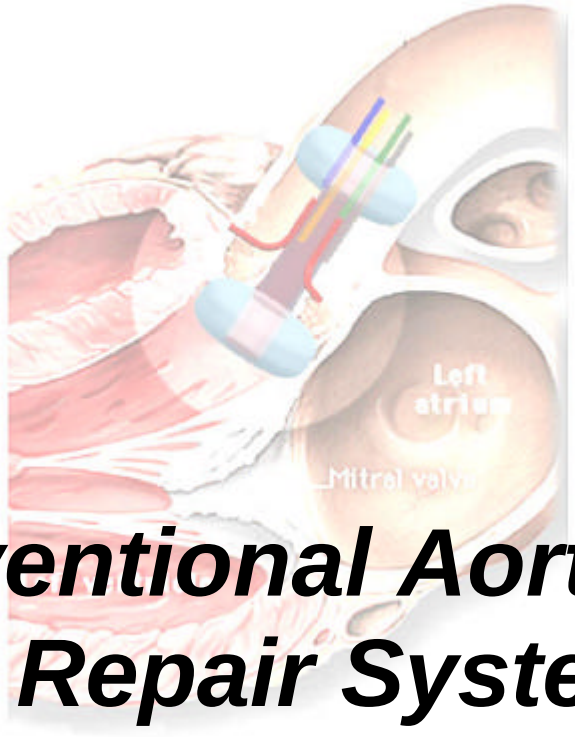

Interventional Aortic Valve Repair System

ME 282: Biomedical Product Design and Evaluation
Biomechanical Engineering Division
Mechanical Engineering Department
Stanford University

March 15, 2002

Project Sponsor
Corazón Technologies, Inc.

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I Executive Summary

Aortic stenosis is a disease characterized by calcification and thickening of the aortic valve. This results in a decreased orifice valve area and a narrowing of the opening of the valve. Aortic stenosis is a serious concern because the decreased blood flow leaving the left ventricle can lead to a heart attack and death. The current treatment for severe aortic stenosis is valve replacement. The main drawback of a mechanical valve replacement is that patients need to be placed on anticoagulants. Bioprosthetic valves have limited durability. Therefore an improved approach to treat aortic stenosis is needed to treat those patients who cannot deal with the complications associated with a valve replacement.

The goal of our project is to design an interventional aortic repair system that uses Corazon's CDS solution to dissolve and remove calcification present on the aortic valve. Our device will isolate the aortic valve region, while at the same time maintaining normal heart functioning. This includes an adequate blood supply from the left ventricle to the aorta and the coronary arteries.

This quarter a detailed market and engineering specifications list for the device was made. Using this list initial design concepts were generated and evaluated. For the isolation unit, an umbrella structure, a springy mesh structure, and a pressurized balloon were considered. Several lumens are needed for the device: one for main blood flow through the device, two for blood supply to the coronary arteries, one for inflation of the device, one for CDS, one for buffer, and one for aspiration. A cellular structure and inflatable central lumen were the design concepts generated for the various lumens.

Using a Pugh analysis, an inflatable central lumen with pressurized balloons for isolation was chosen for the current design. A central lumen for the main blood flow will be inflated, making the diameter of the device large enough to maintain a sufficient blood supply to the aorta. Lumens for inflation, CDS, buffer, and aspiration are attached to the upper outside region of the central lumen. The two lumens for the coronary blood supply are attached to the lower part of the central lumen. On both sides of the device pressurized balloons will be inflated to effectively isolate the aortic valve region. This will prevent blood seepage into the isolation unit and CDS leakage into the circulatory system.

Our future steps for next quarter are to prototype our current design and test how well our device works. Exact dimensions of each component of our device must be determined and materials for fabrication of the device must be chosen. In addition, a membrane valve for the device must be designed. Testing and validation of the device will be accomplished using a pulsatile flow model.

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III Background

Sponsor Background

Corazón Technologies was founded by Brent R. Constantz in December 1998. Corazón is a privately held corporation located in Menlo Park, California. Corazón is an innovative company that develops systems to dissolve and remove calcifications of the cardiovascular system. Their Corazón Demineralizing Solution (CDS) is an inorganic acidic solution that mimics the behavior of osteoclasts, a specialized cell type that dissolves and resorbs bones. Osteoclasts secrete solutions and enzymes that break down calcium phosphate and bone matrix components. CDS is able to dissolve calcium phosphate deposits responsible for calcification present in arteries and on heart valves.

Corazón's first products include: 1) an interventional arterial treatment system for the treatment of peripheral arterial occlusions, and 2) a surgical aortic valve treatment system for the treatment of calcific aortic stenosis during on-pump coronary artery bypass grafting. Corazón is currently working on an interventional approach to treat aortic stenosis using CDS to dissolve calcification present on the aortic valve.

Clinical and Scientific Background

Aortic stenosis is a serious condition characterized by calcification and thickening of the heart's aortic valve, which separates the left ventricle from the aorta. Calcium phosphate deposits form on the three leaflets of the aortic valve (Figure 1). These deposits are made of a highly insoluble mineral, carbonated hydroxyapatite, which is also known as Dahlite. Dahlite binds tightly to collagen, the main component of heart valves. When the aortic valve becomes calcified, it does not open properly, impairing the ability of the left ventricle to pump oxygenated blood out of the heart and into the aorta, which supplies blood to the rest of the body. The walls of the left ventricle initially thicken to generate enough force to eject blood through the narrowed aortic valve. However, with time, the left ventricle dilates and increases in size, losing its contractility and ability to expel blood to the aorta.

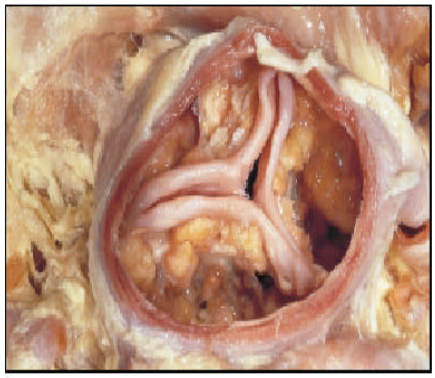

Figure 1. Calcification of the aortic valve.
Shavelle, D.M, and Otto, C.M.

Other characteristics of aortic stenosis are a decreased orifice valve area and increased pressure gradient across the valve (Table 1). A normal valve area in healthy adults is 3.0-

-4.0 cm^2. The valve area is greater than 1.3 cm^2 in mild aortic stenosis, 0.8--1.3 cm^2 in moderate stenosis, and less than 0.8 cm^2 in severe aortic stenosis. If the aortic valve is functioning properly, there should be no pressure gradient across the valve. A peak instantaneous pressure gradient of greater than 70 mm Hg indicates that severe aortic stenosis is present.

Table I. Hemodynamic Degrees of Aortic Stenosis

	Mild	Moderate	Severe
Mean pressure gradient (mm Hg)	<25	25–45	>45
Peak instantaneous pressure gradient (mm Hg)	<40	40–70	>70
Aortic valve area (cm^2)	>1.3	0.8–1.3	<0.8

Note: The normal aortic valve in adults has an area of 3–4 cm^2 and no appreciable pressure gradient. The pressure gradient is proportional to the degree of aortic stenosis, as long as the cardiac output is normal. In patients with low cardiac output, however, the pressure gradient may be deceptively low. In such instances, one should rely on the aortic valve area for the assessment of aortic stenosis severity.

Table 1. Saric and Kronzon

Figure 2 shows the physiology for a normal healthy person. The aortic valve cusp fully opens. As blood flows from the left ventricle to the aorta, turbulent eddies are formed above the valve, redirecting blood flow into the coronary arteries. For a patient with severe aortic stenosis, the valve cusps do not fully open (Figure 3). There is a higher jet velocity of blood flow through the narrowed valve. A high pressure gradient across the valve reduces the blood flow to the coronary arteries. Because there is a lower pressure above the aortic valve than in the coronary arteries, blood is actually pulled back out of the coronary arteries.

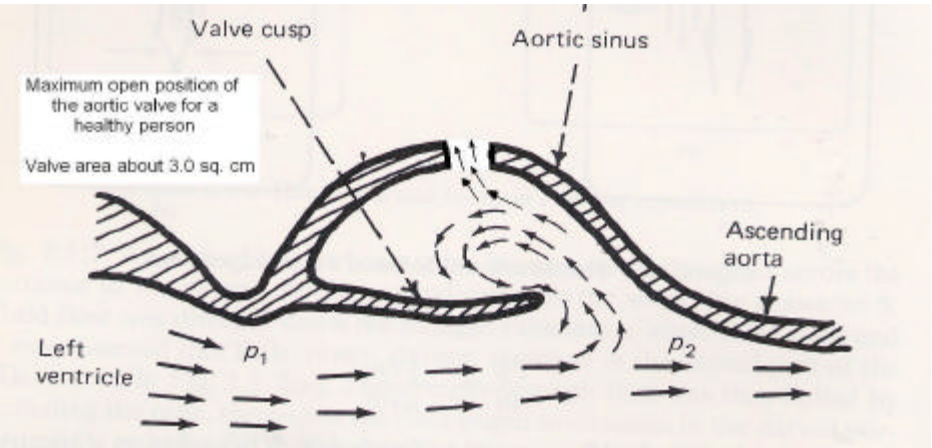

Figure 2. Physiology of the aortic valve for a healthy person.

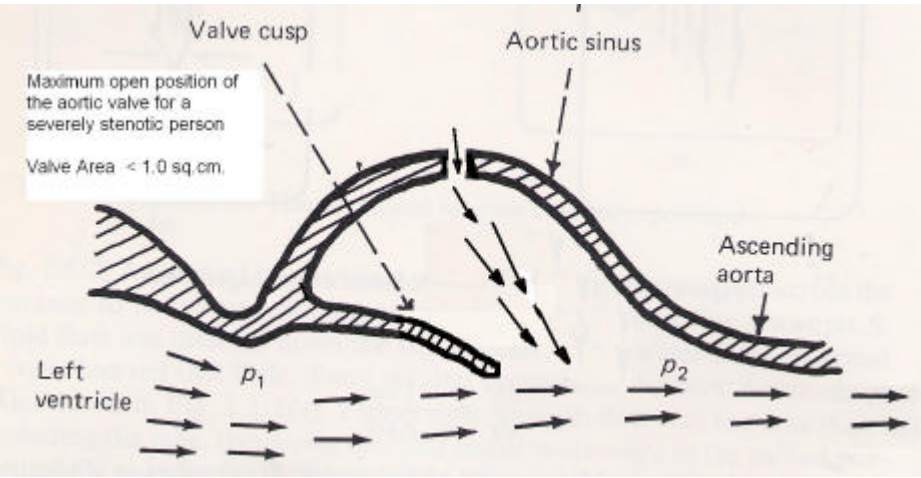

Figure 3. Physiology of the aortic valve for a patient with severe aortic stenosis.

Aortic stenosis has a variety of causes. In the past, rheumatic fever was the most common cause. Rheumatic fever can cause fusion of the aortic cusps and inflammation on the aortic valve, leading to calcification and stenosis. Currently, rheumatic fever is no longer a major cause of aortic stenosis because rheumatic fever has been largely controlled. Congenital defects can also lead to aortic stenosis. About 1% of the population is born with a bicuspid aortic valve made of two valve leaflets instead of the normal three valve leaflets. Blood flow causes trauma to the two cusps, causing inflammation and calcification of the aortic valve over time. Patients with a bicuspid valve usually develop symptoms of aortic stenosis in their 40s and 50s. Today the most common cause of aortic stenosis is calcification and degeneration of the aortic valve. Calcium phosphate deposits accumulate on the aortic valve, and symptoms of aortic stenosis appear when patients are in their 70s or 80s.

