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Hemodynamics of the Aortic Root upon Transcatheter Aortic Valve Implantation

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Hemodynamics of the Aortic Root upon Transcatheter Aortic Valve Implantation

by

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Hemodynamics of the Aortic Root upon Transcatheter Aortic Valve Implantation

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ABSTRACT

Since the start of the twenty-first century cardiovascular therapies have seen a shift towards minimally invasive procedures. Heart disease is the leading cause of death in the United States and it manifests itself in many ways. One crucial aspect of heart disease relates to the calcification of the aortic valve and the valvular insufficiencies that this causes. Traditionally patients with these problems would undergo open heart surgery and a bioprosthetic or mechanical heart valve would be implanted to replace the body’s faulty native valve. A large group of patients who suffer from heart disease, especially the elderly, also suffer from other debilitating diseases and their bodies can be too frail to undergo open heart surgery. Transcatheter aortic valve implantation (TAVI) is a minimally invasive procedure that aims to target this population of high risk patients by using a catheter based approach to deliver a replacement valve. TAVI is a relatively new practice, with the first procedure performed in 2002, and there is still much to learn about the effectiveness, durability, and safety of these valves over time. This study presents experimental and simulation work that aims to examine how TAVs may affect the hemodynamics of the aortic root upon non ideal implantation scenarios. The first portion of this paper demonstrates a methodology of accurately characterizing coronary velocity profiles in an ex vivo environment. The experimental set-up allows for the implantation of a TAV into a native aortic root where hemodynamic conditions, including coronary flow, can be observed. The second portion of this research focuses on a series of simulations that demonstrate how changes in deployment constriction and ellipticity alter the flow patterns of an implanted TAV. With more in depth experimental and simulation studies it is hoped that this research can further the design and development of future TAVs.
1.0 INTRODUCTION

1.1 The Human Heart

The human heart is a complicated organic pump that circulates blood throughout the body. It is comprised of four chambers that are separated by a series of valves. The chambers, in sequence of flow, are the right atrium, the right ventricle, the left atrium, and the left ventricle. The left ventricle can be looked at as a starting point when regarding the direction of blood flow.

Figure 1: Depicts the anatomy of a human heart including the left and right atria and ventricles, the aortic valve, the mitral valve, the tricuspid valve, and the pulmonary valve. [1]
as it is the primary pump that moves blood into the circulatory system. Oxygenated blood is moved through the ascending aorta where it is distributed throughout the circulatory system. Blood then returns to the right atrium via the superior and inferior vena cava.

The blood is now deoxygenated as it re-enters the heart. Flow passes through the tricuspid valve into the right ventricle where it is then pumped into the lungs through the pulmonary valve. While in the lungs, the blood is re-oxygenated and sent back into the left atrium before passing through the mitral valve and reentering the left ventricle. After filling the left ventricle the blood is pumped through the aortic valve out into the circulatory system once again.

A normal cardiac cycle consists of two phases: systole and diastole. Systole is characterized by the contraction of the left ventricle and the beginning of forward flow through the aortic valve. Diastole is characterized by the relaxation and filling of the left ventricle. At the beginning of the diastolic phase the semilunar valves (aortic and pulmonary) close, the atrioventricular valves (mitral and tricuspid) open and the ventricles begin to fill with blood. During mid-diastole the atria and ventricles remain relaxed and the semilunar and atrioventricular valves remain closed and open respectively. At the end of diastole the sinoatrial node and the atria contract and contraction reaches the atrioventricular node. The start of systole begins when the contraction passes from the atrioventricular node to the Purkinje fibers and ventricular wall. The atrioventricular valves close and the semilunar valves open and the ventricles contract and push blood into the arteries.
Figure 2: A depiction of the cardiac conduction system. Electrical signals propagate along the pathways shown, beginning at the sinoatrial node and passing all the way into the purkinje fibers. [2]

1.1.1 Anatomy of the Aortic Root

Throughout this paper there will be references to the aortic root. This term refers to the section of the heart that extends from the outlet of the left ventricle at the annulus of the aortic valve to the area where the ascending aorta ends. For the purposes of this paper this includes the sections of the ascending aorta leading up to the aortic arch and the brachiocephalic artery.
The aortic valve consists of three leaflets that open and close in a passive manner during the systolic and diastolic phases of the heart respectively. Each leaflet is attached in a semilunar fashion to the aortic root. The meeting points of the semilunar leaflets, the commissures, are located at the junctions between the aortic sinuses.

Figure 3: A depiction of the ascending aorta, descending aorta, and coronary arteries with relation to the heart [3]
At the base of the aortic root lies the aortic annulus which serves as the attachment point for the belly of the semilunar aortic valve leaflets. Each leaflet has a corresponding portion of the ascending aorta that bulges away from the belly portion of the leaflet. These bulges are called the aortic sinuses of valsalva [4]. Two of the aortic sinuses serve as the origin point of the coronary arteries and one is a non-coronary sinus. The sinuses serve as an area for the leaflets to be pushed into while the left ventricle is propelling blood through the aortic valve.

Figure 4: A depiction of the aortic root with a cross section examining the leaflets of the aortic valve [5]
1.1.2 MITRAL VALVE

The mitral valve is a bicuspid heart valve that separates the left atrium from the left ventricle. The two leaflets are commonly referred to as the anterior and posterior leaflets [6]. The posterior leaflet extends around approximately two thirds of the atrioventricular junction and is much thinner than the anterior leaflet. The anterior leaflet is much broader than the posterior leaflet and its attachment area lies next to the aortic annulus. The anterior mitral leaflet is in fibrous continuity with the aortic valve [6]. The mitral valve opens downward into the left ventricle during the diastolic filling of the heart. During systole the left ventricle causes the valve to close, preventing fluid from entering the left atrium.

Figure 5: Anatomical representation of the human mitral valve from a cross sectional side view.

(Courtesy of HeartValveSurgery.com)
To prevent leaflet over closure into the left atrium there are fan-shaped chords called chordae tendinae that extend from the papillary muscles to various points on the leaflet surfaces.

### 1.1.3 CORONARY ARTERIES

The left and right coronary arteries (LCA and RCA respectively) act as a network to supply oxygenated blood to the myocardium of the heart. The arteries originate in the left and right coronary sinuses of the aortic root. They extend and branch into smaller arterioles and eventually capillaries as they travel through the epicardium and into the myocardium. The LCA divides into the left anterior descending artery and the circumflex branch.

![Coronary Arteries of the Heart](nyp.org/health/cardiac-arteries.html)

**Figure 6:** Depiction of the coronary arteries and their respective locations around the heart (Courtesy of nyp.org/health/cardiac-arteries.html)
The LCA supplies blood to the left ventricle and left atrium. The RCA divides into the right posterior descending and acute marginal arteries and supplies blood to the right ventricle and right atrium in addition to the sinoatrial and atrioventricular nodes. Since the coronary arteries supply blood to the heart they are arguably one of the most important structures of the circulatory system. If the coronary arteries become blocked the heart muscles will no longer be able to function and the muscles will become ischemic which can greatly reduce the heart's ability to efficiently pump blood.

1.2 HEMODYNAMICS OF THE HEART

When studying the hemodynamics of blood flow around and through the aortic root some of the important values that are looked at are Effective orifice area (EOA), aortic root pressure (AP), left ventricular pressure (LVP), stroke volume, RMS forward flow volume, closing volume, regurgitant volume, total percent leakage per beat, and differential pressure during forward flow between the left ventricle and aortic root (ΔP).

EOA is a standard parameter used by clinicians to determine the severity of stenosis in valves and gives a good idea of how well a valve is functioning during forward flow. EOA is calculated by using the following formula:

\[ EOA = \frac{RMS_{\text{forward flow}}}{51.6 \cdot \sqrt{\Delta P}} \] , [7]

When a valve is fully open the actual orifice area would correspond to the area of the three leaflet free edges in an (almost) circular shape. EOA cannot be measured by looking directly at the valve when it is open because it measures the area of the main forward jet of fluid. Many
factors such as the geometry of the valve, stenotic conditions, angle of the leaflets at the outflow can all contribute to how the fluid passing through the valve is shaped.

