New Concepts in Transcatheter Mitral Valve Replacement

by

Dylan James Ellingham Goode

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis/dissertation entitled:

New Concepts in Transcatheter Mitral Valve Replacement

submitted by Dylan James Ellingham Goode in partial fulfillment of the requirements for the degree of Master of Applied Science in Mechanical Engineering

Examining Committee:

Dr. Hadi Mohammadi, Faculty of Applied Science
Supervisor

Dr. Ray Taheri, Faculty of Applied Science
Supervisory Committee Member

Dr. Zheng Liu, Faculty of Applied Science
Supervisory Committee Member

Dr. Ian Foulds, Faculty of Applied Science
University Examiner
Abstract

The most prevalent form of moderate to severe valve disease in developed countries is mitral regurgitation (MR), which affects ~10% of people older than 75 years of age. Roughly half of patients with severe symptomatic MR are not referred for surgery due to risks of age, comorbid factors and frailty. With these outcomes, a minimally invasive procedural option is required. The emergence of transcatheter aortic valve replacement (TAVR) has segued the development of transcatheter mitral valve (MV) repair devices. Transcatheter mitral valve repair has become a well-established alternative for patients with severe primary and secondary mitral regurgitation (MR) and with a perceived surgical risk. Transcatheter mitral valve replacement (TMVR) could become a more complete form of reduction of severe MR compared to MV repair devices, albeit with significant engineering challenges and all the risks associated with a bioprosthetic heart valve. The development of TMVR devices has become prominent while companies race to become the first commercially available system. Preclinical and clinical trials have shown promising results, showcasing the feasibility of total valve replacement utilizing transcatheter procedure techniques. This thesis is focused on evaluating the feasibility of novel TMVR devices. It is comprised of three major components: design and fabrication of MV leaflets; design of TMVR stents; as well as design and fabrication of a miniaturized heart simulator. Additionally, an extensive literature review of relevant clinical and preclinical designs to fully map out the TMVR landscape.

A novel bileaflet valve was designed for implantation into a TMVR stent. The kinematics of the leaflet motion were evaluated, resulting in a positive feasibility assessment of the design with room for further iterations. An additional bileaflet valve was designed to perform a computational model evaluating wrinkle-induced tearing of prosthetic MVs. A trileaflet valve was designed to evaluate the feasibility of the cryogel material for heart valves. Four stents were designed with intent for
fabrication in the future to evaluate their viability. The heart simulator was designed and fabricated to aid in the evaluation of the kinematics of fabricated heart valves, with plans to further improve the design in the future.
Lay Summary

The most common severe heart valve disease in developed countries is mitral regurgitation (MR), which affects ~10% of people older than 75 years of age. Half of these patients are not referred for surgery due to risks of their age. To solve this issue, catheter-based technology has led to the development of heart valves inserted via a catheter as they reduce surgical risk. Development of these devices has become prominent while companies race to become the first commercially available system. The testing of these devices has shown promising results showcasing the possibility of replacing a diseased heart valve with a catheter.

This thesis showcases the process of creating a catheter-based heart valve. Heart valve leaflets were created, along with a device to evaluate their performance. Additionally, a housing to implant the leaflets were designed for future work. A detailed review of devices being developed is included along with background information.
Preface

This thesis presents the research work conducted originally by the author. Different parts of the work in the current research were developed with collaboration with different research centers. This includes Dr. Mohammadi from the Faculty of Applied Science at the University of British Columbia (Okanagan); Dr. Fradet from the Faculty of Medicine at the University of British Columbia (Vancouver); Dr. Kibret Mequanint from the Department of Chemical and Biochemical Engineering at Western University (London, ON); as well as Ruby Dhaliwal from the Heart Valve Performance Laboratory at the University of British Columbia (Okanagan).

Chapter 1 of this thesis includes a portion of


I gathered relevant background information and wrote the introductory portion of the manuscript. All authors contributed to the editing and revisions of the manuscript.

Chapter 2 of this thesis is a version of


R. Dhaliwal aided in the gathering of relevant transcatheter mitral valve replacement device information. Dr. Mohammadi helped write a portion of the hemodynamics section. I gathered relevant background information, relevant transcatheter mitral valve replacement device
information and wrote the remaining portions of the manuscript. All authors contributed to the editing and revisions of the manuscript.

Chapter 3 of this thesis includes a portion of


I aided Dr. Mohammadi in the design of the trileaflet valve for fabrication. Dr. Mohammadi, Dr. Fradet and Dr. Mequanint all contributed in the writing of the manuscript. All the authors contributed to the editing and revisions of the manuscript.

Chapter 4 includes a transcatheter stent design from Angeleno Medical Ltd.

Chapter 6 of this thesis includes a portion of


I gathered relevant background information and wrote the conclusion portion of the manuscript. All authors contributed to the editing and revisions of the manuscript.
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<th>Full Form</th>
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<tbody>
<tr>
<td>CAVD</td>
<td>Calcific Aortic Valve Disease</td>
</tr>
<tr>
<td>HVD</td>
<td>Heart Valve Disease</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral Regurgitation</td>
</tr>
<tr>
<td>MV</td>
<td>Mitral Valve</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
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<td>TMVR</td>
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<td>TMVI</td>
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<td>TAVR</td>
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<td>AV</td>
<td>Aortic Valve</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>PVL</td>
<td>Paravalvular Leakage</td>
</tr>
<tr>
<td>LVOT</td>
<td>Left Ventricular Outflow Tract</td>
</tr>
<tr>
<td>EOA</td>
<td>Effective Orifice Area</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal Echocardiography</td>
</tr>
<tr>
<td>TVT</td>
<td>Transcatheter Valve Technologies</td>
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<tr>
<td>PET</td>
<td>Polyethylene Terephthalate</td>
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<td>CRT</td>
<td>Cardiovascular Research Technologies</td>
</tr>
<tr>
<td>TCT</td>
<td>Transcatheter Cardiovascular Technologies</td>
</tr>
<tr>
<td>FDM</td>
<td>Fused Deposition Modeling</td>
</tr>
<tr>
<td>ABS</td>
<td>Acrylonitrile Butadiene Styrene</td>
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<tr>
<td>HVPL</td>
<td>Heart Valve Performance Laboratory</td>
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<tr>
<td>PVA</td>
<td>Polyvinyl Alcohol</td>
</tr>
<tr>
<td>BC</td>
<td>Bacterial Cellulose</td>
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a person, and I can’t wait to live a life with you. I am so proud of you and your accomplishments.

You are my better half.
To my family, friends, & loving fiancé.
Chapter 1: Introduction

Although calcific aortic valve disease (CAVD) is the most significant form of heart valve disease (HVD) with regard to mortality, the most prevalent form of moderate to severe valve disease in developed countries is mitral regurgitation (MR), which affects ~10% of people older than 75 years of age [1]–[3]. Furthermore, it is estimated that 2% of the global population displays symptoms of mitral valve (MV) disease.

The mechanism of MR can be classified into two classes, those being primary (organic) or secondary (functional). Primary MR is the inherent damage to the MV apparatus, that being the MV leaflets, the chordae tendineae, papillary muscles and the MV annulus [4]. Secondary MR is accredited to a functional disparity between decreased closing forces and increased tethering forces [5]. Decreased closing forces can be a result of reduced LV contractility or synchrony, while increased tethering forces can be a result of annular and left ventricular dilation causing segmental or global left ventricular dysfunction with papillary muscle displacement/dysfunction [5]. The course of action to treat MR is dependent on the source, development history, pathophysiology, and anticipated treatment effectiveness. The gold standard for treating MR is surgical mitral repair or replacement, but roughly half of the patients with severe symptomatic MR are not referred for surgery due to risks from age, comorbid factors, and frailty [3], [6]. These patients who are not referred for surgery have a mortality rate of up to 50% at the 5 years follow-up mark, along with 90% of the surviving patients having at least one hospitalization within the 5 years after diagnosis [3], [6]. With these outcomes, due to a perceived risk of invasive procedures on these patients, a minimally invasive procedural option is required. Of the patients with severe MR, many are diagnosed with secondary MR and it has been seen that intervention to eliminate MR can reduce
the rate of hospitalization for heart failure when compared to exclusively using medical therapy [7].

Transcatheter mitral valve repair devices modified from various surgical procedures have surfaced to be a viable treatment for patients with MR and high risk of surgical intervention. Prominent mitral valve repair devices under evaluation along with their repair technique can be seen in table 1. Note, there are several other repair devices being developed in various stages. So far, the MitraClip™ is the only FDA approved device; approved for the indication to treat patients with primary MR and also patients who don’t suffer from primary MR but develop signs of heart failure and moderate-to-severe or severe MR due to functional (secondary) MR, regardless of being treated with the most favorable medical therapy [8]. The MitraClip™ device has shown good procedural success at >90%, along with good long-term outcomes [9]. Although, there is a disparity in results between the MITRA-FR [10] (Percutaneous Repair with the MitraClip™ Device for Severe Functional/Secondary Mitral Regurgitation) trial and the COAPT [11] (Cardiovascular Outcomes Assessment of the MitraClip™ Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial [12], which may be due to the differences of patient enrollment requirements. All the other listed mitral repair devices have shown good early clinical results [13]–[18].
<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Repair Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>MitraClip™</td>
<td>Abbot Laboratories, Illinois, USA</td>
<td>Edge-to-edge apposition</td>
</tr>
<tr>
<td>PASCAL Mitral Valve Repair System</td>
<td>Edwards Lifesciences, Irvine, USA</td>
<td>Edge-to-edge apposition</td>
</tr>
<tr>
<td>Carillon Mitral Contour System</td>
<td>Cardiac Dimensions, Washington, USA</td>
<td>Coronary sinus annuloplasty</td>
</tr>
<tr>
<td>Cardioband System</td>
<td>Edwards Lifesciences, Irvine, USA</td>
<td>Direct annuloplasty</td>
</tr>
<tr>
<td>Mitralign Transcatheter Annuloplasty System</td>
<td>Edwards Lifesciences, Irvine, USA</td>
<td>Direct annuloplasty</td>
</tr>
<tr>
<td>IRIS Transcatheter Annuloplasty Ring System</td>
<td>Boston Scientific, Massachusetts, USA</td>
<td>Direct annuloplasty</td>
</tr>
<tr>
<td>ARTO™ System</td>
<td>MVRx, San Mateo, USA</td>
<td>Direct annuloplasty</td>
</tr>
<tr>
<td>DS1000 System</td>
<td>NeoChord, Inc., Minnesota, USA</td>
<td>Synthetic support chords</td>
</tr>
<tr>
<td>Harpoon</td>
<td>Edwards Lifesciences, Irvine, USA</td>
<td>Synthetic support chords</td>
</tr>
<tr>
<td>ChordArt™</td>
<td>CoreMedic AG, Biel, Switzerland</td>
<td>Synthetic support chords</td>
</tr>
<tr>
<td>Mitral Butterfly</td>
<td>Angel Valve Vienna, Vienna, Austria</td>
<td>Artificial papillary muscle</td>
</tr>
</tbody>
</table>

Table 1.1 Transcatheter mitral valve repair devices

Transcatheter mitral valve replacement (TMVR) may propose benefits over MV repair devices.

Due to the complex structure of the MV, along with the diversity and intricacy of MV disease, creating a MV repair device that is tailored to all anatomical disparities can present several issues. This is where TMVR devices pose the opportunity to create a ‘one valve fits all’ ideal, with more predictable MR reduction, and less technically demanding procedures [19]. Though, TMVR procedures pose a greater risk of injury as complications can become more catastrophic and less forgiving. MV repair devices allow for a greater safety profile, as there is less change to the native valve anatomy and physiology. Further development of TMVR systems needs to be done to rival the MV repair devices in their efficacy and safety profile, but the TMVR landscape is showing great promise going forward.
1.1 Purpose & Overview of This Thesis

The purpose of this thesis is to introduce multiple novel TMVR designs for the treatment of MR. Furthermore, this thesis also showcases the use and feasibility of a hydrogel material for leaflet design.

This thesis includes multiple components that lead to the design, fabrication, and simulation of a catheter-based heart valve for the mitral position. In addition to this introductory chapter, this thesis includes 5 chapters. The outline of each chapter is described below:

- **Chapter 2 (Background & Literature Review):** Describes the design challenges and criteria for the design of catheter-based valves for the mitral position. Furthermore, a detailed literature review of current valve designs in the industry in both clinical and preclinical trial stages.

- **Chapter 3 (Leaflet Design and Fabrication):** Describes the iterative design process of designing two bileaflet valves, and one trileaflet valve. The design process includes the initial design, mold design, silicone fabrication, and hydrogel fabrication.

- **Chapter 4 (Stent Design):** Describes the Angeleno Medical stent, with two alterations to the original design to provide a release mechanism. Additionally, novel stent designs are described.

- **Chapter 5 (Heart Simulator):** Describes the design process of creating a system to pressurize and simulate cardiac function to evaluate the kinematics of the heart valves, with further options for evaluating mechanical heart valves. First and second-generation heart simulator designs are described.
• Chapter 6 (Conclusion & Future Work): Summarizes the future of TMVR devices, along with the work conducted in this thesis. Suggestions for future work to be conducted are included.
Chapter 2: Background & Literature Review

This chapter will detail factors that need to be taken into consideration when designing and fabricating TMVR devices, along with the landscape of the TMVR industry by reviewing current designs in clinical and preclinical stages.

2.1 Design Challenges & Criteria

When comparing the TMVR intervention to the transcatheeter aortic valve replacement (TAVR) intervention, there are substantially more design challenges that need to be addressed. These challenges are what has hampered the development of TMVR, as the complexity has proved to be cumbersome. In addition to challenges, certain design criteria are ideal for successful implantation.

After thorough studies into the physiological and anatomical components of the mitral valve, along with studying designs in clinical and preclinical stages, we can outline a criterion for the transcatheeter MV design. The specific criteria chosen for the designs are as follows:

- **The design must be able to be crimped.** For the catheter-based insertion, it is crucial to have a design that can conform to a low profile to aid in the ease of insertion for the surgeons. The lower the profile, the more ideal.

- **The design must have an anchoring system.** The development of an anchoring system that can withstand the dynamic pressures felt within the heart during systolic and diastolic pressures is important. The valve must stay in place after the final placement, without any migration, for optimal performance.

- **The design must not have Left Ventricular Outflow Tract (LVOT) obstruction.** Minimizing obstruction and allowing for the maximum amount of blood flow through the left ventricular outflow tract is vital for the patients’ health.
• **Reduction of stagnation flow.** Optimizing proper blood flow washout to prevent stagnation flow and resulting thrombosis (blood clot) initiation is imperative to design success.

• **Maximize mitral annulus sealing.** Improved sealing around the mitral annulus from proper conformation prevents leakage and resultant turbulent blood flow which can cause thrombosis initiation.

• **Maximize mitral orifice shape.** Closely matching the natural MV orifice shape will allow for optimal valve performance like a healthy native MV.

• **Made for established TMVR surgical approaches.** The design should be made to utilize surgical methods and approaches that are familiar to the surgeons performing the transcatheter procedures.

• **Readjustment during intervention.** A design that can be fully retracted and readjusted during surgery will aid the surgeons and allow for the ideal placement of the valve.

Designing these TMVR prosthetic devices with these certain aspects in mind will lead to designs with high technical implantation success along with superior performance. These challenges and design criteria are outlined in further detail below.

### 2.1.1 Anatomical Structure

Firstly, the anatomical structure of the MV is far more complex than that of the aortic valve (AV). The AV consists of a three-leaflet structure, in the tubular ascending aorta, allowing for ease of access, along with the ability to exclusively use radial forces, due to the heavy calcification present from CAVD, to seat TAVR devices. The MV apparatus first consists of the MV annulus, which can be described as the convergence of the left ventricle and the left atrium that takes on a 3-
dimensional (3D) saddle-shape [20]. The saddle-shape has an anterior peak that is continued with the aortovalvular complex, and a posterior peak that gives attachment to the posterior MV leaflet. The connection between the left atrium, the posterior MV leaflet, and the left ventricle is defined as a fibrous ring structure [21], [22]. The anterior portion of the MV annulus tends to be more challenging to classify, as there are various perceptions among disciplines and imaging modalities [23], [24]. This can be contributed to the continuous transition from the anterior MV leaflet into the intervalvular fibrosa, which can also be described as the “aortomitral curtain” or “continuity” [25]. The anterior portion of the MV annulus is not the pivot point of the anterior MV leaflet, but the leaflet rather pivots closer to the left ventricle, most often beneath the fibrous trigones [25].

As stated, The MV has two leaflets, those being the anterior and posterior MV leaflets, but relative to anatomical axes of the body a more accurate leaflet description would be the anterosuperior and posteroinferior leaflets [26]. Further titles for the MV leaflets are the aortic leaflet for the anterior MV leaflet and the mural leaflet for the posterior MV leaflet. The anterior MV leaflet is rounded and occupies a third of the MV annulus circumference, while the posterior MV leaflet is semilunar shaped and occupies two-thirds of the MV annulus circumference. The posterior MV leaflets have identifiable clefts that create scallops on the leaflet. The anterosuperior segment of the posterior MV leaflet is defined as P1 under Carpentier’s nomenclature, while the central segment is defined as P2, and the posteroinferior segment is defined as P3. The anterior MV leaflet does not have identifiable clefts, but the leaflet is still defined with three segments, as A1, A2, A3, corresponding to the opposite posterior MV leaflet segment. The leaflets can additionally be divided into three zones: the basal zone is detailed as the zone where the leaflets attach to the atrioventricular junction; the clear zone is detailed as the thin mid-zone of the leaflet; the rough zone is detailed as the thick rough zone at the free edge of the leaflet [27]. The rough zone is the central region for
chordal attachment, while also being the area of leaflet coaptation and apposition. Changes to the MV leaflets or MV annulus can lead to primary MR.

The MV leaflets have attachments to a dense collagenous connective tissue known as the chordae tendineae. The chordae tendineae are a “tree-like” structure that protrudes from the papillary muscles, which makes up the sub-valvular apparatus [28]. The chordae tendineae can be defined as three different types of chords, those being primary, secondary, and tertiary chords. Primary chords attach to the MV leaflet’s free edge of the rough zone, while the secondary chords attach to the body of the MV leaflet’s rough zone [27]. Finally, the tertiary chords attach to the basal zone on the posterior MV leaflet and affix straight to the ventricular wall. The ratio of chordae origin to insertion to the MV leaflets has been shown to be 5:1 [29]. The papillary muscles can be defined as the anterior (anterolateral) papillary muscle and the posterior (posteromedial) papillary muscle. The anterior papillary muscle gives chordal attachment to the lateral half of the MV leaflets, while the posterior papillary muscle gives attachment to the medial half of the MV leaflets [27]. The lateral half of the MV leaflets include the anterolateral commissure, A1, P1 and half of A2 and P2. Likewise, the medial half of the MV leaflets include the posteromedial commissure, A3, P3, and the other half of A2 and P2. The sub-valvular apparatus gives structural assistance to the MV leaflets during ventricular contraction [28], and changes to the sub-valvular apparatus can lead to secondary MR.

2.1.2 Valve Fixation and Sealing

Valve fixation techniques cannot exclusively rely on radial forces similar to TAVR due to the usual absence of calcification and a shorter annular region, so more advanced anchoring techniques must be utilized. A variety of different anchoring techniques have been proposed [25], [30]: using tethers to achieve counteracting axial forces; native leaflet grasping to fixate the prosthesis in
place; docking systems to allow radial forces sufficient enough for fixation; atrial and ventricular flanges to grasp the MV annulus and leaflets; atrial cages that use the full anatomy of the left atrium to prevent valve migration; subannular hooks that pierce the native MV tissue; cork-like effects that produces radial forces to aid in the anchoring of the prosthesis; and partial replacement devices that affix to the MV annulus. Some studies suggest that supra-annular fixation with an apical tether shows promising results when compared to sub-valvular fixation techniques [31]. The MV is subjected to high pressures (~120 mmHg) during the systolic phase when the valve is closed [32], so late migration of the TMVR device is of concern. Additionally, the dynamic motion over the cardiac cycle should be considered [33] as a newly protruding anterior MV leaflet due to the implanted TMVR device may create LVOT obstruction, or device dislodgement if the system utilizes leaflet capturing, under the high systolic pressures. Examples of TMVR anchoring mechanisms can be seen in Figure 2.1.
When compared to TAVR, which implants to a hardened stenotic AV that is a tubular shape providing radial reaction forces that are sufficient to seat the prosthesis into place, TMVR devices are implanted to treat MR, needing the designs to be seated to a noncalcified construct that is both dynamic and D-shaped in one plane and saddle-shaped overall. On top of proper anchoring, TMVR devices need to conform to the native MV annulus to apply proper sealing required to prevent leakage through the interface of the valve stent and the native annulus, also known as paravalvular leakage (PVL). It has been seen that D-shaped TMVR stents have produced better PVL results than circular shaped TMVR stents, as expected [35]. Though better sealing with a circular TMVR
stent is plausible when the stent is oversized for the MV annulus, as the discrepancy between oversized D-shaped stents compared to circular stents is far less than the discrepancy between stents that are not oversized [35]. There should be careful consideration when it comes to the oversizing of TMVR stents, as other potential challenges may become more apparent. Additionally, to achieve oversizing of TMVR stents, circular stents create larger septal-lateral forces and smaller inter-commissural forces when compared to the D-shaped stent [36]. As for D-shaped stents, studies show that they expand more along a possibly less compliant inter-commissural axis than circular stents, and less along a possibly more compliant septal-lateral axis [36]. Furthermore, radial expansion forces are significantly less uniform for D-shaped stents than circular stents. TMVR devices that generate sealing from contact between native tissue and a straight tubular section, the radial force is not the primary determinant of sealing. D-shaped stents sealing stems from its ability to better reach commissural features of the MV annulus, which supports the concept of the use of fabric casing the whole region of potential stent-leaflet contact [36]. Stents that expand and conform to the MV annulus seem to be more effective than stents that have circumferentially uniform forces against the MV annulus [36], though further studies should be conducted to validate this concept.