People with aortic stenosis usually develop the following symptoms: angina, syncope, and shortness of breath. Angina, or chest pain, is the result of the heart not receiving a sufficient amount of oxygen. The heart's demand for oxygen increases as the left ventricle thickens and works harder to pump blood through the narrowed aortic valve into the aorta. However, because of the stenotic aortic valve, there is decreased blood flow to the coronary arteries, which branch off the aorta and supply blood to the heart. Syncope, or loss of consciousness, results from the brain not receiving enough oxygenated blood. This is caused by the decreased blood flow into the aorta and the rest of the body. Shortness of breath is the result of accumulation of fluid in the lungs. As the left ventricle thickens, it becomes stiff and loses its ability to contract, so that some blood may be backed up into the lungs. Fluid accumulation in the lungs interferes with proper oxygenation of blood, creating the sensation of shortness of breath.

Need/Market Analysis

Of the 521,000 aortic valve disease diagnoses, 350,000 are due to aortic stenosis. 1.2 million people, or 2-3% of the adult US population, are affected with this disease. When aortic stenosis becomes so severe that the symptoms of angina, syncope, or shortness of breath are present, the mortality rate is greater than 90% within a few years

(Bokros et. al, 1991). Currently only 11% of patients with aortic stenosis receive treatment via an aortic valve replacement. The majority of the remaining patients are placed under "watchful waiting", where their conditions are carefully monitored until their symptoms become so severe that an aortic valve replacement is necessary. The challenge in treating aortic stenosis is finding an effective way to make earlier intervention possible without having to perform a highly invasive aortic valve replacement surgery.

Benchmarking and Related Technology

Aortic valve replacement (AVR) is the current treatment of choice for 11% of the 100,000 patients who are hospitalized due to aortic valve complications annually in the U.S. Currently available replacement heart valves generally fall into two categories: mechanical, and bioprosthetic. While mechanical valves are constructed entirely of synthetic materials, porcine valves are the typical choice for a bioprosthetic.

Mechanical valves were introduced in 1961 with the Edwards-Starr ball and cage valve (Figure 4). Bileaflet valves, as seen in Figure 5, entered the market in the 1970s and remain the most commonly used mechanical valves. However, valvular thrombosis and thromembolism have hampered the success of mechanical valves, due to traditional thrombogenic contributors that are inherent in mechanical AVR (Lund, *et al.*, 1999 and Rosengart, *et al.*, 1998). Patients with mechanical valves are thus required to take anticoagulants such as warfarin or camoudin for the duration of their lives, which can lead to subsequent bleeding complications. Furthermore, mechanical valves cannot grow with the recipient and mismatch may lead to either further occlusion or insufficiency. (Gonzalez-Juanatey, *et al.* 1996). Nonetheless, mechanical valves are used for younger patients due to their durability.

Figure 4. Edwards-Starr ball valve

Figure 5. Bileaflet Valve
St. Jude Medical

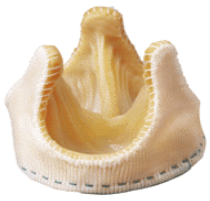

Figure 6. Porcine bioprosthetic valve
St. Jude Medical

Bioprosthetic valves were developed in the 1970s and heralded as allowing normal blood flow (Figure 6). To prevent an immunologic response and rejection from the recipient, bioprosthetic valves are fixed with gluteraldehyde. However, gluteraldehyde also has the adverse effect of decreasing durability by preventing normal cellularization and remodeling of the valve. Bioprosthetic valves are also susceptible to calcification, which may be increased by remnants of gluteraldehyde fixation. Thus, these valves do not maintain the durability found in mechanical valves and are viable only for 10-15 years.

Figure 7.
Balloon Valvuloplasty
Indo-American
Cardiovascular Center

Percutaneous aortic ballon valvuloplasty (PABV) was developed as an interventional method to treat aortic stenosis. This procedure involves a ballon catheter that is passed through the groin, inateratrial septum, mitral valve and into the left ventricle. Once advanced across the valve, the ballon is inflated using a stepwise dilatation technique (Figure 7). Inflation continues until the desired aortic annulus diameter is reached or until aortic regurgitation appears during the operation. The end result is a re-opening of the hardened valve. However, valvuloplasty merely provides temorary relief with hemodynamnic improvements and often results in restenosis within 6 months.

Corazon Technologies, Inc. has applied its demineralizing solution (CDS) interventionally to peripheral arterial occlusions (Figure 8) as well as surgically to aortic valve surgery. In the treatment of total occluded arteries, a total occlusion catheter (TOC) is threaded through an aspiration catheter. The CDS is then cycled through the region along with a buffer solution. Aspiration then removes superficial calcification particles. Partially occluded arteries are treated via a partial occlusion catheter (POC) inserted through the aspiration catheter. Balloons are inflated on either side of the treatment region to prevent blood from buffering the CDS. As in the treatment of total occlusions, the CDS is then cycled through the lesion and the superficial particles are aspirated.

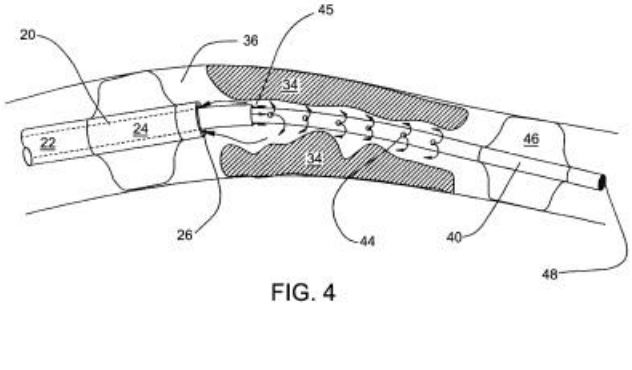

Figure 8. Corazon Arterial Treatment
U.S. Patent 6,290,689

Corazon's surgical aortic valve treatment is performed during coronary artery bypass graft (CABG) procedures. While the patient is on full cardiopulmonary bypass, the CDS is continually supplied to a foam structure, which is positioned on the aortic valve for the duration of the CABG, which typically lasts for half an hour. This approach is simpler than an interventional approach due to the blood-free environment provided by

the cardiopulmonary bypass. Thus, the pump can maintain the normal output of the heart while the surgeons are able to treat the diseased valve.

Problem/Needs Statement

For this project Corazón would like us to design an interventional aortic repair system. Such a system will allow the interventional cardiologist to treat aortic stenosis and remove calcified deposits on the aortic valve without performing open-heart surgery. A catheter system will be used to isolate the aortic valve region and will contain a high-pressure solution delivery device (HPSDD) that delivers the CDS used to dissolve any calcification present on the leaflets of the aortic valve. It is important that normal functioning of the heart is maintained while the decalcification procedure is being performed. This includes maintaining an adequate level of cardiac output and a sufficient blood supply to the coronary arteries, which are located directly above the aortic valve.

Project Team

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 796 Escondido Road, 14E Stanford, CA 94305 (650)799-9959	Beverly is a first year Masters student in Chemical Engineering. She grew up in the Los Angeles area and did her undergraduate degree at MIT in Chemical Engineering. Her focus is on bioengineering, and she would like to pursue a career in the biotechnology industry or the medical device industry. Her previous research has focused on growing cells in different types of bioreactors to optimize the production of monoclonal antibodies.

MARIEL FABRO	mariel@stanford.edu
 436 Mayfield Ave, Florence Moore Hall, Mirlo 212 Stanford, CA 94305 (650) 497-5992	Mariel is a senior receiving a B.S. in Biomechanical Engineering. She is currently collaborating on a mandibular distraction osteogenesis project with the research groups of Michael Longaker, M.D., Ph.D. and Dennis Carter, Ph.D. As a visiting researcher at UCLA, Mariel worked on early developments of a minimally-invasive laser liposurgery. She is also the co-designer of a lesion measurement device for use during cath lab procedures. Mariel is interested in the innovation of medical devices for any and all applications

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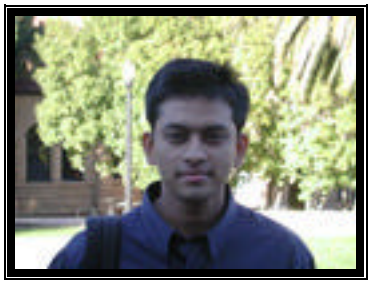 750 Escondido Road, Bldg #141K Stanford, CA 94305 (650) 497-9397	Rajan is a first year Masters student in the Biomechanical Engineering division. He received his undergraduate degree in mechanical engineering from PSG Tech, India. Rajan's focus is on biomedical devices (especially in the cardiovascular field). His previous research was mainly in the development of CFD solvers (Flow simulation) and software for aircraft modeling (Parametric modeling).

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IV Design Definition

Purpose of Design

In addition the current surgical method of applying the CDS to the aortic valve during a coronary artery bypass graft procedure (CABG), Corazón is interested in developing an interventional treatment for aortic stenosis. Such a procedure differs from the surgical method in that it is a minimal invasive procedure performed on the beating heart by an interventional cardiologist in the cardiac catheterization lab.

The purpose of this project is to design an interventional aortic valve repair system including a device to deliver the CDS to the diseased valves and the protocol necessary to use the system. Thus, this system will allow the cardiologist to remove calcified deposits from the diseased valves, leaving the patient with their native valve. Being a non-surgical method, the treatment will result in shorter hospital stays and recovery periods. Furthermore, this procedure will save the patient from problems indicated for valvuloplasty and valve replacement. Interventions can also be performed for those patients labeled as "watchful waiting" without further progression of aortic stenosis.

Project Goals

With the design of an interventional aortic repair system, the goal of the treatment is the following:

- ?? Increase aortic valve cross-sectional area,
- ?? Decrease the pressure gradient across the aortic valve
- ?? Decrease the clinical impact of calcific aortic stenosis.

We will first compile a detailed set of engineering specifications derived from more general market specifications. Using these engineering specifications, we will design an interventional device/delivery system for CDS application that will accomplish the following:

- ?? Isolate the aortic valve region for treatment
- ?? Deliver and apply CDS to the aortic valve leaflets
- ?? Supply blood to the ascending aorta for circulation
- ?? Supply blood to the coronary arteries for myocardium perfusion

We will also develop a protocol for proper usage of the new device such that can be adopted into the catheterization lab environment. In culmination of the design, we will prototype the device and release it to Corazón for further development.

Scope of the Project

The potential for complexity is inherent in the design, and we have limited our scope to the following:

1. Treatment of non-severe aortic stenosis
2. Develop and design a method for simultaneous CDS and buffer application and aspiration
3. Develop and design a method for isolating the aortic valve region.
4. Develop and design a method for supplying blood to the aorta and the coronary arteries
5. Design for anatomical variability in adults
6. Design the device to incorporate points 1-4, and produce a functional prototype
7. Testing of the device to verify functional performance requirements have been met

The following are not included in the project:

1. Treatment of aortic valve commissure
2. Design for pediatrics
3. Pumping blood into or out of the region

Functional Performance Requirements

The following requirements are market specifications identified by the customer for the procedure and application of CDS. The document of engineering specifications derived from these requirements can be found in the Appendix.

?? ***The procedure must be performed via percutaneous methods using a catheter-based system inserted into the right femoral artery and guided to the heart to treat patients who have mild to moderate aortic stenosis with the presence of calcification. Furthermore, the procedure must be compatible with current techniques and procedures used by interventional cardiologists. The catheter-based system must also provide for indirect visualization of the procedure***. Femoral access is common for the catheterization lab environment. As an interventional method, the procedure should follow common catheterization lab procedures to ensure a high adoption rate. Indirect visualization is a key element of catheterization lab procedures, mainly with the use of angiography and echocardiography that allows the cardiologist to maneuver the devices through the blood vessels.

?? ***The applicator must be designed for easy setup and use within the cardiac catheterization lab environment.*** Extra time in the catheterization lab is undesirable for the cardiologist, technicians, as well as the patient.

?? ***The device must maintain normal heart functioning.*** The left ventricle is responsible for pumping blood supply to the rest of the body as well as to the coronary arteries to ensure myocardial perfusion. The device must allow for a reasonable cardiac output and blood supply to the coronary arteries.

?? ***Completion of the procedure must provide a clinically significant increase in the aortic valve area (AVA).*** Without an increase in AVA, the treatment does not meet its purpose

and the problems associated with aortic stenosis will persist. Furthermore, the increase must be sufficient enough to lead to a noticeable improvement in the patient's condition.

