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Implementation of A Helically Contracting Assist Device To Mitigate Advanced Heart Failure

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical Engineering

by

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DEDICATION

To

My Beloved Family

Whose love, encouragement and endless sacrificial care and support let me get such an honor

My Friends

and

All my hard working successful and respected Teachers

in recognition of their love and support

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ABSTRACT OF THE THESIS

Implementation of A Helically Contracting Assist Device To Mitigate Advanced Heart Failure

By

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Master of Science in Biomedical Engineering

University of California, Irvine, 2018

Professor Arash Kheradvar, Chair

Current treatment options for advanced heart failure patients are either heart transplantation or mechanical heart assist device systems with their advantages and disadvantages. This thesis examined the use of helically structured design for novel heart assist device which is inspired by the heart`s own intrinsic helical muscle fiber structure. The study device utilizes a novel external system that assists the heart`s natural helical motion outside the pericardium without direct blood contact. The proof of concept of the helically inspired assist device is also examined on the bench and ex vivo studies. The test VAD was verified twice on bench testing using an excised pig heart having moderate rigor mortis. A cradle was constructed for us to put the dissected pig heart on top of it and placed our pump around the heart. The pump is rotated by an attached motor to lower ring, which was controlled with an Arduino system. A flow tube was connected to the output of the pig heart aorta to observe volume changes through it. In these bench tests, although not a fresh harvest, a dissected pig heart was tested; we were able to see how the pump helps contract the ventricle. An early prototype, which has no adjustable upper ring, shows slight damage

onto the endocardial heart muscle whereas the latest design where the upper ring can be adjustable showed none. The helically fashioned design exhibits promising candidate for future of the heart assist device technology and the people who suffer from advanced heart failure.

CHAPTER 1

Introduction

1.1. Advanced Heart Failure Disease

Cardiovascular diseases (CVD) are the number one cause of death in the world among several types of diseases (see figure 1.1). The number of people who died from heart diseases was 635,260 (23.1% of total deaths in 2016) in the United States alone [1,2,3]. Like other cardiovascular diseases, heart failure is a major public health issue with a rising prevalence. This is due to the aging population and epidemics of diabetes, obesity, and hypertension. Its prevalence is over 5.8 million in the U.S. alone, and almost 23 million worldwide [3]. CVDs include stroke, rhythm disorders, coronary heart diseases, heart failure, and congenital heart disease, etc. Additional contributors to these diseases include smoking and tobacco use, physical inactivity, overweight, and obesity. These contributors may lead to issues such as high blood pressure, diabetes mellitus, and high blood cholesterol [4].

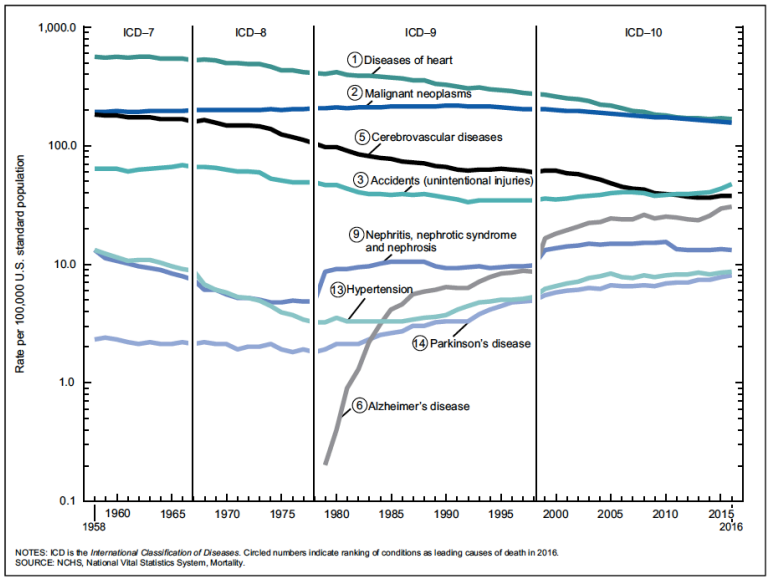

Figure 1.1: Age-Adjusted death rates for selected leading causes of death: United States, 1958-2016. Taken from Xu, J., 2018[1].

Heart failure (HF) is a complicated clinical syndrome that is caused by any functional and/or structural disorder of ventricular filling or ejection of blood out of the heart. Some of the symptoms of HF are fatigue and dyspnea, which can lead to a limitation of exercise tolerance, and fluid retention, which may cause pulmonary congestion or peripheral edema [3,5,6]. Some patients can have multiple symptoms while others present only one. Unfortunately, there is no single diagnostic test. Thus, clinical diagnosis, which formed on physical examination and careful consideration of patient history, carries importance. The clinical disorder may result from several sicknesses of the heart valves, myocardium, pericardium, endocardium, or great vessels, yet most patients with heart failure have symptoms because of impaired left ventricular (LV) myocardial function.

Moreover, several reasons cause HF; dilated cardiomyopathies, familial cardiomyopathies, endocrine and metabolic cause (obesity, diabetes, and thyroid disease , etc.), toxic cardiomyopathies, tachycardia-induced cardiomyopathies, and myocarditis and so on [5]. To be able to help HF disease patients, instead of categorizing them we focused on assisting the heart with a heart assist device, which covers most of the patient profile with HF. Although there are few different types of HF, which is associated with an LV functional abnormalities grouped as heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HfrEF), we are going to focus on only EF itself at this moment. To simplify, we can refer the HfpEF as "diastolic HF" and the HfrEF as "systolic HF". The reason why we focus more on EF is that it is considered significant in terms of the classification of HF patients. Even in patient selection for clinical trials are based on EF. As per the classification, patients whose EF range between 40% and 50% are considered as an intermediate group [5]. One needs to be in Stage D (ACCF/AHA) or Class III and IV (NYHA Functional Classification) to be considered as a possible mechanical support device recipient (see table 1.1. below). In other words, they need to have EF lower than 40%. In 2009 ACCF/AHA guideline for heart failure, stage D was defined as "patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as MCS, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice [5,7].

ACCF/AHA Stages of HF (38)		NYHA Functional Classification (46)	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

Table 1.1: Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications. Taken from Yancy, C., 2013[5]

Heart failure notably decreases the quality of life in terms of health-related factors such as physical and vital functioning. Unfortunately, HF is a progressive sickness[8], and its prevalence and incidence are increasing at widespread proportions. Improvements in terms of survival from HF overall and the aging population are the reason why prevalence rises. The incident has been around the same level over the last few years, with more than 650,00 new HF cases annually [2,4,5]. Like it is mentioned above, "HF incidence increases with age, rising from approximately 20 per 1,000 individuals 65 to 69 years of age to >80 per 1,000 individuals among those ≥85 years of age [5]". Projections indicate that the prevalence of HF will increase by 46% by 2030, resulting in affecting more than 8 million Americans, and 28 million worldwide [3]. Also, according to Framingham heart study, developing an HF for the lifetime at the age of 40 is one in 5 no matter what the gender is. The mortality due to HF is more than 70,000 Americans and 300,000 worldwide, yearly [2][3][4]. Sadly, almost 50% of HF patients die in a period of 5 years after the diagnosis [4].

Furthermore, there is also another big impact of heart failure besides health: economic burden. Like as other CVDs, HF is a reason for vast health and economic burden

globally. Projections show that the total amount of HF will rise almost 127%, between $69.7 billion and $97 billion by 2030[4] (see figure 1.2). This total cost is consist of medications, health care services and lost productivity. To sum up, among all the types of HF patients like HFpEF, HFrEF etc., almost 5% to 10% HF patient population has advanced (end-stage) heart failure (NYHA – Class III to IV and ACCF/AHA – Stage D) who we focus on to assist their heart to solve their symptoms [3,9].

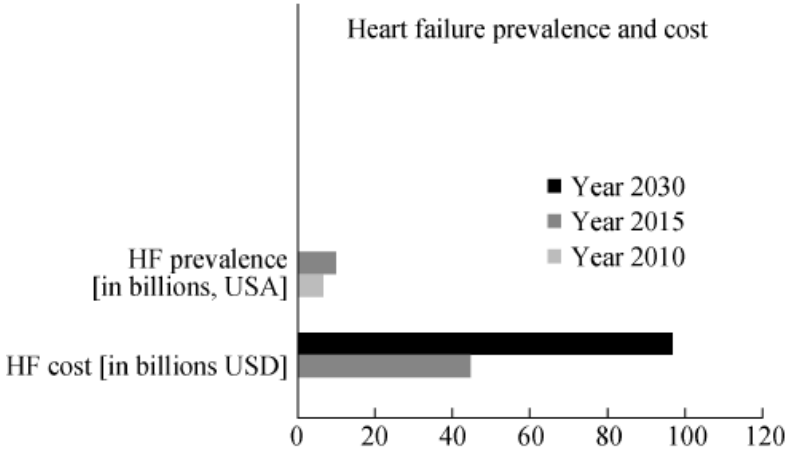

Figure 1.2: Heart Failure prevalence and cost projections by 2030. Taken from Chen-Scarabelli, C., 2015 [3].

1.2. Heart Failure Treatment Options: Medication, Cardiac Transplantation (HTx) or Ventricular Assist Devices (VADs)

Advanced heart failure treatments refer to cardiac transplantation or mechanical circulatory support systems (MCSS). After the state-of-art pharmacological therapy (medication) that consists of beta blockers or diuretics etc. , and cardiac resynchronization treatment are failed, HTx remains as the last option [10]. In early stages of heart failure, correction of the lifestyle in a healthy way and medications can help to manage the

sickness. However, since heart failure is a gradual health problem and as it progresses, treatments vary from pacemaker application for less severe patients as to correct their electrical issues of the heart to more complex treatments like the total artificial heart (TAH) or heart assist devices, MCSS in general, for end-stage heart failure patients. MCSS can be used for from a few days to months [9]. These devices allow patients to have cardiac recover as well as other vital organs` recovery like brain, kidney etc. There are MCSS for a short-term purpose such as intra aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) etc. and long-term purpose such as total artificial heart or ventricular assist devices –which is our focus in this study-.

On the other hand, heart transplantation is another therapy option for end-stage heart failure. Unfortunately, the main limitation of HTx is that there is a limited number of donor hearts available as opposed to millions of patients with heart failure [10]. The need for heart greatly exceeds the number of donated heart led us to produce and use these mechanical devices to save patients life. With the improvements in technology, recipient and donor selection, immunosuppression and medical practices post-transplant survival has increased. Thus, even though there is a shortage of organ donor, HTx is considered as the gold standard treatment for HF [5,9,10,11]. Survival rates after the HTx are excellent in comparison to medical therapy. According to International Society for Heart and Lung Transplantation (ISHLT), HTx has reached its highest of all time (between 1982 to 2015) at a total number of 5,074 in 2015 (see figure 1.3). As per the survival, among 126,753 HTx procedure between these years, it was better in pediatric patients than in adults with a median survival of 16.1 years and 10.7 years, respectively [12]. Also, as ISHLT indicates 1-

year survival is 84.5% [10]. Luckily, post-transplant survival rates did not get affected negatively by pre-implanted mechanical support devices [12].

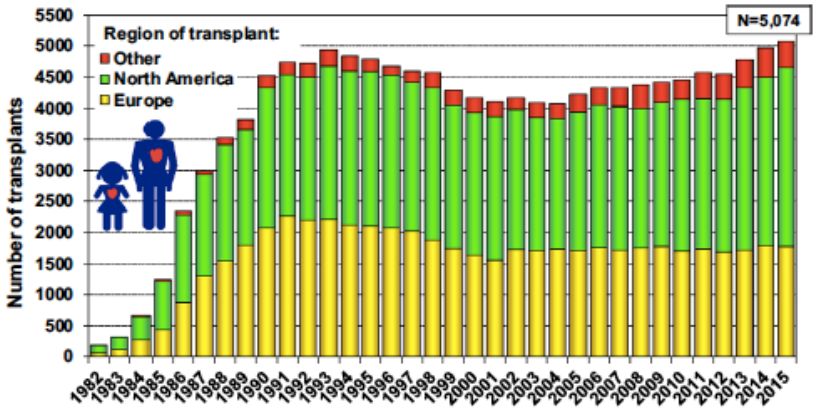

Figure 1.3: Number of adults and pediatric HTx by year and geographic region. Taken from Lund, L. H., 2017[12].

However, no matter what HTx comes with its risk and disadvantages as well. The utmost risk is that the possibility of rejection of the donor heart, which accounts for almost 10% of deaths within the first three years post-transplantation [10][12]. Because the body may see this newly transplanted heart as a foreign object and want to attack it. So, patients are going to be under life-long immunosuppression therapy to keep their immune system from attacking the transplanted heart.

Another problem of HTx is with coronary arteries. The walls of the arteries can thicken and harden, which may restrict the circulation of blood through the heart difficult and cause heart failure or rhythm problems. Lastly, renal dysfunction (accounts for 30% of patients affected), infections, diabetes and other organ insufficiencies can grow, and cause post-transplant morbidities [10][12].

