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Quantification and comparison of the mechanical properties of four human cardiac valves

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ABSTRACT

Objective: Although having the same ability to permit unidirectional flow within the heart, the four main valves—the mitral valve (MV), aortic (AV), tricuspid (TV) and pulmonary (PV) valves—experience different loading conditions; thus, they exhibit different structural integrity from one another. Most research on heart valve mechanics have been conducted mainly on MV and AV or an individual valve, but none quantify and compare the mechanical and structural properties among the four valves from the same aged patient population whose death was unrelated to cardiovascular disease.
Methods: A total of 114 valve leaflet samples were excised from 12 human cadavers whose death was unrelated to cardiovascular disease (70.1 ± 3.7 years old). Tissue mechanical and structural properties were characterized by planar biaxial mechanical testing and histological methods. The experimental data were then fitted with a Fung-type constitutive model.
Results: The four valves differed substantially in thickness, degree of anisotropy, and stiffness. The leaflets of the left heart (the AV leaflets and the anterior mitral leaflets, AML) were significantly stiffer and less compliant than their counterparts in the right heart. TV leaflets were the most extensible and isotropic, while AML and AV leaflets were the least extensible and the most anisotropic. Age plays a significant role in the reduction of leaflet stiffness and extensibility with nearly straightened collagen fibers observed in the leaflet samples from elderly groups (65 years and older).
Conclusions: Results from 114 human leaflet samples not only provided a baseline quantification of the mechanical properties of aged human cardiac valves, but also offered a better understanding of the age-dependent differences among the four valves. It is hoped that the experimental data collected and the associated constitutive models in this study can facilitate future studies of valve diseases, treatments and the development of interventional devices.

Statement of Significance

Most research on heart valve mechanics have been conducted mainly on mitral and aortic valves or an individual valve, but none quantify and compare the mechanical and structural properties among the four valves from the same relatively healthy elderly patient population. In this study, the mechanical and microstructural properties of 114 leaflets of aortic, mitral, pulmonary and tricuspid valves from 12 human cadaver hearts were mechanically tested, analyzed and compared. Our results not only provided a baseline quantification of the mechanical properties of aged human valves, but a age range between patients (51–87 years) also offers a better understanding of the age-dependent differences among the four valves. It is hoped that the obtained experimental data and associated constitutive parameters can facilitate studies of valve diseases, treatments and the development of interventional devices.

1. Introduction

The four heart valves share the same function of directing blood flow, but exhibit different mechanical and structural characteristics. The semilunar valves, the aortic valve (AV) and pulmonary valve (PV), have nearly symmetrical tri-leaflet configurations and

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are positioned in the outflow tracts of the left and right ventricles to the elastic arteries. The atrio-ventricular valves, the mitral valve (MV) and tricuspid valve (TV), on the other hand, are far more complicated in structure and function due to their asymmetrical structure and the presence of tethering chordae tendineae and papillary muscles. These four valves function primarily as passive structures, i.e., they open and close due to the differential blood pressure on each side of the valve leaflets [1]. Under normotensive conditions, the peak differential pressures across the closed AV and MV are about 100 mmHg and 120 mmHg respectively, much higher than their right heart counterparts (i.e., 13 mmHg to 35 mmHg for PV and TV) [2]. These differences in physiological conditions result in differing structural and mechanical properties among the valves.

Over the past two decades, major advances have been made in the diagnosis and treatment of valvular heart disease [3]. The increase in the development of new surgical or percutaneous valve repair and replacement techniques and devices highlights the need for a deeper understanding of the mechanical and microstructural properties of the native, aged human heart valves. Unfortunately, most biomechanical studies of heart valves have focused on the individual MV and AV valves, partially due to the prevalence of their treatment compared to those for the TV and PV valves [3]. The recent explosive use of transcatheter valve techniques for AV [4–8] and MV [9,10] diseases also brings the hope that the largely untreated patient population of TV [11,12] and PV [13] patients can be treated by transcatheter approaches. An in-depth understanding of the biomechanical differences between the four valves can facilitate the transition of the transcatheter AV and MV experience to the PV and TV valve space. However, due to the scarce availability of fresh human heart valves, wide variations in tissue preparation, testing protocols, and determination of mechanical parameters, a cohesive consensus regarding the comparative mechanical properties of the four human heart valves has not been established.

The objective of this study is to therefore characterize the planar biaxial material properties of the MV, AV, TV, and PV from the same aged human patients. Utilizing planar biaxial testing, the mechanical properties of the valve cusps were characterized for each of the four valves and their microstructural properties were examined through histological analysis. Constitutive modeling with the Fung-type elastic model was utilized to describe the biaxial mechanical response. Results were compared both by valve and by age in order to understand the comparative age-dependent changes in mechanical properties in the four heart valves as well.