2.1.3 Left Ventricular Outflow Tract Obstruction

LVOT is the region of the left ventricle between the anterior cusp and the ventricular septum that blood passes through to enter the aorta through the aortic valve. There have been cases of a decrease in LVOT following surgical implantation of annuloplasty rings and prostheses [37], and reports of LVOT obstruction following surgical mechanical MV replacement [38]. With the larger prosthetic size of the TMVR, in addition to being anatomically close to the LVOT, LVOT obstruction is a large design hurdle to overcome [39], [40]. To produce a TMVR prosthesis that
does not encroach upon the LVOT, many factors need to be taken into consideration [41], [42]: The TMVR device protrusion into the left ventricle, and subsequently projection into the LVOT; the prosthesis flaring created from the anchoring method may extend into the LVOT; the angle between the aortic and mitral valve annular planes, also denoted as the aortomitral annular angle, will determine if the prosthesis extends into the LVOT; septal bulging can create narrowing of the LVOT, especially when a TMVR prosthesis juts from the other side creating a bottleneck effect. When compared to the native LVOT, the new altered LVOT can be greatly reduced in size. This newly altered LVOT can be described as a “neo-LVOT” [42]. The listed factors are illustrated and can be seen in Figure 2.2.
When predicting the neo-LVOT on pre-procedural time-resolved computed tomography (CT) with the above-listed factors, observational registries suggest a simulated neo-LVOT area of under 170 to 190 mm$^2$ predicts a high risk of LVOT obstruction [43], [44]. These factors can be described as fixed obstruction as the anterior MV leaflet is pushed towards the interventricular septum, or the septum bulging towards the anterior MV leaflet. The neo-LVOT can also be subjected to a dynamic obstruction, as the anterior MV leaflet can be drawn towards the interventricular septum during systole from generated Bernoulli forces [45]. A long anterior MV leaflet with redundant chordae is a risk factor [46], while additionally, a long anterior MV leaflet may prolapse back into the
TMVR valve, obstructing the valve from properly closing and initiating acute valve failure [47]. LVOT obstruction is identified as an LVOT gradient of $\geq 30$ mmHg and can be deemed a severe obstruction if the pressure gradient is greater than $50$ mmHg [48]. The LVOT gradient can be determined by taking the variance between peak systolic left ventricle pressure and the peak central aortic pressure [49]. The emergence of the intentional laceration of the anterior MV leaflet to prevent LVOT obstruction (LAMPOON) technique has proved to be a feasible means of increasing neo-LVOT, decreasing LVOT gradients and preventing LVOT obstruction. Furthermore, utilizing the LAMPOON technique for TMVR procedures has proven to be a sufficient means of preventing LVOT obstruction [45], [46], [50]. TMVR designs should consider the possible neo-LVOT area created due to the implanted prosthesis, along with utilizing the LAMPOON technique to further increase the neo-LVOT area and decrease LVOT gradients.

2.1.4 Delivery Method

TAVR procedures have the option to utilize a transfemoral approach that provides a minimally invasive method that would be ideal to use for TMVR procedures, but due to the location of the MV, exclusively transaortic implantation is difficult. TMVR designs are currently restricted to four approaches: a transapical approach, which is a puncture through the apex of the heart giving access to the left ventricle, and a direct shot to the MV; a transseptal approach, which is a puncture through the atrial septum and is most often accessed via a transfemoral approach to the right atrium; a transatrial approach, also known as a left atriotomy, which is a puncture through the left atrium to give access to the MV; a transaortic approach, where a minimally invasive surgical incision into the aorta is made to insert the device. Current TMVR delivery approaches are illustrated in Figure 2.3.
The transapical approach has been an alternate for TAVR procedures due to the short distance of travel along with good alignment with the implantation location. However, there have been reports of suboptimal results with the transapical access for TAVR implantation when compared to the transfemoral approach, which can be related to the harmful effects of a thoracotomy in high-risk patients, and to a greater degree of myocardial injury [51]–[53]. Though, in the early stage development of TAVR larger bores were used, along with a learning curve to conduct the TAVR surgery. Additionally, first-generation TAVR devices were larger in size, making them unsuitable for transfemoral insertion, leaving the transapical approach as the only means of insertion. These components may have led to suboptimal performances. Early TMVR designs have utilized the transapical approach, but next-generation devices have had a push towards employing the transseptal approach to avoid similar issues with myocardial injury and the harmful effects of a thoracotomy on high-risk patients. Careful design modifications will have to be considered to employ the transseptal approach, due to the increased travel length, and a higher amount of turns.
2.1.5 Hemodynamics

TMVR devices are employed to operate during both systole and diastole. Furthermore, an aspect to consider is for the TMVR devices to create the largest effective orifice area (EOA) possible during diastole to refrain from mitral stenosis initiation [33]. Additionally, a mitral pressure gradient $\geq 5$ mmHg is deemed to be a characteristic of mitral stenosis [33]. Thrombosis (blood clot) initiation in TMVR devices is also of concern, as there have been reports and cancellation of trials due to thrombosis presence [54]. In the vicinity of prosthetic valves where blood flow maintains a very slow velocity in a relatively small circulation zone, the possibility for blood to clot increases [55]. One of the main reasons for clot formation is an intensified exposure time of red blood cells to large variants in shear stresses, even if shear stress values are not significant. It has been evidenced that pulsation in blood flow is substantial in the regulation of stagnation areas and also blood clot formation [55], [56]. Moreover, blood clotting is proven to be triggered from both jet-like velocity where turbulent shear stresses are high, i.e. Reynolds number being high, as well as stagnation regions [57]. Factors that are known to be overriding in the triggering of blood clot formation are listed in Table 2.1.
Factor | Triggering criteria for blood clots
--- | ---
**Cavitation**<br>Reynolds shear stress | Water hammer and squeeze flow<br>\(>>200 \text{ dynes/cm}^2\) [58]
**Cardiac output** | Slow movement of leaflets (A low cardiac output will cause a reduction in the movement of the leaflet. This will promote the potential for the formation of blood clots by reducing the washout and dilution of the activated platelets)
**Stagnant flow** | If occurring adjacent to prosthetic valves, can promote the deposition of damaged blood elements, leading to thrombus formation on the prosthesis [59]
**Vortex shedding** | Yields repeated vortex pairing within the wake, which is responsible for the formation of larger platelet aggregates [60]
**Recirculation** | Allows many platelets to be trapped [61]
**Pressure drop** | A larger pressure drop means that the heart with the MHV prosthesis has to work harder [62], thereby reducing cardiac output. In fact, heart must maintain the cardiac output and does not lower it in order to keep the output up to the required level and thus is strained harder

*Table 2.1 Blood clot factors*

The procedure of blood clotting starts with activated platelets aggregating to an injured blood element. The level of platelet activation and red blood cell lysis are considerably linked to the level and length of the applied shear stress, also known as the residual time [63].

Measuring residual time has been reported in a few works as outlined in Table 2.2
<table>
<thead>
<tr>
<th>Model</th>
<th>Expression</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear damage accumulation/BDI</td>
<td>$\sum_{t=0}^{t=\text{end}} (\bar{\tau} \times \Delta t)$ dynes/cm²</td>
<td>[64]</td>
</tr>
<tr>
<td>Platelet activation state (PAS)</td>
<td>Non-dimensional level of platelet activation within the interval of [0, 1], in which 0 and 1 correspond to non-activated and fully activated platelets, respectively</td>
<td>[65]</td>
</tr>
<tr>
<td>Power-law model</td>
<td>$C \tau^\alpha \tau^\beta$</td>
<td>[66]</td>
</tr>
<tr>
<td>$\lambda_2$ criterion</td>
<td>$\lambda_2 = 20.0 s^{-2}$ is responsible for blood clot formation</td>
<td>[67], [68]</td>
</tr>
<tr>
<td>Adhesion model</td>
<td>$S \leq S_{th}$, where $S_{th}$ is shear rate threshold, taken as 100</td>
<td>[69]</td>
</tr>
</tbody>
</table>

Table 2.2 Accessible models for the approximation of blood clot formation and threshold

In particular, TMVR clots form between the native leaflet and the valve due to blood stagnation or lack of washout. It is well known that a certain amount of shear stress or wall shear stresses must be provided in the vicinity of the prosthetic heart valve to avoid blood stagnation or blood clot formation which could happen behind the leaflets in TMVR or around the hinges in mechanical heart valve prostheses. Regarding TMVR, the vortex created in the left ventricle during the diastolic phase can be translated into a kinetic energy resource for assisting propulsion and redistribution of blood flow in the systolic phase. In fact, diastolic dysfunction resulting from the design of prosthetic devices may be characterized by the breakdown of the vortex with amplified dissipation of the stored energy which may take away the positive effects of vortex formation. In other words, the shape and mechanical design of prosthetic devices for the mitral position plays an important role and may cause non-physiological hemodynamics within and in the left ventricle which is not desirable.

2.1.6 Prosthetic Valve Leaflet Degeneration

A factor when it comes to TMVR development is the focus on the valve tissue composition. Conventional surgical and transcatheter bioprosthetic valves utilize animal tissues such as bovine
(cow) pericardium or porcine (pig) pericardium, treated by glutaraldehyde [70]. Glutaraldehyde helps decrease immunogenicity and preserves the pericardium tissue [71]. Durability data for TMVR valves do not exist currently, but there are certain factors that need to be taken into consideration when contemplating the possibility of valve leaflet degeneration. The first being that surgical bioprosthetic valves for the mitral position have a higher chance of suffering early structural valve degeneration when compared to surgical bioprosthetic for the aortic position [34]. Secondly, surgical bioprosthetic valves have a higher rate of failure in younger patients than that in elderly patients [72]. Though TMVR for younger patients is of less concern for now, as the technology develops, more thought needs to be put into place towards valve durability for patients with long life expectancies. New insights on durability and structural valve deterioration learned from TAVR and surgical bioprosthetic valves will be beneficial for TMVR device development due to the use of the same materials. Surgical bioprosthetic valves are shown to have good durability towards the 10-year follow-up mark with a greater increase of incidence thereafter, while TAVR devices have shown good durability towards the 5-year follow-up with limited data at the 10-year follow-up [73]. There needs to be careful monitoring of patients undergoing TMVR over the next several years, to collect consistent valve durability data to provide developers with more insight into the longevity of their devices.

2.1.7 Readjustment & Re-Capturability

Going forward with the design of the TMVR devices, the ability to design a device that can be readjusted during implantation can plausibly improve the technical success of the procedure. Due to the multiple recorded events of early death in patients due to TMVR malposition and failed deployments [54], the ability to readjust and recapture the device after it has been implanted and had post-implantation performance tests conducted can prove to be a valuable asset. With new
devices being created, with their individual implantation complexities, failsafe abilities should be considered when applicable. Despite these challenges and restrictions, many TMVR systems have been designed and have had positive first-in-human implantations and are currently in further clinical assessments, while other designs are in research stages. These systems will be described.
2.2 Clinical Evaluation

For the sake of this review, a clinical evaluation will include devices that have had first-in-human implantation, or further human implantation trials. Only current device designs that have achieved the first-in-human implantation will be included in this section, with any device redesigns that have not achieved this feat included in the preclinical evaluation section. Devices that have been discontinued development and have led to the further development of other designs will also be included.

2.2.1 FORTIS (Edwards Lifesciences, Irvine, USA)

The Edwards FORTIS (Figure 2.4) is composed of a circular cloth-covered (to promote endothelization) self-expanding nitinol frame, with a trileaflet bovine pericardial valve. The non-recapturable frame includes an atrial flange and two opposing paddles that fold out at the base and capture the native mitral leaflets to the frame (anatomical anchoring system). During the deployment, surgeons align the paddles to the A2 and P2 sections of the MV leaflets under transesophageal echocardiography (TEE) direction. Once the paddles are discharged, they secure the native mitral leaflets for valve attachment.

The first-in-human implant of the FORTIS device was performed in 2014 by Bapat’s team from London, UK, and had excellent technical and initial clinical outcomes [74]. Overall, there were 13 cases of very high-risk patients performed on with an implant success of 10/13 (76.9%), though the all-cause 30-day mortality was reported to be 5/13 (38.5%) [34], [75]. Due to reports of valve thrombosis, the clinical trial was stopped at the end of 2015 [74], [76].

This system has a good novel anchoring system but the leaflet capturing techniques may have led to thrombosis initiation from created stagnation flow areas. Additionally, the circular stent design does not conform to the natural MV annulus. Certain components of the valve could be utilized
for future designs, but with reports of valve thrombosis, certain issues need to be evaluated before any further iterations of this system are created.

2.2.2 CardiAQ-Edwards TMVR System (Edwards Lifesciences, Irvine, USA)

This first generation of the CardiAQ-Edwards TMVR system had the first success in terms of implantation of a TMVR apparatus in a clinical setting. Søndergaard et al. delivered the valve transseptally in 2012 [77]. The CardiAQ-Edwards TMVR system is a non-recapturable, self-expanding, foreshortening nitinol frame, trileaflet bovine pericardial valve, with two sets of circumference-oriented anchors; one on the ventricular side and one and the atrial side. The ventricular anchors sit behind the valve leaflets and sub-valvular device, using the leaflets for support while also conserving the chords. The principal body of the prosthesis is located in the left atrium, denoted as a supra-annular position, allowing for minimal LVOT obstruction. The circular/symmetric design requires no rotation to conform to the natural mitral annulus. Additionally, the frame is enclosed in a polyester fabric skirt which aids in the reduction of paraprosthetic leakage. A second generation of the CardiAQ-Edwards TMVR system was developed with improved delivery for the transapical approach, and Søndergaard et al. showed good technical success in implantation in 2015 [78].

Early clinical trials (RELIEF) results showed a technical success of 12/13 (92.3%) and all-cause 30-day mortality of 7/13 (53.8%). Though the RELIEF trial began in 2016, it was put on hold in early 2017 to reevaluate the device design. Enrollment was reinitiated in 2018 with transseptal access being the sole delivery mode [79].

This system is one of the more prominent valves in the industry. The design offers effective anchoring through its MV annulus clamping technique but poses a possibility of LVOT obstruction with its large ventricle profile. Furthermore, the device utilizes a circular stent design and does not
conform to the MV annulus. This may reduce the device's PVL performance, though proper oversizing of the device may allow for sufficient results. The move to sole transseptal delivery should improve clinical results.

2.2.3 EVOQUE TMVR System (Edwards Lifesciences, Irvine, USA)

At the Transcatheter Valve Therapy (TVT) structural heart summit in September 2019, Dr. Howard Herrmann presented a second-generation valve, named the EVOQUE TMVR system (Figure 2.4) [80]. This valve utilizes designs from the FORTIS system and the CardiAQ-Edwards TMVR system, with a similar aesthetic look to the CardiAQ-Edwards TMVR system. The EVOQUE TMVR system has a unique anchoring mechanism that preserves the native MV anatomy while also utilizing the MV annulus, leaflets, and chords [81]. The system provides a low profile for both the atrial and ventricular sides to aid in the reduction of procedural complications. The system comes in a 44 mm size or a 48 mm size that is compatible with a single size delivery system and features an intra-annular sealing skirt and frame that allows for the minimization of PVL [81]. The transseptal delivery system has a low profile of 28 Fr, that the Edwards team believes may reduce the need for septal closure [81].

An early feasibility study of the EVOQUE TMVR system is currently recruiting and underway with an estimated study completion date of December 2024 [82]. It is believed that Edwards Lifesciences is going forward with its focus on the EVOQUE TMVR system and the SAPIEN M3 system.

As the EVOQUE TMVR system is a combination of two prominent TMVR designs, the best components of each system were funneled into this valve. The system, similar to the CardiAQ-Edwards valve, uses MV annulus clamping as its anchoring technique and has a large LV profile which again poses a threat to cause LVOT obstruction. Additionally, the circular stent design can
also impede PVL performance. It’ll be interesting seeing how the clinical trial goes with this new design.

2.2.4 SAPIEN M3 System (Edwards Lifesciences, Irvine, USA)

The Edwards SAPIEN M3 system (Figure 2.4) is an adaptation of the SAPIEN 3 system that is utilized for the aortic position. The valve includes a shape memory nitinol stent with a trileaflet bovine pericardial valve, much like the SAPIEN 3 system. The SAPIEN M3 valve has an addition of a polyethylene terephthalate (PET) skirt to minimize paravalvular leakage, and the SAPIEN M3 system has an additional shape memory nitinol dock which encloses the native mitral leaflets to anchor and seals the valve into place.

In March 2018 and June of 2019, John Webb, MD, presented the early feasibility results at both the Cardiovascular Research Technologies (CRT) 2018 Conference and the 2019 TVT Structural Heart Summit, which included 10 patients. All patients were hemodynamically stable throughout the procedure, all had the device successfully implanted, and none had LVOT obstruction [83]–[85]. Additionally, there was no mortality observed at 30 days. Raj Makkar, MD, at the Transcatheter Cardiovascular Technologies (TCT) 2018 scientific symposium in September 2018, showcased the SAPIEN M3 system and displayed results from 15 patients. He showcased the system having high technical success (13/15, 86.7%), 14/15 (93.3%) reduction in MR to 0 or 1+ and no death, LVOT obstruction and hemolysis [84]. Edwards Lifesciences plans to continue the early feasibility study with a plan to initiate a U.S. pivotal trial in late 2019 [80].

The early feasibility results for the SAPIEN M3 system is very promising, proving that alterations to TAVR devices with an addition of a docking system are a feasible means of TMVR. Due to the small sample size, the jury is still out on the design. As the anatomical structure of the MV is far more complex than the AV, adding a docking system may not be enough to overcome the TMVR
design hurdles. The design solely uses radial forces, which it will be interesting to see how repeated cyclic systolic forces applied to the closed valve will affect the implantation position. As the design has a docking system, the circular stent seems to be sufficient when it comes to PVL performance. The docking system does have the possibility of impeding on the LVOT. Above all, this is a system to watch closely, especially with its promising early feasibility results.

2.2.5 Cardiovalve TMVR System (Cardiovalve Ltd., Or Yehuda, Israel)

The Cardiovalve TMVR system (Figure 2.4) is a trileaflet valve that includes two frames; an atrial frame and a ventricular frame. The valve is fixed into the mitral annulus by employing over 24 central “sandwiching” sites, utilizing a circular design that foregoes the need for rotational alignment [34]. The valve has a crimped height of 32 mm and the deployed valve protrudes approximately 12 mm into the left ventricle. The system is implanted using a transfemoral/transseptal approach and comes in three different size variations ranging from 40 to 50 mm. The valve is deployed using a three-step procedure; first is grasping the mitral valve leaflets which is followed by the atrial flange delivery, and finally a full release of the valve to seat it into place. The first five in-human cases of implantation had perfect technical success (5/5, 100%) along with no LVOT obstruction, and no mitral regurgitation [86]. The first 30 days after implantation had a mortality of 3/5 due to access site bleeding, retroperitoneal bleeding, and deep vein thrombosis [87].

The AHEAD European early feasibility study is currently enrolling with a target of 30 patients was started in April of 2018 with an estimated primary completion date of December 2019, and an estimated study completion date of December 2021 [88]. The AHEAD USA early feasibility study is currently enrolling with a target of 15 patients started in March of 2019 with an estimated
primary completion date of April 2020 and an estimated study completion date of September 2025 [89].

The Cardiovalve TMVR system offers a low-profile device to avoid LVOT obstruction, along with no need for rotational alignment. This circular approach may prove to have greater complications with sealing, as it doesn’t conform to the natural MV annulus. The sandwich anchoring system allows for the low-profile and may prove to be a suitable means of fixating the valve into place. Both the European and USA early feasibility trials should be monitored closely, to evaluate the technical success of the device, along with patient selection.

2.2.6 Tiara TMVR System (Neovasc Inc., BC, Canada)

The Tiara TMVR system (Figure 2.4) is a D-shaped device, consisting of three bovine pericardial leaflets with a self-expanding nitinol frame. On the ventricular side, the valve boasts three anchors (2 anterior and 1 posterior). The ventricular anchors are fit to secure the valve against the fibrous trigone anteriorly and posterior shelf of the MV annulus [91]. On the atrial side, the valve has an atrial skirt that helps fix the valve into the atrial segment of the mitral annulus. The valve comes in two sizes: the 35 mm valve has internal diameter dimensions of 30 mm and 35 mm (area: 6.3 cm² to 9.0 cm²), and the 40 mm valve has internal diameter dimensions of 34.2 mm and 40 mm (area: 9.0 cm² to 12.0 cm²), implying that the valve has a tapered shape with minimum and maximum diameters and cross-sectional areas [34]. The Tiara TMVR system is delivered through a transapical approach [92].

The first-in-human implantation of the Tiara TMVR system was reported in early 2014 [92], [93]. The early feasibility trial named TIARA I (started in December 2014) and additional cases, totaling 33 cases, were performed with a 90% implant success and an early mortality rate of 12% [91]. A multicenter international feasibility trial named TIARA II is now ongoing and recruiting with a
target of 115 patients with estimated primary results by January 2020, and an estimated study completion date of January 2025 [94].

One of the intriguing design elements of the Tiara TMVR system is that it takes on a D-shape, to aid the device in conforming to the natural MV annulus. For sealing purposes, this may be the most optimal approach to prevent PVL. The device has effective ventricular anchors, with the right positioning, but may have issues with protruding into the LVOT. Furthermore, the device is only designed for the transapical approach, which increases the chances of surgical complications. The development of this device to be able to be delivered via the transseptal approach would be of great value to this system. The TIARA II trial will be a suitable test and provide good data on if the system is good enough for commercial applications.

2.2.7 Tendyne Mitral Valve System (Abbott Laboratories, Illinois, USA)

The Tendyne mitral valve system (Figure 2.4) utilizes a 30Fr transapical delivery casing for their self-expanding double frame device and adjustable tether with a trileaflet porcine pericardial valve. The outer stent is D-shaped to conform to the natural mitral annulus while the inner stent is a circular shape. The outer stent can come in a variety of sizes, while the interior stent is a singular size to preserve an EOA of greater than 3.2 cm$^2$ [34].

The system has an atrial cuff to aid in anchoring and prevent the valve from entering the ventricle when the tether is under tension, along with providing sealing to prevent paravalvular leaking during diastole. The left ventricular apical tether system has an apical pad that affixes the apparatus to the apex of the heart and helps promote apical closure.

With the success of the first-in-man implantation of the Tendyne mitral valve system in February 2013 [95] and October of 2014 [96], an initial feasibility study between November 2014 and November 2017 was performed on 100 patients, and reported with a technical success of 96 (96%),
30-day all-cause mortality of 6, and 1-year all-cause mortality of 26 [97]. Due to the success of the global feasibility study, a U.S. approval (SUMMIT) trial was approved with a target of 1010 patients and began recruiting in June of 2018, with an estimated primary completion date of June 2022, and an estimated study completion date of June 2026 [98]. The SUMMIT trial is currently being redesigned to address the control arm for functional MR and to include mitral annular calcification [99]. The mitral annular calcification feasibility study began in October 2018 with a goal of 30 patients at 10 sites [100]. The first implantation occurred in November of 2018, with 7 subjects treated as of June 2019 [99].

