Project Number: GRG1102

A CARDIAC CATHETERIZATION DEVICE FOR THE DELIVERY OF HUMAN MESENCHYMAL STEM CELLS

A Major Qualifying Project Report:
Submitted to the Faculty
Of the
WORCESTER POLYTECHNIC INSTITUTE
In partial fulfillment of the requirements for the
Degree of Bachelor of Science
By

Evan J. Costa

Brittany E. Hanna

Alexander T. Madden

Trevor M. Olsen

Date: April 28, 2011

Approved:

Prof. Glenn R. Gaudette, Advisor

1. catheter
2. myocardial infarction (MI)
3. biological microthreads

Table of Contents

Authorship

Each team member contributed the same amount of effort to both the MQP report and project. Each member accepts responsibility for all content of the report, and wishes to decline individual authorship.

Acknowledgments

The group would like to extend its appreciation Worcester Polytechnic Institute for allowing its resources and facilities to be used for the completion of this project. In addition, the group would like to thank Professor Glenn Gaudette, Ph.D for his continued guidance throughout the design process. Lastly, the group would like to thank Zeus Inc ©, High Tech Turning Co. ©, Worcester Medical Center, Michael Madden, Selçuk Güçeri, Ph.D, Jacques Guyette, Billy Siebold, Neil Whitehouse, Lisa Wall, Brian Buonomo, John Burford, Mark Kowaleski for their support in providing resources to us in the design and development of our device.

Abstract

Myocardial infarctions are the leading cause of death for both men and women in the United States. Current treatment techniques return blood flow to the infarcted tissue, but do not replace the dead cells with contractile cells. Research pertaining to human mesenchymal stem cells has shown promise in the ability to regrow and proliferate cardiac myocytes. Biological microthreads have been shown to efficiently deliver cells to the heart. However, a minimally invasive device to deliver cell seeded biological threads is needed to move the technology into the clinic. Therefore, we developed a cardiac catheterization device to deliver microthreads seeded with human mesenchymal stem cells to the left ventricular wall.

Table of Figures

Table of Tables

Executive Summary

Myocardial infarction (MI) is the leading cause of death for both men and women in the United States. Each year, an MI affects approximately 1.7 million people with 460,000 cases being fatal (NHLBI, 2010). Myocardial infarction occurs when the cells of the heart muscle begin to die from inadequate blood supply due to plaque buildup inside the arterial walls.

Despite current treatments involving stents and clot buster drugs, over 2,000 people require heart transplants, with only 50% of those in need able to receive a heart transplant (American Heart Association, 2009). Furthermore, current surgical methods for heart transplantation require invasion of the chest cavity at an expensive cost which comes with a long-term recovery period. The heart muscle that has died remains inactive and reduces the overall functionality of the heart; thus there is a need for new techniques which would allow for the rehabilitation of the heart after a myocardial infarction.

Human mesenchymal stem cells (HMSCs) show great potential for research in the realm of cardiac regeneration. Recent research shows evidence that HMSCs can produce the cardiac specific protein actinin, which suggests the HMSCs ability to differentiate into cardiac myocytes and/or induce existing myocytes to proliferate (Jiang, 2006). Biological microthreads, comprised of collagen and/or fibrin, have been shown to improve efficiency of cell retention compared to other commonly used techniques (Proulx, 2011). It is the goal of this project to develop a catheter system to allow for the minimally invasive delivery of cell-seeded microthreads to the left ventricular wall, which may aid in repairing the damaged heart tissue caused by an MI. It is the goal of this project to develop a catheter system to allow for the delivery of fibrin microthreads to the wall of the left ventricle. A system that is capable of delivering hMSCs to the

heart without an invasive surgery will greatly reduce the time needed for the procedure as well as the healing time for the patient.

It was determined that a catheter-based system would efficiently deliver HMSCs to the left ventricular wall. This design aimed at correcting multiple problems existing with suturing microthreads into the heart wall. Currently, delivery of cell-seeded microthreads relies on an epicardial approach to suture the microthreads into the heart wall. This approach can create shear stress that removes cells from the microthread at the point of entry on the heart wall. This results in dramatically lower engraftment rates. Therefore, reduction of shear stress on cells seeded on a microthread was a function considered in this design. Furthermore, a successful design would be minimally invasive, able to deliver the catheter and cell-seeded microthreads to the left ventricular wall, be visible with current technology, maintain cell viability and be easy to use. While navigating through the arterial system, starting at the femoral, the catheter cannot damage the vessels.

With these constraints and functions in mind, preliminary SolidWorks CAD models of the device were generated. Pros and cons of each of the designs were weighed so that the device could capture all of the most promising aspects in one final design. It was established that a capsule type system would be most ideal for this application so that the stem cells could remain seeded on the microthreads and encapsulated until the point at which they would be deployed inside the flesh of the heart wall. A needle would first be deployed, piercing through the chamber and into the heart, then retracting and allowing the microthreads to be inserted completely.

Using all of these requirements and considerations, the final design incorporates a needle and core delivery mechanism protected by an outer sheath lumen. The inner core is capable of holding 14mm of biological microthreads for delivery to the endocardial wall. The inner core is

placed within a 16gauge needle. The entire assembly is attached to a 9Fr catheter. Materials used are of conventional medical grade. The needle is made of 316L stainless steel and the lumens are made of nylon and polyethylene terephthalate. This design is compatible with current technology for visualizing the catheter within the body, for example fluoroscopy and only the biological microthread is left behind within the heart wall.

The primary goal of this project was to create a minimally invasive device that was capable of delivering stem-cell seeded biological microthreads to the left ventricular wall. In order to accomplish this, we designed a novel cardiac catheter device which allows the hMSCs to be shielded as they enter the heart tissue. Once the entire mechanism was within the wall of the ventricle the outer core was safely retracted without any shear stress on the microthreads. Once the threads were embedded within the tissue, the entire mechanism was retracted, the needle was sheathed, and the entire catheter was removed from the patient. This procedure could be repeated as necessary with a singular incision at the groin, rather than requiring the chest wall to be opened for open-heart surgery. Thus, this device can serve as a successful minimally invasive alternative to current treatments and will provide repair of the damaged heart tissue for people suffering from the once thought irreversible effects of myocardial infarctions.

Chapter 1: Introduction

Every year more than 450,000 people die from heart attack related deaths in the United States (NHLBI, 2010). It has also been reported that myocardial infarctions (heart attacks) are the leading cause of death for all Americans, and that 1.2 million will suffer from them each year (NHLBI, 2010). Myocardial infarctions (MI) are generally caused by plaque buildup inside the arterial walls which creates an inadequate blood supply to the heart tissue. Over time, this inadequate blood supply, called ischemia, leads to the death, or infarction, of the cardiac myocytes. This problem has been commonly fixed by clot buster drugs and surgical stents being placed within the artery. Despite these attempts, over 2,000 people require heart transplants every year, and with each year that number increases. Unfortunately, only around half of those in need of a viable heart are able to receive one due to the lack of donor supply (American Heart Association, 2009). As a result of these statistics, work has been done to discover less invasive and more readily available approaches to regenerate damaged tissue caused by MI.

Advancements in tissue engineering include using human mesenchymal stem cells (hMSCs) in the realm of cardiac regeneration as a way to regenerate and propagate the growth of new living tissue (Barbash et al., 2003). Human mesenchymal stem cells have the ability to differentiate into cardiac myocytes and stimulate existing myocytes to thrive in an area. This method allows for an expedient alternative to long-term surgical options which involve higher risks and more side-effects (Jiang et al., 2006). One newly discovered approach involves the use of fibrin microthreads as a biological cell scaffold to embed these hMSCs directly into the epicardial surface of the left ventricle. Once the stem cells are accurately delivered to the tissue,

they are able seed within the dead tissue and differentiate into cardiac myocytes to stimulate new cardiac tissue.

Fibrin microthreads possess a unique ability to promote tissue growth faster than traditional materials, like collagen, in that they stimulate cell migration, attachment, and proliferation (Cornwell, 2007). In addition to their ability to quickly commence natural tissue healing, fibrin microthreads possess exceptional mechanical properties allowing for them to be tougher and stronger than traditional fibrin hydrogels (Cornwell, 2007). Fibrin microthreads are also biodegradable and biocompatible, making them an excellent cardiac regeneration material (DiTroia et al., 2008). Due to all of these properties, it can thus be understood why fibrin microthreads are an advantageous material for the regeneration of cardiac tissue.

Delivery of stem cells via the use of a catheter has proven to be a successful and efficient procedure. There are various types of catheters, including various fixed and “hockey-stick” catheters; however, steerable catheters prove to be more advantageous in that they allow the user to steer to the destination with far more accuracy and precision (Boston Scientific, 2010). With a steerable catheter, the fibrin microthreads will be able to precisely reach the left ventricular wall and deliver the microthreads to the damaged tissue to promote quick healing and regrowth.

Due to the increasing number of Americans suffering from myocardial infarctions, it is clear that a method to deliver cellular therapies to regenerate damaged cardiac tissue is imperative. A catheter that can successfully deliver fibrin microthreads seeded with stem cells to the wall of the heart can serve as a minimally invasive alternative to current invasive procedures. The stem cells will stimulate proliferation and propagation of cardiac myocyte growth in place of the dead tissue. This catheter will be able to remove the long-term side effects of traditional

invasive surgeries and can be pursued as a clinically viable option for the delivery of cellular therapies.

Chapter 2: Background

2.1 Myocardial Infarction

Myocardial infarction (MI), more commonly referred to as a heart attack, is the leading cause of death for both men and women in the United States. There is an estimated 460,000 deaths occurring annually (NHLBI, 2010). Including survivors, approximately 1.2 million Americans will suffer from an MI each year (NHLBI, 2010).

Myocardial infarction occurs when the cells of the heart muscle began to die as a result of inadequate perfusion of oxygen-carrying blood to the heart, a condition called ischemia. The inadequate flow of oxygen-rich blood is a result of plaque or fatty material that can build up inside the walls of the arteries. Over time, fat, cholesterol and platelets continue to build up and harden. This process is called atherosclerosis and it greatly reduces the area that the blood can travel through resulting in impeded flow. In addition, if the fatty buildup breaks open, a thrombus can form resulting in the cutting off of the oxygen rich blood supply to the heart.

Current methods of treatment for heart failure, including myocardial infarction, require that intervention occur as soon as possible. If a myocardial infarction is identified early enough, the affected artery must be unclogged immediately. Clot buster drugs can be used to dissolve the clot and thereby open the blocked artery. A more permanent fix is to place a stent in the artery. The use of an inflatable balloon and stent can be used to further open the artery and to keep it open.

Each year more than $35 billion is spent in the United States on heart failure cases (Cowie, 2000). Approximately 4,000 people at any given time are in need of a heart transplant (Mayo). Of these people, only 2,210 heart transplants were performed in 2007 as a result of a

limited supply of heart donors as well as an increasing need for heart transplants (American Heart Association, 2009). There is an obvious need for an alternative to heart transplants due to the limited number of heart donors and the large number of heart failure deaths each year. Recently, tissue engineering and regenerative medicine has been researched as an alternative to heart transplants.

2.2 The Heart

The heart is a hollow involuntary muscular organ under control of the autonomic nervous system made of a specialized muscle tissue called myocardium. This organ has its own electrical system that is able to function even without the control of the central nervous system. The myocardium is unique from other muscle tissues in that it requires a constant supply of oxygen and nutrients in order for the muscle cells to stay viable. The heart must function continuously from birth to death and can only tolerate a serious interruption in blood supply for a few minutes before the cells of the heart begin to die (American Heart Association, 2009).

The heart is divided into four chambers: the left and right atria and the left and right ventricles. The left side of the heart pumps blood to the body while the right side of the heart pumps blood to the lungs. The right side of the heart receives blood from the veins of the body. The blood enters from the inferior and superior vena cava into the right atrium. From here, blood flows through the tricuspid valve until the right ventricle is filled at which point the valve closes. Contraction of the right ventricle causes the blood to flow out through the pulmonary valve into the pulmonary artery and into the lungs. The left side of the heart receives the oxygenated blood from the lungs through the pulmonary veins into the left atrium. At this point, the blood flows through the mitral valve into the left ventricle. Contraction of the left ventricle expels the blood through the aortic valve into the aorta and finally into the arteries of the body (American Heart Association, 2009). Any of the previously described mechanisms cannot function effectively if any damage occurs to the heart. Since the heart is unable to regenerate contractile cells on its

own, an approach is needed to heal and regenerate damaged heart tissue as a result of MI. Research shows that stem cells and regenerative medicine proves to be an effective solution to this problem.

2.3 Adult Stem Cells and Regenerative Medicine

Adult stem cells are regarded as a promising possibility in regenerative medicine and tissue repair. Adult stem cells are undifferentiated cells that primarily serve in the maintenance and regeneration of their tissue of origin. They exhibit the ability to both renew themselves and differentiate into a specialized cell of a particular tissue type or organ (Krause D. et al., 2001). For example, research shows that the adult bone marrow cells can differentiate into mature liver cells and skeletal muscle. Adult stem cells can be found throughout the human body in bone marrow, blood vessels and skeletal muscle (Bethesda, 2010). These cells can be harvested with relative ease thus the use of adult stem cells in regenerative medicine avoids the ethical controversy as seen with embryonic stem cell research.

2.4 Human Mesenchymal Stem Cells and Cardiac Regeneration

A particular type of adult stem cell, human mesnechymal stem cells (hMSCs) show the greatest potential for research in the realm of cardiac regeneration. hMSCs can be isolated from harvested bone marrow and propagate in vitro exemplifying their convenience as a source for cell-based therapies (Barbash et al., 2003). Recent research shows evidence that hMSCs can produce the cardiac specific protein actinin suggesting their propensity to differentiate into cardiac myocytes and/or induce existing myocytes to proliferate (Jiang, 2006). Current therapies introducing hMSCs extend little beyond myocardial injections of the cells into the infracted myocardium, or intravenous injections of cells. These methods however fall short, and display low rates of cell engraftment (Freyman et al., 2006). One method that has shown success in past

studies and experiments has been the use of microthreads to deliver stem cells into the cardiac tissue as a way to regenerate tissue caused by myocardial infarction (DiTroia et al., 2008).

