tr>
<td>1 - 16</td>
<td>99.5</td>
<td>1.48</td>
<td>1.38</td>
</tr>
<tr>
<td>0 - 16</td>
<td>93.5</td>
<td>2.14</td>
<td>1.42</td>
</tr>
</tbody>
</table>

The second flow examined was a shearing flow. Velocities were in the x-direction and varied with the y-coordinate from a $U^* = 0$ to $U^* = 8.0$. This corresponds to a maximum of 4 pixels over $\Delta t_1$, or 64 pixels over $\Delta t_2$. 50 frame pairs total were processed, with a grid spacing of 8 pixels. For each y location, the vectors from that entire row and each of the 50 frames (a total of 6350 vectors per y position) were combined to derive the error statistics. Errors are reported versus the average velocity at that height.

Figure 3.6 shows the results of this analysis. Once again, the pair straddling method is able to accurately capture the velocity across the entire range of velocities, equaling or beating a DWO method optimized only for high or low velocities. Error levels are comparable to that for uniform flow, in the range of 5%. At lower velocities the errors are slightly higher than for uniform flow, but still better than the 10-15% developed by CC1-2 alone. The peak-locking effect is also somewhat suppressed. One effect present for these results not seen in the uniform flow analysis is the large peak in the errors for the lowest displacement measurement. This is attributable to the fact that this measurement was taken at a location only 8 pixels into the image, reducing the usable area of the interrogation window to only 24x32 pixels. This makes the measurement more sensitive to loss of correlation, which is more likely the higher the displacement is that is being measured. This explains why the CC1-3 and the pair straddling results are more affected than the CC1-2 results, which have much lower displacements between frames. A similar peak can be seen for the last measurement at the upper end of the displacement scale.
The final flow field examined was a rotational flow consisting of a single large vortex centered in the frame. The rotational velocity profile was of the form

$$U_\theta(r) = U_{\text{max}} \frac{r}{R} \exp \left[ \frac{1}{2} \left( 1 - \frac{r^2}{R^2} \right) \right]$$

(7)

where $U_{\text{max}}$ is the maximum velocity at a radius of $R$. The core motion within $R$ is very nearly solid body rotation, and the velocity drops exponentially outside $R$ towards 0 as the distance increases toward infinity. Radial velocity was 0. A plot of this profile can be seen in Figure 3.7. $U_{\text{max}}$ was equal to a $U^*$ of 16.

Figure 3.6. Relative percent total error for the pair straddling method in shear flow. Velocities reported are the average at each sampling location.
To calculate errors, 500 image pairs were correlated on an 8x8 grid, and for every point in the resulting vector field, the estimated velocities were compared to the exact velocities and error statistics calculated.

Errors for this case are slightly higher than for uniform or shear flows alone, since this flow field combines both rotational and shearing floors. Nevertheless, the combined pair straddling equals or betters both CC1-2 and CC1-3 across the entire range. Within and near the vortex core, CC1-2 and pair straddling both successfully capture the rotational motion, while the displacements are too high for CC1-3 to resolve. As the velocities drop towards 0 in the periphery, the error on CC1-2 climbs to about 12%, while the error for the pair straddling stays lower. Past a radius of about 500 pixels the displacements are extremely small, and relative errors for all three methods climb quickly. However, the error on CC1-3 and the pair straddling remain significantly smaller than for CC1-2. One other effect to note is that because within a few pixels of the center of the rotation the velocities are very small, the pair straddling method follows CC1-3. However, since the path radius is also small, flow is mostly rotational, and the correlation quite poor, causing the errors for both methods to be much worse than using CC1-2 alone would be. On the whole, however, pair straddling still results in better performance than optimizing only for high or low velocities would.

A possible solution to the problem of lost correlations in high shear when switching from the CC1-2 to the CC1-3 correlation is to examine the relative magnitude of the peak in CC1-2 and CC1-3. If the correlation peak in CC1-3 is significantly weaker than the peak found for CC1-2, then the estimate at CC1-3 may not be valid, and should not be used. Another check would be to examine the displacements found from CC1-2 and CC1-3. They should agree to some extent in magnitude and direction at each point. If they are significantly different, the measurement in
Figure 3.7. Relative percent total error on velocity magnitude for the pair straddling method in rotational flow. As a reference, the flow profile of the vortex is also plotted.

CC$_{1,2}$ may be a better estimate because the particle images are displaced less between sequential frames, and are less susceptible to loss of correlation effects.

**Experimental Test**

To evaluate qualitatively the effectiveness of the method in a real experimental setting, images from the stent data set described in Chapter 2 were used. The example case chosen was
flow at the inlet of an Abbott Vascular XIENCE V™ stent (3mm diameter, 18mm length) overexpanded by 10% into a compliant, 3.0 mm vessel. The average flow rate in the vessel had a time-averaged Reynolds number of 160 based on the bulk flow rate. For this case, the field of view was 3.56x2.44 mm at a resolution of 1.73 µm/pix. Reflections and background illumination were blocked using a dichroic filter fixed to the camera lens, and to compensate for the low levels of fluorescent emission a 4 megapixel light-intensified camera (X5i, IDT) was used. The working fluid was seeded with 7 µm red fluorescent polystyrene beads, and illumination was provided by a frequency-doubled (532 nm) Nd:YAG pulsing laser (LDP-100MQG, Lee Laser). For this dataset image pairs were acquired at 300 pairs per second with a pulse separation between pairs of 50 µs. The acquired frames were filtered in blocks of 10 (separated into odd and even frames to allow for differences in illumination between the first and second image of every pair), and the median intensity at each pixel was subtracted from each image to further reduce any background noise.

The resulting images were then processed using a multi-pass, DWO algorithm [12,21] to yield a 128x88 vector field. A robust phase correlation (RPC) algorithm was used for the displacement kernel [26] with a first pass using an effective window size of 512x16 pixels on a grid of 256x64 pixels to obtain a bulk window offset corresponding to the spatially-averaged flow profile. The velocity fields were then interpolated to a 16x16 pixel grid, and a second RPC pass was performed using an effective window size of 32x32 pixels.

Correlations were performed within each image pair, and between the second image of each pair and the first of the next pair (giving a image separation of 3283 µs). To maintain 2nd order accuracy in a central difference sense, to obtain a velocity field at matching timepoint to the original correlation pair (pair B), velocity field obtained from the backwards correlation (2nd
frame of pair a to 1st frame of pair B) and the velocity field from the forward correlation (2nd frame of pair B to 1st frame of pair C) were averaged. The resulting time-resolved fields were then phase averaged over the 4 periods of flow data acquired.

To reconcile the two correlations, the cutoff displacement was calculated based on 1/5 of the largest theoretically resolvable displacement in the long time delay pair ($L/2=256$ pixels) instead of $\frac{1}{2}$ as recommended above in equation (4) to maintain reasonable displacements.

$$\varepsilon_{\text{threshold}} \leq D_c \leq \frac{L}{10} \cdot \frac{\Delta t_1}{\Delta t_2}$$

(8)

This yielded $D_c=0.78$ pixels, and assuming $\varepsilon_{\text{threshold}}=0.5$ pixels and a maximum resolvable displacement of 32 pixels, a DVR of 4202:1, an enhancement at low velocities of approximately $65.6\times$ from correlating on the original image pairs alone.

A comparison of the results of the standard and pair-straddling correlation using this methodology is shown in Figure 3.8 for one snapshot take during the beginning of flow reversal in the channel. As can be seen from the instantaneous streamtraces plotted, the vortical structures emanating from the wall are much better resolved with the improved techniques. However, without an exact solution to compare to, no quantitative evaluation is possible.

Complete results for the use of this methodology applied to the stent experiment outlined in the previous chapter will be described in Chapter 5.
CONCLUSIONS

This method has been applied to synthetic and experimental data and its performance has been characterized through error analysis. Results indicate that the method can increase the dynamic range by a factor of $\Delta t_2/\Delta t_1$, typically one to two orders of magnitude, as compared to traditional techniques, while retaining similar total error and spatial resolution characteristics.

The pair straddling method yields almost identical total errors as the optimized component measurements in uniform, shear, and rotational flows. Initial tests on experimental datasets are qualitatively quite promising, and appear to be a useful enhancement almost any
time TRDPIV is performed. The methods appear to hold great promise in experimental investigations of flows containing large dynamic velocity ranges.

ACKNOWLEDGMENTS

The authors wish to thank Ali Etebari for his help and suggestions. The original idea for the pair straddling method was developed jointly during discussions with him.

Also, the support of the Virginia Tech ASIPRES program and the MRI: “Development of a Spatiotemporal Velocimetry with Simultaneous Size Measurements for Polydispersed Multi-Phase Flows”, CTS 0521102, program officer Michael W. Plesniak, is gratefully acknowledged.
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Chapter 4: In-Vitro, Time-resolved PIV Comparison of the Effect of Stent Design on Wall Shear Stress

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The original publication is available at www.springerlink.com.

ABSTRACT

The effect of stent design on wall shear stress (WSS) and oscillatory shear index (OSI) was studied in-vitro using time-resolved digital particle image velocimetry (DPIV). Four drug-eluting stents [XIENCE V™ (Abbott Vascular), TAXUS® Liberte™ (Boston Scientific), Endeavor™ (Medtronic), and Cypher® (J&J Cordis)] and a bare-metal stent [VISION™ (Abbott Vascular)] were implanted into compliant vessel models, and the flow was measured in physiologically-accurate coronary conditions featuring reversal and realistic offsets between pressure and flowrate. DPIV measurements were made at three locations under two different flow rates (resting: Re=160, f=70bpm and exercise: Re=300, f=120bpm). It was observed that design substantially affected the WSS experienced at the vessel walls. Averaged values between struts ranged from 2.05 dynes/cm² (Cypher®) to 8.52 dynes/cm² (XIENCE V™) in resting conditions, and from 3.72 dynes/cm² (Cypher®) to 14.66 dynes/cm² (VISION™) for the exercise state. Within the stent, the WSS dropped and the OSI increased immediately distal to each strut. In addition, an inverse correlation between average WSS and OSI existed. Comparisons with recently published results from animal studies show strong correlation between the measured WSS and observed endothelial cell coverage. These results suggest the importance of stent design on the WSS experienced by endothelial cells in coronary arteries.

Key Terms: Coronary arteries, blood flow, phase offset, oscillatory shear index, drug-eluting stent, bare metal stent, endothelial cells
INTRODUCTION

One in five Americans suffer from some form of Cardiovascular Disease (CVD), which is responsible for nearly one million deaths in 2006 and creating health-care costs of $430 billion per year.[1] Of these deaths, coronary artery disease (CAD) accounts for 54%, stroke 18%, and congestive heart failure 8%. It has been estimated that eliminating CVD would extend the lifespan of the average American by 7 years. Clearly, improvements in the prevention, diagnosis, and treatment of these diseases are among the most acute and important health challenges we face today.

One of the most popular treatments for CAD is the implantation of coronary stents. The use of stents has dramatically increased since their approval by the United States Food and Drug Administration in 1994, largely because of therapeutic and technological advances. In 1998 over 800,000 stents were implanted in more than 500,000 patients in the United States.[2] By 2003 this number had already climbed to well over one million total stent procedures per year.[3] However, traditional bare metal stents (BMS) are subject to high failure rates due to restenosis and thrombosis[4-8], which are believed to be influenced by abnormal wall stresses and disruption of the blood flow around the stent.[9] Although the estimates of restenosis vary widely, rates of 10-30% over 6-12 months following a stenting procedure are typical.[10] Drug-Eluting Stents (DES) were introduced as a remedy to these problems, and while initial trials were very promising[11], recent controversial results triggered extensive investigations to re-examine whether they are as safe and successful as initially anticipated.[12-15] In particular, DES have been implicated in higher rates of Late Stent Thrombosis (LST), which often manifests as excessive fibrin formation coupled with incomplete re-endothelialization in the stented region. LST has been linked to increased risk of myocardial infarction and mortality.[14]
It has been repeatedly shown that links exist between patient outcome, stent design\[16,5,6\], and implantation strategy\[17,5,7\], and also between wall shear stress and neointimal formation, thrombosis, re-endothelialization, and restenosis.\[18,9,19-21\] Therefore it is widely believed that these trends can be explained in part by alteration in wall shear stress levels as a result of differing stent design and implantation configurations, although the exact biochemical and hemodynamic pathways by which this occurs remain unclear. Furthermore, despite the successes of DES in reducing restenosis rates, their tendency toward incomplete re-endothelialization means that stent-induced flow disturbances will play a role in the hemodynamics for a much longer period than would be expected in BMS. It is for these reasons that research into the effect of coronary stents has been and continues to be an active area of research.

Despite recent advances in \textit{in-vivo} flow measurement, understanding the fluid dynamics at work still requires using computational and \textit{in-vitro} studies. Of the two, the majority of the work in this area has been done using CFD. However, a large number of confounding factors, including moving, compliant walls, complex stent geometries, and unsteady transitional flows make obtaining numerical solutions very challenging. Published studies have utilized simplified stent strut geometries, idealized flow curves, ignored the phase offset between pressure and flow in the coronary circulation, or failed to consider compliant walls (one of the most common simplifications).\[22,23\] With continuing advancement in computational power and CFD algorithms, these restrictions are rapidly easing. For example, early simulations like those by Berry et al. used a time-varying 2D simulation of a wire mesh stent in a straight-walled rigid vessel, neglecting overexpansion and the pillowing of the vessel wall between struts.\[24\] Similarly, Natarajan and Mokhtarzadeh-Dehghan also used 2D axisymmetric models of rigid
walled vessels with time-varying flow, in their case modeling a single segment of deformed stented artery.[25] Later, LaDisa and his various collaborators performed a series of 3D simulations on a model of a simplified slotted tube stent in a rigid vessel. Beginning with rigid walls and steady flow[26] they went on to add the effects of stent deployment ratio in time-varying flows[27] and finally a comparison of the effects of different vessel pillowing, strut spacing, and strut cross section.[28] Tortoriello and Pedrizzetti examined the effect of a sinusoidal time-varying flow on compliant vessels with varying diameter and stiffness, but limited their analysis to one- and two-dimensional finite difference models and a 1D perturbative solution.[29] Their work did not explicitly model the presence of a particular stent design. More recently, Balossino et al. performed a detailed 3D simulation of four commercial stent designs.[30] To generate their geometries, they performed a FEM simulation of the expansion of a single stent segment into a compliant plaque-coated artery, and then used the resulting rigid geometry to perform a time-varying CFD simulation of the flow. However, they still neglected the effect of the phase offset for the pressure, as did the other studies mentioned.

In contrast, fewer experimental investigations into the hemodynamics of stented arteries are available,[22,23] for many of the same reasons that made computational studies difficult. An additional difficulty for experimental studies is matching the physical scaling of the small coronary vessels, as it is often difficult to fully match dynamic similarity with a scaled-up model, while achieving sufficient spatial resolution and accuracy at a 1:1 scale is challenging. Previous studies have overcome these difficulties in working with compliant models by using dye visualization in large-scale models,[31,24] or performing quantitative measurements in idealized, scaled-up, rigid fixtures.[32,25] Yazdani et al. did perform PIV measurements in stented compliant vessels, but they also used a large-scale model (as compared to coronary circulation)
and used a rigid tube and Cordis S.M.A.R.T.® biliary stent as models, instead of a current coronary stent designs.[33] Many of these studies used idealized velocity profiles, and none took into account the effect of the phase angle between the pressure and flow, which occurs in the coronary arteries.[34]

The goal of this study was to overcome the limitations of previous experimental studies and accurately quantify the hemodynamic behavior of the flow in coronary arterial models stented with different commercial stent designs. This was successfully accomplished through in-vitro measurements of the flow field within stented artery models. Physiologic flow conditions and compliant vessels were considered and the performance of the stents designs were compared using the well defined hemodynamic indices: Wall Shear Stress (WSS) and Oscillatory Stress Index (OSI). Although these synthetic indices have not been fully linked in a one-to-one relationship with the biological mechanisms responsible for sensing changes in coronary blood flow and translating them into the chemical signals responsible for the health and remodeling of the surrounding vessel, there is sufficient evidence to suggest that they can serve as a useful proxy of the effect of disturbed flow on the endothelial cell response.

**METHODOLOGY**

In order to simulate coronary flow conditions, a flow loop has been designed as seen in Figure 4.1. The test section has mounting points for compliant vessels constructed out of Sylgard 184 (DOW Corning) with an I.D. of 3.0 mm, wall thickness of 0.4 mm, and a modulus of elasticity similar to that of human arteries[35] (testing yielded values near 1.0 MPa).[36] The compliance chamber is used to simulate the effect of the systemic circulation, and the solenoidal valve clamped the flow in phase with the flow generated by the pump, similar to the contractions of the myocardium. A small air bubble was left in the damping chamber to suppress the
upstream reflection of waves when the clamp valve closes. The working fluid was a 60/40 mixture of water and glycerine approximating the viscosity and density of human blood \((\nu=3.72\times10^{-6} \text{ m}^2/\text{s}, \rho=1099.3 \text{ kg/m}^3)\). This fluid also filled the test section, and matched the index of refraction of the vessel walls, nearly eliminating optical distortion caused by curvature of the vessel walls and minimizing light reflections at the vessel wall. Instantaneous flow rates and pressures were monitored just upstream of the test section. Flow conditions, as documented in Table 4.1, were designed to duplicate resting and exercise conditions within the large coronary arteries, including the phase offset between pressure and flow rates, as seen in Figure 4.2. This offset of peak flow into diastole is especially important when the effect of compliant walls is included in a simulation, since the walls will be expanding during the low flow part of the
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Re</th>
<th>Heart rate (bpm)</th>
<th>Womersley parameter</th>
<th>Flow Rate (mL/min)</th>
<th>Pressure Range (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>resting</td>
<td>160</td>
<td>70</td>
<td>2.09</td>
<td>85</td>
<td>80 – 140</td>
</tr>
<tr>
<td>exercise</td>
<td>300</td>
<td>120</td>
<td>2.73</td>
<td>160</td>
<td>80 – 190</td>
</tr>
</tbody>
</table>

Table 4.1: Flow conditions

Figure 4.2: Pressure and flow. Left, Re=160; Right, Re=300

coronary cycle, instead of the peak flow conditions as is usual for systemic circulation.

Reynolds numbers were calculated based on time-averaged bulk flow velocities and nominal vessel diameter.

To test the effect of variations in stent design, four commercially-available DES [XIENCE V™ (Abbott Vascular), TAXUS® Liberte™ (Boston Scientific), Endeavor™ (Medtronic), and Cypher® (J&J Cordis)] and a single bare-metal stent [VISION™ (Abbott Vascular)] were inflated to 10% above their nominal diameter (3.0 mm) within a mounted vessel, replicating common clinical practice. The VISION™ and XIENCE V™ stents share the same stent geometry. The vessel section in each case was stretched to 5% greater than its resting length. The stents were deployed using an endeflator according to the enclosed manufacturer-recommended protocols, leaving at least 60 mm (>20 diameters) between the proximal end of the
stent and its upstream mounting point. The VISION™, XIENCE V™, Endeavor™ and CYPHERR® stents had deployed lengths of 18 mm, while the TAXUS® Liberte™ was 20 mm in length. See Table 4.2 for exact geometric and deployment details.