The tethering system utilized for the Tendyne MV system is quite novel, and though the device is only delivered via the transapical approach, the apical pad allows for a reduction of surgical issues and aids in the sealing of the access puncture. Additionally, this system utilizes a D-shaped stent to conform to the natural MV annulus, which should prevent PVL. The device does limit itself to patient selection with only having the transapical approach as an option, but due to the design of the device, there aren’t other delivery options available. Furthermore, the tethers may contribute to hemodynamic and flow changes within the LV. Though, one component that this device has over its competitors is the fact that it can be fully retrieved even after surgery, as the tether aids in grasping the device and removing it at a later date if necessary. This system is one of the furthest along regarding clinical trials and will be interesting to watch how the SUMMIT trial will go, especially with the addition of mitral annular calcification for implantation options.
Figure 2.4 TMVR systems in clinical evaluation 1/2

(A) FORTIS (Reprinted from [75] with permission from Elsevier). (B) EVOQUE TMVR System (Reprinted from [81] with permission from Edwards Lifesciences LLC). (C) SAPIEN M3 System (Reprinted from [83] with permission from Elsevier).

(D) Figure 2.4D has been removed due to copyright restrictions. It was an image of the Cardiovalve TMVR System. Original source: [86]. (E) Tiara TMVR System (Reprinted from [92] with permission from Elsevier). (F) Tendyne Mitral Valve System (Reprinted from [101] with permission from Elsevier).

2.2.8 INTREPID TMVR System (Medtronic, Minnesota, USA)

The INTREPID TMVR system (Figure 2.5) was first named the TWELVE TMVR system from Twelve Inc. until Medtronic purchased the company and renamed the valve. The system employs a dual nitinol self-expanding stent design, which contains an individual annular fixation structure with a suspended circular valve stent. The system includes a 27 mm trileaflet bovine pericardial valve in the circular stent, and the outer stent which is fixated to the sub-annular apparatus by means of cleats comes in three sizes (43, 46, and 50 mm). Due to the system being circular with
no paddles or anchors, the valve does not need to be oriented to the natural mitral valve annulus. The outer stent also includes a flexible atrial brim to facilitate visualization under echocardiography [79]. The valve takes on a ‘champagne cork-like’ configuration (narrow neck and wider body) to oppose valve migration during high systolic pressures [34]. The design is meant to preserve and leverage the native leaflets along with the chordae to seal around the device. The device is delivered transapically and new design iterations have made the system to be recapturable up to the point of final release [102]. The system length was increased for larger patients to enhance ease of use and changed the sheath aesthetics and hub design to improve hemostasis and usability.

Bapat et al. outlined the early experience with the INTREPID TMVR system describing the first 50 patient’s implantation along with 30-day follow-ups. One patient did not undergo implantation due to apical site bleeding complications, while 48 of the other 49 had successful implantations resulting in a reduction of MR to mild or none at all [103]. 7 deaths occurred within the first 30-days; 3 deaths related to apical site bleeding at or immediately after the initial implantation, 1 due to malposition of the valve, and 3 others due to refractory heart failure early after the procedure (<30 days). There were 4 additional patients that died between days 54 and 122, but there were no deaths after 4 months [103]. The secondary clinical trial, the APOLLO trial, is currently recruiting with an enrollment goal of 1380 patients with an estimated primary completion date of October of 2021 and estimated study completion date of October of 2025 [104].

The INTREPID TMVR system is another device that is far along regarding clinical trials. The device needs no rotational alignment and utilizes a combination of radial and axial forces to anchor the device into place. With the device being delivered transapically and seeing the early feasibility results, it is safe to say that redesigning the device for a transseptal approach would be of great value. Also, the device doesn’t conform to the natural MV annulus, which puts it at risk of PVL.
2.2.9 Caisson TMVR System (LivaNova PLC, London, United Kingdom)

The Caisson TMVR system (Figure 2.5) was originally created by Caisson Interventional, LLC, but was purchased by LivaNova PLC in 2017 to aid in LivaNova’s entry into the TMVR space [105]. The Caisson TMVR system consists of a two-stage deployment system; the anchor component and the valve. The anchor component is made of a self-expanding nitinol frame and is D-shaped to fit the mitral annulus. The anchor component has four ventricular sub-annular anchoring feet that provide axial fixation onto the mitral annulus, while the three atrial grasping components interact with the atrial surface of the MV annulus [34]. Once the anchor component is deployed, the trileaflet pericardial tissue nitinol-based valve stent is positioned and deployed within. The valve stents additional anchors to provide further fixation, minimizing PVL. The system is deployed using a transseptal approach and both the anchor and valve stent components are repositionable and fully recapturable [106]. The Caisson TMVR system is an atrially-biased system to prevent LVOT obstruction and the 3-leaflet circular valve provides an EOA of greater than 3.0 cm².

The Caisson TMVR early feasibility study (PRELUDE) began in June of 2016 and was completed in August of 2018 [107]. The study had 23 patients enrolled, with 18 patients getting the system implanted, 4 converting to surgery and 1 being retrieved [106]. There were two deaths during the first 30 days post-surgery; one due to septicemia and the other due to drug-induced hypotension. Due to the success of the PRELUDE trial, the LivaNova team moved forward with its European approval trial (INTERLUDE), which is currently active, but not recruiting [108]. A total of 30 patients have been enrolled in the INTERLUDE and PRELUDE studies showing encouraging results, with current work being done on improving the ease of use of the system [109]. INTERLUDE has an estimated primary completion date of August 2020, and an estimated study
completion date of August 2025. The protocol is currently being finalized for its US approval trial (ENSEMBLE) [110].

With the Caisson TMVR system being atrially-based, the possibility of LVOT obstructions is greatly reduced. Additionally, the D-shaped stent conforms better to the native MV annulus and should provide acceptable PVL performance. The ventricular anchoring feet may provide sufficient anchoring to the MV apparatus with good performance. The attributes that the device is repositionable and fully recapturable are intriguing and very beneficial for surgeons. The complexity of implantation is detrimental to the technical success of the device. As Liva Nova looks to improve upon the ease of use of the system, this device is a device to watch.

2.2.10 HighLife TMVR System (HighLife Medical, Paris, France)

The HighLife TMVR system (Figure 2.5) consists of two components; a sub-annular implant ring that acts as a docking system, and a prosthetic valve that sits inside the ring. The sub-annular implant consists of a polymer tube covered in a polyester graft with nitinol hooks for ring closure, to create a single definite ring length of 31 mm [111]. This sub-annular implant is deployed using a transfemoral transaortic method, placing it around the prosthesis which hinders any displacement of the device into the left ventricle. The prosthetic valve consists of a 31 mm nitinol frame with a trileaflet bovine pericardial tissue valve and can be delivered via a transapical or transseptal approach. The valve is circular, allowing it to self-center and align, and includes a pre-formed indentation in the annular section to allow for the sub-annular implant to interact with the valve for satisfactory sealing and fixation. The native valve leaflets sit between the prosthetic valve and the sub-annular implant to minimize PVL. The device is non-recapturable once it is deployed. The HighLife TMVR system study began in July of 2017 and is currently recruiting patients with a goal of 20 patients, even though their estimated primary completion was for July of 2018 [112].
In October of 2017, Dr. Nicolo Piazza outlined the first 11 patient implants. The results included 9 successful implantations, with one causing LVOT obstruction resulting in an in-hospital death [113]. The two other patients were converted to surgery due to chordal entanglement, one ending in an in-hospital death, and the other having greater than 12 months follow up. The estimated study completion date is for December of 2023 [112], with a new generation transseptal delivery system to undergo clinical study around quarters 2 and 3 of 2019 [114].

The HighLife TMVR system provides a surgically complex anchoring system that may be cumbersome for surgeons. Though the device is circular and does not conform to the native MV annulus, the sub-annular implant allows for satisfactory valvular sealing to prevent PVL. Additionally, the sub-annular implant provides effective anchoring for the system. LVOT obstruction will be a question with this design, as the device protrudes into the LV. The use of the LAMPOON technique may prove to be beneficial for this device.

2.2.11 NAVI System (NaviGate Cardiac Structures Inc., Lake Forest, USA)

The NAVI system (Figure 2.5) is comprised of a circular self-expanding nitinol stent-frame that takes the shape of a truncated cone with a height of 21 mm. The system utilizes a trileaflet pericardial tissue valve, and the catheter implantation system has a diameter of 30 Fr at the distal end, and 18 Fr at the level of the catheter shaft [34]. Implantation can be done via the transatrial, transapical and transseptal approaches. The system anchors using annular winglets to secure the valve to the mitral annulus.

The first-in-human implantation was done in October of 2015 using the transatrial approach, with a reduction to zero MR [115]. The NaviGate team received approval to implant the NAVI system from the Krakow, Poland, Ethics Committee in July of 2016 and planned to perform a 30 patient transatrial feasibility study [116]. No further information has been posted regarding the NAVI
system, though the development of the NaviGate team’s GATE system for the tricuspid valve position has been progressing with the first-in-human procedure done in April 2017, and with excellent leaflet mobility and valve function at the one year mark [117]. The NAVI system and the GATE system take on the same design features but are meant for their respected annulus locations. Through the first 27 implantations of the GATE system, there was a 30-day mortality rate of 2/22 (9%) in a compassionate use patient population [118].

The NAVI system utilizes annular winglets to anchor the device to the MV annulus and thus does not protrude into the LV which reduces chances of LVOT obstruction. The stent is circular and does not conform to the native MV annulus, which may cause PVL. It’ll be interesting to see how the device handles the dynamic systolic pressures in the LV and how robust the annular winglets anchoring is. The movement to the tricuspid valve application may be due to the dynamic systolic pressures in the LV.

2.2.12  Cephea TMVR System (Abbott Laboratories, Illinois, USA)

The Cephea TMVR system (Figure 2.5) utilizes a self-expanding double disk assembly that seats the trileaflet bovine pericardial valve. The system boasts a low-profile frame structure to allow for minimal LVOT obstruction and sparing sub-valvular anatomy. The structure has a multilevel conformity design that isolates the leaflets from non-circular distortions, which allows for scaling of the valve sizes with a single valve core [119]. The center column of the prosthesis creates leaflet support by providing a stable platform, to allow the valve to adapt to diverse anatomies. The prosthesis is delivered using an antegrade (transatrial or transseptal) approach and is seated with the atrial disc secured to the floor of the left atrium, while the ventricular disc is anchored to the sub-annular region [34].
The first-in-human was set to begin in the first quarter of 2018 [120]. The early procedural experience with the Cephea TMVR system has shown favorable results, allowing the strategy for the early feasibility study to be in development [121].

Though the Cephea TMVR system does not conform to the natural MV annulus, the double disk design may prevent it from PVL. Additionally, the low-profile design will be beneficial in deterring LVOT obstruction, though careful monitoring of the system will need to be conducted. The use of the LAMPOON technique may be beneficial for this device if LVOT obstruction occurs.

2.2.13 AltaValve TMVR System (4C Medical Technologies, Inc., Minnesota, USA)

The AltaValve (Figure 2.5) has a spherical shaped nitinol stent design that encompasses the entire left atrium. The system applies a supra-annular and atrial anchoring mechanism to seat the device into place, which provides acceptable paravalvular sealing with the PET skirt that interacts with the native supra-annular apparatus. The stent comes in multiple sizes to fit the left atrium and is made to be compliant with the left atrium anatomy [122]. The device is comprised of a 27 mm diameter trileaflet bovine pericardial tissue valve and is implanted using transseptal or transapical approaches [123] by way of a 34 or 32 Fr catheter, respectively [122]. Due to the exclusive supra-annular placement of the device and the minimized annular ring, there is total sub-annular preservation, leading to no LVOT obstruction and total preservation of the native MV.

Animal studies have produced remarkable results, with a total of 45 animals receiving implantations [124]. The device has good endothelization along the stent, with full attachment to the atrial roof, along with no evidence of thrombosis or damage to the sutures or valve tissue [123]. The first-in-human implantation was showcased at TCT 2018 and utilized the transapical approach with good technical success, and no postoperative complications [124]. 7-month follow up showed
great improvement for the patient, along with great improvements from the patients' baseline statistics. An AltaValve early feasibility study for up to 30 patients has been approved to begin in the second half of 2019 and will be performed in Canada, the United States, and in Japan [122]. Initial experience with the transseptal approach will also be taking place in the second half of 2019. The supra-annular and atrial anchoring that the AltaValve TMVR system employs is quite novel and could be the answer to LVOT obstruction. The sealing of the stent does come into question, as though the device is exclusively supra-annular, the interaction between the device and the MV annulus is important. Because the device is circular fit into the MV annulus, there may be PVL issues. Better conforming to the MV annulus could be a possible solution if PVL arises. Monitoring on the AltaValve will be interesting to see how the device interacts over the long term to the atrial wall of the LA. Even though the pressures felt in the LA are less than the LV, LA flow dynamics will also need to be monitored and evaluated.
2.3 Preclinical Evaluation

Preclinical evaluations include systems under preclinical animal studies, along with systems in research stages. Devices with plans of the first-in-human implantation with no updates are also included in this section.
2.3.1 AccuFit TMVR System (Sino Medical Sciences Technology Inc., Tianjin, China)

The AccuFit TMVR system (Figure 2.6) is a self-expanding, circular, self-centering valve with a nitinol frame. The system comprises of an atrial flange and ventricular flange with annulus support. The ventricular flange has a maximum height of 14 mm, with an added covering on the ventricle commissural tips and an added protective suture layer on the left ventricle anchors [127]. The annulus support has an annular clipping space that is between the atrial flange and a ring of anchors that extend radially [128]. The valve is composed of three bovine pericardial leaflets in a tubular shape to avoid central leakage. The Sino Medical team attempted an initial design with reversed leaflets, but have since abandoned that design and gone with the conventional leaflet design [127]. The valve is implanted with a 38-F caliber system via the transapical approach [128].

Preclinical animal (LYD cross-breed Yorkshire swine) studies were done on 87 acute and 32 sub-chronic and chronic animals. For 30 sub-chronic and chronic implantations, the success rate was 80% with a procedure range from 7 to 15 minutes [129]. PVL occurred in 7 cases, with greater than mild PVL in one case, along with LVOT obstruction in a single case. Out of 23 pathological studies, 21 cases (91%) resulted in non-traumatic anchorage with complete sealing and 9 cases (39%) of injury to chordae [129]. First-in-human studies were said to begin in the first quarter of 2017 [34], [127], [130], with no results posted to date.

2.3.2 Epygon TMVR System (Affluent Medical SA, Paris, France)

The EPYGON TMVR system (Figure 2.6) consists of a monoleaflet pericardial tissue that is combined with a D-shaped annular ring. The asymmetric stent shape allows for a minimization of LVOT obstruction due to the protrusion towards the AV, along with a reduction in interference with the left ventricle wall [131]. The D-shaped monoleaflet is designed to cope with the left ventricle shape providing optimal fitting to the valve stent and having a large coaptation surface
against the prosthetic posterior wall. The system is anchored by way of an atrial flange that seats the valve into position, and the left ventricle engagement arms that maintain traction over the papillary muscles to prevent any left ventricle sphericity [131]. The anchors capture and block the anterior leaflet, allowing for no LVOT obstruction. The system is implanted using the transapical approach and is designed to create similar flow dynamics than that of the native MV, creating a rotary flow (vortex) that minimizes energy loss and propels blood toward the LVOT [132].

Preclinical trials performed on 14 sheep models assessed the flow dynamics within the left ventricle and showcased that vortex properties were unchanged, other than the intensity that decreased [131]. Technical success for the preclinical trials was greater than 90%, and the system produced excellent hemodynamics with no prosthetic migration, no LVOT obstruction, no left ventricle to aorta pressure gradients, and no intra or paravalvular thrombosis initiation. The implant also had low atrio-ventricular gradients (1-2 mmHg) while only having traces of PVL [131]. An early feasibility study for the transapical approach in high-risk patients with severe MR was planned for early 2019.

2.3.3 Saturn TMVR Technology (InnovHeart SRL, Milan, Italy)

The Saturn technology (Figure 2.6) consists of an annular structure that encircles the MV to aid in both the anchoring sealing of the prosthetic valve. The device is implanted using a three-step procedure that includes insertion of the annular structure by way of guidewires for the first two steps, then the connection to the self-expanding central valve body [133]. The annular structure also prevents LVOT obstruction by holding the native MV leaflets in place, along with the low profile of the prosthesis. The central valve body utilizes a trileaflet pericardial tissue valve, and InnovHeart states that the system provides surgical-like anchoring to the annulus [133].
Good laboratory practice in-vivo preclinical trial was started in the first quarter of 2018 for the transapical approach, while the transseptal approach is still under development. To date, no trial results have been released.

2.3.4 Corona Mitral Valve Replacement System – (ValCare Medical, Tel Aviv, Israel)

The Corona Mitral Valve Replacement System (Figure 2.6) is a complementary approach that utilizes the AMEND percutaneous annuloplasty ring developed by ValCare Medical. The AMEND ring is a closed ring that takes on a D-shape, is semi-rigid, and provides roughly 15-25% septal-lateral reduction [134]. The AMEND ring is used to offer a solid landing zone for the Corona valve. The Corona valve is a dedicated D-shaped self-expanding stent-based valve with a 4-pericardial-leaflet concept [134], [135]. The bioprosthesis can be crimped to a small profile (21 Fr) and boasts a short stature (27 mm) which provides minimal protrusion into both the left atrium and left ventricle, and thus targeted to produce little to no LVOT obstruction. The system can be implanted using both the transseptal and transapical approaches while preserving the native valve geometry. Due to the Corona valve being fitted to the AMEND ring, the combined systems allow for minimal PVL [134], [135]. The Corona valve is meant to be implanted either utilizing a one-stage approach, meaning the AMEND ring and Corona valve are implanted in a single procedure with two steps or a two-stage approach that uses the AMEND ring to reduce MR with the Corona valve being implanted at a later date if there is a late occurrence of MR.

The AMEND ring has shown good initial clinical experience on a total of 16 cases utilizing the transapical approach [136]. The transseptal approach is undergoing final validation, with plans of being in clinical use later in 2019 [137]. The Corona valve is currently undergoing chronic preclinical trials, with no results posted to date [138].
2.3.5 MValve System (MValve Technologies Ltd., Herzliya, Israel)

The first generation of the MValve system is a docking system for the mitral position, to allow other transcatheter prostheses to be implanted and anchored. The system allows for a true chordal-sparing as it preserves the native leaflets’ function and is inserted using a transapical approach. The system is designed to be accordant to several commercially available transcatheter valves. The device is able to be recaptured along with being fully retrieved after full deployment [139].

The first-in-human implantation of the MValve system was performed in September of 2015, with acceptable technical success. There were no complications, good valve positioning resulting in no residual MR [34]. The MValve Technologies company first planned to begin their first-in-human trial, titled DOCK 1, in the 4th quarter of 2016 [140], but the development of the second generation of the MValve system (Figure 2.6) but those plans on hold. The second-generation system has leaflets sewn to the dock, providing single-step implantation, along with adjusting for the transseptal approach with a 22-24 Fr delivery profile [139]. The group planned to complete final long term durability testing on the newly enhanced device, with plans to start DOCK 1 at approved centers in the EU and South America in the 4th quarter of 2017 [139]. There are no updates to date.

2.3.6 Permavalve TMVR System (Micro Interventional Devices, Inc., PA, USA)

The original name of the Permavalve TMVR system (Figure 2.6) was the Endovalve and was renamed after the purchase of Endovalve Inc. in April of 2011 by Micro Interventional Devices Inc. [141]. The Permavalve TMVR system comes with PolyCor anchors to fix the device to the native mitral annulus. Micro Interventional, Inc. also states that the Permavalve is the first and only TMVR system that has an active fixation, which is achieved by the PolyCor anchors [142]. Dacron cloth is used for the stent skirt that includes integral billows that ensure biological integration while also eliminating PVL. The device is delivered via a transapical approach with a
28 Fr delivery system [142]. The PermaValve utilizes the Permaseal system developed at Micro Interventional Devices, Inc. which aids in the sealing of the transapical access point by way of soft-tissue anchors and advanced biocompatible elastomers [143].

**Figure 2.6** TMVR systems in preclinical evaluation 1/2

(A) AccuFit TMVR System (Reprinted from [130] with permission from Sino Medical Sciences Technology Inc.).
(B) Epygon TMVR System [132]. (C) Saturn TMVR Technology (Reprinted from [133] with permission from InnovHeart SRL).
(D) Figure 2.6D has been removed due to copyright restrictions. It was an image of the Corona Mitral Valve Replacement System. Original source: [137]. (E) MValve System (Reprinted from [139] courtesy of Boston Scientific. © 2020 Boston Scientific Corporation or its affiliates. All rights reserved). (F) Figure 2.6F has been removed due to copyright restrictions. It was an image of the PermaValve TMVR System. Original source: [142].

### 2.3.7 MitrAssist Device (MitrAssist Medical Ltd., Misgav, Israel)

The MitrAssist device (Figure 2.7) is a valve-in-valve approach to treating MR, meaning rather than full replacement of the native MV, the system aids the native MV and increases functionality.
The device comes with a nitinol frame with a pericardial tissue in an asymmetrical bileaflet design [143]. Because the system works in unison with the native MV there is a reduced risk of valve migration, LVOT obstruction, and the system preserves the natural MV functionality. The device is anchored to the papillary muscles to further help MitrAssist work in unison with the MV, as the papillary muscles move in synchrony with the MV apparatus [145]. Preclinical animal trials have shown promising results, with no trauma to leaflets, no thrombosis initiation and no leaflet adhesion [143], [145].

2.3.8 Sutra TMVR System (Dura Biotech, Connecticut, USA)

The Sutra TMVR system (Figure 2.7) is a hemi-valve concept, meaning it targets replacing only one of the mitral valve leaflets, more specifically the posterior leaflet. The systems ideology is to take the benefits from both valve replacement and valve repair to create a seamless device. The system has a crescent-shaped stent frame, allowing it to be crimped to a small profile, have no LVOT obstruction and allows normal anterior leaflet function [146]. The leaflet is comprised of a trileaflet design, emulating the scallops on the native posterior leaflet, which improves coaptation with the native anterior leaflet and reduces leaflet stress to enhance durability. The system is anchored using a dual-guiding-fixation method [146] that is deployed from the left atrium, securing the system to the annulus with cinching capabilities [147].