**Figure 7:** A representation of EOA with respect to the anatomic orifice area (AOA) within the aortic root.

(modified from springerimages.com) [8]

The flow waveform for a normal “ideal” heart beat can be seen in figure 8. This wave form covers the range of one heartbeat from the beginning of systole to the end of diastole. The systolic duration comprised all of the positive flow values. At the beginning of systole these is a sharp increase in the velocity of the flow, it then peaks and steadily declines until the start of systole. This forward flow region is also referred to as the stroke volume and is used when calculating the percent leakage. The negative portions on the graph correspond to the diastolic phase when the valve is closed. Flow values are negative in this region due to paravalvular
leakage and backflow and can be broken up into two parts. At the beginning of diastole the left ventricle relaxes and the aortic valve closes. As the valve closes the leaflets travel towards

![Graph of fluid flow waveform through an aortic valve.](image)

**Figure 8:** This graph represents a normal fluid flow waveform through an aortic valve. The positive regions correspond to forward flow during the systolic phase. The negative regions correspond to closing volume (1) and regurgitant volume (2) respectively. [7]

the ventricle pushing blood backwards through the annulus of the valve. This can be seen as a brief, sharp, spike in negative velocity that (for a healthy individual) should just as quickly return to approximately zero flow. This region is referred to as the closing volume. The remainder of the curve corresponds to the paravalvular leakage while the valve is closed and is referred to as the regurgitant volume. The regurgitant volume for a healthy valve should be minimal while diseased valves that are unable to fully close will demonstrate large regurgitant volumes. These
three values (Stroke volume, closing volume, and regurgitant volume) can be used together to calculate the total percent leakage though the valve per cycle. Total percent leakage per cycles is defined below:

\[
\% \text{Leakage} = \frac{\text{Closing Volume} + \text{Regurgitant Volume}}{\text{Stroke Volume}} \times 100
\]  

(2)

LVP and AP are important pressure waveforms that can be looked at to determine how well a valve is functioning. The LVP waveform has two main portions to it as well that correspond to systolic and diastolic phases. At the start of systole there is a sharp increase in pressure that eventually peaks and steadily decreases until the start of diastole. During diastole the pressure is generally very low and can sometimes show up as negative briefly when taking measurements due to the vacuum effect the filling left ventricle has.

The AP pressure waveform follows a similar trend to the LVP curve during systole. It follows a similar path while remaining at a value lower than its LVP counterpart. A typical healthy valve could have a forward flow differential pressure of around 5 mmHg. With an increase in stenotic conditions and or regurgitant leakage this differential pressure value will increase. Unlike the LVP curve, the AP curve does not drop down as drastically in pressure and will remain pressurized during diastole. The phrase 120 over 80 is a commonly known term regarding blood pressure. The 120 value corresponds to peak pressure at systole and the 80 value corresponds to the minimum pressure value during diastole. As a valve becomes more diseased and ineffective these two numbers will steadily grow further apart from one another.
Figure 9: Normal left ventricular and aortic pressure waveforms for one normal human heart cycle.[9]

Essentially the heart must work harder to pump blood through a faulty valve so the systolic pressure increases. Since a faulty valve is generally leaky it cannot hold the normal pressures gradient and the AP is significantly lower during the diastole phase. An example of a diseased valves LVP and AP waveforms is shown below in figure 10.
Figure 10: Theoretical LVP and AP waveforms for an aortic valve with heavy stenosis. The LVP is much higher than the AP during forward flow. [9]

1.3 HEART DISEASE

Heart disease is a broad term that includes diseases such as coronary artery diseases, heart failure, heart valve diseases and many more. It is credited as the leading cause of death for both men and women in the United States [10, 11]. It is estimated that in 2006 nearly 7235 000 inpatient cardiovascular operations were performed in the United States alone [12]. Heart valve disease is characterized by two main types of problem: valvular stenosis and valvular insufficiency. Valvular stenosis refers to any situation involving the stiffening, narrowing, fusion, or blockage of one of the heart valves. The aortic valve in particular often gathers large calcium deposits on its leaflets as shown below in figure 11.
Having one or more of these symptoms creates a situation where the valve does not function normally and the heart has to work much harder to pump blood through the stenotic valve. An easy way to think about this is to imagine that a healthy heart pumps 100% of the blood needed for the body to function normally per beat. If a stenotic valve restricts flow by say 50% the heart must now work twice as hard to supply the same amount of blood that the body would be getting from a healthy heart. To compensate for the lower blood supply per beat the heart will either have to speed up its normal rhythm or the left ventricle will begin to stretch as the heart tries to pump more blood per beat [14]. This is a disease that usually propagates and gets worse over time. Some of the symptoms include shortness of breath, fatigue, chest pain, dizziness, and eventual heart failure. While it is possible to live with valvular stenosis it can
greatly decrease the quality of your life as simple tasks such as walking up stairs may become too taxing for your heart and body to handle.

Valvular insufficiency is also referred to as valvular regurgitation and is characterized by a valve that is unable to completely close. Incomplete closure of the valve results in back flow of the blood that was just pushed through the valve. For example, with regards to the aortic valve, blood would be pulled back through the aortic valve during diastole filling the left ventricle with both blood from the atrium and blood from the ascending aorta. This is incredibly inefficient and once again the heart has to work much harder to supply an appropriate amount of blood to the rest of the body. Similar symptoms such as fatigue and shortness of breath are common for valvular regurgitation and it is not uncommon for a patient to have both of these conditions contributing towards their “heart disease” in some degree.

Coronary artery disease is characterized by situations where the coronary arteries become damaged, blocked, or diseased [15]. A common cause of coronary artery disease is the build-up of plaques in the arteries (atherosclerosis) [16]. Plaque build-up can begin at a very early age and may not be noticeable until the mid to late stages of life. Cholesterol laden plaques begin to deposit on the arterial walls which then release chemicals that end up making the walls easier for other substances such as calcium to attach to. These substances will build up over time which in turn restricts the blood flow through the vessels. The restriction and potential blockage can prevent blood from being absorbed by sections of the heart muscles. If
Figure 12: Representations of normal and diseased sections of a coronary artery. The image on the right shows an arterial segment that is greatly narrowed by atherosclerotic plaque. [17]

blood is unable to reach portions of the heart and ischemic condition may occur where sections of the heart effectively die and are unable to function. Coronary artery disease may display many of the same symptoms as valvular diseases such as shortness of breath and fatigue. Treatment options for coronary artery disease involve methods including angioplasty [18] and coronary stenting [19].

1.4 HEART VALVES

1.4.1 Surgical Heart Valves

The valves of the heart all ideally act as one way valves. They are oriented in such a way that when blood is pushed through them, such as during ventricular contraction, the leaflets are easily pushed open by the moving blood. As an example of this the left side of the heart
will be discussed. At the beginning of diastole, when the ventricle begins to relax and fill, it creates a back pressure on the blood in the aortic root and attempts to pull it into the left ventricle. Due to the geometry and one-way nature of the valves this back pressure pushes the leaflets together creating a seal. Anatomically the valves cannot open in the other direction so this increase in pressure causes them to close together instead. The mitral valve on the other hand opens inward directing flow into the left ventricle. The increase in fluid volume created by the relaxing left ventricle effectively draws blood through the mitral valve from the left atrium. During systole the left ventricular contraction creates a sharp increase in pressure. This pressure increase pushes the mitral leaflets up towards the atrium where chordae prevent it from traveling too far. This creates a seal and forces blood to move towards the aortic valve. The blood forces the leaflets open and pushes them towards the aortic wall.

![Figure 13: A Bi-Leaflet mechanical heart valve](image)

Artificial heart valves try to mimic the one way nature of native heart valves but have taken many different approaches when attempting to accomplish this goal. Surgical heart
valves, ones that require open heart surgery to implant, fall into two broad categories: Mechanical and bio-prosthetic heart valves. Mechanical valves usually employ a bileaflet design as shown in Figure 13.

These leaflets are commonly made from pyrolytic carbon and have the ability to last a patient's entire lifespan. These types of valves, with their known durability, are usually implanted in patients who have a life expectancy that is greater than 10-15 years [cite]. The downside to the mechanical heart valves is that the metals used for the leaflets are not as compliant as tissue and have been found to cause blood damage that can result in clots. To combat this effect, recipients of mechanical heart valves are required to take anticoagulation medicine for the rest of their life.

Bioprosthetic, or tissue valves, attempt to more closely mimic the native human valves. Biological tissue use has ranged from entire porcine heart valves that have been dissected and mounted to stents to leaflets that have been made from bovine pericardial sacs which are then sewed to a skirt and stent. An example of a bioprosthetic heart valve, one that is used in this study, is the Carpentier-Edwards Perimount (CEP) bioprosthetic valve(Edwards Lifesciences Corporation, Irvine, CA) (figure 14)
The advantage of using a tissue valve is that it more closely mimics the functionality of native heart valves. The tissues are much more compliant that the mechanical leaflets and have less likelihood of causing blood damage which in turn means there is a lower requirement for anticoagulation therapy. The downside is that the tissues used are no longer living and have to be treated with a chemical such as glutaraldehyde to prevent deterioration and to prevent rejection by the host. These treated tissues have still been found to have a life span of approximately 10-15 years before failure which is a fine time frame for patients who are not projected to live that long regardless.