<table>
<thead>
<tr>
<th>Stent</th>
<th>Stent Length (mm)</th>
<th>Strut Thickness, metal + polymer (µm)</th>
<th>Vessel Length (mm)</th>
<th>Entrance Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISION™</td>
<td>18</td>
<td>81</td>
<td>146</td>
<td>60</td>
</tr>
<tr>
<td>XIENCE V™</td>
<td>18</td>
<td>81 + 7.6</td>
<td>184</td>
<td>90</td>
</tr>
<tr>
<td>Endeavor™</td>
<td>18</td>
<td>91 + 5.3</td>
<td>174</td>
<td>87.5</td>
</tr>
<tr>
<td>TAXUS® Liberte™</td>
<td>20</td>
<td>97 + 16</td>
<td>185</td>
<td>87</td>
</tr>
<tr>
<td>Cypher®</td>
<td>18</td>
<td>140 + 12.6</td>
<td>178</td>
<td>90</td>
</tr>
</tbody>
</table>

Digital Particle Image Velocimetry (DPIV)[37] was used to acquire snapshots of the velocity field within these stented vessels at three locations or regions of interest (ROI), each centered downstream of a stent strut. These regions were behind the first strut (upstream or US), behind the middle strut (mid-stent or MS), and behind the last strut (downstream or DS) and are shown schematically in relation to the stents length in Figure 4.3, and in relation to the major features of each stent design in Figure 4.4. As can be seen in these figures, each region imaged included the entire vessel diameter as well as portions of the vessel immediately proximal and distal to the strut of interest, so that the development of the flow around that point could be captured. The goal was to choose regions behind a representative strut as it crossed circumferentially through the field of view so that the region of interest measured was as similar between stent designs as possible. This goal was complicated by the wide diversity of the four designs, and the obstructions to view caused by the portions of the stent falling in front of the imaging plane, meaning that correspondence was approximate. The vessels and laser planes
Figure 4.3: Diagram of the relative positions of the three regions of interest along the stent lengths. US: upstream, proximal; MS: mid-stent; DS: downstream, distal

Figure 4.4: Location of the ROI for each stent relative to its design features. A representative segment of each is shown, with the location of the laser plane marked by a line, and the region where WSS was measured marked by a circle.
were oriented in each case so that the laser plane bisected the vessel vertically along the axis of
the vessel, and the camera was placed to view the stented region perpendicularly to this plane.
The field of view was 3.56x2.44 mm at a resolution of 1.74µm/pix. The working fluid was
seeded with 7µm polystyrene fluorescent flow tracers, and the flow was illuminated using a
pulsing Nd:YAG laser (LDP-100MQG, Lee Laser). To compensate for the low light levels
available at these conditions, a 4 megapixel light-intensified camera was used (X5i, IDT) in
conjunction with an optical filter placed between the lens and the camera sensor tuned to exclude
the 532 nm laser light. Image pairs were acquired at 300 Hz, with a 50 µs pair separation for the
Re=160 cases, and 25 µs separation for the Re=300 cases. Using these images, a grid of
255x175 vectors was calculated for each pair using a multi-pass, iterative, DWO
algorithm.[38,39] 2,570 images were collected for each combination of stent, flow condition,
and location, covering either 5 or 8.6 periods of the flow. It should be noted that this study
accomplished the highest reported to-date spatial and temporal resolution.

From the resulting images, the discrete pixel locations of the wall as a function of time
and position were identified using a correlation-based template-matching algorithm. These
positions were parameterized using a cubic smoothing spline to allow tracking of the vessel wall.
This surface was then used in conjunction with the measured velocity vectors to calculate the
tangential WSS and OSI between the stent struts in each vector field. Wall shear stress is
defined here as the product of dynamic viscosity ($\mu$) and the component of the fluid strain rate
tensor oriented tangential to the wall, $\varepsilon_{12}$.

$$WSS = \tau_w = \mu \varepsilon_{12}$$  \hspace{1cm} (1)
This tangential component of the strain rate tensor in a wall-oriented coordinate system can be found by first computing the strain rate tensor from the planar components of velocity, \( u_i \), in a Cartesian, image-oriented coordinate system, \( x_i \),

\[
\dot{\varepsilon}_{ij} = \left[ \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right]
\]  

(2)

A rotation matrix transforming between the two systems can then be specified at each point along the wall in terms of the rotation angle \( \theta \) between the image- and wall-oriented systems.

\[
a_{ij} = \begin{bmatrix}
\cos \theta & \sin \theta \\
-\sin \theta & \cos \theta
\end{bmatrix}
\]  

(3)

Finally, this transformation is applied back to the Cartesian strain rate tensor to yield the tangential component at each location, and thus the WSS.

\[
\dot{\varepsilon}'_{mn} = a_{mi} a_{nj} \dot{\varepsilon}_{ij}
\]  

(4)

The oscillatory shear index is then determined in terms of the WSS by the following equation, where \( t \) is time and \( T \) is some multiple of the period.

\[
OSI = \frac{1}{2} \left( \frac{1}{T} \int_0^T \tau_w dt \right) - \frac{1}{2} \left( \frac{1}{T} \int_0^T |\tau_w| dt \right)
\]  

(5)

Gradients were calculated from a surface fit of the velocity using generalized multiquadratic radial basis functions (GMQ-RBF), optimized to minimize the surface roughness of the resultant fit [40]. At each wall location, a 5x5 vector grid with one of its edges centered on that point was used to derive a surface fit. The obtained function was then differentiated analytically to obtain the wall gradients. This method has been demonstrated to be more resistant to experimental error than traditional finite differencing and polynomial interpolation.
schemes, both of which were tried here and yielded qualitatively poorer results. Assuming a 10% normally-distributed random error on the DPIV velocity estimates, it was calculated that standard deviation of the errors on the resulting velocity gradients (and therefore the WSS values) using the GMQ-RBF method would be contained within 20% of their true values. This error can be further reduced by averaging the instantaneous, local values in either time or space. Application of simple propagation of error formulas for the mean to a theoretical WSS profile modeled as constant in space and sinusoidal in time with a min and max of -10 and 40 dynes/cm² (respectively), and assuming a normally distributed 20% relative error on each WSS measurement, results in expected errors with a standard deviation of 1-3% on the spatially-averaged values, and under 0.5% for time-averaged values. Averaging over both yields error levels below 0.05%. The principal remaining error in the reported values will be the result of errors in wall detection and any bias in the determined velocity values, which should be of similar magnitude to the random velocity errors (less than 10%).

RESULTS

Analysis of the flow for the five stent designs tested revealed several trends that were shared for all cases. The first is the formation of a vortex just downstream of each strut and its subsequent separation from the stent strut and migration toward the center of the vessel as the flow reverses during each cycle. This process is illustrated in Figure 4.5 using instantaneous streamtraces extracted near the wall from the XIENCE V™ mid-stent ROI for the Re=160 condition. Figure 4.5a shows the relative positions within the flow cycle from which these particular snapshots were extracted. In order to verify the curved streamtraces represent the presence of vortical structures in the flow, a vortex identification scheme based on the eigenvalues ($\lambda$) of the velocity gradient tensor was adopted. It has been observed that the
presence of locally cyclic motion in a flow is associated with these eigenvalues containing a complex conjugate pair \((\lambda_c \pm i\lambda_{ci})\). The imaginary part of this pair, \(\lambda_{ci}\), can be interpreted as a measure of the swirling strength in a plane defined by the associated eigenvectors.[41] This has the advantage over a measure based on local vorticity in that it is frame-invariant and separates the effect of flow straining from the rotation. Strictly speaking, the presence of any non-zero complex eigenvalues should be sufficient to indicate the presence of a vortex, but it is often
convenient to set some minimum threshold for $\lambda_{ci}$ to exclude regions where the rotation is small, especially when using such methods with experimental data where measurement error may give rise to spurious structures. In addition, due to the presence of large variations in velocity over each of our ROI, it is difficult to set a single threshold for all areas of the flow. To overcome this, we have normalized each of the measured $\lambda_{ci}$ values by the magnitude of the local flow, $\|\vec{U}\|$. This is equivalent to normalizing the velocity gradient tensor by the same value, and yields the same eigenvectors and relationships between the eigenvalues while insuring the final eigenvalue magnitudes are independent of the local flow. Without such normalization, structures in the low velocity regions near the wall during flow reversal have eigenvalues so much smaller than the centerline flow that no single threshold can capture both regimes. These values have been plotted as color contours behind the streamtraces, with a value of 1000 chosen as the threshold for $\lambda_{ci}$.

Returning to Figure 4.5, as the flow begins to decelerate (snapshot I) a vortical perturbation can be seen developing just downstream of the strut where it crosses the imaging plane. As the flow in the vessel continues to decelerate, the fluid nearest the wall changes direction to match the rotation of the vortex behind the stent strut, separating it from contact with the wall and strut and causing it to “lift off” (snapshot II). This process continues as more of the fluid within the vessel reverses direction, drawing the vortex further into the lumen of the vessel (snapshot III), where it grows in area, combines with adjacent vortical structures, and stretches out into what appears to be a vortex sheet. Taking into account the three-dimensional nature of the vessel, it is likely these 2D vortices observed are part of more complex vortex tubes that wrap the vessel and interact with each other throughout each cycle. It is also important to note that the process is repeated as the flow changes direction from retrograde to forward in the second half of
each cycle. It appears that vortices may be present upstream of the stent struts as well, but they are harder to observe due to the visual obstruction of the flow by adjacent struts, and evidence for their presence is less clear in all cases.

Secondly, as can be seen in Figure 4.6, it was observed that the average WSS measured in the viewable area downstream of each strut followed closely the imposed mean flow rate. The main difference between locations and designs was in the magnitude of the measured WSS and OSI values. Instantaneous values over all tests ranged between approximately -10 and 30 dynes/cm² for the resting conditions, and -25 to 70 dynes/cm² for the exercise cases. The WSS values during the forward flow appeared to be more sensitive to changes in design and position than the values from the reversed flow. This caused the absolute mean of the shear stress to reduce more than the mean of the absolute shear stress in equation (5), resulting in an overall negative correlation between the time-averaged WSS and OSI. This negative correlation has also been observed by previous researchers.[42] Spatial variability over each ROI was small, and most of the variation was temporal.

Spatially, it was observed that the over-expansion of the stent into the vessels created a divergence at the proximal end and a convergence at the distal end, leading to corresponding decreases and increases in WSS over the axial direction, respectively. This is demonstrated for the XIENCE V™ stent in Figure 4.7 by the X<1 mm region in the upstream ROI (the WSS here drops from near 16 dynes/cm² to under 10), and in the downstream ROI for X>1.75 mm (where it recovers from around 3 dynes/cm² back to 16), but was seen for all designs under both resting and exercise flow conditions. Within the stent, time-averaged WSS values were lower as compared to the unstented portions, as was the magnitude of oscillations observed over the course of a cycle. Additionally, immediately downstream of the strut crossing in each ROI a
Figure 4.6: Time history of spatially-averaged WSS values behind a XIENCE V™ stent strut in each of the three ROI tested for the Re=160 flow conditions. Maximum, minimum, and standard deviation of spatial variability across each region are also shown.

Figure 4.7: Spatial profile of time-averaged WSS values in a XIENCE V™ stented vessel for the three ROI tested under Re=160 conditions. Standard deviation of the time history at each point is also shown to give an indication of the relative temporal variability at each location. The downstream edge of each crossing strut is labeled. Wall regions marked as “blocked” were obscured by other struts in the field of view, making measurements unreliable.
localized decrease in WSS was observed, with a corresponding increase in OSI for those regions. This drop may be related to the vortex lift-off process observed in the instantaneous velocity snapshots.

Finally, despite the similarities in the trends of the WSS values between each stent design, there were noticeable differences in the magnitudes. For simplicity, these differences are summarized here by taking the instantaneous WSS and OSI behind each of the struts marked in Figure 4.7 and averaging along the vessel wall until the next stent strut, both in time and space to get a single value for WSS and OSI for each stent design, ROI, and flow condition. Figure 4.8 and Figure 4.9 show the results of this analysis. The Cypher® and Liberte™ stents showed the lowest WSS values (0.63 - 4.58 dynes/cm² for Re=160; 0.18 - 13.48 dynes/cm² for Re=300) and the XIENCE V™ and VISION™ stents were higher (3.31 – 14.36 dynes/cm² for Re=160; 7.56 – 22.28 dynes/cm² for Re=300). The Endeavor™ stent had low WSS values behind the first strut (2.74 for Re=160 and 4.24 dynes/cm² for Re=300) and high behind the last (13.85 for Re=160 and 25.37 dynes/cm² for Re=300). OSI levels were consistent between the resting and exercise conditions (falling mostly between 0.1 and 0.3), but differences between the stent designs tested are less clear for OSI, aside from the persistence of an inverse correlation between WSS and OSI measured in the vessel.

**DISCUSSION**

The results of this study highlight the importance of considering as many physical elements of the stent-artery system as possible when conducting experimental or computational studies. In particular, it was observed that the overexpansion of the stent into a compliant vessel caused significant changes in the final geometry, creating a diverging channel at the proximal end of the stent and convergence distally to it. This led to a drop in WSS upstream of the stent
Figure 4.8: Effect of stent strut design on WSS behind struts
Figure 4.9: Effect of stent strut design on average OSI behind struts
followed by a subsequent rise downstream. This intuitive result has been previously observed in the computational work of LaDisa et al., which showed an increase in the WSS gradients in the inlet and exit regions of the stent and a reduction in WSS as the stent is progressively over expanded relative to the reference vessel.[27] While not tested here, it would be expected then that the degree of influence for this effect will be heavily dictated by the degree of overexpansion used, a parameter that often varies between patients.

Further work by the same group demonstrated that altering the amount of vessel prolapse between struts also influenced the measured WSS.[28] This prolapse, or pillowing, effect between struts was also observed here. Of particular interest is that the degree of pillowing was clearly time-dependent, as the entire vessel expanded and contracted in rhythm with the passing pressure waves. The diameter change was most noticeable between the struts, but could also be observed at each stent strut. Neglecting its effects could be expected to lead to incorrect estimation of the forces experienced by the cells at the vessel wall, especially closest to the struts. This makes one-to-one scale simulations even more important for experimental work, as attempting to simultaneously match all the relevant material and fluid parameters in a scaled-up compliant model is difficult.

This time-varying diameter change will also interact with the flow waveform, meaning that replicating the large phase offset between the pressure waveform (which will control the vessel diameter) and the flow rate is critical. Even if the time history of the flow rate is physiologically accurate, not properly constraining the pressure to pulse out-of-phase with the flow will lead to different WSS values. In both computational and experimental work, the inlet and exit boundary conditions must be carefully controlled to simulate the effect of the remainder of the systemic and coronary circulations on the region of interest. In computational work this
can be accomplished through Windkessel-type models at the boundary conditions; for experimental work a combination of fixed resistances, dynamic restrictions, and capacitive sections should be adopted as was done here. It is not sufficient to simply impose the desired flow rate with no consideration of the pressure effects, though determination of the extent of the differences could prove informative.

Examination of the WSS histories for the different stents tested revealed noticeable differences in behavior between the different DES designs. However, it is difficult to estimate whether the differences between the designs were statistically significant, since the compared average values were derived from measurements, which vary in space and time. As mentioned previously, based on our estimate of error propagation for these values the expected standard deviation of error for the final averages was very low, and we therefore feel confident that comparisons are valid. The two designs with the thickest struts, the Liberte™ (113 µm) and the Cypher® (153 µm), had the lowest time-averaged WSS values. The Endeavor™ DES (96 µm) had intermediate values, while the two stents with the smallest strut thickness, the XIENCE V™ (89 µm) and the VISION™ (81 µm) had the highest. It appears that for thicker struts, there is a greater velocity deficit near the wall behind the struts, depressing the near-wall gradients and therefore the measured WSS values. However, the correspondence is not exact, indicating that design as well as strut thickness plays a role. For example, the denser network of struts in the Liberte™ stent versus the Cypher® allows less distance for the flow to recover before the next strut, and could be the reason for the TAXUS® Liberte™ having a lower WSS even though the Cypher® has 35% larger struts. The CFD work of Berry et al. showed a similar linkage, demonstrating lower overall WSS for more closely spaced struts.[24] Supporting this, the XIENCE V™ and VISION™ stents shared the same design, and also had very similar WSS
distributions in space and time. Differences between them are likely attributable to slight variations in deployment, rather than the drug coating and small associated thickness change. Overall, though, it is hypothesized that the presence of the stent struts along the vessel wall disturbs the flow there, making it more receptive to direction changes and depressing the peak WSS experienced.

*In-vivo*, these differences in WSS become relevant because studies have linked lowered WSS to up-regulation of various growth-related proteins,[18] leading to vascular remodeling and neointimal growth.[21] Conversely, normal levels of WSS (15-20 dynes/cm²) have been shown to lead to a shift in endothelial cell (EC) phenotype from one having a random, cobblestoned appearance with proliferative behavior to a more slow-growing, flow-aligned fusiform type, in addition to increased expression of atheroprotective compounds such as endothelial nitric oxide synthase (eNOS).[43] One of the primary mechanisms used by the ECs to sense these changes in WSS appears to be the glycocalyx, a layer of macromolecules bound to the outside of the cell membrane. Recent results have shown its removal eliminates or reduces the expression of many shear-associated protective behaviors such as the production of nitric oxide[44] and a shift to a flow-aligned phenotype with reduced cell motility and turnover.[45]

Of particular interest to this study is the finding of Simon et al. who observed that for objects similar in size to stent struts (≥75 µm) under arterial flow conditions endothelial coverage was significantly reduced at 24 hr, and that a 250 µm object completely disrupted it.[46] This parallels the recent results of Joner et al. which examined in a rabbit iliac model the same five stent designs as were tested in this study.[47] They noted clear differences in endothelial cell coverage (both in amount and distribution) between designs at 14 and 28 day end points, both above and between stent struts, with the models having larger struts having less complete
coverage. In fact, if the WSS as measured here is spatially averaged over all three locations and plotted against the endothelial cell coverage as measured between struts using SEM by Joner et al. (Figure 4.10), very close agreement can be seen, although it is important to note for these in-vivo tests the drug coatings will influence cell response as well. These results both reinforce the idea that larger stent struts can lead to less endothelial coverage, and that reduced WSS may be a primary mechanisms for this effect. Future research should attempt to further elucidate the mechanisms by which these differences develop, but the current results illustrate the continued importance of hemodynamics in the development of new stent designs, and should provide a useful benchmark for validation of continuing computational studies.

Figure 4.10: average WSS over all stations for resting conditions from this study plotted against cell coverage between stent struts as measured by Joner et al. [47]
One final note should be made concerning the choice of a glycerine-water mixture as a Newtonian blood analog and its effects on the WSS measured. Blood is of course, a non-Newtonian fluid, and this difference will tend to lead to blunter flow profiles and slightly higher WSS in-vivo as compared to the results given here. However, CFD comparisons of various non-Newtonian blood models applied to steady flow through right coronary arteries has shown that distribution of WSS is largely unchanged between models. Only the relative magnitudes shift, and for sufficiently large velocities (>0.2 m/s centerline in a 2-3 mm vessels) the WSS is nearly identical to the Newtonian case.[48] In comparison, the average centerline velocity for resting conditions in this experiment was near 0.4 m/s, and approximately 0.75 m/s for exercise. Similar results were found when the simulations were extended to transient analysis.[49] We believe therefore that our choice of a Newtonian blood analog was reasonable in this case.

CONCLUSIONS

This study has shown for the first time, as far as the authors know, an in-vitro measurement of the flow within stented compliant arteries on a 1:1 scale under physiologically realistic flow conditions. These measurements were used to make comparisons of four different current-generation drug-eluting stents and a matching bare metal stent. Examination of the flow patterns noted some common features between all five designs, including a vortex lift-off phenomenon that occurs downstream of circumferential stent struts during each flow reversal, an inverse correlation between WSS and OSI (both locally and globally), and a drop in WSS upstream of the stent followed by a subsequent rise downstream of it, corresponding to the overexpansion of the vessel material. Furthermore, clear differences could be seen in the magnitude of the WSS between these four designs despite the small size of the struts in relation to the overall vessel diameter (~50-100 µm vs. 3.0 mm). Although the predicted standard
deviations of error on these averages is much less than the differences measured, the statistical significance of the variation remains unclear due to the nature of the signal being averaged.