The Sutra TMVR system has shown adequate early preclinical results at 120 days post-implantation with good leaflet coaptation, no central MR, and no PVL [146]. Currently ongoing is the accelerated wear testing at over 200 million cycles, and the 28 Fr transseptal delivery system development with the next goals of in vivo implantation into chronic animals [148].
2.3.9 Polares (Polares Medical, Inc., Ecublens, Switzerland)

Polares (Figure 2.7) stands for posterior leaflet augmentation and restoration, denoting it focuses on the partial replacement of the posterior mitral valve leaflet. The Polares device has an anchoring base with leaflet extension curving into the left ventricle. The technology is targeting restoring coaptation for both primary and secondary MR [149]. The Polares device is implanted exploiting a transfemoral transseptal approach and is anchored with primary and secondary anchors [150]. The primary anchor fastens the hemi-valve to the supra-annular apparatus of the MV, with four secondary anchors further securing the system. The system is fully repositionable and retrievable while preserving options for further TMVR implantations in the future. The ventricular hemodynamics are preserved providing no impingement on the LVOT, while also preserving the MV annulus and causing no damage to the MV leaflets [149].

In July of 2018, the Polares Medical Inc. team closed financing to enter clinical validation [151], with confirmed plans of first-in-human implantation soon [150].

2.3.10 Gorman TMVR System (Gorman Cardiovascular Research Group, PA, USA)

The Gorman TMVR system (Figure 2.7) is part of the Annulon startup company that the Gorman Cardiovascular Group founded to focus on catheter-based technologies used for the replacement of the mitral valve [152]. The device is comprised of a supporting frame and the tissue valve mechanism. The frame is a self-expanding nitinol wire woven into a three-dimensional shape. The frame provides a radial expansion force, along with a grasping force, while still providing a casing for the valve mechanism [153]. The system produces the grasping forces by way of the ventricular arms that collect the posterior and anterior leaflets of the native MV onto the bulk of the device. The atrial arms seat the valve in the atrial space while collecting the supra-annular tissue centrally [153]. The device uses a trileaflet pericardial tissue valve and is designed for both transseptal and
transatrial approaches [154]. The system provides no LVOT obstruction, with a good perivalvular seal.

The sutureless device has shown good preclinical results, and the Annulon team is working to bring their devices to clinical practice [152].

2.3.11 Direct Flow TMVR System (Direct Flow Medical, Inc., Santa Rosa, USA)

The Direct Flow TMVR system (Figure 2.7) is an adaptation from their existing TAVR device. The TAVR device is a non-metallic double ring design, that is inflated with saline that allows the device to be seated into place with good sealing [155]. Once the functionality is achieved the saline is removed and replaced with a high strength polymer. The design utilizes a bovine pericardial trileaflet within the inflatable stent. Initial implantations of the TAVR device with minor alterations for the mitral position were performed to showcase feasibility [156]. Further adaptations for the mitral position provided a conforming anatomical atrial sealing flange that is additionally inflated with saline for sealing [157]. The flange provides a smooth surface for sealing and is fully retractable and repositionable during the procedure. The device is implanted using either a transseptal or transaortic approach with a short valve height. The first-in-human implantation with the newest adaptation was hoped to be done in late 2016, but due to the main financial lender for Direct Flow Medical, Inc. refusing to extend their funding arrangement, the company had to shut down [158], [159]. There are no updates on whether the TAVR and TMVR devices will be picked up and further developed.

2.3.12 MitraCath TMVR System (Emory University, Atlanta, USA)

The MitraCath TMVR system is a self-expanding stent docking system that allows for the implantation of circular aortic and pulmonary catheter-based valves to be implanted into the non-
circular D-shaped MV annulus [160]–[162]. Due to the lack of information and updates, it is unsure if the MitraCath TMVR system is being further developed.

Figure 2.7 TMVR systems in preclinical evaluation 2/2

(A) Figure 2.7A has been removed due to copyright restrictions. It was an image of the MitrAssist Device. Original source: [145]. (B) Sutra TMVR System (Reprinted from [148] with permission from Dura Biotech). (C) Figure 2.7C has been removed due to copyright restrictions. It was an image of the Polares device. Original source: [149].

(D) Gorman TMVR System (Reprinted from [153] with permission from Elsevier). (E) Direct Flow TMVR System [157].
Chapter 3: Leaflet Design & Fabrication

This chapter details both the design and fabrication processes for the valve leaflets. The design process includes the iterative valve design procedure, followed by the iterative mold design process to produce the most optimal valve. The leaflets were initially fabricated with silicone, and once satisfied with the result they were made using the novel cryogel material. A detailed description is included for each of the design stages from which two bileaflet valves and a trileaflet valve were designed and fabricated.

3.1 Leaflet Design

Three leaflet designs were created for the sake of this thesis. A bileaflet valve for the implantation into a TMVR stent, a bileaflet valve for a computational model, and a trileaflet valve for evaluation of the cryogel material and the implantation into a TMVR stent. Each of their design phases are described in the following sections.

3.1.1 Duckbill (Bileaflet) Valve

The duckbill valve was an original proposed idea, and for the sake of this thesis, the duckbill design is the main focus for the leaflet designs. The name duckbill comes from the valve looking similar to an open bill of a duck. Extensive details on the design is included. The valve was to be an elliptical shape, with two symmetrical valve leaflets. The original dimensions posed were that it was to be 27 mm on the long side and 25 mm on the short side. These dimensions were later changed and scaled for different stent sizes. However, the ratio of the long side to the short side remained the same. The elliptic valve shape is directed towards better fitting the natural MV annulus, rather than the circular trileaflet valve construct. Also, the two-leaflet valve is a more accurate match to the natural MV when compared to trileaflet valve designs. Preliminary hand drawings of the bileaflet valve can be seen in Appendix A.1.
Provided the design constraints, the design process was conducted using Solidworks™ as the 3-dimensional design software. The originally posed design constraints are as follows:

- Long side measurement of 27 mm.
- Short side measurement of 25 mm.
- Leaflet thickness tapers from 1.2 mm at the base to 0.8 mm at the leaflet edge.
- Completely symmetrical along the leaflet free edge plane.
- The base brim of 1.5 mm outward and 2.2 mm down for suturing to the stent.
- Side towers of protruding 1.5 mm outward, 1.8 mm wide and 1 mm upwards from leaflet free edge for suturing to the stent.

With the addition of the base brim, the total measurements of the bileaflet valve was 30 mm on the long side and 28 mm on the short side. The original bileaflet design was focused on the leaflets being in a closed position with a gap of 0.2 mm between the leaflets to ensure they were two separate leaflets. This is a similar technique used in the trileaflet valve. Due to the trileaflet valve having a semilunar commissure (leaflet contact), it is possible for the leaflet to be functional as the leaflet can be opened to the right position from being closed. The first iteration of the bileaflet valve can be seen in Figure 3.1.
The elliptic shape of the bileaflet valve can be seen in Figure 3.1, along with the base brim and towers that are targeted as spots to suture the valve to the applied stent. This design fulfilled the requirements given, but under evaluation, it was realized that the valve leaflets would not be able to open a sufficient amount to allow for the optimal amount of blood flow. This is due to the leaflet free edge length being too short and not opening fully. It was decided that to create a functional bileaflet valve, the design would have to reflect the open state of the valve. This method differs from trileaflet valve mold techniques. This refers to the trileaflet valves commissure being a semilunar shape, allowing for the leaflet to be in a closed state and able to transition to an open state. The bileaflet valve in its closed state has a straight leaflet free edge, and thus a straight commissure. This restricts the valve leaflets from opening. With these thoughts in mind, the bileaflet valve was redesigned in an open state.

The second iteration of the bileaflet valve would utilize a circular shape along the bottom of the leaflets that would transition to $bump$ contour at the leaflets’ free edge. This $bump$ contour was put into place due to the leaflets free edge needing to have the ability to close properly. The $bump$ contour is what brings the duckbill name to the valve. If the leaflets free edge followed the same
pattern as the base of the leaflets, the leaflets would not have proper contact with each other. The duckbill valve was iterated two times due to issues that arose during the mold making process. Leaflet thickness had to be adjusted, with adjustments to the side tower thickness and upward protrusion. The first iterations of the duckbill valve can be seen in Figure 3.2, while the final version of the duckbill valve design can be seen in Figure 3.3.

Figure 3.2 Isometric render of 1st iteration of duckbill (bileaflet) valve design

Figure 3.3 Isometric render of final duckbill (bileaflet) valve design
As seen in Figure 3.2 and Figure 3.3, slight changes were made to the bileaflet valve design. These changes allowed for better extraction of the leaflets from the molds, along with more material to allow for the valve to be sutured to the stent. The values of these changes can be seen in Table 3.1.

<table>
<thead>
<tr>
<th></th>
<th>Closed Bileaflet Valve Iteration 1</th>
<th>Duckbill (Bileaflet) Valve Iteration 1</th>
<th>Duckbill (Bileaflet) Valve Iteration 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Leaflet Thickness</td>
<td>1.20 mm</td>
<td>1.20 mm</td>
<td>1.59 mm</td>
</tr>
<tr>
<td>Leaflet Free Edge Thickness</td>
<td>0.80 mm</td>
<td>0.78 mm</td>
<td>1.49 mm</td>
</tr>
<tr>
<td>Base Side Tower Thickness</td>
<td>1.80 mm</td>
<td>2.40 mm</td>
<td>2.40 mm</td>
</tr>
<tr>
<td>Leaflet Free Edge Tower Thickness</td>
<td>1.80 mm</td>
<td>1.60 mm</td>
<td>3.00 mm</td>
</tr>
<tr>
<td>Side Tower Upward Protrusion</td>
<td>1.00 mm</td>
<td>2.00 mm</td>
<td>4.00 mm</td>
</tr>
</tbody>
</table>

Table 3.1 Bileaflet Valve Design Changes

As seen in Table 3.1, the final iteration of the duckbill valve has a near-constant leaflet thickness, with a slightly thinner free edge thickness when compared to the leaflet base thickness. The tower thickness at the leaflet free edge increased from 1.60 mm to 3.00 mm, along with protruding an extra 2.00 mm than the previous iteration. This gave more opportunity for the valve to be sutured to the stent, with the option to remove excess material once the valve was secured. A good illustration of the bump contour that gave shape to the duckbill valves leaflet free edge and elliptic base shape can be seen in Figure 3.4, along with side profiles of the valve seen in Figure 3.5.
With the duckbill valve design process complete after multiple iterations and adjustments to better suit performance and mold making ability, the focus was directed towards designing molds to create the valve. The end goal was to create a cryogel prototype of the valve. This meant a 3D printed mold would have to be created to fit inside an aluminum case. This is essential in the cryogel making process that will be described in a later subsection. Multiple mold iterations were conducted until an ideal design was created. The mold design process will be described in subsection 3.2.1.
3.1.2 Human (Bileaflet) Valve

A MV leaflet design was created to closely match the anatomical shape of the native MV. Similar to the previous duckbill (bileaflet) valve, the titled human (bileaflet) valve has two-leaflets. The purpose of this valve design was for it to be used in a computational model to evaluate the stress concentrations on a prosthetic MV induced by existing wrinkles during the closing (systolic) phase. The computational paper can be seen in Appendix Error! Reference source not found.. Additionally, the human valve was fabricated using the novel cryogel material as a proof of concept. The design was not implanted into a TMVR stent, as the purpose was solely for the computational model.

Instead of being symmetrical, the design utilized varied sizes between the two leaflets, like the native MV. The larger leaflet emulates the native anterior MV leaflet, while the shorter emulates the native posterior MV leaflet. The scallops normally seen on the posterior MV leaflet were not incorporated into the design for simplicity. The annulus of the human valve maintains a flat D-shaped orifice and the total dimensions can be seen in Figure 3.6. The total annular length of the human valve was set to 86 mm, while the height of the leaflets are 28 mm and the top plane of the leaflets are located 7.0 mm above the annular plane.

![Figure 3.6 CAD of the human (bileaflet) valve from the ventricular (left) & front (right) view](image-url)
The human valve design utilizes realistic contours to closely match the native MV leaflets. The design was created using multiple contours within varying planes on Solidworks™. The loft function was used to connect each contour to create the final design. The contour of the leaflet free edge proved beneficial for the computational model. Realistic apposition of the leaflets was realized, with additional realistic wrinkles induced. Additional renders of the human valve in an isometric and side view, and ventricular and atrial views can be seen in Figure 3.7 and Figure 3.8, respectively. The mold design will be briefly discussed in section 3.2.2.

![Figure 3.7 Isometric (Left) & side (Right) view of human (bileaflet) valve renders](image)

![Figure 3.8 Ventricular (Left) & atrial (Right) view of human (bileaflet) valve renders](image)

### 3.1.3 Trileaflet Valve

The trileaflet valve design was created to emulate a porcine AV to reduce stresses within the leaflets during the systolic and diastolic phases. As most TMVR devices utilize the trileaflet design
[34], it warranted creating a trileaflet design with the novel cryogel material, and applying it to the TMVR stents designed in the next chapter.

Hyperboloid design of leaflets has been shown to improve the hemodynamic performance of heart valves [163]. A hyperboloid of the revolution was utilized for the trileaflet valve design, and the geometry is characterized by the following equation:

\[

d + d_0 = \frac{m^2}{m^2 - (x^2 + y^2)^{1/2}} = 1 \tag{Eq. 3.4}
\]

Here, x, y, and z are Cartesian coordinates and z is a shift from coordinate z (Figure 3.9(a)). The ratio of ±n/m (asymptote) is in fact an influential factor controlling the amount of gap (g) between two nearby leaflets at the commissure. Given that the proposed design has symmetrical leaflets, the angle between asymptotes is 120°. In this case, a gap (Figure 3.9(a)) was approximated to be 2gsin60°, or:

\[
g = \left[ (n^2 + \frac{R^2}{16})^{0.5} - 0.25 \right] \tag{Eq. 3.5}
\]

Where, R refers to the radius of the valve orifice. To eliminate the gap, the surfaces were replaced by a set of control points defining a smooth approximating surface by repeated linear interpolation [164], which fundamentally leads to the development of Bezier. Bezier surfaces were selected because they only pass through the boundary control points. The other control points in fact adjust the quality of leaflets, because Bezier surfaces are always contained within the convex structure of the control points and never oscillate extensively away from the control points surfaces [165]. By displacing the control points on the free edge and analyzing the new geometry with the finite element procedure, the gap between the two adjacent surfaces was removed and the final geometry was confirmed (Figure 3.9(b)).
Figure 3.9 (a) Design of leaflets using hyperbola. (b) The final design of the trileaflet valve [70]

It can be seen that when comparing Figure 3.9a to Figure 3.9b, the gap between the leaflets was reduced. The elastic nature of the cryogel material would additionally aid in reducing the gap when the design was in the closing phase. Once satisfied with the trileaflet valve geometry, additional valve renders were created. Top and bottom views can be seen in Figure 3.10, while isometric and side views can be seen in Figure 3.11. The natural shape of the trileaflet valve lends itself to being implanted into a TMVR stent due to the side towers created. These towers provide great ability to
suture the design into a stent. The mold design of the trileaflet valve will be discussed in section 3.2.3.

Figure 3.10 Top (Left) & bottom (Right) view of trileaflet valve renders

Figure 3.11 Isometric (Left) & side (Right) view of trileaflet valve renders

3.2 Mold Design

Once leaflet designs were completed, the focus was turned towards creating molds for the fabrication of the three valve designs. The following sections will detail the mold design processes for each design.
3.2.1 Duckbill (Bileaflet) Valve

To be able to fabricate the duckbill (bileaflet) valve design, a mold had to be created. This mold would first be tested by being filled with silicone to provide a proof of concept. Once satisfied with the results, a cryogel prototype would be created using the mold.

3.2.1.1 Valve Calculations

For the cryogel creation process, the 3D printed mold must be inserted into a concealed aluminum box. The aluminum box insert dimensions for the different valve sizes can be seen in Table 3.2.

<table>
<thead>
<tr>
<th>Insert Dimensions</th>
<th>Valve Sizes (radial) Accommodated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Box 1</strong></td>
<td>35.80 x 25.50 x 23.35 mm</td>
</tr>
<tr>
<td><strong>Box 2</strong></td>
<td>43.10 x 43.00 x 32.00 mm</td>
</tr>
</tbody>
</table>

Table 3.2 Aluminum Box Insert Dimensions & Valve Size Accommodation

Valve size accommodated is the conversion of the elliptical base circumference of the duckbill valve to a radial circumference. The valve sizes are stated as radial sizes, even though they are an elliptical circumference. The radial circumference of a stent would be given, and the elliptic duckbill valve would need to sized to fit. The circumference of the valve can be calculated using equation 3.1. Figure 3.12 gives reference to the variables in equation 3.1.

\[
\text{circumference of ellipse} = \pi \left(3(a + b) - \sqrt{3a + b(a + 3b)}\right)
\]

Eq 3.1

![Figure 3.12 Ellipse shape reference for circumference calculation](image)
A key factor in calculating the required respective values of $a$ and $b$ to fit the circumference of the ellipse to a circular stent is the ratio of $a$ and $b$ from the original duckbill valve design. With a long side measurement of 30 mm and short side measurement of 28 mm, values of 15 mm and 14 mm for $a$ and $b$, respectively, are obtained. Solving for the ratio to produce equation 3.2 can be seen below.

$$\frac{a}{b} = \frac{14}{15}$$

$$a = \left(\frac{14}{15}\right)b$$  \hspace{1cm} \text{Eq. 3.2}

By knowing the radius, $r$, of the circular stent provided, the circumference can be calculated by using equation 3.3.

$$\text{circumference of circle} = 2\pi r$$  \hspace{1cm} \text{Eq. 3.3}

Solving equation 3.3, then equating equation 3.3 to equation 3.1 will produce the same circumference values between the ellipse and the circle. By inserting equation 3.2 into the equation 3.1 the value of $b$ can be solved. Once $b$ is solved for, using equation 3.2, $a$ can be solved. Using these equations, the proper elliptic shape can be conserved while scaling the duckbill valve to fit different circular stent sizes.

### 3.2.1.2 First Iteration

Going forward with the accurately scaled duckbill valve sizes, the first iteration of a mold to fabricate silicone and hydrogel valves was created. The first iteration design was targeted at the ability to fit into box 1, along with being comprised of 8 parts to extract the fabricated valve easily. Air holes were applied to the bottom blocks, while excess material holes were applied to the top blocks. These attributes were targeted to ensure the mold was filled with the material, with no air
pockets. Note, the first iteration mold design was used on the first iteration of the duckbill valve. The first iteration mold design can be seen in Figure 3.13.

![Figure 3.13 First iteration duckbill valve mold design isometric view render](image)

As seen in Figure 3.13, the bottom brim of the valve is located in the top blocks, while the entirety of the leaflets and side towers is located in the bottom blocks. When this mold design was put into practice with silicone, the extraction of the leaflets became difficult. The areas where material could leak out (block contact points) became an apparent weakness. The biggest issue was that the leaflets from the first iteration of the duckbill valve were too thin near the leaflets' free edge. Additionally, the side towers were also too thin near the leaflets' free edge. Due to the thinness of the material, the leaflets would tear as they were extracted.

### 3.2.1.3 Second Iteration

With alterations to the new valve design, a second iteration of the mold design was created. This design brought the brim of the valve closer to the surface allowing for the excess material to travel less. Also, the excess material holes were increased and moved away from block contact points. The additional holes were to provide more opportunity for the mold to be completely filled with no air pockets, while the repositioning of the excess material holes was to refrain from having the
excess material created blending with the excess material at the block contact points. The second iteration of the mold design can be seen in Figure 3.14.

Figure 3.14 Second iteration duckbill valve mold design isometric view render

The second iteration of the mold design produced far better results with the silicone mold when compared to the first iteration. The leaflet design changes seemed to produce a more desirable valve. However, the brim of the silicone valve still tore when extracting the valve from the mold. Additionally, the excess material that was created from the block contact points resulted in undesirable bumps along the leaflet, which may cause issues when in use. Because of these issues, a third iteration of the valve mold was created.

3.2.1.4 Third Iteration

The target for the third iteration of the mold design was to reduce the number of parts in the mold but to maintain ease of extracting the valve from the mold. The brim of the valve would not be separated from the main body of the valve. The third iteration of the mold design can be seen in Figure 3.15 and Figure 3.16.
The third iteration of the mold design provided a valve that reduced the amount of excess material created due to the decrease in block contact points. The design utilized three components: the main external body block, the internal body block, and the centering block. The main external body block and the internal body block make up the entirety of the valve mold, while the centering block aids in centering the internal body block. The centering block also allows excess material to flow out, preventing air pockets within the mold. Air holes were again attached to the main external body block, at the lowest point, which was the top of the side towers of the duckbill valve. The
connection between the main external body block and the internal body block consists of a lock and key model. This was targeted to reduce any rotation of the internal body block.

3.2.1.5 Fourth Iteration

Though the third iteration design was close to producing a desirable result, the centering block was not sufficient enough to keep the internal body block centered. The fourth and final iteration of the mold design was aimed at combining the internal body block and the centering block, making a two-piece mold. Additionally, the lock and key model was made more robust, to fully lock the pieces together. The two-piece mold would provide the most efficient means of filling the mold, along with extracting the valve, while maintaining the highest quality for the valve. The fourth iteration of the design mold can be seen in Figure 3.17 and Figure 3.18.

Figure 3.17 Fourth iteration duckbill valve mold design isometric view render
By having two pieces, rather than three, the ability to extract the valve from the mold became easier, along with far less excess material created. The final iteration of the mold design produced desirable results with the silicone model, that the hydrogel prototype could be created. The hydrogel prototype was also a desirable result and will be discussed in later subsections. The lock and key model were adjusted from a single tooth to two teeth. This design created a tighter and more secure fit, that ensured the two pieces of the mold would seat perfectly and not have any play to create a distorted valve. The lock was a diameter of 5 mm, with teeth protruding 1 mm inwards with a width of 1.5 mm. To create this secure fit, there was a tolerance of 0.1 mm applied between the lock and key. The air pinholes were a diameter of 0.5 mm. The more robust lock and key model, along with the air pinholes can be seen in Figure 3.19.
With the final iteration of the mold design created and established, the design was applied to different sized duckbill valves. The design renders shown are for the 23 mm duckbill valve. The design was additionally used for the 25, 30, 31- and 33-mm duckbill valves. The 23 mm and 25 mm duckbill valves were fit into box 1, while the 30 mm, 31 mm and 33 mm duckbill valves were fit into box 2 (dimensions shown in Table 3.2). The difference of boxes used was based on the accommodation of the box size for the duckbill valve size. The same design principle and measurements were constant between the box 1 and box 2 designs. The only difference between the designs was the accommodated valve sizes and external dimensions. The external body and internal body components of the final mold design (23 mm accommodated valve) can be seen in Figure 3.20 and Figure 3.21, respectively.
In Figure 3.21 the excess material holes can be seen. The excess hole diameter was set to match the thickness of the base brim to create the perfect amount of excess material that could easily be removed from the final product. Due to the extensive iterative process in the design of the mold, the finished product has become ideal. Going forward, the mold design will not need to be altered, but rather if the duckbill valve has changes made, the same design principles for the mold can be used. The next step in the design process was to create the silicone model for a proof of concept. This step was intertwined with the mold design process as the mold was tested after each iteration, and when the mold didn’t create a desirable product, the mold would be redesigned to create a new silicon model. Section 3.3.1.1 and 3.3.1.2 details the silicone and cryogel fabrication of the duckbill valve, respectively.