Ventricular assist devices (VADs), on the other side, have been developed and design to assist and provide mechanical circulatory support the native heart with reduced ejection fraction since the original VAD design by Dr.Michael DeBakey in 1960s. Multiple different devices for circulatory support have been developed that range from VADs to TAH. The very first aim of VADs is to unload the blood from failing intrinsic heart and take it to aorta as to maintain forward cardiac output and systemic perfusion. These VADs are differentiated by the flow characteristic (pulsatile and continuous), pump mechanism (axial, centrifugal and displacement of volume), the location of the implant (intracorporeal and extracorporeal) and the supported ventricle (right, left or biventricular) [5](see table 1.2 and figure 1.4). Patient selection for MCSS protrudes with the candidacy of HTx, however, since HTx still is considered as gold standard for advanced HF implantation of VADs should be given in the light of the possible benefits to the patients [9]. Therefore, with respect to the previous statement; MCSS can be used in short-term or long-term, however, because of the issues that were mentioned like other therapies and lack of HTx procedure due to the shortage of donor, more common way of using them are long-term consists of bridge to heart transplantation (BTT), bridge to decision/candidacy (BTD), bridge to myocardial recovery (BTR) and destination therapy (DT) [5,13,14]. BTR is for a patient who needs a temporary assist from few days to weeks. BTT is reserved for a patient who meets the HTx criteria but needs extra circulatory support prior to transplantation. The last group, DT, is referred for a patient who is not a candidate at all for transplantation whereas still requires support until death [8]. MCCS can bridge some patients to HTx who are excessively sick and have high-expected mortality while on the waiting list for a donor heart. Also, the purpose for a bridge, MCSS can be used for patients who are ineligible for

HTx like who have a cardiogenic shock or end organ insufficiency. Thus, it saves patients time to stabilize their hemodynamics and organ perfusion [9].

Volume Displacement	Thoratec 'HeartMate I XVE/IP'
	Thoratec 'IVAD/PVAD'
	Abiomed 'BVS5000/AB5000
Rotary - Axial Flow	Thoratec 'HeartMate II'
	Jarvic Heart 'Jarvic 2000 FlowMaker'
	MicroMed 'Heart Assist 5 Adult VAD'
	Berlin Heart 'InCOR'
Rotary – Radial Flow	WorldHeart 'Levacor'
	Terumo 'DuraHeart'
	HeartWare 'HVAD'
Rotary – Mixed Flow	Abiomed 'Impella'
	CircuLite 'Synergy'

Table 1.2: Types of clinical ventricular assist devices. Adapted from Timms, D., 2011[13].

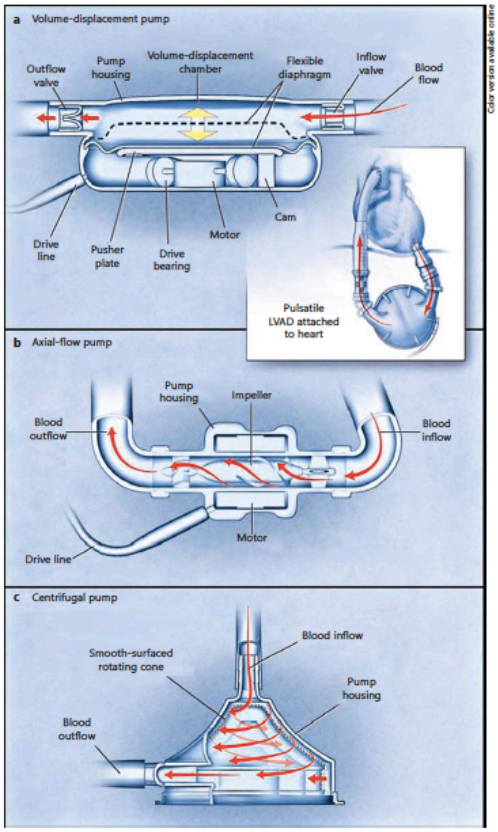

Figure 1.4: Simplified schematic of LVAD designs. a) volume displacement pump, b) axial flow pump and c) centrifugal pump Lee, S., 2013[11].

Basically, how the VAD works is that it is connected to the apex (bottom of the heart) by an inflow cannula that vacuums blood out of the ventricular cavity and an outflow cannula that take blood mostly to ascending aorta. To provide power the VAD, a percutaneous driveline that consists of power and control wires is sent through the skin of the abdominal wall somewhere above the diaphragm. Then, it connects the VAD to an externally attached portable driver that contains electronic controller and batteries (see figure 1.5). In a best descriptive way, VAD assists the failing heart by unloading of which ventricle is attached and generate flow to both pulmonary and systemic circulation. Usually, right ventricular assist device (RVAD) implantation is a rare occasion. Most of the time, an RVAD may be implanted after an LVAD to provide bi-ventricular support to the

native heart [8]. Some studies have demonstrated that ventricular function improved with an implantation of LVAD (Cohen, Thomas, Freed, Rich, & Sauer, 2015)[15].

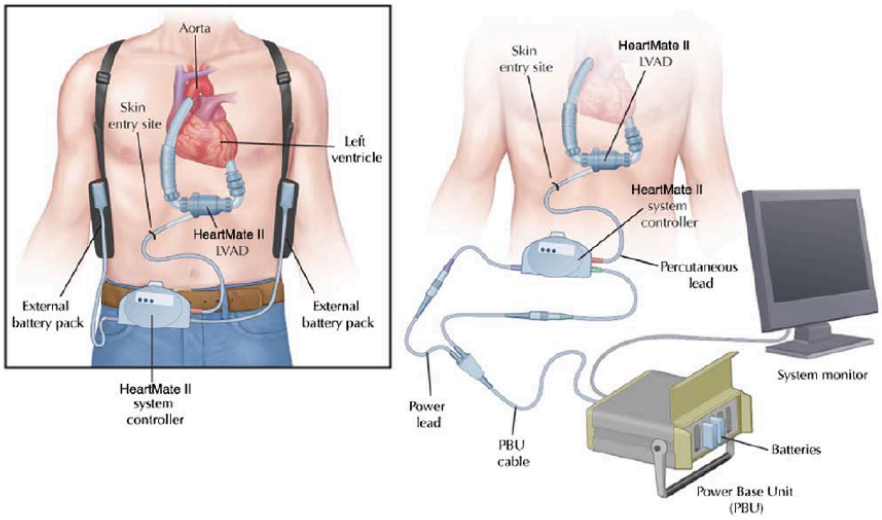

Figure 1.5: Components of a VAD. Figure illustration by Rob Flewell. Taken from Wilson, S. R., 2009[8].

When first generation VADs started to develop, the initial purpose was to reproduce the pulsatile outflow mimicking the physiological function of the intrinsic heart. However, even though the one-year survival rate improved, these devices were flawed in reliability and durability issues. Also, these types of devices played a role as a high infection source due to its large tissue and blood-contacting surface [13]. In addition to these, the structural disadvantages, blood trauma, and high mechanical failure rates led to a push to the development of continuous flow VADs (CF-VADs). These second-generation CF-VADs have demonstrated advantages over first-generation VADs such as durability, a decrease in size, lower infection rates, and increased survival [14]. Yet, due to the lack of understanding of the long-term effects, non-physiological and low pulsatile blood flow trace of CF-VADs, has brought up some major adverse event that includes bleeding, thrombosis, hemorrhagic

strokes, renal impairment and multi-organ insufficiency. Although these concerns above regarding CF-VADs, a distinct advantage of smaller size, easier surgical implantation, quieter vibration-free operation [8], and better mechanical longevity make them accepted form of therapy over the PF-VADs [13]. In terms of technicality, CF-VADs also offer us less power needs to operate with a smaller driveline, which can reduce the incidence of infection.

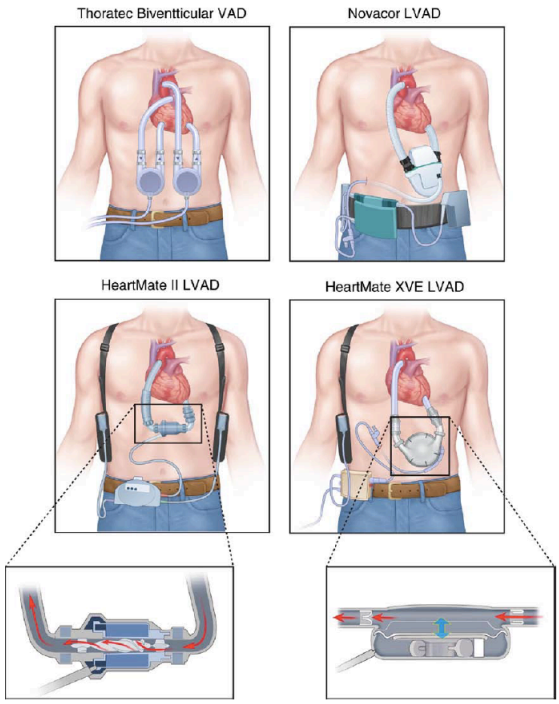

Figure 1.6: Schematics of Commonly Used VADs. Mechanical support systems: Thoratec VAD (top left), Novacor LVAD (top right), HeartMate II LVAD (bottom left), and HeartMate XVE LVAD (bottom right). Taken from Wilson, S. R., 2009[8].

1.2.1. Risk of Ventricular Assist Devices (VADs)

Each type of these VADs comes with its own sets of risks and complications. The important thing is selecting the right therapy and device depending on each patient's situation [16]. One of the major prevailing complications is right ventricle failure after left ventricle assist device implantation whose reported incidence ranges between 13% and 40% [15]. In addition, development of de-novo aortic insufficiency (AI) has been reported associated with LVAD treatment. AI occurs due to combination decrease in left ventricular end-diastolic pressure (EDP) and the increase in aortic root pressure, due to unloaded left ventricle and output of the device, respectively. AI is normally a hint for valve replacement or over sewing. If it were at a severe level, the LVAD would not be able to completely unload the ventricle. Thus, AI may end up causing a dangerous loop of decompensated HF [11,15].

There are perioperative and long-term complications; perioperative complication including right heart failure, sepsis, hemorrhage, air embolism and kinking of the flow grafts (grafts that maintain the by-pass between pump and aorta) whereas long-term complications are mechanical device failure, infection and neurologic event [8].

Device malfunction is one of the important causes of mortality and morbidity for patients with VAD. A study, the REMATCH trial [8], demonstrates that 35% of VAD patients happened to have a component failure within two years of implantation. These failures can arise from any components of the device from controller to the inflow and outflow cannula

grafts, batteries, impeller of the pump and even drivelines that carry the wires outside of the body. Because of the foreign surfaces implanted inside the body can active one`s immune system, coagulation cascade, and the platelets, VADs are prone to thromboembolic events. And if we consider high blood-contact and turbulent blood trace that increase the risk of shear stress on blood, all may cause thrombi formation [8]. Also according to some major studies (New England Journal of Medicine and the Journal of Heart and Lung Transplantation), thromboembolism incidence has raised sharply in VAD patients. Pump thrombosis is a primary cause of death, frequently causing necessity to change the pump [15]. The neurologic problems due to VAD are transient ischemic attacks and cerebrovascular events along with intracranial hemorrhage, seizure, brain abscesses, even though patients have to take anticoagulation drugs.

One of the other most critical complications is the infection, which is a common problem can occur at any time. Unfortunately, VAD is susceptible to infection from the incision site, device pocket (if the VAD requires one), valves, conduits, and drivelines. It is an issue that can be manageable with careful wound care and antibiotics, however, can result in bacteremia, sepsis, and endocarditis if it starts to diffuse too much [8,17].

1.2.2. Limitations And Unmet Clinical Needs Related With VAD

Despite the technological development in VADs, there are distinct limitations and disadvantages associated with the current state of the art of cardiac assist devices that need to be taken into account.

Those limitations include:

- Irreversible modification of heart structure: A hole at the bottom of the heart, apex, needs to be surgically opened as to implant the inflow cannula (see figure 1.7). Therefore, any device malfunction can result in immediate death.
- Right heart failure: As mentioned before, it may also occur due to a mismatch between right and left ventricles.
- Blood thinner (anticoagulation) drug usage: Since VAD implantation is a highly invasive process; there is a high blood-surface contact that may lead to clot formation. To reduce this risk, patients need to take anticoagulation medications. Despite the fact that it looks like this is in favor of patients, blood thinners increase the risk of internal bleeding.
- Blood clots: Due to the nature of VADs, the blood needs to go through the pump and is distributed to the body by aorta. In case of blood clot formation in heart, the pump may send it to anywhere inside the body that may lead to stroke or heart attack, or even cause the VAD`s impeller (see figure 1.7) to stop working.
- Hemodynamics problems; which are associated with the change in blood flow pattern from intrinsic pulsatile to continuous.
- Driveline infections: This can occur since the driveline goes out of the body to connect the pump to an external power source and control panel.
- Frequent recharge need: To provide a certain amount of cardiac output as to maintain regular body requirement, the pump needs to work constantly.

That`s why there is always need for major power supply, and this is powered by the batteries the patients carry with themselves.

All these limitations and unmet clinical needs have led to the development of more minimally invasive methods like such as a helically oriented heart assist system.

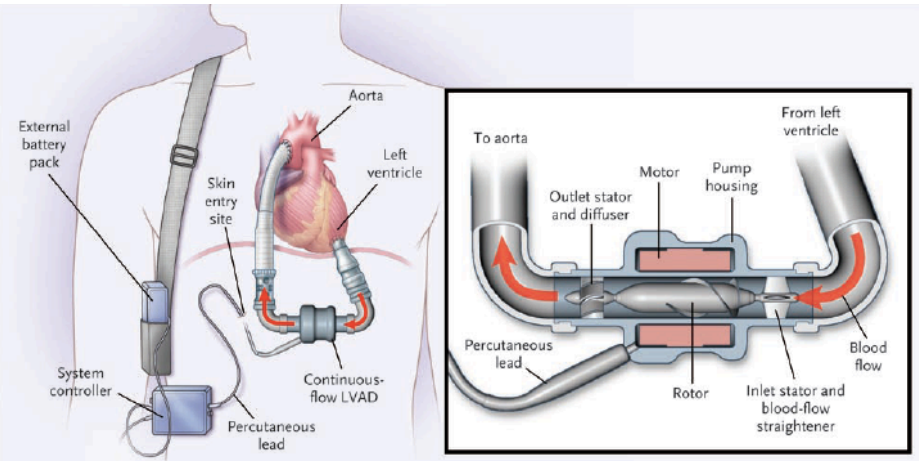

Figure 1.7: Components of the Continuous-Flow LVAD. The inflow cannula is placed into the bottom of the left ventricle after a hole is poked, and the outflow cannula is anastomosed to the aorta. Blood travels from the left ventricular apex through LVAD pump. The LVAD is placed within the abdominal wall or peritoneal cavity above the diaphragm. A percutaneous lead carries the electrical cable to an electronic controller and battery packs, which are worn on a belt and shoulder holster, respectively. Figure taken from Miller et al., 2007[18]

1.3. Helically Oriented Heart Assist Device

The solution we offered with this study is that a novel and true “heart assist” device that will wrap the heart externally and provides an additional contraction force with its patented (U.S. Patent No. 9,656,009 B2, 2017)(U.S. Patent No. 8,794,937 B2, 2014)(U.S. Patent No. US 2009/0131740 A1, 2009) helically oriented wire mechanism, which we

believe it will improve both systole and diastole function of the heart. This device eliminates and provides a better solution to the unmet needs of current technologies since it does not require direct blood contact, and thus, it is anticipated anticoagulation therapy may not be needed. In addition, there will not be a surgical modification to heart, which will remain intact, so even with the device malfunction patient can stay alive till he/she receives further treatment. Moreover, the device is going to be implantable via minimally invasive procedure through rib cage with a small incision, is synchronized with a commercially available pacemaker, and only work to assist the heart when needed. Therefore, the device is more power-efficient since there will be a reduced need for endless power supply. Lastly, it is planned to have this system to be fully implantable, which means that the batteries will be subcutaneous (under the skin) and wirelessly rechargeable for us to eliminate potential driveline infections. Further details are discussed in the next chapters.