2.5 Fibrin Microthreads

Microthreads have many biological advantages as a scaffold for seeding cells. These biological materials function with excellent mechanical properties with regards to tissue growth and integration into an injury site. Microthreads can also function as advanced hydrogels, providing better integration into tissues and more efficient cell adhesion than current technologies. Furthermore, microthreads have important delivery potential in cardiac repair. This is primarily due to their ability to mimic organic tissues, which give them additional advantages when requiring biocompatibility and biodegradability. Lastly, microthreads play a major factor in cell migration, orientation, and proliferation; this is integral in tissue regeneration and repair (DiTroia et al., 2008).

2.5.1 Promoting Tissue Growth and Mechanical Properties

Some advantages of microthreads include their ability to promote tissue growth while concurrently achieving excellent mechanical properties (Cornwell, 2007). Microthreads are commonly made out of a substance known as fibrin, and its structure can been seen in Figure 1 below:

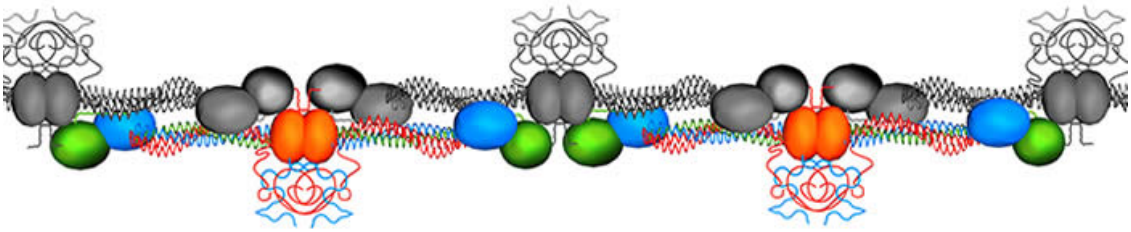

Figure 1: Fibrin Assembly (Marquette University, 2010).

Fibrin is a complex protein, requiring the assembly of double stranded twisting fibrils containing lateral sections of fibril links (Marquette University, 2010). This combination of components makes the fibers very thick and an ideal material composition for microthreads. Additionally, this material is heavily involved in natural wound healing (Cornwell, 2007). Fibrin must be slightly altered, however, before it can be used in microthread applications. Altering the protein can affect the mechanical stability of the material, decreasing the rigidity and strength. By modifying the concentration of natural fibrinogen with fibrin, higher mechanical strengths can be achieved (Cornwell, 2007). Cells can be seeded on this fibrin assembly, resulting in better mechanical seeding techniques compared to traditional cell delivery methods. In a study done by Professor Cornwell, fibrin microthreads proved to be stronger and tougher than fibrin hydrogels (Cornwell, 2007). This application benefits the area of tissue regeneration by providing mechanical rigidity and strength while also effectively promoting the body's natural tissue to repair its dead and damaged tissue (Cornwell, 2007).

Promoting tissue regrowth while maintaining sufficient mechanical properties are extremely important characteristics of a material used for delivering cells to dead cardiac tissue. Allowing for a strong, yet flexible structure that can promote efficient cell growth is crucial to the overall success of the tissue regeneration (DiTroia et al., 2008). Microthreads, although typically delivered in bundle formation, can be cross-linked and woven into forms that make the structure stronger, while providing more available surface area for cell delivery and other such applications (DiTrioa, Hassett, Roberts, 2008). Additionally, fibrin structures are advantageous in supporting differentiation, propagation, and movement of stem cells. This is important to the survival and effectiveness of renewing damaged and dead cardiac tissue. With these fibrin

microthreads, a higher engraftment rate of the stem cells potentially yielding better tissue regrowth can occur.

2.5.2 Microthreads as a More Efficient Scaffold

In addition to microthreads providing excellent mechanical properties that can guide tissue regrowth in dead and damaged cardiac tissue, microthreads can be used as a cellular platform due to their ability to be constructed into larger shapes and sizes and their strengths. A study demonstrating this theory was performed with fibrin microthreads acting as a scaffold for wound healing (Murphy, 2008). In the experiment, the microthreads were prepared in a gel formation, being conducive to attachment of cells (particularly fibroblasts). The microthreads proved to be effective in maintaining the overall attachment of the cells, in addition to their constant proliferation and viability.

With this newly developed method of cell delivery, scaffolds can deliver cells to the problem site with better mechanical strengths and control (which is shown below in Figure 2) than scaffold methods, making fibrin microthreads far more advantageous than traditional means (Murphy, 2008). The threads proved to have high tensile strengths and stiffness, actually being enhanced when exposed to ultraviolet light (Cornwell 2006).

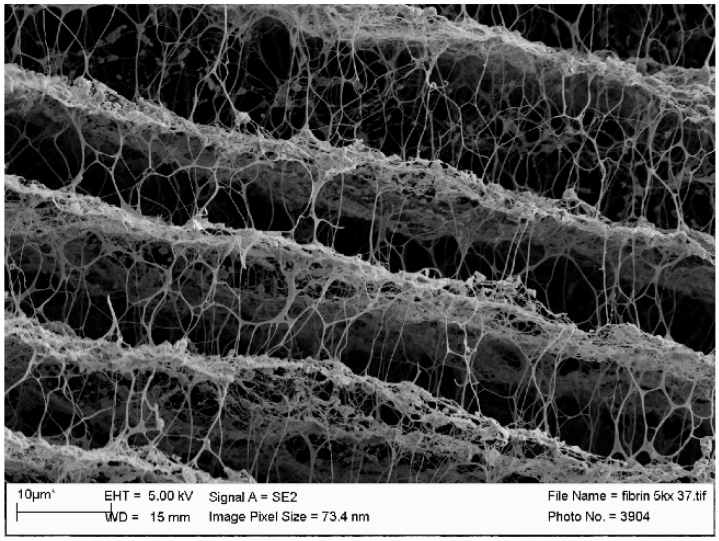

Figure 2: Oriented Fibrin Hydrogel (Manufacturing Chemist, 2010).

Similarly, cross-linked threads show greater values of mechanical properties compared to the tested uncross-linked threads. Even after being seeded with fibroblasts, it has been shown that microthreads are capable of cell proliferation. This study proves that bundled microthreads are an acceptable means of tissue regeneration (Cornwell et al., 2006). Fibrin microthreads, as compared to fibrin hydrogels, have greater mechanical properties and can support cell adhesion and cell proliferation (Cornwell et al., 2006).

2.5.3 Microthreads Mimicking Tissues

Along with being beneficial as scaffolds, microthreads have a unique ability to mimic organic tissues; this provides extra value to using microthreads in that they are both biocompatible and biodegradable (DiTroia et al., 2008). The main component of fibrin microthreads (fibrin) is an essential component of natural wound healing and, therefore, of damaged tissue regrowth (Cornwell, 2007). Collagen, like fibrin, can be assembled into structured patterns to allow for more strength and stiffness in biomedical applications. Collagen

Type I is a major functioning component of extra-cellular matrix (ECM) in tendons and ligaments. Collagen is not a major protein in damaged tissues upon immediate harm, like fibrin. Fibrin matrices provide natural regrowth of tissues due to their similarities to collagen and ability to repair damaged tissue (Cornwell, 2007).

In vivo, fibrin gels present a low elastic modulus and a variety of binding sites for signaling proteins and integrins in order to stimulate an emergency reaction to the damaged tissue site (Flanagan et al., 2009). Additionally, fibrin gels activate an immediate immune response to the patient in a reaction to the foreign material.

2.5.4 Effects on Cell Orientation, Migration, and Proliferation

Additionally, microthreads mimic the functions of scaffolds in that they have the ability to direct the movement and direction of the cell in order to properly repair damaged tissue (Murphy, 2008). In a study performed by Professor Cornwell and Professor Pins ten fibrin microthreads were bundled together and soaked with cells and media (Cornwell, Pins 2007). After approximately one week of culturing and incubation, fibroblast attachment and proliferation was noticed with recordable data regarding the actual viability of the cells. It was noted that the fibroblasts had successful attachment to both cross-linked and uncross-linked ultraviolet (UV) stained microthreads. The success of this study proves fibrin an acceptable material for scaffolding in tissue engineering studies and applications (Cornwell et al., 2007).

Furthermore, fibrin microthreads which are organized into a bundled structure stimulate cell proliferation and attachment (DiTroia et al., 2008). This structure allows for a tight alignment of the scaffold; the scaffold can form into larger structures, which would allow for a more accurate and efficient cell migration. The cells align in the longitudinal direction when they

are constructed in this fashion, allowing for a stiffer and more rigid scaffold material that could promote cell proliferation to regenerate tissue (DiTroia et al., 2008).

These fibrin microthreads would require a minimally invasive method of delivery in order for the patient to have a shorter recovery time. One method of achieving this goal would be to use a catheter to deliver the microthreads, due to the fact that it would not require invasive surgery.

2.5.5 Delivery of Cellular Therapies via Microthread Scaffold

Recent work has shown success in the delivery of cellular therapies seeded on biological microthreads. These studies show cell engraftment rates in the targeted tissue up to 70%, when sutured into the epicardial surface of the heart (Fakharzadeh et. al, 2010). One existing technique to deliver cellular based therapies is intramyocardial injection where a stem cell solution is injected into the epicardial surface (Sherman, 2006). This technique, however, only results in cell engraftment rates of up to 10%. The comparison in engraftment rates between the two therapies can be seen in Figure 3 below:

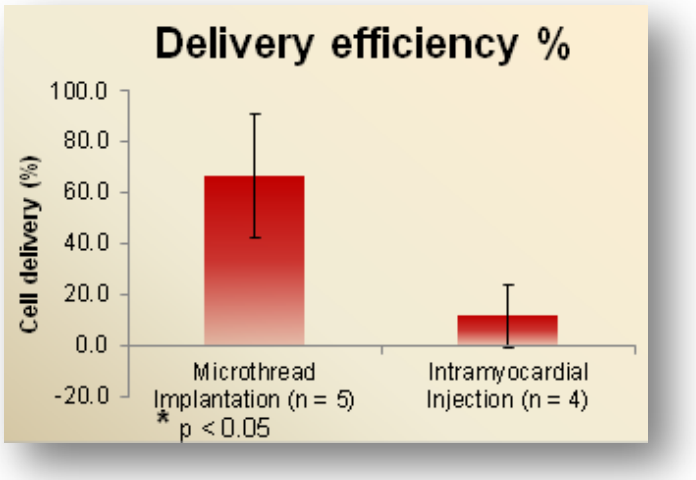

Figure 3: Delivery efficiency% of Microthread Implantation vs. Intramyocardial Injection (Image courtesy of Gaudette lab, 2011).

This graph demonstrates the comparison in efficiency of cell engraftment rates of microthread implantation versus intramyocardial injection, showing an improvement of 60% with the microthread implantation technique.

2.6 Advantages of a Catheter-Based System

A minimally invasive technique for accessing the heart is cardiac catheterization. Currently there are many commonly performed procedures completed with the use of a catheter. These procedures can be either diagnostic or therapeutic or a combination of both. The therapeutic catheterization procedures repair the defects diagnosed such as problems with the heart valves or opening blocked arteries. Recent research has looked into delivering cells to the heart wall for regenerative purposes (Sherman, 2006).

2.11 Catheter System Examples

Tissue damaged by myocardial infarction makes the heart much less effective. Heart tissue does not make use of the regenerative properties of the body, and therefore cells must be

delivered to the damaged tissue in order for repair to begin. Currently, there are different catheter devices in clinical trials which deliver cells to the heart for this purpose. Cardiac catheterization is a common procedure performed in today's healthcare. Catheters were design to perform a critical task inside the body while being operated outside of the body. As illustrated in Figure 4 below, the distal portion of a catheter is the portion which performs the task internally, while the proximal portion is the end actuated by the physician.

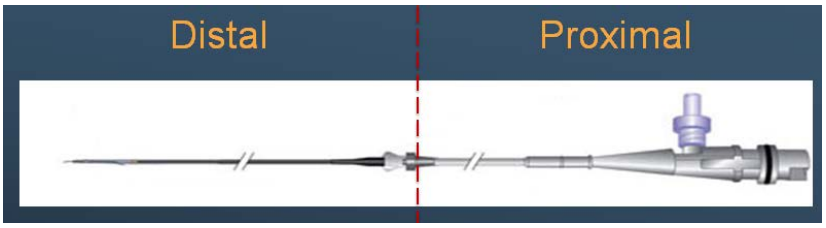

Figure 4: Standard Catheter (medgadget, 2011).

There are two different methods for cell delivery into the heart: intramyocardial injection and intracoronary infusion. The difference between the two delivery mechanisms can be seen in Figure 5 below:

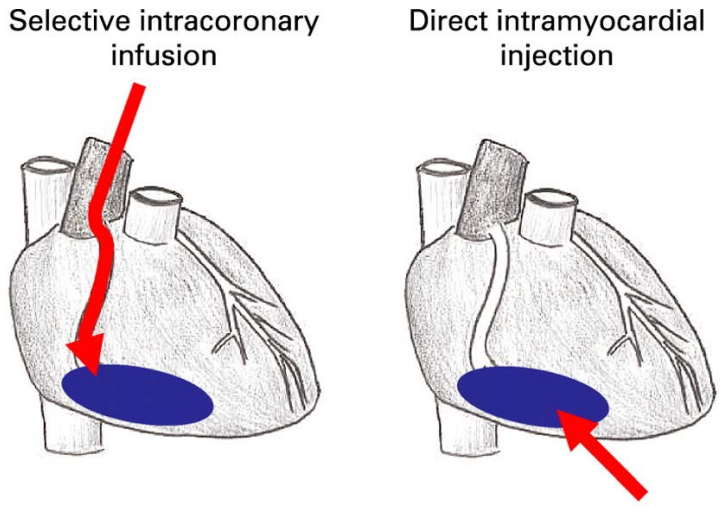

Figure 5: Intramyocardial Injection of Cell Suspension (Beeres et. Al, 2008).

Both of these methods inject the cells into the heart, but approach the damaged tissue from different anatomical structures. Both methods are inherently flawed due to low cell retention after the procedure (Sherman, 2006). Even with this problem, it is important to see how current technology approaches the problem in order to find a more viable solution.

