Models of the Aging Cardiovascular System for the Study of Degenerative Diseases

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Abstract

Tools to aid in the design and testing of prosthetic hearts valves include cardiac pulse duplicators and computational fluid dynamics simulation. Typically, conditions in the pulse duplicators are well defined and controlled based on established guidelines for prosthetic valve testing. We have created a pulse duplicator to simulate the physiologic effects of the aging and diseased cardiovascular system, including increased aortic impedance (decreased compliance and increased resistance), and cardiac outputs representing heart failure as well as normal states. In this paper we will describe the design and validation of this cardiac pulse duplicator, and its use to study degenerative aortic valve disease. This is a progressive disease with an unpredictable rate of progression characterized by increased leaflet thickness, stiffening and calcification without commissural fusion. These changes increase resistance to cardiac outflow and hence the workload on the left ventricle. This will cause left ventricular hypertrophy and if untreated, heart failure and death. It is believed that “wear and tear”, including mechanical stress injury to the endothelium on the valve, mediates the disease process. Risk factors for valve disease are similar for other cardiovascular disease (e.g., age, smoking, hypertension, and hyperlipidemia). Current hemodynamic measurements of the severity of aortic valve disease have little value in predicting progression or onset of symptoms. Early changes in the degenerative process include thickening and stiffening of the leaflets, reflected in altered rates of opening and closing, before becoming restrictive to flow. In this study, we tested the hypothesis that changes in ambient hemodynamic forces associated with aging and related cardiovascular disease (such as hypertension) affect valve mechanics and independently classic measurements of disease severity. For example, hypertension creates increased afterload for the left ventricle, due to increased peripheral resistance, decreased arterial distensibility, and early wave reflections because of increased wave propagation velocity. These contribute to a more rapid initial rise in aortic pressure, a higher systolic peak, and a more rapid fall in pressure during diastole compared to normal. These changes alter forces on the aortic valve and thus stress patterns within it. Data obtained in the pulse duplicator, combined with computational simulation, will be used to develop markers of the properties of the valve itself, independent of ambient hemodynamic state. Such measurements, if validated clinically, would be useful in predicting disease progression and in the design and assessment of new therapeutic strategy.

Introduction

Cardiac pulse duplicators have been developed, primarily with the aim of testing prosthetic devices such as artificial heart valves. These apparati are designed to conform to certain guidance documents or testing standards, but due to differences in design including input waveforms, working fluid, location of measurement sensors for pressure and flow, geometry of testing chamber, and the material properties of the testing chamber, different results can be obtained for a similar valve tested in different systems [1].

In this paper, we present results from an *in vitro* study using a cardiac pulse duplicator that can be used to generate the data outlined in the Food and Drug Administration guidance documents, but also can be used to model hemodynamic conditions associated with cardiovascular pathology and aging. For example, both aging and hypertension create increased afterload for the left ventricle, due to increased peripheral resistance, decreased arterial distensibility, and early wave reflections because of increased wave propagation velocity. These contribute to elevated mean blood pressure, a more rapid initial rise in aortic pressure, a higher and later systolic peak, and a more rapid fall in pressure during diastole compared to normal [2]. Hyperlipidemia, hyperinsulinemia, obesity, diabetes mellitus, and cigarette smoking all affect the vascular system in ways that resemble accelerated aging [3-13].

The experimental apparatus described below allows us to tune these parameters through normal and pathologic ranges. In this way we can test hypotheses regarding the effects of changes in hemodynamics on the performance of the aortic valve, as it relates to degenerative aortic valve disease. Degenerative aortic valve disease is characterized by increased valve leaflet thickness, stiffness and calcification. These changes increase resistance to cardiac outflow and hence the workload on the left ventricle. This will cause left ventricular hypertrophy and, if untreated, heart failure and death. It is an increasingly common disease in the elderly, with degenerative changes seen in up to 75% of patients greater than 85 years old [14]. Degenerative aortic valve disease is progressive, and there is variability in the rate of progression between subjects. Thus, prediction of disease progression in an individual is difficult [15-18].