Based on these results, it is hypothesized that the presence of the stent struts along the vessel wall disturbs the flow there, making it more receptive to direction changes and depressing the peak WSS experienced. These differences are important because previous studies have shown linkages between altered WSS and areas of endothelial cell damage and atherosclerosis, especially when average WSS values are lower than the normal range. The close correlation between the average WSS values measured here and the cell coverage around those stents as measured by Joner et al. further reinforces the continued importance of hemodynamics in the development of new stent designs. Future research should continue these efforts both to understand how differences in stent design leads to changes in the fluid dynamics, and to discover how the endothelial cells sense and respond to those changes.

ACKNOWLEDGEMENTS

Abbott Vascular provided partial support for this research. This material is also based upon work supported by the National Science Foundation under CAREER award #0547434. The authors would also like to thank Alpasian Kosoglu for his help running the processing software.
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Chapter 5: In-Vitro Comparison of the Effect of Stent Configuration On Wall Shear Stress Using Time-Resolved PIV

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To be submitted to the Annals of Biomedical Engineering

ABSTRACT

Time resolved particle image velocimetry was used to measure wall shear stress (WSS) and oscillatory shear index (OSI) within a 3.0 mm diameter compliant vessel model implanted with an Abbott Vascular XIENCE V™ stent in five configurations: baseline, over-expanded, increased diameter, two overlapped stents, and increased stent length. Flow through unstented vessels was also tested for comparison. Flow conditions featured a realistic coronary pressure-flow offset and reversal at average flow rates corresponding to resting (Re=160, f=70 bpm) and exercise conditions (Re=300, f=120 bpm). Comparisons revealed that the WSS was similar for all cases behind the first strut and downstream of the device, indicating that changes in configuration have little effect downstream. However, there were notable differences within each stent revealing reduced WSS values for all cases due to the stent-imposed expansion of the vessel wall (3.29-9.39 dynes/cm² for Re=160 and d=3.0mm). Over-expanding the stent with a second balloon affected the alignment of the stent geometry, and led to higher WSS at the inlet and lower values at mid-stent. The overlapped stents showed disturbed flow and a WSS deficit region downstream of the overlapped region. Analysis of the longer stent showed that the WSS within the vessel recovers with distance. An overall correlation was noted between decreased WSS values and elevated OSI. Results of this study are important because decreased WSS has been implicated in endothelial cell changes and increased restenosis, and clinical research has shown that a link exists between deployment configurations and negative patient outcomes.

Key Terms: Coronary stents, Wall Shear Stress, time-resolved DPIV, design comparison, blood flow
INTRODUCTION

The goal of this paper is to explain the differences seen *in-vitro* due to the effect of variations in implantation strategy for a particular drug-eluting coronary stent on the fluid dynamics within the vessel, and in particular the wall shear stress (WSS) experienced at the vessel walls. This problem is of considerable interest since the implantation of coronary stents is among the most widely used treatments for coronary artery disease (CAD), which is the most common cause of death from cardiovascular disease. In general, cardiovascular disease (CVD) is among the leading causes of death throughout the developed world. In the United States, one in five Americans suffer from some type of CVD and in 2006 alone these diseases accounted for nearly one million deaths and $430 million in health care costs [1]. If achieved, NCHS estimates indicate that a complete elimination of CVD might lead to an increase in the lifespan of an average American of almost seven years [2]. It is clear that improvements in the treatment, diagnosis, and prevention of these diseases are among the most important health challenges faced today.

Among deaths from cardiovascular disease, CAD accounts for just over half (54%), much more than stroke, the second leading cause, (18%). Many treatments exist for CAD, but the use of coronary stents is one of the most popular. Beginning with their approval by the United States Food and Drug Administration in 1994, usage of these devices in the US alone has grown from 800,000 devices in 500,000 patients in 1994 [3] to over one million procedures per year in 2003 [4], and has continued to grow since. However, concerns regarding high failure rates from restenosis and thrombosis [5-12] have long plagued bare-metal stents (BMS), with typical rates of restenosis over the first 6-12 months of 10-30% [13]; these effects are believed to be influenced by abnormal wall stresses and disrupted blood flow around the stent [14]. To combat
these problems, Drug-Eluting Stents (DES) were introduced, showing very promising results in initial trials [15]. However, some recent and still controversial studies have led researchers to re-examine their long-term outcomes in comparison to BMS [16-19]. Late stent thrombosis (LST), which often involves excessive fibrin formation and incomplete re-endothelialization of the stented area, is the most common problem observed and has been linked to an increased risk of myocardial infarction and death [18].

This incomplete re-endothelialization also suggests that the direct interaction of the stent struts with the flow may play a greater role in the success after implantation for DES than for traditional BMS (which are typically quickly covered by a layer of cells). It has long been known that a connection exists between stent design, implantation strategy, and patient outcome [6-9,12,20,21], and also between wall shear stress and neointimal formation, thrombosis, re-endothelialization, and restenosis [10,14,22-25]. Therefore it is widely believed that these trends can be explained in part by alteration in wall shear stress levels as a result of differing stent design and implantation configurations, although the exact biochemical and hemodynamic pathways by which this occurs remain unclear.

Although recent advances in *in-vivo* flow measurement now allow a more detailed examinations of the flow within the body than ever before, for the moment, full understanding of the fluid mechanics involved still requires the use of computational and *in-vitro* studies. Historically, the majority of detailed work on the hemodynamics of stented arteries has been done using CFD [26,27]. However, a variety of complicating details make exact numerical replication of in-vivo conditions difficult, including moving, compliant walls, complex stent geometries, and unsteady transitional flows. To overcome these problems, published studies have used simplified stent strut geometries, idealized flow curves, ignored the phase offset
between pressure and flow in the coronary circulation, or failed to consider compliant walls (one of the most common simplifications) [26,28-35]. With continuing advancement in computational power and CFD algorithms, these restrictions are rapidly easing.

In contrast, fewer experimental investigations into the hemodynamics of stented arteries are available [26,27], for many of the same reasons that made computational studies difficult. An additional difficulty for experimental studies is matching the physical scaling of the small coronary vessels, as it is often difficult to fully match dynamic similarity with a scaled-up model and achieving sufficient spatial resolution and accuracy at a 1:1 scale is challenging. Previous studies have overcome these difficulties in working with compliant models by using dye visualization in large-scale models [28,36], or performing quantitative measurements in idealized, scaled-up, rigid fixtures [29,37]. Yazdani et al. [38] did perform particle image velocimetry (PIV) measurements in stented compliant vessels, but they also used a large-scale model (as compared to coronary circulation) and used a rigid tube and Cordis S.M.A.R.T.® biliary stent as models, instead of coronary stent designs. Many of these studies used idealized velocity profiles, and none took into account the effect of the phase angle between the pressure and flow, which occurs in the coronary arteries [39]. In our previous work on this topic [40] we attempted to eliminate some of these difficulties by using physiologically-scaled compliant vessels implanted with commercial stents. Using high speed, high resolution PIV measurements, five different current commercial designs were compared under realistic, offset pressure and flow conditions and clear differences in WSS were observed between the models. These variations were observed to correlate well with the endothelial cell coverage measurements of Joner et al.[41] for the same five designs.
The goal of this study was to extend our previous work from a design comparison between different stents [40] to a comparison of the use of one of these stents when implanted under different configurations commonly used by surgeons for treating different vessel and lesion types. These included changes in total stent length, overlapping multiple stents, overexpansion of the stent during implantation, and differing vessel diameters, all of which have been previously implicated in affecting patient outcomes. As before, PIV was used to examine the in-vitro hemodynamics in each of these configurations under realistic offset flow and pressure waveforms, and the hemodynamic indices of WSS and oscillatory stress index (OSI) were focused on as the basis for comparison. Such a study has never before been described. An additional advancement of this work over our previous effort was the incorporation of a new PIV correlation method, the robust phase correlation (RPC) in our processing algorithm [42-44]. Further details on these methods are described below.

**METHODOLOGY**

To simulate and measure coronary flows in stented arteries, a flow loop was constructed and digital particle image velocimetry (PIV) was used to quantify the near-wall flows as has been previously described [40]. In brief, a computer controlled gear pump was used in conjunction with a pressurized capacitance chamber and a solenoidal clamp valve to simulate coronary flows, including the clinically observed phase offset between the flow rate and pressure wave forms of ~220° [39]. Figure 5.1 shows a diagram of this setup. Testing was conducted in straight transparent vessels manufactured from Sylgard 184 (DOW Corning), and the working fluid was a 40/60 blend of glycerin and water (by volume) selected to yield a viscosity and density similar to that of human blood (\(\nu=3.72 \times 10^{-6} \text{ m}^2/\text{s}, \rho=1099.3 \text{ kg/m}^3\)). The test section was immersed in a bath of the same solution to minimize mismatches in the index of refraction,
greatly reducing reflection and refraction from the vessel walls. Flow conditions were selected to replicate resting and exercise conditions as given in Table 5.1, and instantaneous flowrates and pressures were monitored during the experiment by an ultrasonic flow meter and a pressure gage placed just upstream of the test section, as can be seen in Figure 5.2. Reynolds numbers were calculated based on time-averaged bulk flow velocities and vessel diameter before deployment.

To test the effect of stent deployment on wall shear stress (WSS), a current-generation drug-eluting stent (Abbott Vascular’s XIENCE V™) was deployed according to the manufacturer’s recommendations using an endeflator into the simulated arteries (pre-strained to +5% of their resting lengths) to create five different configurations, as shown in Table 5.2. The stents were each inflated to 110% of their nominal diameters, replicating common clinical
practice, except for the over-expanded configuration, which was inflated to 125%. After the balloons were withdrawn, the stents were allowed to recoil to their final diameters (approximately 3.2-3.25 mm and 3.3-3.4 mm lumen diameter for the two conditions, respectively). To compare the effect of longer stent deployments, both a single 28 mm stent and a series of two overlapping 18 mm stents were chosen. For the overlapping stents, the distal device was deployed first, followed by the second proximal stent inside the first with an overlap of 2.75 mm (two strut patterns). To test for dependence on vessel size, a 4.0 mm stent was also used. For all cases, at least 60 mm was allowed between the stent and its upstream mounting point. Vessels used for each test had an lumen diameter matching the stent size, and a wall thickness of 0.4 mm. The modulus of elasticity was previously found to be approximately 1 MPa [45], similar to that of human coronary arteries [46]. Tests were also conducted on each vessel diameter with no stent present.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Re</th>
<th>Heart rate (bpm)</th>
<th>Womersley parameter</th>
<th>Flow Rate (mL/min)</th>
<th>Pressure Range (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>resting</td>
<td>160</td>
<td>70</td>
<td>2.09</td>
<td>85</td>
<td>80 – 140</td>
</tr>
<tr>
<td>exercise</td>
<td>300</td>
<td>120</td>
<td>2.73</td>
<td>160</td>
<td>80 – 190</td>
</tr>
</tbody>
</table>

Table 5.1: Flow conditions

Figure 5.2: Pressure and flow. Left, resting (Re=160); Right, exercise (Re=300)
Table 5.2: Stent deployment. Abbott XIENCE V™ stents were used for all tests.

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Diameter, design/deployed (mm)</th>
<th>Covered length (mm)</th>
<th>Vessel length (mm)</th>
<th>Entrance length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference</td>
<td>3.0 / 3.3</td>
<td>18</td>
<td>184</td>
<td>90</td>
</tr>
<tr>
<td>over-expanded</td>
<td>3.0 / 3.75</td>
<td>18</td>
<td>198</td>
<td>85</td>
</tr>
<tr>
<td>long stent</td>
<td>3.0 / 3.3</td>
<td>28</td>
<td>202</td>
<td>87.5</td>
</tr>
<tr>
<td>overlapping stents</td>
<td>3.0 / 3.3</td>
<td>33.25</td>
<td>200</td>
<td>78</td>
</tr>
<tr>
<td>large vessel</td>
<td>4.0 / 4.4</td>
<td>18</td>
<td>161</td>
<td>80</td>
</tr>
</tbody>
</table>

Figure 5.3: Diagram of the relative positions of the various ROI along the stent lengths. US: upstream, proximal; MS: mid-stent; DS: downstream, distal

Flow was measured using PIV, a well-established non-invasive optical technique [47] at either three or four regions of interest (ROI) oriented parallel to the vessel within each configuration. These regions, as shown in Figure 5.3, were centered just downstream of the first strut (upstream or US), near the middle of the stent (mid-stent or MS) and downstream of the final stent strut (downstream or DS). The laser illumination plane on which measurements were taken was centered within the vessel lumen, and the camera was placed perpendicular to it. Each ROI was positioned to focus on a region of wall just downstream of where a link connected two adjacent rings of struts within the stent, but also included adjacent upstream regions and the entire vessel width so that the measured velocities at the wall could be placed in context with the
Figure 5.4: Location of the ROI relative to the strut pattern. A) Overhead view of the ROI with the laser plane marked by a line, and the region where WSS was measured marked by a circle. B) Side view of the ROI showing relative size of ROI in relation to the stent struts and vessel.

overall flow patterns (see Figure 5.4). For the 3.0 mm vessels, the field of view was 3.56x2.44 mm at a resolution of 1.73 µm/pix; for the 4.0 mm vessels, the field of view was 4.73x3.25 mm at a resolution of 2.31 µm/pix. The working fluid was seeded with 7 µm red fluorescent polystyrene beads, and illumination was provided by a frequency-doubled (532 nm) Nd:YAG pulsing laser (LDP-100MQG, Lee Laser). Image pairs were acquired at 300 pairs per second, with 50 and 25 µs pair separations for the 3.0 mm vessels, and 70 and 45 µs pair separations for the 4.0 mm cases (resting and exercise conditions, respectively). Reflections and background illumination were blocked using a dichroic filter fixed to the camera lens, and to compensate for the low levels of fluorescent emission a 4 megapixel light-intensified camera (X5i, IDT) was used. The acquired image pairs were processed using a multi-pass, DWO algorithm [48,49] to yield a 128x88 vector field. A robust phase correlation algorithm was used for the displacement
kernel [42], and was supplemented by the use of a multi-frame correlation technique [50-52] to compensate for the large dynamic range between the high velocity at the centerline during peak forward flow and the low velocities near the wall during reversal. For each combination of stent, flow rate, and ROI, 1,285 image pairs were captured yielding either 5 or 8.6 periods of the flow.

To calculate the fluid shear stress at the walls (WSS) the discrete pixel wall location for each data set was found as a function of time using a CUMSUM test for change point analysis [53] based on the local value of the horizontal standard deviation of image intensity [54]. This data was parameterized using a cubic smoothing spline to allow tracking of the vessel wall. This surface information was then combined with the phase-averaged velocity vectors to calculate the tangential WSS and OSI between the stent struts in each vector field. For this work, WSS was defined as the product of the dynamic viscosity ($\mu$) and the component of the fluid strain rate tensor oriented tangential to the wall, $\dot{e}_{12}$ as shown in Equation (1).

$$WSS = \tau_w = \mu \dot{e}_{12}$$

(1)

To compute this quantity, the strain rate was calculated in a Cartesian camera-oriented coordinate system (the gradient calculation is described below), and transformed using the local wall normals at each horizontal location into a wall-oriented system to find the tangential strain component. Further details of the transformation were given in [40]. From these values, the oscillatory shear index is then determined in terms of the WSS by the following equation, where $t$ is time and $T$ is some multiple of the flow period.

$$OSI = \frac{1}{2} \left( \frac{1}{T} \int_0^T \tau_w \, dt \right) \left( 1 - \frac{1}{T} \int_0^T |\tau_w| \, dt \right).$$

(2)
Velocity gradients were calculated from a surface fit of the velocity using thin plate spline radial basis functions (TPS-RBF)[55]. At each wall location, a 5x5 vector grid with one of its edges centered on that point was used to derive a surface fit. The obtained function was then differentiated analytically to obtain the wall gradients. This method has been demonstrated to be more resistant to experimental error than traditional finite differencing and polynomial interpolation schemes, both of which were tried here and yielded qualitatively poorer results. In their paper, Karri et al. showed that for Womersley-type flow, the gradient schemes used here, and assuming 10% random error on the velocity measurements, the instantaneous gradient errors should be contained under 20%; applying that variance to the current study for averages over one period in time or along the vessel length suggests that WSS error should be less than 3%. The principal error in the reported WSS and OSI values will be therefore due to errors in the wall detection or bias in the velocity fields, which should be similar in magnitude to the random error (< 10%). The effects of random errors in the velocity fields were further reduced during processing by using proper orthogonal decomposition (POD) to automatically construct a low-order model of the flow field based on first few modes, again as described by Karri et al. [55] except that here the differentiation was done at each time step on the reconstructed flow fields, instead of on each spatial mode as was suggested in that work. Typically only 3 spatial modes were required to capture the behavior of the flow near the walls, and were sufficient to capture at least 99.5% of the original energy of the flow. A full description of POD is beyond the scope of this text, but a good introduction to the method may be found in a review by Berkooz et al. [56] and the tutorial of Smith et al. [57].

Tests of this POD filtering procedure for differing numbers of modes indicated that the calculated average values for WSS and OSI typically varied less than 10% for a reconstruction
using only 3 modes as compared to reconstructions using some or all of the remaining modes, comparable to the estimated error level of the PIV velocity determination and gradient estimation procedures.

Results for the baseline case (XIENCE V™ stent, 3.0 mm diameter, 18 mm length) are based off the same image sets used in our previous work [40]. However, the analysis reported here was repeated from the beginning using the modified methodology described above to allow direct comparison to the new test cases that are the focus of this paper.

RESULTS

Spatial and temporal wall shear stress distributions were similar between the five configurations tested. In each case, the WSS pattern at each point generally followed the overall imposed flow rate profile in shape, and was similar between tests, which implies that the overall dynamics are dominated by the driving flow waveforms and the large-scale vessel geometry. However, important differences were observed primarily in the relative magnitudes of the curves. A summary of the WSS and OSI values for each case tested can be found in Table 5.3, and these results are plotted in Figure 5.5 and Figure 5.6. The reported means are averaged over the stated ROI in space and time for WSS and OSI, and the minimum and maximum WSS values were computed by first taking the spatial mean over the given ROI, then selecting the min or max WSS value in time for that average curve.

In regards to spatial variation, due to their overexpansion during implantation into a compliant vessel all the cases demonstrated a divergence of the vessel wall upstream of the first stent strut, and a convergence downstream of the final strut (as seen in Figure 5.4). Accordingly, time-averaged WSS decreased upstream of the stent, and recovered in the region downstream of it. For the baseline case shown in Figure 5.7, the WSS started around 11 dynes/cm² outside the
Table 5.3: Summary of WSS and OSI values for each case

<table>
<thead>
<tr>
<th>Stent</th>
<th>Re#</th>
<th>ROI</th>
<th>WSS (dynes/cm²)</th>
<th>OSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mean</td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>min</td>
<td>max</td>
</tr>
<tr>
<td>XIENCE 3x18 reference</td>
<td>160</td>
<td>US</td>
<td>7.21</td>
<td>-13.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS</td>
<td>3.29</td>
<td>-6.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DS</td>
<td>10.32</td>
<td>-10.31</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>US</td>
<td>11.28</td>
<td>-22.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS</td>
<td>3.23</td>
<td>-13.73</td>
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<td></td>
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<td></td>
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<td>MS1</td>
<td>3.88</td>
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</tr>
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<td></td>
<td></td>
<td>MS2</td>
<td>8.60</td>
<td>-9.32</td>
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<td></td>
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<td>13.27</td>
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<td></td>
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<td></td>
<td></td>
<td>MS1</td>
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<td></td>
<td></td>
<td>MS2</td>
<td>12.85</td>
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<td>DS</td>
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<td>-11.36</td>
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<td></td>
<td></td>
<td>MS2</td>
<td>4.30</td>
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<td></td>
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<td></td>
<td></td>
<td>MS1</td>
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<td></td>
<td></td>
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<td>DS</td>
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</tr>
<tr>
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<td>-6.21</td>
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<td>24.05</td>
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<td>-4.97</td>
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<td></td>
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<td>MS</td>
<td>1.33</td>
<td>-2.79</td>
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<td>5.01</td>
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<tr>
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<td></td>
<td></td>
<td>DS</td>
<td>10.04</td>
<td>-3.66</td>
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</table>
Figure 5.5: Effect of stent configuration on average WSS behind struts for XIENCE™ stents
Figure 5.6: Effect of stent configuration on average OSI behind struts for XIENCE™ stents
stent and declined to near 5 dynes/cm², and recovered more quickly downstream of the last strut to near its original values (over 0.9 vs. 0.5 mm). Downstream of the first strut, the average WSS was stable around 7 dynes/cm². However, moving to the mid-stent location values were lower, with average WSS distal to that strut at about 3.3 dynes/cm². In the downstream ROI within the stent values increased and became similar to the ones in the upstream location.

