Engineering Approaches to Cardiovascular Disease: Development of Markers of Heart Valve Disease Severity and Progression

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Abstract— **Fluid mechanical principles can be applied to biologic systems. The flow of blood must obey conservation of mass, momentum, and energy. Application of these principles, combined with the knowledge of the anatomy and physiology of the heart and blood vessels, establishes the relationship between pressure and flow that permits us to understand phenomena such as the perfusion of organs, the control of blood pressure, and the operation of heart valves [1]. The endothelial cells that line the blood vessels act as sensors, responsive to the fluid environment to which they are exposed, and transducers of signals to initiate responses from subjacent tissue. A host of cellular processes are affected by mechanical stresses [2] and deleterious stress patterns are implicated in disease processes.**

As our understanding of the interaction between blood flow, the mechanics of cardiac and heart valve motion, and disease processes has increased, our ability to track and predict disease progression has improved. Still, there are significant clinical quandaries in the interpretation of hemodynamic data, and robust markers to predict progression and determine the benefits of therapeutic strategy are still needed.

This paper discusses the fluid mechanics of degenerative valve disease, classical ways to assess disease severity, and ongoing studies to find markers representing early stages of the disease that may improve prognosis and allow benefits of new therapeutic strategies to be assessed.

Keywords—**Aortic valve, Doppler echocardiography**

I. Introduction

The aortic valve sits between the left ventricle and aorta, and is designed to permit forward flow during ventricular contraction with little resistance, and to close to permit no retrograde flow during relaxation. Aortic stenosis is a condition in which the valve is obstructed (Fig 1). Aortic stenosis may be the result of a congenital defect, rheumatic disease, or a degenerative process thought to be related to aging and sclerosis [3]. The presence of obstruction leads to an increased pressure difference between the left ventricle and the aorta, reflected by a rise in left ventricular pressure. Chronic elevation in left ventricular workload leads to hypertrophy of the cardiac muscle [4]. This results in decreased left ventricular distensibility and impairment of diastolic filling [5-8]. Symptoms of this condition often appear most pronounced with exercise [9], and progress with age [10]. Untreated, aortic stenosis can quickly lead to left ventricular failure and death [11].

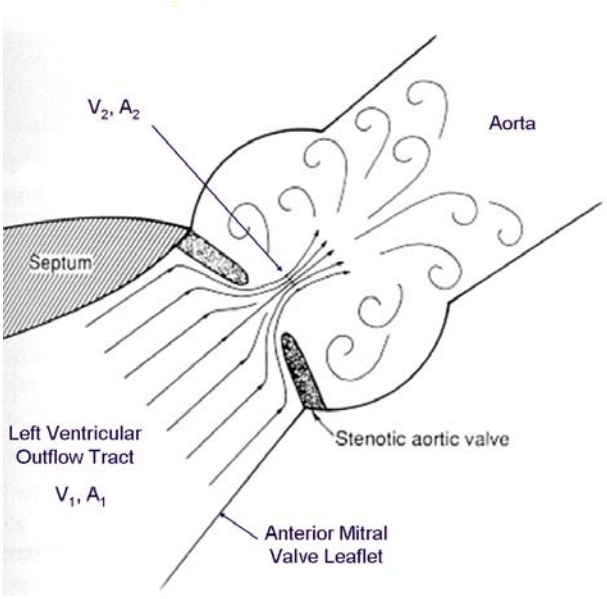

Fig 1. The left ventricular outflow tract and ascending aorta. Pulsed and continuous-wave Doppler measure v_1 and v_2. The cross-sectional area of the left ventricular outflow tract (A_1) is determined by 2D echocardiography. The effective valve area (corresponding to the *vena contracta* velocity) is calculated as $A_2=v_1A_1/v_2$.