Both of these types of valves require open heart surgery to implant. During the surgical procedure the patient is placed on general anesthesia and is put to sleep. The surgeon makes a large cut in the chest that passes through the breastbone. The ribcage is then held open and the heart is stopped while the patient is connected to a heart-lung bypass machine. The bypass
machine acts oxygenate blood that enters it then it pumps the blood throughout the body, effectively replicating the main functions of the heart without having the blood actually pass through the heart. This machine also flushes the heart with a potassium solution that effectively “freezes” the heart in place and prevents it from beating. The surgeon then removes the native valve and sews the new valve to the annulus of the native aortic root.

1.4.2 Transcatheter Heart Valves

When a patient is deemed too sick to undergo open heart surgery they may opt to receive a transcatheter aortic valve (TAV) via a minimally invasive procedure called Transcatheter Aortic Valve Implantation (TAVI). TAVs are different than surgical valves in that the doctor is not required to do open heart surgery to implant them. Instead, the valve is cramped and mounted into a catheter which is then guided into place and used to release the TAV inside the native valve. The main differences between TAVs and surgical valves are that TAVs are able to be cramped down to a size much smaller than the normal aortic annulus and they are able to secure themselves in the aortic annulus without sutures.

There are two types of TAVs used, balloon expandable valves and self-expanding valves. Balloon expandable TAVs are generally made with a steel stent with a skirt and leaflets sewn onto attachment lines along the stent. The valves are cramped over a balloon and inserted into a catheter. A well-known balloon expandable valve is the Edwards Sapien XT (Edwards Lifesciences Corporation, Irvine, CA) [22] as shown in figure 15.
Figure 15: Edwards SAPIEN XT (Image from www.cxvascular.com)

Figure 16: Medtronic CoreValve [23]
Self-expanding stents are made from shape memory alloys such as nitinol and do not require a balloon to expand them into place. They are still mounted in a catheter but expand into the aorta when released. An example of a self-expandable TAV with a nitinol stent is the Medtronic Core Valve (Medtronic, Inc., Minneapolis, MN).

The self-expandable valve in Figure 17 can be seen to have a wide flaring stent design past the aortic leaflets. This section is designed to flare out as an anchor for the stent to prevent it from migrating. The steel stents are expanded into place and have little chance of slipping from their positions once mounted. Nitinol stents are highly flexible and the likelihood of stent migration is much higher. To combat companies have come up with unique stent designs to attempt to create the most efficient anchor. Some of which can be seen in the figures below.

![Figure 17: The Jenavalve, a porcine root sewn into a Nitinol stent [24]](image)
The JenaValve (JenaValve Technology GmbH, Munich, Germany) [24] has a stent design that incorporates three “feelers” that are used to align the valve in an anatomically correct position. The feelers are placed into the native sinuses of the patient prior to the rest of the valve being removed from the catheter. Once the feelers are in place the valve is released and it acts to secure the leaflets between the feelers and the rest of the stent. The resulting placement should allow the commissures of the TAV to align perfectly with the commissures of the native leaflets.

1.4.3 TAVI Procedure

Transcatheter aortic valve implantation is a relatively new medical procedure that has gained popularity in the past decade. It is a minimally-invasive method of implanting a heart valve when compared to the standard procedure involving open heart surgery. The procedure involves guiding a TAV through the body via a catheter then expanding this valve inside the native aortic valve, pushing the diseased leaflets to the side. TAVI is still a relatively new procedure and currently is only performed on patients that are too sick to or unhealthy to undergo the full open heart procedure. Since TAVI is generally performed on elderly populations with multiple comorbidities who are not projected to survive for more than a couple years, the devices are implanted to help improve quality of life for their remaining time rather than to present a long term solution to valve disease. Being a newer technology there is not much data on how long these valves will actually last in the human body. While older technologies such as the surgical tri-leaflet bioprosthetic valves are projected to last approximately twenty years the early TAVs are believed to have lifespans of approximately five
years. This is hard to gauge because most recipients of TAVs will die of heart related or other causes long before they would reach a time frame where these valves would normally fail. Surgical valves have been traditionally used in younger patients as well which allows them to be monitored for fatigue damage over time as the younger patients are less likely to die from age related comorbidities.

![Figure 18](image_url)  

**Figure 18:** A step by step representation of transcatheter aortic valve implantation. (Image courtesy of http://my.clevelandclinic.org)

TAVI involves taking a TAV and crimping so that it is able to fit inside a catheter. There are also two common ways that TAVI is generally performed: Trans-femoral or trans-apical. The type of valve used and the approach usually depends on doctoral preference.

For the trans-femoral procedure a small incision is made in the upper thigh straight into the femoral artery. A guide wire is then laced through the femoral artery, through the aortic arch until it reaches the aortic valve. At this point a balloon angioplasty is performed on the
calcified valve. This step is more important for the self-expanding stents as the balloon expandable ones will essentially perform an angioplasty during deployment. Balloon angioplasty is a procedure in which a balloon is placed in between the leaflets of the valve then rapidly expanded and deflated. This acts to open the valve if it has been sealed shut by something such as heavy calcification. Freeing the leaflets in this manner allows the self-expandable stents to deploy in a more natural manner rather than be restricted by an anomaly such as having two leaflets temporarily fused together. After the angioplasty is performed the catheter containing the valve is moved into position. Throughout these procedures the valve and catheter can be tracked with radio-opaque markers using xray fluoroscopy. When the valve is in position it is released from the catheter and pushes the native aortic leaflets to the side as it is deployed. There are many different types of TAVs and while following the basic procedure detailed above each may have a slightly unique mounting procedure.

The trans-apical approach to TAVI involves making a small incision in the apex of the left ventricle. The catheter is then pushed through the ventricle and through the aortic valve from the opposite direction compared to the femoral approach. This procedure is slightly more invasive as it requires a hole to be cut in the left ventricle. It is generally used when the ascending aortic is too heavily calcified and the catheter is not able to be pushed through. Although being slightly more invasive compared to the femoral approach it is still minimally invasive compared to open heart surgery and aortic valve replacement.
**Figure 19:** Fluoroscopy image of an aortic root during a TAVI procedure. The darkened area shows the aortic root while dye is being injected into the area. Image courtesy of (http://www.mentice.com/our-procedures)
2.0 Project Rational

2.1 Overview

Coronary flow is difficult to accurately replicate in an ex vivo environment. The coronary system supplies blood to the myocardium through a constantly branching network of arteries, arterioles, capillaries, venules and veins. During systole the myocardium of the ventricles contract to propel blood out of the heart. During left ventricle contraction the myocardium muscle fibers act to constrict the coronary arteries [25]. Velocity of blood while exiting the aorta will generally peak at the start of systole then decrease steadily until the start of diastole where the aortic valve will close and flow velocity will be zero or negative (depending on the state of the Aortic valve). Comparatively, the velocity waveforms of the coronary arteries peak at the start of Diastole as the myocardium relaxes and the ventricle re-fills with blood [26, 27]. During systole the contraction causes the coronary velocity waveform to be at its lowest point in the cycle and it will generally not fluctuate higher or lower.

When attempting to accurately measure coronary flow in an ex vivo environment an external system must be developed to replicate the resistance provided by the myocardium. A left heart simulator (LHS) was developed with the capability to mount a native aortic root with cannulated coronary arteries. To accomplish this task a stepper motor was used to change the coronary resistance in rhythm with the pneumatic pump. Using this system substantial testing can be done on heart valves to see how they perform in an ex vivo environment that accurately mimics the in vivo hemodynamic conditions of both the aortic root and coronary arteries.
The topic of TAV deployment was also studied. The bulk of the research was focused on examining how the flow patterns through the valve were affected at different deployment scenarios. Due to the flexible nature of self-expanding TAVs it is highly likely that they will not deploy in a perfectly circular orientation. Calcified leaflets can be very rigid and hard to displace which can cause the TAVs to be under expanded or deployed in an elliptical shape. The effects of ideal and non-ideal deployment were studied in both the ex vivo model and through fluid simulations.

2.2 Specific Research Goals

Goal 1: The first goal of this project is to develop and validate a LHS that is capable of replicating a wide range of hemodynamic conditions found in the human heart. The LHS must be able to test bioprosthetic heart valves and produce similar experimental results as other studies. The LHS needs to have the capability to mount a native aortic root in the position that the aortic valve would normally be mounted. The aortic root needs to be able to be run at standard flow conditions without leakage. For both prosthetic valve and aortic root testing; flow rate, LVP, and AP measurements must be able to be recorded.

Goal 2: The second goal of this project is to develop a coronary resistance system that is capable of accurately characterizing in vivo coronary velocity waveforms. This system must be compatible with the LHS and must be useable with native aortic roots. The system should be able to replicate both healthy and diseased coronary flow conditions.
Goal 3: The third goal is to mount a transcatheter aortic valve (TAV) into a native aortic root that has been mounted in the LHS. The coronary artery flow of this native root will be recorded during varied deployment orientations of the TAV.

