PERCUTANEOUS AORTIC VALVE PROPOSAL/PROTOCOL

I. GOALS:

The main objective of this pilot study is to demonstrate the feasibility of percutaneously placed aortic valve. This study is designed to show that such a device can be placed without the need for a sternotomy or circulatory bypass.

II. HYPOTHESES:

1. We speculate that we can disperse the forces that are required to seat an artificial aortic valve utilizing stent technology.
2. We speculate that this procedure can be done safely and effectively utilizing percutaneous technologies.
3. We speculate that the ascending aorta can withstand a stented structure without dissection or rupture.
4. We speculate that the intraluminal valves can properly function within a stented system

III. Equipment and Supplies

1. We propose that we use 10 pigs to place the percutaneous devices and to derive the needed data. This would require the facilities to house and provide upkeep. Our veterinarian facilities have these capabilities. Moreover, the facility has a catheterization laboratory which can be utilized with proper funding to derive the primary set of data. The collaborators and I will perform the procedures and interpretation necessary to publish our series. There will be a need for computers and software for the analysis.
2. We will be making the valves and stents at the University of Missouri unless it is found that we have neither the expertise nor equipment. Thus far we have found our chemical engineering department invaluable in this area.

Expand Detail

Therefore, much of the expense will logically be in the development of the prototypes. The materials will include, but will not be limited, to different polymers, metals, and ceramics to initiate in a fluid model the exact valves we will pursue in the animal models. We estimate that the first 10 weeks of research will be the construction of adequate prototypes.

3. It is invaluable to have adequate visualization of the aortic valve for the successful completion of this project, and in pursuit of this visualization we will utilize to an extent not previously utilized, echocardiography. We will place, as will be discussed in the procedures section, 3 echoprobes for the adequate visualization of the aortic valve. These will be placed in the esophagus, the right atrium, and transcutaneously. Also, an intravascular ultrasound will be utilized in the data acquisition portion of the study. This could represent a substantial portion of our budget in securing these devices.
4. We will also be developing and modifying known catheters and peripheral equipment as seen necessary for the successful completion of this project. Excitingly, this may lead to a multitude of novel devices, which will be needed to visualize and deliver the stent/valve. Further, there will be the need for novel debulking devices to percutaneously (please see submitted background material for further explanation) remove the native aortic valve structure sufficiently to relieve the stenosis. This may require testing on a delivery device for precise biotome resection, percutaneous ultrasound and laser debulking and new more effective balloon valvuloplasty. However, debulking devices would not be necessary in this protocol because the pigs would not have aortic stenosis.
5. Finally, staff will be instrumental in the timely completion of this project. These will include maintenance staff for the pigs as well as catheterization personnel. The

engineering department will need partial funding for post-doctoral candidates to help in the development of the valve. As well, the cardiology department and I will need secretarial support to help in the clerical and organizational demands placed upon a rigorous study protocol. This staff is fortunately available with a high level of experience within this institution and would only need allocation of said monies to properly establish their work roles.

IV. COLLABORATION

1 This project will be a multidiscipline effort including the collaborative efforts of representatives from the Cardiology, Biophysics, Chemical Engineering, Engineering, Pathology and Veterinary departments. Representatives from each department have, to date, been utilized in a peripheral manner to gain more knowledge and insight to bring about the project to its issuance. This working relationship will be needed to successfully complete this project.

V. PROCEDURES

1. The project can be roughly divided into 3 phases. The first phase will be the successful assembly of working prototypes with subsequent fluid model testing. The second phase will be the placement of the devices into the pigs with subsequent data acquisition. The final stage will be the analysis of the data with subsequent conclusions.

TIMELINE:

1. PHASE 1	8 TO 10 WEEKS
2. PHASE 2	1 TO 2 WEEKS
3. PHASE 3	6 TO 8 WEEKS

This timeline may be influenced positively or negatively dependent upon initial successes/failures encountered at each stage.

VI. DATA ACQUISITION

1. The most important data will be the initial success of placing the device without excess mortality in the pigs. Subsequently, we will collect data confirming the valves' function and durability through a variety of ways. These will include the use of the echo devices to precisely monitor the function of the valve in-vivo under a variety of stress conditions. Specifically, we will infuse vasopressors and chronotropic chemicals into the pigs to provide different rate and pressure situations and assess each devices' tolerance to these conditions. An intravascular ultrasound device will be utilized to assess the stent deployment within the ascending aorta, and a similar intracardiac echo will assess the coaptation of the aortic valves within the native aortic valve structure. This will provide crucial data as to the devices' ability to open and close without impinging upon vital structures, namely, the coronary arteries. The hemodynamic equipment within the catheterization lab will be utilized to provide information as to the effect of deployment upon the pig's circulatory system. These measurements will include instantaneous gradients across the valve and stent combination, along with standard measurements of cardiac output and systemic resistance. A hematologic profile will be collected from each valve to assess its rheostatic effects upon the circulating blood pool. In addition, fibrin assays will be drawn to assess the activation of the coagulation cascade. Cardiac enzymes will be periodically drawn to assess for microembolization or delayed trauma upon the cardiac circulation. Finally, the

pigs will be sacrificed after these data have been collected, and tissue sections from the ascending aorta, heart, brain, lungs, kidneys, spleen and liver will be taken to assess for structural alterations which may be related to the percutaneously delivered valves.

VII. FUTURE DIRECTIONS

1. From this pilot study we will have the information needed to pursue more ambitious projects which will lead ultimately to trials in humans with inoperable aortic stenosis. From census data there were approximately 50 million Americans over the age of 65. Among this population there is an annual incidence of 2 to 9%, depending upon age, of aortic stenosis. This could mean that as high as 4.5 million elderly persons could suffer from this disease. Among those who are older, especially over 75, they are less likely to be operative candidates. This could represent a tremendous amount of patients who could be helped by this procedure. For the investor, this could represent a tremendous previously untapped market, which could lead to substantial profits. For the physician, more importantly, it could lead to definitive treatment where previously there were few options besides palliation.