In this country, a form of this disease referred to as "degenerative aortic valve disease" is increasing in frequency. Degenerative aortic valve disease is characterized by increased leaflet thickness, stiffening and calcification without commissural fusion. Of patients older than 70 years who undergo aortic valve replacement, the majority are for aortic stenosis [12]. Systemic risk factors for aortic valve disease are similar to coronary artery disease (including smoking, hypertension, hyperlipidemia, and diabetes), and the magnitude of association of these risk factors is also similar [13]. Similar to atherosclerosis, mechanical stresses mediate biochemical changes and development of valve lesions. However, the fluid mechanical environment surrounding the aortic valve leaflet is more complex than at the site of atherosclerosis. Fluid forces act upon both sides of the leaflet, which undergoes flexion and large-scale deformations through the cardiac cycle. This cyclic loading leads to "repetitive stress injury". Calcification occurs exclusively on the aortic side of the leaflet in areas of maximal flexural stress [14,15]. Degenerative changes appear to be accelerated in congenitally bicuspid aortic valves [16], perhaps because the abnormal structure is less able to accommodate detrimental stress patterns. Mechanical stresses are also im-

plicated in lipid uptake and calcification in bioprosthetic valves [17,18].

Figure 2 shows a conceptualization of the progression of the disease: deleterious stresses cause structural damage and mediate changes in composition and material properties of the leaflets. This results in altered valve leaflet motion, reflected in changes in local fluid mechanics and valve hydraulics. This leads to further changes in stress patterns and therefore more remodeling.

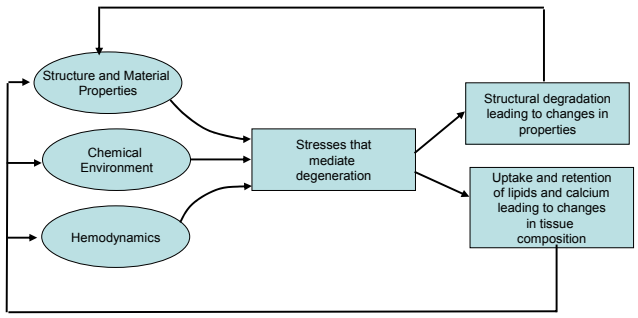

Fig. 2. Feedback mechanisms that lead to valve degeneration.

II. CLINICAL ASSESSMENT OF AORTIC VALVE HEMODYNAMICS

Traditionally, clinical assessment of aortic stenosis, therefore, includes measurements of effective orifice area and transvalvular pressure drop. The gold standard for these measurements is by cardiac catheterization. Pressure proximal and distal to the valve is directly measured, and the effective orifice area of the valve (A_o) is calculated by the Gorlin & Gorlin equation [18]:

$$A_o = \frac{SV / SEP}{44.3\sqrt{h}} \quad (1)$$

In this equation, SV is the stroke volume, SEP is the systolic ejection period, and h is the mean pressure drop across the valve.

Aortic valve function may also be assessed noninvasively with Doppler echocardiography. Echocardiography allows visualization of cardiac structures and geometric measurements. Ultrasound provides velocity measurement based on the Doppler principle; the frequency shift between the emitted beam and the signal reflected by a red blood cell is proportional to the speed of the cell. Two modes of spectral Doppler ultrasound are pulsed-wave and continuous-wave Doppler. Pulsed-wave Doppler provides a velocity measurement within a sample volume, but is subject to aliasing based on the Nyquist effect. Continuous-wave Doppler provides the maximum velocity along the sight of the beam, but provides no spatial resolution.

The effective valve area may be calculated noninvasively using the continuity equation [19]:

$$A_o = \frac{\pi D_{LVOT}^2}{4} \frac{VTI_{LVOT}}{VTI_{AV}} \quad (2)$$

In this equation, D_{LVOT} is the diameter of the left ventricular outflow tract, measured from a standard echo-cardiographic image, and VTI_{LVOT} and VTI_{AV} are the velocity-time-integrals of the pulsed-wave Doppler trace in the left ventricular outflow tract and the continuous-wave Doppler trace through the aortic valve, respectively. Because the maximum velocity provided by continuous-wave Doppler must occur at the vena contracta of the stenotic jet, this equation represents a statement of conservation of mass applied between the left ventricular outflow tract and the vena contracta, and therefore A_o represents the effective orifice area of the valve.