Below we describe experiments involving aortic valves of different material properties that model the spectrum of aortic valve disease. An echocardiographic method has been proposed to predict an individual's risk for rapid progression, based on the rate of change of the aortic valve area through the cardiac cycle. According to this method, the ratio of the aortic valve area halfway through deceleration to that halfway through acceleration is an indicator of risk [19]. However, changes in ambient hemodynamics, reflected in changes in the pressure and flow waveforms, due to hypertension and aging should affect the distribution of forces on the valve and hence affect its mechanical performance, ***independent*** of changes to the valve itself. Thus, we tested the hypothesis that changes in hemodynamics related to changes in aging and hypertension, such as increased afterload, alter aortic valve mechanics, and that these effects can be measured by observing aortic valve motion during opening and closing phases of the valve and therefore independently influence the proposed echocardiographic method of assessing risk.

Experimental Methods

The pulse duplicator (Figure 1) is essentially a mechanical analog of a modified Windkessel model of the systemic circulation [20, 21]. It 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 resistance elements are used to "tune" the system to produce physiologic pressure and flow waveforms.

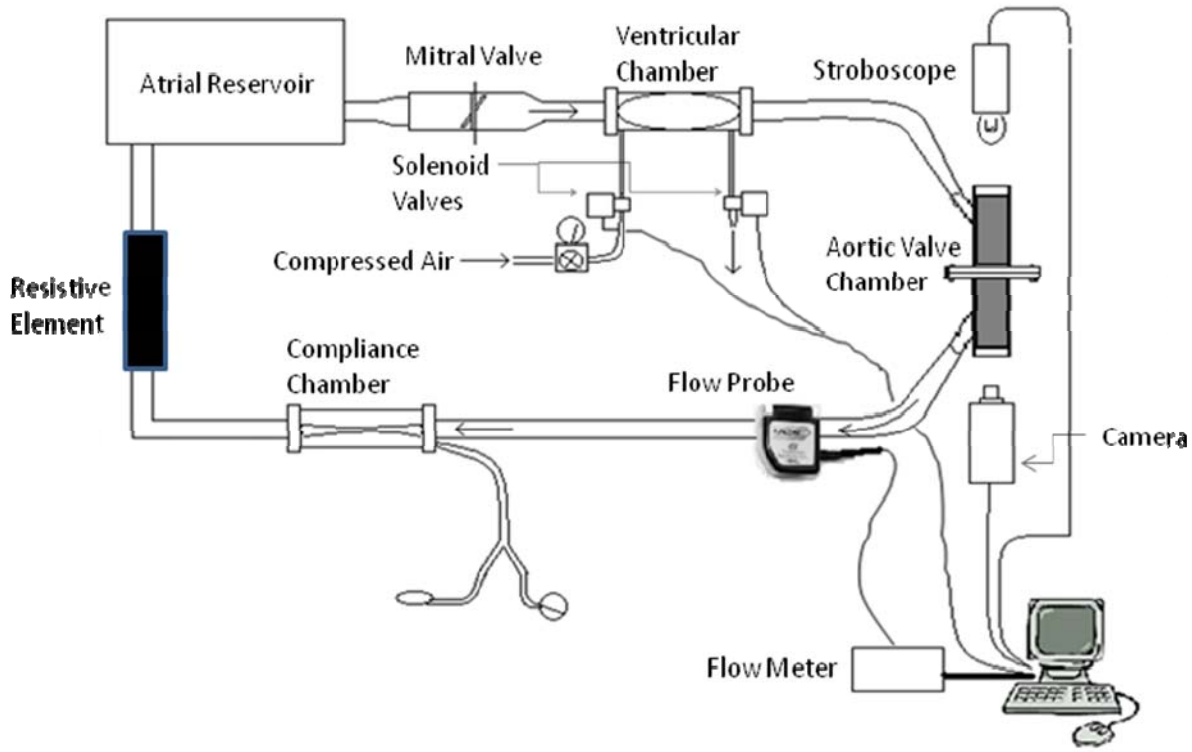

Figure 1. Schematic of the pulse duplicator system (not to scale). Adapted from Ref. 15.

