PERCUTANEOUS AORTIC VALVE REPLACEMENT

This proposal for a project to advance the development of a technique and prosthetic value to be used in percutaneous aortic value replacement is divided into seven sections. The section on anatomy describes the native aortic valve and its function while the following section on the valve's dynamics and physics discusses the implications of the anatomy for the valves successful function. The sections on aortic stenosis and regurgitation describe the valve dysfunction and the section on surgical therapy discusses current surgical replacement therapy and its problems. The final two sections outline the study goals and stages. The purpose of the study is to advance the development of a potential percutaneous technique and prosthetic valve that would mimic the function of the native valve and avoid the problems associated with current methods for surgical replacement of the native aortic valve.

I. Aortic Value Anatomy

The aortic valve directs the flow of blood from the left ventricle into the systemic circulation through the aortic artery. It accomplishes this function by opening during the contraction of the left ventricle and closing when the left ventricle relaxes.

In a normally functioning valve, three leaflet-shaped cusps open widely to allow the unimpeded transference of blood, and then close tightly, not allowing any blood back into the left ventricle. Significant restriction to blood flow is called stenosis, and blood leakage back into the left ventricle is called regurgitation.

The aortic valve is a tricuspid structure. Each cusp folds up toward the aorta during the contraction phase and then folds back against the others in the relaxation phase. [Figure 1 show a picture] However, it is important to understand that the structure of the aortic valve is complex, with integral relationships beyond its three-leaflet valve structure. For instance, each leaflet sits directly opposite an out pouching of the proximal aorta. This dilated segment, called the sinus of valsalva, is part of an anatomic relationship that assists the repetitive opening and closing of the valve while minimizing the stress on any point within this valvular apparatus. Further, the proximal portion of the aortic valve is highly elastic, which allows it to dilate during the contraction phase of the left ventricle.

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Moreover, these valvular structures are integrally related to the coronary arteries, which supply blood supply to the heart. These arteries, as represented in Figure 2, are located within 2 of the three sinuses Thus, each component plays a vital role in the function and durability of the valve.

The first components of the aortic valve I would like to discuss are the leaflets.

As stated, the number of leaflets within a normal aortic valve is three. Any congenital variation in the number of leaflets causes significant problems with function. When there are less than three valves, the valve undergoes rapid stenosis and restriction. An individual with a unicusped valve rarely survives beyond the first year of life. Among individuals with congenital alterations in the valve number, the most frequently encountered is a bicuspid aortic valve. Individuals with this variations in valve number can survive into adulthood. However, this valve combination becomes more and more stenotic and regurgitant by the 4th and 5th decade, which usually results in the need for surgical replacement. (See figures 3 and 4). Rarely, an individual with a quadricusped valve will survive into adulthood. This alteration in design also results in marked stenosis.

The anatomy of a normal aortic valve (three cusps, sinues, aortic arteries) permits the dispersion of pressure over a larger surface area in the structure. This dispersion resists the exhaustion of any one component of the valve. Moreover, the curvature of the cusp structure allows the leaflet to reverse curvature. An ability needed in order to fold and allow the maximum opening diameter during contraction. Finally, a curved design allows a redundancy in the coaptation area of the leaflets. The area of coaptation is the valve edge that must meet and close in order to prevent regurgitation. Hence, both the number of leaflets and their overall shape is important in the function and durability of the valve.

As mentioned earlier, the valve leaflets have a direct relationship to the sinuses of valsalva. The sinus diameter is almost twice that of the aorta. This cavity plays an important role in the mechanism of valve closure. [referenced Mano Thubrikar] An oblique section through the leaflet-sinus assembly shows this remarkable relationship. (See Figure 4). This section reveals that the sinus and leaflet form a circle when the valve is in a closed position. Furthermore, it is angulated to a degree as to allow pressure transduction along the entire surface of this unit. All this suggests that

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the shape of the leaflet-sinus assembly is important in determining how stresses are developed within the valve. This relationship also allows the valve leaflets to close without straining the aortic valve, as has been suggested. Finally, this relationship of the sinuses and valve allow for the efficient flow of blood in the coronary ostia.

Another structure, the aortic root, has been observed to expand during ventricular contraction. The dilatation of this structure (predicted by Poisselles' law, which describes the relationship of resistance to vessel diameter, length an fluid viscosity) reduces tension, which in turn reduces resistance to flow. This phenomenon also allows for complete opening of the aortic valve. Interestingly, when the cusps open, a circular dimension is maintained that is at least the same diameter as before contraction. Moreover, it is has been observed to be even larger than the original orifice. (Medical Engineering & Physics 19(8): 696-710,1997). This behavior reduces circumferential stress on the valve and generates a reduced Reynolds shear stress number (the number used to evaluate the amount of stress in a confined fluid system). In a similar manner, the inner lining of the cusp of the valve, the lamina ventricularis, extends into the ventricular myocardium when the valve is in an open position. A confluence of fibers at the base, called the fibrous coronet, is a distinct structure separating the elastic fibers above, and the myocardium below. However, this structure is not static. It is a very dynamic structure, which bends and molds to the forces exerted from the ventricular myocardium (Cardiovascular Research, 22,7,1988)(Journal of Biomechanics33 (6): 653-658, 2000 June). In a fashion similar to the aortic root, this structure allows the valvular apparatus to open with the least amount of strain.