1.4. Summary of The Thesis

Implementation of helical contractile concept into the heart assist device as to development, design and in-vitro studies for a novel helically oriented heart assist device is the main objective of this thesis. The helically fashioned wires that reinforce the contraction of the ventricles along with the upward movement of the lower ring of the device are of utmost importance. The development of such a heart assist device would eliminate lots of disadvantages of current ventricular assist device treatment for end-stage heart failure patients and promotes improvements in patients` quality of life. In this

research, previous concept studies, evaluations and different type of materials were first studied to develop an understanding of the type of design needed for the best contraction support by the device. Materials were investigated according to their biocompatibilities and other mechanical specifications for them to be used in the living body properly. Chapter 2 describes these concept investigations and design selection.

Once a proper design was chosen, ideal materials such as wires, lower and upper rings were investigated. Furthermore, research for other components such as motor and its control system has been done. After gathering all the material in proper design criteria, few in-vitro tests have been conducted to show the proof-of-concept for this helically oriented heart assist device. After confirming the design, few prototype options are created using 3D design software and then printed using 3D printing technology. There have been several testing after optimizing the prototypes to have better contraction outcomes. These are discussed in detail in Chapter 3. After all these efforts to produce the best proper prototype, the overall system structure which is synchronization with a commercially available pacemaker and implantation methods also had been discussed in Chapter 4.

Future research on this topic includes maximum possible minimalized pump and motor design and their fully implantable methods. These may be optimized to improve the pump efficiency and increase durability. In addition to in-vitro and ex-vivo testing, in-vivo studies will also be performed using a large animal model, heart failure disease-induced sheep or porcine, for the assist device. The conclusion and the future topics of research are discussed in Chapter 5.

CHAPTER 2

Helical Contractile Concept

2.1. Background

As we discussed in the previous chapter, advanced heart failure (HF) treatment still remains a dominant clinical challenge, and the currently available medical therapies are somehow limited or ineffective for some patients situation. Therefore, this led the community to use mechanical circulatory support systems (MCSS) like ventricular assist devices, which has evolved from short-term extracorporeal and pulsatile system to more durable, smaller and cost-effective intracorporeal continuous flow system [19] over the last 20 years. So, these durable systems are the new era in the treatment of end-stage HF. However, most of this variety of support systems still requires direct blood contact; thus, thromboembolic events and blood thinning medication need, and carries risk such as immune reactions to the foreign body, hemolysis and right heart failure due to mismatch etc. Accordingly, there is a new interest in developing techniques, cardiac compression systems (CCS), to assist the circulation by simply compressing the failured heart from its epicardial surface [20]. Before the usage of these compression systems, there is a procedure called cardiomyoplasty, which includes wrapping the patients' skeletal muscle around the heart and stimulate with myostimulator as to contract it with the native heart. Yet, this technique also comes with its risk and consequences such as high peri-operative mortality rate or conduction disturbances and arrhythmias since the stimulator makes it unable to use of pacemakers or internal cardiac defibrillators [20].

Our proposed method, bio-inspired helically-fashioned assist device, that externally wraps the heart around and actively twist and causes mechanical compression of the surface of the heart in harmony with intrinsic heart with the help of pacemaker synchronization has the potential to truly assist the native ventricular contraction without the complications associated with other devices or techniques. Because no direct contact between the blood flow and artificial or non-biological surfaces means no need for blood thinner drugs and no additional complication arises from contact.

2.2. Understanding The Nature Of The Heart: Effect of Cardiac Fiber Geometry on Torsion Motion

The reason why we called it bio-inspired assist device is that the natural myocardial fibers of the heart fiber also form helical structure (see figure 2.1). Anatomical studies have indicated that cardiac muscle tissue has a specialized structure. It shows a continuously altering fiber orientation through the wall; circumferential near the midwall and more inclined toward the epicardium and the endocardium [21]. The epicardial and the endocardial regions have different fiber orientation in terms of direction (see figure 2.3) [22]. In mammalian LV, myocardial fiber orientation alters smoothly from a left-handed helix on the outer layers to a right-handed helix on the inner layers. Therefore, this creates perpendicularly oriented fibers on the LV wall and contraction of these fibers results in twisting motion or "wringing" [23]. It is also accepted that this fiber architecture has an important role in several aspects of the heart functionally like ventricular contraction and

electrical propagation etc. In addition, some experimental studies have suggested that it plays a major role in the LV filling by storing energy that released during systole as elastic recoil energy and uses it as a potential energy as to create more suction effect [21]. In other words, during ejection as the LV twist: subepicardial and subendocardial fibers contract in opposite directions creates shear forces between layers of the wall, and when these forces are released it creates elastic recoil during diastole as the ventricle untwists. Thus, LV stores potential energy that is released during early diastole (elastic recoil energy) to support ventricular filling [23]. Unfortunately, it is known that myocardium and its fibers can be structurally altered due to many heart diseases, which makes it inefficient in functioning [24]. With our proposed mechanism by assisting the twist motion that has a role in contraction and ejection, we probably make it possible to save the heart its energy as well along with the assist on ejecting the blood out of the heart.

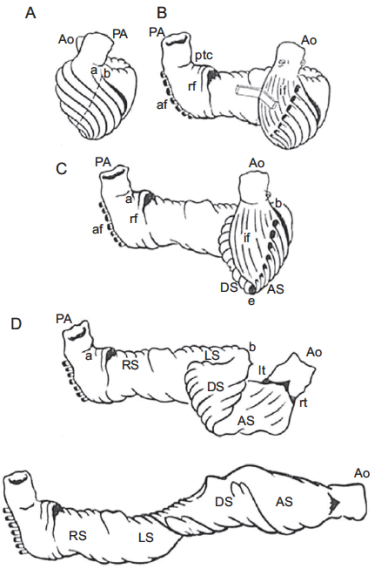

Figure 2.1: Schematic presentation of the helically structured ventricular myocardial band. af, aberrant fibers; Ao, aorta; AS ascending segment; DS, descending segment; if, intraseptal fibers; LS, left segment; lt, left trigone; PA, pulmonary artery; ptc, pulmonary-tricuspid cord; rf, right septal fibers; RS, right segment; rt, right trigone. Taken from Poveda et al., 2013 [24].

Fiber orientation mentioned above is important because left ventricular (LV) torsion that contributes ventricular filling and ejection is directly related to it [22,25,26]. When the helically fashioned fibers contract in LV, it results in torsion as the apex rotates in regards to the base over the long axis [27]. LV torsion mechanic is described as systole begins with a small negative (also called clockwise as viewed from apex) torsional deformation. When it reaches end-ejection isovolumetric relaxation (IVR) it is followed first by sudden torsional recoil in early diastole (this rapid negative untwisting occurs during the IVR and makes diastole begin)[23], then by more gradual untwisting during mid and late diastole [27] (see figure 2.2).

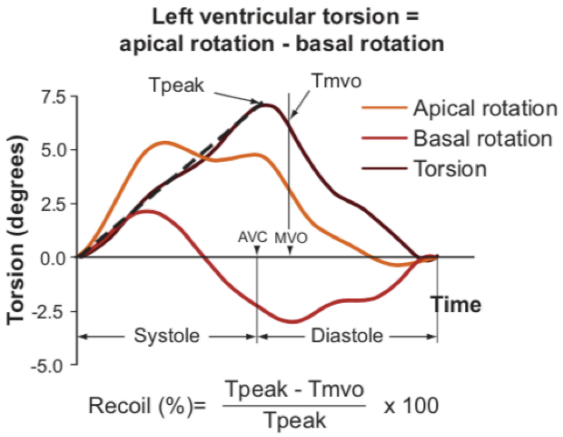

Figure 2.2: Torsion versus Time plot. "Left ventricular torsion (black line) was calculated by subtracting basal rotation (red line) from apical rotation (orange line). Positive torsion rate (dashed line) was the slope of the torsion versus time curve from the beginning of systole to peak torsion (T_{peak}). Recoil was the percentage decrement from peak torsion to torsion at mitral valve opening (T_{mvo}), and recoil rate was calculated as recoil divided by the time from T_{peak} to T_{mvo}." Taken from Burns, A.T., 2009 [28].

To picture it simpler, we can explain the situation like during initial isovolumetric contraction (IVC), both apex and base rotate in the counterclockwise direction as one views from the apex. Afterward, during systole, the apex keeps rotating in counterclockwise whereas the base changes its direction into clockwise. Some sources explain this as the ventricle undergoes an initial slight clockwise torsional deformation, then twist in the counterclockwise direction of ventricle follows it through the end of systole. LV torsion motion is then followed by abrupt isovolumetric untwisting of the ventricle; diastole. As per the diastole, there is a quick clockwise untwisting that occurs before the mitral valve opens and continues still 15% to 20% of LV is filled (See figure 2.4). Then as the last step, more gradual untwist happens for the rest of the diastole at where ventricle has fully filled [23]. The elastic recoil energy stored in the fibers during contraction releases and causes this untwist motion that contributes to active vacuuming of blood from atrium [22].

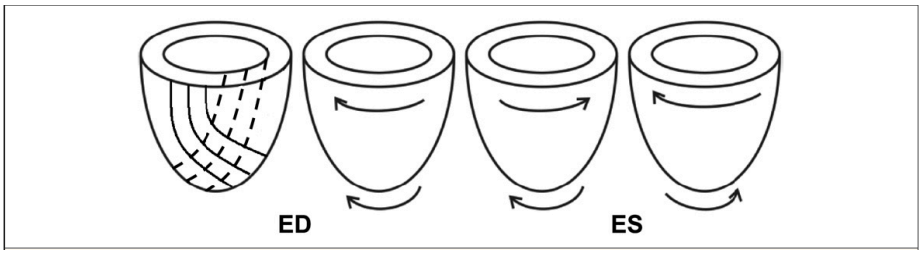

Figure 2.3: Schematic Drawing of LV Torsion. The image on the left shows the myofiber directions. Solid lines indicate epicardial region; dashed lines indicate endocardial region. The image on the right shows untwisting. ED = end-diastole; ES = end-systole; LV left ventricle. Taken from Rüssel et al., 2009 [22].

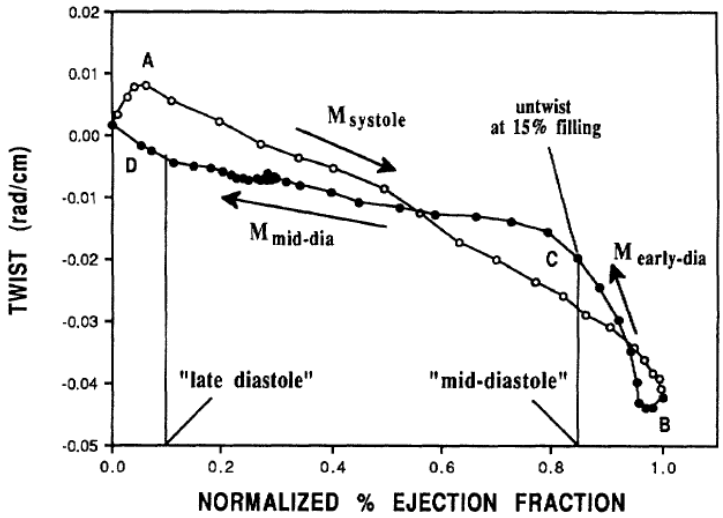

Figure 2.4: "Plot of twist-normalized percent ejection fraction (%EF) relation. After an initial clockwise chamber twist (A), the relation is relatively linear during systole (o) from A to B. In contrast, diastole (o) can be divided into two separate phases, each displaying a different slope. There is an early, rapid recoil (B to C) with little chamber filling (15-20% of normalized EF), followed by a slower chamber untwist relative to ventricular filling (C to D). $M_{systole}$, slope between minimum and maximum twist (A to B); $M_{early\text{-}dia}$, slope between end systole (normalized %EF, 1.0) and mid diastole (normalized %EF, 0.85) (B to C); $M_{mid\text{-}dia}$, slope between mid-diastole and late diastole (normalized %EF, 0.10). Left ventricular untwist during early diastole (first 15% chamber filling) is expressed as percent of maximal twist". Taken from Yun et al., 1991[29].

When we look at LV torsion in patients with specific diseases such as pressure overload due to aortic stenosis, ischemic heart disease, cardiomyopathy or heart failure, we see that LV torsion is affected in different ways. For example, in pressure overload basal rotation reduced but apical rotation increased and delayed in terms of the twist angle at the point of maximum apex rotation (see figure 2.5). Furthermore, in myocardial ischemia (MI), the systolic rotation was less at the apex and diastolic untwisting was delayed. Also, MI would cause a significant decrease in LV pumping function [25]. As for our focus group, heart failure, it was found that decreased twist angle during increased end-systolic volumes (ESV). They also suggested that LV untwisting rate relates to the peak twisting angle and the LV-ESV [22].