Figure 5.8 shows a comparison of the spatial profiles and time histories for stent configurations of varying total length under resting (Re=160) conditions. As can be seen, the profiles behind the first strut at the inlet were very similar for all three configurations tested, with the overlapping stent case having slightly higher WSS versus the baseline and 28 mm length cases, as were the profiles past the final downstream strut. However, the patterns within the middle of the stent were different. At the first midstent location (behind the 7th ring of struts for each of the three cases) the 18 mm baseline and 28 mm stent both continue to show substantially decreased WSS patterns (3.29 and 3.88 vs. 7.21 and 6.80 dynes/cm²). In contrast the overlapping stent case shows WSS decreased from the values near the inlet 8.50 vs. 9.39 dynes/cm². This change is primarily attributed to higher peak WSS for the overlapping case, as
Figure 5.8: Effect of stent length and overlap on the WSS for each ROI under resting conditions. a) time-averaged WSS versus position b) time histories of spatially-averaged WSS
the minimum value during each cycle is practically unchanged. At the second midstent location (which has no correspondence in the 18 mm stent results), the WSS in the 28 mm stent has recovered to a value higher than the upstream ROI. In the overlapping stent case, the second midstent location was recorded at the same distance from the inlet as in the 28 mm stent (and the same distance as the downstream ROI in the 18 mm stent), but directly distal to the area of overlap between the upstream and downstream stent. For this configuration the average WSS is much lower than the first midstent ROI (4.30 dynes/cm²). Trends for the exercise conditions were similar, and are not shown here.

Changes in the overexpansion ratio of the stent implantation and vessel diameter also altered the WSS profiles within the stent (see Figure 5.9 for resting conditions). Both the over-expanded and large diameter cases showed similar WSS profiles and means at the first ROI. These values were approximately 45% smaller than the baseline case at that location. At the midstent location, the WSS value dropped for the 4.0 mm diameter stent (from 4.05 to 1.33 dynes/cm², or 67%), similar to the drop seen in the baseline 3.0 mm stent (7.21 to 3.29 dynes/cm², 54%). Examining Figure 5.9b it can be seen that these drops in mean were caused by consistent decreases in WSS throughout the flow cycle. In contrast, the average WSS in the over-expanded 3.0 mm stent rose at this ROI to a value of 7.21 dynes/cm², comparable to the mean value and spatial profile measured for the upstream region in the baseline stent. Values at the downstream location (measured just distal to the final strut in each stent) were similar for the two 3.0 mm stents (10.32 and 9.03 dynes/cm²), but were much lower for the 4.0 mm stent (5.01 dynes/cm²), which is to be expected in a larger diameter vessel. For comparison, tests of empty vessels under identical conditions to those studied here resulted in average WSS and OSI values of 21.08 dynes/cm² and 0.12 for Re=160 and 33.74 dynes/cm² and 0.10 for Re=300 in a 3.0 mm
Figure 5.9: Effect of stent overexpansion and diameter on WSS for each ROI under resting conditions. a) time-averaged WSS versus position b) time-histories of spatially-averaged WSS
vessel, and 8.23 dynes/cm² and 0.12 at Re=160 and 12.38 dynes/cm² and 0.09 at Re=300 in a 4.0 mm vessel.

Although OSI did vary between configurations and positions, trends were less clear than for the WSS values. OSI values for the resting conditions generally stayed in the 0.1 to 0.2 range. For the exercise conditions almost all cases illustrated a reduction in OSI approximately 30% in average across all cases. However the exact reduction varied widely from 6% (XIENCE 3x28 MS2) to 64% (XIENCE 4x18 MS). In contrast, it should be noted that the reference case (XIENCE 3x18) was the only one to present an increase in OSI for exercise conditions.

Comparing the OSI values between US and DS locations across all configurations we note that the US OSI is noticeably higher (approximately 40%) compared to the DS value for resting conditions. For exercise conditions although the trend is the same only a 4% reduction is estimated. Also, comparing OSI values between resting and exercise conditions an overall reduction is observed (almost 10%) but it substantially more pronounced at the stent proximal and distal ends.

The most noticeable observation was an overall inverse correlation between OSI and average WSS values. This relationship was initially suggested in our previous investigation [40] for arteries stented with different commercial stents however it was not explored in more depth in that work. Other researchers have posed a similar argument about the relationship between time averaged WSS and OSI (Fiedman and Deters [58] in aortic bifurcations, Huo et al. [59] coronary bifurcations, Steinman et al. [60] and Lee et al. [61] for carotid bifurcations). Huo et al. in particular noted a power law relationship to the localized measurements, and quantified the relationship for each of their test cases [59].
To visualize this relationship, averaged WSS and OSI results are plotted in Figure 5.10. As the experimental setup and conditions for this work are identical to our previous study of the effect of stent design, values from that analysis [40] are also included for completeness. A linear regression line for the entire ensemble was calculated for each of the resting and exercise conditions, and is also marked. The standard errors on the slope and intercept for the resting conditions were 0.0018 and 0.0144, respectively, and were 0.0015 and 0.0235 for the exercise conditions, with all measures having a p-value less than or equal to 0.0001, indicating a high degree of significance for the fits. As can be seen, the spread of data points from both studies are
reasonably consistent with each other. The correlation coefficients for the linear regressions do not indicate exact correlation between OSI and WSS ($R^2$ values are 0.482 and 0.3438); however, this is to be expected since the goal of both studies was to test the effect on WSS of various changes in stent design or implant configuration. Therefore, the low correlation merely indicates that for a given input flow the resulting changes in OSI cannot be determined solely by the changes to the WSS magnitude. Also, a linear regression is probably not the most appropriate fit for the data, as it implies that for sufficient WSS, OSI will drop to zero, and that for zero WSS the OSI will be less than one-half. However, by definition the OSI must be 0.5 at zero WSS, and for the flow conditions tested, reversed flow (and therefore a non-zero OSI) will almost certainly be present.

DISCUSSION

Overall trends observed for the stents tested here were similar to the previously observed results for these stents [40], with a vortex appearing downstream of each stent strut and lifting off during flow reversal into the mean. As before, the over-expansion of the stent into the vessels caused the formation of diverging and converging sections at the proximal and distal ends of the stents, respectively. Spatially averaged WSS values downstream of the strut in each ROI followed the imposed flow rate closely, and the previously observed inverse relationship between mean WSS and OSI was also observed here.

In regards to the particular conditions studied in this work, variations in implantation strategy for this stent design did not have much effect on the OSI and WSS measured distal to the device, as the WSS profiles all appear to converge to the same Figure 5.8 and Figure 5.9). Additionally, for the three tests where the stent was deployed to the same diameter (baseline, long stent, and overlapped stent) the values for WSS behind the first strut in the upstream ROI
are all substantially similar, and this agreement extended to the second ROI for the baseline and long stents. However, using overlapping stents in place of a single longer stent appears to disrupt the flow within the stented region, as WSS values were higher than baseline at the first midstent ROI, and substantially lower than in a single long stent at the second midstent ROI (which was located at the same distance from the inlet for both configurations). Since the second midstent measurement location is just distal to the overlapped region, it appears that the overlapping of two stents just upstream is creating a larger flow obstruction near the walls, leading to greater velocity deficits and lower WSS values. This can have significant ramifications since the accepted clinical procedure is to implant the most distal stent first so that subsequent implantation does not disturb the first device. This procedure can lead either to the first (downstream) stent being expanded further than was planned (during the second balloon inflation) or to the second stent not being able to expand fully as it pushes against the first, and being left protruding further than designed into the flow. Either could contribute to a WSS deficit downstream of the overlap region, and since low WSS values have been linked to restenosis and plaque deposition, might indicate a region more prone to these effects. Additionally, the second scenario could explain the slightly higher WSS upstream of the overlapped region as well, as incomplete expansion would leave the vessel lumen narrower, and thus subject to higher flow rates and WSS values.

Regarding the long stent as compared to the baseline case, after an initial decrease in WSS from the upstream ROI to the first midstent location, it appears that the WSS behind each strut begins to recover to a higher value with distance. This may indicate that flow is recovering from the divergence at the inlet. Typically, expansions such as this create a velocity deficit in the flow profiles near the wall that requires a certain distance to recover. It may be that the
shorter baseline stent is too short to exhibit this behavior, while the longer 28 mm stent is not. Interestingly, previous clinical research has indicated that longer stents are correlated with negative patient outcomes. Examination of the WSS and OSI between the two cases, however, does not reveal any major differences that might account for this behavior. One possible explanation is that vessel injury from implantation could be more responsible, or that patients with more challenging lesions received the longer stents. However, the use of two stents to cover a given vessel length as compared to a single long stent was associated with increased disruption of the flow patterns and WSS values, indicating that the use of a single stent might be preferable clinically.

In comparing the effect of implanting stents of varying diameter into matching vessels, WSS values for the 4.0 mm stent and vessel were decreased as compared to the baseline 3.0 mm case, however, changes were consistent with the drop observed for vessels with same diameters in which no stent was implanted (about 60%). Analysis of changes in WSS for a hypothetical Poiseuille flow in pipes of the same diameter yields a 42% drop, reinforcing the suggestion that the primary driver of the differences between these cases is the change in diameter. Any differences caused by the change in ratio between the strut size and vessel radius (strut size and layout are identical for the two stents) are concealed within this more dominant effect.

In contrast, the expansion of a second balloon catheter into the stent to inflate it to 125% of its design size yielded clear differences versus the baseline, a 10% over-expanded stent. This variation is of interest clinically because doctors frequently over-inflate the stents in order to assure patency within the vessel, or use multiple balloons to insure that the plaque in sufficiently compressed to reopen the vessel. Testing only a standard inflation regimen would not reveal any differences this might cause. Most notably, the pattern of WSS was changed, with the values
behind the upstream strut being depressed versus the baseline, and those behind the midstent strut being elevated. It was observed that the strut pattern appeared visually to be less regular as compared to the baseline configuration. This could have resulted in the struts and links being aligned differently within the vessel, leading to the changes measured.

An overall comparison of the OSI trends showed that the values are consistently higher in the proximal end compared to the distal end. This phenomenon can be explained by the fact that at the proximal end the flow is diverging therefore it is more receptive to adverse pressure gradients ultimately becoming unstable and with higher fluctuations. In contrast, the distal end is converging therefore will be subject to favorable pressure gradients and more stable. Such higher OSI values could be linked to detrimental effects and this behavior is in agreement with clinical observations suggesting higher prevalence of edge restenosis at the proximal versus the distal end of the stent.

A similar argument holds for explaining the overall reduction of OSI for exercise versus resting conditions. Although the baseline configuration showed increase in OSI for the higher Reynolds number, which is intuitively consistent, all other cases resulted in reduced values. Increase of OSI with Reynolds number suggests that the flow fluctuations are inertia dominated and will be controlled by the microscale interactions with the stent struts. In contrast, a reduction of OSI suggesting, less unsteadiness in the flow, implies that the stent struts (which are the same for all cases) no longer dominate the near wall flow and the large scale geometrical distortions induced by the different deployment strategies are the culprit.

In summary, this work addresses the effect of different stent deployment configurations on the time averaged WSS and OSI and represents an advancement of our previous effort [40] where we studied the effect of stent design and the corresponding micro geometry on the WSS
and OSI. Clear differences were observed between different implantation configurations even when the same stent design is used for all tests. This was consistent with previous clinical research on patient outcomes. Supporting this, our previous study of stent design showed that the WSS values we measured were well-correlated with the extent of for in-vivo cell coverage as previously reported by Joner et al. [41] for the same set of designs. This suggests that differences in WSS seen in this study might give rise to similar changes in the recovery of the endothelial cell layer between stent implantation configurations. It is well known that low WSS leads to up-regulation of various growth-related proteins [22] and is linked to vascular remodeling and neointimal hyperplasia [23]. Similarly, there appears to exist a normal range for WSS in the vasculature of about 15-20 dynes/cm² that creates a more regular endothelial cell layer and induces atheroprotective signaling pathways [62-64]. However, in this case, the origin of these differences is not dominated by the stent design and strut geometry, but by large-scale geometrical features that are attributed to the deployment procedure.

Work is ongoing to further analyze these measurements to better understand the flow changes that gave rise to the measured WSS values and the link between OSI and WSS, and how these values can be used to create better stent designs and guide physicians to the best choice of implantation configuration to treat a given lesion.

ACKNOWLEDGEMENTS

Abbott Vascular provided partial support for this research. This material is also based upon work supported by the National Science Foundation under CAREER award #0547434.
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Chapter 6: Comparison of Methods to Calculate Pressure Fields from Noisy Time-Resolved Experimental Velocity Fields

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To be submitted to the journal Measurement Science and Technology

ABSTRACT

This paper explores the challenges associated with the determination of pressure from DPIV-measured planar velocity fields for time-dependent incompressible flows. Several methods that have been previously explored in the literature are compared, including direct integration of the pressure gradients, and solution of different forms of the pressure Poisson equations. Their dependence on grid resolution, sampling rate, and velocity measurement error levels was quantified using artificial data of two ideal sample flow fields – a decaying vortex flow and pulsatile flow between two parallel plates. The need for special attention to mitigate the velocity error propagation in the pressure estimation is also addressed using a physics-preserving method based on Proper Orthogonal Decomposition.

The results demonstrate that there is no unique or optimum method for estimating the pressure field and the resulting error will depend highly on the type of the flow, but the virtual boundary, omni-directional pressure integration scheme first proposed by Liu and Katz performed consistently well. Estimated errors can vary from less than 1% to over 100% with respect to the expected value. However, the analysis offers valuable insight that allows optimizing the choice of methods and parameters based on the flow under consideration.

Key Terms: Digital Particle Image Velocimetry, Error Analysis, Pressure Estimation, Poisson Equations
INTRODUCTION

Since its introduction, DPIV, a non-invasive optical method for the measurement of fluid velocities, has become a standard technique in experimental fluid dynamics [1]. Recently, with high repetition rate (>1 kHz) pulsed lasers and cameras becoming more widely available, time-resolved DPIV has become more popular, allowing researchers to observe the spatio-temporal development of flow structures.

For investigating and understanding the dynamics of complex flow fields the interplay between pressure and velocity and their respective fluctuations is of paramount importance. Unfortunately, non-invasive pressure field measurements have been unattainable and pressure measurements have been limited to traditional methods such as probes and pressure ports.

Examination of the Navier-Stokes equations for incompressible flows indicates that derivation of these pressures from the PIV data is possible. In fact – as it will be discussed in the following section – previous works by other researchers have proposed and demonstrated several methods for estimating the pressure field from DPIV velocity data. However, little work has been done to determine the most effective methods or their dependence on grid resolution, sampling rate, and velocity measurement error, in particular for time-varying flows. More importantly, to the best of the authors’ knowledge there are no published works offering an in-depth quantification of the error involved with these methods. This paper tackles these challenges, and performs a detailed comparison of the best form of the governing equations to use, compares several proposed smoothing functions, and studies the effect of velocity error level, grid resolution, and sampling frequency on two synthetic flow fields.
BACKGROUND

Three main approaches have been popular so far in deriving pressure fields from velocity data. These are direct integration of the pressure gradients in the Navier-Stokes equation along a path [2-4], global solution of the pressure Poisson equation [5-10], or a CFD-based flow modeling approach [11,12].

Line integration approaches typically start by rewriting the Navier-Stokes equations with the pressure gradient term on the left side, and the remaining acceleration and viscous terms on the right. Due to difficulties with estimating variations in the fluid density, this type of analysis is usually constrained to incompressible flows. Equation 1 shows one way this might be written, with $P$ representing pressure, $\rho$ a constant density, $u$ the velocity field, $t$ a time, $\mu$ a constant dynamic viscosity, and $F$ a vector field. The contributions of body forces such as gravity have been ignored but could be easily included.

\[
\nabla P = -\rho \left( \frac{\partial u}{\partial t} + u \cdot \nabla u \right) + \mu \left( \nabla^2 u \right) = F
\]

Equation 1

These equations then describe a conservative vector field ($F$, the entire RHS) equal to the gradient of a potential function (pressure), and therefore any line integral between two points will describe the relative pressure difference between them. In practice, the pressure field can be reconstructed over the entire velocity field, starting from a known or assumed pressure measurement, by numerical integration over a single path [2], or averaged between multiple paths [3,4]. Averaging tends to smooth out the effect of any errors in the velocity field.

The pressure Poisson equation is typically derived by taking the divergence of Eq. 1 above. This can then be written as

\[
\nabla^2 P = \nabla \cdot \left\{ -\rho \left( \frac{\partial u}{\partial t} + u \cdot \nabla u \right) + \mu \left( \nabla^2 u \right) \right\} = \nabla \cdot F
\]

Equation 2
or by applying the incompressible form of the continuity equation,

$$\nabla \cdot \mathbf{u} = 0 \quad (3)$$

then Eq. 2 becomes

$$\nabla^2 P = -\rho \nabla \cdot (\mathbf{u} \cdot \nabla \mathbf{u}) = \nabla \cdot \mathbf{G} \quad (4)$$

with $\mathbf{G}$ being a new vector field. Equations 2 and 4 are both Poisson boundary value problems, which are well known, and the appropriate boundary conditions are either a Dirichlet condition for known pressure, or a Neumann form using Eq. 1.

The line integration of the pressure gradient field (Eq. 1), and the solution of the pressure Poisson equation (Eq. 2) are closely related, and several researchers have proposed refinements that could easily be adapted to either method. Baur and Koengeter [3] recognized that although the 2D flow recorded by PIV is typically nearly planar, there exist out-of-plane velocities and velocity gradients that should be considered. They rewrote the Navier-Stokes equations in a conservative form

$$\frac{\partial \rho \mathbf{u}}{\partial t} + \nabla \cdot (\rho \mathbf{u} \mathbf{u}) = -\nabla P + \nabla \cdot \nabla^2 (\rho \mathbf{u}) \quad (5)$$

and then expanded the convective terms, preserving the Cartesian $\partial w/\partial z$ term, as calculated by the continuity equation from the known 2D components of the velocity field. The out-of-plane velocities were still considered negligible, as were the out-of-plane components of the viscous term. They did not provide any comparisons of this approach to solutions in which the conservative form was not used, however.

Gurka et al. [5] presented a Reynolds-averaged form of the pressure Poisson equation, which contained an additional Reynolds stress gradient term, and compared solutions obtained with this form for time-averaged pressure to the time-average of pressures obtained with the instantaneous form of the equation (Eq. 4). They found that the Reynolds-averaged form
appeared to give better results, and reasoned that this was because the relative sizes of the errors on derivates of the averaged terms were smaller than on time-averaged spatial derivatives.