?? ***The applicator must consist of a single use, disposable device.*** Since the device is used in situ, it is not feasible to re-sterilize and reuse. Furthermore, most devices used in interventional procedures are single-use.

?? ***The applicator must allow for the controlled application and removal of Corazón's proprietary solution to an isolated region that includes the AV, left ventricular outflow tract, and proximal region of the ascending aorta in patients with aortic valves between 19 mm and 31 mm.***

?? ***The applicator must be compatible with aortic valves between 19 mm and 31 mm.*** This is the range of anatomic variability obtained from Corazon and the literature review.

?? ***The applicator must create a demineralizing zone on the aortic side of the AV and in the region of the aortic root.*** The demineralizing zone is essential for proper reaction between CDS and the calcified aortic valve. When the CDS dissolves the calcification during initial contact, the reaction has a propensity of producing a basic composition, which will simply buffer the entire surface of the valve. It is important to maintain a steady flow of H^+ ions to the valve surface to keep the pH on the valve surface at an acidic level.

?? ***The applicator must be designed to provide an appropriate gross margin.*** This requirement deals with the cost of the device and results from business decisions made at Corazon.

?? ***The applicator must be biocompatible.*** Since the device is inserted into the arterial system and deployed in the aortic route, biocompatibility with blood and the left ventricular tissue is absolutely necessary.

?? ***The applicator must be sterile.*** Since the device will come into contact with the patient, the device must be sterilizable.

?? ***The applicator must be functional and sterile upon arrival in the catheterization lab.*** As a product delivered to the catheterization lab, the device should not need excessive assembly. Furthermore, the device must be sterilized during the manufacturing process to avoid unnecessary inconvenience to the technicians.

?? ***The applicator must be compatible with Corazón's high-pressure pressurization system.*** A high-pressurization system will be used to deliver the CDS through the catheter-based device. The device must be able to withstand the conditions imposed by this high-pressurization system such that the delivery of CDS is not compromised.

?? ***The applicator must be compatible with Corazón's proprietary solutions for the duration of the procedure.*** The method of CDS application must last the duration of the

procedure. Since the CDS is acidic, the applicator must not degrade or allow leakage of CDS.

?? ***The applicator must be compatible with aspiration.*** Due to the demineralizing action of the CDS, superficial particles will dislodge and be released into the treatment region. Aspiration will remove these particles as well as all of the solutions (CDS and buffer) delivered to the treatment region. The device must allow for this aspiration, and furthermore must not be negatively affected by the method of aspiration.

Regulatory Considerations

The interventional aortic valve repair system will be considered a medical device, under the definition stated by the FDA. The device will deliver a chemical solution that will biologically and pathologically alter the area of treatment. As such, the device will be a Classification III device. There are no other products that are similar to the device in regards to the intended use and further development of the device, beyond our scope, will follow the pre-market approval regulatory pathway. A brief regulatory checklist can be found in the Appendix

V Design Development

Vision/Strategy

The main goal of the project is to provide an effective isolation zone and maintain normal physiology during the procedure without causing any harm to the patient. During the procedure CDS will be used for the dissolution of calcium deposits on the aortic valve cusps and commissures. The valvuloplasty technique is modified with drastic changes that allow for blood flow through a central lumen.

Overview of Work Completed

The preliminary designs for the isolation unit and different lumens have been completed. Options considered for the isolation unit were an umbrella, a springy mesh, and a pressurized balloon. Options considered for the lumen design were a cellular type lumen and an inflatable central lumen. The current design chosen is an inflatable central lumen with pressurized balloons for isolation. These ideas were chosen because they meet the requirements of supplying an adequate cardiac output and effective isolation of the aortic valve.

Design Concepts Generated and their Evaluation

The design concepts generated for the device are split up into two main sections, the design of the isolation unit and the design of the various lumens.

Design of the isolation unit

The primary purpose of the isolation system is to prevent blood seepage into the isolation unit and CDS leakage into the circulatory system. A constant pressure must be maintained inside the isolation unit, but the pressure across the isolating module will continually fluctuate. In the lower part of the isolation unit that contains the left ventricular outflow tract, the pressure fluctuates from as low as 5 mm Hg during diastole to the maximum systole pressure in the left ventricle. Design of the isolation unit must take into account this pressure fluctuation. Axial movement of the device due to the fluctuating pressure must be prevented.

Three main design concepts were generated for the isolation unit: an umbrella structure, a springy mesh structure, and a pressurized balloon.

The umbrella type isolator consists of a member framework over which a web like material is fitted (Figure 9). Each member contains springs that distense radially into the aortic walls and the left ventricular outflow tract. This structure might allow slight seepage of blood into the isolation unit and slight leakage of CDS into the circulatory system when there is slight axial movement of the device. The umbrella structure can be easily deployed. However, since the structure fits tightly across the walls, its retractment may cause damage to the walls. Due to the wide ranges of aortic root diameters that are found in patients undergoing the procedure, it will be necessary to have different umbrella sizes. This would increase the manufacturing cost of the device. In addition, manufacturing of the umbrella tips is complicated.

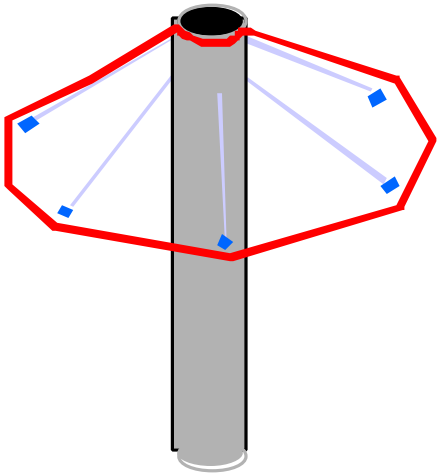

Figure 9. Umbrella structure

The springy mesh structure consists of a stent like device with a web material covering the mesh to prevent blood flow across the structure (Figure 10). After deployment the springy characteristic allows a tight fit across the blood flow tract. The structure is flexible and adapts to how the blood flow tract contracts and expands. This provides a very good isolation of the demineralizing zone. Sufficient normal forces at the walls of the mesh are present, eliminating the need for the device to be fixed externally during pressure variations of systole and diastole. The springy mesh structure addresses anatomic variability better than the umbrella structure. However, retraction of the springy mesh structure can be problematic if the wires in the mesh get stuck. Manufacturing of the structure therefore requires more detail and accuracy and will be more costly than the umbrella structure.

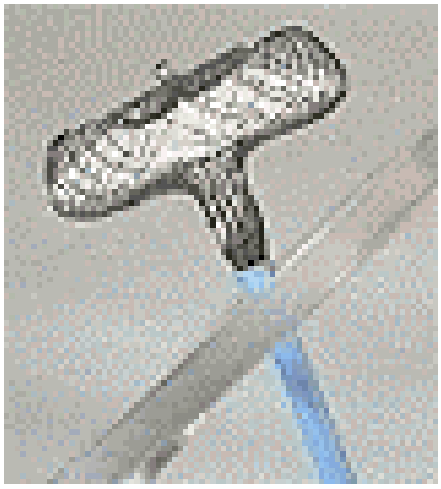

Figure 10. Springy mesh structure

Saline or air is used to inflate the balloons in the balloon type isolater (Figure 11). Interventional cardiologists are comfortable in using balloons. A wide range of anatomic variability can be accounted for by varying the pressure inside the balloons, therefore making treatment of a wide range of aortic root diameters possible.

Compared to the umbrella structure and springy mesh structure, the balloon type isolater is easy to manufacture. Deployment and retraction of the balloon type isolater is also feasible.

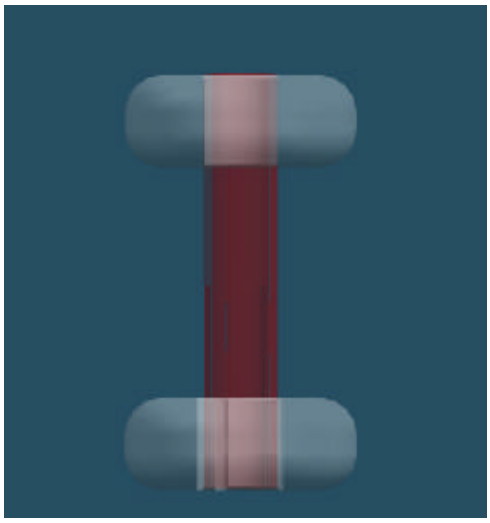

Figure 11. Pressurized balloon

An evaluation of the design concepts for the isolation unit is shown below in the Pugh Chart. The best design concept appears to be the pressurized balloon.

Isolation Design Requirements	**Criteria Weighting**	**Design Concepts**		
		Umbrella	**Springy mesh**	**Balloon**
No seepage of blood into isolation unit	20	7	9	8
No seepage of CDS into circulatory system	20	7	9	8
Anatomic adaptability	16	7	8	10
Ease of manufacturability	15	6	7	9
Ease of deployment	15	7	7	10
Ease of retraction	15	6	2	10
		0.670	0.721	0.906

Table 2

Design of Various Lumens

A total of seven lumens are needed: one for main blood flow, two for blood supply to the coronary arteries, one for inflation, one for CDS, one for buffer, and one for aspiration. Among these various lumens, the ones that pose a major challenge for design are the lumens for the main blood flow and for blood supply to the coronary arteries since flow in these lumens is pulsatile. There are also various complications that arise in designing the lumens that supply blood to the coronary arteries since the coronary arteries are located in the isolation unit. The lumens for CDS, buffer, and aspiration involve steady

flow and fixed pressures, and are therefore straightforward to design. All six lumens must fit into the given maximum device diameter constraint of 10 F.

Two different design concepts have been generated for design of the central blood lumen that allows for main blood flow from the left ventricle into the aorta. Blood flow through this lumen must be maintained at an adequate physiological rate. In addition, the pressure at the distal end of the lumen must be maintained at 60 mm Hg or greater for proper perfusion of blood to the systemic circulation.

The first design concept is a cellular type lumen (Figure 12) made of an elastic material. One advantage of this approach is that it effectively utilizes the available space since double walls are unnecessary. The elastic lumen can be attached to the isolation unit. As the isolation unit is deployed, the lumen will stretch and open up radially. This cellular type lumen has a low manufacturing cost due to its simple design.

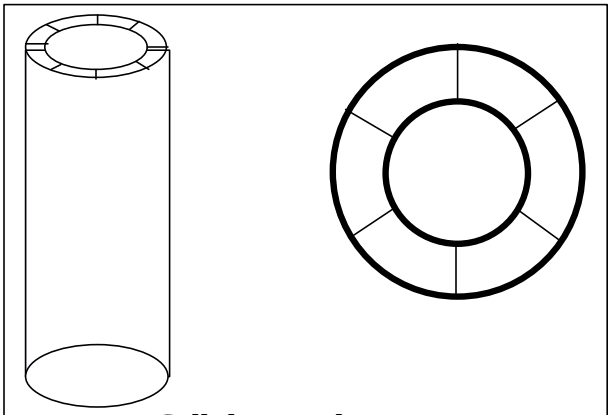

Figure 12 ***Cellular type lumen***

The second design concept is an inflatable central lumen (Figure 13). The central lumen is a double walled chamber, made of a plastic type polymer which can be inflated. All other lumens are situated surrounding this central lumen. After the lumen structure is positioned across the aortic valve, the central lumen is inflated to open up the narrowed aortic valve. This part of the procedure is similar to valvuloplasty. Afterwards the dissolution procedure is performed. The inflated lumen allows for a large enough diameter to provide for adequate blood flow.