Goal 4: The fourth goal is to develop computational models of abnormal TAV deployment. TAV deployment will be analyzed by looking at how the shape of the annulus impacts flow. The parameters are the ellipticity and constriction of the TAV during deployment. The simulations will be validated through experimentation on a steady flow loop by comparing the centerline pressure drop of the flow profile.
3.0 MATERIALS AND METHODS

3.1 Left Heart Simulator

All of the experimental testing detailed in this paper was completed on a Left Heart Simulator (LHS) that was fabricated in the UConn tissue mechanics laboratory. A LHS is a mechanical system designed to replicate the hemodynamic pressure and flow conditions found in the body to allow the study of artificial heart valves. The main components consist of an atrial reservoir, the mitral valve, the left ventricular chamber, the aortic valve, aortic compliance chambers, and a peripheral resistance device. This LHS was designed to have certain functionality that was not available to us in our older LHS model from ViVitro (ViVitro Systems, Victoria, B.C.). The main difference between this LHS and others is implementing an easy way to mount and test native aortic roots. Other added functionality is the ability to view both the aortic and mitral valves from both the front and back while running the system.

The atrial reservoir is a large open topped chamber that receives flow after it passes through the peripheral resistance. It fluctuates in volume as the simulator transitions between systole and diastole – rising during systole and falling during diastole. It also serves as the access point to the system where it is filled with testing fluid, generally saline.

The second component of the system is the Mitral Valve and its housing chamber. For all of the testing detailed a mechanical heart valve was used in this location. It was mounted in a 0.25inch thick rubber gasket that was fit into an aluminum holding piece. The gasket was secured with two setscrews. Due to supply limitations and the overall effectiveness of the
mechanical valve in this position, no other valve is used in the mitral position during any of the
testing described throughout this paper.

Flow then travels into the left ventricle chamber. This chamber is a two part acrylic
chamber that houses a silicone bladder. The bladder splits the chamber so that one side is
exposed to an air filled chamber that connects to a pneumatic pump. The bottom portion of
the chamber has a port that connects to the pneumatic pump via a rubber tube. The
pneumatic pump pressurizes the bladder during systole, causing it to push fluid out of the
ventricle. During diastole a vacuum like effect is applied to the bladder and it expands and fills
with fluid. The beats per minute and the corresponding systolic duration per beat can be
controlled on the pump interface. The left ventricular chamber also features two viewing ports
to look at the aortic valve and mitral valve respectively. The LHS is horizontally oriented which
allows easier viewing of the valves and the capability to view both the mitral and aortic valves
from both sides of the valves. Attached to the top of the left ventricular chamber is another
two-part chamber that houses a silicone bladder. This chamber acts as compliance in the
ventricle which helps to smooth out pressure curves. The two-part chamber is cylindrical in
shape; the top portion can be opened to the outside via a stopcock valve, and the bottom
portion can be temporarily opened to the outside to allow air to drain from the system.
**Figure 20:** a) Overview of the LHS system showing the experimental set up during coronary flow testing; b) Shows a top down view of the ventricular chamber with the compliance removed to show the geometry. Viewports were machined into the acrylic block to allow viewing of the aortic and mitral valves from the ventricular chamber; c) image of a native ovine aortic root mounted in the LHS; and d) image of the bladder compliance used in the ascending aorta portion of the LHS.
Fluid exits the left ventricle through the aortic valve. The aortic valve is mounted in a cylindrical silicone holder that is custom made to fit the specific type of valve mounted in it. The outer design of the holder is based off the ViVitro holder and seems to be a standard fit between their different devices. The inner potions of the holders along with the material type are the parts that are unique to each valve holder.

**Figure 21:** Two types of valve holders used during testing. The holder on the left is for CEP and has an indent along the inside wall that the sewing ring of the valve protrudes into. The holder on the left is made from much more compliant silicone compared to the CEP holder and is used to secure TAVs. It has a cylindrical inside.

One of the materials used was a silicone rubber base (Silicones, Inc. High Point, NC) and is used as a standard in ViVitro devices. This silicone cures with a blue color and tends to be relatively ridged. This is optimal for mounting of bioprosthetic valves that have a sewing ring.
The sewing ring slips into a circular notch that spans the circumference of the holder. The second type of holder is made from Dragon Skin silicone rubber (Smooth-on Inc., Easton, PA). Silicone is used throughout this project for many things such as gaskets, compliance bladders, and valve holders. It was found to be highly compliant and with a cure time of approximately 90 minutes it proved to be a quick and effective solution to many of the issues encountered during the development of the LHS. The second valve holder is used to hold TAVs and the inner portion is cylindrical with a 23mm diameter.

After flow passes through the aortic valve it enters the ascending aorta and the compliance chambers. This breaks down into several sections in sequence. The first of which is a rectangular chamber that serves three functions in addition to enclosing the valve mounting area. A brass port extends from the top that enables air to be released from this chamber while also acting as a grounding point for the electromagnetic flow meter. There is also a high pressure braided tubing line (3mm outer diameter) that extends outward at approximately the same height as the center of the valve while being approximately three valve diameters downstream of the annulus. This line connects to a stopcock valve that enables connection with a pressure sensor.

After flow passes through this chamber it enters a chamber referred to as “turn after aortic”. This chamber changes the direction of the overall fluid flow by ninety degrees. Flow enters the component and is faced with a four way intersection. It has another bladder compliance chamber attached along the top of the component that works in the same way as the ventricular compliance bladder. This acts to soften the pressure waveforms in the
components analogous to the ascending aorta. This compliance chamber is able to be moved and mounted along axis of the flow direction. When mounted along this axis it functions more effectively as it is in the direct path of the fluid flow exiting the aortic valve. Mounting the compliance in this location limits the viewing capabilities of the system and is generally not the mounting orientation used.

Following the path of the fluid flow from the “turn after aortic” component the next piece of the system is a tubular compliance chamber meant to imitate the aortic root. This “balloon compliance” chamber is an air tight cylindrical chamber with a port connected to a stopcock. A rubber balloon spans the inner length of the chamber and fluid passes through this balloon. As the aortic pressure increased this balloon channel with expand and soften the pressure waveforms. It acts in a similar yet more exaggerated manner to the actual ascending aorta. The stopcock connected to the cylindrical chamber is attached to a hand pump that is able to regulate how much the balloon expands. This allows the balloon compliance to have degree adjustability to help create more accurate pressure waveforms.

The last component of the LHS is the peripheral resistance valve. A rubber tube connects from the outflow of the “balloon compliance” chamber to the input port of the resistance valve. The outflow of the resistance valve connects to the atrium via another rubber tube. Along the length of this tube the flow passes through a floating ball flow meter. The peripheral resistance device is meant to replicate the effects of the blood dispersing though the arteries and veins and acts in the LHS to maintain a high pressure in the ascending aortic area and a low pressure in the atrium.
3.2 Coronary Resistance Device

Due to the inhibitory biomechanical interaction of the myocardial muscles on the perfusion of blood from the coronary arteries to the heart, this phenomenon requires a unique approach when developing an experimental model. There has been much research on experimental coronary flow but few studies try to accurately replicate the in vitro coronary velocity waveforms. Some studies such as the one performed by Geven et al. measure coronary flow but do not attempt to recreate a dynamic coronary resistance [28]. Others such as Gaillard et al use a pressure driven coronary resistance [29]. This has actually proven to be a moderately effective way of replicating the flow waveforms but it lacks a degree of control in that the waveforms appear to be inaccurately time shifted compared to in vitro data.

3.2.1 Stepper Motor

To achieve the kind of control needed to vary the resistance appropriately, a LabView (National Instruments Corporation, Austin, TX) controlled stepper motor was used. The stepper motor manually rotates a stopcock valve attached to an extension of the ex vivo coronary artery.

A cylindrical aluminum extension was machined to fit to the end of the stepper motor. It had a set screw hole made in the side and was slightly drilled out to fit the tip of the stepper motor. The end of the extension had an insert machined into it that was the approximate size of the knob of the stopcock valve. The insert is shaped like the stopcock knob to prevent slippage when rotating. When the body of the stopcock valve is secured in a fixed position the stepper motor is able to quickly and precisely rotate the knob to any angle desired.
3.2.2 LabView Program

The main component of the coronary resistance device, the stepper motor, is controlled by a LabView program. The program is structured to have two main case structures within a while loop that alternates between true (systole) and false (diastole). The systolic and diastolic cases are both structured very similarly and relate to the speed and angular distance rotated by the stepper motor during the two cardiac phases. The start of the program initializes the stepper motor and resets it to a specific position that can be changed. This position relates to the angle of the stopcock valve (SV1) with respect to it being fully open, where open corresponds to $\theta_0 = 0^\circ$. This is an important parameter as it can be used to change the baseline
opening position of the valve. The program then alternates between systolic and diastolic phases by rotating the stopcock valve between its “open” and “closed” states. The open phase corresponds to the angular position of SV1 during systole and the closed phase relates to the angular position of SV1 during diastole.