Experiments have also been performed with reconstructing pressures from multiple planes of PIV data in order to get access to out-of-plane information. Fujisawa and Sato [7] took 3 planes of PIV data in a combustion chamber, and integrated the $\partial w / \partial z$ term estimated from Eq. 3 in the out-of-plane direction to estimate the magnitude of the out-of-plane velocities. More recently, Fujisawa et al. [10] took numerous 2D µPIV measurements across the depth of a micro channel, and reconstructed the total 3D field using B-splines before calculating the pressure fields.

Notably missing from previous research is a more in-depth error analysis comparing different approaches, and the sensitivity of the pressure solutions to noise or errors in the given velocity fields. Most verification was provided only in an ad-hoc manner. This paper attempts to address these considerations in the context of resolving time-varying flow fields using TRDPIV measurements.

METHODS

**Numerical Techniques**

Different combinations of the governing equations and solution methodology were tested and compared for suitability and robustness. The first of the three solution methodologies tested was line integration, similar to that employed by Baur and Koengeter [3]. In order to minimize the effect of the choice of starting location and integration path on the final results, the result was computed for all eight possible combinations of corners and integration directions, and the resulting fields averaged at each time step. The second methodology was to solve the Poisson
Equation boundary value problem using the pressure gradient equations with Neumann boundary conditions.

The third methodology tested was an advanced, multi-path line integration adapted from the work of Liu and Katz [13]. In their methodology, a virtual boundary was established outside the measured domain, some distance from its edges and a series of nodes was established along its perimeter. In this work, the boundary chosen was a circle with a diameter equal to 1.5x the diagonal of a rectangle enclosing the velocity measurement domain, and the number of nodes was equal to the number of velocity nodes on the perimeter of that measurement domain. To compute the pressures, starting values were established by integrating along a path tracing the perimeter of the flow domain. Then, integration was performed along paths stretching between every combination of nodes on the virtual boundary, beginning when the paths cross the measurement domain and ending at its edges so that no information is used from outside the measured velocity field. Information from all integrations is averaged together during the solution process. After all paths are computed, new values of pressure along the boundary were taken from this average field, and the process was repeated until the final solution converged.

Based on the experience of Liu and Katz and testing during this study, it was noted that 10 iterations was sufficient to converge most fields below a residual of $10^{-2}$ (calculated from the $L_2$ norm of the point-by-point pressure difference divided by the $L_2$ norm of the previous pressure field). The $L_2$ norm of some arbitrary vector quantity, $\alpha_i$, is typically defined as

$$ L_2(\alpha_i) = \| \alpha_i \|_2 = \sqrt{\sum a_i} $$

(6)
The omni-directional integration scheme is intended to localize the effects of errors in the velocity fields so they do not contaminate the entire field, while maximizing the uniform spread of information throughout the pressure solution and minimizing the effect of path dependence.

All solutions assumed 2D incompressible flow.

The combinations tested were the following:

**Line Integration and Omni-Directional Integration:**

- **“Standard”** – the pressure gradient term from the standard Navier-Stokes equations (Eq. 1).
- **“Conservative”** – the pressure gradient term from the Navier-Stokes equations constructed with a more conservative form of the convection terms (Eq. 5). \( \partial w/\partial z \) is estimated from the continuity equation (Eq. 3).
- **“Conservative2”** – the pressure gradient term from the Navier-Stokes equations constructed by preserving the numerically derived \( \partial w/\partial z \) in both the convective and viscous terms of Eq. 5.

**Poisson Equations:**

- **“Simple1”** – the pressure Poisson Equation for 2D flow with continuity applied to eliminate most of the derivative terms (Eq. 4) and the standard Navier-Stokes equations as boundary conditions (Eq. 1).
- **“Simple2”** – the same as “Simple1,” except that the \( \partial w/\partial z \) term in Eq. 4 is preserved, and calculated from the continuity equation (Eq. 3).
- **“Standard”** – the divergence of the standard Navier-Stokes equations (Eq. 2) with Eq. 1 as the boundary conditions.
- **“Conservative”** – a conservative form of the Navier-Stokes equations (Eq. 5) was used for both the Poisson equation, with the standard form of the equations for the boundaries (Eq. 1).
• “Conservative” – a conservative form of the Navier-Stokes equations (Eq. 5) was used for both the Poisson equation and the boundary conditions.

Calculation of the derivatives in the source terms was performed using second order central differences within the domain, and second order forward differences at the boundaries. The gradient and Poisson terms were discretized by means of second order central differences and pressures were calculated at the velocity node locations. To solve the discretized Poisson equations the use of an alternate direction implicit algorithm with adaptive successive over-relaxation (ADI-SOR) was tested initially, but convergence was extremely poor and often failed entirely. MATLAB’s implementation of the GMRES algorithm was tested as well, and converged fairly quickly and consistently, but ultimately for the size matrices considered here a direct solution was found to be much quicker and more robust, and was therefore used throughout testing.

**Velocity Field Smoothing**

For all the solvers, noise in the measured velocity fields was a significant problem. Although all schemes worked nearly equally well for noise-free velocity fields, as soon as random errors were introduced into the original data - even for very small error levels - the results became unusable. Therefore it is evident that a methodology is required for eliminating or minimizing the effect of measurement noise on the estimated pressure.

For the case of steady flows, time averaging of the velocities or the resulting pressures removes this problem [2,5,7,8]. Other techniques that have been explored are phase averaging of unsteady data [6], filtering and smoothing of the velocity fields [3,9], fitting a spline surface to the velocity field [10], or the use of velocity reconstruction schemes based on the application of the Navier-Stokes equations to the measurements [11,12].
In this work we explored three approaches. First, we designed an 10th-order “Maximally Flat” lowpass FIR filter with a -3dB gain at a normalized cutoff frequency of 0.49 using MATLAB’s “sptool”. This filter was then run on the vector fields in the X and Y directions using the zero-phase forward/backward filtering operation “filtfilt.” This squared the filter response, and eliminated problems with phase-shifts in the spatial frequencies.

Second, we smoothed the field by minimizing the least-square differences of the smoothed velocity field to the original field while satisfying the constraint of the incompressible continuity equation. The problem was solved using Lagrange multipliers as described by Suzuki et al. [14]. The resulting Poisson problem is then written as

\[
\frac{\partial^2 \lambda}{\partial x^2} + \frac{\partial^2 \lambda}{\partial y^2} = -2\left( \frac{\partial U_{\text{raw}}}{\partial x} + \frac{\partial V_{\text{raw}}}{\partial y} \right) \\
U_{\text{smooth}} = U_{\text{raw}} + \frac{1}{2} \frac{\partial \lambda}{\partial x} \\
V_{\text{smooth}} = V_{\text{raw}} + \frac{1}{2} \frac{\partial \lambda}{\partial y}
\]

(7)

Finally, we used Proper Orthogonal Decomposition (POD) and the method of snapshots to capture the most important (energetic) modes of the flow from the data. POD, also known as Karhunen-Loéve decomposition, is too complex technique to fully explain here, but the interested reader is referred to review articles by Berkooz et al. [15] and Smith et al. [16]. In essence POD constructs the most efficient spanning of an ensemble so that the maximum amount of energy is captured in the smallest number of orthogonal modes. POD has been applied to a wide variety of problems in fluid mechanics and other disciplines. For the purposes of this work POD acts as a physics-based filter were only the most energetically significant modes of the flow are retained. These most energetic modes in many cases tend to be smoother and less affected by
errors in the velocity field, in contrast to the lower energy modes, which were heavily contaminated by random noise, and therefore discarded.

For the flows studied here, we set the threshold to discard modes that contributed less than 1% to the total energy of the system, unless they were needed to bring the total above 95%. This resulted in keeping approximately 3 modes for the pulsatile slot flow cases, and 6 modes for the Taylor vortex flow. These flow fields are explained in greater detail below.

**Model Flow Fields**

Two different flows with exact analytical solutions to the Navier-Stokes equations for pressure and velocity were used to validate the solvers tested here. The first is pulsatile flow between two infinite parallel plates. The flow is driven by a combination of a single steady and sinusoidal component, given in terms of the pressure gradient as:

$$\frac{dP}{dx} = \rho K + \gamma \rho K \cos \omega t$$  

(8)

where \(P\) is the pressure, the \(x\) coordinate is along the direction of the flow, \(\rho\) is the fluid density, \(\gamma\) is the ratio between the strength of the steady and oscillating pressure gradients, \(\omega\) is the frequency of the oscillation, and \(t\) is time. The velocity profile across a channel of half-width \(h\) is then:

$$u = u_{\text{max}} \left(1 - \frac{y^2}{h^2}\right) + \frac{\gamma K}{i \omega} \left(1 - \frac{\cosh \left(\frac{y}{h} \sqrt{i \lambda}\right)}{\cosh \left(\sqrt{i \lambda}\right)} \right) \exp(i \omega t)$$  

(9)

with \(u_{\text{max}} = Kh^2/2 \nu\), where \(\nu\) is the kinematic viscosity of the fluid. The pressure gradient due to a constant flow with a velocity of \(u_{\text{max}}\) on the centerline is then \(\rho K\). The pressure distribution along the channel is then simply the integral of the gradient along the flow direction, with respect to time-varying inlet pressure.
Results from this flow field will be presented in the rest of the paper in non-dimensional variables, with the characteristic scales being $L_0 = h$, $U_0 = u_{\text{max}}$, $T_0 = \omega t$, and $P_0 = \rho U_0^2$. For this paper, the channel half-width was chosen to be $h = 4$ mm, the velocity was $u_{\text{max}} = 1$ m/s, the viscosity $\nu = 1 \times 10^{-6}$ m$^2$/s, the pulsatile frequency $f = \omega/2\pi = 1$ Hz, and the magnitude of the pressure oscillation to be $\gamma = (1/2)\omega h^2/2\nu$, or about 25 times the steady pressure gradient. This was chosen to obtain oscillating flow velocities of $\frac{1}{2}$ of the steady centerline speed. For such conditions, the centerline velocity is approximately $1.5 \ u_{\text{max}}$ at peak flow, and falls to $0.5 \ u_{\text{max}}$ at mid-channel during the peak adverse pressure gradient, with a reversed region near the walls up to $0.25$ of $u_{\text{max}}$. Figure 6.1 shows examples of these profiles at 10 evenly spaced instances within a single cycle.

![Figure 6.1: Ten example U-velocity profiles for pulsatile flow, equally spaced over one period](image-url)
The second flow tested was a decaying Taylor vortex at the origin,

\[ u_\theta(r) = \frac{H}{8\pi} \frac{r}{vt^2} \exp \left( -\frac{r^2}{4vt} \right) \]  

(10)

where \( u_\theta \) is the tangential velocity, \( r \) is the radial position, and \( H \) is the strength of the vortex. All other velocity components are zero. Using the Navier-Stokes equations for cylindrical coordinates, the pressure distribution is found to be

\[ P(r) = \frac{\rho H^2}{64\pi^2 vt^3} \left[ -\exp \left( -\frac{r^2}{2vt} \right) \right] + P_\infty \]  

(11)

where \( P_\infty \) is the pressure at an infinite distance from the origin. Results using these formulas will be presented later based on non-dimensionalized variables, with \( L_0 = \sqrt{H} \), \( U_0 = v\sqrt{H} \), \( T_0 = L_0/U_0 = H/v \), and \( P_0 = \rho U_0^2 \). The vortex strength was chosen to be \( H = 1 \times 10^{-6} \text{ m}^2 \), the viscosity \( v = 1 \times 10^{-6} \text{ m}^2/\text{s} \), and the density \( \rho = 1000 \text{ kg/m}^3 \), yielding characteristic scales of \( L_0 = 1 \text{ mm} \), \( U_0 = 1 \text{ mm/s} \), \( T_0 = 1 \text{ s} \), and \( P_0 = 1 \text{ mPa} \).

**Validation and Comparison of Methods**

In order to test the performance of the various numerical models in combination with time varying velocity fields, several studies were conducted to examine their dependence on filter choice, integration scheme, grid spacing, time resolution, and velocity measurement errors.

**Pulsatile Flow:** For the pulsatile flow case, the accuracy of each method was evaluated by comparing the pressure gradient at each time instant to the exact values. Pressure fields were computed by each method and a least-squares fit was then used to match a line to the predicted pressures at every time instant, with the slope of this line being the experimentally determined pressure gradient. The error relative to the exact amplitude of the pressure gradient oscillation was calculated, and an overall measurement was found by taking the RMS value of the errors measured at each time instant. To more closely simulate real experimental data, errors were
imposed on the input velocity field by adding to each exact value a normally distributed random component with a standard deviation equal to a percentage of the magnitude of the steady flow midline velocity, and a random direction. In each case a physical domain size 5h long by 2h wide was tested over 3 periods, except in the filter comparison, in which the testing was only performed on a single period. In most cases the grid used was 101x101 points in space, with 61 samples in time, equivalent to a grid spacing of 200 µm along the channel length, 80 µm across its width, and a sampling frequency of 20 Hz (\(\Delta t=50\) ms). Unless otherwise specified, the noise level was 1%.

**Vortex Flow:** The ability of each method to resolve correctly the shape and magnitude of the pressure drop induced by a stationary, decaying vortex was evaluated using velocity fields matching the Taylor vortex described above. Errors were calculated by measuring at each point and instant in time the deviation of the predicted pressure from the exact solution, relative to the peak pressure drop at the center of the vortex for that instant in time. The RMS of these relative errors was then found for each method over all the points at every time step. The domain tested in each case was \(6L_0 \times 6L_0\), centered on the origin, and the flow fields at times ranging from \(0.05T_0\) to \(0.30T_0\), by which time the majority of the vortex had spread to fit within a radius of approximately \(L_0\). The imposed errors on the velocity field were calculated similarly to the pulsatile flow case, except that the magnitude was scaled at each point as a percentage of the exact value to simulate more closely the form of actual PIV measurement error. In most cases the grid used was 101x101 points in space, with 26 samples in time, equivalent to a grid spacing of 60 µm in each direction, and a sampling frequency of 100 Hz (\(\Delta t=10\) ms). As before, the default noise level on the artificial velocity fields was 1%.
RESULTS

Comparison of Governing Equations

The effect on proper pressure estimation of the various governing equations when paired with the solution methodologies in both pulsatile and vortex flows was examined first. The data presented by first smoothing using the Lagrange minimization technique, but trends were similar for the other smoothers tested. The results of this testing are plotted in Figure 6.2. As will be shown later, Lagrange smoothing had little advantages over no smoothing at all, and so all the error levels are very high.

For both pulsatile and vortex flows, the Poisson solvers were nearly unusable when paired with a Lagrange solver with any form of the equations, with errors quickly climbing into the thousands of percent (Figure 6.2a and d). As expected, the two simple forms were better than the standard form, as not applying the continuity equation to the divergence of the Navier-Stokes equations creates third-order derivatives that tend to amplify the experimental error. Also, the “simple” form performed better than “simple2,” likely because interpreting non-zero field divergences as out-of-plane velocity gradients introduced an additional source of error. It is uncertain whether this would continue to hold for flows in which out-of-plane flows do exist. However, unexpectedly, the “conservative” form performed far better than any other method, even though in its construction it was the most complicated, and theoretically is more susceptible to error propagation. Instead, pressure errors for the pulsatile and were “only” 60% at 1% velocity error and 2000% at 10% velocity error, but were better for vortex flow (5 and 53%, respectively). This led to the “conservative” form of the Poisson solver being selected for the remainder of the work.
Figure 6.2: Comparison of the different governing equation constructions for the various solution methodologies over several error levels. Errors on pressure gradients in oscillating slot flow are on the left, and RMS errors on the pressure field for a decaying Taylor vortex are plotted on the right. From top to bottom, the solvers used were a Poisson equation, multi-path line integration, and Omni-directional integration. Velocity fields were smoothed with Lagrangian minimization.
For the multi-path and omni-directional line integrations, results were similar for each of the three computational forms, with perhaps a slight advantage to the “standard” construction (Figure 6.2b, c, e, and f). This slight difference, when paired with its greater computational simplicity led to the “standard” form’s adoption for use with the multi-path and omni-directional integration schemes throughout the rest of the paper.

**Comparison of Smoothing Techniques**

Based on the results of the previous section, pressure fields calculated with the three available smoothers and the case of no smoothing were compared in both synthetic flow fields when paired with the “conservative” Poisson solver, and the “standard” multi-path and omni-directional line integrations. Errors levels were slightly different for the Lagrange multiplier-based smoother as compared to the previous section as new velocity fields were generated for this analysis. As results were similar for all solvers, only the values from the multi-path line integrals will be discussed, as shown in Figure 6.3.

Examining the results, it is clear that POD filtering performed the best by far over a variety of error levels, and that no filtering led to the worst errors. While all methods produced the lowest errors at zero input noise, lowpass filtering performed the worst for clean data, with 12.6% gradient error versus 1.25% for all other methods in pulsatile flow, although at 0.25% pressure error in the slot flow it was comparable to the other methods which ranged from 0.05% to 0.4% error. For pulsatile flows, POD filtering yielded 5.38% error at 1% velocity error and 27.7% error at 10% velocity noise, and for the vortex flow led to 4.3% error at 1% velocity noise and 56% pressure error at the 10% noise level. Also, it can be noted that in the pulsatile slot flow, lowpass filtering performed better than no filtering or Lagrangian minimization, which were equivalent, but in the decaying vortex the trend was reversed, with the Lagrangian
minimization performing better than the equivalent cases with low pass filtering or no smoothing.

Based on these tests, it was determined that POD-based low order model with an appropriately chosen number of modes was the best choice for smoothing the data before integration.

![Figure 6.3](image)

**Figure 6.3:** Comparison of the 4 smoothing techniques when paired with the “standard” form of multi-path line integrations. a) Errors on pressure gradient in oscillating slot flow. b) Errors on pressure values in decaying vortex flow

**Effect of Velocity Error Level**

Based on the previous determination of the best set of governing equations to use with each solver in 2D planar flow, and the selection as low-order modeling using POD as the best smoother, the effect of various error levels from 0-10% on the accuracy of the pressure estimation was tested on the two synthetic flow fields of interest. The results of these tests are plotted in Figure 6.4. For pulsatile slot flow (Figure 6.4a), the omni-directional integration performed clearly better than either multi-path line integration or the solution of the pressure Poisson equation. While for no velocity error, the error on pressure gradient was slightly worse for the omni-directional scheme compared to regular integration or the Poisson equation (1.9%
vs. 1.2% and 1.1%), by 1% velocity deviation the error for the other two methods had already climbed to 6.1% and 16.9% while for the omni-directional scheme it remained only 1.8%. In fact by 10% velocity noise, the error on pressure gradient was still under 3%, while for the other two methods it had climbed to around 75% and 150%. In contrast, for the decaying vortex all three methods showed a linear increase in pressure error with imposed velocity noise. Here, the omni-directional scheme was slightly poorer than the other two methods (ranging from 0.1% to 47%), while the multi-path integration (0.4% to 40%) and the Poisson equation (0.1% to 32%) performed approximately equivalently, with the Poisson solver better by a slight margin.