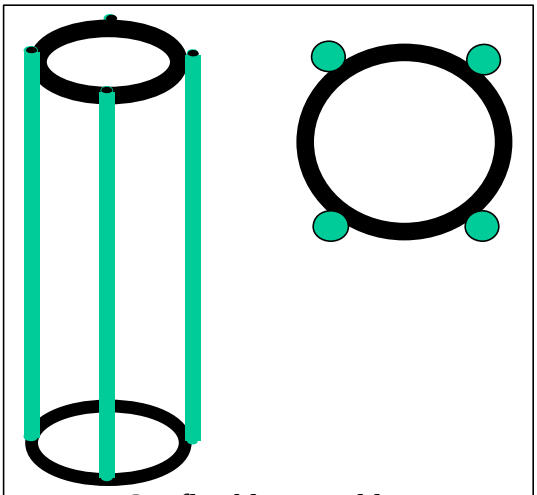

Figure 13 Inflatable central lumen

Evaluation of the cellular type lumen and the inflatable central lumen are summarized in the Pugh chart below. The inflatable central lumen proves to be a better design concept.

Lumen Design Requirements	Criteria Weighting	Design Concepts	
		Cellular	Inflatable central lumen
Large enough diameter to allow for adequate blood flow (2L/min)	20	5	8
Dimensional constraint for passing through the femoral artery	10	9	8
Ease of manufacturability	10	8	7
		0.675	0.775

Table 3

Valve Design

A membrane valve that mimics the behavior of the aortic valve will be attached at the bottom of the isolation unit around the central lumen. The details of this component of the device are yet to be determined.

Current Design

Our current design is to use the inflatable central lumen and pressurized balloons for the isolation unit. To minimize the number of lumens surrounding the central lumen so that the diameter of the device is not too large, optimal positioning of the surrounding lumens is done. The lumens for CDS, buffer, aspiration, and inflation are evenly spaced around the central lumen. The lumens for the coronary blood supply are attached to the lower portion of the central blood lumen. The central lumen has a guide wire entry for both coronary guide wires, so that the two lumens for coronary blood supply can be positioned into the coronary arteries.

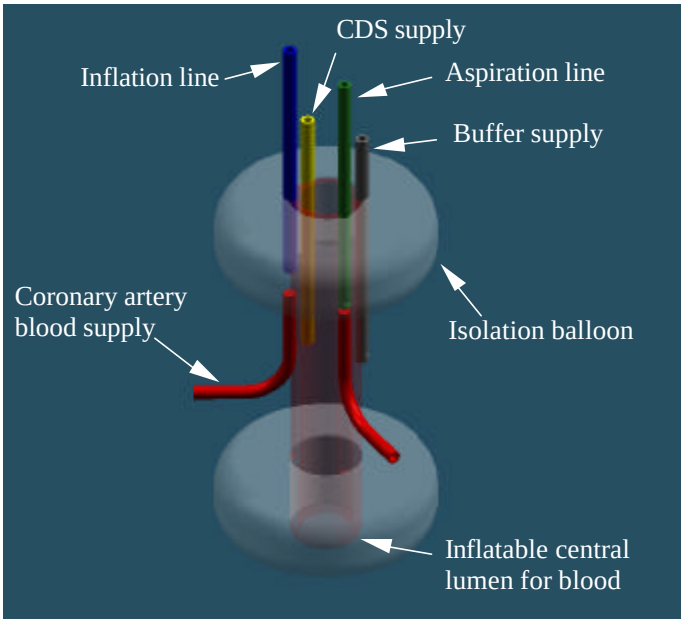

Figure 14. Upper guide wire approach

Two configurations were developed for blood supply to the coronary arteries: the upper guide wire configuration, and the lower guide wire configuration. The upper guide wire approach (Figure 14) is relatively easy to use since the guide wires for the coronary arteries can be easily positioned.

The lower guide wire approach (Figure 15) is more difficult to use. The guide wires for the coronary arteries are first directed towards the left ventricle and then must be reversed in the opposite direction to enter the coronary arteries.

Below is a Pugh analysis of the two different guide wire approaches. The upper guide wire approach is advantageous because it is easier for the doctor to use.

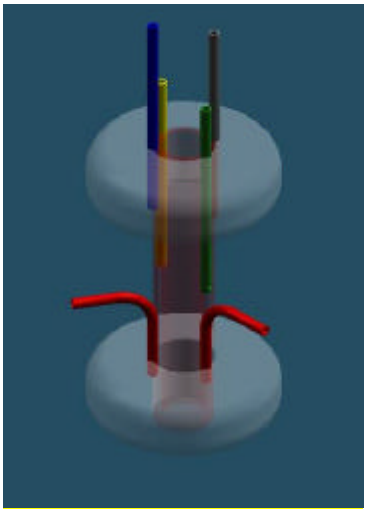

Figure 15. Lower guide wire approach

Coronary Design Requirements	**Criteria Weighting**	**Design Concepts**	
		Lower guide wire approach	**Upper guide wire approach**
Blood perfusion	20	8	8
Doctor's ease of usage	15	7	9
Ease of manufacturability	15	8	8
Positional and dimensional advantage	15	7	8
		0.891	0.973

Table 4

VI Development of Treatment Protocol

Vision/Strategy

The interventional cardiologist performing the procedure should be completely at ease with his own standard procedures and should not have to undergo unnecessary training to do the new proposed procedure.

Protocol for the procedure

The upper guide wire configuration is discussed as it is considered easier to use than the lower guide wire configuration device. Fluoroscopy is also assumed as the method of visualization in this protocol.

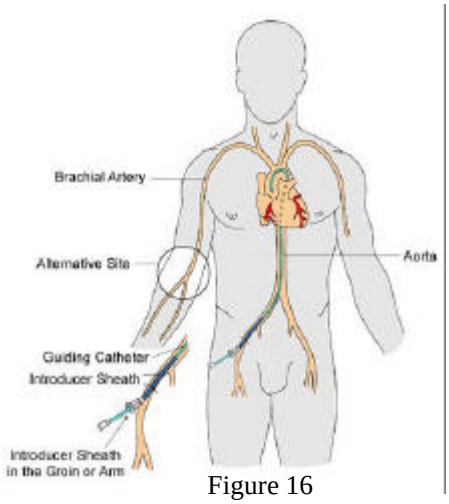

Figure 16
Stanford University Medical Center

Step 1: First, percutaneous access to the femoral artery is obtained. Protocols will differ depending on hospital guidelines and the cardiologist's preference. A sample protocol for this procedure has been attached in the Appendix.

Step 2: The cardiologist then uses a dilator to maintain sufficient access to the femoral artery while the various devices are threaded into the artery lumen. An alternative site is available through the radial artery, but this procedure does not have the option of taking the alternative route.

Step 3: A central guidewire is threaded through the aortic valve and into the left ventricle. This is used as a rail for the catheter-based device and helps to ensure safe passage to the area of treatment.

Step 4: The device, packaged into a 10F sheath, is threaded over the guidewire. The sheath is positioned in the ascending aorta, between the treatment region and the aortic arch. The sheath is maintained in this position for the duration of the procedure. The deflated device is advanced from the sheath to the treatment region.

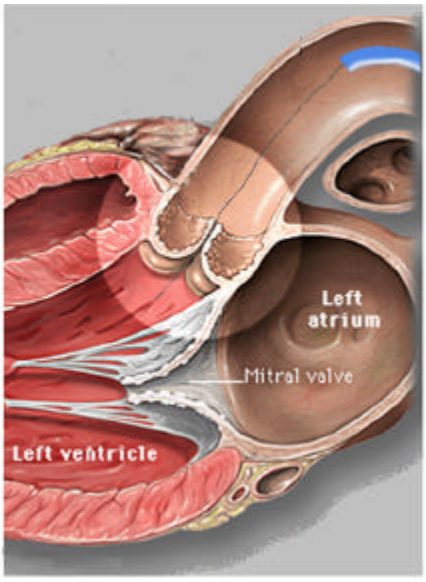

Figure 17

Step 5: Once the device is about 2 cm above the level of the coronary ostia both the guide wires that have been packaged into the coronary blood lumens are guided into the corresponding coronary ostia. It is imperative to ensure that the orientation of the coronary guide wires is correct, as the device assumes an angle of 120º between the left and right coronary artery. If the coronary blood lumens stray too far from this orientation, the device will become entangled or twisted when inflated. More importantly, the coronary arteries have different perfusion requirements and the lumens will most likely reflect this difference.

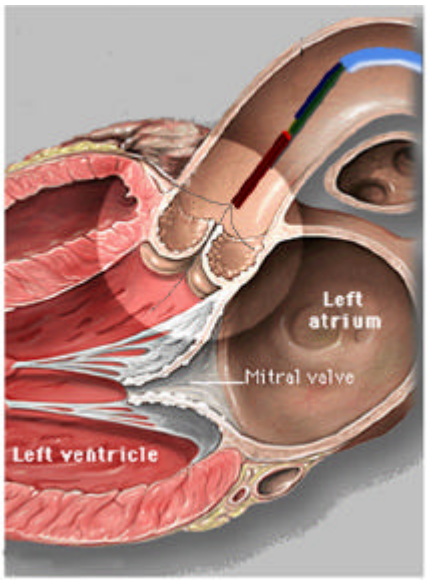

Figure 18

Step 6: The device is then advanced such that the deflated central lumen and deflated lower isolation balloon enter the left ventricle. The coronary blood lumens should follow their respective guidewires into the coronary arteries. Once the appropriate orientation is achieved, the cardiologist secures the device by clamping it at the site of percutaneous entry. The various supply lines of the device are connected to their corresponding external devices used in the cath lab: CDS line is connected to the power injector, buffer line is connected to an IV, inflation line is connected to a valved syringe, the aspiration line is connected to a vacuum source.

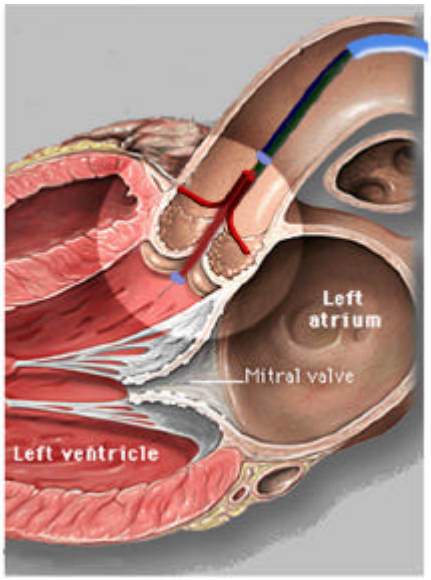

Figure 19

Step 7: The balloons in the isolation unit and the central lumen are partially inflated and the blood flow is established to the coronaries through the coronary blood lumens via the central blood lumen. At this moment, blood flow through the central lumen and partially through the aortic valves.

Step 8: Once blood flow to the coronaries is established through the central blood lumen small balloon seals at the tip of the coronary blood lumens are inflated and sealed off.

Step 9: The isolation balloons are inflated to the recommended level based on the aortic root diameter, completely occluding the aortic valve zone.

Step 10: After the isolation unit is completely deployed, the blood in the isolation zone is flushed out and the decalcification procedure is initiated. The buffer and CDS are continuously circulated over the aortic valve simultaneously. Aspiration is also done during the entire cleaning procedure. In the event of a pink streak in the aspiration collection solution, the supply of CDS should be cut off immediately and the balloon deflated gradually.

Step 11: After the decalcification procedure is complete, the contents are flushed out with saline solution and the isolation balloons and coronary balloons are deflated to allow the device to be retracted.

Step 12: After the device is retracted the normal arterial closure protocols are followed.

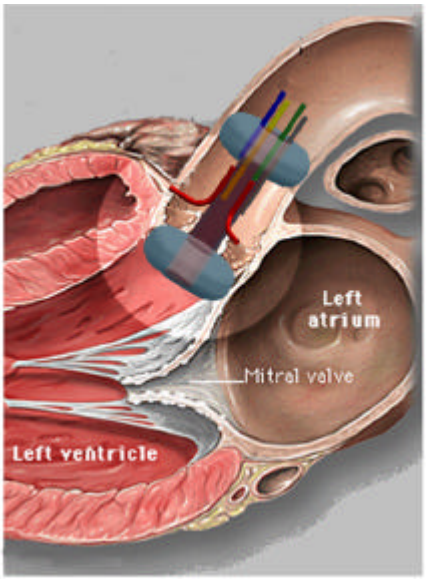

Figure 20

VII Project Plan

Overview

Corazon presented the team with a challenging project in the field of interventional cardiology. In order to provide ourselves with a substantial background in the disease state of aortic stenosis and the practice of interventional cardiology, we performed an extensive research of the literature, procedures, as well as the engineering side of medical devices. Our initial objective was to collect information on the particulars of the anatomy of the treatment region and hemodynamics of the disease state. Our frequent meetings with the sponsor provided an introduction to the many factors that must be considered when designing a medical device, and subsequently lead to a framework for the development of detailed engineering specifications. With the background and research, we aimed to design to a device that would meet the requirements posed by both the cardiologist and physiologic demands. While we have chosen a design concept we are still refining the functional and physical aspects of the device.