The transvalvular pressure drop can be estimated by a form of the Bernoulli equation in which accelerative and viscous effects are neglected:

$$\Delta P = 4\left(v_2^2 - v_1^2\right) \quad (3)$$

In this equation, P is expressed in mm Hg and v in m/s. The coefficient 4 represents the viscosity of blood and an appropriate conversion factor. V_2 is the continuous-wave Doppler velocity through the aortic valve, and v_1 is the pulsed-wave Doppler trace obtained in the left ventricular outflow tract. Often, v_1 is neglected because it is much smaller than v_2. This form of the equation is often referred to as the simplified Bernoulli equation [20].

Because Doppler ultrasound fundamentally measures velocity, and the catheter measures pressure, and the precise locations of measurement sites cannot be controlled [21], discrepancies exist between the two measurement techniques. The Doppler-derived pressure drop commonly overestimates that measured by catheter [21-23]. Several factors have been identified that account for this. First, catheter-derived pressure drops often represent peak-to-peak measurements, because pressure pulses measured in the left ventricle and downstream of the valve will be slightly out of phase due to the compliance of the aorta [24,25]. A Doppler technique represents an instantaneous measurement. Omission of terms from the full mechanical energy balance in the derivation of the simplified Bernoulli equation is a second source of discrepancy. Omission of the proximal velocity will cause overestimation if it is abnormally elevated. Omission of viscous losses could actually lead to underestimation of the true pressure drop [27]. Third, and most importantly, pressure recovery has been identified as the main cause of discrepancy in aortic stenosis [21,27-29].

Pressure recovery occurs because of re-expansion of flow downstream from the vena contracta of a jet. At the vena contracta, velocity is a maximum and pressure is a minimum. In principle, continuous-wave Doppler records this velocity. Downstream, flow expands, velocity falls and pressure rises. This corresponds to the conversion of kinetic energy back to potential energy. The catheter is usually placed somewhere downstream of the vena contracta, and

therefore measures recovered pressure. The catheter-measured difference will also record a small amount of viscous losses (a function of the distance between sensors).

Attempts have been made to account for the differences between Doppler and catheter measurements, and to correct the Doppler-derived pressure drop. Clark showed that pressure recovery is a function of receiving chamber geometry [30]. Based on Clark's analysis, Voelker proposed a geometric correction factor to the Doppler measurement [31]:

$$C = 2\left[\left(\frac{A_o}{A_A}\right) - \left(\frac{A_o}{A_A}\right)^2\right] \quad (4)$$

In this equation, A_A is the anatomic area of the aortic root. The simplified Bernoulli equation corrected for geometry is written:

$$\Delta P = 4v_2^2(1 - C) \quad (5)$$

Studies have shown that this correction improves agreement [29,32], but is insufficient to fully explain errors. Orifice geometry itself can affect the measured pressure drop, even for a constant anatomic area [33-34]. Jet orientation with respect to the axis of the aorta can also affect the measured pressure drop [34]. Finally, the amount of turbulence in a flow field can affect the amount of pressure recovery, because turbulent dissipation represents energy loss to irrecoverable forms [27]. Dimensional analysis has shown patterns in the clinical data. For instance, a plot of Doppler/catheter error versus Reynolds number shows underestimation at low Reynolds number, when viscous forces dominate. Overestimation occurs at higher Reynolds numbers, when viscous effects vanish and the basic phenomenon of pressure recovery predominates. At the highest Reynolds numbers, a trend toward agreement is seen, associated with greater turbulent dissipation and obliteration of pressure recovery [27,36].