![Figure 6.4](image)

**Figure 6.4:** Effect of noise level on accuracy of pressure gradients in pulsatile flow using POD-based smoothing.  
a) Pulsatile slot flow.  
b) Decaying vortex

**Effect of Grid Resolution**

In these tests, the spacing of the computational grid was varied while the physical domain size was kept constant, and the velocity noise level was set to 1%. For the pulsatile slot flow, only the resolution across the width of the channel was varied, with the total nodes varying between 11 and 501, since except for noise, the flow did not vary in the streamwise direction. For the decaying Taylor vortex, the resolution was varied simultaneously in both directions, with resolutions ranging from 11 to 301 grid points. Results are plotted in Figure 6.5.
With the slot flow, it appears that the velocity field begins to be under-resolved below about 101 grid points, though the errors do not increase rapidly until about 25 points. In this case, the omni-directional scheme performed the best, with errors through most of its range around 1-2%. For finely sampled data (above 101 points) the Poisson solver performed better than the multi-path integration (errors around 6-7% versus 3.5% to 26%), but for under-resolved data the Poisson equation failed badly, while the multi-path line integrals returned results similar to omni-directional integration.

With the slot flow, the flow appears to be under-resolved at 11 grid points, but for 25, errors were at a minimum. Interestingly, in this case error increased for all methods with increasing grid resolution, opposite what one would expect. For resolutions at 25 grid points and above, the multi-path method performed the same as the Poisson solver (varying between approximately 2-3% and 11-12%, while the omni-directional method, as before, was slightly worse (2.7% to 15%). For under-resolved fields, however, while the error on the Poisson solver and the omni-directional integration remained reasonable (16.5% and 14.3%) the error on pressure measurements with multi-path line integration show upwards to over 34%.

![Figure 6.5: Effect of grid resolution on accuracy of pressure measurements using POD-based smoothing at 1% velocity error. a) Pulsatile slot flow. b) Decaying vortex](image)
**Effect of Time Resolution**

The final study on these synthetic fields examined the dependence of the pressure solvers on adequate temporal resolution. Velocity error was kept fixed at 1% for all tests. Here, the temporal span of the flow fields being studied was held fixed (3 periods for the slot flow, and 0.25T₀ for the vortex), while the number of time steps was varied between 201 and 11. The pressure errors calculated for these tests are plotted in Figure 6.6.

![Figure 6.6: Effect of time step size on accuracy of pressure measurements using POD-based smoothing at 1% velocity error. a) Pulsatile slot flow. b) Decaying vortex](image)

For the pulsatile flow, the two line integration techniques performed the best, with multi-path integration performing slightly better for under-resolved flows, reaching a minimum error of 0.9% at 17 snapshots per period, and the omni-directional directional scheme was slightly better above that point, continuing to decrease toward 1% error for small time steps. The conservative Poisson solver performed worse than either throughout nearly the entire range, though the error for the omni-directional method was slightly higher at the coarsest sampling.

For the decaying vortex, the Poisson solve was the best performing method, decreasing from 5.5% to 1.6% error with increasing sampling rate. The multi-path line integration performed similarly at low sampling rates, but reached a minimum error at 400 time steps/T₀ of
2.9%, and then increased again to 4.7%. The omni-directional scheme was slightly worse over most sampling rates, decreasing from 8.3% pressure error at 44 timesteps/$T_0$ to around 2.8% at 800 timesteps/$T_0$. On the whole, though, error levels remained quite low for all sampling rates for the decaying vortex.

**DISCUSSION**

The present analysis reveals that for different types of flows, different methods appear to give better results; there is not a single method that works best in all cases. For cases of no noise in the velocity fields, all methods gave almost equivalent results, but as soon as errors were applied to the “measured” velocities, differences began appearing. It was observed that the form of the Navier-Stokes equations chosen made a significant difference to the error levels obtained using each of the three pressure solvers tested. The most consistent results were obtained using the “conservative” form with the pressure Poisson equation, and the “standard” form with either of the line integration approaches. Choice of smoother was also critical to controlling the error obtained. No filtering yielded very high errors in all cases, while lowpass filtering and a Lagrange multiplier-based smoothing technique which attempted to minimize the least-squared difference of the flow from the measured data while satisfying the incompressible continuity equation both yielded inconsistent results that in some cases were no better than no filtering at all. The failure of the lowpass filtering, appears to be explained by distortions it causes in the relative contributions of different wave numbers of the flow. Qualitatively, filtering sometimes altered the original velocity profiles, while only smoothing out the affects of large transient errors, not removing them. The idea behind the Lagrange minimization technique was to create a field that was similar to the measured field, but satisfied in a discretized sense the divergence free condition assumed for incompressible flow. It’s failure in suppressing the effect of velocity
noise suggests that the main source of error in the pressure calculation using line integration is probably not violation of this assumption, but instead spurious gradients caused by finite differencing. In particular, as can be seen in Figure 6.2, the Poisson equation failed spectacularly when paired with this smoother, even though it would be assumed that it would be the most sensitive to violations since it depends on a matrix inversion of the discrete form of the governing equations. The use of proper orthogonal decomposition to create a low-order filter provided the best results. One explanation for this is that the decomposition selected for the modes with the highest kinetic energy, and that these are the flow structures that contribute the most to the final pressure fields at each timestep. Although generally beneficial, it suggests that care must be taken to include any smaller modes that have flow physics of interest in the final velocity field even if their magnitude is relatively small, so as not to exclude them from the pressure analysis.

For the internal flow case, pulsatile flow between two infinite plates, the two line integral approaches gave clearly superior results when predicting the pressures within the channel. Error levels were lower, and the solutions were less sensitive to spatial grid resolution, sampling rate, and error levels. Qualitatively, the solutions were better as well, being less prone to returning pressure distributions that were curved instead of linear. In contrast, the Poisson formulation gave results with consistently higher error.

On the other hand, for the external flow case tested (the decaying Taylor vortex), the “conservative” form of the Poisson equation were the most accurate, giving more accurate solutions. The multi-path line integration performed almost as well, and the omni-directional scheme was only slightly worse. All three approaches gave similar results overall.
More testing is needed to determine if this difference in applicability holds up in general for time-varying flows, but at least given these results, it appears that computing the pressure based on an omni-directional pressure integration scheme returns the most consistent results over the widest range of resolutions, flows, and error levels. One effect that was not examined, though, is the influence of real out-of-plane velocities; all the flows tested were purely 2-D. This could serve to differentiate better the various schemes and might change the results of the initial comparison of governing equations, as certain constructions might be more robust in the face of unresolved velocity components. Several approaches to studying this suggest themselves, including use of CFD data, repeating the tests here with an angled offset of the measurement plane from the 2-D axis, and use of other flow fields for which a 3-D solution for the pressure and velocity is known exactly.

One interesting result observed here, mainly in the grid tests (Figure 6.5), but also in the sampling rate tests (Figure 6.6), is the existence of an optimal resolution, beyond which additional measurement points actually increase the final error on the calculated pressure. This can be explained by examining the form of the derivative estimator. Typically, the derivatives are found by constructing a relationship between measurements of the function at adjacent points, and dividing by the step size. In the case of exact measurements of the function, this gives rise to errors that are proportional to the derivative of the function times the step size raised to an appropriate power. In other words, as the step size decreases, so does the error.

However, the presence of imperfect measurements of the underlying function introduces another error term that has the same form as the derivative estimator itself – the total error on the derivative is proportional to a function of the errors on the measured points, divided by the step size. In this case, the derivative error actually increases as the measurement points become
closer together, assuming that the error on each measurement is independent and roughly of the same magnitude. Taken together, the total error on the derivative scheme becomes a balance of these two effects, as is shown in Eq. 12.

\[ E_{of/\Delta n} = G\left( \frac{\epsilon_f}{\Delta n}, f^{(r)}(\Delta n)^s, \ldots \right) \]  

(12)

Here \( E \) represents the total error on the derivative estimation for a function \( f \), \( \epsilon_f \) is the measurement error for samples of the function, \( f^{(r)} \) is \( r \)-th derivative of that function, \( \Delta n \) is the step size on the discrete grid, and \( s \) is the exponent governing the formal order of the method. The exact form of the function \( G \) will depend on the derivative scheme used, but in general there should be a value below which the grid size is too coarse and the sampling term dominates, and above which the grid becomes too fine and the measurement error on the function begins to dominate.

While it would be ideal to determine this point, in practice this will depend on many factors, including the error propagation characteristics of the scheme in which the derivative estimator is used, the exact form of the derivative formula, and the shape of the underlying function. This makes the analytical prediction of the optimum resolution impractical. From the results shown here, however, it appears that oversampling may be better than undersampling, as the errors increase more slowly. One option for controlling these errors may be to interpolate the measured values for the velocity field to fit on a different grid more suitable for the calculation of pressures.

CONCLUSIONS

The first detailed comparison of various methods for calculating pressure from 2D time-resolved velocity fields in incompressible flows was performed. The effects of grid resolution,
sampling frequency, and velocity error were examined for their effect on the calculated pressure fields. The use of a smoothing technique for the velocity fields was critical for the success of time-resolved measurements. A new approach using Proper Orthogonal Decomposition was proposed as an improved way to preserve the physical features of the flow, and in tests it appeared successful as compared to low pass filtering or a Lagrange multiplier-based approach. From the error analysis of this method it was found that there is often an optimum grid resolution, probably due to the interaction of the discretization errors of the finite difference schemes and the propagated errors from the velocity measurements. Similar results appear to apply for sampling rates. Also, pressure errors scale linearly with errors on the velocity measurements. Overall, the line integral methods may be superior for internal flows, while the Poisson equations gave better results for external flows, but overall the virtual boundary, omni-directional line integration scheme gave the most consistently low error levels, and is recommended for use in future work.

ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. 0521102 and CAREER Grant No 0547434.
REFERENCES


ABSTRACT

Left ventricular diastolic dysfunction (LVDD) is a disease in which the heart is unable to completely fill the left ventricle before ventricular systole, and can eventually lead to heart failure. In this study, 2D phase contrast MRI velocity scans were taken of 8 patients (2 normals, 6 diseased, one also with dilated cardiomyopathy). Using these scans, an omni-directional pressure integration algorithm was applied to study the pressure differences in the left heart throughout the filling process. It was observed that the peak early filling pressure difference between the atrium and apex was larger in normal patients than diseased (2.87±0.56 vs. 0.95±0.56, p<0.05) and that the subsequent peak late filling pressure difference was smaller (1.04±0.03 vs. 1.21±0.72), mostly due to an elevated peak atrial-to-mitral pressure difference (0.68±0.19 vs. 1.01±0.51). This created a clear difference in the ratio of peak pressure differences (measured from the left atrium and ventricular apex) between early and late filling (2.74±0.46 vs. 0.97±0.76, p<0.05). This ratio could be useful clinically if derived from color m-mode echocardiography. Qualitative observations of the velocity fields showed that the mitral inflow jet generated a pair of vortices near the base of the ventricle, beyond which the jet expanded outward. An adverse pressure gradient was seen at this location due to increased local and convective acceleration, while within the vortex-confined jet region, a strong jet and favorable pressure gradient was maintained.

On the basis of these observations it is hypothesized that the increased suction of blood in healthy patients as compared to LVDD could be attributed to interaction of wall motion with the
inflow jet, specifically to increased apical and mitral annulus wall movement which could contribute to the formation of a larger and stronger vortex pair at the base, helping to sustain a favorable pressure gradient in front of the mitral valve and leading to improved filling of the left ventricle during early diastole. In contrast, it is suggested that during late filling and for diseased patients, this mechanism is attenuated, requiring increased left atrial pressure differences in order to compensate for the impaired ventricular relaxation.

**Key Terms:** phase contrast magnetic resonance imaging, left ventricular diastolic dysfunction, pressure estimation, ventricular wall motion, blood flow
INTRODUCTION

Left Ventricular Diastolic Dysfunction (LVDD) is a disease in which the heart is unable to properly fill the chamber of the left ventricle before the systolic contraction pushes the blood out of the heart into the rest of the body [1]. It is frequently characterized by elevated filling pressures within the heart. Over 70 million people in the United States with high blood pressure are at risk for LVDD [2], and numerous studies have shown a link between LVDD and heart failure [3-6]. However, due to compensatory mechanisms early stage dysfunction can be difficult to diagnose. One survey of asymptomatic individuals in Olmsted County, Minnesota revealed that 21% have mild diastolic dysfunction and 7% have moderate or severe LVDD. Either condition was associated with increased risk for heart failure and was predictively correlated with death [7]. Despite numerous advances in clinical modalities the prognosis and diagnosis of LVDD has remained unchanged over the past 20 years; clearly, better tools and understanding of the disease are required. Correct diagnosis of the causes of heart failure is important to the proper treatment of the condition, and can be confounded by the presences of other factors such as heart disease and age-related changes that cause apparent filling abnormalities without actually reflecting an underlying ventricular dysfunction [1].

Several previous investigations have postulated the significance of vortex dynamics and the vortex formation from the mitral valve jet to the efficiency of the left ventricle filling [8]. The hypothesis that an optimum vortex formation process governs the heart stroke has received particular emphasis, and has been studied extensively \textit{in-vitro} [9-12].

Another hypothesis is that the development of this disease is linked to alterations in the pressure gradients between the left atrium and ventricle at different points during each heartbeat. It is believed that in normal hearts most of the work of filling the left ventricle during diastole
(the relaxing or filling part of the heart cycle, known as early filling) is achieved by a suction effect created by the active relaxation of the myocardium and the consequent enlargement of the left ventricle [13]. In contrast, in unhealthy hearts this effect is diminished, and more of the work needs to be done by an active contraction of the left atrium during early atrial systole (so-called late filling) [1], or an increased left atrial pressure during diastole [13].

*In-vivo,* investigation of LVDD using quantitative velocity measurements has mostly been constrained to echocardiography, particularly color M-mode. Although the use of phase contrast MRI (pcMRI) is well established in the study of left ventricular flows, examination of the fluid mechanical concepts has been limited, especially in the context of LVDD. As of yet this quantitative tool has mostly been used to derive qualitative visualizations featuring vector fields, or blood element pathlines [14-20]. One of the more sophisticated analyses attempted to quantify residence times for the injected volumes as well as changes in the kinetic energy of the blood as it travels through the heart [21]. Expanding on line integration for pressure commonly used in echocardiography, pressure differences within the left heart have also been found between two points and across the entire 2D field [22,15,23]. Additionally, available pathophysiological studies of the left ventricle using pcMRI appear to be limited to considerations of dilated cardiomyopathy [21,15]. No previous pcMRI studies of LVDD appear to have been undertaken.

Over the past decade, pcMRI has emerged as a proven technique for accurately measuring the velocity of tissues and fluids in-vivo [24]. While issues of temporal and spatial resolution, long acquisition times, motion artifacts, and proper gating or phase-locking techniques remain, overall, pcMRI is now capable of providing useful measurements at a variety of scales, in both planar and 3D scanning modes; the type and quality of the data is directly
comparable to digital particle image velocimetry (DPIV) methods more familiar to the fluid dynamics community [10,11,25,12].

Phase contrast velocity encoded MRI works by acquiring pairs of images encoded by magnetic fields of opposite gradient, imparting opposite phases to the spin information. These two images are then compared. If no motion has occurred between the two images, then the phases will exactly cancel. However, if the tissue has shifted between the scans, then the phases of the corresponding voxel will have changed, leaving a value proportional to the velocity of that motion [24]. The process must be repeated for each component of the complete velocity vector that is to be measured, though the initial reference can be reused, meaning that 3-component measurements take at least twice as long as sampling a single component. In practice, a single “image” is actually acquired over several heartbeats, and reconstructed in a phase-average sense into individual time instants after the scan is complete. Improved methods that leverage this fact are available for both 2D and 3D scans [26-28].

This work will attempt to validate the hypothesis that development of LVDD is linked to changes in the pressure gradients between the left atrium and ventricle at different points during each heartbeat. Illuminate the dynamics that give rise to the observed gradients. Because technical and ethical problems exist with direct measurements of intra-cardiac pressures \textit{in-vivo}, the pressure gradients will be calculated from non-invasive phase contrast Magnetic Resonance Imaging.

\section*{METHODOLOGY}

\textbf{Phase Contrast MRI}

Phase contrast MRI measurements were performed on a Avanto 1.5T Scanner from Siemens Medical Solutions, located at the Wake Forest University Baptist Medical Center in
Winston-Salem, NC. 2D pcMRI scans were acquired of 8 patients in various stages of LVDD (as determined by physicians) in accordance with IRB guidelines pre-established for the study (see Table 7.1). Velocity encoding (VENC) for each scan was 100-130 cm/s seconds, with a TR of about 20 ms and 40, 45, or 50 reconstructed phases (depending on patient heartrate). TE was 3.3, and there was 1 view per segment. Flip angle was 20 degrees, and the resolution was 320x256 at 1.25 mm/pixel in-plane with a 5 mm slice thickness. Three signal averages were used for each scan.

In addition, a separate high-SNR imaging scan was acquired immediately following each pcMRI over the same field of view and used to perform image segmentation on the velocity portraits, as noise in the real part of the pcMRI images often made boundary detection difficult. These images were registered to the pcMRI scans via common anatomical landmarks, and the boundaries of the left ventricle (LV), left atrium (LA), aortic outflow tract, right ventricle, and descending aorta were mapped and transferred to the pcMRI images.

### Table 7.1: List of patients tested

<table>
<thead>
<tr>
<th>#</th>
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<th>notes</th>
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<tbody>
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<td>-</td>
</tr>
<tr>
<td>9</td>
<td>diseased</td>
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<tr>
<td>11</td>
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<td>12</td>
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<td>-</td>
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<tr>
<td>13</td>
<td>diseased</td>
<td>Dilated LV</td>
</tr>
<tr>
<td>14</td>
<td>normal</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>diseased</td>
<td>-</td>
</tr>
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**Pressure Calculations**

A number of different methods have traditionally been used with pcMRI data to derive relative pressure data, including line-integration along a single path [15,23], iterative approaches [22,23,29], and the solution of a Poisson equation minimizing the curl of the resulting pressure
gradient field. However, our previous work with derivation of pressure fields from noisy particle image velocimetry fields indicated that the iterative, omni-directional line integral pressure solver as suggested by Liu and Katz [30], when applied to a particle image velocimetry fields and paired with a reduced order model derived from proper orthogonal decomposition (POD), yielded superior results to many other similar algorithms [31]. Consequently, this was the method chosen for this study.

In brief, the algorithm begins with the construction of low-order model using proper orthogonal decomposition [32]. This method constructs an efficient spanning of the sampled field, sorted by relative contribution to the total kinetic energy of the flow, from which can be selected the modes of interest. In practice, this usually involves solving some variant of an eigenvalue problem over the velocity fields.

\[
\int_\Omega \left( u(x) \otimes u^*(x') \right) \Phi(x') \, dx' = \lambda \Phi(x)
\]  

(1)

The eigenvalues, \( \lambda \), then represent the relative kinetic energy contribution of each eigenvector field, \( \Phi \). These eigenvectors can then be projected back onto the original velocity fields, \( u \), to obtain time varying coefficients \( a \) for each mode that allow reconstruction of the original field.

\[
u(x,t) = \sum_{i=1}^{N} a_i(t) \Phi_i(x)
\]

(2)

By summing over a subset of the original modes a reduced order model of the original flow field can be constructed.

Typically in noisy experimental data, the primary modes contain most of the flow information, while the higher modes contain information about the random noise, and can therefore be excluded. In this case, the time-average field was initially subtracted, and POD performed on the remaining time-varying components. From this decomposition, the 4 to 10 of
the most energetic modes were kept, in most cases spanning ~60-90% of the remaining energy in
the flow. Selection of the exact modes kept was performed based on a qualitative examination of
the fields and their relative contribution for each patient. An example of the energy distribution
for patient 8 is shown in Figure 7.1. Pressure calculations were then performed on this reduced-
boundary outside the flow field, and then integrating along straight paths between all possible
combinations of points on this boundary. This is shown schematically in Figure 7.2. Only
integrals within the fluid domain are performed, and the solution is initialized by integrating
around the true fluid boundaries. The resulting pressure information is averaged between all
paths. This information is then used to update the pressure boundary information, and the
process is repeated until the field converges. This method has the advantage of localizing the
effect of any errors in the velocity field.