Deliverables

The deliverable for Winter Quarter is a packet of engineering specifications shown in Appendix. Some specifications are yet to be determined and are marked as such.

The deliverable for Spring Quarter is a design of the interventional device for aortic repair. This device will meet the purpose and goals described in the Design Definition. We will present the device itself in the form of a functional prototype. CAD drawings of the device as an assembly and separate parts will also accompany the device. Due to the high complexity of the procedure, we will also include a diagram of the catheterization lab setup as well as written instructions. Lastly, we will submit the results and analysis from validation tests.

Methodology

Identification of engineering specifications involved a literature review, meetings with Corazón, and conversations with interventional cardiologists.

SolidEdge was used for the CAD drawings included in this report. We will continue to use this software for solid modeling and drafts. Our current option for manufacturing is Vesta, Inc., which fabricates custom silicone rubbers components of medical device OEMs. This company is able to convert our CAD drawings into various lumen components and balloon components through extrusion and molding, respectively. The silicone rubber used in Vesta's manufacturing processes has the following benefits:

?? Temperature resistance through a range of –75ºF to 500ºF

- ?? Sterilizable by ethylene oxide, gamma, E-beam, steam autoclaving, and other methods
- ?? High tear and tensile strength and flexibility
- ?? Biocompatible and formulated to comply with FDA and ISO
- ?? Chemical resistance

We will submit the deliverables to Corazón for further development. The company will then perform additional test methodology on the device and redesign accordingly. As we will not likely run animal tests, Corazón will take the project further to incorporate animal models and possible clinical trials in the future.

Design Validation

Physiology testing

The functional prototype is to be validated by testing the flow characteristics of the device in a pulsatile flow model. A porcine aortic valve fitted across a cylindrical elastic pipe is to be used in line with a system, which contains a pulsatile flow pump and air chambers (to adjust compliance of the tubing mimicking ascending aorta). The flow conditions at the inlet to the device can be altered and the effectiveness of the central blood lumen and the coronary lumens can be determined by having individual pressure probes in all of them. Pressure at the exit, which is to be maintained at 60 mmHg for normal physiologic conditions and flow rates at the coronaries, should be determined for a wide range of expected left ventricular outflow conditions. Both healthy and stenotic patient outflow conditions will be studied to examine the efficiency of the device.

Dissolution testing

A similar setup to the previous system will be used, with the addition of porcine valves with holes. CDS and buffer would be continuously pumped as in the actual cath lab procedure. The pH of the surface of the valves from the inferior direction should be 1. This would indicate that CDS is properly being administered and it has a favorable demineralizing zone.

Major hurdles

We expect to encounter many difficulties, due in part to the complex physiological and functional requirements detailed in the prior sections. The first problem will likely manifest itself in the assembly of individual units of the device. The ensemble of separate components will requires functionality of all components with each other to ensure the overall functionality of the device. Even a single failure mode presented in a single component will compromise the entire device. Secondly, supplying blood to the coronary arteries is a primary concern. The difficulty consists of diverting flow from the central lumen to the coronary branches. There is also anatomic variability once the coronary arteries have actually been accessed. The supply lines for the coronary arteries

must not block a bifurcation, or the heart will not be sufficiently perfused. However, patients will vary in the distance to the first bifurcation. We have not yet been able to address this problem of anatomic variability. An obvious problem also presents itself in the physical scale of the device. An interventional method, while less invasive, places strict constraints on the size of the device. If we are unable to maintain the limited size of the device, it cannot be used for its intended purpose. However, there is a trade-off between size and logistics. Smaller lumen diameters are more difficult to manufacture, maneuver, and assemble.

Timeline

The Gantt Chart in the Appendix represents our updated timeline for accomplishing the project goal. Earlier this quarter we accomplished mostly background research on the anatomical, physiological, and clinical implications of aortic stenosis. Data from various references was also collected for future calculations on hemodynamics. We have met regularly with Corazón and interventional cardiologists to orient ourselves with available facilities as well as the resources that have been made available to us. The remaining of the winter quarter was devoted to identifying design specifications based on research and input from Corazón and cardiologists. Upon the increased emphasis on engineering specifications for this quarter, the timeline was changed to reflect the time required to collect the necessary information. This left is with less time than anticipated to generate and assess design concepts, which lead to our choice for the current design.

The spring quarter will involve much of the prototyping and verification. We are planning to perform a simulation of our proposed device with a computational model. This will aid us in determining if the design, particularly the central lumen, allows for proper blood flow. Furthermore, the design will likely undergo alterations due to input from Corazón. Prototyping will then begin with at least two rounds of large-scale prototyping. The first will consist of a "looks like" prototype made of rigid materials to demonstrate the assembly and configuration of the device. The second prototyping stage will also be at large scale, but with materials closer to the final deliverable. We would like to use this larger scale for validation tests in a pulsatile flow model and this may require outsourcing to Vesta so that the prototype functions within the test conditions. It is important that we accomplish this phase of the prototype as early as possible, to account for a possible lengthy manufacturing time. Our final prototype will then be a scaled model, also outsourced to Vesta. We have allotted at least a month for the final manufacturing, leaving a week for validation testing of the scaled prototype.

Individual responsibilities of team members

As we approach the project as a team, much of the research and development will be accomplished in collaboration. In addition, we have suggested the following roles for ourselves:

Beverly will coordinate information regarding proper usage of the CDS, including its potency, duration of effectiveness, handling, and compatibility with materials. She will

also coordinate validation methods for the team, including experimental set-up and evaluation.

Mariel will coordinate much of the prototyping needs for the group. This involves locating manufacturing and fabrication sites and materials, machining, rapid prototyping, as well as any research associated with these topics in regards to medical devices. As a frequent user of SolidEdge, Mariel will provide CAD drawings of the device. She will also be the main contact for the Dr. Aaron Kaplan.

Rajan will use his fluids expertise to formulate much of the hemodynamic factors involved in the device. Thus, he will ensure the device meets the physiological needs and the validation methods also correlate with physiologic behavior. He will also be the main contact for the Corazón representatives and Dr. Issam Moussa.

Interventional Aortic Repair System: Updated Timeline (2002)

Milestones

Task	Fri 2/8	Fri 2/15	Fri 2/22	Fri 3/1	Fri 3/8	Fri 3/15	Fri 4/5	Fri 4/12	Fri 4/19	Fri 4/26	Fri 5/3	Fri 5/10	Fri 5/17	Fri 5/24	Fri 5/31	Fri 6/7
Background Research																
Project Plan Due																
Identify Design Specifications																
Pig Heart Workshop																
Brainstorm Ideas																
Evaluate Ideas and Pick Direction																
Finish Winter Presentation																
Research Manufacturing Possibilities																
Submit Winter Report																
Submit Engineering Specs to Corazon																
1st Prototyping Stage (Large Scale)																
Finalize Design and CAD Drawings																
Survey Cardiologist on Protocol																
2nd Prototyping Stage (Scale Down)																
Test, Evaluate, and Redesign																
Manufacture Final Prototype																
Pulsatile Flow Validation Tests																
Finish Final Presentation and Report																

Completed milestones =

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Presentation slides

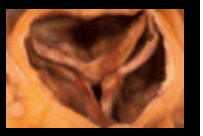
CORAZÓN

Interventional Aortic Valve Repair System

Beverly Bangayan
Mariel Fabro
Rajan Prakash

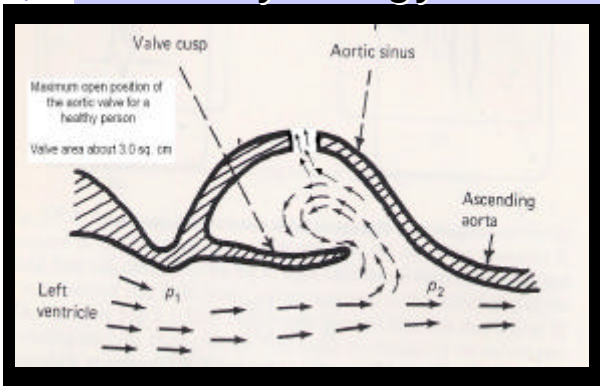
Aortic Stenosis

- Calcification of the aortic valve, causes the commissures to stick together, reduces the valve area
- So why is this a concern?

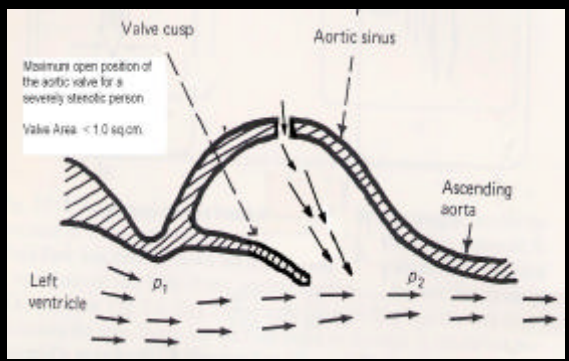


Joey Bravo

Physiology



Physiology



Targeted Market

- Women of child-bearing age
- Patients with mild stenosis
- Elderly patients - risk in valve replacement surgery
- Patients who need valve replacement due to stenosis

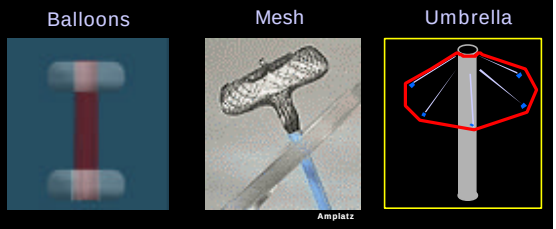
Deliverables

- Detailed Engineering Specifications
  Example: must create a demineralizing zone on the aortic side of the AV and in the region of the aortic root. -Market Spec provided
  - pH < 1.0
  - CDS and buffer flow rates and pressure
- Functional Prototype
  Interventional device to deliver Corazón CDS solution to aortic valve

Design Requirements

- Maintain heart function
  - Blood supply to body - Blood lumen
  - Blood supply to heart - Coronary guides
- Isolation of aortic valve - CDS does not work in the presence of blood
- Individual supply lines for CDS, buffer and aspiration
- Compatible with Cath Lab procedures

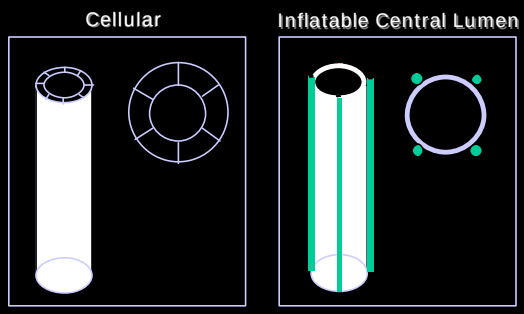
Design Concepts - Isolation



Design Concepts - Isolation

Isolation Design Requirements	Criteria Weighting	Design Concepts: Umbrella	Springy mesh	Balloon
No seepage of blood into isolation unit	20	7	9	8
No seepage of CDS into system	20	7	9	8
Anatomic adaptability	16	7	8	10
Ease of manufacturability	15	6	7	9
Ease of deployment	15	7	7	10
Ease of retraction	15	6	2	10
		.670	.721	.906