Catheters can be constructed in multiple ways; for instance, an integrated system combines a core and support catheter to form a single structure. This design allows for repeated injections into the heart wall. The disadvantage of an integrated system is that it is unable to use a guide wire for navigating to the heart. Therefore, the navigation tools used to navigate the catheter to the left ventricle must be dependable. MyoCath and Myostar catheter systems, made by Bioheart Inc. © utilize an integrated system (Bioheart, 2009). Straight needles made of either stainless steel or nitinol allow for repeated injections of cells into the wall of the left ventricle (Sherman, 2006).

A non-integrated device separates the core catheter from the support catheter thereby enabling the use of a guide wire for the navigation to the heart. The core catheter is then inserted through the support catheter allowing for the injection of cells. There are two catheters that use this kind of assembly: the Helix and the Stiletto (BioCardia ©, 2007-2009). The Helix catheter system uses a corkscrew-like needle which increases the stability while inserted into the heart tissue and can be seen in Figure 6 below:

Figure 6: Helix catheter (BioCardia, 2007-2009).

The Stiletto uses a spring loaded needle which injects to a fixed depth for delivering the cells to the heart wall. A spring loaded system is advantageous in delivering cells through fibrotic tissue. A non-integrated system allows for a more complex delivery system with the core catheter (Sherman, 2006).

Currently, the only minimally invasive way of delivering cells to the heart wall is intra coronary injection. Another way to deliver cells to the heart is to suture threads seeded with cells into the heart through open heart surgery. The procedure of suturing threads is not optimal due to the healing time required for such an extensive surgery. The aforementioned benefits of fibrin microthreads for cell adhesion and viability make this an approach worthy of further research and development. A catheter-based approach for delivering microthreads seeded with cells to the heart would combine the advantages of microthreads with the known success of catheter-based systems.

2.12 Visualization and Delivery of the Catheter

Catheters are non-invasive and therefore require imaging techniques to direct the device's operator through the body and within the heart. There are many different ways that a catheter can be tracked in the body. Fluoroscopy is an imaging method that uses x-ray images to guide the operator to the correct portions of the heart (Fluoroscopy, 2010). In combination with the fluoroscopy, radiopaque dye is used to highlight portions of the heart's anatomy. The radiopaque dye is a contrast material that does not allow x-rays to pass through it. This is helpful to visualize arteries, veins or the location of structures like the heart wall. As there is with any procedure that involves x-rays there are risks involved with the radiation exposed to the body. While the risk is small the duration and intensity of the x-rays can be cause for concern with fluoroscopy (Fluoroscopy, 2010).

Using fluoroscopy, the catheter can be guided to the heart and provide some imaging within the heart. If more defined structures are needed, however, other techniques must be explored. For this reason, another way of visualizing the inner anatomy of the heart is the use of ultrasound. Ultrasound uses sound waves to identify the structures within the body. One of the catheter systems that uses this is the AcuNav catheter developed by Biosense Webster © (Biosense Webster Inc., 2010). The use of ultrasound allows the mapping of the heart so that different anomalies can be identified (Ren, 2002).

The company Stereotaxis developed a technology that utilizes magnetic fields to guide the catheter through the body and heart. This type of system allows for a more detailed control than conventional methods. Since the catheter system is activated by a computer the operators do not have to be in the same room as the patient, reducing the amount of radiation they are exposed to which is crucial (Stereotaxis, 2010).

2.13 Fixed Versus Steerable Catheters

Catheters can either be fixed or steerable. A fixed catheter has a constant defined curve. Many different curves can be formed depending on the application of the catheter. Figure 7 shows multiple examples of possible catheter curves as developed by Boston Scientific (Boston Scientific, 2010).

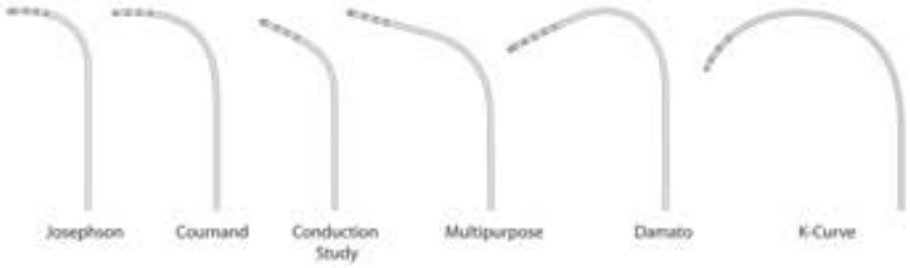

Figure 7: Examples of Fixed Catheter Curves (Boston Scientific, 2010).

A steerable catheter allows for a change in the shape of the distal end while inside the heart. This can be done from the proximal end of the catheter and can provide the operator with a greater range of motion while navigating to certain structures (Boston Scientific, 2010). Figure 8 shows how the curve is capable of changing while inside the heart. The major advantage of a steerable catheter is the ability to fix the position more accurately during the procedure.

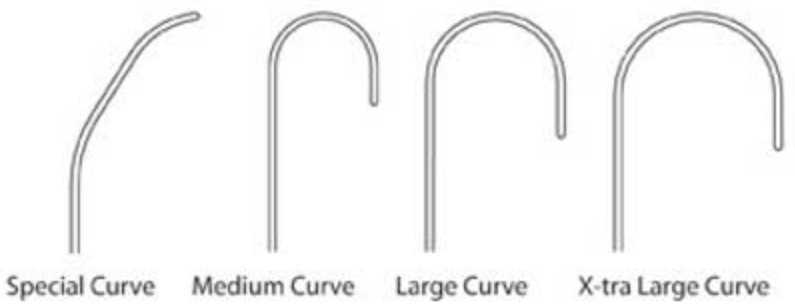

Figure 8: Curves obtainable with a steerable catheter system. (Boston Scientific, 2010)

Biosense Webster developed the "EZ Steer Bi-Directional Catheters" which utilizes their proprietary micro-tensioning system for precise control of the catheter's distal end (Biosense Webster Inc., 2010). Several joints are located at the end of the catheter and by moving a dial at the distal end the operator is capable of making fine, incremental adjustments to the catheter's position. This kind of control is important for procedures that require precision and accuracy (Boston Scientific, 2010).

Chapter 3: Project Approach

3.1 Project Assumptions

There were multiple assumptions made in order to simplify the client statement into a solvable problem with the time and resources available. All assumptions made were based on prior research and have been shown to be reasonable in their respective areas. The following are assumed to be true within the scope of this project:

1. Human Mesenchymal Stem Cells (hMSCs) have been shown to regenerate cardiac function.
2. Microthreads are an appropriate scaffold system for the delivery of cells.
3. Catheters are an appropriate and accepted system for cardiac therapies.
4. A bovine heart is an acceptable model for cardiac tissue.

3.2 Project Stakeholders

There are multiple stakeholders in the outcome of this project. Stakeholders are the people affected by the use or presence of this device either directly or indirectly. The list of stakeholders is as follows:

- Doctors
- Hospital personnel
- Patients
- Patients' family

In order for the device to be found useful it must be intuitive for the doctor's performing the procedures. If the device does not function in a similar fashion to other catheters it most

likely will not be a success. Therefore, the design must take this into account and create a user friendly device. A “user friendly device” means that the device should act as a help not a hindrance to the procedure.

Additionally, it must be understood that doctors will not be the only people handling the device. Other staff will need to move the catheter system from a storage place before the procedure and dispose of it after it is no longer needed. The device must be durable enough to be handled by many people prior to the procedure taking place. The safety of the staff is a necessary consideration in the design of the device and the reasoning why the hospital personnel must be considered.

The patients having the procedure performed must be considered in the design of the device. The use of the device provides live saving therapy to the patient and must not debilitate the person further. For this reason the patients’ family must also be considered. If the device results in a recovery time the patients’ family or care giver will most likely be responsible for helping the patient with their daily activities. The longer time period in which the person is recovering from the procedure the more the family or care giver will be needed.

3.3 Project Goals

The overall goal of this project is to restore cardiac function to a patient who has suffered from a myocardial infarction. In order to simplify the goal into something obtainable and within time and money constraints, it was decided to use a catheter system to deliver the therapy that will restore cardiac function. A more specific list of primary and secondary goals is as follows:

1. Design catheter system for insertion into the femoral artery

2. Create device that allows protection of (hMSCs) until delivery
    a. Capsular design to allow for protection of cells during transport and non-use
    b. Capsule design in order to quickly reload catheter to deliver cells to multiple sites
3. Safely implant cells into the wall of the left ventricle in the target area
4. Use preexisting technology to guide the catheter to its desired location
    a. Radiopaque dye
    b. Guide wires
5. Restore cardiac function without increasing injury in the heart or elsewhere in the body

Chapter 4: Design

4.1 Initial Client Statement

The group received the following initial client statement from client, Glenn R. Gaudette, Ph.D.:

"Design a method to delivery microthreads that are seeded with stem cells. The microthreads will be approximately 1 mm in diameter and 17 mm in length."

The client statement was analyzed and discussed with the client to receive more details pertaining to the expected device design. It was concluded that in addition to the statement, the device needed to be minimally invasive, as good as or better than what is currently out there, and cause as little side effects as possible. Additionally, the device must allow for at least 17mm of microthreads to be deployed into the heart wall.

4.2 Objectives, Functions, Constraints, and Specifications

After analyzing the initial client statement, the group determined what components of the design were crucial for satisfaction of the client, what components would make the design more successful and appealing, and what functions would be required for the device to work properly. Together, the objectives, functions and constraints act as guidelines for all experimental designs that are created and tested. Section 4.5 (Developing Design Alternatives) details all preliminary designs that were developed in the brainstorming process and what aspects of each preliminary design were extracted and implemented into the final conceptual design.

4.2.1 Objectives

In the design process, objectives indicate what exactly the design should do, rather than what it must do. Objectives help to make a basic and completely functional design more attractive and alluring to the patient and can make a procedure safer, more ergonomic, and produce less pain for the patient. Keeping the initial client statement in mind and top priority, the group brainstormed all possible design objectives. The objectives were determined based on five major components: ease of use, safety, location, maneuverability, and minimal invasiveness.

Safety is the most important objective our group identified for this device. If the safety of the patient or the surgeon is jeopardized, the success of the device is likewise at risk. Additionally, if the device is not safe to use on the patient, the reputation of the surgeon using it may also be at danger; therefore, a device that is devoid of risks and harm is essential. Sub-objectives of the objective safety include that the device should not damage the coronary wall, be safe for the patient and for the user. With regards to safety for the patient, the device should not result in a long recovery time and should not cause harmful side effects.

Ease of use is an important objective because if it is easy to use for the surgeon then the surgeon will be more inclined to select our design rather than one that is complicated and perhaps riskier to practice with. Subsets of this objective include making the device easy to load, easy to insert, easy to use/handle on proximal end, and ease of making insertion. These four subsets ensure that the surgeon will have minimal to no problems initially use the catheter device and navigating the device into the left ventricular wall so that the microthreads can successfully be delivered and the device can be inserted and removed without flaw.

The delivery location of the catheter must be considered as a third objective when designing the device. The device must be accurate and arrive at the exact location of the infarction in order to effectively place the microthreads for tissue repair. Precision is another subset of location and is similar to accuracy; the difference between accuracy and precision is that accuracy identifies an exact location whereas precision identifies exactly how often that accuracy can be performed. Lastly, repeatability of the device with both accuracy and precision make this a required objective.

A maneuverable and minimally invasive device encompasses the last two design objectives that the group established was important for the success of the design. Making the devices steerable, contain a bend, and ensuring mechanical stiffness are subsets of making the device maneuverable enough to get to the correct destination in the heart. Furthermore, by making the device minimally invasive it will make the procedure an outpatient procedure and decrease costs, time out of work, recovery time, and surgical risks.

The objectives of the final conceptual design for the cardiac delivery device can be viewed in Appendix B.

4.2.2 Functions

In order to allow the device to carry out the specific objectives which have been determined, functions are required. Functions establish how the device is going carry out certain tasks, and with respect to this device, how it will perform effectively and accurately and satisfy the client's demands and needs. The group brainstormed all of the functions the device needed to be able to do and established the following list:

- Deliver Catheter to Wall
    - Be steerable
    - Be visible
    - Be non-obstructive
    - Be removable
    - Be Safe
- Deliver Cells to LV Wall
    - Push/Expel cells and thread
    - Be Safe
- Navigate to Insertion Location
    - Be precise
    - Be accurate
- Maintain Cell Viability
    - Reduce shear stress
    - Provide nutrients
    - Allow gas exchange
    - Maintain cell adhesion to thread
    - Allow for cell engraftment to heart

As shown in the above list, the required functions have been categorized into four specific groups: deliver catheter to wall, deliver cells to the LV wall, navigate to insertion location, and maintain cell viability. Each category is then divided up into subcategory to understand what aspects of that category are important.

Delivering the catheter to the wall would be easy with the help of a steerable catheter; this means in order to deliver the cells to the wall it should deform with a specific angle, contain the necessary degrees of freedom, and the distal end of the catheter should have different mechanical properties than the remainder of the catheter in order to steer the catheter properly. Delivering the catheter also requires visibility of the device and to be non-obstructive; therefore, the visibility resolution and the diameter of the entire catheter are important to the functionality of the device. The device must be removable in order to take out all materials from the body, with the exception of the microthreads seeded with stem cells. Lastly, safety is another component of this function. The needle should not be too sharp and should not be exposed until it is user-activated, it should maintain mechanical stability, and it should not impede blood flow.

Delivering cells to the left-ventricular (LV) wall is the second function that requires several sub-components to ensure complete functionality. Both the cells and thread should be expelled from the device via a user-interface that can deliver the catheter into the LV from the proximal end of the device. This function can be accomplished via a proximal end interface. Additionally, the safety of this operation should not be compromised in that the design should minimize destruction and the stability of the implantable should be ensured.

The third function deals with navigating to the insertion location which requires absolute precision and accuracy. With regards to precision, repeatable placement of the microthreads must be validated and guaranteed simultaneously with accurate placement of the threads in the target location.