3.2.2 Human (Bileaflet) Valve

The human valve’s mold design was closer to that of the first iteration of the duckbill valve mold design process. The mold utilized multiple layers to extract the complex geometry of the human valve. The design consisted of six parts to fit into box 1 (Table 3.1) that had dimensions of 35.80 x 25.50 x 23.35 mm. The layer heights for the three layers are 9.68 mm for the bottom layer, 5.24
mm for the middle layer and 8.09 mm for the top layer. The three layers were split down the middle of the long side making each side symmetrical for each layer. Renders to aid in visualization of the human valve’s mold design can be seen in Figure 3.22.

Figure 3.22 Human (bileaflet) valve mold design renders

Further iterations of the human valve mold design were not conducted, as the resulting models were satisfactory for a proof of concept. If the human valve design was to be implanted into a TMVR stent and a higher grade of models were needed, further iterations of the mold design would have to be conducted. Molds similar to that of the final iteration of the duckbill valve mold and trileaflet valve mold would be the targeted design.
3.2.3 Trileaflet Valve

The mold for the trileaflet valve was made for a 33 mm diameter valve. The mold was fit into box 2 (Table 3.2) which had dimensions of 43.00 x 43.00 x 32.00 mm. The mold design benefited greatly from the duckbill valve as it emulated a similar design as the final mold iteration, thus, eliminating the need of multiple iterations for the trileaflet valve mold. The top component of the mold is comprised of a 6 mm square block that attaches to the internal shape of the trileaflet design. The bottom component of the mold is comprised of a 26 mm square block that provides the outer shape of the trileaflet design by way of a cavity. Due to the shape of the trileaflet valve leaflets, it was deemed unnecessary to have holes for excess material to flow out of. The shape of the leaflets would create a direction of flow towards the interaction between the internal and external pieces of the mold, and thus refraining from pockets of air to be trapped within the mold. Renders of the trileaflet mold design can be seen in Figure 3.23 and Figure 3.24.

![Figure 3.23 Trileaflet mold design isometric view render](image-url)
Additionally, the trileaflet valve mold does not utilize the lock and key component that was created in the duckbill valve mold iterations. This was due to the satisfactory centering of the external body component in the aluminum box. Further iterations could exploit the lock and key component if centering is of issue. As the resulting models were satisfactory, no further iterations were needed for the trileaflet valve mold.

### 3.3 Fabrication

Fabrication of the leaflet designs would follow the successful design of the molds. The design valves utilized a silicone material to test the feasibility of the molds before moving to the novel cryogel material. The following subsections will detail the fabrication process for both designs.

#### 3.3.1 Duckbill (Bileaflet) Valve

The duckbill valve’s mold design process was intertwined with the silicone fabrication of the design. Poor silicone valve results would be corrected in the mold design process and then evaluated again. After the fourth iteration of the mold design produced a satisfactory silicone model, the design was fabricated utilizing the cryogel material.
3.3.1.1 Silicone

For each iteration of the mold design, a prototype was 3D printed using the Stratsys Mojo 3D printer. The Stratsys Mojo 3D printer uses fused deposition modeling (FDM) technology, printing acrylonitrile butadiene styrene (ABS) thermoplastic material. The Stratsys Mojo also uses SR-30 soluble support to create detailed prototypes. SR-30 is a dissolvable FDM support material that allows for hands-free removal of the material. The silicone material used was a two-part platinum cure silicone rubber from Smooth-On. The mix ratio for the silicone was a 1A:1B by weight or volume. The part A would be initially poured and stirred thoroughly before adding equal parts of part B. The two parts would be stirred thoroughly before being poured into the molds. The molds would be sealed within the aluminum box and allowed to sit and cure for ~24 hours. As the molds weren’t exposed to air, the cure time was increased from the suggested 4 hours to ensure a completed product. The material used can be seen in Figure 6.12 in Appendix C.1.

The first iteration of the mold design, as described above, is an 8-part mold that was aimed at easily extracting the valve model from the mold. The top blocks had the brim of the duckbill valve, while the bottom blocks comprised of the leaflets and side towers of the valve. This design utilized the first iteration of the duckbill valve, which was further iterated and improved. The 3D printed first iteration mold design along with the silicone model created from the mold can be seen in Figure 3.25.
As seen in Figure 3.25 above, the produced silicone model was not a desirable result. The brim of the duckbill valve was not extracted properly due to the mold design and silicone material, along with the leaflets being too thin for a quality prototype. The excess material created from the mold can also be seen on the leaflets and side towers due to the 8-part mold design. Due to these undesirable results, the second iteration of the mold design was created, utilizing the second iteration of the duckbill valve design. The second iteration of the design mold had similar attributes when compared to the first iteration. The main difference was the top blocks were reduced in size, allowing for less travel for the excess material created. The 3D printed second iteration of the design mold along with the produced silicone model can be seen in Figure 3.26.

The silicone model did improve from the first iteration to the second, but the excess material produced that can be seen on the model in Figure 3.26 was not sufficient. Additionally, the bottom
brim of the duckbill valve was also not created and extracted properly due to the design and material. The design was changed from an 8-part mold to a 3-part mold, to reduce the amount of excess material created. The third iteration of the design mold and its created silicone model can be seen in Figure 3.27.

Figure 3.27 Third iteration mold design & silicone model

The third iteration of the design mold created a more desirable silicone model. The leaflets had continuity without excess material ridges, along with no excess material on the side towers of the valve. A brim was semi-created but was torn during extraction. Furthermore, the internal body was not able to maintain a central location within the exterior body. The fourth and final iteration of the design mold would improve upon the third iteration by changing from a 3-part mold to a simplistic 2-part mold. The lock and key components were made more robust to ensure the part would seat exactly where it should. The silicone model extracted from the mold produced a very
desirable prototype. The fourth and final iteration of the design mold along with the silicone model created can be seen in Figure 3.28.

As seen in Figure 3.28 above, the silicone model created is by far the best quality model out of all the iterations. The brim of the valve was torn during extraction, which was not ideal. However, it was determined that the hydrogel material to be used for the duckbill valve would have higher strength properties and would be able to handle the extraction process better than the silicone models. With this knowledge along with a quality silicone model, the next steps of using the final design mold for the fabrication of the hydrogel model of the duckbill valve could be conducted. A comparison of iterations one through four of the design mold and silicone models can be seen in Figure 3.29.
Figure 3.29 Iterations 1 through 4 of mold design with produced silicone models

3.3.1.2 PVA-BC Cryogel

Once a quality silicone model was created from the final iteration of the mold design, the attention was directed towards fabricating a model utilizing the novel cryogel material developed in the Heart Valve Performance Laboratory (HVPL) at UBC’s Okanagan campus. The cryogel material is a polyvinyl alcohol (PVA) cryogel reinforced by bacterial cellulose (BC) natural nanofibers. The PVA-BC cryogel valve provides a one-piece fabrication with excellent biocompatible properties [70]. The PVA-BC cryogel used had larger viscous properties when compared to silicone, which aided in providing better model results by discouraging leakage when filling the mold.

The cryogel applied was PVA, 99+% (Sigma-Aldrich) hydrolyzed, which has a molecular weight of 146,000–186,000. A suspension of 0.877 wt% BC in distilled water was implemented. The bacterium used for producing this suspension was Acetobacter xylinum which took place in shake flasks by a fermentation process [166]. The PVA solution was transferred to the BC suspension to make a 15% PVA with 0.5% BC hybrid solution by weight fraction. The PVA-BC solution was transferred into the duckbill (bileaflet) final design mold that was fit into an aluminum box and sealed. Next, the aluminum box was placed in a thermal unit that acts as a heated/refrigerated...
circulator (15L Heating Bath Circulator Model SD15H170-A11B). The thermal unit was filled with an antifreeze methanol-based fluid that was rated to handle up to -40°C [167]. The sample was cycled between 20°C and -20°C at 0.1°C/min. The molds were cycled in the thermal unit using the freeze-thaw process. The freeze-thaw process creates physical cross-links that provide mechanical properties similar to that of soft biological tissue, while also not leaving any toxic residual amounts of chemical agents that may be left behind with other PVA solidification methods [166], [168]. Previous studies determined that four cycles were enough to achieve maximum anisotropy of the PVA-BC cryogel [70]. Once the freeze-thaw process was complete, the aluminum box was removed from the bath, and the PVA-BC cryogel duckbill valve was extracted. Excess material was trimmed from the valve before the valve was sutured to a valve stent. An extracted sample PVA-BC cryogel duckbill valve can be seen in Figure 3.30.

![Figure 3.30 Multiple views of PVA-BC cryogel duckbill (bileaflet) valve](image)

As stated, the PVA-BC cryogel valve offers excellent biocompatible properties along with a one-piece fabrication. The one-piece fabrication allows the valve to not be provisionally compacted, like those of a bioprosthetic valve, when crimped down to a small profile. This is important for transcatheter valves that need to be crimped to a small profile to fit into a catheter.
Once a quality PVA-BC cryogel duckbill valve model was created, the valve was sutured to a simple circular stent to evaluate the kinematics of the valve leaflets. The kinematics of the valve leaflets is discussed in chapter 5. The PVA-BC cryogel duckbill valve sutured into the simple stent can be seen in Figure 3.31.

![Figure 3.31 Multiple views of PVA-BC cryogel duckbill (bileaflet) valve in simple stent](image)

### 3.3.2 Human (Bileaflet) Valve

The fabrication of the human valve was not essential for its evaluation, as it was created with a main purpose for a computational model. A silicone and cryogel model were created for the sake of future research. The following sections will detail the fabrication of the silicone and cryogel models.

#### 3.3.2.1 Silicone

The human valve mold was 3D printed using the Stratsys Mojo 3D printer, printing the mold in an ABS thermoplastic material using its FDM technology. The SR-30 soluble support allowed for the difficult contours of the mold cavity to be realized. The same silicone was used as the duckbill valve, which was the two-part platinum cure silicone rubber from Smooth-On. Once the silicone was prepped to be poured into the mold, the bottom pieces of the human valve mold were inserted into box 1 (Table 3.2) to begin the pouring process. The silicone was poured into the first layer to
fill the bottom of the cavity. Then, the middle layer of the mold was inserted into the box and filled with the silicone with additional silicone added to ensure the top layer would be sufficiently filled. Once satisfied with the amount of silicone, the final layer was added to the box, and squeezed into position allowing for the excess silicone material to be pushed out of the added holes for removal of any existing air pockets. The excess silicone material was collected, and the aluminum box was sealed to allow for the model to cure. The model was cured for ~24 hours to ensure for a solid structure. Once satisfied with the amount of curing time, the model was extracted from the mold. The 3D printed human valve mold along with the silicone model extracted can be seen in Figure 3.32.

![Figure 3.32 Human (bileaflet) valve mold design and silicone model](image)

The silicone model was extracted delicately, and all excess material created from the gaps between each block was removed for a clean model. The silicone material provided enough rigidity within the system to allow for the design to stand freely on its own. If the design was to be implanted into a TMVR stent, the mold would perhaps be iterated to reduce the imperfections created from the multi-block mold design. For the scope of this design, further iterations were not needed. The resulting silicone model was satisfactory to continue towards fabricating utilizing the PVA-BC cryogel material. That fabrication is detailed in the next section (subsection 3.3.2.2).
3.3.2.2 PVA-BC Cryogel

The next and final step in the fabrication process for the human valve was to fabricate the design using the PVA-BC cryogel material developed in the HVPL. Detailed descriptions of the PVA-BC cryogel material along with the cycling process can be seen in subsection 3.3.1.2. The same PVA-BC cryogel material was used for the human valve. Similar to the fabrication of the human valve utilizing the silicone, the bottom layer of the human valve mold was inserted into box 1 (Table 3.2). The bottom cavity was filled with the liquid state of the PVA-BC cryogel material. The middle layer of the mold was then inserted and filled. Additional material was added to allow for the top component of the mold to be filled. The top layer of the mold was inserted, and pressure was applied to allow for the excess PVA-BC cryogel material to flow out of the excess material holes and discourage any air pockets within the cavity. The excess material was collected, the mold was wiped clean and the aluminum box was sealed. The aluminum box was placed within the thermal unit which was filled with antifreeze methanol-based fluid. The sample was cycled between 20°C and -20°C at 0.1°C/min, which utilizes the freeze-thaw process that creates the physical cross-links within the material. Once the freeze-thaw process was completed, the aluminum box was extracted from the thermal unit, and the PVA-BC cryogel model of the human valve was removed. Excess material was trimmed from the PVA-BC model, and the model was submerged in water to allow for greater visualization. Due to the limited thickness of the human valve leaflets, it was difficult to visualize the design when not submerged. Photos of the submerged PVA-BC human valve model can be seen in Figure 3.33.
The PVA-BC cryogel human valve model extracted was satisfactory for the proof of concept. If the design was to be sutured into a TMVR stent, the leaflet and mold design would have to be altered. The addition of a brim would be ideal to allow for the model to be sutured sufficiently. Additionally, increasing the leaflet thickness may be beneficial, while also scaling up the design. The mold should take on a similar design to that of the final duckbill valve mold iteration. This design would create less excess material attached to the final model. Because the design was meant for a computational model, these changes were not made, but will be included as recommendations for the future work section.

3.3.3 **Trileaflet Valve**

The trileaflet valve was fabricated with the intent to evaluate the feasibility of implanting into a TMVR stent. Additionally, as most TMVR stent designs utilize a trileaflet configuration, creating a cryogel model was essential to further evaluate the cryogel material. The following sections will detail the fabrication of the silicone and cryogel models.

3.3.3.1 **Silicone**

Like the duckbill valve and human valve molds, the trileaflet mold was 3D printed using the Stratsys Mojo 3D printer that extrudes ABS thermoplastic material using FDM technology. The
support material used was SR-30 soluble support allowing for detailed contours for the mold. The silicone used was the same as for the previous valves, the silicone rubber offered by Smooth-On. The silicone material was mixed and then added to the bottom of the trileaflet valve mold that was seated within the aluminum box. The bottom component was filled enough to allow for excess material to spill out the sides of the mold once the top component was pushed into place. Excess material was collected, and the aluminum box was sealed. The trileaflet mold was then set aside and allowed to sit for ~24 hours to ensure the entire structure was fully cured. The closed 3D printed trileaflet valve mold along with the silicone model and separate components can be seen in Figure 3.34.

![Figure 3.34 Trileaflet valve mold design and silicone model](image)

The silicone model produced from the trileaflet mold was satisfactory to continue towards fabrication using the cryogel material. The model had the leaflet free edges fused together, so simple cutting had to be done to allow for the free motion of the leaflets. Apposition of the leaflets
was ideal for cardiovascular testing, while the structure held itself up due to the rigidity of the design and leaflet thickness. The next steps were to fabricate the design using the cryogel material.

**3.3.3.2 PVA-BC Cryogel**

The silicone model produced for the trileaflet valve was ideal, and focus was turned towards fabricating the design using the PVA-BC cryogel material developed at the HVPL. Detailed description of the PVA-BC cryogel material along with the cycling process can be seen in subsection 3.3.1.2. The bottom component of the trileaflet valve mold was placed within box 2 (Table 3.2). The PVA-BC cryogel material was poured into the bottom cavity, allowing for a sufficient amount to fill the total cavity and allowing for excess material to flow out once the top component was inserted. The top component was inserted, and pressure was applied to allow the excess material to flow out. The excess material was collected, and the aluminum box was sealed. The aluminum box was inserted into the thermal unit filled with antifreeze methanol-based fluid. The sample was cycled between 20°C and -20°C at 0.1°C/min using the freeze-thaw process to create the physical cross-links in the material. Once the freeze-thaw process was completed, the aluminum box was removed from the thermal unit, and the PVA-BC cryogel trileaflet valve model was extracted from the aluminum box. Excess material was trimmed from the model, and the free edges of the leaflets were sliced to create free motion of the leaflets. The PVA-BC cryogel trileaflet valve model can be seen in Figure 3.35.
The PVA-BC cryogel trileaflet valve model extracted from the mold was perfectly fabricated and was sufficient to suture into a TMVR stent. The model itself had good rigidity within the material and could stand on its own. Leaflet thickness was also ideal, as the model did not feel fragile and was resistive to tearing. The PVA-BC cryogel trileaflet valve model was sutured into a simple stent to display the feasibility of the design. The model in a simple stent can be seen in Figure 3.36 and Figure 3.37.
Figure 3.37 Bottom (left) & isometric (right) view of PVA-BC cryogel trileaflet valve in simple stent

The PVA-BC cryogel trileaflet valve model sutured into the simple stent better displays the gap created between the leaflets. The radial forces from the sutures pulling the valve towards the inner diameter of the stent are what cause this realistic gap formation. Under performance, the backward pressures towards the closed leaflets would create a stretching of the leaflets to reduce the gap even more. This was a good showcase of the feasibility of this trileaflet design and the quality of the PVA-BC cryogel material and lends itself well to further research and utilization for different TMVR stents that are designed.
Chapter 4: Stent Design

After the design and fabrication process for the valve leaflets, the focus was directed towards the design of transcatheter stents. As stated in chapter two, there are design criteria and challenges to overcome when it comes to TMVR designs. The design of the stent is crucial for the success of the device. The design criteria described in chapter 2.1 is:

- **The design must be able to be crimped.** For the catheter-based insertion, it is crucial to have a design that can conform to a low profile to aid in the ease of insertion for the surgeons. The lower the profile, the more ideal.

- **The design must have an anchoring system.** The development of an anchoring system that can withstand the dynamic pressures felt within the heart during systolic and diastolic pressures is important. The valve must stay in place after the final placement, without any migration, for optimal performance.

- **The design must not have Left Ventricular Outflow Tract (LVOT) obstruction.** Minimizing obstruction and allowing for the maximum amount of blood flow through the left ventricular outflow tract is vital for the patients’ health.

- **Reduction of stagnation flow.** Optimizing proper blood flow washout to prevent stagnation flow and resulting thrombosis (blood clot) initiation is imperative to design success.

- **Maximize mitral annulus sealing.** Improved sealing around the mitral annulus from proper conformation prevents leakage and resultant turbulent blood flow which can cause thrombosis initiation.
• **Maximize mitral orifice shape.** Closely matching the natural MV orifice shape will allow for optimal valve performance like a healthy native MV.

• **Made for established TMVR surgical approaches.** The design should be made to utilize surgical methods and approaches that are familiar to the surgeons performing the transcatheter procedures.

• **Readjustment during intervention.** A design that can be fully retracted and readjusted during surgery will aid the surgeons and allow for the ideal placement of the valve.

With these design criteria and challenges outlined, stent designs can be created with the target to achieve this criterion. Angeleno Medical LLC has worked closely with the HVPL in the design and fabrication of TMVR stents. The original Angeleno Medical stent will be described, along with alterations that were made to the design. Additionally, complete novel designs will be described.

### 4.1 Angeleno Medical Stent

This section will detail the original Angeleno Medical stent, along with two alternative designs based on the original stent design. The alternative stent designs focus on release mechanisms for the original Angeleno stent design.

#### 4.1.1 Original

The original Angeleno Medical stent is composed of several parts. Those parts include: a deployable frame; a mesh band that forms the interface between the device and valvular apparatus; a deployable hooking mechanism that allows the prosthetic to securely attach to the valvular apparatus and subvalvular apparatus; and a retrieval hook allowing for the repositioning and removal of the prosthetic valve once it has been initially positioned [169]. There are several
embodiments of each component written in the U.S. provisional patent (WO/2018/112276). Figure 4.1 showcases one embodiment of the Angeleno Medical stent along with a side view.

![Figure 4.1 Multiple views of Angeleno Medical stent (Reprinted from [169] with permission from UCLA Technical Development Groups)](image)

The deployable frame is comprised of a plurality of struts that connect proximally to a proximal collar and distally to a distal collar that is aligned with the central axis of the frame. The deployable frame is comprised of a non-ferromagnetic flexible material, such as a shape-memory material like nitinol. The deployable frame gives the structure to the overall apparatus. Additionally, the deployable frame is the main distorting component when reducing the apparatus to a small profile. The mesh band is attached to the deployable frame by exploiting a seam along each strut. The mesh band may be comprised of a plurality of fibers or a plurality of leaflet struts that are focused on supporting the formation and coaptation of the leaflets, along with flexible tethers that extend from the leaflet struts that are adjoined to the frame struts [169]. The mesh band is employed to provide an interface between the prosthetic and the valvular apparatus. This interface is intended
to discourage PVL. As seen in Figure 4.1, denoted as 400 and 416, anchoring hooks are a component of the stent to secure the prosthetic to the valvular apparatus. The anchoring hooks may be attached to the deployable frame, embedded in the frames outside of the mesh band or embedded within the mesh band. The anchoring hooks are aimed at fixating the prosthetic valve to the valvular and subvalvular apparatus. The retrieval hook is attached to the deployable frame by way of the proximal collar. The retrieval hook is rigid to allow for retrieval or readjustment of the prosthetic valve. The material of the retrieval hook will emulate the deployable frame, as a non-ferromagnetic material. A close-up image of the retrieval hook can be seen in Figure 4.2.