![Diagram of stopcock orientation](image)

**Figure 23:** A diagram detailing stopcock (SV₂) orientation with respect to the adjustable parameters: dθ and θ₀

To start the motor there is a trigger built into the program that activates the secondary part of the program after a certain time delay. The first part of the program sets the stopcock to a certain predetermined angle and the second part of the program is a continuous while loop that alternates between “open” and “closed” at each iteration. The trigger is used to sync the stepper motor so its resistance follows and appropriate pattern to alter the flow waveform. Since the motor and pump must be started independently of one another this trigger is crucial in regards to syncing the two devices. A third pressure tap is attached to the system in a place where the pressure waveforms are constant every beat (in this case the left ventricle).
pressure, say 70 mmHg, is chosen at the threshold value and an initial time delay is chosen. The pump is turned on and the lab view program is set to run at the start of one of the heart cycles. When the threshold pressure is reached the time delay is initiated and the secondary component of the program begins. If the stepper motor is found to be not in sync with the pump the time delay value can be changed until the systolic resistance phase matches exactly with the forward flow systolic phase. The two key components of this trigger system, the threshold value and the time delay, are fully adjustable to enable the system to adapt to any flow condition.

Beats per minute is a controllable variable on the pneumatic pump, however the coronary resistance device runs independently from the pump system. As an example we will examine the case where the BPMs are set to 70 with a systolic duration of 350ms. This heart rate gives a cycle that lasts approximately 0.857 seconds with systole lasting 0.350 seconds and diastole lasting 0.507 seconds. The labView program has two time delays built into its “open” (T1) and “closed” (T2) phases that correspond to the durations of systole and diastole respectively. In the given case T1 and T2 are equal to 0.350s and 0.507s respectively. When the BMPs of the system are changed the T1 and T2 values must be changed accordingly for the coronary resistance motor to match the pattern of the pneumatic pump.

3.3 Data Collection

A square wave electromagnetic flow meter was used to measure aortic and coronary flow velocities. Two different sized probes were used to take the aortic flow (88 mm circumference, Carolina Medical Electronics, East Bend, NC) and coronary flow (10 mm circumference, Carolina
Medical Electronics, East Bend, NC) respectively. Before every use the flow meter had to undergo the same process. The probe switch would be set to “null” and the null value would be changed until the lowest value was attained. The probe switch was then set to “+” and the flow meter was zeroed using the “zero” knob. The probe factor was set to 460 and the balance was set to 500.

Immediately before the aortic valve mount rests the probe for the electromagnetic flow meter. The LHS system was primarily build out of acrylic blocks that are compression fit using stainless steel threaded rods. The flow probe is sensitive to pressure so housing was made out of rubber gaskets. When the LHS is compressed to prevent fluid leakage the rubber gaskets are subjected to the pressure rather than the flow probes.

Pressure values were recorded using several pressure transducers (World Precision Instruments, Sarasota, FL). Two sensors were used simultaneously during the majority of the testing so that aortic and ventricular pressure could be recorded at the same time. The voltage signals from the pressure sensors are recorded and analyzed in LabScribe2 data collection software (iWorx Systems, Inc., Dover, NH).

3.4 LHS Validation

The LHS was validated by testing a bioprosthetic valve with previously published data and comparing this date with our collected experimental data. The valve used was a 25mm CEP bioprosthetic valve. The valve was mounted in the aortic position using an industry standard silicone ring valve holder (ViVitro Systems, Victoria, B.C.) made from silicone [30]. The valve holder secured the sewing ring of the CEP and prevented leakage from occurring around the
sides of the valve [30]. The CEP was tested at 70 BPM, 5 L/Min, and approximately 100 mmHg
average aortic pressure. The fluid used in the test system was 9% saline solution which was at
room temperature. Henceforth in this paper these flow testing conditions (70 BPM, 5 L/min,
100 mmHg, 9% saline) will be referred to as the standard testing conditions or STC.

Figure 24: Image of the CEP used during testing mounted in its corresponding valve holder

3.5 TAV Testing and Validation

A TAV was provided by Dura Biotech (Storrs, CT) for use in these experiments. The Dura
Biotech TAV is a 23mm tri-leaflet bovine pericardium bioprosthetic valve. It consists of a woven
nitinol wire stent, a sewing skirt, and gludaraldehydye treated pericardial leaflets. Based on
previous studies the wire thickness used for the stent was 0.017”[31]. A picture of this valve is
shown below in figure 25. The TAV used is a prototype. The TAV was tested at STC. The valve
mounting is different compared to the CEP mounting because the TAV has no sewing ring. A
separate valve holder was used that has a 23mm inner geometry of a cylinder. The nitinol stent design allows the valve to expand into the cylindrical holder and rest in place.

![Image of aortic root preparation](image)

**Figure 25:** Dura Biotech TAV prototype

### 3.6 Aortic Root Preparation

Mounting an aortic root into the LHS proved to be a difficult task that involved some trial and error before a method could be relied on. The inherent difficulty in mounting the aorta into a flow loop stems from the anatomy of the aortic root. Fluid must be able to pass through the aortic valve without the device hindering normal valve movement or flow in any significant way. When the fluid passes through the valve it must then travel though the ascending aorta. Since this part of the geometry is relatively cylindrical the attachment method is fairly simple. A hose barb and hose clamp apparatus can be used to secure this section.
The only issue that has arisen for this attachment point is when the ascending aorta is cut too short and the hose barb extends downwards and hinders leaflet movement. The real difficulty comes from attaching the other end of the aortic root. The most logical place to attach the aortic root to a flow loop is along the aortic annulus. However the aortic annulus does not have uniform geometry along its circumference and there is no cylindrical section that is analogous to the ascending aorta that could be attached by a hose clamp. Approximately two thirds of the annulus connects to the thick myocardium of the left ventricular wall and the other third connects to the Mitral valve leaflet. The myocardial sections tend to be significantly thicker than the mitral valve section. The connection point needed to be air tight and able to handle the normal pressures found in the body without breaking or leaking. The optimal way to attach the annulus to the LHS utilized a method that connected the annulus tissue to a rubber gasket that was then compression fit onto the LHS to create a tight seal.

![Figure 26: ovine heart pre-dissection](image-url)
The first step of this method was to dissect the aortic root from the heart. The hearts used were ovine and were stored in a -80°C freezer to preserve the tissue. Ovine hearts are anatomically similar to human hearts and were deemed acceptable for this study [32]. Upon removal from the freezer the heart was placed in a water bath that was set to 37°C to allow it to warm to body temperature. Three main tools were used during the dissection process: Forceps, scissors, and a scalpel. All dissections were performed on rubber dissection boards. To begin the extraction of the aortic root the heart was cut in half in a plane parallel to the aortic annulus.

Sections of the myocardium are then slowly excised until there is approximately half an inch of tissue extending down from the annulus. The Mitral valve is initially left intact but is then cut to extend the same distance as the myocardial section. The myocardial muscle is then trimmed in a manner that thins the section of tissue so that the thickness disparity between the leaflet and myocardium is not so drastic.

A circular piece of rubber gasket is cut out with a center hole that is approximately the size of the annulus. The annulus of the root is lined up over this center hole and then sutured to it. The sutures act to pull the tissue towards the gasket and secure it in place. After the sutures have been added a layer of cyanoacrylate based adhesive glue is used to seal the gaps between the tissue and the gasket. The cyanoacrylate based adhesive is generally used for tasks such as sealing wounds in a veterinary setting and attaching coral to the bottoms of salt water aquariums. It is optimal for connecting tissue to surfaces as the tissue is generally wet.
A significant amount of work must also be done to free the coronary arteries to allow them to be extended and cannulated. The coronaries extend from the aortic sinuses and wrap around the ventricular chambers embedded in the myocardium. Depending on the coronary attachment method there needs to be a certain amount of artery extending from the sinus. One method of attachment involves leaving an approximately one cm long extension which can then be attached to a small hose barb/leur lock attachment.

![Dissected ovine aortic root](image)

**Figure 27:** Dissected ovine aortic root that has been mounted to a gasket and fitted with attachments to the coronary arteries. This valve is ready to be mounted into the LHS

This method did not always prove to be the most efficient due to the fact that the hose barb was prone to being ejected from the coronary artery during periods of high pressure. The more efficient method involved trimming the coronary arteries so that there was approximately 1-2 mm extending from the aortic sinus. A 3mm inner diameter rubber tube was then glued to
the coronary artery extension. This rubber tubing then allows connection to a flow meter probe and the coronary resistance device. The tissues along with the rubber gasket it is attached to is then placed in 0.625% Glutaraldehyde solution overnight. This is a process that causes deformation of the alpha-helix structures in proteins which creates a sample that is more rigid but will not degenerate as quickly as untreated tissue [33].