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 for data acquisition and display (National Instruments, Houston, TX). Flow measurements are made with an ultrasonic flow meter with cannulating probes (Transonic Systems, Inc., Ithaca, NY). Pressure measurements can be made with fixed-mount pressure transducers at various locations in the flow loop; typical locations include proximal to the aortic valve (P_1), at the vena contracta of the valvular jet (P_2), and downstream at the site of recovered pressure (P_3). High fidelity catheters (Millar Instruments, Inc., Houston, TX) can also be introduced into the system to measure pressure at any location.

Pulse duplicator control is achieved using an external control system. This consists of a stamp, programmable in Visual Basic, to generate signals to control the solenoid valves. In this way, cardiac cycle rate and systolic ejection time can be varied. The pulse duplicator is also equipped with a camera and stroboscope for analysis of the valve motion. A second stamp controls the camera, and the stroboscope is controlled by a temperature compensated crystal oscillator external to the PC. 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. Photographs were acquired by oversampling every millisecond through the cardiac cycle and correlated with instantaneous

pressure and flow data from that cycle. The instantaneous valve opening area is obtained from planimetry using MATLAB, with functions supplied in the Image Processing Toolbox.

The working fluid was a 41% (by volume) solution of glycerin in phosphate buffered saline (PBS), which at room temperature has viscosity and density (0.037 poise and 1.08 g/cm^3, respectively) similar to the Newtonian properties of whole blood. Blood flow in the heart and great vessels behaves essentially as a Newtonian fluid [22] due to the high shear environment. Because of the sensitivity of the viscosity of the solution to environmental factors such as humidity and temperature, fluid viscosity was repetitively monitored using a Canon-Fenske viscometer and the viscosity of the working fluid was kept at 0.037 ± 0.001 poise throughout the experiments. The cardiac output was varied between 2 and 8 liters per minute, the heart rate was held constant at 70 beats per minute. The systolic ejection period was 35% of the cardiac cycle. Resistance and compliance downstream was varied from a range representing normal blood pressure (120/80 mm Hg, systolic/diastolic) to hypertension (approximately 180/120 mm Hg).

Fresh aortic valves were harvested from pigs (25 to 50 kg) at the Vivarium at USF Health. Approval to use these tissues was obtained from the Institutional Animal Care and Use Committee at the University of South Florida. These were treated either with 2% or 4% glutaraldehyde in PBS or 70% ethanol to produce a range of valve leaflet stiffness. Glutaraldehyde fixation forms crosslinks between carboxyl groups and the lysine groups of the collagen in the valve. This renders a change in leaflet stiffness without a change in valve area. Valves were mounted to sewing rings provided as a generous gift by St. Jude Medical and then set in the aortic chamber of the pulse duplicator (Figure 1).

From the flow and pressure data, peak instantaneous and mean systolic pressure drops, effective orifice area, and valve resistance are calculated. The effective orifice area is calculated by the formula of Gorlin and Gorlin [23]:

$$A_{AV} = \frac{Q}{44.3 \times RS\sqrt{\Delta P_m}}$$

where A_{AV} is the effective aortic valve area (cm^2), Q is the cardiac output (ml/min), R is the heart rate (beats/minute), S is the systolic ejection period (in seconds), and ΔP_m is the mean pressure drop across the valve (mm Hg). Valve resistance is determined by an equation proposed by Ford [24]:

$$R_{AV} = \frac{1333 * \Delta P_m}{Q \diagup 60}$$

It is important to note that the anatomic opening area of the valve determined by photography will in general not agree with that calculated by the Gorlin equation from the hemodynamic data. This is due to the fact flow through a stenotic aortic valve forms a turbulent jet (Figure 2). Using the pressure difference in between left ventricle and the *vena contracta* pressure tap will yield an effective area that reflects the coefficient of contraction of the jet, which *in vivo* approaches 0.60 for severely stenotic valves [25]. On the other hand, using the downstream, recovered pressure in the formula more accurately represents the overall energy loss due to the obstruction caused by the valve; therefore, there is an inverse relationship between the amount of pressure recovery and the Gorlin-derived aortic valve area [26]. The

result from the Gorlin equation is also flow dependent. Therefore, this data will also be used to elucidate the relationship between anatomic area, calculated area, and hemodynamic state.