Finally, maintaining cell viability of the stem cells requires a reduction of shear stress, provision of nutrients, gas exchange, cell adhesion to the thread, and cell engraftment to the

heart. For this application, decreasing the shear stress both entering the wall and when the microthreads are leaving the delivery device are essential. Providing nutrients for the stem cells that are on the microthreads will help to maintain the cell viability, as the cells will need to remain at the tip of the catheter until placement inside the cell wall. Likewise, the cells are going to need to perform gas exchange. With regards to cell adhesion on the thread, a majority of the cells are going to have to maintain viability prior to being injected; therefore, there cannot be a large percentage of cells that die prior to placement.

4.2.3 Constraints

In addition to determining what functions the device needs to be able to carry out, constraints must be set in place. Constraints state exactly what the device must do. If the device fails to successfully qualify a constraint, the device will ultimately fail. Below lists the design constraints the group developed:

- Must not exceed time budget (August 27th-April 21st)
- Must not exceed monetary budget ($624)
- Must not puncture aortic valve
- Must not be thrombogenic
- Must not fully penetrate thickness of ventricle wall
- Must be biocompatible
- Must be manufacturable
- Must not create an immune response
- Must be seen with current available technology
- Must release entire microthread into LV wall

- Must be able to retract needle without retracting the thread
- Catheter must take direct course to LV wall
- Catheter must not break
- Thread should be completely embedded in damaged tissue region
- Cells must remain intact and on microthread

Once it can be said with confidence that the cardiac delivery device meets all of these constraints, the device can then be deemed successful.

4.2.4 Specifications

Specifications define exactly what the tolerances are for each established function. Once the device has been confirmed to meet the objectives and constraints, specifications are set in place to make sure that the device can meet its desired functions; otherwise, the device may be unable to fulfill both safety and functional requirements.

The steerable catheter must have a minimum of two degrees of freedom. The diameter of the catheter must not exceed 4 mm to qualify it as non-obstructive. The catheter must not impede blood flow up to 30% in order to ensure safety of the patient. In order to expel/push the cells and threads into the LV wall, the catheter must have a dual lever interface. To ensure safety, the control depth must not exceed 4mm-15mm. The stability of the implantable material must be ensured to the extent of the project. The catheter must be precise and accurate in navigating to the insertion location. The accuracy of the insertion location must be within 3mm of the target location. With regards to maintaining cell viability of the stem cells, there must be a decrease in shear stress compared to current technology. Provision of nutrients and gas exchange is crucial for maintaining cell viability; therefore, the cells will be able to sit inside the catheter for 24

hours before they are no longer living. Cells have no more than a 10% loss during adhesion to the thread before injection into the heart. Lastly, there can be no more than a 30% loss of cells overall during the cell engraftment to the heart procedure.

4.3 Revised Client Statement

After taking the objectives, constraints, functions and specifications into mind, the team worked to develop a more specific and more precise client statement that contained all necessary details pertinent to the success of the device:

The ultimate goal of this project is to create a device that enables the delivery of microthreads seeded with stem cells *to the wall of the left ventricle. For the procedure to be successful the device must be able to deliver* microthreads 1mm in diameter and 17mm in length *to the heart wall. The device must be minimally invasive, allow for a short recovery time, maneuverable to enable maximum control, safe for both the user, patient, and heart, and must allow for easy loading of microthreads. The device must also allow easy insertion into the heart in both an accurate and precise method. Costs to manufacture the device must not exceed the department budget of $624 and must be completed by April 21st, 2011.*

4.4 Pairwise Comparison

We created a pairwise comparison chart (which can be viewed in Appendix B) in order to rank the objectives relative to each other. In this chart, if the objective in the left column is determined to be more important than the objective in the top row, it receives a score of “1” (one). If it was found to be less important, it received a score of “0” (zero). The numbers in the horizontal rows were added up to give each objective a total score. The total scores of each objective for each group member and advisor were summed to create a complete pairwise comparison chart as shown in Table 1. The objectives were then ranked from most important, with the highest score, to least important, with the lowest score.

Table 1: Filled Out Pairwise Chart

Objective (Ease of Use)	Alex	Brittany	Evan	Glenn	Trevor	Total
Easy to load	0	0	0	0	0	0
Easy to insert (reach LV)	2	3	2	3	2	12
Easy to use (proximal end)	1	2	3	2	3	11
Ease of making insertion	3	1	1	1	1	7

Objective (location)	Alex	Brittany	Evan	Glenn	Trevor	Total
Accuracy	2	1.5	2	1	0.5	7
Precision	0	1.5	0	0	1.5	3
Repeatability	1	0	1	2	1	5

Safety (Patient)	Alex	Brittany	Evan	Glenn	Trevor	Total
Does not damage coronary well	2	2	2	1	1	8
Does not result in long recovery time	0	0	0	0	1	1
Does not cause harmful side effects	1	1	1	2	1	6

4.5 Morphological Chart

In order to create a variety of design alternatives, a morphological chart was used that displayed the desired functions of the cardiac delivery device and different means of obtaining each of these functions. Various design alternatives were considered, and the multiple combinations can be seen below in Table 2:

Table 2: Morphological Chart

	1	2	3	4	5	6	7	8
Deliver Catheter to Wall	Deflectable Guide catheter	Integrated: multiple curves	2 guide catheters	Transvenous	Guidewire	material make-up for proper deflection	Alex's crazy suction cup idea	hockey-stick
Delivery Cells to LV Wall	Syringe injection	Smart polymer	Smart alloy	Sewing Machine mechanism	Suture mechanism at end of wire	Arched hollow needle with cradled thread	Biodegradable polymer sheath	Bundled thread suspension injection
Naviate to Insertion Location	Steerable catheter	Nitinol smart alloy	Nonsteerable, curved catheter tip	Fiber optic line	Radio opaque imaging/marker bands	Side port at proximal end for die injection		
Keep Cells Viable	Expose cells to blood	Encase cells in cell media	Procedure done quickly	Arched hollow needle would protect cells	Biodegradable polymer sheath			

4.6 Developing Design Alternatives

Based on the functions, objectives and specifications that had been previously defined, multiple design alternatives were created to solve the problem at hand. The early stages of the design focused on the distal tip of the catheter as it was decided to be the most important part of the design. The functions the distal tip ultimately ended up performing indicate how the catheter lumen would be designed and by extension the proximal end. The following sections define the design alternatives that were explored and the advantages and disadvantages of each. The feature taken from the design to be implemented in the final design is also indicated.

4.6.1 Biodegradable Capsule

The first preliminary design incorporated microthreads within a biodegradable capsule. The structure of the microthreads sometimes makes them difficult to handle. This design was a

way to get around that problem. The capsule would become the item needing to be handled and therefore easier to maneuver and deliver.

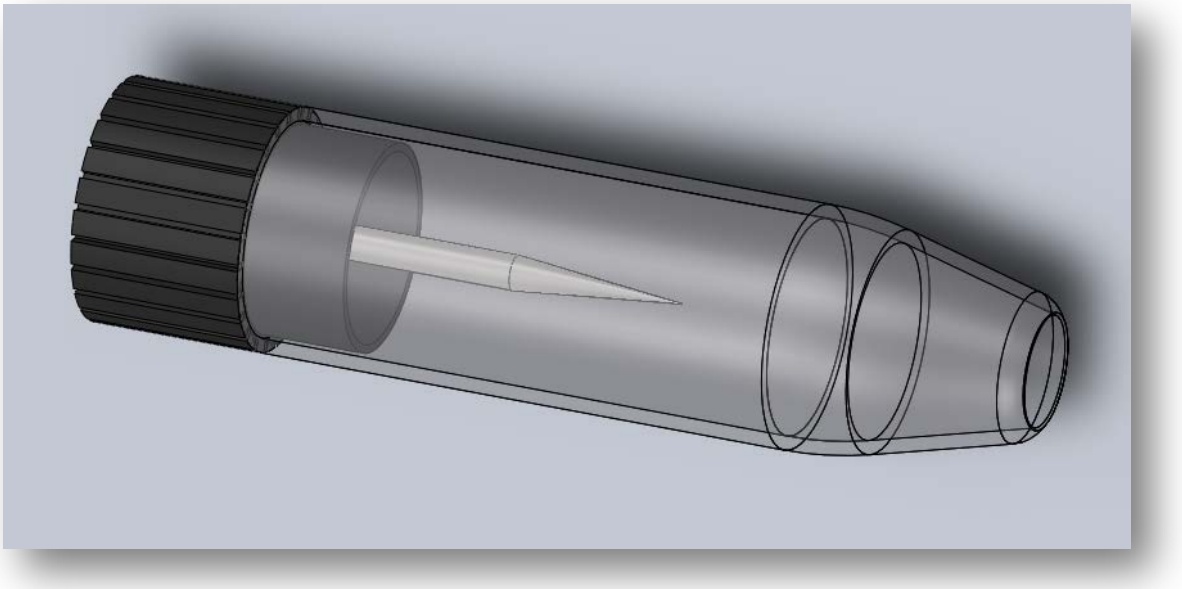

Figure 9: Biodegradable Capsule with the grey section being left behind in the heart and the dark grey section being attached to the catheter.

The design is depicted in Figure 9. The light grey section found on the right side of the device would be made of a biodegradable material and filled with microthreads and cell media, while the needle pushes through the heart tissue. The capsule would be injected into the heart wall and left there as the biodegradable material dissolved. The threads would then be left behind and able to start rehabilitation. There are both advantages and disadvantages to this design. The capsular approach allows the threads to be handled in a different way and allows for easy loading of the catheter in the procedure room. The problem with this design comes with leaving a foreign material inside the heart wall. Multiple problems could have presented themselves, for example,

cardiac function could have been impaired or the capsule could have come dislodged from the tissue.

4.6.2 Auto Injector

One way preliminary designs were created was to look at currently existing technologies. These technologies could then be modified to solve the current problem. A technology that was looked at was an auto injecting syringe as seen in Figure 10. Similar to the first preliminary design this approach looked to remove the thread architecture from the problem. The microthreads would be tied into balls and injected into the heart wall as a kind of pellet. The size constraints of the catheter system would have made this design very difficult to manufacture.

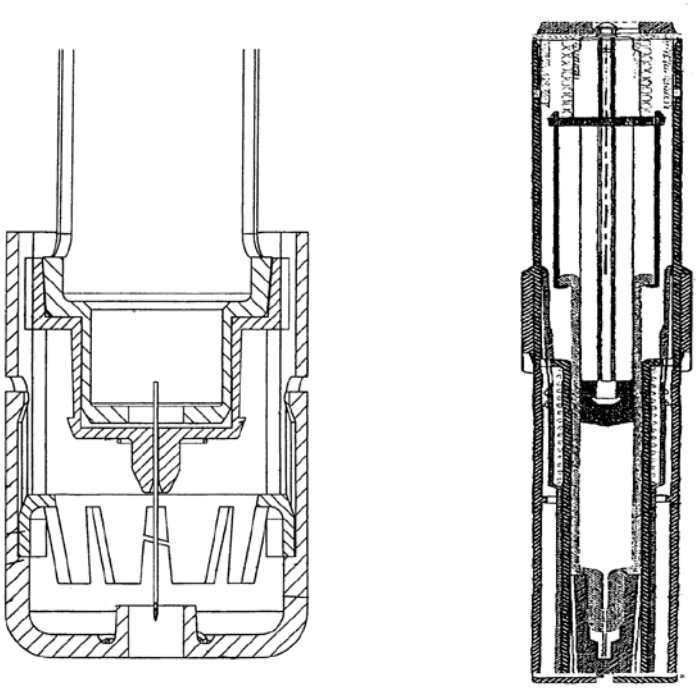

Figure 10: Sample Auto Injector Design

4.6.3 Suture Needle

The last preliminary design utilized the microthreads as threads. The symmetrical mechanism utilized three needles to deliver the microthreads to the heart wall. As can be seen in Figure 11 the green structure was the main needle body and the two blue needles would actually deliver the threads to the wall. The thread would be stored in the middle portion of the green needle and an end of the thread would be attached to each blue needle. While the needle structure was being maneuvered to the heart wall the blue sections would be enclosed within the green. Once at the heart wall, the blue needles would be advanced into the wall pulling the thread through the heart tissue. The problem with this design was that it would have been very difficult to manufacture. There are also many moving parts and therefore a more difficult proximal end would need to be designed.

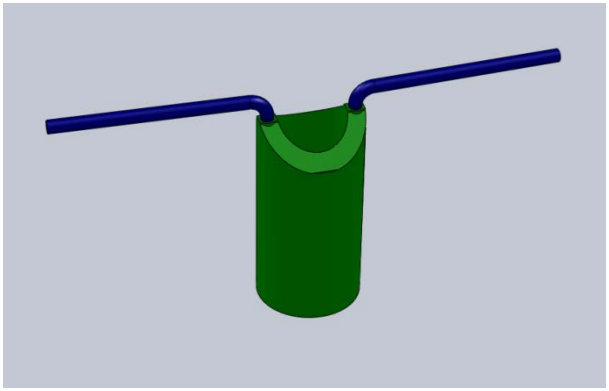

Figure 11: Three Needle Preliminary Design

4.7 Initial Design

After looking through conceptual designs and the revised client statement, it was devised that the protection of the patient was the most important aspect of our design. To fill this requirement we looked into many ways of reducing sharp edges on the distal end of the catheter. From our preliminary and conceptual designs we knew that our delivery mechanism would utilize a needle. In order to encapsulate this into a safe structure, a capsule was decided upon.

A capsule is a sheath like replaceable portion of the distal catheter. By having a distal end that is detachable and replaceable the physician would be able to load microthreads easily into the device. The premise for the capsule was to provide a physiological environment for the cell-seeded biological microthreads for a period of about 24 hours. The capsule could be placed at the distal end at the time of the procedure. If more than one procedure is needed at one time the used capsule can be replaced with a new one and the procedure can be repeated.

The capsule could provide many benefits to all of the stakeholders involved. First, for the cells, an expanded polytetrafluoroethylene (ePTFE) barrier would be placed between the outside environment and the cells. This ePTFE barrier would allow for the retention of cell media within the capsule and an area for gas exchange. Particulates would be kept out of this environment reducing the possibility of destroying the viability of the cells. Second, the patient would also be protected. The intricate design of the capsule would provide mechanical safety stops to ensure the needle would not be overexposed into the heart wall. These stops would be extruded rings on the inside of the capsule that would not allow the needle to move past. The heart wall has a finite thickness so under no circumstance would the needle need to be exposed more than that distance.