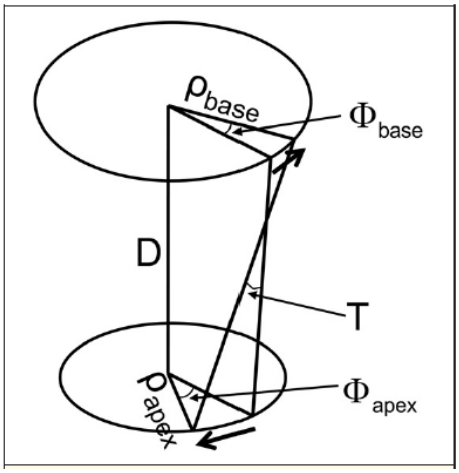

Figure 2.5: A sketch of a basal and an apical plane and the torsional deformation. Twist is defined as (Φ_{apex} - Φ_{base}), twist per unit length as (Φ_{apex} - Φ_{base})/D, and LV torsion T (circumferential-longitudinal shear angle) as (Φ_{apex} - Φ_{base})(ρ_{apex} - ρ_{base})/2D. Taken from Rüssel et al., 2009 [22].

2.3. Design Around Helical Fiber Architecture

The goal of this research was to develop a novel heart assist device that utilizes helical orientation, which is inspired by the nature of the heart itself. While designing this idea from scratch, one needs to consider several indexes that will have primary or secondary effects on the cardiac system. For example, the device needed to restore maladaptive changes like cardiac output or stroke work (SW) inefficiency that caused by cardiac remodeling (i.e. decline in pumping capacity). Or, besides from being produced with biocompatible materials, size, implantation method etc., the device also should be providing an energy savings and less damage to the hemodynamics of heart, and improving the ejection fraction (EF) and/or stroke volume (SV). Hence, we had to take in consideration of the fundamental principles of cardiac mechanics and ventricular-vascular-device interactions with several other design criteria. We know that the current VADs employ a different mechanism to send the blood out to the body and the similar principles govern their hemodynamic effects.

The effect of helical fiber structure for torsional behavior on LV performance is already discussed above. Another important subject when it comes down to design an assist device is the energy efficiency and hemodynamics like stroke volume or ejection fraction. The place where we can find details regarding these is ventricular pressure-volume loops (PVLs) (see figure 2.6). It gives us an idea of how the heart actually is doing under normal or other specific conditions, because events occurring during a single cardiac cycle can be characterized by PVL.

Under regular conditions, it is trapezoidal with a rounded tip [30]. It has four sides what describe: isovolumetric contraction, ejection, isovolumetric relaxation and filling. Also, its boundaries are an end-systolic pressure-volume relationship (ESPVR), and end-diastolic pressure-volume relationship (EDPVR) that shifts due to alteration in ventricular contractility and diastolic properties, and what determines the shape and position of the loop are ventricular preload and afterload.

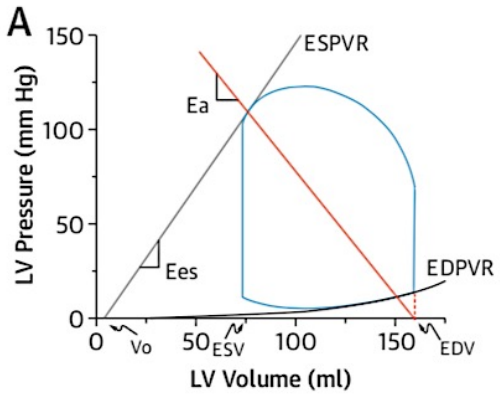

Figure 2.6: Overview of normal pressure-volume loops. PVLs are bounded by the ESPVR and EDPVR. ESPVR is approximately linear with slope end-systolic elastance (E_{es}) and volume–axis intercept (V_o). Effective arterial elastance (E_a) is the slope of the line extending from the end-diastolic volume (EDV) point on the volume axis through the end-systolic pressure–volume point of the loop. Taken from Burkhoff, D., 2015 [30].

The PVLs can be used to understand how key cardiovascular parameters (i.e., SV or EF) are determined by contractility, pre-load, after-load, etc. The stroke volume can be calculated according to $SV \approx (EDV\text{-}V_0)/(1+E_a/E_{es})$ or SV= EDV-ESV. In addition, cardiac output (CO) and ejection fraction are obtained with simply multiplying SV by heart rate, and by dividing SV by end-diastolic volume (ED), respectively. Myocardial oxygen consumption (MVO_2) can also be explained by PVLs; MVO_2 is linearly related to ventricular

PV area (PVA) that is the summation of external stroke work (the area under the PVL) and the potential energy: PVA = SW+PE [30] (see figure 2.7). So, In order to produce an energy saving device, we need assistance that can make the area of PE (or mechanical energy) less by helping the twist motion as we mentioned at the end of section 2.2 above.

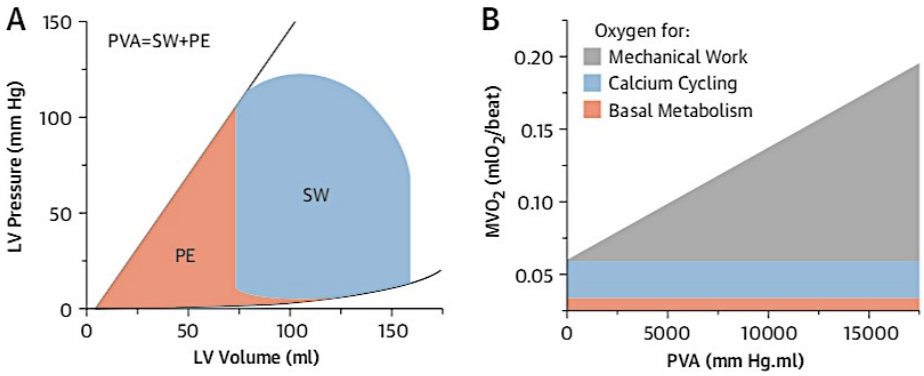

Figure 2.7: Myocardial Energetics Assessed on the Pressure-Volume Diagram. A.Pressure–volume area (PVA) is the sum of the stroke work (SW) and potential energy (PE). B. Myocardial oxygen consumption (MVO_2) is linearly correlated with PVA and is divided into 3 major components, as indicated in the figure. LV = left ventricular. Taken from Burkhoff, D., 2015 [30] .

As per the work required to achieve an EF with your device in which twist can be optimized for obtaining the greatest EF, Grosberg A. et al. shows twisting has better results than the squeezing in terms of work efficiency with using the analytical model of cylindrical tube for pumping [25]. Also, they indicate that the helical fiber orientation has nothing to do with work against the internal pressure since EA is considered linear. Therefore, the work for overcoming the internal pressure would be the same with both squeezing and twisting methods.

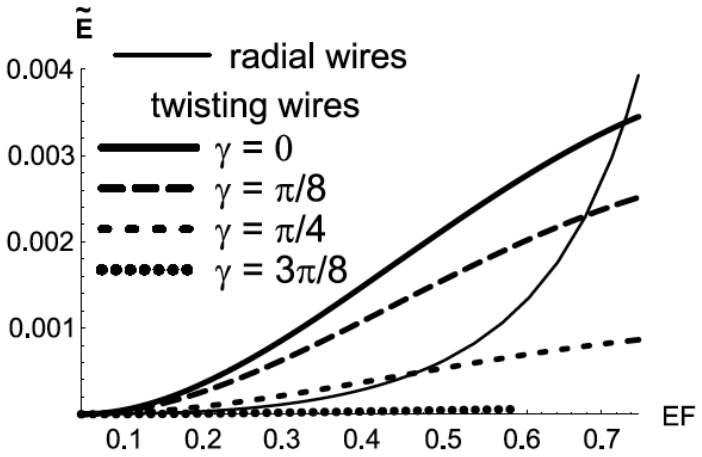

Figure 2.8: The plot of work required vs. the ejection fraction achieved for both the twisting of the bottom of the tube and circumferential shortening of fibers. There are multiple curves for several initial twist angles, γ values. Taken from Grosberg, A., 2009[25].

In the same study with a different analytical model that is more close to the ventricular function of the intrinsic heart by having a half-ellipsoid shell approximation, they suggested that this model could be used in designing of such a device as ours. As it is shown in figure 2.9, they actually created a model that is mimicking the twisting motion and slight upward movement of the apex that is the exact characteristic of the native heart [25]. This approximation fits in our model since Grosberg A. et al. solved the equations assuming the base is static whereas the apex turns with a certain angle as we planned to apply this to our prototypes. In our future studies, what we need to find is that how much force and torque need to be applied over the fibers to obtain maximal EF.

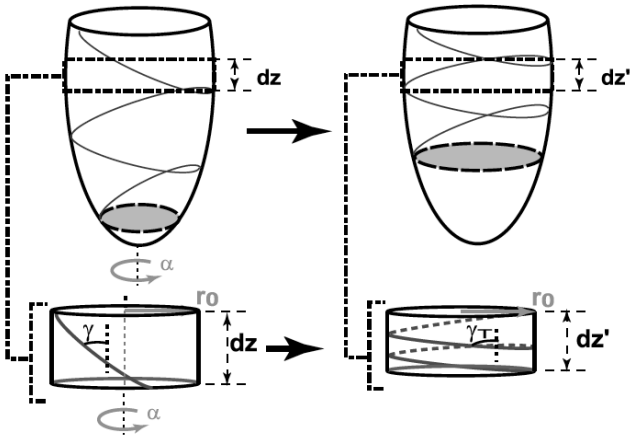

Figure 2.9: A sketch of an ellipsoid that is twisting. The small disk at the bottom is for an example. γ indicates the angle between longitudinal plane and helical fiber which has a turning angle as α. Taken from Grosberg, A., 2009[25].

To sum, since a device utilizes twisting helical fibers formation could reduce energy requirement for pumping [25], and its assistance to torsion movement that has positive effects on ventricular filling and ejection we decided to use this helically oriented design with our system. Thus, ideal helix structure/design was chosen, the overall system was determined and explained in detail in chapter 3.

2.4. Method

After the helically fashioned wire use is decided, we started to think around the possible prototypes. We settled on a design, which is explained in Chapter 3 in detail, consist of one upper ring, one base that connects to the motor, helical wires between upper ring and base, and a felt that acts as a buffer between the device and the heart (see figure 2.10).

Figure 2.10: Drawing of primary components of the prototype

Basically, what will happen when the device senses a trigger signal from the pacemaker is that the motor starts to rotate and this causes the base twist while the top ring remains static. The wires and base turn in the same direction, and because the top ring is stationary the twist causes the base to be pulled upwards as the helical wires shorten (see figure 2.11). The upward motion is also demonstrated in figure 2.12 as well.

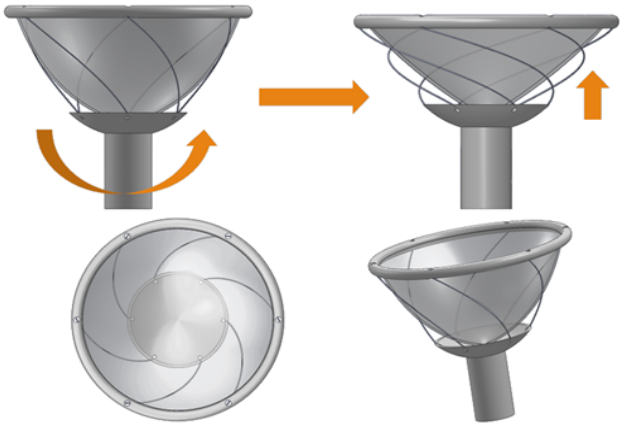

Figure 2.11: A drawing illustrating the physical action of the device. While the base turns, the helical wires twist and shorten, which in turn forces the base to go upward.

Since the twist and upward motion mimic the intrinsic heart pumping mechanism we will be assisting heart naturally instead of bypassing heart with taking the blood out of

the ventricle and send it to the body through the aorta. This also can prevent the heart from getting weaker during the treatment, so in case of pump failure native heart still is enough to support blood consumption for vital functions of the body.

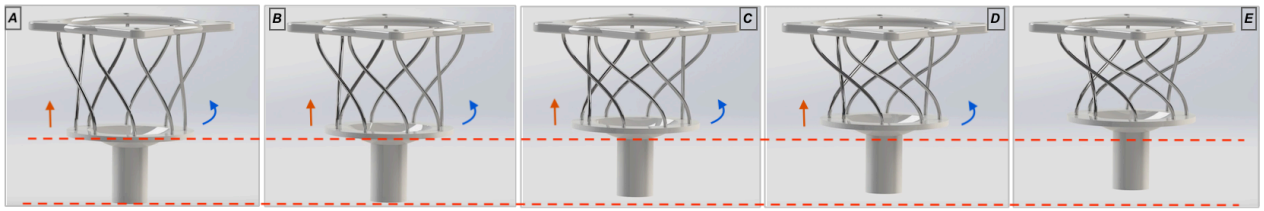

Figure 2.12: Demonstration of upward motion of the pump prototype throughout the photos A to E. Adjusted from the 3D model created by Daryl Nguyen.

In conclusion, as it is seen in the figure above, while the base rotates by the motor (motor is not shown in it) it moves upwards and helical wires get shorten that help the diastole by simply applying pressure the outer wall of the heart. In the next chapter, proof of concept testing is explained.