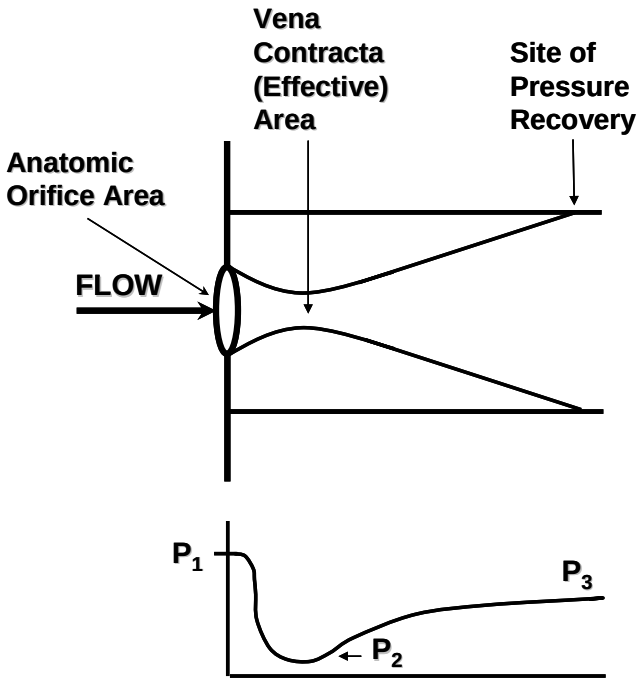

Figure 2. Jet flow through a stenotic valve, showing the relationship between the anatomic and the effective orifice area.

Results

Instantaneous anatomic area was measured from the individual photographs showing the opening of the aortic valve (Figure 3). Plots of anatomic area versus time were then generated (Figure 4). The rate of valve opening was affected by flow rate, whereas valve closing was affected by valve treatment; the stiffer valve would close faster. A higher afterload

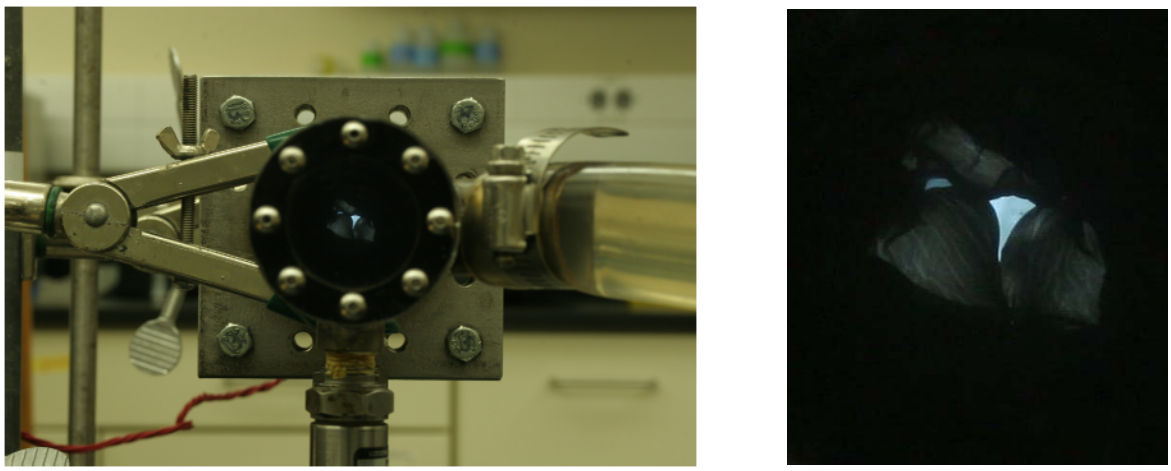

Figure 3. Photographs taken of the instantaneous position (left) are processed in MATLAB (right). From these pictures, valve opening area is measured.

also leads to faster valve closure. Therefore, factors extrinsic to the properties of the valve itself will affect the valve area ratio measured by echocardiography.