Lastly, the physician is protected by being insured that the needle cannot puncture too far beneath the endocardial surface.

The delivery mechanism enclosed in the capsule would utilize two primary parts: the outer needle and the inner core. This mechanism was meant to reduce the amount of shear placed on the cells and microthreads while passing under the endocardial surface. The current technique of delivering microthreads to the heart wall is to suture them in place from the epicardial surface. As the suture needle pulls the threads the tissue acts as a kind of “squeegee” wiping the cells off the threads. Studies have shown that a higher density of cells can be found at the surface of the tissue comparatively to the deeper infarcted region (Fakharzadeh, 2010). As can be seen in Figure 12, the inner core is placed within the outer needle. The microthreads are draped over the inner core and exposed only when the outer needle is retracted.

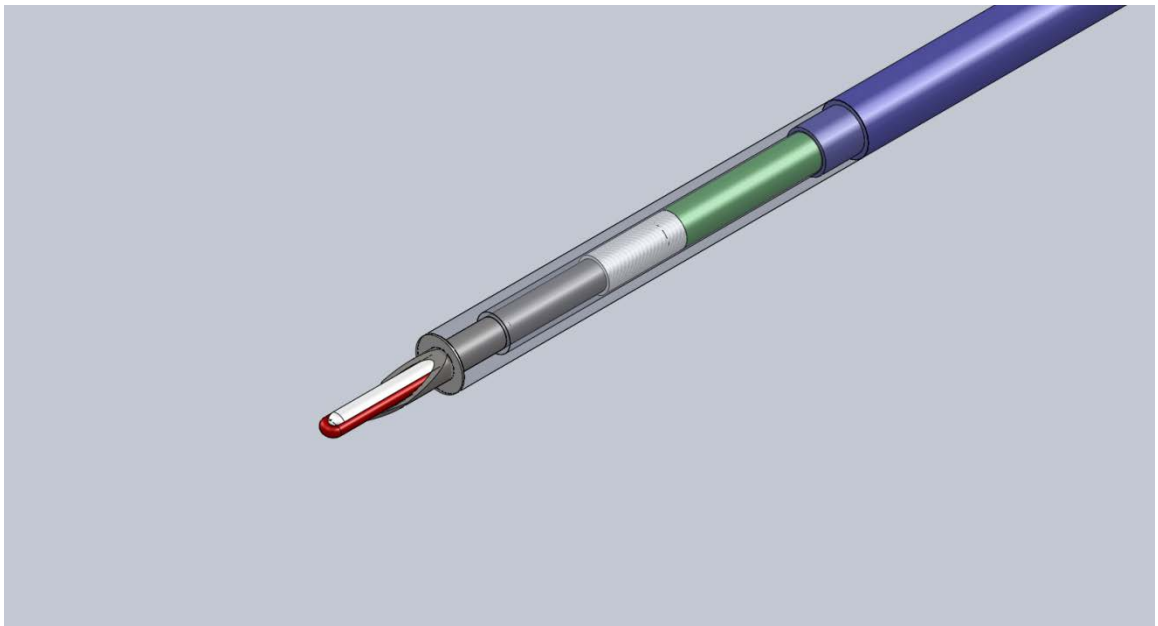

Figure 12: Close-up of how the distal delivery mechanism is assembled. As shown the device would have just passed under the endocardial surface.

The actuation of the catheter would take a four step process. This process can be visualized in Figure 13:

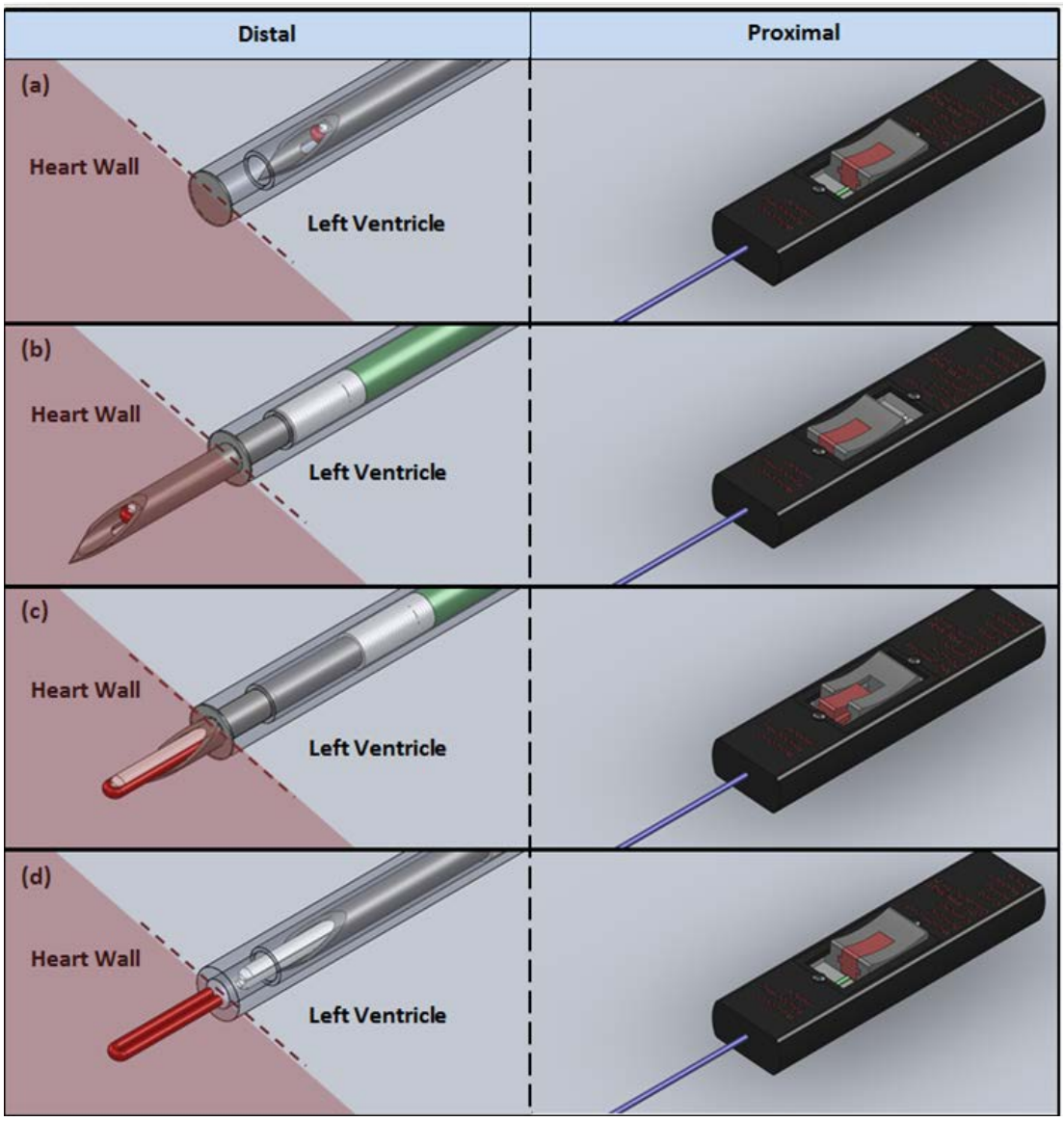

Figure 13: Distal and Proximal actuation in the initial design.

The four step process would be as follows. Figure 13a depicts the proximal end completely retracted at the "starting position" and the distal end located at the heart wall. Notice that both slides are moved to the back of the handle casing. Figure 13b has both slides on the handle

moved fully forward. The action at the proximal end results in both the outer needle and the inner core plunging under the endocardial surface. By moving both the outer needle and inner core into the tissue together it is believed that the microthreads will be protected from shear stresses produced by the endocardial wall. Figure 13c shows the primary gray slide pulled back on the proximal handle which retracts the outer needle. As the outer needle is retracted the inner core and threads are exposed to the infarcted heart tissue. Figure 13d shows the final step of retracting the inner core by pulling back on the red slide at the proximal end. As the inner core is removed from the tissue only the biological microthreads are left behind. After the delivery mechanism successfully leaves the microthreads in the infarcted region the catheter is tracked back out of the left ventricle and through the incision made in the femoral artery.

One of the primary drawbacks to this design was the handle. It was rapid prototyped by a three-dimensional printing technique. This manufacturing technique has a limited resolution requiring the simplification of the design. What resulted was a non-ergonomic design found to be unusable by industry professionals. The handle utilized a two slide mechanism which would actuate the outer needle and inner core separately. The handle can be seen as designed in Figure 14.

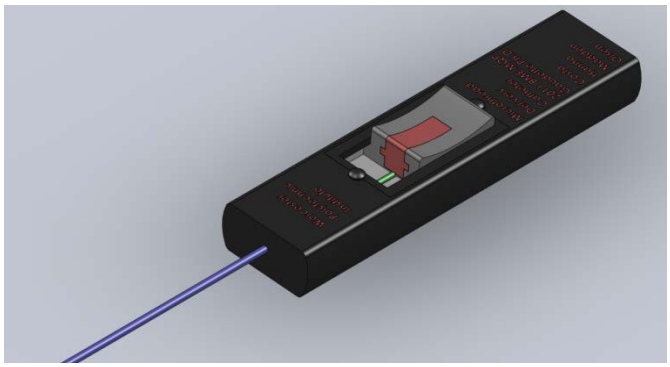

Figure 14: The handle found at the proximal end in the "starting position".

[52]

Another drawback of this design was the plausibility of machining the required parts. One of the constraints set at the beginning of the design process was the ability to create a working prototype. This involves all parts being manufacturable within the time and monetary budget. Given the scale of the distal end of the catheter it would be necessary to have the parts created off campus. This would entail extra costs. For this reason we decided to simplify our design by taking the most essential pieces of the initial design into our final design.

4. 8 Final Design

In order to address the flaws in the initial design we created a new final design that addressed the concerns expressed by our client as well as industry professionals. After these discussions we determined that the handle was the most pressing problem in need of addressing. The initial design featured a rectangular handle. A more ergonomic, circular design was used in the final design as a result of suggestions from industry professionals. The catheter is comprised of five primary components, as shown in Figure 15. The red dotted line running through the center of the next series of figures shows the separation of the distal and proximal ends of the catheter.

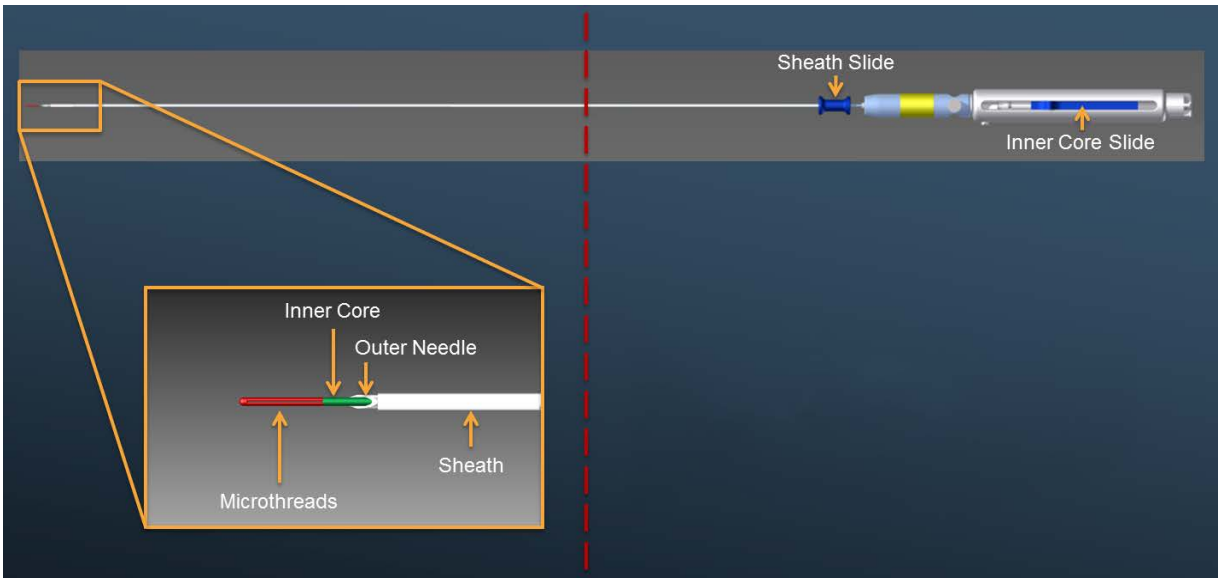

Figure 15: Labeled diagram of key components found in the final design.

The first step in using the device is to track the catheter to the left ventricular wall. As seen in the detail view of Figure 16, the distal end is sheathed so that the sharp edge of the needle is not exposed. The sheath took the place of the capsule for providing a level of safety for both the patient and physician.