2. Materials and methods

2.1. Sample procurement

Twelve human cadaver hearts were obtained from the National Disease Research Interchange (NDRI, Philadelphia, PA). The hearts were selected based on cause of death, wherein the patients were defined as having a cause of death unrelated to cardiovascular disease. Research on human cadaver tissues was approved by Biological Materials Safeguards Committee (BMSC) at Georgia Institute of Technology. The hearts were obtained fresh within a post-mortem recovery interval (15.32 ± 6.51 h). Upon arrival at the laboratory, all hearts were cryopreserved in a solution of 10% DMSO and 90% Roswell Park Memorial Institute (RPMI) 1640 medium and stored at −80 °C until testing. Samples and cryopreservation solution were thawed by submerging in 37 °C for approximately 2 h, followed by progressive 2.5% dilution of the DMSO using saline solution. All valve leaflets were explanted from the hearts. Previous studies have shown that the mechanical properties of vascular tissues are preserved when stored in cryoprotective agents at low temperatures (−80 °C) [14–18].

2.2. Patient characteristics

The study consisted of 12 hearts from individuals between 51 and 87 years of age (70.1 ± 3.7 years), a relatively aged patient population. The patient population consisted of 8 females and 4 males; 8 patients had a history of smoking, 3 suffered from diabetes, and 4 had previous cardiovascular diseases (Table 1). In addition, 5 patients were under and 7 were over the age of 65. It should be noted that the age of 65 has been identified as a cutoff age for analysis of many cardiac events and treatments, such as aortic sclerosis, which is present in about 25% of adults over age 65, and a bioprosthetic valve replacement is recommended for those over the age of 65 [19].

2.3. Sample preparation

A total of 114 leaflet samples were harvested from these twelve hearts, and tested (Table 2). Each leaflet was removed from the annulus and labeled according to valve type and location (Fig. 1).

Tissue samples were subjected to planar biaxial testing for the quantification of mechanical properties. While uniaxial testing data can elucidate individual material properties along each testing direction, biaxial tensile testing can analyze the coupling of the response in each direction, particularly important for the anisotropic nature of heart valve tissue. As physiological valvular loading conditions incorporate multiaxial loading, biaxial tensile testing can provide more accurate mechanical characterization than uniaxial testing [20] (see Fig. 2).

The details of testing sample preparation and planar biaxial tensile testing techniques can be found in Sacks and Sun [20]. Briefly, the chordae tendineae on the ventricularis side of the MV and TV leaflets were removed to maintain a smooth and planar surface for biaxial testing. The natural shape of each leaflet was preserved for testing (a). Four fish hooks were mounted at each of the four edges, forming a square testing area not less than $10 \times 10\ \text{mm}^2$ in size. Four graphite markers were attached to the leaflet surfaces, demarcating a $2 \times 2\ \text{mm}^2$ area at the center of each leaflet testing region for optical marker tracking—atrialis for MV and AV and ventricularis for AV and PV leaflets. The sample was then mounted in a 37 °C phosphate-buffered saline (PBS) testing solution bath in a trampoline fashion (a). The leaflet circumferential (CIRC) and radial (RAD) directions were aligned with the primary axes of the biaxial testing device. The sample thickness was measured prior to testing and averaged at five locations near at the center of the leaflet.

2.4. Biaxial tensile testing and analysis

A stress-controlled test protocol was utilized to characterize the leaflet tissues, wherein the ratio of the normal Lagrangian stress components, T_{11}: T_{22}, was maintained constant, and the shear components are free of load ($T_{12} = T_{21} = 0$) [21]. A load range of 40–80 g was applied to each sample without causing tears at the edges of the specimens. Forty continuous cycles of preconditioning with T_{11}:T_{22} = 1:1 were conducted. The reference markers were obtained after preconditioning at zero load for both axes and were used for strain calculations. A complete test consisted of seven successive protocols: T_{11}:T_{22} = 1:0.3, 1:0.5, 1:0.75, 1:1, 0.75:1, 0.5:1, and 0.3:1. This range was chosen for extensive coverage of the in-plane stress state [20].

The mechanical properties of valve leaflets were assessed and compared across groups by means of extensibility (EXT), tangent modulus (TM), and degree of anisotropy (DA). From the equibiaxial protocol, the TMs at two linear regions of the stress-strain curve—the low load pre-transitional and high load post-transitional regions— were calculated in order to provide a comparative measure of stiffness between the heart valves (b). The data points

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