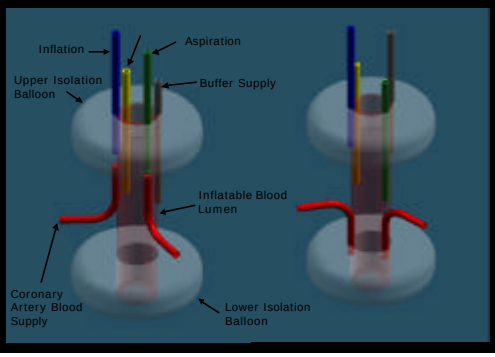
Design Concepts - Lumens



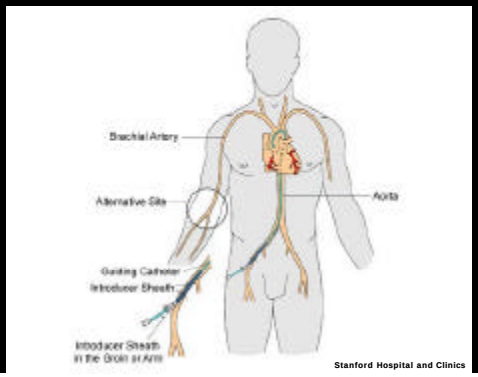
Design Concepts - Lumens

Lumen Design Requirements	Criteria Weighting	Design Concepts: Cellular	Inflatable central lumen
Large enough diameter to allow for adequate blood flow (2L/min)	20	5	8
Dimensional constraint for passing through the femoral artery	10	9	8
Ease of manufacturability	10	8	7
		.675	.775

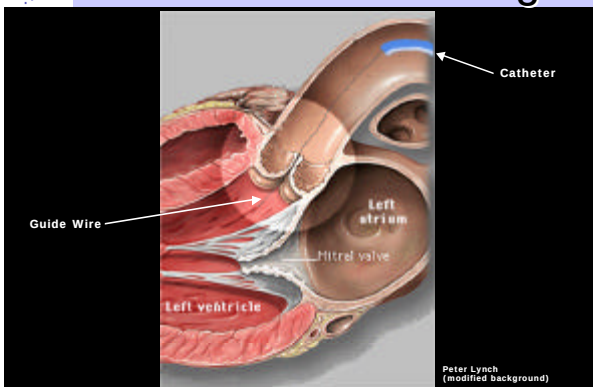
Current Design



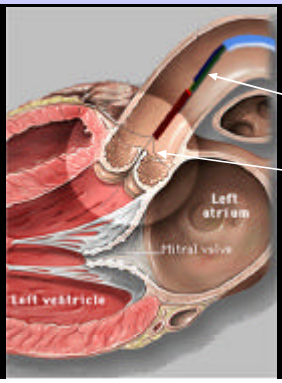
Percutaneous Entry



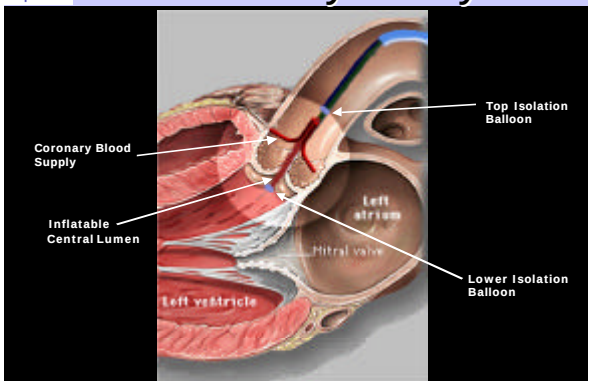
Catheter Positioning



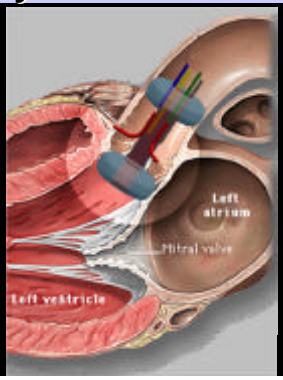
Advancement



Coronary Entry



Fully Inflated Device



Future Steps

- Exact dimensions and material selection
- Membrane Valve Design
- Prototyping
- Testing - pulsatile flow model

Expenses

Expenditures to date: none

Projected expenditures for next quarter:

Item	Cost	Balance
Prototype 1	$200	$4800
Prototype 2	200	4600
Machine Shop Passes	180	4420
Equipment	2000	2420
End Fabrication Device	2000	420
Validation Model	400	20

Resources

The following is a list of resources already used and/or needed in the future to complete the project:

- ?? Dr.Issam Moussa, Interventional Cardiologist, has consulted the team this quarter regarding heart anatomy, expected cardiac function, and product feasibility in the cath lab environment
- ?? Dr. Aaron Kaplan, Director of Interventional Cardiology at Palo Alto's VA Hospital, will replace Dr. Issam Moussa next quarter as the team's mentor
- ?? Brent Constantz, Corazón President and CEO, provides guidance and direction to the team
- ?? Phil Houle, Corazón Project Manager, assists us in our formulation of both engineering and market specifications
- ?? Kevin Ohashi, Corazón Director of Research, will assist us in testing and validation of our designs
- ?? Sarah Pestieau, Corazón, manages the pulsatile flow machine at Corazón and will be essential in our validation models
- ?? Joey Bravo, Corazón, is our main contact in utilizing porcine hearts and wet lab facilities
- ?? Nitin Patel, Corazón, provides insight and advice on our design concepts
- ?? Corazón facilities, Stanford University PRL, and additional manufacturing facilities will provide us with the ability to accomplish early-stage prototypes, as well as a fully-functional final prototype

Patent Search Information

Patent number	Patent title	Patent relevance
6234971	Vascular catheter having low-profile distal end	small tipped catheter
6132417	Right coronary artery catheter	approach of right coronary lumen
5971974	Left coronary artery catheter	approach of left coronary catheter
5599306	Apparatus for providing external perfusion lumens on balloon catheters	balloon catheters external perfusion
6159219	Stent retrieval device	balloon catheters for removing springy mesh
5868753	Stent retrieval catheter	springy mesh retrieval
6027508	Stent retrieval device	springy mesh retrieval
5733302	Stent retrieval device	springy mesh retrieval
6070589	Balloon catheter with adjustable shaft	deploying springy mesh

GENERAL CUSTOMER REQUIREMENTS – PROCEDURE AND APPLICATOR

?? The procedure must be performed as a percutaneous method using a catheter-based system inserted into the right femoral artery and guided to the heart to treat patients who have mild to moderate aortic stenosis with the presence of calcification. Furthermore, it must fit into the current techniques and procedures used by interventional cardiologists. The catheter-based system must also provide for indirect visualization of the procedure.
?? The applicator must be designed for easy setup and use within the cardiac catheterization lab environment.
?? The device must maintain normal heart functioning.
?? Completion of the procedure must provide a clinically significant increase in the aortic valve area (AVA).
?? The applicator must consist of a single use, disposable device.
?? The applicator must allow for the controlled application and removal of Corazón's proprietary solution to an isolated region that includes the AV, left ventricular outflow tract, and proximal region of the ascending aorta in patients with aortic valves between 19 mm and 31 mm.
?? The applicator must be compatible with aortic valves between 19 mm and 31 mm.
?? The applicator must create a demineralizing zone on the aortic side of the AV and in the region of the aortic root.
?? The applicator must be designed to provide an appropriate gross margin.
?? The applicator must be biocompatible.
?? The applicator must be sterile.
?? The applicator must be functional and sterile upon arrival in the catheterization lab.
?? The applicator must be compatible with Corazón's high-pressure pressurization system.
?? The applicator must be compatible with Corazón's proprietary solutions for the duration of the procedure.
?? The applicator must be compatible with aspiration.

GENERAL CUSTOMER REQUIREMENTS – HIGH-PRESSURE PRESSURIZATION SYSTEM

?? The high-pressure pressurization system must be a reusable device.
?? The high-pressure pressurization system must be a non-electric, non-electronic, pneumatic device.
?? The high-pressure pressurization system must deliver a constant pressure to the solution bags.
?? The high-pressure pressurization system must be designed to ensure that the flow rate of buffer and CDS are equivalent and consistent.
?? The high-pressure pressurization system must have an indicator that indicates the pressure.
?? There must be no fluid contact between the high-pressure pressurization system and Corazón's proprietary solutions.

?? The high-pressure pressurization system must be designed for easy setup and use within the surgical environment.
?? The high-pressure pressurization system must use common functionality available within the surgical environment.
?? The high-pressure pressurization system must be designed to provide an appropriate gross margin.
?? The high-pressure pressurization system must be compatible with Corazón's applicator.
?? The high-pressure pressurization system must be compatible with Corazón's proprietary solutions.

GENERAL CUSTOMER REQUIREMENTS, SPECIFICATIONS, SOURCE, AND OUTPUT – PROCEDURE AND APPLICATOR

?? The procedure must be performed via percutaneous methods using a catheter-based system inserted into the right femoral artery and guided to the heart to treat patients who have mild to moderate aortic stenosis with the presence of calcification. Furthermore, must be compatible with current techniques and procedures used by interventional cardiologists. The catheter-based system must also provide for indirect visualization of the procedure.

#	Specification	Rationale	Source	Output
1	The device must fit in a 10F (3.5 mm diameter) sheath.	Physician preference for the maximum catheter size for femoral access is 10F.	Phil Houle, lab notebook, Physician input	In-line verification
2	The delivery shaft of the device must be kink resistant for R $\geq$ TBD in.	The pathway from the femoral artery to the aortic valve can be very tortuous, particularly in the region of the iliac arteries. Physician experience states that the smallest curve through which the device must pass is TBD	Physician input	Kink Test
3	The device must be compatible with a guide wire of TBD diameter.	Physician preference for the guide wire is TBD, allowing for maximum maneuverability and minimum harm	Physician input	In-line verification

		to the arteries.		
4	The procedure must not exceed a duration of TBD	Cath lab time is costly and the procedures are complex. Furthermore, it is not desirable to allow the device to maintain heart function for extended period of times, nor is it desirable to maintain the patient's transvalvular pressure gradient at high levels for extended periods of time	Physician input	Cadaver heart protocol, cadaver protocol
5	The device must cross the aortic valve with an opening no larger than 6 mm in diameter	The physician must be able to maneuver the device into the left ventricle. As the heart is still beating, device will have to fit into the opening provided by the stenotic valve. The smallest valve opening that may be encountered in the intended procedure was determined to be TBD.	Phil Houle, lab Notebook, Physician input	Cadaver heart protocol, cadaver protocol
6	Applicator working length = 12 +/- 0.5 in	The applicator must be long enough to reach the treatment area, but not so long as to become a nuisance to the clinical staff.	Physician input – lab notebook 31, pages 14-15	In-line verification
7	Solution Delivery Tubing working length = 174 +/- 1 in	The tubing must be long enough to reach from the IV pole to the proximal	Physician input – lab notebook 31, pages	In-line verification

		end of the applicator, but not so long as to become a nuisance to the clinical staff. The solution bags will initially hang on the IV pole opposite the surgeon.	14-15; Physician input – lab notebook 29, pages 34-35	
8	Solution Delivery Tubing kink resistant for R $\geq$ TBD in.	The tubing must not kink when it is manipulated and positioned during the procedure.	Physician input – lab notebook 31, pages 14-15	Kink test
9	Radiopaque materials	Fluoroscopy is a common visualization method in the cath lab.	Lab notebook	Material verification

?? The applicator must be designed for easy setup and use within the cardiac catheterization lab environment.

#	Specification	Rationale	Source	Output
10	Installation must be less than TBD minutes.	Cath lab time is costly and the procedures are complex. The applicator installation should not significantly add to the time or complexity of the procedure.	Physician input – lab notebook 31, pages 14-15	Cadaver heart protocol, cadaver protocol
11	Should not require adjustment by physician during procedure.	Catheterization is complex and requires careful attention. The applicator should not add to the complexity by requiring that it be constantly monitored and adjusted	Physician input – lab notebook 31, pages 14-15	Cadaver heart protocol, cadaver protocol, animal protocol

		throughout a procedure.		
12	The CDS and buffer tubing must not be interchangeable.	The tubing setup should be obvious so that the solutions are directed into the lumens that were designed to deliver them.	Physician input – lab notebook 31, pages 14-15	Cadaver heart protocol, cadaver protocol, animal protocol

?? The device must maintain normal heart functioning.