Sample pressure and flow traces obtained from are displayed in Figure 5. These data are correlated to the photographic data, and instant-aneous flow/pressure/valve area relationships can be studied. The flow dependence of the Gorlin equation is demonstrated with these data; however, the data suggest that valve resistance may be a robust marker of valve stiffness. A marker of the properties of the valve that is independent of other hemodynamic factors may prove valuable in predicting outcome, as well as in evaluating therapeutic strategy designed to slow the progression of the degenerative disease.

Acknowledgments

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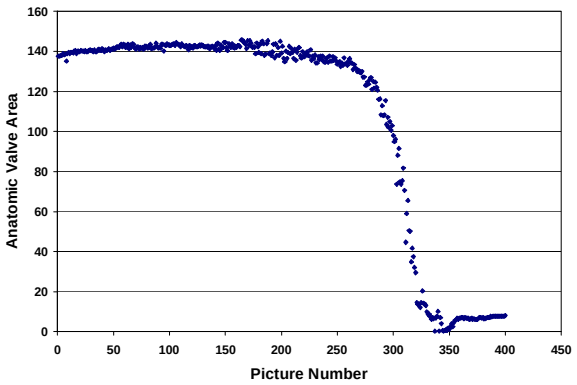

Figure 4. Anatomic area for an ethanol-treated valve at 6 l/min. The closing phase of the cycle is captured. In this graph, Area is in mm^2 and the time between each picture is 1 ms.

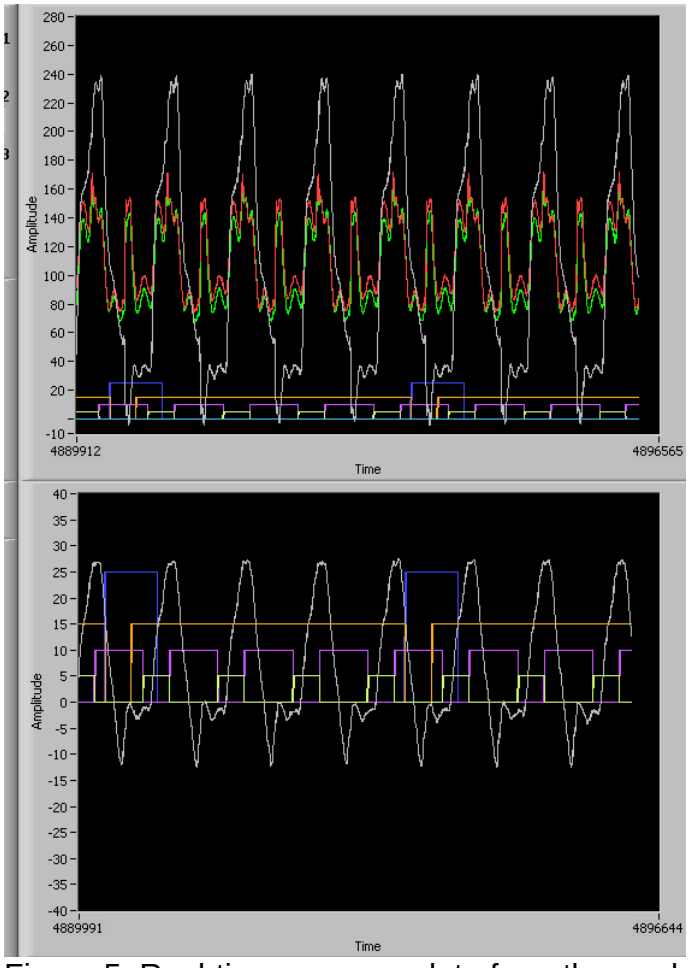

Figure 5. Real-time pressure data from the model ventricle and aorta (top) and flow rate (bottom). Superimposed on the flow waveform iare signals from solenoids, stroboscope and camera shutter.

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