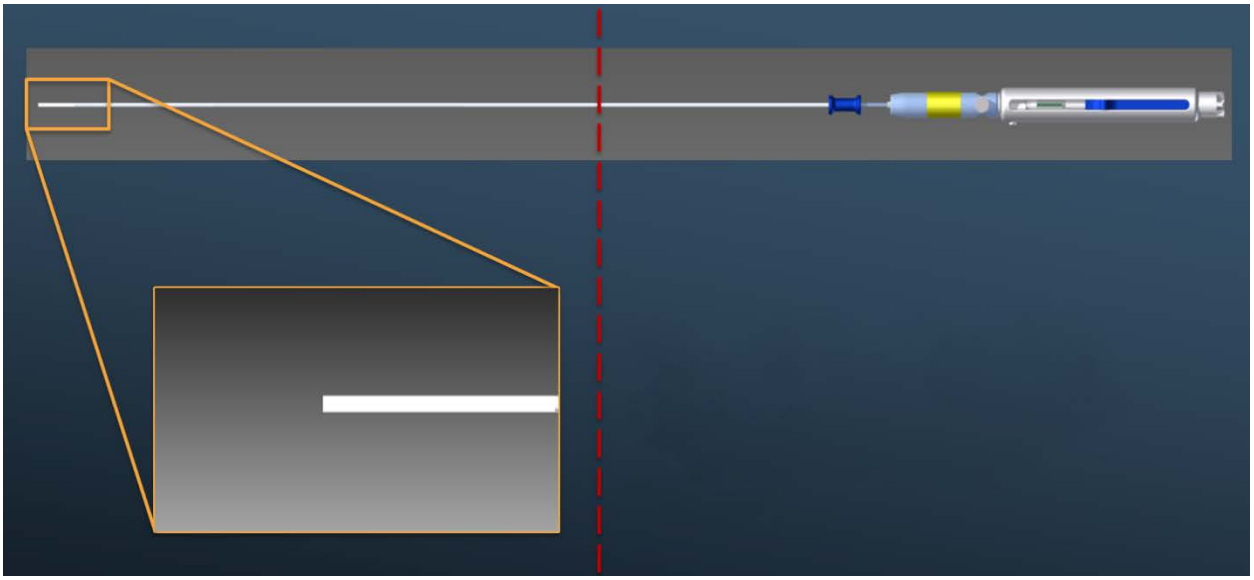

Figure 16: Catheter Actuation Step 1

Once located at the proper location, the outer needle can be introduced into the infarcted tissue region. This is first done by unsheathing the outer needle by pulling back on the sheath slide at the proximal handle. The sheath slide is pictured as a blue cylinder in Figure 17. The handle is then moved forward by the physician who will plunge the outer needle and complete delivery mechanism under the endocardial surface. As can be seen in Figure 17, only a minimal portion of the needle is exposed. The sheath slide stop pictured as the light blue cylinder with a yellow stripe prevents the needle from being over exposed. Again, this provides a level of safety for the patient by limiting the depth the needle is allowed to penetrate the ventricular wall. It also provides a means of insurance for the physician not to move too far under the endocardial surface.

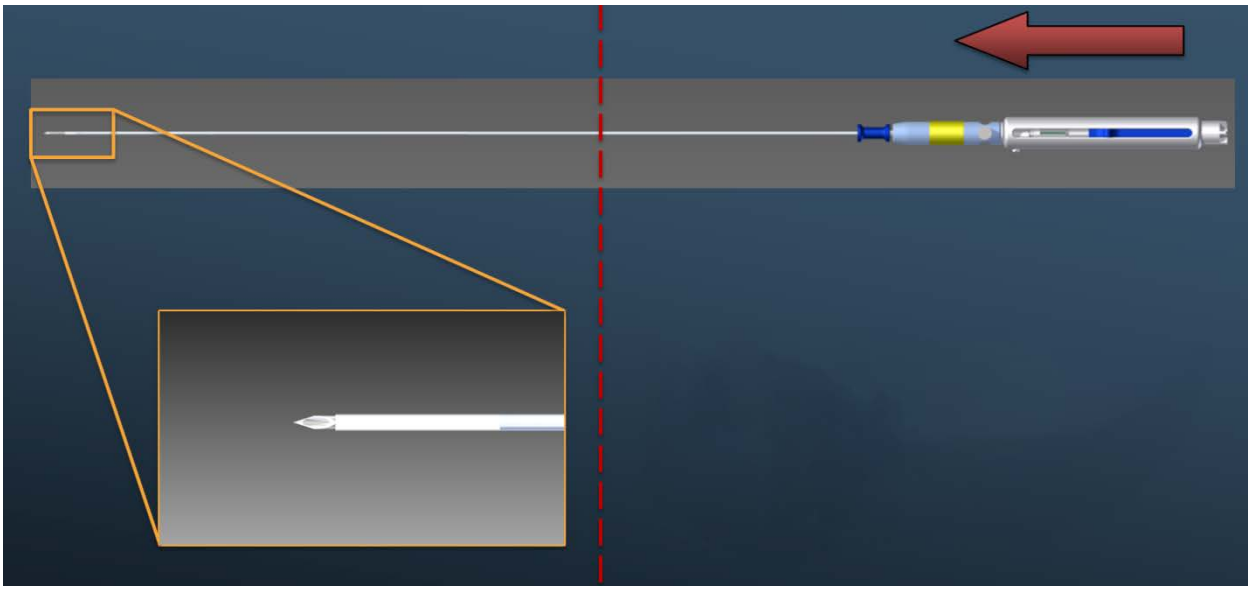

Figure 17: Catheter Actuation Step 2

Figure 18 depicts the next step of the actuation process, microthread delivery. At the proximal end of the catheter the physician moves the inner core slide forward. By doing this, the inner core and microthreads are deployed within the infarcted tissue at the distal end. As in the initial design, the outer needle/inner core delivery mechanism is believed to reduce shear on the microthreads as it passes under and through the endocardial surface.

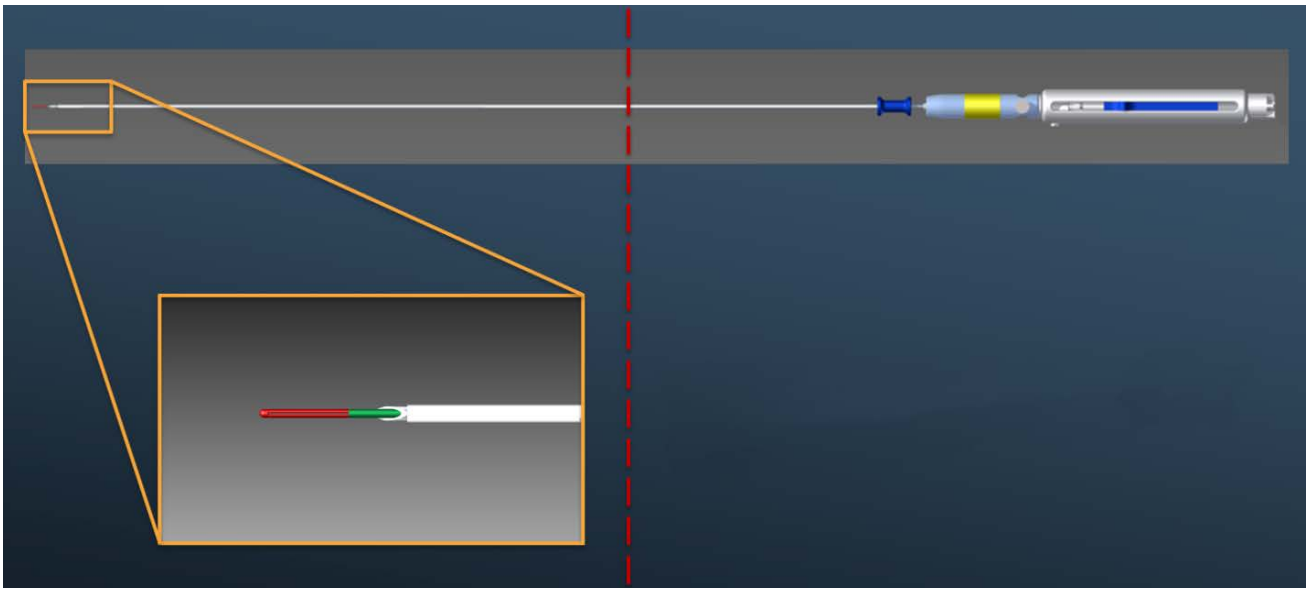

Figure 18: Catheter Actuation Step 3

Once the inner core has been deployed the biological microthreads have been delivered. The next step is the removal of the delivery mechanism from the infarcted tissue region as seen in Figure 19. In order to do this, the physician pulls back on the proximal handle thereby retracting the delivery mechanism from the tissue. The goal is to leave only the biological microthreads behind in the desired tissue region.

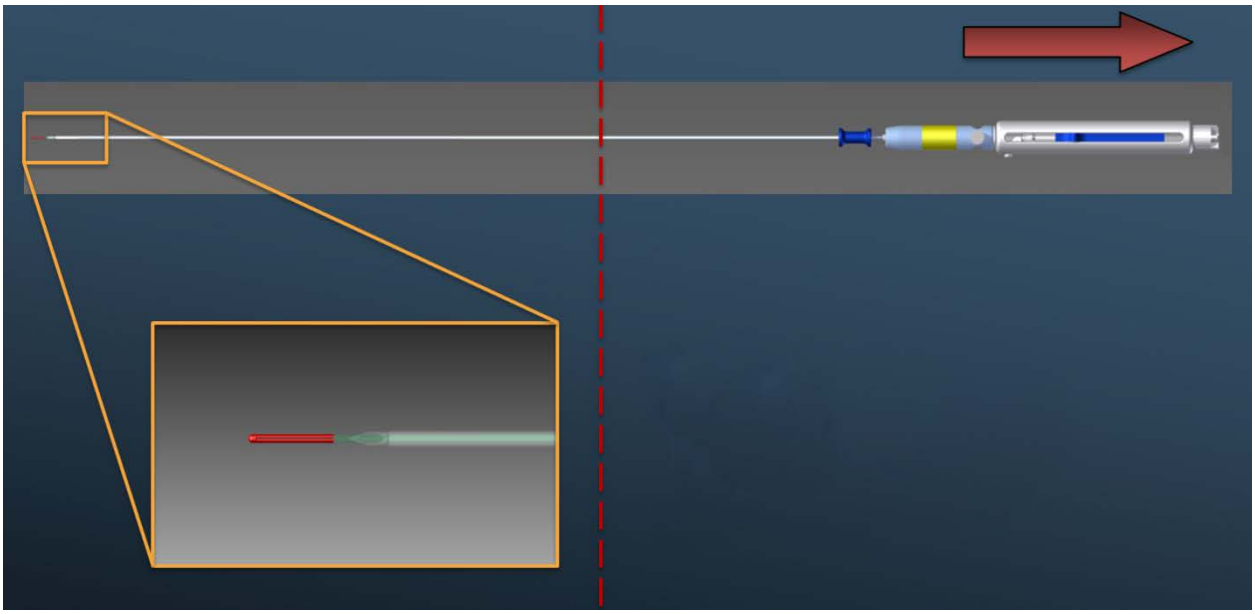

Figure 19: Catheter Actuation Step 4

The final step, shown in Figure 20, involves re-sheathing the needle while the distal end of the catheter is still located within the left ventricle. The re-sheathing process should take place once the delivery mechanism is removed from the ventricular wall. The physician does this by pushing forward on the sheath slide in a reversal of step one in this process. Once the sheath is covering the outer needle, it is safe for complete device retraction. The procedure is now complete, but can be repeated as many times as necessary until the appropriate amount of therapeutic cells have been delivered.

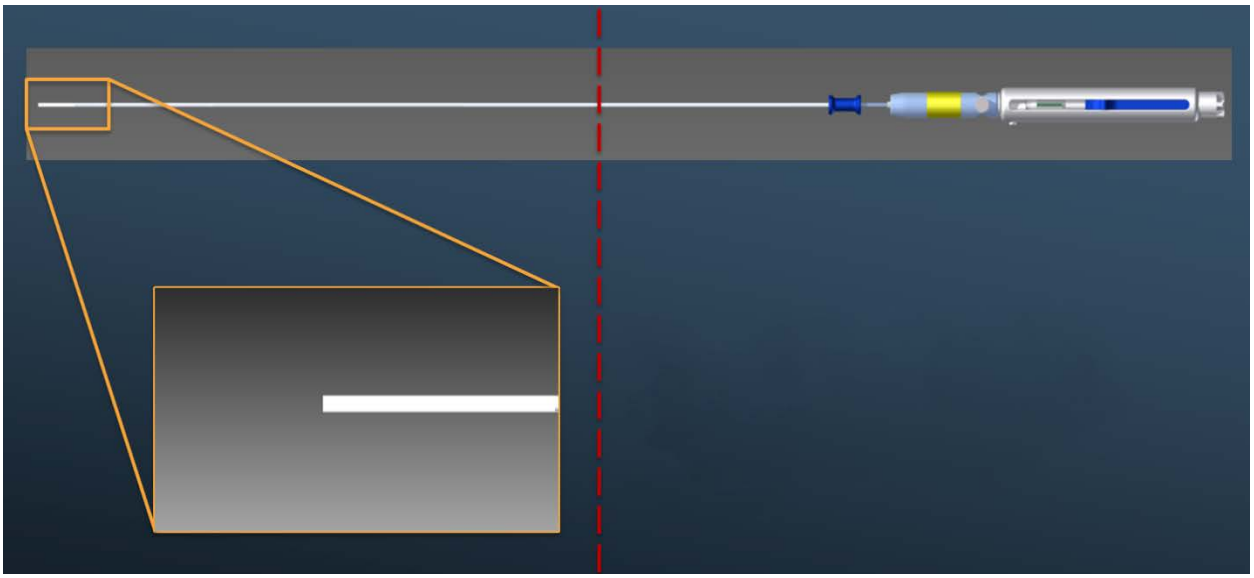

Figure 20: Catheter Actuation Step 5

Chapter 5: Methodology

5.1 Materials

The materials used for the device must be rigid enough to withstand the process of delivering the catheter into the heart, in addition to delivering the stem cells to the left-ventricular wall. Manufacturability of the material is important since most medical devices are very small and require special manufacturing. In addition to fulfilling mechanical and manufacturing conditions, all materials must be biocompatible and safe for the patient.

Based on the above requirements, materials were selected. Starting at the proximal end the handle is created from hard plastic and Delrin. The lumen connecting the proximal handle and distal delivery mechanism are created from several different materials. The inner lumen, which actuates the inner core, is a polytetrafluoroethylene (PTFE) coated stainless steel wire. The center lumen, which creates the main body of the catheter, is made of polyethylene terephthalate (PET). The sheath lumen is created of nylon. Lastly, the outer needle found in the delivery mechanism is 316L stainless steel.

5.2 Testing

5.2.1 Design of Testing

In order to test the feasibility of some concepts and the functionality of others, testing protocols must be devised to obtain reliable data. These protocols are conceived from literature and will serve the purpose of validating the final design. The tests should be designed to be a binary pass/fail. In the event that the device fails a test the reasoning behind the failure will be looked into and the correct course of action taken.