![Figure 7.1: Example reduced-order reconstruction of patient 8 using nine of the 40 available modes.](image)

**Statistics**

Comparisons were made using a Wilcoxon signed-rank nonparametric test in order to
avoid assumptions on the distribution of values (such as Gaussian, etc.). Differences were
defined as statistically significant if the p-value was less than 0.05.
RESULTS

Based on the phase contrast MRI data acquired, flow and pressure fields were calculated for each patient. Figures 7.3 and 7.4 show representative velocity vectors and relative pressure fields for a healthy and diseased patient at several instants in time during LV filling. From these pressure fields, time histories of the pressure differences between three stations (the base of the atrium at the top of the heart, the throat of the mitral valve, and the bottommost portion of the ventricle at the apex of the heart) were extracted and plotted for each of the eight patients in this study (Figure 7.5). In these plots, a positive pressure difference represents the presence of a net favorable pressure gradient between each of the three locations (one tending to accelerate the
Figure 7.3: Color contours of pressure relative to pressure at the mitral valve for patient 8.  
a) $t/T_0=0.325$, opening of mitral valve; b) $t/T_0=0.375$, peak ventricular gradient;  
c) $t/T_0=0.425$, peak diastolic flow; d) $t/T_0=0.725$, diastasis;  
e) $t/T_0=0.875$, peak atrial systole; f) $t/T_0=0.95$, mitral regurgitation
Figure 7.4: Color contours of pressure relative to pressure at the mitral valve for patient 9.
a) $t/T_0=0.489$, opening of mitral valve; b) $t/T_0=0.533$, peak ventricular gradient;
c) $t/T_0=0.6$, peak diastolic flow; d) $t/T_0=0.778$ diastasis;
e) $t/T_0=0.889$, peak atrial systole; f) $t/T_0=0.978$, mitral regurgitation
Figure 7.5: time histories of pressure differences within the left heart during systole for the various patients a) patient 8, healthy; b) patient 9, diseased; c) patient 10, diseased; d) patient 11, diseased; e) patient 12, diseased; f) patient 13, dilated LV, diseased; g) patient 14, normal; h) patient 15, diseased
flow and push it into the ventricle), and a negative value corresponding to a net adverse gradient (one tending to decelerate the flow or draw it back into the atrium). For reference, blood velocity in the center of the mitral annulus in a direction normal to the base of the left ventricle is also plotted. From this data, the peak pressure differences across the ventricle during early and late filling were tabulated for both early and late diastole (Table 7.2). Averages and standard deviations for various subcategories are presented in Table 7.3.

**Table 7.2**: List of peak pressure differences between various points within the left heart during filling. Total: superior atrial wall pressure minus ventricular apex pressure; Atrium: superior atrial wall pressure minus mitral valve pressure; Ventricle: mitral valve pressure minus ventricular apex pressure.

<table>
<thead>
<tr>
<th></th>
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<th>Systolic Filling</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Atrium</td>
</tr>
<tr>
<td>Early filling</td>
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</tr>
<tr>
<td>∆P_{ventricle} = P_{mitral} - P_{ventricle}</td>
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<td>1.43</td>
</tr>
<tr>
<td>Late filling</td>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>∆P_{atrium} = P_{mitral} - P_{atrium}</td>
<td>0.68</td>
<td>0.91</td>
</tr>
<tr>
<td>∆P_{ventricle} = P_{mitral} - P_{ventricle}</td>
<td>0.20</td>
<td>-0.03</td>
</tr>
<tr>
<td>Atrial pressure ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.84</td>
<td>0.49</td>
</tr>
</tbody>
</table>

**Table 7.3**: List of average pressure differences and their standard deviations for early and late filling in each of the three regions measured.

<table>
<thead>
<tr>
<th>Peak Pressure Difference (mmHg)</th>
<th>Healthy (n=2)</th>
<th>LVDD (n=6)</th>
<th>non-DCM (n=7)</th>
<th>DCM (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early filling (E wave)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆P_{total} = P_{atrium} - P_{apex}</td>
<td>2.87±0.56*</td>
<td>0.95±0.56*</td>
<td>1.61±0.97</td>
<td>0.20</td>
</tr>
<tr>
<td>∆P_{atrium} = P_{mitral} - P_{atrium}</td>
<td>2.14±0.64*</td>
<td>0.70±0.51*</td>
<td>1.22±0.75</td>
<td>-0.03</td>
</tr>
<tr>
<td>∆P_{ventricle} = P_{mitral} - P_{ventricle}</td>
<td>1.42±0.99*</td>
<td>0.36±0.26*</td>
<td>0.68±0.69</td>
<td>0.23</td>
</tr>
<tr>
<td>Late filling (A wave)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆P_{total} = P_{atrium} - P_{apex}</td>
<td>1.04±0.03</td>
<td>1.21±0.72</td>
<td>1.22±0.65</td>
<td>0.81</td>
</tr>
<tr>
<td>∆P_{atrium} = P_{mitral} - P_{atrium}</td>
<td>0.68±0.19</td>
<td>1.01±0.51</td>
<td>0.94±0.50</td>
<td>0.79</td>
</tr>
<tr>
<td>∆P_{ventricle} = P_{mitral} - P_{ventricle}</td>
<td>0.50±0.02</td>
<td>0.49±0.44</td>
<td>0.54±0.37</td>
<td>0.12</td>
</tr>
<tr>
<td>E/A pressure ratio</td>
<td>2.74±0.46*</td>
<td>0.97±0.76*</td>
<td>1.58±1.58</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*denotes statistically difference between groups (p<0.05)
Examination of this data revealed several notable features. In both healthy and diseased patients, the opening of the mitral valve during early diastole coincided with development of a modest pressure difference across the length of the left ventricle and atrium (Figure 7.3a and Figure 7.4a) caused primarily by the relaxation and expansion of the myocardium of the left ventricle. This pressure difference grew in time through early filling, reaching a maximum during peak acceleration of the mitral inflow jet (Figure 7.3b and Figure 7.4b). A large unfavorable pressure gradient then developed, first in the ventricle (Figure 7.3c and Figure 7.4c), then in the atrium. During this time, two recirculation regions formed, the first (typically larger) between the inflow jet and the aortic outflow tract, and the second (often much smaller) between the inflow jet and the lateral wall of the ventricle. These structures typically extended approximately half the distance between the mitral wall and the apex of the heart, but could be smaller in the case of weaker inflow jets. In healthy patients, both the mitral jets and the associated total pressure gradients were more vigorous than in cases with diastolic dysfunction, with $\Delta P_{\text{total}} = 2.87 \pm 0.56$ vs. $0.95 \pm 0.56$ (p<0.05), as seen in Figure 7.3b and Figure 7.4b. Following early diastole, the pressure difference tends to decrease and in many cases the flow through the mitral valve and within the ventricle slows greatly (Figure 7.3d and Figure 7.4d). This is followed by a renewal of the pressure gradient during atrial systole, and the subsequent development of a second mitral inflow jet, vortex pair, and finally an adverse pressure gradient which brings the filling of the left ventricle to a conclusion. One notable feature of all eight cases is that this negative pressure difference between the atrium and the ventricle persisted long enough to cause minor mitral regurgitation. It appears that this was assisted by the migration of the medial inflow vortex toward the lateral wall, causing fluid returning from the apex to flow through mitral valve into the atrium, and likely assisting in the final closing of the leaflets.
Further examination of the time histories for the eight cases also shows that before each filling jet enters the left ventricle, development of the pressure difference across the ventricle tends to lead the pressure difference developed across the atrium. This pattern tended to be more pronounced for the diastolic relaxation than for the atrial contraction, and more notable in healthy patients than diseased. However, due to the limited temporal resolution and short duration of these pressure pulses, the exact difference was difficult to quantify.

As mentioned previously, the two healthy patients demonstrated a stronger pressure difference during ventricular relaxation than did the patients with diastolic dysfunction (Table 7.2 and Table 7.3). Additionally, the pressure difference in the left heart was slightly higher for diastolic dysfunction patients during late filling and atrial systole than for healthy ($\Delta P_{\text{total}} = 1.21\pm0.72$ vs. $1.04\pm0.03$ mmHg), mostly due to an increase in the atrial pressure difference ($\Delta P_{\text{atrium}} = 1.01\pm0.51$ vs. $0.68\pm0.19$ mmHg, and $\Delta P_{\text{ventricle}} = 0.49\pm0.44$ vs. $0.50\pm0.02$ mmHg). This led to a clear difference in the ratio of peak pressure difference during relaxation to the peak pressure difference during atrial systole, $P_{E/A}$. For healthy patients, this ratio was large, $2.74\pm0.46$, while for diastolic dysfunction patients, it was much smaller, $0.97\pm0.76$ ($p<0.05$) (Figure 7.6).

In comparison to the patients who were healthy or only had diastolic dysfunction, the flow patterns and pressure history for the patient suffering from dilated cardiomyopathy in addition to diastolic dysfunction, were notably different (patient 13, Figure 7.5f). The initial pressure difference developed during ventricular relaxation was very weak ($0.20$ mmHg), resulted in very little inflow, and did not cause a negative pressure difference across the mitral valve or the formation of vortical structures adjacent to the jet. The atrial contraction which followed occurred very early during the cardiac cycle as compared to the other patients.
($t/T_0=0.65$ for peak late filling pressure, vs. $t/T_0=0.85\pm0.03$), and was larger than the early filling pulse but still somewhat small (0.81 mmHg). Unlike the initial early filling, this contraction did lead to the development of a vortex medial to the jet, and was larger than in other cases, while the lateral vortex was nearly non-existent. This vortex did not remain fixed against the base of the left ventricle, and instead convected downward with the flow in to the ventricle, where it persisted (as did the rotation in the other seven patients) until the ventricle contracted, forcing blood from the heart.

![Figure 7.6: Plot of ratio of peak atrial-to-apical pressure differences between ventricular diastole and atrial systole for healthy and diseased patients. The circles indicate measured values; the bars, means for each category; and the whiskers, standard deviations.](image)
Finally, comparison of pathlines for blood entering the left ventricle revealed changes in trajectories between different parts of the cycle and between healthy and diseased patients. Some of these pathlines are plotted in Figure 7.7 for a healthy (top) and diastolic dysfunction patient (bottom). For most patients, blood entering the heart during early, diastolic filling (left) exhibited more direct paths, traveling farther towards the apex than they did during atrial systole (right). In both cases, after passing mostly straight between these two flanking vortices, the flow begins to spread outwards as the jet dissipates. For blood entering with the first inflow jet, the pathlines indicate that most of this fluid was pumped out of the heart with the next ventricular contraction. In contrast, the blood that entered in the second atrial-driven pulse spread more quickly, with more getting caught in the flanking vortices, and this fluid was less likely to be pumped out in the next contraction cycle. This was true even for cases with strong atrial contractions and pressure differences, although the differences were less noticeable.

DISCUSSION

The results of this study demonstrate clear differences between the flow and pressure gradients in patients with and without left ventricular diastolic dysfunction. In particular, for diastolic dysfunction patients, pressure differences during early filling were depressed as compared to healthy patients, and increased during late filling. This change was largely attributable to a decrease in pressure difference across both the LA and LV during early filling, and an increase in LA pressure gradients during late filling. As a result, the ratio of peak pressure differences between the atrium and apex appears to be a useful predictor of left ventricular diastolic dysfunction. Given the expense and effort required to obtain these values from phase contrast MRI, determination of pressure differences in this manner probably has little clinical usefulness at present and will remain most useful in research, especially as the pressure
Figure 7.7: Pathlines of blood through the heart for patients 8 (top) and 11 (bottom). Pathlines are colored with instantaneous velocity magnitude. (left) blood entering the LV during diastolic filling; (right) blood entering the heart during atrial contraction.

Differences largely correlate with the magnitude of mitral inflow during each part of the cardiac cycle[8], a value easily measurable through less expensive modalities[33]. However, good results have also been shown with similar pressure measurements obtained from color m-mode echocardiograms[33]. If the results of this study are substantiated in larger trials, relative peak pressure ratios could prove to be a useful supplement to existing ultrasound-based parameters.
such as the ratio of peak early inflow to mitral annulus speed ($E/E'$) or ratio of peak velocities between early and late filling ($E/A$).

Physically, these filling patterns appear to originate from differences in the LV expansion and geometry. As has been previously described, blood flow into non-dilated left ventricle tends to follow a nearly straight path towards the apex before beginning to diverge toward the ventricle walls. It appears that the location that this spreading begins at is tied to the formation of the vortices that flank the mitral jet, which previous 3D studies have indicated are part of a vortex ring[21]. As can be seen in Figure 7.3b and Figure 7.4b, this inflow jet initially travels down a favorable pressure gradient, with the flow at the apical end of the ventricle expanding outward or quiescent. As the inflow pulse passes the ring vortex, it begins to spread out, and a localized pressure minimum appears at the level of the vortex ring, leading to an adverse pressure gradient just beyond its furthest extents. In normal-sized hearts, this vortex remains fixed at the base of the ventricle throughout the filling process. In essence, the vortex ring is acting as a virtual channel or nozzle for the inflow jet, preserving its coherency and delaying its expansion into the full width of the ventricle. Once the jet passes the end of this “channel,” it suffers the same fate as any flow entering a diverging nozzle, and the increase in local and convective acceleration terms causes a corresponding rise in the pressure relative to the nozzle throat. Beyond this point, the pressure gradients measured are minimal, meaning that diastolic suction shifts from acting along the entire ventricle to only a small region near the base. Eventually, this acts to decelerate the flow entering through the mitral valve and is responsible for the development of the large negative pressure differences measured after each mitral inflow. A similar effect can be seen in both early and late filling for both healthy and non-dilated diastolic dysfunction patients, and the
size of the vortices observed seems to correlate qualitatively with the measured pressure differences developed and the magnitude of the inflow jet.

The question then becomes, what controls the size of these vortices, and therefore the development of the mitral inflow? One possible explanation is that this development is related to the motion of the LV walls and the mitral annulus during different stages of filling. It is well known that in a healthy heart the relaxation of the myocardium begins near the apex during isovolumetric expansion (while the base may still be contracting), and then progresses toward the base with an untwisting motion during early filling[34]. This preferential expansion will create localized accelerations at the apex downward and away from the centerline of the ventricle, while the flow near the base will mostly flow downwards. In addition, as the mitral jet develops, the mitral annulus moves upwards into the LA, away from the LV. This necessitates an upward motion of fluid towards the base of the LV to fill the increasing volume there. Taken together, this initial diverging flow pattern at the apex, coupled with the initial downward flow needed to replace the displaced apical blood, followed by the beginning of the inflow jet and the upward flow at the walls needed to support motion of the mitral annulus upward, creates the conditions necessary for the creation of a large vortex ring fixed to the base of the LV and surrounding the inflow jet. Essentially, this means the size and location of this vortex ring would be dictated by the LV geometry and dynamics of its expansion.

In contrast, during late filling the preferential expansion of the apex of the heart is absent, and filling is driven mainly by the contraction of the LA. As a result, the walls of the LV should expand more uniformly along its entire length, leading to an initial outward acceleration of fluid throughout the ventricle. As this second inflow jet develops, without the initial preferential
downward motion near the base, flow is more likely to begin recirculating closer to the mitral valve, leading to a smaller vortex ring.

In diastolic dysfunction, the initial relaxation is delayed, and the compliance of the ventricle is decreased[35,33]. Upward motion of the mitral annulus (E’) is also diminished[33]. Additionally, there is evidence that the untwisting or recoil of the LV is diminished for patients with diastolic dysfunction[33]. With decreased wall recoil, the initial velocity gradients that form during isovolumic relaxation and predispose the incoming filling jet to form a large vortex near the base will also decrease. As a result, expansion of the ventricle in response to the mitral inflow jet will be more spatially uniform, creating increased off-access convective acceleration and leading to the formation of a smaller vortex ring. Impaired motion of the mitral annulus will augment this effect, requiring less upwelling of fluid towards the base of the ventricle, denying the vortices an additional source of energy. Overall, this would cause early filling in diastolic dysfunction to more closely resemble typical, atrial-driven late filling.

Although wall motions were not measured in this study, the observed flow patterns are consistent with this hypothesis. For healthy patients, we observed that the vortices formed during early filling were larger, the inflow jet began diverging further into the ventricle, and the initial favorable pressure gradient in the LV was larger and had a greater distance over which to act on the blood, leading to higher filling velocities and greater volumes displaced. The atrial pulse then need not be as large to complete ventricular filling, and the vortices are smaller. For patients with diastolic dysfunction, the vortices formed around the mitral jet were smaller and the adverse pressure gradient formed closer to the base of the LV. To compensate for the decreased filling, the LA contracts more strongly, leading to the observed increase in peak LA pressure differences. This also could explain why the LV pressure difference does not increase versus
healthy patients during late filling, despite the increased flow, since the formation of the
favorable pressure differences there remains dominated by a uniform expansion of the ventricle.

This is very different from the flow observed here for the patient with dilated
cardiomyopathy. In that case, the ventricle width is over twice the width of the mitral valve
(about 45mm versus 19mm), much larger than is normal in undilated hearts. This moves the
mitral inflow jet away from the ventricle walls, and makes the flow less wall-bounded,
diminishing the effect of the mechanisms described above. Instead, the flow acts more like a jet
in a semi-infinite domain, with the development of a vortex at the tip of the mitral jet which then
propagates downward into the LV. This structure continues to develop until the blood is
circulating smoothly throughout the ventricle. This is consistent with the flow reported in MRI
scans of DCM patients by Gharib et al.[9] and by Bolger et al.[21]. This agreement means that
the work of Gharib, Kheradvar, and collaborators done in-vitro with particle image velocimetry
exploring the linkages between vortex pinch off, formation time, and mitral recoil force in
patients with and without DCM is applicable to the case studied here[10,11]. In that work, they
noted that conditions which lead to maximal recoil force coincide with vortex pinch-off
occurring at a non-dimensional formation time (a concept representing the equivalent motion of
a piston) of 3.5-4.5, a value previously reported to be the optimum for effective momentum
transport. This value occurs for mitral valves near the typical healthy diameter, and are lower for
larger and smaller valves. However, the applicability of those results to un-enlarged hearts is not
clear, as the flow patterns observed in this study are very different, and their experimental setup
used a “ventricle” with a width of 13 cm, much larger than physiological, and approximately 5x
the diameter of their mitral opening. This severely attenuates any wall effects, something which
the current study appears to indicate is a primary driver in the development of flow patterns in LV filling.

CONCLUSIONS

2D phase contrast MRI data of the 3-chamber view of the heart was acquired for 8 patients, (2 healthy, 6 with diastolic dysfunction, one of which is suffering from dilated cardiomyopathy). Pressure fields were derived from the measured flow fields, and pressure differences between the atrium, mitral valve, and apex were calculated as a function of time. From this data it was observed that healthy patients had larger peak pressure differences during early filling than late filling, and that compared to patients with diastolic dysfunction, pressure differences were higher during early filling, and lower during late filling. The ratio of peak transmitral pressure during early filling to peak transmitral pressure during late filling was explored as a diagnostic tool to differentiate between healthy and diseased patients, and appeared to give good results, with high values (above 2) indicating normal function, and lower values (below 2) indicating diastolic dysfunction. However, given the complexity of the measurements necessary to derive this value and its close association with the existing parameter E/A (peak early filling velocity versus peak later filling velocity), its clinical utility is unclear.