![Figure 4.2 Hook view of Angeleno Medical stent (Reprinted from [169] with permission from UCLA Technical Development Groups)](image)

The prosthetic described is targeted towards implantation via a catheter, and to do so, the ability to be crimped to a small profile is essential. The curvature of the struts allows for the prosthetic to deform into a small profile. The memory shape alloy material is also essential in allowing for this deformation to a small profile. A partial deployment illustration of the prosthetic can be seen in Figure 4.3. Note that this is a simple illustration that does not include the mesh band, anchoring hooks, or leaflets.
The Angeleno Medical stent offers design components that are absent from many of the current designs in clinical and preclinical trials. For example, the prosthetic allows for the re-capturability of the device, even after full release. Also, the retrieval hook is an essential and valuable component of the apparatus. Further studies and iterations of the above design are being conducted to create an optimal TMVR system.

### 4.1.2 Flower Release Mechanism

The flower release mechanism developed for the Angeleno Medical stent is targeted for the ability to utilize Angeleno Medical’s novel hook and deployable frame apparatus that allows for readjustment of the stent when it is in position during implantation, but to also be able to release the stent and remove the deployable frame apparatus used. To achieve this, the deployable frame apparatus was reduced to a one-sided approach to allow for the possible release of the apparatus. The mechanism is targeted to be set up for both anterograde and retrograde release. The signature hook was kept on the stent to allow for the readjustment of the valve before the final release. The isometric view of the rendered mechanism and stent can be seen in Figure 4.4, which showcases the signature hook, along with the mechanism’s components. The original hand drawing of this design can be seen in Appendix A.2.
The whole stent and mechanism consists of five parts: the valve stent that anchors the valve to the MV annulus using radial forces and the structure on which the valve leaflets are sutured; the deployable frame apparatus which allows for the readjustment and control of the whole system; the four thin wires that are directed towards the center, allowing for the stent to be fully captured by the apparatus; the center pin that allows for rigidity for the release mechanism; the flower release wire that sits inside the release pin, and protrudes out while also curling around the wire loops to provide a fully closed system that aids in the capturing of the apparatus. For denotation, the end with Angeleno Medical’s novel hook will be titled the hook end, and the end with the wires will be called the wire end. The wire end and side view of the device can be seen in Figure 4.5.
From Figure 4.5 it can be seen that the four wires are separate pieces from the deployable frame apparatus. The wires have butt ends to ensure they do not slip through the holes at the end of the deployable frame apparatus. Another example of the four wires being a part of the deployable frame apparatus can be seen in the following section (subsection 4.1.3). Both are suitable and interchangeable designs for their needs. The wires have the ability to deform and be crimped to a small profile without any plastic deformation which proves to be essential as they are necessary to hold the whole system together. The device's most important component is the flower release wire which holds the four wires at the radial center via the loops at the ends of the wire. The ideology is to be able to pull the flower release wire at the hook end while anchoring to the release pin. Once the flower release wire is pulled, the wire end is meant to fold towards the radial center, thus creating a straightened wire. Once straightened and pulled, the flower release wire is pulled through the four-wire loops, releasing the wires from constraint. Once the four wires are released from constraint, they will be freely moving, allowing for the deployable frame apparatus to now be able to be released from the valve stent. The hopes are that the deployable frame apparatus will slide slowly, without adjusting the position of the valve stent, and be able to be re-sheathed into
the sheath that the valve was delivered in. The flower release mechanism end can be seen in Figure 4.6.

![Figure 4.6 flower release mechanism non-sectioned (Left) & sectioned (Right) view render](image)

This design is meant to mitigate the limitations of the original Angeleno Medical stent, which is the inability to remove the deployable frame apparatus. By leaving this apparatus in position in the patient’s heart, complications may possibly occur with high blood cell shear stresses induced from the apparatus body impeding the central blood flow. Also, stagnation flow points may be created from this apparatus body, which can also cause thrombotic complications. The focus was put into being able to utilize the novel hook and deployable frame apparatus to aid in surgical implantation, while also having the ability to remove the apparatus to improve hemodynamics and deter complications.

### 4.1.3 Candy Cane Release Mechanism

The candy cane release mechanism developed for the Angeleno Medical stent is also targeted to utilize their novel deployable frame apparatus that provides the surgeon with the ability to
maneuver and readjust the stent when it is in position during implantation. This design, much like the flower release mechanism, is focused on the ability to release the stent and remove the deployable frame apparatus. This is another adaptation for a release mechanism for the deployable frame apparatus. To achieve a release of the deployable frame apparatus, the apparatus was reduced to a one-sided approach. This design is set up to be used for anterograde and retrograde release. The signature hook on Angeleno Medical’s stent was removed and replaced with a simplistic, yet sophisticated, twist and pull mechanism. Readjustment of the stent can still be done by the handling of the central removal pin. The isometric render of the candy cane release mechanism rendition of the Angeleno Medical stent can be seen in Figure 4.7, which displays the stent with all its components. Original hand drawings of this design can be seen in Appendix A.2.

Figure 4.7 Isometric render of candy cane release mechanism stent

The candy cane release mechanism boasts a different kind of release mechanism, along with removing the Angeleno Medical’s novel hook. The hook can be added to this design if needed and desired. Control of the stent is done by handling the central pin which is also the main component of the release mechanism. The whole design includes only three components; the adapted deployable frame apparatus, the central pin, and the valve leaflet stent. For reference, the bottom
of the isometric render of Figure 4.7 will be named the wire side, while the top will be named the mechanism side. The deployable frame apparatus and the central pin are the two components that work together to provide rigidity for control of the whole system, along with providing the ability to release the valve leaflet stent. The wires that hold the stent together on the wire side are attached to the deployable frame apparatus as one seamless piece. This discourages any complications with these wires when removing the deployable frame apparatus. A full view of the wires can be seen in Figure 4.9. The mechanism and wire views can be seen in Figure 4.8.

Figure 4.8 Left: Mechanism view render. Right: Wire view render.

Figure 4.9 Side view render of candy cane mechanism stent

The main selling point for the candy cane mechanism design is the release mechanism itself. It features a wire that follows along the hollow center of the central pin. On the wire side, this wire
is guided and attached to the candy cane curved end. When this wire is pulled from the mechanism side, it elastically deforms the candy cane curved end towards being straight. This is the first step in the release process. The candy cane curved end can be seen in Figure 4.10 for reference.

![Figure 4.10 Candy cane release mechanism non-sectioned (Left) & sectioned (Right) view render](image)

The second step of the release process has to do with the mechanism side. In the central pin, there are L shaped notches along the outer diameter. These notches are designed to fit the block extrudes from the deployable frame apparatus. The block extrudes are on the inner diameter of the central ring of the deployable frame apparatus. This allows for control of the whole stent as a rigid object. When the central pin is twisted in a counter-clockwise direction, the block extrudes align with the long side of the L-shaped notches from the central pin. This allows the central pin to be slid back a sufficient distance that allows for the now straightened candy cane curved end to be pulled through the wire loops, and thus releasing the apparatus from the stent. The deployable frame apparatus and central pin are then slowly pulled away from the valve stent, leaving the stent in its
desired location and allowing for the removal of the other components. The deployable frame apparatus and central pin can then be re-sheathed and removed from the patient. The mechanism side can be seen in Figure 4.11 for reference.

The candy cane release mechanism adaptation for Angeleno Medical’s stent was developed to showcase a means of removing the outer stent from the design, while also maintaining the benefits from their original design. This design provides a more complex release mechanism than the flower release mechanism described above but has a more robust means of release. Design components from each design can be interchanged to provide the most optimal stent design.
4.2 Novel Designs

This section will detail the novel TMVR stent designs created. Those include a simple TMVR stent design, and a second novel D-shaped stent designed to better conform to the native MV annulus. The following subsections will describe each design in detail.

4.2.1 Simple Stent

The following stent is titled the simple stent, as it has simplistic characteristics to the design. It consists of a circular apparatus to fit the MV annulus, with arms that create symmetrical atrial and ventricular flanges. The target of the simple stent was to create a stent that can distort to a low profile which is achieved through a symmetrical circular design. The isometric renders of the fully expanded simple stent along with the fully crimped simple stent can be seen in Figure 4.12.

![Figure 4.12 Simple stent open (left) & closed (right) isometric render](image)

Though the atrial and ventricular flanges are symmetrical, the flange would distort to the shape of the subannular apparatus and atrial apparatus to conform and seal. The whole device would be wrapped in Dacron cloth to allow for sealing of the device to discourage PVL. As stated above, the focus of the simple stent was to distort to a low profile. A standard diameter value of 40 mm was applied to the stent when it was fully expanded, with the ability to be crimped down to a
diameter of 4 mm. Note, it is apparent that the system would include leaflets, which would make it difficult to crimp down to such a low profile. The crimped diameter of 4 mm is merely a showcase of its ability to crimp to small diameters. In practice with the full system including leaflets, the diameter would be greater than 4 mm. The open diameter and crimped diameter can be seen in Figure 4.13.

![Diagram of simple stent open (left) & closed (right) top view (with diameter)](Image)

Figure 4.13 Simple stent open (left) & closed (right) top view (with diameter) render

The total height of the simple stent when fully open is 22.03 mm, while the height of the crimped simple stent is 26.19 mm. The height change is due to the deformation of the stent, along with the straightening of the atrial and ventricular flanges. The side view profiles of the simple stent in its opened and closed state can be seen in Figure 4.14. Note, Figure 4.14 does not have the open and closed views to scale, but rather is focused on showcasing the flanges in their open and closed states.
When comparing the simple stent design to the design criteria outlined at the start of this chapter, it does not meet many of the requirements. The design is able to be crimped, as that was the main focus of the design. The design does have symmetrical atrial and ventricular flanges for anchoring of the device. LVOT obstruction may be an issue with a device that does not fully conform to the natural MV annulus, along with being a large apparatus. This device may benefit from the LAMPOON procedure, or by creating an adjustment to the ventricular flange, to allow for a larger LVOT. It is difficult to evaluate the possibility of any stagnant areas on the valve which could lead to thrombosis initiation. Computational studies may bring more light to this criterion. The device does not match the natural MV annulus shape, so sealing and PVL may be of issue. Oversizing of the valve may be a solution but could also produce negative repercussions. The device does have a large orifice area to allow for blood through the valve. The device can be used for all TMVR surgical approaches, as it does not depend on the direction the device is delivered. Finally, it is possible to be able to re-sheath the device when it is semi deployed, but after full deployment, it would be difficult to recapture. Additional components could be added to the design to allow for re-capturability.
This system was good practice in getting acquainted with equations within Solidworks™ to create a device that can be crimped by changing variables. Additionally, practice with simple stent design proved to be very beneficial leading into more complex designs, like the novel sun valve stent that is detailed in the following section (subsection 4.2.2).

4.2.2 Sun Valve Stent

The sun valve stent gets its name from the shape the atrial flanges create when looking at the device from an axial view. The device consists of atrial flanges, posterior and anterior leaflet capture hooks, ventricular anchors and a D-shaped stent shape to conform to the native MV annulus. The focus of the sun valve stent was to create a shape that better conforms to the native MV annulus, while also creating a more complex anchoring system. The isometric view of the sun valve stent render can be seen in Figure 4.15.

![Figure 4.15 Sun valve stent isometric render](image)

The sun valve stent would be encompassed by a biocompatible cloth, Dacron, for example, to prevent PVL. The flanges would be encased in Dacron, along with the leaflet capturing hooks and ventricular anchors. The atrial flange is connected to the stent via every third diamond, allowing for the ability to conform down to a smaller profile when being crimped. Additionally, the stent is
symmetrical along the posterior-anterior axis. The axial view of the sun valve stent render can be seen in Figure 4.16.

The namesake for the sun valve stent comes from the atrial flange that can be seen from the axial view displayed in Figure 4.16. The D-shape of the stent allows for the system to better conform and fit the natural MV annulus, deterring from PVL. The D-shape also allows for the stent to be of a smaller size, refraining from needing to oversize the system to prevent PVL. The sun valve stent can utilize any valve leaflet style, though valve leaflets that are more oval than circular would fit better to the sun valve stent utilizing more of the leaflet space. The duckbill (bileaflet) valve detailed in Chapter 3 would fit well within the sun valve stent. Additional renders of the sun valve stent with the duckbill valve leaflets attached can be seen in Appendix A.3.

The atrial flange is not consistent when it comes to the distance it protrudes from the stent in the axial view. This is created from offsetting the D-shape by 5 mm and by 10 mm and creating a smooth transition from the 5 mm offset on the anterior leaflet side, to the 10 mm offset on the posterior leaflet side. This creates a differing angle for the atrial flange, with hopes to fit the atrial
wall better than a constant angled flange would. Better illustrations of the atrial flange angle, along with the wide and short side views of the sun valve stent render can be seen in Figure 4.17.

The short side view (right) of the sun valve stent render displays the change in angle for the atrial flange from the anterior side to the posterior side. The flange raises up from the D-shaped stent by 5 mm. For the atrial flange, the angle on the anterior side is calculated to be 45°, and the angle on the posterior side is calculated to be 26.56°.

The short side view in figure 4.17 displays both the anterior and posterior leaflet capturing hooks. The leaflet capturing hooks are created using a continuous piece that shapes into making a hook. The angle of the hooks can be altered depending on the clearance needed to capture the anterior and posterior leaflets. The leaflet capturing hooks also act as a secondary anchor, aiding in keeping the sun valve stent from shifting from systolic pressures. Further testing would have to be conducted to evaluate how the leaflet capturing hooks and the overall body of the sun valve stent effect the LVOT gradient, and if the device causes LVOT obstruction. The ventricular anchors can be seen in the wide side view in Figure 4.17, as they protrude a distance of 5 mm from the side of the sun valve stent. The ventricular anchors also extended 1.25 mm in the axial direction. The ventricular anchors, similar to the leaflet capturing hooks, are one continuous piece that shapes to making an anchor shape. The ventricular anchor is meant to prevent shifting of the sun valve stent.
under systolic pressures, as it is tasked with being the primary anchoring system for the device, while the leaflet capturing hooks act as secondary anchoring. Close-up renders of the leaflet capturing hook and ventricular anchor can be seen in Appendix A.4.

When comparing the sun valve stent to the design criteria outlined, the design does well in adhering. The sun valve stent is designed to be able to conform to a low profile to fit into a sheath and be delivered via a catheter to the MV. The design has primary and secondary ventricular anchoring, while additionally having an atrial flange that is aimed to fit properly to the atrial wall. Further evaluation needs to be conducted to determine if LVOT obstruction is of an issue with this design. If there are high LVOT gradients, alterations can be made to allow for proper blood flow through the LVOT. Additionally, evaluation on determining possible areas of stagnant flow would have to be conducted, and alterations made to decrease any areas where thrombosis initiation occurs. As the sun valve stent takes a D-shape, the device is aimed at better conforming to the natural MV annulus, and thus aimed at preventing PVL along with maximizing the MV orifice shape. The device can utilize all surgical TMVR approaches, as it does not rely on the direction of implantation. The device can be readjusted during partial deployment, though it is unable to be recaptured after full deployment. Further design components could be added to provide the ability to recapture the device after full deployment.
Chapter 5: Heart Simulator

The next step in the transcatheter heart valve design process is to be able to see how the designed leaflets function. As costs of heart simulators that meet ISO requirements are very high, a means of being able to evaluate the kinematics of the leaflets in a cost-effective manner was important for the design process. The challenge was posed to pressurize the valve to evaluate its kinematics to be able to streamline the design and prototype manufacturing process. The design was to utilize a two-valve apparatus, similar to that of a frog’s heart. A pump would be applied to produce a pulsatile flow, while a balloon would handle the volumetric changes. A design schematic can be seen in Figure 5.1.

![Figure 5.1 Heart simulator original design schematic](image)

As seen in Figure 5.1, the design is to have both an AV and an MV to be under evaluation. This is aimed at creating a realistic environment simulating the left side of the heart. The pump was to perform pulsatile strokes to simulate the main squeezing of the heart while the balloon is meant to handle the volume and pressure changes within the system. The design uses water to simulate blood flow and provide good visualization of the valves. With these design attributes in mind, a
heart simulator was designed and fabricated. Two generations of the HVPL Miniature Heart Simulator were created and will be described in the following sections.

5.1 First Generation

The first-generation design for the heart simulator, titled the HVPL Miniature Heart Simulator 1.0, was focused on creating a modular device that can come apart in multiple pieces, along with the option of further expansion by adding additional parts. Viewing windows on the device was key to allow for the visualization of the valves during the performance. The pump had to be oriented so that it would not impede the ability to see the valves when the system was in use. The device had to be cost-effective, so the ability to 3D print all parts was important. The first-generation heart simulator isometric and exploded views can be seen in Figure 5.2.

![Isometric view + exploded view of HVPL miniature heart simulator 1.0 render](image)

**Figure 5.2 Isometric view + exploded view of HVPL miniature heart simulator 1.0 render**

5.1.1 Design & Fabrication

These subsections will describe each component with its design attributes, along with how each component was fabricated. All the parts printed using the Prusa MK3 3D printer were printed using...
PLA at 30% gyroid infill, with 4-layer walls. The parts printed on the Stratsys MOJO used ABS, which create a solid part.

5.1.1.1 Center Box

The center box is the central piece of the HVPL Miniature Heart Simulator 1.0. All the additional components attach to the center box. Seating for gaskets was created to allow for sealing at attachment points to prevent leakage of the device. The fabrication of the gaskets will be detailed in section 5.1.1.5. The seating for the gaskets can be seen in Figure 5.3, along with the overall isometric view and the annulus attachment face of the center box. The goal was to produce a box that allows the circulation of water to facilitate the opening and closing of the heart valves.

Figure 5.3 Isometric and annulus attachment view of center box render

Figure 5.3 displays all the viewing windows that are a component of the center box. The viewing windows were put in place to allow for proper lighting to aid in observing the valves. Additionally, flanges were created for attachment to the other components. The annulus attachment flange allows for 4 bolts to anchor the component to the center box, while the balloon and pump attachment parts each has 8 bolts to attach to the center box. All bolts used were M8x35mm bolts, which are designed for 9 mm holes. The interior of the center box allows for circulation of water
flow, encouraging the flow through the attached valves. Due to printer size constraints, the center box was separated into multiple components to be able to print the device. The balloon and pump attachment flanges were printed with PLA using a Prusa MK3 3D printer, while the rest of the body was printed using ABS on a Stratsys MOJO 3D printer.

5.1.1.2 Annulus Attachment

The annulus attachment slides into the center box from the side, which is fastened using M8x35mm bolts and then sealed by way of the gasket, which is seated into the center box. The annulus attachment has a realistic MV annulus, created from real MRI scans, for the evaluation of catheter-based valves, while also having an attachment site for mechanical AV. The annulus attachment allows for the proper function of the heart valves, giving the system two valves. Isometric and side views can be seen in Figure 5.4.

![Figure 5.4 Isometric and side view of annulus attachment render](image)

A mechanical heart valve gasket was created to allow for proper sealing around the valve, while also fitting the mechanical heart valve into the annulus attachment. This allows for the freedom to create individualized gaskets for multiple different mechanical heart valve designs and sizes. The annulus attachment can be adjusted and reprinted to support multiple catheter-based valves or
multiple mechanical valves. Multiple annulus attachments can be printed and quickly switched out for any situation that is preferred. The annulus attachment was printed using PLA material on a Prusa MK3 3D printer.

5.1.1.3 Balloon Attachment

The balloon attachment is used to aid in the volumetric change from the pump, along with elastic bounce back to simulate the left ventricle during systole. The bottom of the balloon attachment has a large viewing window and legs to allow for video footage of the functioning heart valves. The side tube allows for interchangeable elastic material to be used for the simulation of the left ventricle. The isometric and bottom view can be seen in Figure 5.5.

![Figure 5.5 Isometric and bottom view of balloon attachment render](image)

As seen in Figure 5.5, the balloon attachment has a flange to connect the component to the center box. The balloon attachment was separated into two components to be able to print. The side tube was printed using ABS on the Stratsys MOJO 3D printer, while the rest of the body was printed with PLA on the Prusa MK3 3D printer.
5.1.1.4 Pump Attachment

The pump attachment provides for water flow within the whole system. The first-generation pump is set to be a 60 mL chamber and plunger, while further iterations are planned on including an automated system. The water flows out of the cylinder toward the MV annulus. Both the mitral and aortic side have viewing windows to view the performance of each valve. The isometric and top view of the pump attachment can be seen in Figure 5.6.

![Figure 5.6 Isometric and top view of pump attachment render](image)

The pump attachment includes a flange to connect the part to the center box, while a side tube gives attachment to the pump cylinder. Figure 5.6 showcases the viewing windows for the AV and MV. The pump attachment was separated into two components to be able to print. The side tube was printed using ABS with the Stratsys MOJO 3D printer, while the rest of the body was printed using PLA with the Prusa MK3 3D printer.

5.1.1.5 Gasket Molds & Gaskets Fabrication

For the system to be watertight, gaskets had to be created to provide a seal at attachment areas. To do so, a soft deformable material would have to be utilized to handle the pressure created from the bolts and prevent water from leaking. Attachment areas include the securing of the balloon attachment to the exterior box, the annulus attachment to the exterior box, and the pump attachment
to the exterior box. Seating for the gaskets was designed onto the exterior box to allow for the gasket to sit within the exterior box, while also protruding outward to allow for the soft material to be deformed, and thus creating a seal. Additionally, an apparatus had to be created to hold a mechanical valve into place on the annulus attachment. To do so, a mold was created to allow the mechanical valve to securely sit in the annulus attachment. The molds made for the attachment point gaskets along with the mold made for the mechanical heart valve seating can be seen in Figure 5.7.

![Figure 5.7 Isometric and top view of gasket molds render](image)

The large attachment point gasket mold’s outer dimensions are 110 x 110 mm with a thickness of 5 mm. The annulus attachment gasket mold’s outer dimensions are 55 x 105 mm with a thickness of 5 mm. Finally, the mechanical heart valve gasket mold’s dimensions are a 50 mm outer diameter, with a 30 mm inner diameter. The inner seating for the mechanical heart valve is 40 mm. The deformable material used was Mold Max™ 30, a silicone rubber compound from Smooth-on. The material had a medium hardness and was able to go from a viscous liquid that would encompass the entirety of the molds to a solid object that could be extracted and utilized. The Mold Max™ 30 material used can be seen in Figure 6.13 in Appendix C.2.
5.1.1.6 Fabricated System

The fabricated version of the HVPL Miniature Heart Simulator 1.0 can be seen in Figure 5.8. The system was sealed using clear RTV silicone adhesive sealant offered by Permatex, rated for a temperature range of -60°C to 204°C and targeted for waterproof sealing. The RTV silicone adhesive sealant provides a cost effective water tight seal on the viewing windows while be graded to handle harsh conditions. The system was additionally sealed with the custom silicon rubber gaskets that were described in subsection 5.1.1.5. The balloon was created using a large balloon that was cut to shape the balloon attachment and was secured using a worm gear clamp. The windows are made of acrylic glass to ensure viewing capabilities and were cut to size to be glued and sealed to their respective parts. The 3D printing of each individual part is detailed in their respective subsections. Further design improvements will be detailed in section 5.1.2.
A towel was used between the balloon and the worm gear clamp to ensure the balloon did not tear. Additionally, a small hole was drilled into the chamber of the pump to provide a means of bleeding the system to extract all the air that could be trapped within. The performance of the system and the design improvements are discussed in the following subsections.