#	Specification	Rationale	Source	Output
13	The mean pressure in the aorta must be maintained at a minimum level of 60 mmHg	This the pressure necessary for proper perfusion of blood to the systemic circulation	Physician input – lab notebook	Biomechanical flow testing
14	The applicator must maintain a minimum mean pressure of 70 mmHg	Pressure drop in ascending aorta has been observed to be 10 mmHg in cases of sedation. (sedation is not always used)	Physician input – lab notebook	Biomechanical flow testing
15	The applicator should maintain a minimum cardiac output of 2 liters/minute	At least 2 liters/minute of blood supply is required to prevent brain ischemia.	Physician input – lab notebook	Biomechanical flow testing
16	Treatment time should not exceed 120 minutes if blood flow to the lower limbs is reduced considerably	Time limit for lower limb tissues to resist ischemic attack without blood supply	Physician input – lab notebook	Biomechanical flow testing
17	3.75% of the cardiac output should be diverted to the left coronary artery, 1.25% of the cardiac output should be diverted to the right coronary artery.	Approximately 5% of the cardiac output is normally directed to the coronary arteries for myocardium perfusion. 75% of this amount is taken by the left	Physician input – lab notebook	Biomechanical flow testing

		coronary artery while 25% is taken by the right coronary artery		

?? Completion of the procedure must provide a clinically significant increase in the aortic valve area (AVA).

#	Specification	Rationale	Source	Output
18	Aortic valve area must increase at least 25%.	To provide a clear benefit to the patient, the procedure must increase the aortic valve area by at least 25%.	Physician input – lab notebook 29, pages 34-35	Biomechanical flow testing, clinical trial

?? The applicator must consist of a single use, disposable device.

#	Specification	Rationale	Source	Output
19	Single use, disposable device	The applicator is difficult to clean and sterilize once it has been used in a patient.	Engineering decision	IFU, labeling

?? The applicator must allow for the controlled application and removal of Corazón's proprietary solution to an isolated region that includes the AV, left ventricular outflow tract, and proximal region of the ascending aorta in patients with aortic valves between 19 mm and 31 mm.

#	Specification	Rationale	Source	Output
20	Under standard manipulation of the heart, no more than 100 ml of blood must leak into the treatment area (aortic valve, left ventricular outflow tract, and proximal region of the ascending aorta) over a TBD minute period of time when the procedure is performed on aortic valves between 19 mm	When blood is introduced into the treatment area, the pH increases. However, to maintain the demineralizing zone, the pH must be maintained at the proper level.	Physician input – lab notebook 31, pages 14-15	Cadaver heart protocol

	and 31 mm			
21	Under standard manipulation of the heart, no more than xx ml of fluid must leak out of the treatment area over a TBD minute period of time when the applicator is deployed.	Isolation of the therapy will reduce potential procedural, physiological, and regulatory issues.	Physician input – driven by outcomes of hemotoxicity studies	Cadaver heart protocol, hemotoxicity studies
22	Must not be able to initiate CDS flow without initiating buffer flow.	The buffer neutralizes the aspirated CDS and the treatment site in the event of aspiration loss.	Physician input – lab notebook 29, pages 34-35	Cadaver heart protocol, cadaver protocol, animal protocol
23	Flow of CDS and buffer into applicator must be visually verifiable during use.	Need to provide feedback that applicator is still functioning.	Physician input – lab notebook 29, pages 33, 34-35	Cadaver heart protocol, cadaver protocol, animal protocol
24	Aspiration of CDS and buffer must be visually verifiable during use.	Need to provide feedback that applicator is still functioning.	Physician input – lab notebook 29, pages 33, 34-35	Cadaver heart protocol, cadaver protocol, animal protocol
25	Isolation device must function for at least 3 deployment/retraction cycles	The cardiologist may need to deploy and retract the isolation device a number of times during the procedure in order to place it in the right location.	Physician input – lab notebook 31, pages 14-15	Isolation device deployment/retraction test
26	Deployment of isolation device must be visually verifiable during use.	Need to provide feedback that applicator is still functioning.	Physician input – lab notebook 29, page 33	Cadaver heart protocol, cadaver protocol, animal protocol

?? The applicator must be compatible with aortic valves between 19 mm and 31 mm.

#	Specification	Rationale	Source	Output
27	Applicator must easily cross 19 mm or larger aortic valves without damaging them.	The procedure is designed to treat patients who have mild to moderate aortic stenosis with the presence of calcification. Aortic valves range in size from 19 to 31 mm. The applicator must cross the aortic valve to treat the patients and should not harm them.	Physician input – lab notebook 31, pages 14-15; Capps SB, et al. "Body surface area as a predictor of aortic and pulmonary valve diameter." J Thorac Cardiovasc Surg, 119(5): 975-82 2000	Cadaver heart protocol, cadaver protocol, animal protocol
28	Isolation devices must not damage the left ventricle or coronary ostia.	The isolation devices will be deployed in the left ventricle and coronary ostia to help contain the solutions in the treatment area. They should not harm the patients when it is deployed.	Physician input – lab notebook 31, pages 14-15	Cadaver heart protocol, cadaver protocol, animal protocol

?? The applicator must create a demineralizing zone on the aortic side of the AV and in the region of the aortic root. A demineralizing zone is considered essential to the removal of mineral, which is believed to be the key to improved aortic valve performance.

#	Specification	Rationale	Source	Output
29	Treatment area must be maintained at a pH no greater than 0.2 pH units above the pH of CDS solution being administered.	A pH of less than 1.5 has been determined to provide high rates of mineral	Physician input – lab notebook 31, pages 14-15; Engineering	Cadaver heart protocol

		dissolution. The current CDS specification is for a pH of 0.8 to 1.2. Furthermore, it is difficult to measure a change in pH of less than 0.2 pH units in a system involving flow.	decision	
30	When no more than 3.5 ml of blood is applied to treatment area, pH must return to pH no greater than 0.2 pH units above the pH of CDS solution being administered in less than 10 seconds.	When a buffer is introduced into the treatment area, the pH increases. However, to maintain the demineralizing zone, the pH must be returned to the proper level.	Physician input – lab notebook 31, pages 14-15 Get engineering input.	Cadaver heart protocol
31	The pH in the remainder of the vascular site must be greater than 6.0.	pH elevating solution must be used in the remainder of the vascular site to increase the pH so that there is no damage to normal tissues.	Corazon arterial treatment patent, lab notebooks	Cadaver heart protocol, cadaver protocol, animal protocol
32	Flow rate of CDS & buffer must be in a range of TBD ml/min.	This flow rate ensures that 1-liter of solution will last for at least 30 minutes.	Engineering decision	Cadaver heart protocol, cadaver protocol, animal protocol
33	The overall pressure in the local environment must be constant at 1-2 psi.	The pressure in the local environment needs to be isometric, not varying by a significant amount, so that the local environment is stable.	Corazon arterial treatment patent, lab notebook	Cadaver heart protocol, cadaver protocol, animal protocol

?? The applicator must be designed to provide an appropriate gross margin.

#	Specification	Rationale	Source	Output
34	Target cost (direct material) $\leq$ $175.00	Business requirement	Management decision	BOM

?? The applicator must be biocompatible.

#	Specification	Rationale	Source	Output
35	Must be biocompatible.	Non-compatible materials can damage a patient's tissues, blood, or organs.	ISO 10993-1; FDA Blue Book Memorandum #G95-1	Biocompatibility testing

?? The applicator must be sterile.

#	Specification	Rationale	Source	Output
36	Must be sterile to a sterility assurance level (SAL) of 10^{-6}.	Non-sterile devices can introduce pathogens into the treatment area, resulting in patient harm.	ANSI/AAMI/ISO 11137, AAMI TIR 13409	Sterilization validation testing

?? The applicator must be functional and sterile upon arrival in the catheterization lab.

#	Specification	Rationale	Source	Output
37	Must pass bubble leak test	The pouch must provide a proper sterile barrier.	Packaging engineer; ASTM E515-95	Bubble leak test
38	Must withstand a 1 lbf peel test	During shipping, the contents of a pouch can shift and apply a load to the seal. The pouch must withstand this load.	Packaging engineer	Peel test
39	Must pass a manual handling test	During handling, a package with a sterile device may be dropped or hit.	Packaging engineer	Manual handling test

?? The applicator must be compatible with Corazón's high-pressure pressurization system.

#	Specification	Rationale	Source	Output
40	Fluid delivery lumens must withstand a pressure of 40 psi.	The pressurization system pressurizes the fluid in the solution bags to a pressure of 200 mmHg. This fluid is then delivered through the applicator's fluid delivery lumens. These lumens must withstand this pressure without bursting. They will be tested at a much higher pressure to ensure a factor of safety.	Get engineering input (10x operating pressure)	Lumen burst test

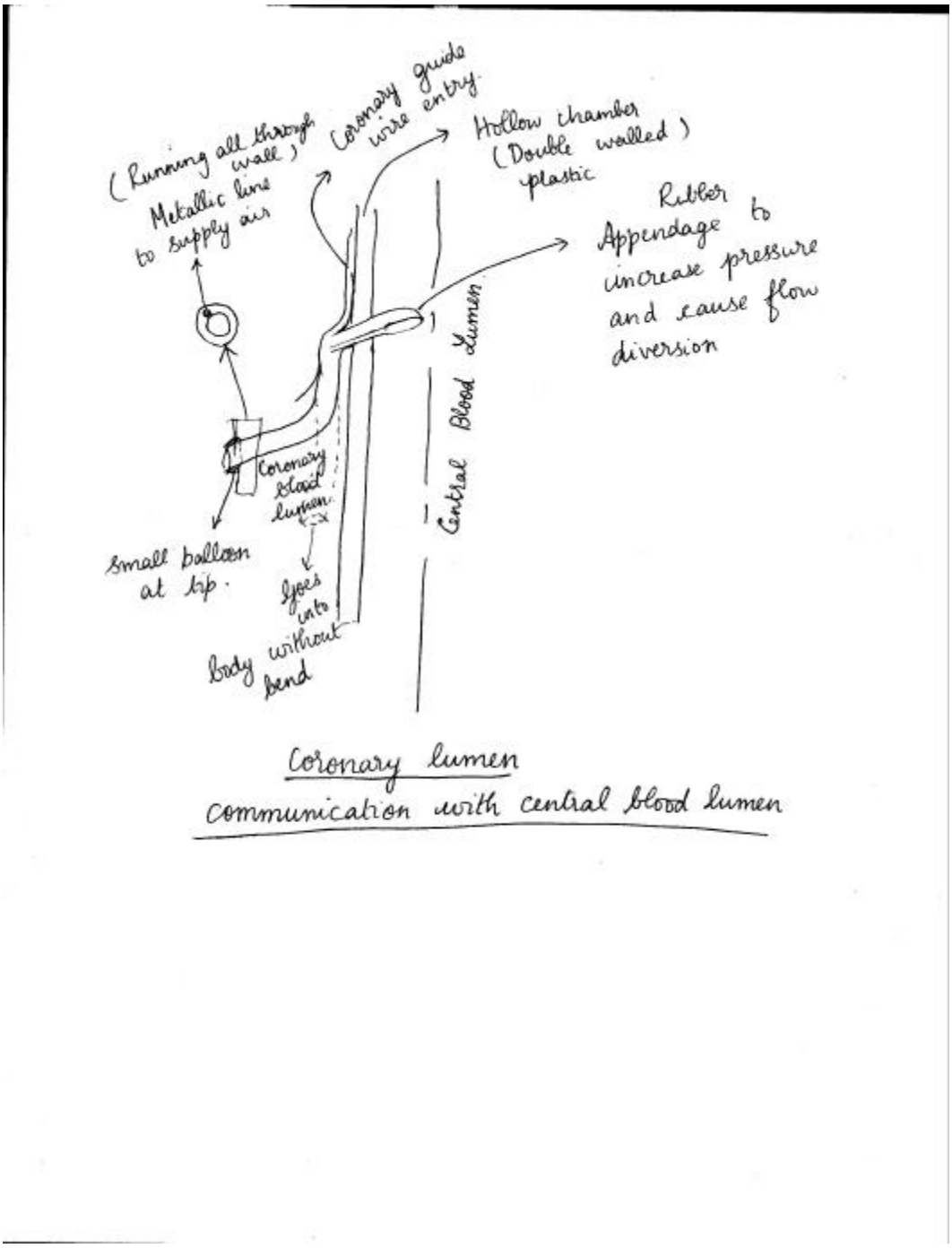
?? The applicator must be compatible with Corazón's proprietary solutions for the duration of the procedure.

