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Leaflet Mechanical Properties of Carpentier-Edwards Perimount Magna Pericardial Aortic Bioprostheses:

Surgical Bioprosthetic Leaflet Biomechanics

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Abstract

Background and Aim of Study: Transcatheter aortic valve replacement (TAVR) has recently been shown to be equivalent to surgical aortic valve replacement (SAVR) in intermediate-risk patients. As TAVR expands to SAVR population, TAVR vs. SAVR durability becomes increasingly important. While TAVR durability is unknown, valve design, particularly leaflet stress, impacts durability. While leaflet stress cannot be measured directly, stress can be determined by finite element modeling. Such models require leaflet mechanical properties. Balloon-expandable TAVR is comprised of bovine pericardial leaflets treated in the same fashion as surgical bioprosthetic leaflets. Our aim was to determine leaflet mechanical properties of Carpentier-Edwards bioprostheses for future TAVR and SAVR computational models.

Materials and Methods: Leaflets (n=35) from twelve Carpentier-Edwards Model 3000TFX Perimount Magna aortic bioprostheses (21mm, 23mm, and 25mm) were excised and subjected to displacement-controlled equibiaxial stretch testing. Stress-strain data were fit to Fung constitutive model to describe material properties in circumferential and radial directions. Leaflet stiffness was calculated at specified physiological stress, corresponding to zero pressure, systemic pressure, and between zero and systemic pressure.

Results: Bioprostheses 21mm had significantly thinner leaflets than larger bioprostheses. Non-linear stress-strain relationship was observed in all leaflets along circumferential and radial directions. No significant difference in leaflet stiffness at systemic pressure or between zero and systemic pressure was found among the three bioprosthetic sizes. However, 23mm bioprosthetic leaflets were significantly more compliant than 21mm and 25mm leaflets at zero pressure in circumferential direction. No differences in leaflet stiffness in circumferential vs. radial directions were observed.

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Conclusions: Bovine pericardial leaflets in Carpentier-Edwards Perimount Magna bioprostheses showed no differences in material properties among different sizes at systemic pressure. The thinner 21mm leaflets did not lead to any corresponding differences in leaflet stiffness, suggesting that the thinner TAVR leaflets may have similar stiffness as their thicker SAVR counterparts.

Keywords

Aortic Valve; Surgical Bioprosthesis; Experimental

Introduction

Transcatheter aortic valve replacement (TAVR) has become a viable alternative to traditional surgical aortic valve replacement (SAVR) surgery in intermediate-risk patients(1). As TAVR expands into the traditionally SAVR population, understanding TAVR relative to SAVR durability becomes increasingly critical. Surgical bioprostheses have documented long-term durability of 20 years or greater in reported series(2–4). Transcatheter aortic valve (TAV) durability, however, is unknown; and the concept of waiting for years clinically to observe degeneration seems impractical. Since durability is impacted by valve design, primarily leaflet stress, determining leaflet stress can be used as a surrogate for relative durability. Unfortunately, leaflet stress cannot be measured directly, but requires finite element analyses of models with accurate geometry, leaflet thickness, and leaflet mechanical properties. The Edwards TAVs, SAPIEN, SAPIEN XT, and SAPIEN 3, (Edwards Lifesciences, Inc, Irvine, CA) were developed using bovine pericardium with the same proprietary fixation and anti-calcification treatment processes as their surgical bioprostheses, Carpentier-Edwards Perimount Magna aortic bioprostheses. The primary difference between Edwards TAVs and their surgical valve leaflets is leaflet thickness, since TAVs must have thinner leaflets to allow crimping of TAV into small delivery catheters. Prior studies investigating bovine pericardium for bioprosthetic leaflet mechanical properties have mainly utilized nonindustrial bovine pericardium that investigators cut and treated with glutaraldehyde(5–8), or industrial glutaraldehyde-fixed bovine pericardial sheets not selected to be of the same quality as those used for leaflets(9). Edwards bioprostheses have highly stringent and specific requirements for their bovine pericardium used for valve leaflets, with special proprietary fixation and the latest anti-calcification treatment process, which is utilized in both their surgical and transcatheter valves. In order to appropriately understand leaflet stresses in current generation surgical and transcatheter bioprostheses, our aim was to investigate leaflet mechanical properties from Carpentier-Edwards Perimount Magna pericardial aortic bioprostheses. Additionally, we sought to determine the effect of bioprosthetic size on leaflet properties. Description of these material properties allows accurate future computational modeling of SAVR and TAVR.

Materials and methods

Three sizes, 21mm, 23mm, and 25mm, of Carpentier-Edwards Model 3000TFX Perimount Magna aortic bioprostheses (Edwards LifeSciences, Irvine, CA) were obtained (n=12). There were four bioprostheses for each size and three leaflets of each bioprosthesis were tested. Specimens of 1cm × 1cm were excised from the central region of valve leaflets, and

care was taken to align specimen edges in the circumferential and axial directions. Sample thicknesses were measured using Mitutoyo Digital waterproof caliper (Model 500-754-10) by lightly sandwiching the tissue between two glass slides. Excised samples were stored in phosphate buffered saline solution without calcium and magnesium.