The complex interactions of these phenomena make a robust method for achieving agreement between Doppler and catheter measurements difficult. Therefore, one aim of our ongoing studies is to develop a method to determine the recovered gradient from Doppler data, and to directly determine energy loss associated with stenosis. This is fundamentally the quantity of interest in determining left ventricular work and the mechanical efficiency of the left ventricle as a pump. Although both the maximal and the recovered gradient have physiologic significance, it has been shown that the recovered gradient more accurately reflects the left ventricular workload induced by the stenosis [37]. Development of a non-invasive method of determining the recovered gradient would be attractive for several reasons. First, the presence of the catheter itself within the valve lumen creates obstruction, and increases the apparent gradient [38]. Second, care must be taken to ensure that the distal catheter is sufficiently downstream to record fully recovered pressure [39]. Third, a noninvasive measurement is more desirable, especially in a pediatric population, than an invasive one, and the trend toward eliminating diagnostic catheterization in favor of Doppler echocardiographic studies is influenced by the reliability of the Doppler technique and the faith the cardiologist has in the Doppler data [40].

III. Hemodynamic Markers of Aortic Valve Disease Progression

Currently, patients are monitored by periodic echocardiograms. A "wait and see" approach is taken in which intervention is contemplated either after the measurements indicate severity of disease, or after symptoms develop. The rate of progression of aortic stenosis in an individual is nonlinear and standard clinical assessments have little prognostic value (in predicting the rate of progression or the onset of symptoms). Aortic stenosis is classified as severe if the jet velocity exceeds 4 m/s and A_o is less than 1 cm^2 [41]. Fewer than 26% of the patients diagnosed with severe stenosis remained symptom-free after 5 years of follow up [42].

Early in the course of the disease, degenerative changes (reflected in leaflet "thickening") can progress with little changes in A_o or pressure drop, and the patient can remain asymptomatic for years. The average hemodynamic progression of aortic stenosis is roughly a 0.1 cm^2 decrease in valve area and a 10 mm Hg increase in pressure drop per year [43]. However, this can be highly variable from patient to patient, and deterioration of hemodynamic performance can occur rapidly [44]. The absolute and percentage reduction in A_o per year in those with aortic stenosis is greater in those with milder stenosis and is accelerated in presence of smoking, hypercholesterolemia and elevated serum creatinine and calcium levels [43].

In a retrospective study, Lester, et al. suggested that the rate of change in A_o within a cardiac cycle can be used as an additional measure of disease severity and may be used to predict an individual's risk for subsequent rapid disease progression [44]. This is based on the fact that the rate of opening and closing of the valve is affected by valve stiffness. This was quantified from Doppler echocardiography by measuring the time to half of the peak velocity during acceleration and deceleration. The A_o was determined at those points in time ($A_{o½d}$ and $A_{o½a}$ for the valve area halfway through deceleration and acceleration, respectively). The ratio of $A_{o½d}$ / $A_{o½a}$ would be larger for those with delayed opening times.

Our fluid mechanic experiments demonstrate that this measure is also confounded by other hemodynamic factors [45]. Model aortic valves whose hemodynamics represent the range of mild to critical aortic stenosis were tested in a pulse duplicator (Fig 3) that reproduces physiologic waveforms. This system consists of an atrial reservoir that feeds a ventricular chamber by gravity. The ventricular chamber houses a compressible bulb. Solenoid valves allow compressed air into the chamber to produce systole, and release the air to produce diastole. Between the model atrium and ventricle is the mitral valve section. Downstream of the ventricular bulb sits the aortic valve section. Compliance and

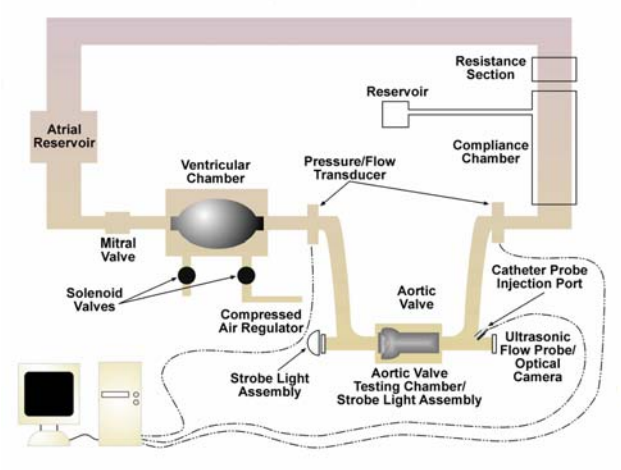

Fig. 3. The pulse duplicator system.

resistance elements are used to "tune" the system to produce physiologic pressure and flow waveforms. The compliance section consists of an outer chamber connected to a pressurized air reservoir, surrounding an elastic tube through which the fluid travels. Increased afterload can be simulated in the pulse duplicator by increasing the resistance and/or increasing the external pressure in the compliance chamber, rendering the elastic tubing stiffer.