CHAPTER 3

Prototyping and Testing Helically Oriented Heart Assist Device and Proof of The Concept Testing

3.1. Background

Mechanical support systems have long been investigated and tried as to idealized as the solution to many medical problems ranging from the kidney to heart or neurologically controlled limbs to lungs. Although they have been studied over a long time of period,

progress stays relatively slow due to the fact that these are extremely complicated areas. Despite some of the efforts in the above areas have turned into a device, kidney for instance, still has too much way to go as to be finalized as an artificial organ [31]. To be able to come up with properly working mechanical support systems along with the native organ(s), the organ(s) structure and function even at a cellular level need to be well understood. As per the cardiovascular area, mechanical circulatory support system (MCSS) is also still being under investigations, and everything I mentioned above is completely valid for the cardiovascular and extremely important. One who would want to build an MCSS needs to know everything about heart system from top to the bottom, and effects of it to the body to estimate possible outcomes either positive or negative. For instance, thromboembolic events, hemolysis, immune reactions, infections and the need for blood thinner drugs need to be considered since those contribute significantly to mortality and morbidity. From previous studies, it is found that compression applied to the weakened heart over its epicedial surface, direct cardiac compression (DCC), may provide ventricular support and also help to avoid blood and foreign body interactions. Researchers gained a lot of insight about the effect of DCC on ventricular pumping function from a cardiomyoplasty which is a dynamic biomechanical compression technique applied for patients with heart failure [32]. DCC device technology was also trying to avoid the complications that arise due to a device and blood interactions encountered with the use of the current ventricular assist device (VAD) technology. John H. Artrip et al. showed that the DCC device can increase LV and RV pressure generating capability and, may significantly improve systemic hemodynamics along with avoiding some complications associated with VAD [33].

In this part of the study, materials selection, design of the pump prototype and components for the whole device are examined and, a few ex vivo tests that are conducted with pig hearts were explained.

3.2. Methods and Materials

Few different pump design and motor selections were examined. The main aim of the study was to prove that our design would assist the heart to produce a pump to eject the blood out of the ventricles and improve the ejection fraction. The attachments of the pump are upper/lower rings (or the base) and connection apparatus between motor extension and lower ring, produced with a 3D printer by using PLA. Along with the design of the pump, to find a proper motor type a small DC motor and a relatively bigger stepper motor were also tested. The motor and the pump itself were tested with a harvested porcine heart in a few different sets of experiments. The system was optimized regarding the results gathered in each experiment.

Once the parts for the pump were printed, the wires are attached between lower ring (base) and upper ring by hand and stabled with a knot in each end as the knots stay inside of the rings. The key point was to give the helical structure while leading the wires thorough rings; by means, the initial cross-section should not look alike the wires are straight between rings. The desired look is given in figure 3.1.

Figure 3.1: Helix Cardia visual demonstration. Image by Grant Harrison Barnes

One of the advantages of our design is that the pump part can be tailored to the patients` heart size because we would like to be able to design our pump according to the shape and size of the patient in the end product so that we can provide better assist to the native heart. After the part seen in figure 3.1 was prepared, the motor was attached to the lower ring. There were two different motors we tested our system. The detail about motors is given under the “motor selection” section below. Those motors were controlled with the same set of a circuit but different codes inside. We used an Arduino and a motor driver to control the motor and another Arduino to mimic the Pacemaker, which we called it pacemaker stimulation circuit. With the help of 3 buttons at the stimulation circuit, we were able to set 3 different heartbeats 60, 120 and fluctuating between 60 and 120, accordingly.

In order to have a clear understanding of the process I need to consider materials and methods under different sections, which are hardware, electrical, and software, since this is a complete project that arises from a patented idea to an actual working device. Before starting to design a medical device properly, it is extremely important to

understand the behavior of the material under realistic in-vivo conditions and how some characteristics of this material influence the material response.

3.2.1. Hardware

3.2.1.a. Attachments

The PLA (Polylactide) is selected for attachments parts, which will form the main part of the device that encapsulates the heart. PLA is utilized due to its ease of manufacturing and its low cost per gram of filament to print. PLA is an ideal material because of its low cost in prototyping parts of the pump. Even though PLA does not provide great strength properties as much as other metal alloys which range from 8840 to 9500 psi, it still works for most of our prototypes since the part does not go under a huge amount of pressure while it operates [34]. I must note here that end product is thought to have different materials with a high biocompatibility rather than PLA like titanium. Bioabsorbable polymers, like PLA -one of the most widely produced polymer-, have a progressively important role in BME application because of its abilities such as mechanical, microstructural degradation properties and chemical. Also, it has a unique ability to be resorbed in-vivo specific to the material time frame starting from months to a few years. As it is indicated by J. Bergström and D. Hayman “PLA is used in a wide range of biomedical applications such as stents, sutures, screws, nails, pins, anchors, spinal cages, soft-tissues implants, tissue engineering scaffolds, drug delivery devices, and craniofacial augmentations in plastic surgery” [35]. Even though PLA can be directly used in-vivo, we only aim to use it for prototyping. PLA has good mechanical properties –tensile young

modulus, tensile strength, flexural strength- as opposed to other polymers like polypropylene (PP) or polyethylene (PE) etc. Those mechanical properties determine the material`s behavior under different stress modes (tensile, impact shear, pressure) [36]. At the end, PLA was a good choice for us to start printing our prototypes.

3.2.1.b. Wires

The characteristic of Nitinol, which contains Nickel and Titanium metals, can be manipulated by changing this Nickel and Titanium ratio. It usually is around %50-%50. The more nickel there is, the more elastic behavior known as “superelasticity”. The well-known feature of superelastic (SE) Nitinol is; its flexibility, which is almost 10-20 times greater than stainless steel, and its strains, can be as high as 9-11%. [37,38]. This superelastic Nitinol shows large but fully recoverable strains compared to 316 stainless steel (another popular option to use in medical devices). Figure 3.2 shows a regular stress/strain curve for Nitinol vs. 316 stainless steel. Figure 3.3 also shows the stress/strain relationship for Nitinol vs. stainless steel along with other tissues such as bone and tendon. One may see that the similarities of behavior between organic materials and Nitinol. This behavior gives Nitinol steerability and torquability, which we need to have for our wires to rotate with the motor attached every time the assist system has to work. Even though there are advantages of using Nitinol, there are some concerns over Nitinol as well such as its toxicity. When it comes down to biocompatibility all materials create a foreign body reaction when implanted, so the matter is its degree related to the reaction. Accordingly, biocompatibility relates to the materials` level of corrosion in a specific solution (body in our case) [38]. It is

known that titanium is not toxic in a human body; however, nickel is. There are some effects like carcinogenic and allergic response and muscle tissue degeneration. Researches generally show that Nitinol has quite good biocompatibility since when titanium and nickel are mixed; fortunately, a passive titanium oxide layer (TiO2) is formed on Nitinol, which acts as a barrier to oxidation of nickel and prevents it from corrosion. As those are mentioned above, due to its characteristics (excellent corrosion resistance, biocompatibility, torquability etc.) and the fit for our purpose we chose to use Nitinol for the wires [37,38].

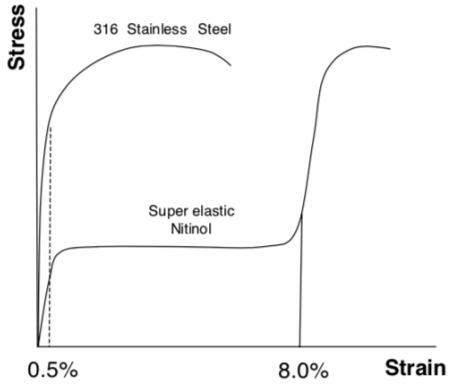

Figure 3.2: The elastic strain range for superelastic Nitinol and 316 stainless steel. Taken from Morgan, N., 2004 [7].

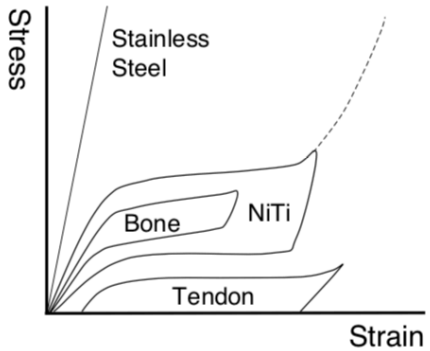

Figure 3.3: The stress vs. strain relationship for superelastic Nitinol, stainless steel, bone and tendon tissue. Taken from Duerig, T., 1999 [38].

3.2.2. Software

For us to be able to rotate the motor, we needed to control it with a microcontroller. For this purpose, Arduino (an open-source computer hardware and software company) is chosen due to its simplicity to use and easy to learn by the researchers who have no prior experiences. There are multiple codes written during the study to find the best fit for the motor in use (DC or stepper motor) and to the pacemaker replication.

3.2.3. Motor Selection

The first two important criteria for motor selection are the size and the torque. The size needs to be small and light enough to make it possible to implant easily inside the chest cavity, and the torque that motor needs to provide has to be high enough to rotate the pump attachment as to assist the heart to send the blood out of the failed ventricles. We first started building our design around a small DC motor that we already have in our laboratory. But the problem with that motor was no specifications for the motor were available since there were no markings on the motor where we can check the features. During our research, we understood that the stepper motor would be a better fit for us; however, we could not find a smaller stepper motor as we desired, which can provide us enough torque. The reason why stepper motors are a better fit is they move in distinct steps. So, because the motor turns pre-set amount each time there is a step occurred, the velocity and the position can be calculated. Knowing these two variables has importance since the pump attachments should not be rotated over some definite angle and velocity to

avoid going against to intrinsic heartbeat and timing. On the other hand, even though we use DC motor, there are some ways to have control over the position and velocity by simply adding encoders to the rear shaft of the motor.

We conducted some more research over the stepper motor option we could use for our purpose and purchased a stepper motor – Anaheim Automation model 34Y106S-LW8-, which can fit in our criteria for motor selection (see table 3.1 below). The reason why we chose the stepper motor over DC motor to start the project with was that stepper motors have some advantages in some applications where the motor has to hold position while still producing full torque. The DC motor also can do this as well but we find out that this will affect its lifespan. When the high-torque stepper motor and a small DC motor were tested first time with a harvested heart, they gave similar results on pumping the heart. The DC motor was 35mm in diameter, 50mm in height, and had a shaft with a 5mm diameter. Both DC and stepper motor were powered with a 12V/500mA power source. Even though we conducted our three ex-vivo tests with both the DC and the stepper motor, we still needed to have smaller but powerful enough (torque wise) motor for us to go for, in order to achieve one of our overall project purposes, miniaturizing. So, after some consideration, we ordered a motor configuration that contains a DC motor (DCX26L GB SL 12V) and a Gear (GPX26 A 103:1) from Maxon Precision Motors (see figure 3.4 and 5.1)(see the table 3.2 below for the details).

Size	Minimum as possible Max up to 2x2x4 (L x W x H)
Voltage	Up to 12V max
Torque	4 N-m or Higher
Type	DC or Stepper preferred
Price	$500 or so

Table 3.1: The criteria for motor selection

DCX26L GB SL 12V	
Power	
Commutation	Graphite brushes
Nominal voltage	12 V
Motor bearings	Sintered sleeve bearings
Electrical connection, motor	
Electrical connection, motor	Cable
Cable length	1000 mm
GPX26 A 103:1	
Power	
Gearhead type	Standard version
Reduction	103:1
Number of stages	3
Overall Product Specification	
Motor Weight	164 g
Motor Length	54 mm
Typical noise level	44 dBA

Table 3.2: Specification of Maxon precision DC motor configuration. Table taken by Maxon brochure

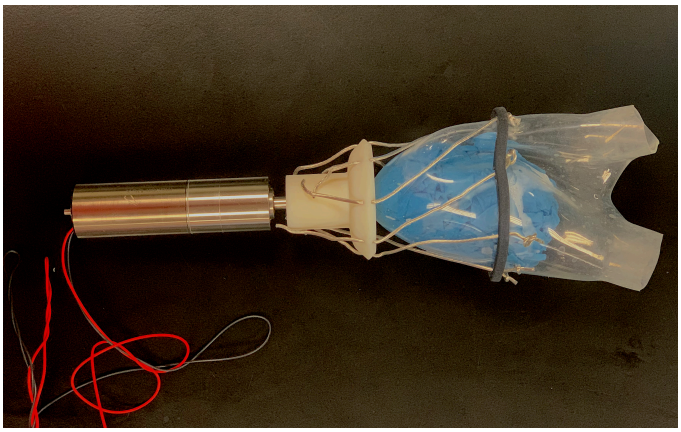

Figure 3.4: Maxon Precision Motor with prototype

In vitro experiments showed that this new DC motor (Maxon Motor) was capable of overcoming certain forces that could prevent it to rotate the base. So it may not be wrong to say that bench test experiments with this motor can help us to acquire ejection fraction on the harvested heart.

3.2.4. Electrical Circuits

The motor that rotates the pump structure is controlled by a circuit comprises motor driver unit, few Arduino processor boards and other necessary circuit parts such as buttons, wires, and power supply (see figure 3.5 and 3.6). We can consider the circuitry system into two different sections: one for controlling the motors (either DC or stepper) and one for Pacemaker stimulation (PMS) part (see the figure 3.5 below for diagram). To start with a second part, at the beginning of the project, we had to come up with a circuit that replicates/mimics the pacemaker since we did not have available commercial pacemaker in hands we can use. This PMS part basically sends a command about the heart rate regarding beat per minute (bpm) to the main part of the circuit as to change the rate of

the motor (see figure 3.5 and 3.6). There were three different bpm options: 60, 120 and fluctuating between 60-120. We set these numbers to see what would the effect of changing bpm on ejection fraction (EF) and cardiac output (CO) during the study. There are no other specific reasons we picked these bpm values. Those could be any numbers between physiological ranges. Of course, as an end product, our device will not be the one, which decides the bpm of the pump but the pacemaker. One of our aim for the end product is to synchronize the pump with a commercially available pacemaker, thus the pump would not work against the heart intrinsic heartbeat. This is also explained in Chapter 4 under synchronization section.