### 5.1.2 Design Performance & Improvements

The HVPL Miniature Heart Simulator 1.0 is the first-generation of the design and is subjected to further improvements. The second-generation device will reduce areas that need sealing, to allow for a more watertight device. To achieve this, the viewing windows on the center box will be removed, as the actual viewing of the valves was minimal. Instead, larger viewing windows on top will be put in to allow for better visualization of the valves to better view their kinematics. Next,
the device will utilize a diaphragm and balloon to control the fluid flow rather than a pump. With careful consideration of angles, bleed lines will be added to ensure no air pockets get stuck within the system. More realistic chambers will allow for accurate valve function. The system will be more streamlined to reduce the size of the device, and the sealing mechanisms will be improved upon. The new system will better reflect a natural heart, with the main pumping being from the bottom of the system, similar to a ventricle, rather than the top. Additional balloons will be added to handle the volume and pressure changes within the system to better replicate the atrium. Finally, the whole system will be 3D printed more robustly to ensure a stronger structure to handle the hydraulic pressures.

### 5.2 Second Generation

The second-generation of the heart simulator, titled the Miniature Heart Simulator 2.0, was aimed at improving upon the deficiencies of the first generation. Making the system watertight proved to be difficult. To discourage leakage within the system, fewer windows were designed for the system, along with fewer areas that needed to be sealed. Additionally, as pockets of air were trapped in the first-generation system, bleed lines were added to allow for the pockets of air to bleed out of the device to further encourage a watertight system. Furthermore, certain components were designed with the ability to allow for air to be released by way of angles. The isometric view of the complete and exploded system can be seen in Figure 5.9.
When comparing the second-generation of the heart simulator to the first-generation, you can notice that the annulus attachment component has been removed and replaced with individual blocks to seat the valves into position. All side viewing windows were removed, as functionality was limited due to the extreme visibility angle and the minimum amount of additional light brought in. Attachment for bleed lines can be seen on the top component and will be discussed more in its respective subsection. A cross-sectional view of the full second-generation heart simulator can be seen in Figure 5.10.
The large gaskets used in the first-generation of the heart simulator were reused for the second-generation. The attachment points of each component are now seated into each other to promote better sealing of the system. The seating of the attachment points can be seen in Figure 5.10. Note that there are two valves in the system, one oriented to open when the flow is going upward, and one oriented to open when the flow is going downward. The goal was to replicate the dynamics of a natural heart by way of pumping from the bottom similar to the LV and having balloons to handle the volumetric and pressure changes at the top similar to the LA.
5.2.1 Design & Fabrication

The design of the second-generation of the heart simulator was aimed at being more simplistic with few areas that the system could leak from. The second-generation of the heart simulator is comprised of four components: The heart chamber where the valve fixation blocks are seated; the valve fixation blocks that constrain the valves in position to evaluate their performance; the ventricle attachment that provides the pulsatile pumping by way of a diaphragm; and the atrium attachment that handles volumetric and pressure changes within the system. Each component’s design, along with how they were fabricated, will be detailed in the following subsections.

5.2.1.1 Heart Chamber

The heart chamber of the second-generation of the heart simulator is similar to the exterior box of the first-generation. For this design, all the viewing windows were removed, along with the height of the component being reduced. The height of the exterior box from the first-generation was 136 mm, which was reduced to a working height of 100 mm for the heart chamber in the second-generation. The flanges that allow for the attachment of the other components remain unchanged and utilize the same M8x35mm bolts used on the first generation of the heart simulator. The M8x35mm bolts are designed for 9 mm holes, which the heart chamber has 8 holes on each flange. The atrial side has a seating to allow for the atrium attachment’s protruded component to fit into the heart chamber, while on the ventricle side the heart chamber has protruded components that seat into the ventricle attachment. These components were added to discourage water leakage in the system, as the water would have to leak around these protruded components. This seating can be seen in the cross-sectional view in Figure 5.10. The heart chamber can be seen in Figure 5.11.
The interior of the heart chamber has shelves to allow for the annulus attachment blocks to seat into the heart chamber. The ventricle side of the shelves angle towards the center of the aortic and mitral valves, to encourage central flow towards the center of the valves. To fixate the annulus attachments into the heart chamber, valve fixation blocks were created, which will be detailed in section 5.2.1.2. Slots were created to allow the valve fixation blocks to slide into position without the possibility of obstructing the central flow. As the center septum that divides the aortic and mitral sides had a small dimension of 5 mm, the center slots for the valve fixation blocks had smaller dimensions than that of the slots on the outer sides of the interior. Fully dimensioned drawings of the heart chamber can be seen in Appendix D.1.

5.2.1.2 Valve Fixation Blocks & Annulus Attachments

As discussed in section 5.2.1.1, valve fixation blocks were created to hold the annulus attachment blocks in place in the heart chamber. To achieve fixation, slots were designed onto the heart chamber that would fit key protrusions on the valve fixation blocks. This allowed for perfect alignment of the fixation blocks while maintaining their position. The fixation blocks were also angled to promote central blood flow towards the anchored heart valves. As the septum of the heart
chamber had a small dimension, the keys for the septal (medial) side of the valve fixation blocks protruded a distance of 1.25 mm, while the exterior (lateral) of the interior of the heart chamber protruded a distance of 2.25 mm. The total height of the valve fixation block is 24.50 mm, while the key height and width are 18 mm and 4.50 mm, respectively. Renders of the valve fixation blocks can be seen in Figure 5.12.

![Figure 5.12 Isometric + top view of valve fixation blocks render](image)

The valve fixation blocks were imposed to fixate the annulus attachment blocks. These annulus attachment blocks were to hold onto the heart valves under evaluation. The first annulus attachment block created was for the mitral position and catheter-based heart valves. This block was created to visualize the bileaflet (duckbill) valve that was designed and fabricated. The block would remain rigid and be shaped to an accurate depiction of the MV annulus. Future iterations would focus on making an MV annulus that was elastic, to better simulate the native annulus. The block dimensions are a length of 89.50 mm, and width of 41.50 mm and a height of 37.00 mm. The MV annulus attachment block can be seen in Figure 5.13.
Once the MV side of the heart simulator was created, the AV side had to be created to produce realistic heart flow dynamics. A block was created that would utilize a mechanical heart valve. The mechanical heart valve applied was the St. Jude Medical valve, an FDA approved valve that has decades of use. Note that any FDA approved valve could be used, as long as it operates without any issues so as the focus can be put onto the other side of the heart chamber. To fixate the mechanical heart valve into position, a locking system for the valve had to be created. The outer dimensions of the block had to be the same as the MV annulus block, with an additional component that would allow the mechanical heart valve to be slid into the center of the block and held in place. The block is opened at one end that would allow this function, with a locking component that would follow the heart valve to hold it into place. The mechanical valve would be fit into a gasket and then slid into position. The mechanical heart valve attachment can be seen in Figure 5.14.
The mechanical heart valve attachment allows for FDA approved function of a heart valve, which allows for the focus of evaluation to be on the other annulus block attachment. The mechanical heart valve attachment block could also be utilized to evaluate mechanical heart valves kinematics while having the FDA valve on the other side of the heart chamber. This system to fixate the mechanical heart valve into the block proved to be a sufficient means of positioning the heart valve in the ideal position, while also not having any worries of the valve coming dislodged under working conditions. Fully dimensioned drawings of the components in this subsection can be seen in Appendix D.1.

5.2.1.3 Ventricle Attachment

The ventricle attachment for the second-generation of the heart simulator emulates the balloon attachment from the first-generation. In fact, the design is identical to the balloon attachment, other than one design change. The ventricle attachment allows for the protruded component from the heart chamber to seat into it by adding a shelf. This was included to discourage leakage in the system. The flange and hole dimensions remain consistent, as does the height of the component at a height of 150 mm. For this design, the balloon was employed to act as the major pulsatile function of the heart simulator, rather than just handling the volumetric and pressure changes. As the balloon became dilated as the heart simulator was filled, the balloon would be pressed to redirect the water flow towards the attached heart valves. This function also acts more closely to that of the ventricle, hence the name of the ventricle attachment. Renders of the ventricle attachment can be seen in Figure 5.15.
From above, the similarities between the balloon attachment from the first-generation of the heart simulator and the ventricle attachment from the second-generation can be seen clearly. The same viewing window was exploited, as it provided maximal viewing of the active heart valves. The only change was the shelf which can be visually seen in Figure 5.15. A fully dimensioned drawing of the ventricle attachment can be seen in Appendix D.1.

### 5.2.1.4 Atrium Attachment

At the other end of the heart chamber is the atrium attachment. The atrium attachment is the replacement for the pump attachment from the first-generation of the heart simulator. This component focused on handling the volumetric and pressure changes created from the ventricle attachment. Two smaller balloons were utilized to manage these changes, while also being tilted to allow for any air pockets trapped within to be funneled towards the top. The angle of the balloons was 5° from the horizontal plane or 85° from the vertical side of the atrium attachment. Renders of the atrium attachment can be seen in Figure 5.16.
Other changes include the singular larger viewing window, rather than the two smaller viewing windows from the pump attachment of the first-generation. This allowed for a better evaluation of the kinematics of the heart valves. Additionally, bleed lines were included to fully allow any trapped air to be fully released from the apparatus. The bleed lines were lined up to be exactly level with the glass, to prevent any air pockets from being trapped between the difference. The attachment component for the bleed lines was replicated from a known attachment piece for PVC tubing. Furthermore, two bleed lines were used for both the inlet of water and the outlet of air. The inlet for water could be directly hooked up to the tap of a sink, while the outlet would drain into the sink. The flange and bolt holes remain the same, but the atrium attachment includes a protruding component that seats into the heart simulator to promote better sealing of the device. A fully dimensioned drawing of the atrium attachment can be seen in Appendix D.1.

5.2.1.5 Fabricated System

Once designs were finalized for the second-generation of the heart simulator, 3D printing was utilized to create each component. All the parts were printed using the Prusa MK3 3D printer using PLA at 30% gyroid infill, with 4-layer walls. All the M8X35mm bolts were reused for the second-generation of the heart simulator. In addition, the gaskets used in the first-generation were also
utilized for the second-generation. The fully fabricated system under pressure can be seen in Figure 5.17.

The ventricle attachment balloon in Figure 5.17 is visibly dilated due to the large hydraulic head, as is the atrium attachment balloons to a lesser degree. The ventricle attachment balloon was the same balloon from the balloon attachment component from the first-generation, while new smaller balloons were cut and fit to the atrium attachment. The ventricle attachment balloon was connected using a towel and worm gear to hold it in place. Due to the low pressure on the atrium attachment, simply stretching the small balloons around the atrium balloon locations while taping them to seal the addition was sufficient and provided no leakage or chance of balloons tearing. The dilated ventricle attachment balloon would be jolted to produce the pulsatile flow, or additionally would be pressed inward and quickly released to produce the pulsatile flow. The whole system was treated with a coating for 3D printed parts to provide more strength to the system, while also preventing
leakage. The system was sealed using the same clear RTV silicone adhesive sealant that was used in the first-generation of the heart simulator. The bleed lines had simple gas valves, designed for lawn mowers, attached for the ability to trap the water in the system and not allow air to flow back in. A closer look at the inlet and outlet bleed lines can be seen in Figure 5.18.

![Figure 5.18 Inlet (left) & outlet (right) flow of bleed lines](image)

The whole fabricated system provided a means of evaluating the kinematics of newly designed heart valves. The performance of the second-generation of the heart simulator along with design improvements will be discussed in the following subsection.

5.2.2 Design Performance & Improvements

The second-generation of the heart simulator was an improvement upon the first-generation. The pulsatile flow created was better than the first-generation, even with how rudimentary it was. Moreover, the addition of bleed lines and consideration of where air pockets would form improved how watertight the system is. The larger viewing windows also made it easier to evaluate the kinematics of the heart valves in working conditions. The balloons on the atrium attachment
seemed to work optimally, with no leakage and allowed for any trapped air to escape by the angle of the balloons.

The system did leak less than the first-generation but did succumb to eventual leakage. The gaskets used at the flange areas were subjected to leakage, while the attachment of the balloon to the ventricle attachment also had leakage problems. It is assumed that the large hydraulic pressure head is too much to be trapped by a worm gear. Further iterations would need to improve upon this attachment, with something more robust to handle large hydraulic pressure. Due to the leakage, air bubbles were consistently in the way of viewing the system, which made for lower quality imaging of the heart valves under evaluation. To counteract the leakage, the bleed line inlet continually provided water flow, as the outlet continually provided an outlet for the air bubbles. With this setup, the evaluation of heart valves was able to be conducted. Conditions weren’t optimal, but sufficient to produce results.

For further iterations of the heart simulator, the system could go in many directions. The most prominent issue to fix is making the system completely watertight. It would be worth investigating if printing every component as a solid part would improve water leakage issues. Furthermore, using a more optimized material for the gaskets may produce better results. A reduction in size and height would also reduce the hydraulic pressure in the system, which may also reduce water leakage. Perhaps creating one part that encompasses the whole system would be beneficial as there would be a reduction in attachment points under hydraulic pressure. Having a simple lid at the top of the apparatus to allow for the annulus blocks to be placed within the system, but also having low hydraulic pressure may be the best option. Moreover, the top viewing window should perhaps be angled to promote air bubbles to flow towards the bleed line outlet. Though there were minimal air pockets trapped within the system, the ones that were created were trapped on the top viewing
window and unable to flow to the bleed line outlet unless the whole apparatus was tilted. Further improvements will be discussed in the kinematics results section, as they pertain to the evaluation of the heart valves.

5.3 Kinematic Results

The first and second iteration of the heart simulator was subjected to watertight issues. The system had a means of preventing leakage, but the system had failures that caused air to enter and water to escape. Even with these failures, which were described in the previous subsection, the evaluation of the kinematics of the bileaflet valve was able to be conducted. The bileaflet valve was sutured into a simple circular stent and then fit into the annulus attachment. As the annulus attachment was rigid, and not sized to fit the simple stent, a soft deformable material was used to fit the simple stent into the annulus. The soft deformable material used was a sticky tack material that could be formed to the desired shape along with sticking to the annulus attachment. Photos of the bileaflet valve in its open and closed state from the heart simulator can be seen in Figure 5.19.
The bileaflet valve was able to be visualized in both its open and closed state from the heart simulator. The key factor that it identified is how the leaflets come together (Figure 5.19A & C). Instead of the leaflets meeting in the center of the EOA, one leaflet protruded over to the other leaflet, acting similar to a monoleaflet as only one leaflet is in motion. There are two believed reasonings as to why this occurs. The first, and most important, is the geometry of the heart simulator itself. The flow of water that is directed from the balloon is believed to be affecting one leaflet more than the other. As the flow moves through the balloon attachment, it is believed that it bounces off the walls and comes at the leaflet on an angle. This is not identical to flow dynamics felt within a real LV. To achieve better visualization, a flow that is directed perpendicular to the valves should produce more realistic results. This factor wasn’t realized until after testing of the second iteration of the heart simulator. A secondary balloon within the system that would segregate
the balloon side of the ventricle attachment from the heart chamber of the ventricle attachment may be the best possible way to direct the flow perpendicular to the annulus blocks.

The second believed reason for this specific kinematics of the leaflets is possibly due to the length of the leaflet free edge. It is feasible that the leaflet free edge is too long, making it difficult for the leaflets to close and meet in the center of the EOA. Further iterations of the bileaflet valve could be conducted to produce a valve that is ideal for leaflet apposition. Careful consideration into the leaflet free edge length should be conducted as a short leaflet free edge may allow for better leaflet apposition but may effectively decrease the EOA to an impractical point. A long leaflet free edge may create a large EOA, but leaflet apposition is lessened. For this reason, it is beneficial to determine an ideal length that will make for sufficient EOA along with leaflet apposition.
Chapter 6: Conclusion & Future Work

Catheter-based technologies are evolving to becoming the new gold standard for repair or replacement of heart valves subjected to valvular heart disease in patients with a perceived surgical risk. The success of TAVR for the treatment of aortic stenosis, along with the MitraClip™ for treating MR, has streamlined the progress and development of catheter-based technologies in the industry. TMVR could potentially become a new option for the treatment of MR for patients with perceived surgical risk. Readily available TMVR is inevitable, but before these systems do become available, further development needs to occur to ensure the safety and efficacy of these implants and implantations. TMVR has many more hurdles to overcome when compared to TAVR, so the trajectory is not as rapid. These hurdles include the increased complexity of the MV anatomy, variability of pathology, durability of the systems, and lack of evidence supporting that TMVR is a sufficient option for the treatment of secondary MR. There have been increased concerns over thrombosis initiation after TAVR [170], along with further research regarding best practices, such as the use of pacing as therapy for aortic regurgitation and its negative impacts on patients [171]. This showcases that even the commercialized options of TAVR still need to be adjusted and fine-tuned to increase the safety for the patients. TMVR device developers can learn from the prior experience and longer development time of the TAVR devices. There is limited data on the risks of thrombosis following TMVR, though the FORTIS system’s clinical trial was stopped due to observed evidence of thrombosis initiation [172]. It is important for these devices to be created with all factors in mind, and to be cautiously developed to make sure the most optimized option is put on the market. The race to create and be the first to market could produce a device that is not completely suitable for implantation on a commercial level, putting many lives in danger. Careful considerations on the course of actions should be taken by these developers. It is suggested that to
create an optimal TMVR device, that the design has a low profile and reduced protrusion into the LV to reduce LVOT obstruction with the possible use of the LAMPOON technique. Additionally, conforming to the natural MV annulus has been suggested to be ideal for the reduction of PVL. With a device that conforms to the natural MV annulus, an increased EOA can also be realized. The anchoring system of the TMVR device should not obstruct LV flow dynamics along with creating areas of stagnant flow. Devices with supra-annular positioning may be the solution to discouraging LVOT obstruction and thrombosis initiation. Though the transseptal approach seems to be the most optimal when it comes to technical success, the increased experience with the transapical approach, along with lower-profile designs have made both approaches feasible. Additionally, TMVR designs that consider the dynamic motion of the MV, the MV annulus and the LV will have a greater opportunity at being successful. Finally, devices should not be overly complex to implant along with the ability to readjust during surgery with the possibility of recapturing will increase technical success.

With all this in mind, TMVR systems are not far away from being readily available and could be a viable option for the treatment of MR in the near future. Further development of TMVR system designs, increased surgical practice for surgeons, and better cardiac imaging will improve the technical success for implantation. Devices to date are showing good promise in their respected clinical and preclinical trials and are pointing towards TMVR becoming a vital therapeutic option in the treatment of MV disease in the not so distant future.

6.1 Work Overview

As trileaflet valve designs are the most utilized leaflet designs for surgical bioprosthetic and transcatheter valves, this work showcased the feasibility of a bileaflet valve design. Though a bileaflet valve design more closely replicates the native MV leaflets than that of a trileaflet design,
the bileaflet valve design proposed was symmetrical and does not employ chords. This difference from the native MV leaflets could prove to be ideal for heart valve hemodynamics, or perhaps a suboptimal choice. Further evaluation is warranted to determine the feasibility of clinical trials of the design. The PVA-BC cryogel material exploited in these studies proved to be a prime method of fabrication for leaflet designs in their development stage. The ability to create a mold that would be filled by a viscous cryogel material that becomes rigid and tissue-like after cycling streamlined the prototyping process. This work was a great example of how ideal the PVA-BC cryogel material is for the design process of valves. When compared to bioprosthetic tissue, the cryogel material is far more time-efficient and ideal for the iterative design process. Additionally, when comparing the cryogel material to other quick manufactured materials such as silicone, the cryogel material has the additional benefit of being closer to that of real tissue and reacting similarly. This made it ideal for the evaluation of the kinematics of the leaflet design. Silicone material was used to evaluate the feasibility of the molds that were designed, but once the final design of the mold was confirmed the cryogel material was exploited.

Once a novel leaflet design was created, the focus turned towards creating novel stent designs to accommodate the leaflets. The Angeleno Medical stent was first used as a base design to further improve upon. When evaluating the design, it was deemed important to remove any impedance to blood flow. The cage on the Angeleno Valve stent is quite useful for its ability to readjust and recapture, so adaptations that allowed for the release of the cage after successful implantation was the focus. Two methods of a release mechanism for the cage was designed for the Angeleno Medical valve. One designed titled the flower release mechanism due to the flower-like shape to the main release apparatus, and one designed titled the candy cane release mechanism as the main release apparatus closely resembles a candy cane shape. Both designs take into account the
difficulties of performing certain maneuvers when visibility and control are limited. The mechanisms were limited to twisting and pulling as their controls, while also not allowing for premature release during implantation. Both designs warrant further evaluation to determine their feasibility in real practice.

Following the development of the release mechanism for the Angeleno Medical valve, the focus was turned towards creating novel designs for a TMVR stent. Two designs were developed, one being a simple circular stent that displayed the ability to crimp a stent to a small profile followed by a D-shaped stent that conformed better to the native MV annulus. The simple circular stent proved to be good practice when brainstorming novel stent designs, which led to the sun valve (D-shaped) stent. The sun valve fits the elliptic shape of the duckbill (bileaflet) valve more ideally than a circular stent. Renders of the duckbill valve within the sun valve stent can be seen in Appendix A. The sun valve stent consists of the D-shaped apparatus, an atrial flange that has varying degrees based on location within the LA, ventricular anchors that impede the stent from moving during systolic pressures and leaflet capturing hooks to add additional anchoring to the system. The design may benefit from the utilization of the LAMPOON technique which lacerates the MV leaflet to open the LVOT to discourage obstruction and LVOT gradients. Fabrication of the design is warranted to perform in vitro testing.