Additionally, it was observed that large vortices formed laterally and medially to the inflow jet during the filling process, and these vortices had the effect of constraining the inflow, and delaying the expansion and lateral motion of the fluid until farther into the left ventricle. As a consequence, the end of the vortices acted like a diverging nozzle, causing an adverse pressure gradient to form in the middle of the ventricle (instead of pressure varying smoothly across its length). To explain these differences, it was proposed that in healthy patients the preferential initial expansion at the apex of the ventricle during isovolumic relaxation, coupled with upward
motion of the mitral annulus during filling allowed for the formation of larger vortices, leading to
more effective suction in the left ventricle. In contrast, it was suggested that late filling in
normal hearts lacked this mechanism, as did both early and late filling in hearts with diastolic
dysfunction, and therefore the inflow jet expanded earlier and was paired with smaller vortices.
As a result, filling during these periods was less efficient, suction was decreased, and to
compensate the diseased hearts had to raise the LA pressure gradients to complete the filling
process.

In contrast, the heart with both dilated cardiomyopathy and diastolic dysfunction showed
substantially different filling behavior. In this patient the vortex that formed at the tip of the
mitral inflow jet traveled with the jet, and appeared to be governed by the vortex roll-up and
pinch-off described in the work of Gharib et al.[9-11]

To verify the hypothesis proposed, it will be necessary to perform simultaneous (or phase
locked), high resolution imaging of ventricular wall motions as well as the velocity scanning
programs used here. Better understanding of this mechanism will significantly enhance our
understanding of the underlying pathologies that give rise to diastolic dysfunction. Confirmation
that changes in wall motion are a significant contributing factor in the development of LVDD
may allow for new treatments that better treat the underlying causes, rather than just the
symptoms.
REFERENCES


Appendix: Additional WSS and OSI Results

These appendices contain a more detailed listing of the results from the complete stent testing. The wall shear stress and oscillatory shear index data presented here were calculated based on the processing methodologies described in Chapter 4, and do not include the robust phase correlation and pair straddling methods described in Chapters 3 and 5.

OVERVIEW OF WSS AND OSI MEASUREMENTS

After testing was complete, for each case examined the regions of the wall visible in the PIV data and directly exposed to the flow were located, and the wall shear stress (WSS) and oscillatory shear index (OSI) were computed as described above. Out of those regions, a single section downstream of a stent strut was isolated for further analysis and comparison for each case. This is the same region, as discussed above, which had been selected prior to the experiment as the target location for that ROI. Table A.1 and Table A.2 list these WSS and OSI values for all cases tested. The quantities in these tables were computed by first averaging at each position along the wall over a single period in time (these curves can be seen in Appendix A in the “WSS: Time Averaging (1 Period), Entire Visible Region” sections for each stent configuration). From this data, the WSS values in each selected region were averaged in space to get a single value for the shear stress experienced at the vessel wall downstream of a strut crossing, and the standard deviation of those values was found to give an estimate of the variability over that region. Similarly, the OSI was calculated from the experimental data along the same region by averaging in time, and from that the spatial average and variability were found in the same way as the WSS.
Table A.1 List of time- and space-averaged WSS values for all conditions tested.
Ranges are spatial variation over the region tested

<table>
<thead>
<tr>
<th>Re #</th>
<th>XIENCE™ 3x18</th>
<th>VISION™ 3x18</th>
<th>XIENCE™ 3.75</th>
<th>XIENCE™ 3x28</th>
<th>XIENCE™ Overlap</th>
<th>Endevor 3x18</th>
<th>Liberte™ 3x18</th>
<th>CYPHER® 3x18</th>
<th>XIENCE™ 4x18</th>
</tr>
</thead>
<tbody>
<tr>
<td>160US</td>
<td>9.14±0.56</td>
<td>3.31±0.46</td>
<td>3.83±1.58</td>
<td>8.72±1.65</td>
<td>9.82±0.31</td>
<td>2.74±3.28</td>
<td>-1.87±2.18</td>
<td>0.63±1.68</td>
<td>6.3±1.13</td>
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<tr>
<td>160MS1</td>
<td>5.43±0.84</td>
<td>3.99±0.68</td>
<td>9.29±2.40</td>
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<tr>
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<td>---</td>
<td>---</td>
<td>8.70±1.69</td>
<td>7.29±1.75</td>
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</tr>
<tr>
<td>160DS</td>
<td>10.99±3.94</td>
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<td>9.93±3.36</td>
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<td>7.85±6.94</td>
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<td>18.37±3.92</td>
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<tr>
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<td>23.38±2.44</td>
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<td>25.37±9.14</td>
<td>-6.93±1.12</td>
<td>13.48±3.72</td>
<td>8.14±7.80</td>
</tr>
</tbody>
</table>

Table A.2: List of space-averaged OSI values for all conditions tested.
Ranges are spatial variation over the region tested

<table>
<thead>
<tr>
<th>Re #</th>
<th>XIENCE™ 3x18</th>
<th>VISION™ 3x18</th>
<th>XIENCE™ 3.75</th>
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<th>XIENCE™ Overlap</th>
<th>Endevor 3x18</th>
<th>Liberte™ 3x18</th>
<th>CYPHER® 3x18</th>
<th>XIENCE™ 4x18</th>
</tr>
</thead>
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<td>0.22±0.07</td>
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<td>0.19±0.01</td>
<td>0.31±0.09</td>
<td>0.40±0.05</td>
<td>0.29±0.09</td>
<td>0.18±0.04</td>
</tr>
<tr>
<td>160MS1</td>
<td>0.18±0.01</td>
<td>0.23±0.03</td>
<td>0.11±0.01</td>
<td>0.14±0.05</td>
<td>0.15±0.01</td>
<td>0.23±0.07</td>
<td>0.27±0.03</td>
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<td>0.16±0.02</td>
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<td>0.17±0.10</td>
<td>0.14±0.09</td>
<td>0.11±0.02</td>
<td>0.11±0.02</td>
<td>0.15±0.07</td>
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<td>0.16±0.02</td>
<td>0.34±0.10</td>
<td>0.34±0.08</td>
<td>0.31±0.07</td>
<td>0.15±0.07</td>
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<td>300MS1</td>
<td>0.18±0.02</td>
<td>0.24±0.02</td>
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<td>0.13±0.01</td>
<td>0.23±0.1</td>
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<td>0.14±0.04</td>
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<td>0.14±0.06</td>
<td>0.24±0.05</td>
<td>0.29±0.06</td>
<td>0.22±0.21</td>
<td></td>
</tr>
</tbody>
</table>
EXPANDED WSS AND OSI RESULTS, INDIVIDUAL STENT CONFIGURATIONS

In this section, detailed breakdowns on the variations of the measured WSS and OSI in both space and time are plotted in several ways. The plots are divided first by configuration. Within each configuration, there are three basic plot types. The first shows the variation of the WSS over a single period of the flow cycle, with the values being averaged over the region behind the strut. The red regions delineate the extent of one standard deviation of the spatial variance at each time instant, and the blue dashed lines outline the maximum and minimum values recorded. For a given Reynolds number these time histories are all synchronized in time to one another, and correspond to the flow profiles seen in the plots below. Timing was not synchronized for comparisons between Re=160 and Re=300 cases, however.

The second group of plots for each stent shows the WSS profile along the length of the vessel for each configuration, averaged in time over one period. In addition, the standard deviation of that temporal variability is outlined by the red regions to give an idea of the amount of change in WSS experienced at each station along the vessel. While the WSS was calculated and plotted along the entire length of the ROI, in some regions flow near the vessel walls was obscured by the stent struts. For those regions, the WSS was extrapolated from the approximate wall locations, and is plotted using dashed lines. However, in many cases this estimate failed, and only values within the marked regions should be trusted for analysis.

Finally, the third set of plots outlines the spatial profile of OSI along the vessel length for each test case, and the presence of the blocked regions is indicated as before.

For each plot type and configuration, either 6 or 8 individual plots are shown per page, representing the two flow rates and 3 or 4 positions tested for each stent configuration.
Figure A.1: Example experimental flow rate and pressure curves for Re=160 (left) and Re=300 (right)
ABBOTT VASCULAR XIENCETM 3X18

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

3x18 US Re160 WSS, averaged on region behind strut (botx18 MS Re160 WSS, averaged on region behind strut (botx18 DS Re160 WSS, averaged on region behind strut (bot

Re160

3x18 US Re300 WSS, averaged on region behind strut (botx18 MS Re300 WSS, averaged on region behind strut (botx18 DS Re300 WSS, averaged on region behind strut (bot

Re300
ABBOTT VASCULAR XIENCE™ 3X18

WSS: Time Averaging (1 Period), Entire Visible Region

US

- xience3x18 US Re160 time-averaged WSS (bottom wall)

- xience3x18 US Re300 time-averaged WSS (bottom wall)

MS

- xience3x18 MS Re160 time-averaged WSS (bottom wall)

- xience3x18 MS Re300 time-averaged WSS (bottom wall)

DS

- xience3x18 DS Re160 time-averaged WSS (bottom wall)

- xience3x18 DS Re300 time-averaged WSS (bottom wall)
ABBOTT VASCULAR XIENCE™ 3X18

OSI: Entire Visible Region

US

Re160

Re300

MS

DS

xience3x18 US Re160 OSI (bottom wall)

xience3x18 MS Re160 OSI (bottom wall)

xience3x18 DS Re160 OSI (bottom wall)

xience3x18 US Re300 OSI (bottom wall)

xience3x18 MS Re300 OSI (bottom wall)

xience3x18 DS Re300 OSI (bottom wall)
BOSTON SCIENTIFIC LIBERTE™ 3X20

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

Re160

liberte3x20 US Re160 WSS - region (top)

liberte3x20 US Re300 WSS - region (top)

Re300

liberte3x20 US Re300 WSS - region (top)

liberte3x20 MS Re160 WSS - region (top)

liberte3x20 MS Re300 WSS - region (top)

liberte3x20 DS Re160 WSS - region (top)

liberte3x20 DS Re300 WSS - region (top)
BOSTON SCIENTIFIC LIBERTE™ 3X20

**WSS: Time Averaging (1 Period), Entire Visible Region**

**US**

[Graph showing time-averaged WSS for US Re160 and Re300]

**MS**

[Graph showing time-averaged WSS for MS Re160 and Re300]

**DS**

[Graph showing time-averaged WSS for DS Re160 and Re300]
BOSTON SCIENTIFIC LIBERTE™ 3X20

OSI: Entire Visible Region

**US**

![](liberte3x20 US Re160 OSI (top wall))

**MS**

![](liberte3x20 MS Re160 OSI (top wall))

**DS**

![](liberte3x20 DS Re160 OSI (top wall))

Re160

![](liberte3x20 US Re300 OSI (top wall))

![](liberte3x20 MS Re300 OSI (top wall))

![](liberte3x20 DS Re300 OSI (top wall))

Re300
MEDTRONIC ENDEAVOR™ 3X18

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

Re160

endeavor3x18 US Re160 WSS - region (bottom)

Re300

endeavor3x18 US Re300 WSS - region (bottom)

MS

endeavor3x18 MS Re160 WSS - region (bottom)

endeavor3x18 MS Re300 WSS - region (bottom)

DS

endeavor3x18 DS Re160 WSS - region (bottom)

endeavor3x18 DS Re300 WSS - region (bottom)
MEDTRONIC ENDEAVOR™ 3X18

WSS: Time Averaging (1 Period), Entire Visible Region

US

endeavor3x18 US Re160 WSS (bottom wall)

Re160

endeavor3x18 US Re300 WSS (bottom wall)

Re300

MS

endeavor3x18 MS Re160 WSS (bottom wall)

DS

endeavor3x18 DS Re160 WSS (bottom wall)

endeavor3x18 MS Re300 WSS (bottom wall)

endeavor3x18 DS Re300 WSS (bottom wall)
MEDTRONIC ENDEAVOR™ 3X18

OSI: Entire Visible Region

US

MS

DS

Re160

Re300
CORDIS CYPHER®, 3X18

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

3x18 US Re160 WSS, averaged on region behind strut

3x18 US Re300 WSS, averaged on region behind strut

MS

3x18 MS Re160 WSS, averaged on region behind strut

3x18 MS Re300 WSS, averaged on region behind strut

DS

cypher3x18 DS Re160 WSS - region (top)

cypher3x18 DS Re300 WSS - region (top)
CORDIS CYPHER®, 3X18

WSS: Time Averaging (1 Period), Entire Visible Region

US

Re160

Re300
CORDIS CYPHER®, 3X18

OSI: Entire Visible Region

US

cypher3x18 US Re160 OSI (bottom wall)

MS

cypher3x18 MS Re160 OSI (bottom wall)

cypher3x18 MS Re300 OSI (bottom wall)

cypher3x18 DS Re160 OSI (top wall)

cypher3x18 DS Re300 OSI (top wall)
ABBOTT VASCULAR XIENCE™ 3X28

WSS: 1 Time period, Spatial Averaging (Region behind Strut)
ABBOTT VASCULAR XIENCE™ 3X28

WSS: Time Averaging (1 Period), Entire Visible Region

US

Re160

Re300

MS1

MS2

DS
ABBOTT VASCULAR XIENCE™ 3X28

OSI: Entire Visible Region

US

MS1

MS2

DS

Re160

Re300
ABBOTT VASCULAR XIENCE™ 3X18 – OVEREXPANDED TO 3.75

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

Re160

Re300

MS

DS
ABBOTT VASCULAR XIENCE™ 3X18 – OVEREXPANDED TO 3.75

WSS: Time Averaging (1 Period), Entire Visible Region

**US**

xience3x18-3.75 US Re160 WSS (bottom wall)

**MS**

xience3x18-3.75 MS Re160 WSS (bottom wall)

**DS**

xience3x18-3.75 DS Re160 WSS (bottom wall)

Re160

xience3x18-3.75 US Re300 WSS (bottom wall)

xience3x18-3.75 MS Re300 WSS (bottom wall)

xience3x18-3.75 DS Re300 WSS (bottom wall)

Re300
ABBOTT VASCULAR XIENCE™ 3X18– OVEREXPANDED TO 3.75

OSI: Entire Visible Region

US

Re160

xience3x18-3.75 US Re160 OSI (bottom wall)

OSI

OSI(x)

blocked regions

x (mm)

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

Re300

xience3x18-3.75 US Re300 OSI (bottom wall)

OSI

OSI(x)

blocked regions

x (mm)

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

MS

Re160

xience3x18-3.75 MS Re160 OSI (bottom wall)

OSI

OSI(x)

blocked regions

x (mm)

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

Re300

xience3x18-3.75 MS Re300 OSI (bottom wall)

OSI

OSI(x)

blocked regions

x (mm)

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

DS

Re300

xience3x18-3.75 DS Re300 OSI (bottom wall)

OSI

OSI(x)

blocked regions

x (mm)

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5

0
0.1
0.2
0.3
0.4
0.5
ABBOTT VASCULAR XIENCE™ 4X18

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

xience 4x18 US Re160 WSS - region (bottom)

Re160

xience 4x18 US Re300 WSS - region (bottom)

Re300

MS

xience 4x18 MS Re160 WSS - region (bottom)

xience 4x18 MS Re300 WSS - region (bottom)

DS

xience 4x18 DS Re160 WSS - region (bottom)

xience 4x18 DS Re300 WSS - region (bottom)
ABBOTT VASCULAR XIENCE™ 4X18

**WSS: Time Averaging (1 Period), Entire Visible Region**

**US**

- xience 4x18 US Re160 WSS (bottom wall)
- xience 4x18 US Re300 WSS (bottom wall)

**MS**

- xience 4x18 MS Re160 WSS (bottom wall)
- xience 4x18 MS Re300 WSS (bottom wall)

**DS**

- xience 4x18 DS Re160 WSS (bottom wall)
- xience 4x18 DS Re300 WSS (bottom wall)

**Re160**

**Re300**
ABBOTT VASCULAR XIENCE™ 4X18

OSI: Entire Visible Region

**US**

![Graph](image1)

**MS**

![Graph](image2)

**DS**

![Graph](image3)

Re160

![Graph](image4)

Re300

![Graph](image5)
ABBOTT VASCULAR XIENCE™ TWO 3X18, 4MM OVERLAP

WSS: 1 Time period, Spatial Averaging (Region behind Strut)
ABBOTT VASCULAR XIENCE™ TWO 3X18, 4MM OVERLAP

WSS: Time Averaging (1 Period), Entire Visible Region

US

Re160

2xience3x18 US Re160 WSS (bottom wall)

WSStime-avg ± time

blocked regions

Re300

2xience3x18 US Re300 WSS (bottom wall)

WSStime-avg ± time

blocked regions

MS1

2xience3x18 MS1 Re160 WSS (bottom wall)

WSStime-avg ± time

blocked regions

2xience3x18 MS1 Re300 WSS (bottom wall)

WSStime-avg ± time

blocked regions

MS2

2xience3x18 MS2 Re160 WSS (bottom wall)

WSStime-avg ± time

blocked regions

2xience3x18 MS2 Re300 WSS (bottom wall)

WSStime-avg ± time

blocked regions

DS

2xience3x18 DS Re160 WSS (bottom wall)

WSStime-avg ± time

blocked regions

2xience3x18 DS Re300 WSS (bottom wall)

WSStime-avg ± time

blocked regions
ABBOTT VASCULAR XIENCE™ TWO 3X18, 4MM OVERLAP

OSI: Entire Visible Region

US

MS1

MS2

DS

Re160

Re300
ABBOTT VASCULAR VISION™ 3X18

WSS: 1 Time period, Spatial Averaging (Region behind Strut)

US

vision3x18 US Re160 WSS - region (bottom)

Re160

vision3x18 US Re300 WSS - region (bottom)

Re300

MS

vision3x18 MS Re160 WSS - region (bottom)

DS

vision3x18 DS Re160 WSS - region (bottom)

vision3x18 DS Re300 WSS - region (bottom)
ABBOTT VASCULAR VISION™ 3X18

WSS: Time Averaging (1 Period), Entire Visible Region

US

Re160

vision3x18 US Re160 WSS (bottom wall)

Re300

vision3x18 US Re300 WSS (bottom wall)

MS

Re160

vision3x18 MS Re160 WSS (bottom wall)

Re300

vision3x18 MS Re300 WSS (bottom wall)

DS

Re160

vision3x18 DS Re160 WSS (bottom wall)

Re300

vision3x18 DS Re300 WSS (bottom wall)
ABBOTT VASCULAR VISION™ 3X18

OSI: Entire Visible Region

US

Re160

vision3x18 US Re160 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)

Re300

vision3x18 US Re300 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)

MS

vision3x18 MS Re160 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)

vision3x18 MS Re300 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)

DS

vision3x18 DS Re160 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)

vision3x18 DS Re300 OSI (bottom wall)

OSI

0 0.1 0.2 0.3 0.4 0.5

x (mm)
EXPANDED WSS AND OSI RESULTS, COMPARISON OF STENT CONFIGURATIONS

In this section the averaged values and spatial variability of the WSS and OSI from Table A.1 and Table A.2 were plotted so that patterns in within and between stent configurations would be more apparent. In addition to the mean values, indicated by the black tick marks, and the spatial standard deviation, indicated by the bar heights (centered on the mean), the breadth of the maximum and minimum time-averaged values are also indicated by the “whiskers” attached to each bar. Here, the green whiskers correspond to the Re=160 case, and the blue to the Re=300 case.
In each plot, the standard deviation of the spatial variation on WSS over the ROI behind the strut is indicated by the height of each bar, and the maximum and minimum WSS over that region are indicated by the “whiskers”. The orange bars and green whiskers correspond to the Re=160 data, and the red bars and blue whiskers describe the Re=300 data.
In each plot, the standard deviation of the spatial variation on OSI over the ROI behind the strut is indicated by the height of each bar, and the maximum and minimum OSI over that region are indicated by the “whiskers”. The orange bars and green whiskers correspond to the Re=160 data, and the red bars and blue whiskers describe the Re=300 data.