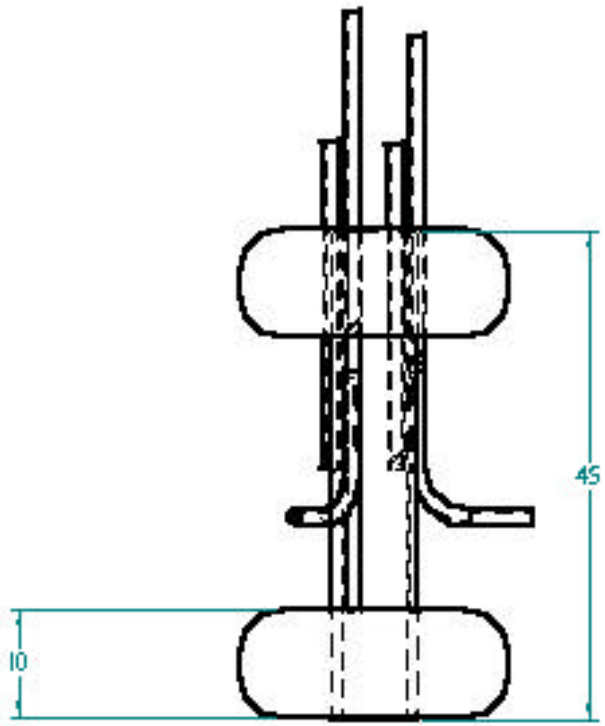
#	Specification	Rationale	Source	Output
41	Applicator tubing with drip chambers must connect to solution bags placed inside low-pressure pressurization system.	The applicator is designed to deliver the solutions to the treatment area. The applicator must connect to the solution bags in order to deliver them to the area.	Engineering decision	Cadaver heart protocol, cadaver protocol, animal protocol
42	Applicator materials must be chemically compatible with solutions.	The CDS is acidic and the applicator materials must not degrade in the presence of the acid.	Engineering decision	Material compatibility testing, biocompatibility testing

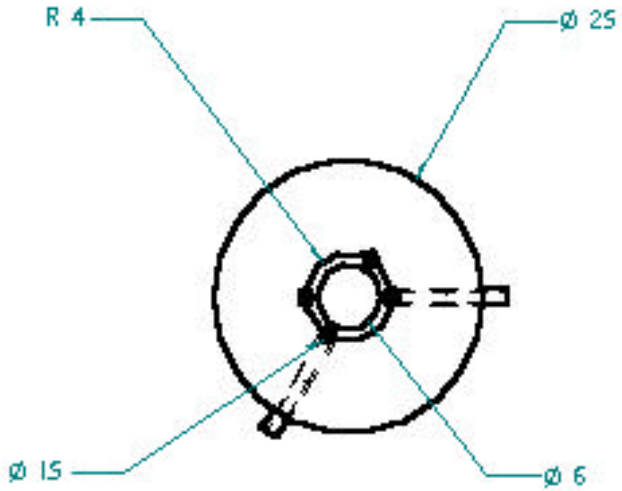
?? The applicator must be compatible with aspiration.

#	Specification	Rationale	Source	Output
43	Applicator must connect to vacuum source in the cath lab	The applicator requires a vacuum source for aspiration.	Physician input – lab notebook 31, pages 14-15	Animal protocol

Design Sketches







Interventional Aortic Repair Device Assembly

Beverly Bangayan
Mariel Fabro
Rajan Prakash

dimensions: mm

March 15, 2002

Title:
Interventional Aortic Repair System

Sponsor:
Corazón Technologies, Inc.

Type of Project: **New Design**

Design Description

This is a project to develop an Aortic repair system to treat calcification of the aortic valve. Calcification of cardiovascular tissues such as aortic heart valve leaflets, arterial wall and atherosclerotic plaque in arteries is a serious problem limiting interventional cardiologists and cardiothoracic (CT) surgeons in their attempts to treat cardiovascular disease. Untreated, these calcific lesions can severely restrict flow through the aortic valve or coronary vessel damaging the heart muscle.

The proposed system will use Corazón Technologie's biomimetic solutions to dissolve and remove calcified deposits and atherosclerotic cardiovascular plaque from heart valves and arteries to restore their native function. The device will enable physicians to remove calcification from stenotic aortic heart valves and improve native aortic valve function without replacing the valve. This novel product technology may allow earlier intervention in more patients and on less diseased aortic valves without waiting to intervene when aortic stenosis (AS) progresses to a point that requires replacement with a prosthetic valve. The goal is to remove calcification that stiffens and welds leaflets, increase aortic valve cross sectional area, decrease the pressure gradient across the aortic valve, and decrease the clinical impact of calcific AS.

Goals of Project – Final Deliverables
The Interventional Aortic Valve Repair System should allow the interventional cardiologist to treat calcific AS in the cardiac catheterization lab. All patients with non-severe calcific AS will be treatment candidates for the interventional application. The System should include a nominal diameter catheter that isolates the aortic valve in a percutaneous approach and, once deployed on the valve with the coronary ostia isolated, maintains a zone of "pure" CDS on the aortic valve surface. The system should include sterile infusion tubing that will connect to a high-pressure solution delivery device (HPSDD) containing CDS and buffering solution.

The Company believes that Interventional Aortic Valve Repair would have a high adoption rate due to the innovative nature of the interventional cardiologist, the expected primary user of this product. In addition, the cardiologist is the specialist who performs valve disease diagnosis and controls the valve treatment patient population.

Resources Available
Corazon Technologies, Inc., Use of laboratory and machining facilities at Corazón Technologies. Bench-top tissue calcification models and human valvular tissue will be provided at Corazón.

Resources Needed
Clinical mentor - Cardiologist

Project Sponsor Contacts

Brent Constantz Ph.D.
Corazón Technologies
191 Jefferson Drive, Menlo Park, CA 94025
(650) 813-5240 x 219
kohashi@corazon-inc.com

Regularities and Standards Checklist

1. What is your project?

Please briefly describe the project you are working on:
Our project is the design of an interventional aortic repair system. We will be treating calcification of the aortic valve using the Corazón Demineralizing Solution (CDS).

Please describe potential solutions that you are considering for your project:
For all our solutions, we are considering using a catheter inserted through the femoral artery and guided to the heart. The aortic valve will then be isolated. The CDS will then be administered. At the same time a blood supply will be delivered to the aorta and the coronary arteries via tubing.

List and briefly describe any potential solutions that have biological or chemical components.
All our solutions to the project will involve the use of the CDS.

List and briefly describe any solutions that emit radiation.
Radiation may be emitted if flouroscopy is used to visualize the system.

2. Project Scope

List which solutions involve developing a completely new device.
All solutions involve developing a completely new device since no such device currently exists.

List solutions reusing a known technology, approach, or process.
All solutions will use Corazón's unique approach of dissolving calcification. All solutions will use the CDS.

Are any solutions based on other devices? Yes

If so which devices?
The solutions will be similar to Corazón's device for treatment of arterial occlusions.

Were the device(s) developed before 1976?
No.

How are they similar?
They are similar because they will both be using CDS.

Does your solution pose any new risks?

Yes, there is the risk that our device will not adequately supply blood to the aorta and coronary arteries.

Utilize any new technologies?
Our solution will use new technology to isolate the aortic valve and supply blood to the aorta and the coronary arteries. It will also use new technology in decalcifying the aortic valve by using the CDS.

Are any of your solutions used with other devices or treatments?

If so, what devices or treatments?
No.

Are they life critical?
Yes, our solutions are life critical because they must supply adequate blood to the aorta and coronary arteries.

3. Safety

Does your project pose any dangers to patients, physicians, or others?

If so, how?
The CDS is an acidic solution and would pose dangers to the patients if it escapes the isolation unit and enters the circulatory system. Another risk to patients is that our solution may not adequately supply blood to the aorta and coronary arteries.

Is it life threatening?
Yes.

4. Sponsor recommendations

What classification does your sponsor want your group to aim for?
Class III

What premarket approval process do they envision for your project?
PMA

5. Assuming your project is a device:

This last section of the checklist is intended to help start your project's FDA identification/ classification process and to document your progress. In order to guide you through this process, this document utilizes the FDA website's device advisor (see step 1). Note: at various points along the process the website offers more information to help you answer questions; these questions/links are not in this checklist.

Steps:

1) Open http://www.fda.gov/cdrh/devadvice/31.html
2) Does the product emit radiation?
   Maybe, if flouroscopy is used to visualize the system.
3) Does Your Product Meet the Definition of a Medical Device? Yes
4) Do you know the class of your device? Yes
   a. If yes jump to 5
   b. If no:
      i. Read section on "How to determine Classification"
      ii. Use the Classification Database or the Device Panels (circle which you used)
5) Record the following information:

   Device:

   Medical Specialty:

   Product Code:

   Device Class: Class III

   510(k) exempt?: No

   Regulation Number (7 digit):

   Device Description:

6) Which are required: 510k / PMA / Exempt
   (circle which apply – known from the above classification)
   A PMA is required.

7) The next steps in the regulatory process depend greatly on your specific project. See the regulatory team for guidance if you are uncertain of your next steps.

Arterial Catheter Insertion Protocol

Obtained and modified from "Los Angeles County & University of Southern California Trauma Surgery and Critical Care "

A. Indications

1. Continuous blood pressure monitoring
2. Frequent blood analysis

Prior to starting the procedure, inform the nurse caring for the patient that a procedure will be done on the patient. They can help in obtaining the necessary equipment and setting up the monitors and transducers. At the completion of the procedure, enter the procedure into the computer under Procedure Notes.

B. Equipment

Femoral Artery Cannulation

1. 18-gauge 5 1/4" angiocath
2. Cordis central line kit (used with above kit for the Seldinger needle and wire)

General

1. A-line insertion tray
2. Suture 2-0 or 3-0 nylon on cutting needle
3. Sterile gauze 4 x 4
4. Local anesthetic - 1% lidocaine (no epinephrine)
5. Medication for sedation (if necessary)
6. Sterile gloves, drapes, gown, mask, cap, eye protection
7. Betadine solution or swabs
8. Pressure transducer, tubing, pressure monitor

C. Technique

Femoral Artery Cannulation

1. Perform the Allen test
2. Complete aseptic technique is to be used
3. Prepare the patient
4. Don mask, cap, eye protection
5. Wash hands
6. Place gown and gloves
7. Create a sterile field
8. Palpate the femoral artery.
9. Infiltrate with local anesthetic
10. Enter the skin over the femoral artery ~1 to 2 cm below the inguinal ligament with the needle using the Seldinger technique.
11. Advance the needle at ~45 degree angle

12. Entry into the artery will be signaled by the appearance of pulsating arterial blood.
13. Immobilize the needle with free hand.
14. Advance the guidewire through the needle
15. Remove the needle leaving the guidewire in the place
16. Pass the arterial catheter over the guidewire.
17. Remove the guidewire
18. Connect tubing to the catheter.
19. Secure the catheter with suture and apply sterile dressing.

Precautions/Complications

A. Contraindications

1. Ischemia of the extremity
2. Infection at the puncture site
3. Raynaud's Disease
4. Prior vascular surgery involving the artery to be punctured

B. Complications

1. Digit, hand, leg, foot ischemia
2. Hemorrhage
3. Arterial air embolism
4. Infection
5. Arteriovenous fistula
6. Arterial aneurysm