To sum up, PMS part acts as a heartbeat detector by gathering the information from the pacemaker sensing lead to give the main circuit the go signal. We can imagine this go signal as a trigger command, which means if there is a successful pace, which is called capture in pacemaker terminology, to the heart by pacemaker this pacemaker detector circuit receives the pacing information from the pacemaker lead, it will trigger the main circuit as to start the motor rotation to assist the heart. On the other side, the first part of the circuitry is responsible to control motor functions to rotate the pump. Since we had 2 different motor types to test, we had several codes within the same set of the circuit by slight changes on connections (see figure 3.6). This changes occurred due to the different needs of connection between motor driver- stepper motor and motor driver-DC motor. As you can see from the diagram shown in figure 3.6, DC motor required two pins connection whereas stepper motor does require eight pins. As long as, we maintain the correct

connections and proper codes (pin initiation/determination was important) there were no problems controlling the motor.

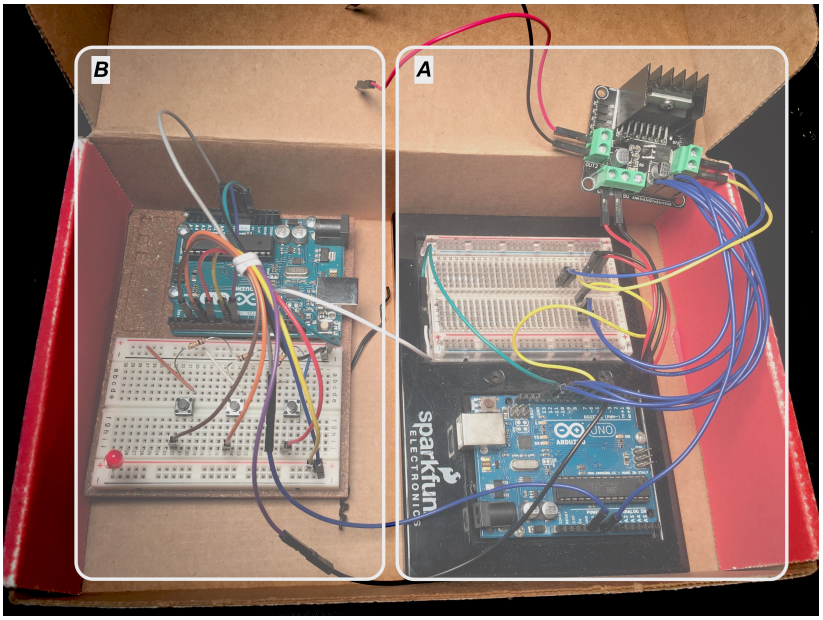

Figure 3.5: Electrical circuitry for motor control and pacemaker stimulator. A) The main part of the circuitry that controls the motor. It consists of motor driver and Arduino. B) The PMS part of the circuitry that mimics the pacemaker and sends a triggering signal to the main part.

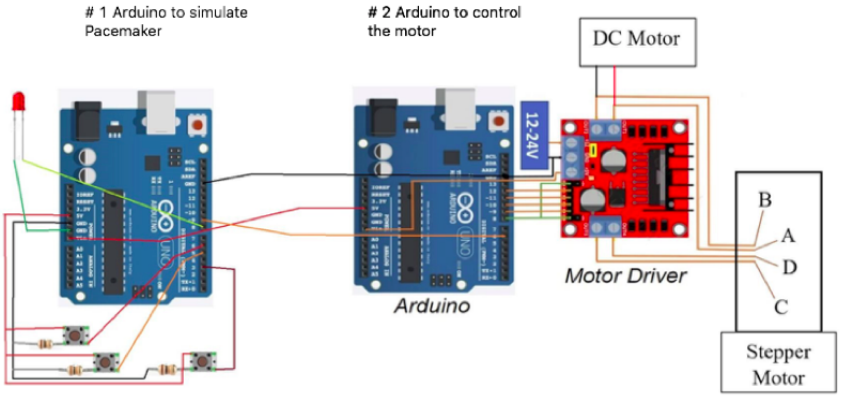

Figure 3.6: Wiring diagram for connection of motor drive vs. motor type

3.3. Results

The first test conducted was at the University of California Irvine Douglas Medical Center on a harvested porcine heart with the purpose of assessing the device fitment. The PLA upper and lower ring parts were attached to midsection and apex of the heart, respectively (see figure 3.7). Rather than being quantitative, this was a qualitative test where we more concerned with just to test the parts and to see how we can fit them around the heart for the first time. What we learned from the first results is a circular design for the top ring attachment was not optimal. It`s because abrasion to the heart tissue can develop due to the mismatch of design and anatomical shape of the heart. Also, issues of rigor mortis was prevalent for us to fit the rings around the heart, especially after the second hour of testing and it made it hard to acquire solid results. As per the shortcomings, the test was difficult to obtain healthy results for several reasons: for one, the heart we were provided had suffered from rigor mortis and had multiple holes in the tissue, which caused leakage during the contractions and made it almost impossible to assess the ejection fraction even though the aim was not to measure it. In addition, we were not well prepared on how to fit the parts around the heart and had no bench tests prior to this test.

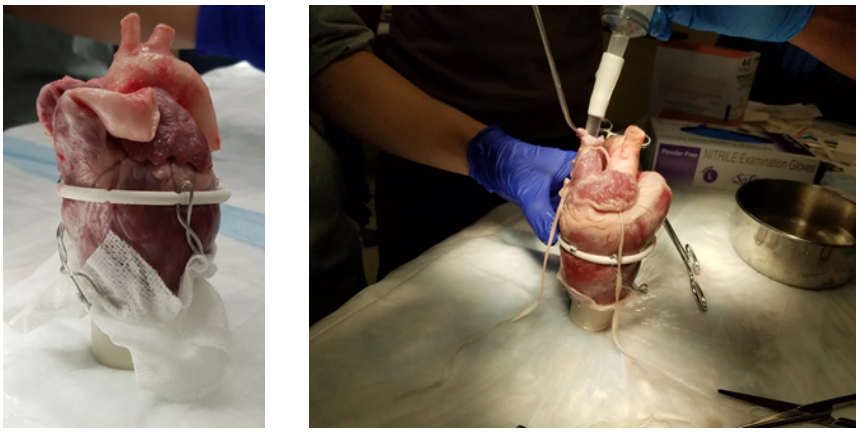

Figure 3.7: Photos from the first test: Test conducted on ex vivo pig heart.

After the first test, attempts were made to improve the design of the rings and the motor. We produced a new upper and lower ring (base) and, bought a new large stepper motor (Anaheim Automation, Model #34Y106S-LW8) that can provide more torque than the previous DC motor we tested. Once we understood the circular upper ring design is not optimal for fitment around the heart, we prepared more elliptic ring (see figure 3.8).

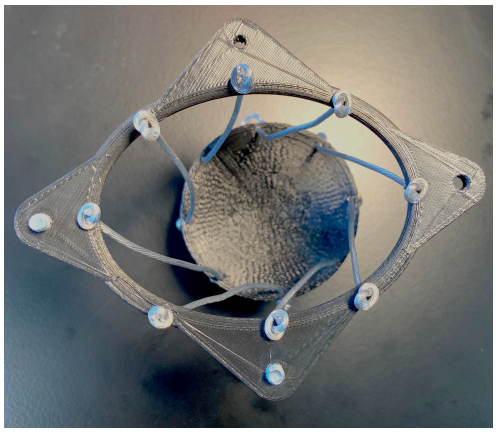

Figure 3.8: Elliptic upper ring design

A second test was conducted with the changes on the design and new stepper motor on a new harvested heart again. The aims of the second test were to quantify the stroke volume and power consumption by measuring how much power was used during the

study, and the water level changes inside the tubes placed in the heart. Also in this second test, Nitinol wires were tested without being treated with heat in advance. Although this may affect its effectiveness, we still wanted to see how it would behave during twist on the heart tissue. This time even though the fitment was better than the previous circular design, we ended up having no place to let the heart extend when it`s filled with saline. Because we 3D printed the parts by forecasting the heart dimensions would be similar to what we had on the first experiment. This is due to the lack of possibility to have imaging of the heart before it is harvested. So, we ended up having a larger sized heart than our upper ring. Thus, there was a clear trace of the upper ring on the surface of the heart as shown in figure 3.10. Unfortunately, we were not able to test power consumption since we did not have any resources for detecting motor power usage. So, the power consumption was estimated based on the data provided on the supplier`s website, by considering how long the motor was active/inactive per twist of the device.

On the other side, we were able to gather some data with respect to stroke volume. To test it, we put a tube into the left ventricle and, filled the heart with saline. Then, with the help of a ruler, we tried to measure the water level changes inside the tube that stays straight upwards with every contraction caused by the twist of the device as it is shown in figure 3.9. The still photos below were taken from a video record show the device causes the heart ejecting the saline inside. In our case, this is considered as a stroke volume changes in every beat of the pump.

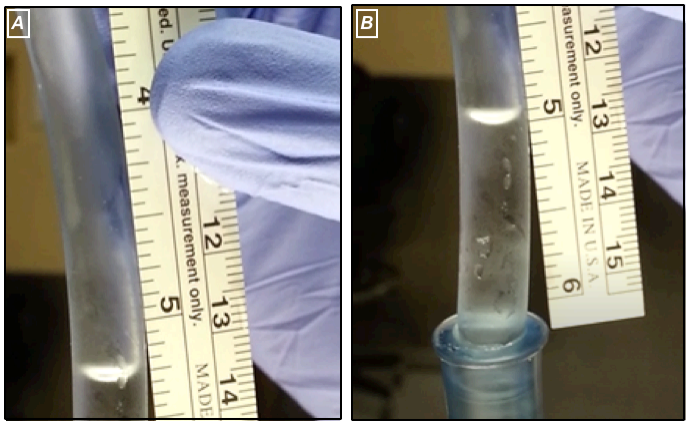

Figure 3.9: Stroke volume (SV) changes. A) SV at diastole, B) SV at systole

We also tried to calculate what cardiac output would be based on our observations by multiplying the stroke volume of the heart by its rpm. The cylindrical tube had 0.35 cm radius and, the water level in this tube changed by 1.016 cm when the heart was full of saline. At this phase of testing, the speed of the motor rotation was set to 60 beats per minute, and the cardiac output is measured 21.336 cm^3. This gives us approximately 0.3556 cm^3 stroke volume value. In terms of ejection fraction (EF), for every single beat the average blood pumps out of the heart is 59 to 89 cm^3 [39], and since the EF is hundred times the difference between the end diastolic volume and end systolic volume divided by the end diastolic volume [40], the EF of the device is 0.29633% by assuming the approximate EDV is 120 ml (124 ± 15 ml) [41]. Unfortunately, this value was not even enough for us to be able to say we have improvement in EF. Again, there could be some negative factors that affect the test why we could not achieve the desired results such: the heaviness of the motor that may led the base not to move upward, improper measurement setup, and rigor mortis of the heart we had. So, even though we redesign the upper ring attachment to fit better in form, the unique shape of each heart (the porcine heart used for the second test was larger than the upper ring we designed) failed us fitment wise. The possibility of being

loose or tight of upper ring attachment was expected because of not having access to the heart dimensions prior to the test. As a result, after removal of the top ring, we realized that the heart was too big for the ring, which caused tissue deformation –indentation- in the midsection of the heart (see Figure 3.10). To sum up, what this second test showed us is that the rigidness of the upper ring was capable of damaging heart tissue and upward movement of the base part was prone to be affected by the weigh of the motor.

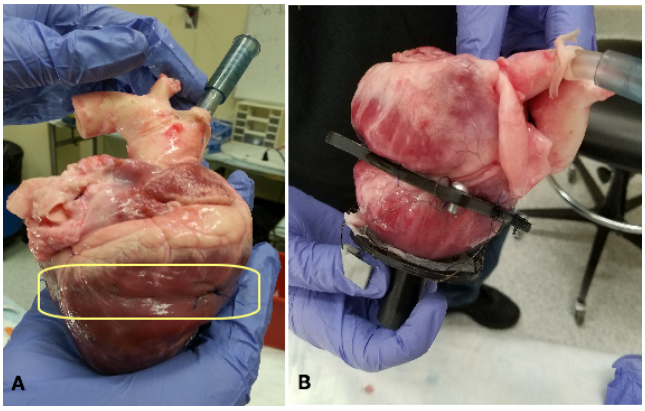

Figure 3.10: Photos from ex-vivo experiment A) Tissue deformation -indicated with yellow rectangle- in the midsection of the heart caused by upper ring, B) the location where the upper ring was attached by sutures.

Following completion of these previous two tests, we came to the conclusion we need to have an upper ring attachment that can be tailored to every different heart size. To achieve this, there should be a mechanism either can be adjustable like a zip-lock or superelastic but durable so that we can slide it around and place it to the upper section of the heart. While researching on the possible elastic material that we may use, we had an opportunity to have an ex-vivo test in a week. So, I came up with a design (see Figure 3.11) that consisted of zip-lock and leather.