3.7 Testing Aortic Root

Upon completion of the curing process the native aortic root was then tested in the LHS. To connect the aortic root to the system two separate sections must be compressed. Normally when mounting a bioprosthetic valve, the length of the device between the left ventricle and the “turn after aortic” compliance section are compressed together. This acts to mitigate leaks in the valve mounting section. As the aortic root has two attachment points, compression must be achieved in two sections. The two areas involve compression of the device between the annulus attachment and the left ventricle component of the LHS and compression between the aortic outflow and the compliance.

To test the hemodynamics of the native aortic root the LHS was run at STC. To prevent leakage, stopcocks were attached to the ends of the coronary artery extensions and were put into the “off” position. The coronary artery extensions were split approximately 6 inches away from the original stopcock and another stopcock was put between the two sections of tubing. This stopcock (SV2) is controlled by the coronary resistance device and is the main contributor towards replicating the coronary velocity waveforms.

3.8 Coronary Artery measurement
Coronary artery flow was measured for the aortic root at STC. In this testing the left coronary artery was investigated. This was achieved by extending the section of coronary artery that was being looked at with 3mm inner diameter rubber tubing. At the outflow of the coronary artery a stopcock was attached to be able to switch the flow from “on” and “off” in between tests. To run the coronary resistance device the following steps were taken. First the pneumatic pump is turned on and baseline flow parameters are recorded. This is important as the lab only owns one flow meter so in order to compare aortic and coronary flow rates the data must be compared post experimentation. The LVP and AP curves are consistently recorded while both the aortic and coronary flows are being recorded so matching up the LVP curves during each portion of the test will allow comparisons between the two corresponding flow curves. After the baseline testing is recorded the electromagnetic flow meter switches from the aortic probe to the coronary flow probe. Once it is verified that the coronary flow probe is collecting data and it is zeroed appropriately, the coronary resistance device is activated. The start button is pressed in LabView and the trigger mechanism in the code waits for the LVP to reach a certain threshold. Once this threshold is met the coronary device initiates a time delay (between 0 and 0.5 seconds) and begins alternating SV2 between the open and closed phases. The period of greatest resistance should occur at the onset of systole. If this was not immediately observed the time delay between the trigger and the start of the oscillations would be altered until an acceptable waveform could be observed.
Figure 28: Experimental set up of LHS during coronary artery flow measurements using a native ovine aortic root.

3.8.1 Coronary Adjustability
To demonstrate the adjustability of the coronary resistance device, the variables $d\theta$, $\theta_0$, and systolic/diastolic time delays were all changed three separate times to show the effects that they have on the coronary waveform while the aortic flow rate remains unchanged.

The first variable, $d\theta$, corresponds to the angular distance of stopcock (SV2) rotation between systole and diastole. Three cases were examined with the variable $d\theta = 9.0^\circ$, $10.8^\circ$, and $12.6^\circ$ respectively. The second variable, $\theta_0$, corresponds to the original angular orientation of the stopcock (SV2) at the start of diastole. Coronary artery flow was examined at three different $\theta_0$ orientations: $\theta_0 = 0^\circ$, $1.8^\circ$, and $3.6^\circ$. The $0^\circ$ orientation corresponds to the condition where the stopcock flow is fully open and unimpeded. As this opening angle increases the stopcock is rotated so that it allows less and less flow through it as the opening becomes smaller. This control is best used as a way to mimic different diameters of coronary arteries due to it representing the unrestricted flow conditions during diastole.

The third major adjustable parameters of the coronary resistance system are the time delays during systole and diastole. Altering these allows the LabView program to function in sync with the pneumatic pump and any physiological heart rate and systolic duration. Three different scenarios were examined with the BPM equaling 45, 70 and 100. $T_1$ was set to 0.45, 0.35, and 0.2 seconds respectively for the three scenarios and $T_2$ was equal to 0.88, 0.51 and 0.4 seconds respectively.

3.8.2 TAV Implantation
One of the uses for the coronary artery resistance device detailed in this work is to examine how a TAV could alter coronary flow when it is deployed. When a valve experiences stenosis there is generally a large buildup of calcium deposits on the leaflets of the native valve. This prevents the valve from functioning as normal and would be reason why a TAV could be implanted. When deployed, TAVs push the calcified native leaflets into the fully open position with the free edges of the leaflets being moved towards the aortic sinuses. When there is heavy calcification on these leaflets the calcified portions will move with the leaflet as the valve is opened. Calcification can sometimes be pushed too far into the coronary sinuses which in turn can cause a blockage of blood flow to the coronary arteries which could result in ischemia of the heart [34, 35].

Using the coronary resistance device at constant settings, TAVs can be implanted into native aortic valves are varying orientations and the resultant effect on coronary flow can be observed. In this test three scenarios were examined. A native ovine aortic root with an annulus diameter of approximately 19 mm was dissected as previously described and mounted into the flow loop. The root was tested at STC.

The LHS was then shut down and the root removed from the system. The Dura Biotech TAV was then implanted into the native root so that that approximately half of the stent lay on either side of the aortic annulus [36]. The TAV was arranged such that the commissures of TAV aligned with the commissures of the native aortic valve. This set up was then tested at STC. The TAV was then removed from the system and re-implanted such that the TAV commissures were rotated approximately 60 degrees from the native aortic commissures. This would place
the commissures of the TAV at a location directly between two commissures of the native valve. This third set up was then tested at STC.

3.9 TAV Deployment study

The goal of this study was to develop computational models of abnormal TAV deployment then validate these models through experimental methods. It has been found in clinical use that self-expanding TAVs have been associated with abnormal deployment at the annulus [37, 38]. The abnormal TAV deployments that were examined were circular deployment, changes in ellipticity, changes in constriction of the annulus, and elliptical configurations while experiencing annular constriction.

3.9.1 Simulation Work

To begin building a geometric model for simulation work first the material properties of the leaflets were determined. Planar biaxial testing was conducted on tissue samples which was then fit with the Fung Model to create a non-linear, anisotropic, hyperelastic material model [39, 40]. Using a generic geometric model of a tri-leaflet heart valve that was created in the UConn Tissue Mechanics Laboratory finite element analysis (FEA) was conducted to warp this base geometry into the various elliptical and constricted configurations that would be tested.

The TAV leaflet geometries were chosen based on two different variables: e and UE where “e” is the ellipticity at the annulus and is defined in equation (3). The elliptical drawing next to the formula represents the orientation of the annulus of the valve.
\[ e = \sqrt{1 - \left(\frac{L_{\text{minor}}}{L_{\text{major}}}\right)^2} \quad \text{Where} \]

\[ UE = 1 - \frac{\text{Actual Area}}{\text{Nominal Area}} \]

UE represents the percent under expansion of the annulus and is defined as follows:

The \( e \) variable was examined for values ranging from 0 to 0.68 and the UE variable was examined for values between 0% and 29%. These ranges were deemed to be the clinically relevant scenarios. The FEA was performed in Abaqus (Dassault Systemes, Velizy-Villacoublay, France) and the valve was constricted along one axis at several distances before being rotated and constricted once again. Figure 29 shows the FEA results of the leaflets being morphed into elliptical and constricted shapes.
Figure 29: Results of FEA simulations for TAV ellipticity and TAV Ellipticity + Rotation

Figure 30: FEA results for TAV annulus constriction
After the finite element analysis was completed these new geometries were imported into Hypermesh (Hyperworks, Altair Engineering, Inc., Troy, MI) to be sealed and prepared for CFD analysis. The FEA results consisted of three leaflets with no inherent mesh thickness and no other mechanical structures. To prepare the geometry for CFD analysis several additional structures needed to be added. The first thing done was to increase the leaflet thickness to 0.2 inches. Two circular gaskets were built into the system which served as the attachment point of the leaflet skirt. Two leaflet skirts, for the outer and inner leaflet portions were built to connect the upper and lower leaflets to the upper and lower gaskets respectively. The upper gasket was then connected to an outlet tube that was three valve diameters long (Approximately 69mm for a 23mm valve). The lower gasket was connected to an inlet tube that extends backwards one valve diameter. Outlet and Inlet faces were also created.

Figure 31: Sealed mesh geometry of FEA results after being imported into Hypermesh
The geometry was then exported from Hypermesh and imported into STAR-CCM+ (CD-adapco, Melville, NY) where a polyhedral volume mesh was created. The CFD simulation was run in STAR-CCM+ with the following physics initial conditions: 30 Liters/minute flow rate, 100 mmHg outlet pressure, unsteady, k-epsilon turbulence, density of 1056 kg/m³, viscosity of 0.0035 Pa-s.