The coronary arteries arise within or above the sinus of valsalva. The blood flow to the heart occurs mostly when the ventricle relaxes. At this time, the cusps of the aortic valve are closed, and, as mentioned, the diastolic forces of the blood against the valve are dispersed along the valve and adjacent sinus. The opening, or ostia, of the coronary arteries, when located near the apex and middle of the sinuses, allows for least turbulent, most laminar flow characteristics. (This optimal location will be important to keep in mind when designing a replacement valve because this relationship promotes the greatest amount of flow with the least amount of resistance.) In disease states where these relationships are lost, it has been proposed that this loss could increase stress at the coronary ostia. (The Aortic Valve CRC press).

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These integral relationships are not only seen in the gross anatomy of the valvular apparatus. The microanatomy shows the integral nature of these structures as well. The amount of elastin shown by staining methods is in a higher concentration than anywhere else in the body. (American Journal of Pathology 445 (7): 1931). This concentration allows a greater amount of dilatation of the structures in this area. Further, scanning electron micrographs have shown the unique arrangement of collagen in the valves, which permits the unique reversal of curvature, which is vital in the function of the valve. (See Figure 6). (Anatomic Embryology 172(61): 1985). The fibers are unusually small and arranged in sheets with unique distances between each strand. In theory, this would give a greater amount of tensile strength while allowing continued flexibility. As always, nature has selected the most efficient machinery, and we have only to discover the reasons why.

II. Aortic Valve Dynamics and Physics

The aortic valve is not a static structure and is better understood in a dynamic state. Full understanding of this structure requires understanding the dynamics and physics of the opening and closing of the valve: the motion of the various parts, the design of the valve in vitro and the hydrodynamics of the valve.

The valve's ultimate function is to allow fluid transfer from the ventricle to the systemic circulation. In order to do this efficiently, it minimizes shear stress, resistance to flow and tensile forces. The opening and closing of the aortic valve depends upon differential pressures, flow velocity characteristics and, as mentioned earlier, the unique anatomic relationship between the valves and the sinuses of valsalva. The most comprehensive model of this process has been developed by Bellhouse et al. In this model, the flow of fluid through the aortic valve was studied by injecting dye within the flow of fluid. Some of the pertinent observations incorporated in this model were as follows: 1) The valve opens rapidly, and as the leaflets move into the sinuses, vortices form between the leaflet and the sinus walls; 2) The flow enters the sinus at the sinus ridge, curls back along the sinus wall and leaflet and flows then back into the main stream; 3) During the end of systole, the vorticeal motion created during contraction forces the valves back toward a closed position. These observations are important because they show that absolute pressure differences created between the

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aorta and ventricle are not the source of initial closure of the aortic valves. In fact, it would be detrimental to valve stress if these forces dictated closure of the aortic valve. For example, if two objects are separated and a set amount of force is applied to each, increasing the distance between them would produce greater velocity and the momentum at impact would be greater. Therefore, if the leaflets are closed or near closure as contraction is coming to an end, then the force used for coaptation would be less. Less force per cycle equates to greater longevity of the valve.

This phenomenon would affect the design for prosthetic valves. The cusps and the relationship of closure for prosthetic valves must incorporate passive closure during systole in order to lengthen the life span of any such device.

To understand how to do this, we must explore The theory of laminar flow as it relates to aortic valve function. Laminar flow is predicted by Reynolds number, which incorporates the laws as described by Outsell and Bernoulli. In general, the lower the Reynolds number, the more likely that flow will be laminar. The equation that describes the Reynolds number in the aorta is as follows:

$$Ua/v = \text{Reynolds number}$$

That is U, which equals the velocity of blood and a, which represents the radius of the aortic valve, is inversely related to the viscosity of blood. As the velocity increases or the viscosity decreases, the tendency towards turbulent flow also increases.

Moreover, the behavior of the system is also predicted by the rate of acceleration or deceleration described by the Strouhal number, which predicts flow characteristics of a given fluid. In a system where viscosity, velocity and radius vary slightly, the rate of acceleration or deceleration predicts laminar versus non laminar flow. When looked at in this perspective, it is easy to see the relevance of this information to valve function. Only a small pressure difference is required to open the native aortic valve. Maintaining a small pressure difference minimizes acceleration to flow. Thus, laminar flow is more likely. The deceleration phase is naturally a gradual process; however, as stated above, it is the relationship between the sinuses and the cusps that allows this deceleration to occur without an abrupt pressure drop. When laminar flow is produced, the resistance to flow, wall stress, shear stress and circumferential

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