The pulse duplicator is interfaced to a personal computer with LabView™ software and input/output board (National Instruments, Houston, TX). Custom-built control circuitry completes the pulse duplicator control and data acquisition system. Parameters such as heart rate and systolic ejection time can be controlled, and pressure and flow data are acquired and displayed. Flow measurements are made with an ultrasonic flow meter with cannulating probes (Transonic Systems, Inc., Ithaca, NY). Pressure measurements are made with fixed-mount pressure transducers at various locations in the flow loop, and with pressure transducers with high fidelity 2F catheters (Millar Instruments, Inc., Houston, TX). A Doppler echocardiographic machine (Acuson Aspen™, Siemens Medical Solutions, Malvern, PA) is used for hemodynamic measurements.

The pulse duplicator is also equipped with a system of cameras and stroboscopes for high speed analysis of the valve motion. The instantaneous anatomic opening area of the valve can be determined by obtaining a digital photograph of the valve viewed in cross section. A timing signal from the camera and stroboscope is acquired by LabView™ to synchronize the photographs with instantaneous pressure and flow data. It is important to note that the anatomic opening area of the valve determined by this method will in general be larger than that calculated by the continuity equation from Doppler echocardiographic data. This is due to the fact flow through a stenotic aortic valve forms a turbulent jet, and the continuous-wave Doppler records the velocity at the *vena contracta* of the jet (refer to Fig. 1). Thus, the difference in the valve areas determined by the two techniques reflects the coefficient of contraction of the jet, which approaches 0.60 for severely stenotic valves.

Our results show that the rate of change of aortic valve area during the opening and/or closing is affected not only by the material properties of the valve, but also by flow rate and afterload (determined by downstream resistance and "stiffness" of the blood vessels). These are reflected in changes in the shape of the aortic pressure waveform (Fig 4) [46]. Valve opening occurs when the left ventricular pressure exceeds that in the ascending aorta, and the retrograde pressure gradient established during deceleration is responsible for bringing the leaflets toward closure [47]. Thus, it is reasonable that changes in the pressure waveforms alter the temporal distribution of pressure (and therefore stress in the valve leaflets). Recent in vivo studies demonstrate the clinical relevance of arterial compliance and therefore increased afterload and decreased left ventricular function on markers of the severity of aortic stenosis [48,49].

A major goal of our research is to develop techniques to determine the properties, and health, of the valve itself, which is robust in light of the confounding factors on hemodynamic measurement. We seek a method that is sensitive to early, subtle changes in the valve before overt stenosis and symptoms develop, that can be determined noninvasively, and is simple and straightforward for the clinician to use.

Fig 4. Aortic pressure waveforms for normotension (left) and hypertension (right). Changes in hypertension include a more rapid rise and higher peak in early systole, and a more rapid decay in pressure in diastole. These may result in different force distributions on valve leaflets during the opening and closing phases.

IV. Conclusion

Dimensional analysis of clinical data demonstrates a potential method of estimating recovered pressure from the continuous-wave Doppler velocity. This method would take into account geometry and the velocity profile of the turbulent jet, two factors that influence current clinical measurements. A method that unifies the two phenomena should be a more robust marker of severity.

To predict disease progression, a method to account for both the changes in material properties of the valve and the hemodynamics (i.e., the interaction between fluid and solid) may be important. In general, any method would need to be tested in clinical studies and data should be analyzed in light of relevant medical history that might suggest increased risk for the disease.

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