![Sealed Hypermesh geometry with inlet and outlet tube sections. This is the geometry that was imported into STAR-CCM+](image)

**Figure 32:** Sealed Hypermesh geometry with inlet and outlet tube sections. This is the geometry that was imported into STAR-CCM+

### 3.9.2 Experimental Validation

In order to validate the simulation results, experimental flow testing was conducted. Each of the sealed geometries were 3D printed to scale excluding the outlet and inlet tubes. The plastic valves were mounted into a steady flow loop and tested at the following conditions: approximately 30 LPM flow rate and 100 mmHg fluid pressure at three diameters downstream of the valve. Using an aluminum extension, centerline flow pressure was recorded at 2mm
intervals from three diameters upstream to one diameter downstream. Pressure was recorded with a pressure transducer.

Figure 33: SLA Valve from Additive manufacturing
4.0 Results

4.1 LHS Validation

In order to validate the left heart simulator a bioprosthetic heart valve with known hemodynamics was tested and the experimental and published results were compared. The Valve used was a 25mm diameter CEP what was placed in the aortic position. Previously published results for the CEP show that it has an EOA of $2.12 \text{ cm}^2$, a systolic differential pressure of 4.8 mmHg, a closing volume of $1.71\pm0.25 \text{ ml}$, and a regurgitant volume of $4.56\pm1.41 \text{ ml}$ [41]. The experimental CEP results for the EOA, systolic transvalvular pressure, stroke volume, closing volume, and regurgitant volume were found to be $2.04 \text{ cm}^2$, 5.7 mmHg, 75.25 ml, 1.49 ml, and 1.94 ml respectively. The percent back leakage across the valve per cycle was found to be approximately 4.5%. These results can be seen in Table 1 below.

<table>
<thead>
<tr>
<th></th>
<th>CEP (25mm) Published</th>
<th>CEP (25mm) Experimental</th>
<th>TAV (23mm) Published</th>
<th>Dura TAV Experimental (23mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Vol (ml)</td>
<td>-</td>
<td>75.258</td>
<td>-</td>
<td>76.896</td>
</tr>
<tr>
<td>Closing Vol (ml)</td>
<td>1.71 ± 0.25</td>
<td>1.493</td>
<td>-</td>
<td>2.698</td>
</tr>
<tr>
<td>Regurg Vol (ml)</td>
<td>4.56 ± 1.41</td>
<td>1.944</td>
<td>-</td>
<td>1.351</td>
</tr>
<tr>
<td>Total Leakage %</td>
<td>-</td>
<td>4.567 %</td>
<td>-</td>
<td>5.26 %</td>
</tr>
<tr>
<td>RMS Fwd Flow (L/min)</td>
<td>-</td>
<td>13.958</td>
<td>-</td>
<td>14.174</td>
</tr>
<tr>
<td>ΔP Systolic Flow (mmHg)</td>
<td>≈ 4.8</td>
<td>4.92</td>
<td>10.0±4.0, 3.88±1.62</td>
<td>7.531</td>
</tr>
<tr>
<td>EOA (cm²)</td>
<td>2.12</td>
<td>2.04</td>
<td>1.61±0.4, 1.97±0.11</td>
<td>1.67</td>
</tr>
</tbody>
</table>
**Table 1:** CEP and TAV hemodynamic data [34, 41-44]

Throughout the course of one cycle the average left ventricular pressure was found to be approximately 49 mmHg while the peak systolic pressure was approximately 118 mmHg. Through one cycle the average aortic pressure was found to be approximately 95 mmHg while the peak aortic pressure was found to be approximately 117 mmHg. The left ventricular and aortic pressure waveforms for the CEP tested in the LHS are shown below in figure 34.

![Experimental LVP and AP for the CEP valve](image)

*Figure 34:* Experimental LVP and AP for the CEP valve
4.2 TAV Baseline Assessment

The TAV used in the study (provided by Dura Biotech) was tested at STC and compared with published results from similar sized valves tested at the same conditions. The results for the experimental testing and for the previously published data can also be seen in Table 1. The EOA for the Dura Biotech TAV was found to be approximately $1.67 \text{ cm}^2$ while the published results for the EOA of the Edwards SAPIEN TAV (Edwards Lifesciences Corporation, Irvine, CA) was found to be $1.61\pm0.4 \text{ cm}^2$ (for 23 and 26 mm valves) [44] and $1.97\pm0.11 \text{ cm}^2$ (23mm valves) [34] for two different studies respectively. The experimental results for the Dura Biotech TAV show an average differential pressure across the valve during forward flow of 7.531 mmHg, an average stroke volume of 76.896 ml, an average closing volume of 2.698 ml, and an average regurgitant volume of 1.351 ml giving a total back leakage percentage of 5.26%. Published results for the Edwards SAPIEN show [cite] show a differential pressure of approximately $10\pm4 \text{ mmHg}$ [44]. ISO-5840 guidelines require that size 23mm TAVs must be able to function with an EOA of at least $1 \text{ cm}^2$ and have a maximum back leakage of 10% per cycle [45].

4.3 Aortic Root Baseline Test

The native ovine aortic root (size 19mm) was tested at STC and was found to have an EOA of approximately $1.2 \text{ cm}^2$. The average systolic transvalvular pressure was found to be approximately 10 mmHg and the total leakage percentage was found to be 5.46% of each cycle. These numbers indicate that the root was functioning as normal and there was no excess of paravalvular leakage or leakage around the attachment points of the root to the LHS.
4.4 Experimental Coronary Artery Flow

4.4.1 Baseline Testing and Validation

Measurements of the coronary artery flow were performed on the same aortic root that is referenced in the aortic root baseline test. Total coronary flow volume was calculated to be approximately 3% of the total aortic flow volume. As the aim of the project is to create a

![Graph showing experimental and previously published in vivo coronary velocity data.](image)

**Figure 35:** A comparison of experimental and previously published in vivo coronary velocity data.

Experimental aortic flow velocity has been included for comparison.
coronary waveform that more accurately mimics in Vivo waveform, a comparison of the experimental waveform for the left coronary artery velocity is compared to previously published in vivo velocity data in figure 35.

4.4.2 Coronary Flow Adjustability

As previously described, the coronary resistance device has three main adjustable parameters $\theta_0$, $d\theta$, and the time delays between systolic and diastolic phases ($T_1$ and $T_2$). Figure 36 shows user varied flow conditions with a change in the $d\theta$ variable at $d\theta = 9.0^\circ$, $10.8^\circ$, and $12.6^\circ$. Altering the $d\theta$ variable will change the maximum diastolic flow rate while keeping the systolic flow rate constant. As $d\theta$ changes it alters the opening angle of the stopcock. An increase in the $d\theta$ value will increase the diastolic flow rate. As an example to how this variability is relevant and useful a case involving a 69 year old patient with 62% diameter stenosis in the mid right coronary artery is examined [46]. In this case the approximate systolic velocity is 0.1 m/s and the approximate diastolic flow velocity is 0.6 m/s peak velocity. In Figure 36, the third test case, where $d\theta = 12.6$ degrees, the coronary velocity waveform very closely mimics these parameters.

Three cases involving a change in the $\theta_0$ variable can be seen in Figure 37. A change in the $\theta_0$ variable will keep the general shape of the graph the same while shifting the entire waveform in a manner that would increase or decrease the total flow. Three $\theta_0$ configurations were chosen: $\theta_0 = 0^\circ$, $1.8^\circ$, and $3.6^\circ$. As $\theta_0$ increases, the total amount of flow allowed into the system is restricted. This means that an increase in $\theta_0$ decreases both the average systolic and diastolic flow rates and an decrease in $\theta_0$ increases the average systolic and diastolic flows.
Figure 36: Experimental coronary flow velocities at three separate values of $d\theta$

Figure 37: Experimental coronary flow velocities at three separate values of $\theta_0$
The third adjustable parameter that was explored is the alteration of the time delay variables T1 and T2. Altering these variables in the LabView program allowed the motor to be synced up with varying heart rates. Three different heart rates were examined: 45 BPM, 70 BPM, and 100 BPM. As can be seen in Figure 38 the coronary waveforms continue to hold their shape and trends while the heart rate is changing.

![Figure 38: Experimental coronary flow velocities at variable heart rates](image)

4.4.3 Ex Vivo TAV Deployment

Figure 39 shows the coronary velocity waveforms for the three scenarios tested involving TAV deployment in an ovine native aortic root. The changes in the waveforms from case to case are similar in shape and magnitude with the average flow between the three of them being approximately 190±13.5 ml/min. It was determined that 60° TAV commissure...
rotation has little to no effect on the coronary flow rate. This testing was done on a completely healthy aortic root, the animal was less than 2 years old when it was slaughtered and had no noticeable calcium build up on the aortic leaflets.