To determine if the duckbill valve could function as a realistic heart valve, an apparatus that could provide gradients of pressures to evaluate the kinematics of the design was necessary. First and second generations of the HVPL miniature heart simulator were created to provide a cost-effective means of evaluating the valve design. The full dimensions of the second-generation of the heart simulator can be seen in Appendix D.1. Results were produced that showcased that further iterations of the duckbill valve are needed. The length of both the leaflet free edge along with the
length of the leaflets should be adjusted to improve leaflet apposition. Additionally, the heart simulator should be further iterated to improve upon the previous designs. Maintaining a water-tight system proved to be difficult, but progress was made between the first and second-generation. The second-generation heart simulator was also utilized to evaluate the kinematics of a novel mechanical heart valve, but that design is beyond the scope of this research.

This thesis showcased an in-depth review of the TMVR industry, background knowledge about TMVR design with a detailed list of design criteria along with proposing a novel design for heart valve leaflets. Additionally, several stent designs were proposed to solve issues within TMVR systems. To be able to evaluate the novel leaflet design, a cost-effective heart simulator had to be created to evaluate the kinematics. The end result of this research is a functioning heart valve leaflet that warrants further iterations and design optimization, along with the sun valve (D-shaped) stent that fits the novel duckbill (bileaflet) valve that warrants fabrication to perform in vitro studies. In addition, novel ideas of release mechanisms were proposed for the Angeleno Medical valve and warrant fabrication to evaluate the practicality of their designs, while the heart simulator warrants further iterations to produce a water-tight device that evaluates kinematics of valve designs with further possibilities to evaluate the hemodynamic performance.

6.2 Recommendations for Future Work

Future work should focus on iterating the duckbill (bileaflet) valve to optimize the leaflet free edge length to create optimal apposition between the two leaflets. Moreover, the length of the leaflets should also be evaluated to further improve the leaflet appositions. Additional evaluation of the optimized duckbill valve design using bioprosthetic tissue instead of the PVA-BC cryogel material may be necessary to see how the design operates when closer to implantation conditions.
Additional work can be done on iterating the mold design for the human (bileaflet) valve. A mold design that closely replicates that of the duckbill and trileaflet valve mold designs would be ideal. Once the duckbill valve has been optimized for performance, the focus can be put on fabricating the sun valve stent to fit the duckbill leaflets into. Ideally, the stent would be fabricated using a shape memory alloy like nitinol, though the cost of fabrication may become quite expensive. The feasibility of the stent design can be initially evaluated using cheaper materials, such as steel, to determine if once fully deployed the design operates satisfactorily. Once satisfied, further prototypes could include the more expensive shape memory alloy.

Once fabricated, in vitro studies can be conducted on the sun valve stent with the duckbill leaflets to iterate and improve upon the novel design. Further computational fluid dynamics (CFD) studies can also be conducted to iterate the sun valve stent design. Utilizing both in vitro testing with CFD should create a feasible design that can be further evaluated using in vivo (animal model) studies. Additionally, testing the sun valve stent under crimped conditions will need to be conducted to determine areas of high stress concentrations. Fitting the stent into a sheath should also be tested, while determining the sequence of how the stent should be released to provide the anchoring.
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Appendices

Appendix A

Appendix A includes hand drawings of the bileaflet valve, stent designs and additional renders of the sun valve stent with the bileaflet valve.

A.1 Hand Drawing Design of Bileaflet Valve

Figure 6.1 Original hand drawn sketches for duckbill (bileaflet) valve
A.2 Hand Drawing Design of Heart Valve Stents

Figure 6.2 Flower release mechanism valve hand drawing
Figure 6.3 Candy cane release mechanism valve hand drawing
Figure 6.4 Novel stent design hand drawn sketches 1 & 2
Figure 6.5 Novel stent design hand drawn sketches 3 & 4
Figure 6.6 Novel stent design hand drawn sketches 5 & 6
A.3 Sun Valve Stent with Bileaflet Valve Render

Figure 6.7 Isometric view of sun valve stent with bileaflet valve render

Figure 6.8 Sub- and supra-annular view of sun valve with bileaflet valve render

Figure 6.9 Anterior and medial view of sun valve with bileaflet valve render
A.4 Leaflet Capture Hook & Ventricular Anchor Renders

Figure 6.10 Ventricular anchor for sun valve render

Figure 6.11 Leaflet capturing hook for sun valve render
Appendix B

B.1 Wrinkle-Induced Tear in the Mitral Valve Leaflet Tissue; A Computational Model

In this study, we offer a numerical platform to detect the locations of high stress zones in the prosthetic heart valve, in the mitral position, during the closing phase due to existing wrinkles. We assume the most high-risk locations for ruptures to either initiate or propagate are at the base of existing wrinkles. We developed a finite element model for the human mitral valve. A mesh model was effectively created to account for the uneven stress distribution and high stress concentration zones in the valve tissue structure. The constitutive material model used in this study are anisotropic and hyperelastic material models such that the membrane elements are used for the leaflets and spar elements are utilized for the mitral valve cords for which it was assumed flexural stiffness is insignificant for both sets of elements. We developed a novel and effective computational model for the simulation of wrinkles in the valve leaflet during the closing phase. The proposed numerical model provided a quick but precise assessment for the detection of locations of rips and tears on the leaflet tissue during the closing phase. The proposed model is an essential step for the design of material and geometry of leaflets of prosthetic heart valves made of polymers or tissue materials in the mitral position.

Mechanics of prosthetic valves in the mitral position has been extensively studied in the past using finite element and other numerical methods [173]–[177], however, less attention has been paid into modeling wrinkles and their effects. More specifically, their effects in causing ruptures in the valve leaflets during the closing phase, especially when the valve is calcified. This study is an attempt to resolve that. The prosthetic valve leaflet can be considered as a membrane or a shell [178]. The flexural stiffness of the leaflets is considered consistently low, or in order words, the bending moments that can be supported by the leaflets are very insignificant due to small leaflet thickness [179], [180]. In such conditions negative in-plane stresses in one principal direction may cause the leaflets to buckle and thus numerous wrinkles are formed parallel to the tensile direction [164], [181]. By characterizing the geometry of these wrinkles, more insight to the mechanics of the valve leaflets may be achieved. For example, due to high stress concentration regions at the basis of wrinkles (geometrical factor), it is hypothesized that the initiation or propagation of rupture in the leaflets occur in those areas.
In this study, we developed a numerical tool by which formation of wrinkles on the valve leaflets were modeled in physiological conditions. We utilized the nonlinear finite element (FE) commercial software ABAQUS (Simulia, RI, USA) which was coupled with the proposed numerical technique written in FORTRAN90 custom-code to simulate wrinkle formation in the mitral valve leaflets in the closing phase. This study is conceptual and fundamental which seems to merit further development and advancement.

**Method**

**Mitral valve model:** The mitral valve model, as shown in Fig. B1, was provided based on anatomical configuration as discussed in [182], [183]. For simplicity, the three scallops on the posterior leaflet have not been incorporated into the geometry of the valve [184]. The annulus of the mitral valve model maintains a flat D-shaped orifice. The total dimensions of the valve are demonstrated in Figs. 1 and 2. As observed, the total annular length of the mitral valve model was set to 86 mm. The height of leaflets is 28 mm while the top plane of leaflets is located 7.0 mm above the annular plane. The primary chordae tendineae are connected to the free margin of the leaflet. These chordae are connected to a static node representing the papillary muscle tip which are positioned in a plane 35 mm directly below the annular plane. Considering an appropriate coaptation between the leaflets, the optimized location was considered for the papillary tip of each chordae tendineae under physiological conditions.

![Figure B1: CAD model of the human mitral valve from the bottom view (left) and front view (right)](image)

Figure B1: CAD model of the human mitral valve from the bottom view (left) and front view (right)
We used membrane (Belytschko-Tsay) and beam (Hughes-Liu) elements for the construction of the mitral valve leaflets and for the chordae tendineae, respectively. The beam elements are in fact spar elements that are designed to withstand tensile force only. In this study, their stiffness for compression and flexural stiffness are set to zero. The elements’ mass density for both beam and membrane elements are all set to 1000 kg/m$^3$. The thickness of the membrane elements is considered uniform and are set to 0.75 mm. The cross-sectional area for the beam elements is considered 0.6 mm$^2$. Elastic modulus of beam elements is set to 40 MPa and a bulk modulus of 33 MPa are considered for the solid state of the implemented model [184].

![Figure B2: Mesh model of the human mitral valve consisting of spar (left) and membrane (right) elements simulating the valve leaflets and chordae tendineae](image)

For the mesh independency study, a computer-generated pressure ramp of 120 mmHg which is approximately equal to 16 kPa was implemented over a period of 325 ms and was kept constant on the leaflets until convergence was achieved. In this study, a global nodal damping factor was utilized and set to 0.997 in ABAQUS [185]. Global nodal damping factor is an ABAQUS term showing how damping property is added in to the model, which is totally optional. We consider a value of 10% of critical damping which is in fact to damp all elements by means of the same damping coefficient (*DAMPING_GLOBAL).

The convergence criterion is considered satisfied when the current global kinetic energy is less than the maximum global kinetic energy multiplied by 1E-6, which is known as the tolerance.
The independency criterion is considered satisfied when there was no noticeable difference in the stress values or the discrepancy in the value of the principal stress was observed to be less than 1% [185]. The final mesh model consisted of 2845 membrane elements and 346 beam elements.

**Mechanics of wrinkle:** For the theoretical work, plane-stress theory is utilized, and flexural stiffness is set to zero. The Cauchy stress tensor \( \sigma \) is written as such: \( \sigma = \frac{1}{J}F.T(E)F^c \) (1) where, \( F \) is the deformation tensor, \( J \) is Jacobian of \( F \), \( E \) is the Green-Lagrange strain tensor and \( T \) is a tensor function of \( E \). Assume vector \( P \) is a vector tangent to the midsurface of the membrane at position \( x \) (Fig 3a). For vector \( P \), the assumption of no negative stresses (due to presence of wrinkle) is written as: \( \vec{P} \cdot \sigma \cdot \vec{P} \geq 0 \) (2). This condition leads to the following finite number of inequality conditions: \( \vec{n}_1 \cdot \sigma \cdot \vec{n}_1 \geq 0 \) (3), \( \vec{n}_2 \cdot \sigma \cdot \vec{n}_2 \geq 0 \) (4), \( \vec{n}_1 \cdot \sigma \cdot \vec{n}_2 = 0 \) (5), here: \( \vec{n}_1 \) and \( \vec{n}_2 \) are normal vectors signifying the principal directions of \( \sigma \) or the directions of principal stresses. Eqs. (3) and (4) are in fact conditions where the two principal Cauchy stresses are positive in direction \( \vec{P} \). This is minimum conditions for the formation of wrinkle in a membrane structure. To determine the stress in this direction, we use: 

\[
\vec{P} \cdot \sigma \cdot \vec{P} = [(\vec{P} \cdot \vec{n}_1)\vec{n}_1 + (\vec{P} \cdot \vec{n}_2)\vec{n}_2] \cdot \sigma \cdot [(\vec{P} \cdot \vec{n}_1)\vec{n}_1 + (\vec{P} \cdot \vec{n}_2)\vec{n}_2] = (\vec{P} \cdot \vec{n}_1)^2 \vec{n}_1 \cdot \sigma \cdot \vec{n}_1 + (\vec{P} \cdot \vec{n}_2)^2 \vec{n}_2 \cdot \sigma \cdot \vec{n}_2
\]

(6)

Two main conditions are considered: (1) The principle stresses are positive which means that the membrane is taut, (2) The principle stresses are zero which means that the membrane is slack. If one of principal stresses is zero and the other one is positive, the new set of conditions are considered as such: \( \vec{n}_1 \cdot \sigma \cdot \vec{n}_1 = 0 \) (7), \( \vec{n}_2 \cdot \sigma \cdot \vec{n}_2 > 0 \) (8), \( \vec{n}_1 \cdot \sigma \cdot \vec{n}_2 = 0 \) (9), here, \( \vec{n}_1 \) denotes the arbitrary direction where the principal Cauchy stress is zero. The key challenge would be determining the principal stress in the direction of \( \vec{n}_2 \). The stresses in the membrane stay unchanged if it is straightened by flexure in the plane defined by \( \vec{n}_1 \) and \( \vec{n}_2 \) (Fig. B3b).
Figure B3: (a) Vector P at position x and its origination with respect to the midsurface, and (b) the fictive non-wrinkled and wrinkled surfaces with respect to \( n_1 \) and \( n_2 \)

Because the membrane part has the same shape (being longer in the direction of \( \vec{n}_1 \) compared to the fictive non-wrinkled part), the new deformation tensor \( (F^*) \) takes the form of: \( F^* = (I + \varphi \vec{n}_1 \vec{n}_1) \). F (10). Given that \( I \) is the unit tensor and \( \varphi \), a positive value, which is the area ratio of the fictive non-wrinkled over real wrinkled membrane parts, \( I + \varphi \vec{n}_1 \vec{n}_1 \) is also a tensor that equalizes the length of the fictive non-wrinkled membrane and real wrinkled membrane parts. It should be noted that \( \varphi \) and the direction of the principal frame are calculated using Eqs. (7) and (9).

**Case Study I (Validation):** A rectangular sample made of rubber sheet with the dimensions of 10 mm x 20 mm x 1 mm was considered. The material properties of the sample were set to \( E = 1.5 \) MPa and \( \nu = 0.45 \) (close to the material properties of the heart valve leaflet tissue). To make an effective model for formation of wrinkles when the sample is stretched, a strip of tape was placed on the midline of the sample. As shown in Fig. 4a, this strip was placed in the transversal direction while stretching occurs in the axial direction. The elastic modulus of the tape was set to 3 MPa and the thickness and the width of the sample were set to 3 mm and 2 mm, respectively. A 13.3% stretch was applied on the sample. These same conditions were used by Takei et al. [186]. In this study, it was indicated wavelength (\( \lambda \)), normalized amplitude (\( A^* \)), and length of formed wrinkles (\( y \)) are connected and follow: \( A^* = \exp(-3.4y/\lambda) \). This equation was used as a basis for the validation of the wrinkle model provided in this study. The results of the FE models are presented in Fig. 4b. In this FE model 38,562 rectangular elements were utilized. The computational results obtained in this study are fully consistent with results discussed by Takei et al. [186] with error being less than 5%, as shown in Figs. 5.
Figure B4 - (a) The rectangular sample used in this study with dimensions of 10 mm x 20 mm x 1 mm) and (b) the finite element (FE) modeling for the simulation of wrinkles formation. As seen, development of five full- and two half-wrinkles in the neighbourhood of the strip tape is identifiable.

Figure B5 - The normalized amplitude of the wrinkles with the relative distance from the strip tape. It should be noted that the relative distance is defined to be the ratio of the wrinkle length to the wrinkle wavelength.

Case Study II (Validation): An elliptic balloon laying on a flat surface under a concentrated force applied at the center from top is considered (Fig. B6a,b,c). For simplicity, we assume the balloon is made up of a linear and isotropic material with a stiffness of 1000 Pa and the Poisson’s ratio of 0.37 which has no flexural stiffness (membrane). Three thicknesses of 5 nm, 10 nm and 15 nm are
considered for the balloon and the diameter of the balloon is set to 5 \( \mu \text{m} \) when viewed from top. From the side view, the balloon is elliptical with a height of 8 \( \mu \text{m} \). The balloon is assumed to be filled with a softer material with a stiffness and Poisson’s ratio of 100 Pa, 0.30, respectively. We apply a semi-spherical tip-indenter with a diameter of 1.67 \( \mu \text{m} \) at the center of the top surface of the balloon. The penetration of indenter was kept constant at 2 \( \mu \text{m} \) (~25% axial deformation) for each thickness.

![Figure B6](image)

Figure B6 – Display of the model used for testing the proposed wrinkle model. (a) Demo of the applied model including the indenter and the balloon, (b) the mesh model used, and (c) the applied boundary conditions. The wrinkle formation as the thickness of the balloon is decreased is demonstrated in (d) thickness is 15 nm, (e) 10 nm, and (f) 5 nm when the balloon is viewed from top. In Fig (d) elements capable of taking wrinkles compared to normal elements are identifiable.
The three-dimensional CAD model of the balloon and the indenter was developed in AutoCAD 2016. Upon an element-independency study, the total number of elements in the mesh model must be at least 8713 if the membrane thickness is 15 nm, otherwise, the proposed model is incapable of capturing wrinkles. A finer mesh model especially around the indenter tip is required as thickness of membrane becomes thinner. We used 15,670 and 35,056 elements, corresponding to the membrane thickness of 15 nm and 10 nm, respectively. As demonstrated in Fig. 6d,e,f, the length and the depth of wrinkles both increased upon the increase of thickness unlike the number of wrinkles. Also, the number of wrinkles increases with decrease of thickness which is consistent with other studies [175], [176], [185].

Results:

Mesh Independence Study: It is done by performing additional computation for each model with greater mesh density. The mesh size is reduced to the point where by increasing the mesh density the results are not affected. It should be noted that since mesh density and wrinkle size are related, therefore, for each model the mesh independency study was done separately.

In this study, the time-dependent simulation of the mitral valve closure was simulated while formation of wrinkles was also taken into consideration. The following constitutive material model was considered for the assessment of stress-strain behavior of the mitral valve. This model is defined based on the following strain energy density function for a hyperelastic and incompressible material model [187], [188]:

$$\phi(I_1, I_4) = C_{10} e^{C_{01}(I_1-3)} - 1 + \frac{c_0}{2} [(1 - \beta) e^{c_1(I_1-3)^2} + \beta e^{c_2(I_4-1)^2} - 1]$$  \(10\)

Here, \(I_1, I_4\) are strain invariants and \(C_{10}, C_{01}, c_0, c_1\) and \(c_2\) are material constants. \(\beta\) is the parameter controlling the degree of anisotropy in the leaflet tissue. For example, \(\beta = 0\) for isotropic material
models and $\beta = 0.5$ for transversely isotropic material models. The second portion of Eq. (10) describes the nature of a fiber reinforced material model whereas; the first portion is responsible for the stability and convergence criteria of the numerical solver used. Table B1 outlines the numerical values used in this modeling work, which were obtained from previous biaxial and uniaxial studies discussed in the method section [189].

Table B1: Numerical values of the constitutive material model parameters used in this study [189]

<table>
<thead>
<tr>
<th></th>
<th>$C_{10}$ (KPa)</th>
<th>$C_{10}$ (KPa)</th>
<th>$C_0$ (KPa)</th>
<th>$c_1$</th>
<th>$c_2$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaflet Tissue</td>
<td>2.85</td>
<td>6.79</td>
<td>32.3</td>
<td>75.95</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(Isotropic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaflet Tissue</td>
<td>0.84</td>
<td>28.68</td>
<td>13.93</td>
<td>79.79</td>
<td>66.03</td>
<td>0.5</td>
</tr>
<tr>
<td>(anisotropic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal Chordae</td>
<td>4.79</td>
<td>137.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strut Chordae</td>
<td>18.55</td>
<td>121.07</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The dynamic of the valve was characterized in three progressive ways. Phase (1) is considered as the early stage of the closing phase. In this phase, leaflets are pushed by the blood stream but neither contact nor wrinkles are formed on the leaflets. Essentially, this motion can be characterized as a rigid body motion of the leaflets due to the gradient of pressure across the valve. Based on our proposed computational model this phase takes ~12 ms and the maximum principal stress of 36 kPa occurs at the commissure of the anterior leaflet and at the free edge of the posterior leaflet. The stress map of maximum principal stresses is shown in Figs. B7a,B7b,B7c. Phase (2) is characterized by formation of friction contact between the anterior and posterior leaflets without formation of any wrinkles. As observed in these figures, even though in the beginning the closing phase of the valve most of the leaflet tissue experiences rigid body motion but due to bending of the leaflet tissues, a small amount of bending stresses are built up in the valve structure. As results show, this phase takes 36 ms where the maximum principal stress falls within the range of 64 kPa to 151 kPa. The locations of the high stresses are more or less the same compared to the first phase with one major difference, high stress zones are also developed in internal nodes on the leaflet away from the free edge of the posterior leaflet as shown in Figs. B7d,B7e,B7f. Phase (3) is characterized as both the friction contact and wrinkle occurrence on the leaflets as the two leaflets
come together, and coaptation takes place. This phase takes around 100 ms. This is the longest of the three phases while the maximum principal stresses fall within the range of 186 kPa to 302 kPa. The results of formation of wrinkles and friction contact are shown in Figs. 6g,6h,6i. There are six identifiable wrinkles which are formed on the anterior leaflet. At the basis of the wrinkles the amount of maximum principal stress is as high as 240 kPa which is quite substantial. As reported by others, the von Mises stresses at the same areas fall within the range of 200 kPa to 225 kPa [12] which is 10% less than the value proposed in this study. It should be noted that since shear stresses in the heart valve leaflets are insignificant, the von Mises and principal stresses are comparable value-wise.

To the best of my knowledge, this is the first ever computational study that accounts for the wrinkle formation for the simulation of mitral valve dynamics during the closing phase. The author of this study offered a numerical technique for modeling aortic heart valve leaflet mechanics in which wrinkle formation was accounted for but in the aortic position [9]. Results of the proposed model strongly show that formation of wrinkle in mitral valve leaflets elevates the maximum principal stresses by a factor of 10%, which is significant. Results strongly support that the basis of wrinkles are likely the high-risk location when mechanical tears may start or an existing tear may grow and propagate. The issue becomes even more intense as the leaflets are prone to calcification. In other words, depending on the degree of calcification in the leaflets, the elevated value for principal stresses at the basis of formed wrinkles are higher. Using the proposed computational model and taking into consideration wrinkle mechanics in the mechanics of mitral valve leaflets may give us more insight into the stability of calcified leaflet dynamics in the opening and closing phases.
Figure B7 – Finite element analysis results of mitral valve dynamics in the closing phase. The Maximum principal stresses are shown on the mitral valve leaflets during the progression of the closing phase. Early stages are characterized by just the rigid body motion of leaflets as shown in Figs a, b and c. The second stage is characterized by the anterior and posterior leaflets making contact, but no wrinkles are formed which is shown in Figs d, e and f. The final stage is characterized by the maximum capitation area between the leaflets and fully developed wrinkles.
Appendix C

Appendix C includes silicone & rubber materials used.

C.1 Silicone Material Used

Figure 6.12 Ecoflex 00-30 platinum cure silicone rubber material used

C.2 Rubber Material Used

Figure 6.13 Mold Max 30 silicone rubber compound used
Appendix D

D.1 HVPL Miniature Heart Simulator 2.0 Engineering Drawings

This subsection of the appendix includes dimensioned drawings for the second-generation of the heart simulator. Drawings include: The heart chamber; Sealing blocks with annulus attachments; Ventricle attachment; and the atrium attachment. All drawings are 98% of their actual size.