5.2.2 Individual Testing

Testing was conducted to examine and validate the device's two most critical objectives: the ability of the catheter to track easily around the aortic arch, and its ability successfully implant fibrin microthreads into the endocardial wall.

5.2.2.1 Bending Radius Testing

To test the catheters bending ability we constructed a model aortic arch. The model was made from simple vinyl tubing purchased from a hardware store. An approximately 2 foot length of tubing was used. One end of the tubing was bent 180 degrees with a bend radius of 3.5cm, as we had previously determined our prototype could not bend significantly more than this without kinking or permanently deforming. The distal portion of the bend (where the aortic arch would enter the left ventricle) was mounted to a riser whereas the beginning of the arch sat approximately 3cm lower; this orientation was similar to the actual aortic arch. Lubricant was applied to the inside of the tube at the location of the bend to better mimic physiological conditions and negate the natural tackiness of the vinyl tubing, which can be shown in Figure 21. Over the course of testing the device was passed through the model 35 times, and the test was conducted on a pass/fail basis centered on its ability to track easily through the model while having all of its mechanical components maintain smooth function.

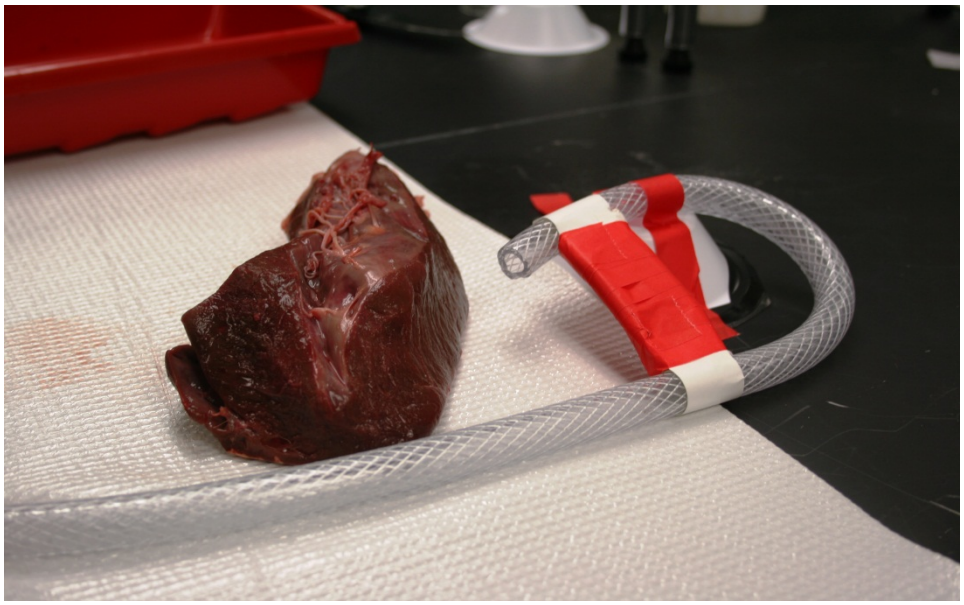

Figure 21: Heart Model

5.3.2.2 Microthread Implantation Test

The primary goal of our testing was to test the prototype's ability to successfully inset fibrin microthreads into cardiac tissue effectively. We acquired bovine heart tissue and placed a section at the end of the model arch to mimic the left ventricle. The prototype was then loaded with length of fibrin microthread approximately 1.5cm long. The threads had been previously hydrated for a minimum of 15 min in PBS. Loading of the microthreads into the needle was conducted with the aid of forceps. The catheter was then tracked through the model to the tissue and deployed, as shown in Figure 22. 35 trials were conducted during this test. This portion of the test was also conducted on a pass/fail basis. A pass was defined as the successful leaving behind of the threads in the section of bovine tissue. A fail was classified as the accidental pulling out of the threads from the tissue as the device is retracted.

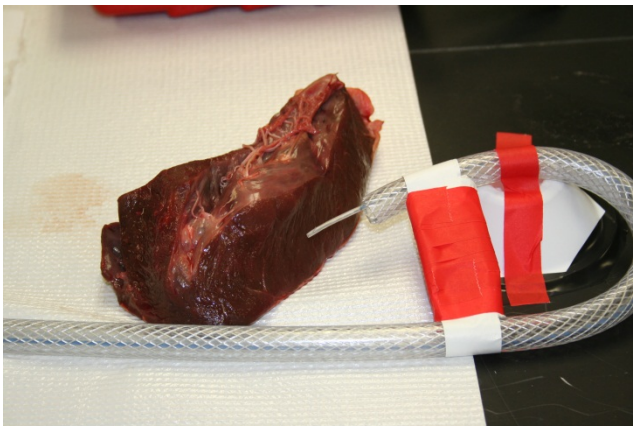

Figure 22: Microthread Deployment Testing

Chapter 6: Results

Preliminary Results

This section explains all of the preliminary testing results performed on the catheter, stem cells, and components of the device necessary to perform the functions essential to the overall success of the catheter. The tests that were performed include the bending radius test and the microthread implantation tests.

6.1. Bending Radius Testing Results

The bending radius test resulted in a 100% success rate. The catheter, when pushed manually, successfully passed through the model arch and the 3.5 cm bending radius. It was noted that a relatively significant amount of force was required to push the catheter around the bend. The force was attributed to the 3.5cm bend being near the non-braided catheter's maximum bending radius.

6.2 Microthread Implantation Results

The thread implantation test resulted in a 91% success rate, as can be seen in Figure 23. The remaining 9% of failures displayed the same consistent failure mode. The failure resulted from the pinching of the microthread between the core and the inner wall of the needle. The consistency of the failure mode allowed the team to note that increasing the diameter of the inner core would likely prevent this occurrence. Of the 91% of successful trials there were some instances of the thread being partially exposed from the tissue sample. This occurrence, although still considered a successful delivery, is believed to be caused by the same "pinching" experienced in tests failures.

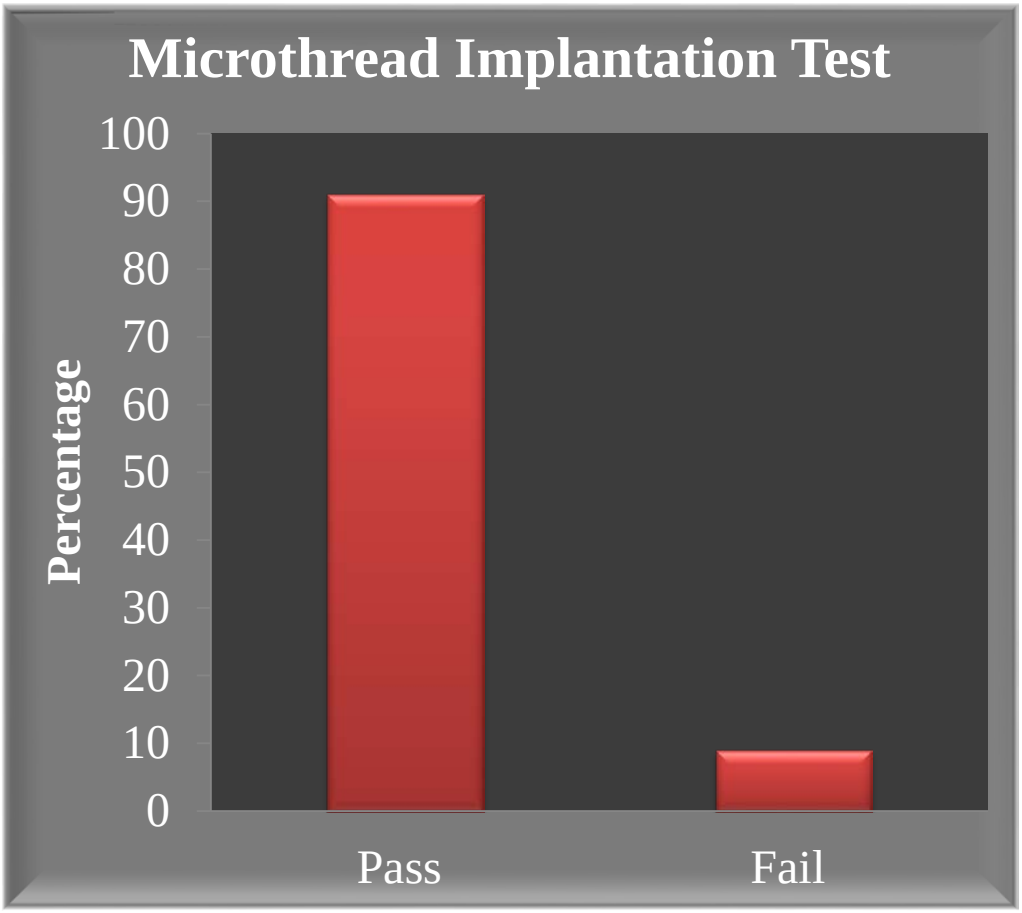

Figure 23: Results of Microthread Implantation Test

Chapter 7: Discussion and Conclusions

The primary goal of this project was to create a minimally invasive device that was capable of delivering stem-cell seeded biological microthreads to the left ventricular wall. In order to accomplish this, we designed a novel catheter system which, in accordance with common, well-established cardiac catheterization procedures, is capable of delivering hMSCs to the heart wall.

The results showed a significant level of success considering it was the first build of a prototype. The success of the prototype testing solidifies that a catheter device such as the one created could in fact be a clinically viable means of clinically delivering cellular therapies to the heart. The novel needle and core design, perhaps the most critical aspect of the device, effectively meets the thread implantation objective. Further honing and perfecting of the needle and core design will likely increase testing success higher than the 91% of the initial prototype. For instance, redesign of the shape and profile of the core may prove more effective in ejecting the threads in tissue.

Testing brought forth the need for an effective method for loading threads. Loading was accomplished with relative ease using forceps. This process, however, was inconsistent. The loading of the thread also played a role in effectiveness of thread insertion. For instance, if loading took more than a few seconds, the thread would begin to dry out and thus be more apt to get stuck when deployed. For initial testing, current loading techniques sufficed, but looking forward to clinical applications a more effective methodology needs to be developed.

The overall design of the catheter proved successful. The handle and its mechanism functioned well mechanically and were ergonomic and easy to use. The sheath and inner lumen portions of the assembly performed as designed and were made from appropriate medical grade polymers. These components' performance showed little need for redesign.

In conclusion, we created a successful working prototype of a cardiac catheter. This minimally invasive device is an endocardial approach to delivering cell seeded biological

microthreads to the heart wall. We believe that our novel needle and core delivery mechanism is capable of reducing shear stresses on the biological microthreads comparatively to an epicardial suturing approach. It is our strong belief that our device shows great promise in its ability to bring cellular therapies to the clinic.

Chapter 8: Future Recommendations

8.1 Enhanced Flexibility

Although our prototype device performed mechanically over a 3.5cm bend, it would not be able to perform over much a tighter bend because of the kinking of the catheter tubes or the permanent bending of the wire. A natural aortic arch has a bending radius closer to 2cm; this means that in physiological conditions our catheter would have difficulty rounding the arch. However, there are some common engineering and manufacturing techniques which exceeded our budget that if employed would significantly enhance the catheters flexibility.

A braided catheter involves compliant materials, such as rubber or silicone based polymers. The soft polymers are more flexible but lack strength and the ability to maintain their shape around a small bending radius. These compliant polymers are than reinforced by small diameter steel coil that is braided over the catheter and then laminated. This creates a catheter that can bend without kinking, yet also maintains its shape and strength. The pitch, pattern, and dimensions of the wire braiding can control the catheters flexion properties. In our particular case, only a small length of our catheter needs to have these highly flexible properties (the section that needs to pass through the arch). Our catheter could have been manufactured in the same manner as our prototype except with addition of a braided portion in the length where the catheter needs to bend. This would ensure our catheter could bend around a natural aortic arch.

The second component of our prototype that needs to have enhanced flexion properties is the solid PTFE coated stainless steel wire that acts as our inner core and runs the entire length of the device. The solid wire would not be able to bend around a natural aortic arch without

permanently deforming. A solution to this design flaw is found in novel hypotube manufacturing. Hypotubes, essentially hollow wire, can now be laser cut perpendicular to their lengths to various depths to enhance their ability to bend. If we were to replaces our solid wire with a PTFE coated and laser cut hypotube that component of the catheter could also bend effectively over an aortic arch.

8.2 Tolerances and Dimensions

Before we proposed a second stage rebuild of our prototype, all the dimensions and tolerances would need to be examined and honed. One of the most important dimensional areas of catheter design affecting mechanical function is excess space between coincidental lumen. This excess space, even a few thousands of an inch, turns to slack when the catheter is applied around a bend and can result in the shortening of the outer most lumen length to a range of even multiple millimeters. For example, when the device is straight and the sheath is retracted the needle becomes exposed 2.5mm, but when around the bend of the aortic arch the needle is exposed 3.5mm. If the sheath were only 2 or 3 thousandths larger than the inner lumen this shortening phenomenon would be negated. This need for tighter dimension also holds true for diameter differences between the needled mounted lumen and the inner core wire. In short, the honing and tightening of dimensions will enhance the catheter's function.

Additionally, the device's single failure mode noted in testing was likely attributed to a dimensional design flaw. Increasing the diameter of the core would rid the distal portion of the catheter of the excess space that the microthread consistently became stuck in.

8.3 Thread Morphology

We would like to perform a study to understand the orientation and shape of a fibrin microthread that has been inserted in tissue with our device. Areas of interest would include a comparative analysis of thread depth relative to the needle and core depth settings. Likewise, we would analyze the shape of the thread, for instance, we would determine if the core pushes the thread into a crumpled structure or a longitudinal orientation. Excising a small portion of tissue that a thread has been implanted in and processing this histologically could provide these details. Specifically, the tissue would be sequentially sectioned via cryostat, mounted and stained, examined by microscopy, and then recreated virtually in three dimensions.

8.4 Shear

We believe our device reduces shear on the threads and cells in particular when compared with the needle and suture approach. To test shear properties we would perform a test similar to those that examine thread morphology. First, hMSC's loaded with quantum dots are seeded onto fibrin microthreads. The threads would be implanted into tissue using the catheter delivery device. The tissue would then be processed as previously explained, stained with Hoescht and examined with a quantum dot filter. We could then examine and the tissue sections and rebuild them three dimensionally with the use of computer software. The quantum dots would allow for the tracking of cells that had been inserted into the tissue, determining if they have sheared off of the thread and if so, what location in the tissue.