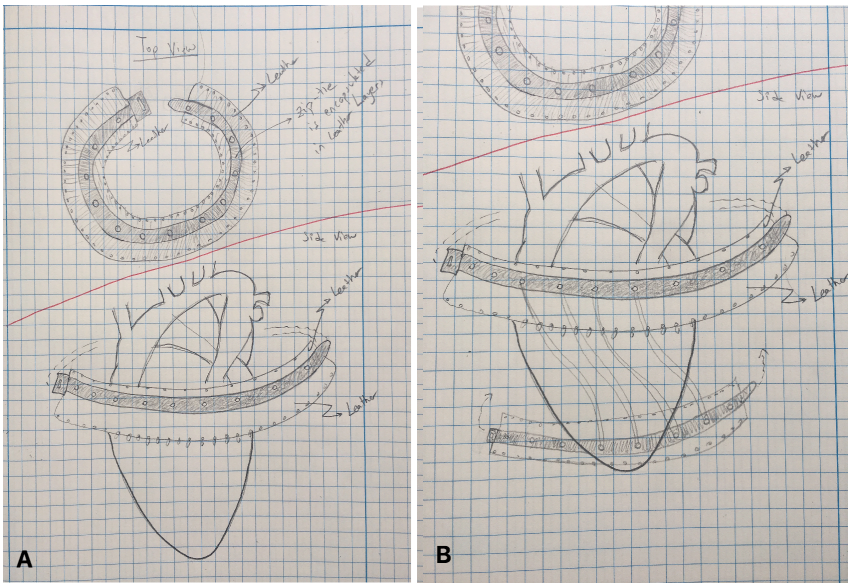

Figure 3.11: Design hand drawing. A) shows different views of upper ring, B) shows possible lower ring attachment

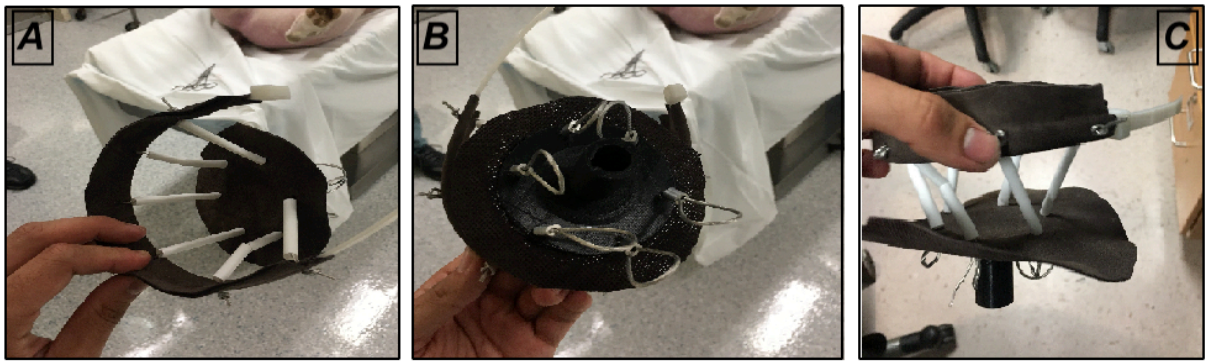

Figure 3.12: Latest attachment prototype that was used in third test. A) Top view before the upper ring adjusted to the size of the heart, B) bottom view with wire length adjusting lock, C) side view; shows the helical wire formation after upper ring is adjusted

What this new attachment (see figure 3.12) did provide us was that leather gave us friction, so we did not need to use sutures to fix the upper ring in place and with the zip-lock like design veterinarian was able to slide one edge of the new upper ring attachment around the heart and tighten it as much as he needed. After sternotomy is done, it is understood that our prototype was larger for the pig`s heart. We still tried to fit it around and started the motor to see the contractions but the upper ring was not stable. That is why

we had to open the lock, cut a small piece of leather to open the zip treads as to be able to tighten it more. However, we also had to cut one of the wires attached in this purpose. After the new adjustments, the upper ring was wrapped around the pig heart nicely. After starting the motor with new adjustment, we have seen that the reduced number of wires cause insufficient contraction to the heart wall. We tried to eliminate this by reducing the length between upper and lower rings. At first, we prepared the first prototype with 5cm of length between rings by looking at the pig heart with Dr. Roger Geertsema, however, pig`s heart we tested on was relatively small. But again, after this new adjustment contraction was still not sufficient to make pulse. The team hand man manipulated the device to determine the amount of rotation required to generate a pulse. The amount of rotation required to generate a low pulse was approximately 220 degrees (which may or may not have the potential to damage the heart.) A small amount of direct pulsing of the ventricle by hand did produce a slight pulse. To duplicate a similar amount of pulse via the device required an amount of rotation that caused the heart to rotate and slightly collapse the left atrium. While testing our device, it was seen that there was no need for suturing the upper ring to the heart tissue. The combination of the zip-tie mechanism and leather provided enough grip properties. We definitely have to consider suturing in long-term testing to make sure rings stay stable where we want them to be. Lower ring, similarly, the texture of the thin leather strips provides a sufficient amount of grip to the heart tissue. Attachment of the lower ring and motor drive plate via suturing was not required for this study. In conclusion of the last test, we realized that how having an adjustable ring could be helpful in terms of implantation.

After the last ex-vivo experiment, we tried to come up with a miniaturized design and 3D printed the base part (see figure 3.13). Although, we prepared it to use in test (see figure 3.14), the test did not happen due to the tear occurs at holes possibly because of the material intensity difference we use between the reinforcements around the hole and base (see figure 3.15).

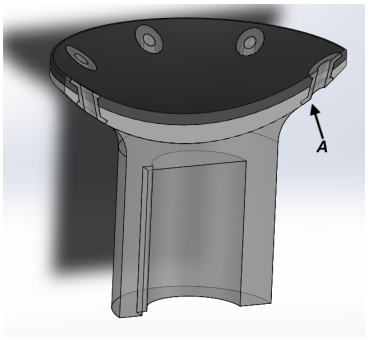

Figure 3.13: 3D drawing for miniaturized base part. Color transition between light gray and dark gray shows the difference in intensity of the material; hard and more elastic, respectively. A) Indicates the reinforcements around the hole.

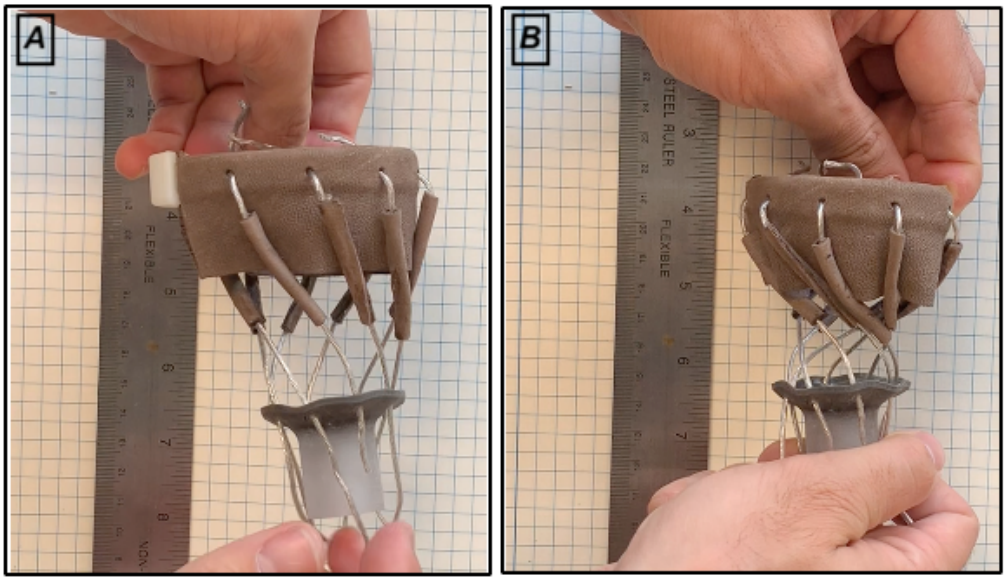

Figure 3.14: Leather coated miniaturized pump prepared for testing. A) neutral helical position (before rotation). B) contraction (after rotation)

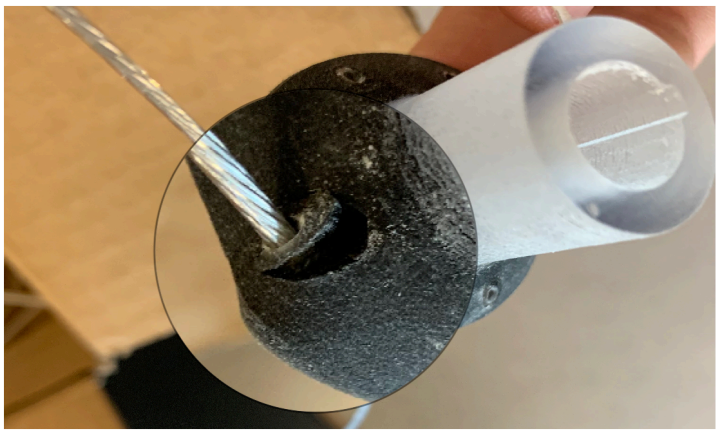

Figure 3.15: The tear occurred around the hole.

CHAPTER 4

Synchronization With The Native Heart

4.1. Synchronization With The Pacemaker

To achieve a properly working heart assist device with the native heart, this assist device should not go against to intrinsic heart motion. The Helix Cardia must be in sync with the cardiac cycle of the patient's heart rhythm to optimize the efficiency of the device. That is why we planned to synchronize our device with a commercially available pacemaker. This will give us an opportunity to assist the heart when it`s needed truly. Because whenever the pacemaker senses that the heart is in need for extra support or correction in electrical activity, and the heart is paced, then assist device will be triggered and start pumping in synchrony with the intact heart. In addition, since the device will only work when it is triggered as needed, the overall system will not require a continuous power supply, which will make it more power-efficient.

So with the device working correctly, the reduced ventricular function of the patient will be improved but will not take over the complete function of the heart. We believe this removes the potential of cardiac atrophy, which has been seen with other heart failure devices. If the device is not working in unison/harmony with the heart's intrinsic motion, it may lag behind or contract prior to the patient's heart. This would cause stress on the heart as the heart could be in diastole, while the device is also trying to squeeze in systole. If this were to occur, the already weakened heart would have a larger force to overcome to draw blood into the ventricles. This could lead to reduced heart function. The worst case would be the force being so high that the heart could not dilate causing the cardiac function to stop entirely. Furthermore, the device may lag behind and not be squeezing at the same time the heart is in systole. In this case, the device is not assisting the heart whatsoever. In either case, the Helix Cardia is not aiding the patient's heart, and in some cases, causing further damage. To alleviate any of the potential issues, it is vital the Helix Cardia is in sync with the heart's intrinsic motion.

The way we plan to make synchronization is that the Helix Cardia will be used with a biventricular pacemaker. The pacemaker will do the entire signal reading and processing of the heart's electrical signals. When the pacemaker deems necessary to signal the ventricles to contract, this signal will also be sent to the Helix Cardia as an input signal to actuate. The device will use a wire linked in a parallel circuit with one of the ventricular leads of the pacemaker. This wire will be connected to an analog input pin on a controller (in this case an Arduino). Complete circuitry is shown in figure 4.2. This input signal will be

analyzed via LabView; if it reaches a certain threshold known as the capture threshold, it will send an output signal to the motor of the Helix Cardia to cause it to actuate like some sort of a go signal. The capture threshold is defined as the minimum required voltage to stimulate the cardiomyocytes to contract and is easily seen as a pacing spike on an ECG [42]. The capture threshold varies per patient, and updates throughout the patient's lifetime as the impedance of the lead changes. The Helix Cardia will actuate only when the correct pacing signal is sent to the native heart to capture the ventricles. The Helix Cardia will only actuate once per pacing signal. Furthermore, the future of the coding will all be integrated into Arduino code, removing the required computational power for LabView. A mathematical model is being developed to calculate the ejection fraction as the motor rotates the helical wires. Once the mathematical model is complete, it will take inputs from the heart, such as heart rate, and create outputs for how fast the motor of the Helix Cardia will rotate and how long it will rotate for. "Programmable oscillator" from block diagram creates the heart rate (see figure 4.1). "Programmable oscillator" is calculated prior to "output pulse generator", so HR will be calculated prior to electrical stimuli being created and sent to the heart. These outputs will create the desired ejection fraction.

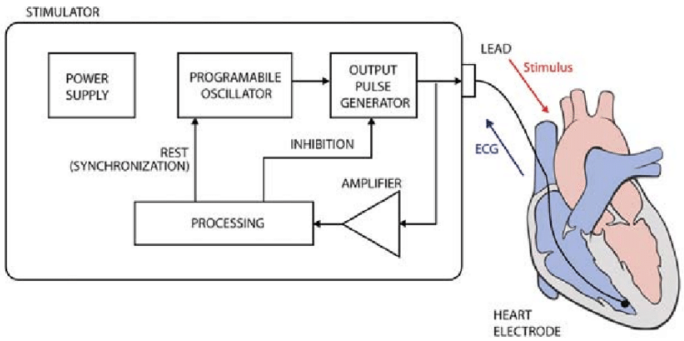

Figure 4.1: Block Diagram to explain how heart rate is sensed and created. Taken from Magjarevic, 2010 [43]

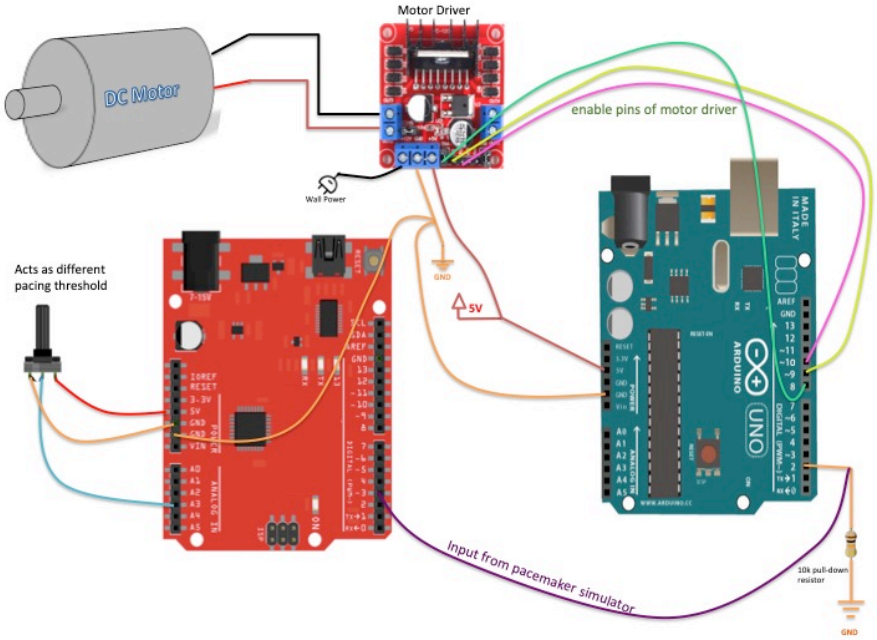

Figure 4.2: The complete circuit diagram.