![Figure 39: Experimental coronary flow velocities during TAV implantation](image)

**Figure 39:** Experimental coronary flow velocities during TAV implantation
4.4 TAV Deployment Study

4.4.1 CFD Simulation results – TAV deployment configuration hemodynamics

Results for the CFD simulations at circular, elliptical, constricted annulus, and constricted annulus + elliptical orientation are shown in figure 40. It can be seen that the circular orientation has the most uniform and smooth flow pattern out of all of the orientations. The irregular orientations all show an increase in velocity magnitude and turbulent kinetic energy of the flow exiting the valve. It can be seen that the constricted annulus + elliptical orientation has the most drastic change in flow profile from the circular geometry.

![Figure 40: CFD results showing circular, elliptical, constricted annulus, and constricted annulus + elliptical configurations](image)
EOA was seen to change for each of the orientations which are detailed in figure 41. The EOA at the circular orientation was taken as the base EOA for the analysis. Two trends can be taken from this set of data. 1) With an increase in ellipticity there was a decrease in EOA and 2) with an increase in annular constriction there was also a decrease in EOA. The change in EOA was much more drastic during changes in the annular constriction compared to changes in the ellipticity. At constant angular constriction the EOA decreased as the ellipticity increased for all cases except for the 15% annular constriction + ellipticity case. The highest reduction in EOA occurred at the highest annular constriction but at an ellipticity of e=0.30.

Figure 41: Degree of Ellipticity/Eccentricity vs. reduction of EOA from nominal circular (%)
At increasing ellipticity and percent annular constriction the turbulent kinetic energy (TKE) was seen to exhibit similar trends to the reduction of EOA. As ellipticity increased (except for the final case where UE = 29%) TKE was seen to increase drastically compared to the base circular geometry. Percent increase in TKE was also seen to rise as the annular constriction increased. As with the reduction in EOA, the scenario with the highest percent increase in TKE occurred at the greatest annular constriction (in this case 29% under expansion) and at an ellipticity of 0.30.

\[\text{Figure 42: Degree of Ellipticity vs. Increase in mean turbulent kinetic energy from nominal circular (\%)}\]

### 4.4.2 Experimental Validation

Experimental validation tests were performed using a centerline pressure drop test for 3D printed valves with the same geometry of the valves in the CFD simulations. It can be seen that the simulated and experimental centerline pressures values follow similar trends. The
peak transvalvular pressures for circular and geometries where e=0.3, 0.5, and 0.68 respectively are shown in the following graph, figure 43. At the circular orientation the flow is the least turbulent and the experimental and simulated peak pressures are very close. The difference in simulated and experimental peak pressure grows as the ellipticity value “e” gets larger. At the value e=0.68 the largest differential in peak transvalvular pressure can be seen with the simulated pressures rising to higher values than the experimental pressures.

![Figure 43: Simulated and experimental peak transvalvular pressure](image)

The following graph (figure 44) shows a comparison of simulated and experimental centerline pressures for the circular valve. It can be seen that the experimental data closely matches the trends of the simulation data. The largest area of error occurred from the annulus of the valve to the outflow region, between approximately 0mm and 20mm along the axial position. This area of error could be attributed to the data collection method. While the probe was placed
inside the valve area it may have affected the flow patterns and pressure recorded for that area. The experimental recordings, while close, may not have been along the exact centerline of the flow profile as the turbulent flow would push the probe around inside the system. Steady measurements along the centerline were attempted but there is always a margin of error that could be attributed to several factors that needs to be taken into account during experimental work.

Figure 44: Centerline pressure drop testing. Simulated vs. experimental results
5.0 Discussion

With the advent of modern imaging techniques and improved surgical resources, humans have been moving towards less and less invasive surgical procedures. TAVI is a relatively new field of medicine yet it has been steadily growing and evolving since the start of the millennium. As this is a relatively new field there is an immense amount of research that still needs to be conducted on the methods and technology as it grows and changes. One of the key issues with recent TAV development has been how these valves interact with the coronary Ostia after deployment. It is not uncommon for a heavily calcified native valve to occlude the coronary arteries post TAV deployment. As it is incredibly difficult and expensive to carry out experiments in vivo, systems such as the one in this paper must be developed to create experimental environments that simulate the in vivo ones.

Due to the nature of the human body no two hearts are exactly the same. While there is an ideal representation of the aortic root and coronary artery system, the reality is that all patients will have a unique anatomy. In order for an in vitro system such as the LHS to mimic these varying parameters it must have a range of adjustability along several components of the system. The adjustable nature of the LHS starts at the pneumatic pump that drives fluid flow in the system and works directly with the peripheral resistance to create an environment where most systolic and diastolic pressure ranges can be met. Some extreme conditions, such as cases where the pressure differential between peak systolic and diastolic pressure is extremely large, are unable to be modeled using this device due to restrictions with the peripheral resistance.
and compliance. This is generally not an issue as all of the ranges examined in this study were easily obtained.

The adjustable nature of the coronary artery flow could be key to creating an environment that more closely mimics in vivo conditions. When back pressure in the aortic arch causes the aortic valve to close the force that the blood exerts on the leaflets is going to vary depending on whether or not coronary flow is occurring. With an LHS system that has been set up to examine coronary flow the regurgitant leakage across the valve may vary compared to a system that does not measure coronary flow. Additionally the flow patterns in that area will differ which could cause different forces to act on the leaflets different directions.

Using the $\theta_0$, $d\theta$, and time delay variables the user should be able to accurately set the diastolic and systolic coronary flow velocities to match most clinical conditions. Previous attempts to experimentally model coronary flow have had the most success when using a pressure driven resistance system. The theory behind this is to have an extension of the coronary artery that passes through an airtight container which is attached to the pressure system that drives the ventricle. During each simulated heart beat the ventricular pressure will pressurize the sealed off chamber which in turn acts to constrict the tubing passing though it which restricts flow. It tries to mimic in vivo conditions with a method that closely mimics that of the human body. The upside to this approach is that no programming is needed but it lacks the precision that is capable with a fully adjustable system. The coronary resistance is also dependent on when each contraction occurs which can cause an inaccurately time shifted coronary resistance waveform.
5.1 Future Directions

Going forward this system could be developed into a way to do patient specific testing using simulations to back up ex vivo or in vitro experimental work. It can also be used as a way to better understand the nature of how and why coronary arteries can be occluded by calcification on the leaflets. First a method must be developed where artificial calcium deposits are added to a native ovine aortic valve. These “calcium” deposits must act and function in a similar manner to actual leaflet calcification. It should make the leaflet much more rigid and it should reduce the overall function of the valve in terms of aortic regurgitation. Different calcification patterns can be created that emphasize build up in different areas of the valve. TAVs can then be deployed into these calcified leaflets and coronary flow can be examined. It may be possible to show that certain patterns of leaflet calcification could be more prone to occlude coronary artery flow. This could be instrumental to cardiac surgeons who have to decide whether or not a patient is a suitable TAVI candidate.

A more comprehensive study can be developed and performed on the effects of TAV deployment orientation on coronary artery flow. In this study only TAV commissure rotation was examined but this could be expanded to cover many more orientations. The TAV can be deployed at varying heights with respect to the aortic annulus. It could be deployed to far into the left ventricle or too far extending into the ascending aorta. The TAV can then be rotated at these locations to examine commissure orientation.

Another direction that this research could take is towards building artificial aortic roots that are capable of being mounted into the LHS. Studies would need to be done to determine a
material that has similar compliant properties to native aortic tissue. This synthetic aortic root could then be mounted into the LHS and TAVs could be implanted. If patient specific data was used this could be used to validate simulation results of TAV expansion into the aortic root. One possible way to create these geometries would be through 3D printing of a mold.
6.0 Conclusion

The LHS created in the UConn TML is capable of testing all kinds of heart valves ranging from native aortic roots to bio-prosthetic and mechanical heart valves. The addition of the coronary resistance device allows the LHS to replicate in vivo coronary velocity waveforms in an ex vivo environment. This can be useful for modeling diseased conditions in an ex vivo environment for TAV deployment testing. Valve testing is generally done in a healthy environment and it is hard to predict how and if a valve will act differently in heavily diseased conditions. The ability to do this in a relatively inexpensive manner could prove invaluable to the future of valve testing and validation. The simulation work examining the differences in flow patterns for TAVs with varying ellipticity and constriction show how important different deployment scenarios can be on the hemodynamic conditions in the Aortic root. Diseased aortic roots, while experiencing similar problems, will rarely look the same of have exact calcification patterns. This annular non-uniformity will cause valves to deploy in non-uniform ways. While the ideal TAV will deploy in a perfect circle it is very rare that this will be the case in an actual clinical setting. TAVs are designed to have their best hemodynamics occur during circular deployment so it is important to study how the hemodynamics will change with varying valve deployment. Heart disease is the leading cause of death in human beings[10] and it is incredibly important to fully understand how current therapies such as TAVs work in ideal and non-ideal conditions. Research such as this will hopefully add to the overall knowledge of heart disease and heart disease therapies which in turn should help to create new, better, devices and therapeutic techniques.
7.0 References