8.5 Thread Loading

The most difficult aspect of using our device is the loading of the threads into the needle. Currently, loading is performed carefully with forceps, and although this worked fine, we expressed concern that the process could damage threads loaded with cells. The development of tooling or better methodology to more effectively load the threads into the catheter would increase its ease of use dramatically.

8.6 Clinical Trials

After performing the aforementioned design improvements and testing, the device would be validated enough to begin animal testing. The procedure would be performed on either a porcine or sheep model, as they are the common standards in cardiovascular device testing. Animal testing would allow us to determine if the device and procedure are clinically viable. Animal testing would be performed under fluoroscopy by a cardiologist who could then provide crucial feedback for visualization, accuracy, and ease of use.

Chapter 9: References

American Heart Association. *Heart Transplant*. 2010. Retrieved October 11, 2010, from American Heart Association web site: http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/CareTreatmentforCongenitalHeartDefects/Heart-Transplant_UCM_307731_Article.jsp

Barbash I, Chouraqui P, Baron J, Feinberg M, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes L, Kloner R, Leor J. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation.* 2003;108(7):863-868.

Beeres, S. L M A., D. E. Atsma, J. Van Ramshorst, M. J. Schalij, and J. J. Bax. "Cell Therapy for Ischaemic Heart Disease." Heart 94.9 (2008): 1214-226. Print.

Bianco P, Riminucci M, Gronthos S, Robey P. Bone marrow stromal stem cells: nature, biology, and potential applications. *Stem Cells.* 2001;19(3):180-192.

"Biocompatibility of Plastics." *Zeus Industrial Products, Inc.* 2005. Web. 12 Dec. 2011. <http://www.zeusinc.com/UserFiles/zeusinc/Documents/Zeus_Biocompatibility.pdf>.

Bioheart Inc. "Product Candidates". 2009. 25 October 2010 <http://www.bioheartinc.com/prod-myocath.html>.

Boston Scientific. Web. 10 Oct. 2010. <http://www.bostonscientific.com/>.

"Cardiac Catheterization: MedlinePlus Medical Encyclopedia." *National Library of Medicine - National Institutes of Health*. Web. 5 Oct. 2010. <http://www.nlm.nih.gov/medlineplus/ency/article/003419.htm>.

Cornwell, K. Collagen and Fibrin Biopolymer Microthreads for Bioengineered Ligament Regeneration. University of Massachusetts Medical School). 2010

Cornwell, K. G., & Pins, G. D.Discrete crosslinked fibrin microthread scaffoldsfor tissue regeneration Wiley InterScience. 2006.

Cowie, M.R., Wood, D.A., Coats, A.J.S., et al. Survival of patients with a new diagnosis of heart failure: A population based study. *Heart*, 83(5), 505-510. 2000.

DiTroia, L., Hassett, H., & Roberts, J. Fibrin Microthreads for Stem Cell Delivery in Cardiac Applications. WPI: http://www.wpi.edu/Pubs/E-project/Available/E-project-042308-220733/unrestricted/Fibrin_Microthreads_MQP.pdf

Fakharzadeh, Michael. Delivering Stem Cells to the Heart. Thesis. Worcester Polytechnic Institute, 2010.

"Fluoroscopy." U S Food and Drug Administration Home Page. Web. 1 Oct. 2010. <http://www.fda.gov/radiation emittingproducts/radiationemittingproductsandprocedures/medicalimaging/medicalx-rays/ucm115354.htm>.

Freyman T, Polin G, Osman H, Crary J, Lu M, Cheng L, Palasis M, Wilensky R. A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. Eur Heart J. 2006;27(9):1114- 1122.

"GORE® Medical OEM Contact Information." *W. L. Gore & Associates, Inc.* 2010. Web. 12 Dec. 2010.<http://www.gore.com/en_xx/products/medical/oem/medicaloem_contact_info.html>.

Griffiths, P.J. et al. "Synchronous In Situ ATPase Activity, Mechanics, and Ca2+ Sensitivity of Human and Porcine Myocardium". Biophysical Journal , 97, 2009, 2503–2512.

"Helix Biotherapeutic Delivery." BioCardia. Web. 18 Dec. 2010. <http://www.biocardia.com/helix/products.shtml>.

Hong, K. Z. (1996), Poly(vinyl chloride) in medical device and packaging applications. Journal of Vinyl and Additive Technology, 2: 193–197. doi: 10.1002/vnl.10123

"Imaging Catheter." New Smoother Imaging Catheter from Boston Scientific. Web. 20 Apr 2011. < http://www.medgadget.com/archives/img/c232ph_icross_02_us_large.jpg>.

ISO - International Organization for Standardization. 2010. Web. 06 Dec. 2010. <http://www.iso.org/iso/home.htm>.

Jiang S, Haider H, Idris N, Salim A, Ashraf M. Supportive interaction between cell survival signaling and angiocompetent factors enhances donor cell survival and promotes angiomyogenesis for cardiac repair. Circ Res. 2006;99(7):776-784.

Kevin R. Siebenlist, Ph.D., Associate Professor. Interactions of fibrin(ogen) with other proteins of the coagulation cascade., October, 2010, from http://www.marquette.edu/chs/bisc/faculty/rsiebenlist.shtml

Krause D, Theise N, Collector M, Henegariu O, Hwang S, Gardner R, Neutzel S, Sharkis S. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell. 2001;105 (3):369-377.

Mayo Clinic Staff. *Heart transplant: How you prepare*. 2008. Retrieved October 11, 2010, from Mayo Clinic web site: http://www.mayoclinic.com/health/heart-transplant/MY00361/DSECTION=how-you-prepare

Murphy, M. (September 3, 2008). Fibrin microthreads promote stem cell growth for localized delivery in regenerative therapy. WPI: http://www.wpi.edu/Pubs/ETD/Available/etd-090208-143505/unrestricted/MMurphy.pdf

Murry C, Field L, Menasché P. Cell-based cardiac repair: reflections at the 10-year point. *Circulation.* 2005;112(20):3174-3183.

National Heart Lung and Blood Institute. *What Is a Heart Attack?* 2008. Retrieved October 11, 2010, from National Heart Lung and Blood Institute web site: http://www.nhlbi.nih.gov/health/dci/Diseases/HeartAttack/HeartAttack_WhatIs.html

Regulating regenerative medicines. Retrieved October, 2010 from http://www.manufacturingchemist.com/technical/article_page/Regulating_regenerative_medicines/43846

Ren, J., F. Marchlinski, D. Callans, and H. Herrmann. "Clinical Use of AcuNav Diagnostic Ultrasound Catheter Imaging during Left Heart Radiofrequency Ablation and Transcatheter Closure Procedures." Journal of the American Society of Echocardiography 15.10 (2002): 1301-308

Sherman, Warren, Timothy P. Martens, Juan F. Viles-Gonzalez, and Tomasz Siminiak. "Catheter-based Delivery of Cells to the Heart." Nature Clinical Practice Cardiovascular Medicine 3 (2006): S57-64

Stem Cell Basics . In *Stem Cell Information* [World Wide Web site]. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2009 [cited Monday, October 04, 2010] Available at http://stemcells.nih.gov/info/basics/defaultpage

"Stereotaxis - Magnetic Navigation." Stereotaxis - Home. Web. 4 Oct. 2010. <http://www.stereotaxis.com/niobe.html>.

Toma C, Pittenger M, Cahill K, Byrne B, Kessler P. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation.* 2002;105(1):93-98.

Uibo, R., Laidmäe, I., Sawyer S., E., Flanagan, L. A., Georges, P. C., Winer, J. P., et al. (May 2009). Soft materials to treat central nervous system injuries: Evaluation of the suitability of non-mammalian fibrin gels., 924-930.

Appendix

Appendix A: Fibrin Thread Making

Materials

Stock Solutions:

-Fibrinogen (Sigman F 4753) = 70mg/ml in HEPES buffered saline (pH 7.4)

-HBSS = 20mM HEPES 0.9% NaCL

-1mL aliquots @ -20^{o}C

-Thrombin (Sigma T 4648) = 8 U/200 µl in HEPES buffered saline (pH 7.4)

-HBSS = 20mM HEPES, 0.9% NaCl

-200µL aliquots @ -20^{o}C

-CaCl2 = 40mM CaCl2 in diH2O stored at 4^{o}C

Solutions (warmed to room temp):

-Fibrinogen = 1mL in a 1mL syringe from stock fibrinogen

-Thrombin = 150 µL of thrombin stock solution + 850 µL of 40mM CaCl2 in a 1 mL syringe.

Methods

1. Place blunt end syringe (20 ½ gauge BD) into 0.86 MM I.D. polyethylene tubing of length 1- ½ feet.
2. Place each 1mL syringe of Fibrinogen and Thrombin solutions into the back end of the blending connector (Micromedics blending applicator, MN)
3. Set the syringe pump to:

   -Infusion

   -4.7mm diameter

   - Rate = 0.23mL/min
4. Place a metal non-stick pan beside the syringe pump and fill with 500mL of 10mM HEPES solution (pH 7.4)
5. Attach the blending connector with the 1mL syringes attached to the syringe pump and run the pump.

6. Drag the polyethylene tubing consistently against the bottom of the pan, as the thrombin and fibrinogen are extruded from the tube.

7. Wait 7-8 minutes after starting extruding the threads to begin removing and hanging them to dry.

Appendix B: Design Tools

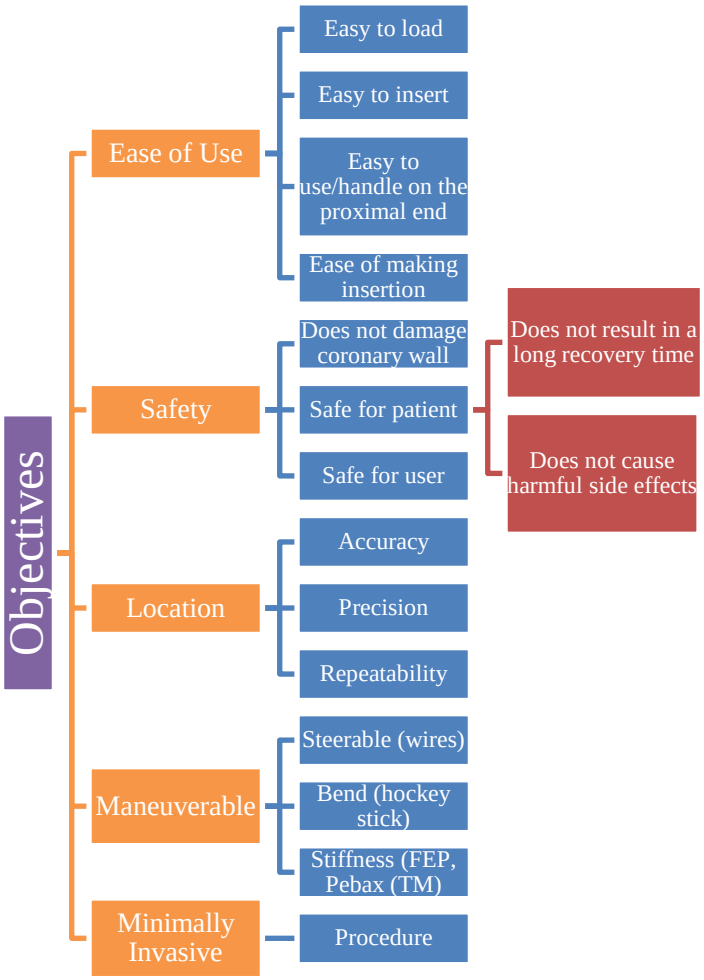

Figure 24: Objective Tree

Table 3: Blank Pairwise Comparison Chart

Objective (Ease of Use)	Easy to load	Easy to insert (reach LV)	Easy to use (proximal end)	Ease of making insertion
Easy to load				
Easy to insert (reach LV)				
Easy to use (proximal end)				
Ease of making insertion				

Objective (location)	Accuracy	Precision	Repeatability
Accuracy			
Precision			
Repeatability			

Safety (Patient)	Does not damage coronary wall	Does not result in long recovery time	Does not cause harmful side effects
Does not damage coronary well			
Does not result in long recovery time			
Does not cause harmful side effects			

Appendix C: Test Results

Trial	Pass/fail	Notes
1	Pass	Perfect
2	Fail	Stuck between core and needle
3	Pass	perfect
4	Pass	perfect
5	Pass	Apprx 2mm of thread exposed
6	Pass	Perfect
7	Pass	Perfect had to actuate core multiple times
8	Fail	User error
9	Pass	Perfect
10	Fail	Thread pinched
11	Pass	Perfect
12	Pass	Perfect
13	Fail	Thread pinched
14	Pass	Negligible exposure
15	Pass	Perfect
16	Pass	Partial exposure of thread
17	Pass	
18	Pass	

19	Pass	Negligible exposure
20	Pass	
21	Pass	
22	Pass	
23	Pass	
24	Pass	
25	Pass	
26	Pass	
27	Fail	Shallow needle angle, partial exposure
28	Pass	
29	Fail	Partial exposure
30	Pass	
31	Pass	
32	Fail	Thread stuck
33	Pass	
34	Pass	
35	Pass	

Appendix D: Glossary and Acronyms

Acronyms

MQP – Major Qualifying Project

MI – Myocardial Infarction

hMSCs – human Mesenchymal Stem Cells

ECM – Extra-Cellular Matrix

LV- Left Ventricle/Ventricular

Glossary

Catheter – a device containing a distal and proximal end, whereby the proximal end is actuated outside of the body by the physician, and the distal end is actuated internally performing a critical task.

Microthreads – biological tissue strands comprised of fibrin and/or collagen

Proliferation – Spreading; Propagation

Radiopaque – Blocks the penetration of x-rays or other types of radiation

Shear stress – Stress applied parallel or tangential to the face of a material

Viability – The ability to maintain a healthy and living state

Thrombogenic – Tending to produce a blood clot

Biocompatible – Being compatible with life and not causing health risks or threats to a living substance.