To sum up, one of the Arduino (the red one) senses through pacemaker lead if there is successful pacing, also known as capture, coming from the pacemaker. If there is, then it sends a trigger signal to the other Arduino to actuate the DC motor as to start the twisting of the pump. For synchronization purpose, reading the pacemaker and controlling the motor studies conducted separately. That is why in current circuitry there are two different processors used. The red one`s initial purpose was to mimic pacemaker and send pre-set bpm values. The blue one is to control the motor. Eventually, these processors will be joined into one, and there will only one processor as it is pictured in figure 4.3. In that desired circuit setup, the processor will read the information about heart through one of its lead (read through one of its analog pins that connected to PM lead). Every time there is a signal coming from PM, our processor assesses if it exceeds the threshold for pacing. Afterward, it will actuate the motor mechanism in case of a successful pacing. Therefore,

cost of the study, a necessity for complex codes to run different processor and possible problems associated with crowded circuits may be reduced.

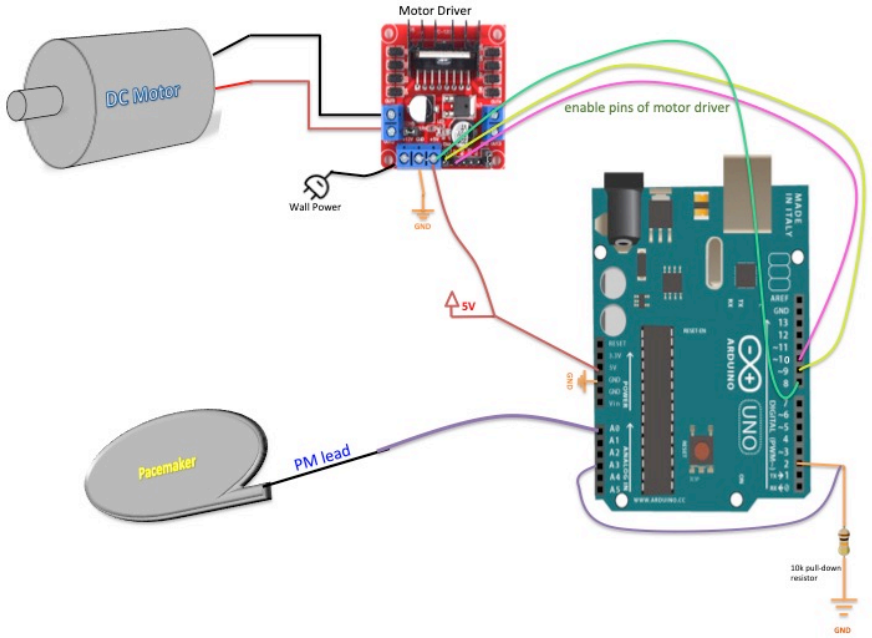

Figure 4.3: Desired circuit diagram.

CHAPTER 5

Conclusion and Future Work

5.1. Conclusion and Future Work

Despite the limitations, these collections of experiments showed the proof of concept of the helically oriented heart assist system would actually work to help ejection fraction for the patient with heart failure. Some of the well-known biocompatible materials were used to produce prototypes for test purposes on a bench test platform. Once all the

components; upper and lower ring, the helically fashioned wire between these rings and motor with electrical circuitry were gathered, the system was tested with harvested hearts to prove that the system can provide extra pumping force with its unique helical motion mechanism.

In those tests, the desired design of the pump showed promising findings on cardiac output; however, due to the unpredictability of heart harvesting schedule and preparedness of the study team for the test and lack of number of tests done, and not having assessment for the dimensions of the heart prior to producing tailored prototypes, expectations of device efficiency could not met. As more data collected and the tests were done, we have concluded that we need to have miniaturized prototypes with adjustable upper rings, and not only small but also powerful enough motor to produce proper torque. Furthermore, a sleeve-like biomaterial would work fine to prevent damaging the heart tissue with the helical wires (see figure 5.1).

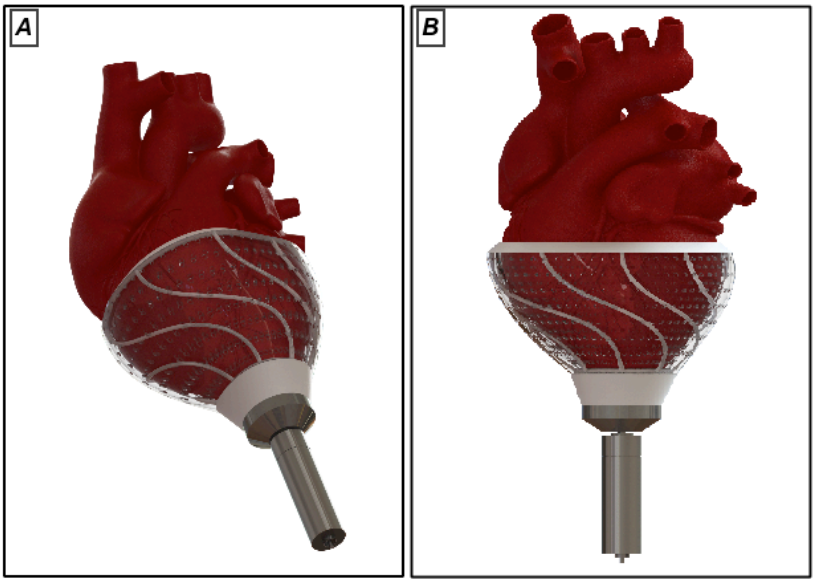

Figure 5.1: Overall 3D pump design. Design A and B represent slightly different view. Model created by Daryl Nguyen

To sum up, as a result of experiments it is shown that the Helix Cardia pump system can assist the heart. With the help of the combination of right material choice and the helical design this device could provide a lot of solution to unmet medical needs of other available heart assist devices have such as need for anticoagulation therapies due to high blood contact, possible right heart failure due to ventricular flow mismatch, infections due to driveline usage, and irreversible modification of the heart due to inflow cannula implantation to the apex of the heart. If device successes, helically oriented heart assist device would eliminate the cost of the overall procedure as per both device and surgery since it can be produced less costly and surgery duration would plummet due to the ease of implantation. All these advantages would allow us to use this device for a wide range of patients from young patients who can not have some of the assist device therapy due to fitting problems to old patients who can not go under a major surgery to have assist device. This project was a heart assist device design and development to treat failure hearts. This

could be undertaken by implementing designs and materials that avoid leading problems associated with current technologies. The possible solutions to these problems are evaluated and compared by the following criteria: technical design spec, cost-effectiveness, ease of implantation, and overall concept. This study aimed to develop a novel & bio-inspired assist device that will contribute to treatment options for HF patients. The results of this research have shown a promising and alternative treatment option for patients with advanced heart failure after most feasible solution for the project had been chosen and feasibility assessments such as technical feasibility, business feasibility, and cost-effectiveness. We believe Helix Cardia is likely to be successfully assisting the failing heart and be a better solution for HF as opposed to current treatment options.

As for the future works, even the results acquired during the tests were enough for us to be able say we did proof of concept, since this is a complete product development project with different aspects such as electrical, hardware and software, there are still tests and researches need to be conducted on few subjects from miniaturizing the system to synchronizing it with pacemaker, and wireless recharge etc. These we can name them such as; biocompatibility test of materials, validation tests on the mechanical properties, and mechanical testing on materials including tensile test or impact tests to assess the strength and elasticity of selected material mentioned for components. All of these testings carry a lot of importance, because the device, if successful, will be considered Class III for FDA (food and drug administration), which is the stringiest level of medical device and require a serious of testing with successful results. In addition to that, the verification test for some components may need to follow a protocol that decided by USO (United States

Pharmacopeia). In terms of level, Class VI is the highest level in which our device may be considered. If so, the components have to be subjected to systemic injection (also known as systemic toxicity), intracutaneous reactivity, and muscle implantation tests to assess if the raw material is safe to use in manufacturing medical devices.

Another critical test would be on Nitinol wires to determine their tendency to breakage and deformation. A tensile test would be suitable in this matter. When we consider the far-reaching effect of failure of the wires; few wires breaking (also depending on the total number of wires) may not cause the device to refrain functioning properly, there could be a decisive physical threat due to the possible risk like cut on the heart tissue during systole/diastole movement by broken wires. There should definitely a long endurance tests to understand at which point wire deformation and deterioration occur and asses the max number of rotation that can wires stand without breaking apart. As per the material we used for prototyping in base and ring components, we need to replace them with a high density and mechanical strength along with biocompatible material such as Titanium or PEEK (Poly-etherether-ketone), which can even replace titanium or its alloys [45].

On the top of necessary testing for the materials planned to for use in bench experiments, there is also another subject that needs to be addressed. It is the fitting of the device. Testing the device in-vivo and ex-vivo for only device fitting study during the development phase cannot always be easy or affordable. And if one does not test the fitting unless one does sure about the dimensions, one may not even acquire healthy results from

testing, which happened to us in our third experiments due to lack of knowledge on the dimension of the heart. To avoid these kind of problems, 3D modeling techniques can be an option to see if one`s device can fit in a cavity of testing animal [44].

Another important topic we already planned and started working on is sleeve-like idea that we can use to prevent contact between the heart tissue and the device itself. It is important to have a sleeve as some sort of buffer because the contact of the components of the device including wires with the heart tissue can increase the risk of an immune response and may lead to undesired reactions. There are different ideas on how we can design around it and what kind of materials we can use. The utmost criteria are, of course, it needs to be biocompatible and elastic enough to let the heart expand during contraction. The materials we might use in that case can be; polyurethane (used in few heart assist devices both commercially available or experimental [46] (see figure 5.2), polypropylene or polyethylene due to its biocompatibility and excellent mechanical properties [47] or Carbothane™ produced by a company named Lubrizol, which is a transparent gel-like material that one can play with its thickness to use it for different purposes.

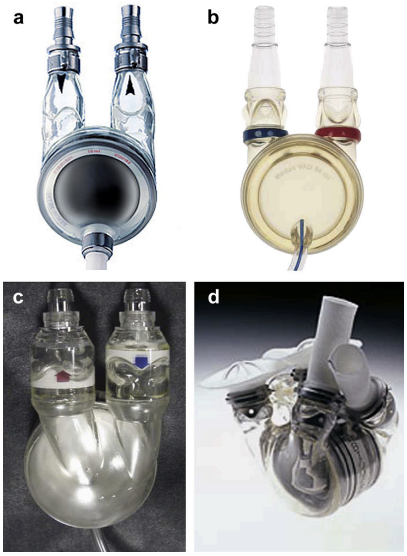

Figure 5.2: Heart assist devices that use polyurethane flexible trileaflet valves: (a) Berlin Heart Excor VAD, (b) Medos VAD III, (c) Abiomed AB5000 VAD and (d) Abiomed Abiocor TAH. Taken from Ma et al., 2011[47].

Due to its high importance in the project, one of the future works needs careful consideration, and hard work is synchronization of the device with the commercially available pacemaker, as I mention in Chapter 4. Even though we started the project by mimicking the pacemaker with electronic circuitry, it needs to be connected directly to the pacemaker itself. There are few limitations with this part of the project such as lack of access to commercial pacemaker truly, since the companies do not tend to reveal their specifications of the device, and also long process to acquire the signal from the pacemaker due to interpretation from the intrinsic heart electrical signals. The very first reason why we want the device synchronized with a pacemaker is that our device should not work against to native heart but in harmony. Imagine a situation where the heart tries to diastole (relaxation) while the assist device in a phase of systole (contraction). This is unacceptable with a device supposedly assist the heart. Another reason is that the assist device will

acquire data or signal from the pacemaker so that it can adjust its rate per minute and speed for rotation according to the heart`s parameter.

As it is mentioned in early chapters, the intrinsic blood flow is pulsatile. So keeping this in the same way with the device carries importance in terms of keeping healthy hemodynamic properties of the heart. Thus, one other major point needs to be studied is the assessment of the ability to maintain healthy pressure/flow rate during ex-vivo experiments. This pressure and flow relationship is critical because for pulsatile flow this relationship is associated with vascular impedance (VI). And the VI assessment is crucial to study loads on the ventricles [48] since it represents the hydraulic workload of LV due to the systemic circulation. Also, it provides quantitative data about the vascular character [49]. However, like other types of impedances (i.e. mechanical or electrical) vascular impedance is also a complex property [49]. So, there should be some quantitative measurements conducted on ex-vivo heart properties such as pressure, flow or ejection fraction (impedance value depends on the pattern of EF) [49] etc. These measurements can be acquired via electromagnetic flow catheter if invasive determination possible, otherwise Doppler echocardiography can be used as well. Furthermore, theoretically computed pressure and flow profiles can be compared with experimental data later on. This kind of study on flow and pressure assessment could have a strong effect to prove that helically oriented device has advantages over others when it comes down to keeping the natural blood flow and maintaining hemodynamics.

Last future work we want to accomplish is a wirelessly charging system for the power need of the device. Since we envisioned the end product as a fully implantable heart assist device, this requires everything is placed inside the thoracic cavity including the power source. Unfortunately, current available ventricular assist devices require a lot of power to pump the blood out from the heart to the body. Thus, as to power these kinds of devices large batteries need to be worn outside the body. In this purpose, a cable protrudes through over the diaphragm and connects to assist device. We do not want to have any electrical cable goes out of the body to connect an outer power source to function and run the pump as current assist devices do. This is one of the high-risk sources of infection for heart assist device patients [50]. For this reason, we can use such a system where we are able to charge our built-in batteries wirelessly over the body tissue like adaptive wireless power charging [51].

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