Planar biaxial testing system

A custom-built planar biaxial stretching system was used to determine mechanical properties of these bovine pericardial valve leaflets (Figure 1). Details of the biaxial tensile testing methods and analyses have been previously described(10). Briefly, three 5–0 silk sutures were anchored to each specimen edge using small, barbless fishhooks. These sutures were attached to four linear arms of the stretcher, aligning circumferential and radial edges with direction of deformation. Five black polymer markers (MO-SCI Corp., Rolla, MO, 250–355 μm) were placed on tissue surface, creating a square grid in specimen center. Tissue was then floated in a phosphate-buffered saline bath at room temperature. Load cells (Model 31/3672–02, Honeywell Sensotec Inc., Columbus, OH, 1000 gm; ±0.1%), located on two orthogonal arms were zeroed and monitored while mounting the sample to ensure that a measurement of zero force corresponded to length of the resting tissue. During extension, data from load cells was amplified and used to determine force on the sample during deformation. Real-time displacement of marker beads on tissue surface were obtained using noncontacting CCD camera placed over tissue surface (30 fps, Model TM 9701, Pulnix Inc., Sunnyvale, CA, USA; 0.1pixels/mm). Images of tissue surface during deformation were digitized in MATLAB (The Mathworks, v. 7.0, Natick, MA), and markers were located based on their contrast to surrounding tissue surface. Coordinates of each marker were tracked through the loading cycle, and their relative movement was used to calculate Green strains in the circumferential and radial directions. Samples were tested over a large strain range using equibiaxial displacement controlled protocols. First, 10 preconditioning cycles of 10% stretch, using a triangular waveform at 0.5 Hz, were applied. Subsequently, a quasistatic stretch cycle of up to 70% peak strain was applied. This was repeated for each specimen.

Fung Constitutive Model

Bioprosthetic leaflet made from bovine pericardial tissue, presents typical nonlinear material properties such as nonlinearity and hyperelasticity. The relationship between leaflet strain and corresponding leaflet stress under physiologic pressure are two parameters used to describe leaflet mechanical properties. Two dimensional Fung strain energy function has been widely used to simulate mechanical behavior of heart valve tissues(11) which defines strain energy function W as

$$W = \frac{c}{2}\left(e^{Q} - 1\right)$$
$$Q = c_{11}E_{11}^2 + 2c_{12}E_{11}E_{22} + c_{22}E_{22}^2 \quad (1)$$

where c and c_{ij} are coefficients to Fung model and E_{ij} are Cauchy stress. In biaxial tensile testing, Cauchy stress is a function of the first derivative of W to E, which is defined as

$$\sigma = \mathrm{J}^{-1}\mathrm{F}\frac{\partial W}{\partial E}\mathrm{F}^{-1} \quad (2)$$

where F is deformation gradient with $\mathrm{F}^{\mathrm{T}}\mathrm{F}=1$ and J is 1 for imcompressible materials. Cauchy stress-Green strain relationship is then expressed by

$$\begin{aligned}\sigma_{11} &= \lambda_1^2 ce^{Q}(c_{11}E_{11} + c_{12}E_{22}) \\ \sigma_{22} &= \lambda_2^2 ce^{Q}(c_{12}E_{11} + c_{22}E_{22})\end{aligned} \quad (3)$$

Data and statistical analysis

Experimental data from biaxial mechanical stretch testing was fitted to two-dimensional Fung strain energy function and Cauchy stress and Green strain were derived from Equation 3. Stiffness, or Young's modulus, is defined as the slope of the stress-strain curve at a particular physiologic stress. In this study, we examined bioprosthetic leaflet stiffness at 3 regions along the stress-strain curve, at zero pressure, at systolic pressure, and within the pressure range between zero and systolic pressure. Stiffness between zero and systolic pressure was defined as the average of the first derivative of stress-strain curve corresponding to the pressure range between zero and end-systolic pressure. Functionally, we examined stiffness in the low-stress, high stress regions of the stress-strain curve as well as averaged between those regions in the non-linear aspect of the curve. Left ventricular (LV) pressure increases to 17.5kPa and drops to 0kPa over one cardiac cycle, while aortic pressure increases to 15.5kPa from minimum 10kPa over a cardiac cycle. Pressure difference between the aorta and LV represents the pressure applied on the leaflets. Magnitude of pressure exerted on the leaflets is −15kPa (inward closing the leaflets) to 2kPa (outwards opening the leaflets). Given the dimension and thickness of the bioprosthetic leaflets, leaflet stress can be estimated based on Laplace equation ranging from 0kPa to 807.69kPa. Stiffness at zero, systolic pressure, and between zero and systolic pressure were measured at 0kPa, 807.69kPa, and between 0 and 807.69kPa, respectively. When tissue specimens were not stretched to the desired stress level, tissue stiffness was obtained from extrapolated curves based on the Fung strain energy function fitted to the raw data. For statistical analysis, normal distribution of tissue stiffness at physiological stress was first verified for all regions using the Kolmogorov–Smirnov test. Consequently, paired t-tests were utilized to compare stiffness of different sample directions. Paired t-tests were also used to compare stiffness between size groups. Reported values are quoted as mean ± standard deviation (S.D.) and $p< 0.05$ was considered statistically significant.

Results

Square samples were cut from the center of each leaflet. Average thickness and dimension of the samples from Carpentier-Edwards Magna pericardial aortic bioprostheses are listed in Table 1. Leaflet of 21mm bioprothesis was significantly thinner compared to 23mm leaflets ($p=0.0312$). Similarly, there were significant differences in thickness between 21mm and 25mm bioprosthesis ($p=0.0002$). In contrast, leaflet thickness from 23mm bioprosthesis was not significantly thinner than that of 25mm bioprosthesis ($p=0.0901$).

Raw experimental data from biaxial tensile testing of 35 leaflet samples are shown as Cauchy stress versus Green strain curves along circumferential and radial directions (Figure 2). Leaflets exhibited nonlinear hyperelastic behavior in both directions. After fitting the experimental data to Fung constitutive model, stress-strain curves were developed using the average and median coefficients (Figure 3) according to each bioprosthetic size. Average and standard deviation of coefficients for the Fung model are listed (Table 2).

Stiffness obtained between pressure range of 0kPa (*ex vivo* 0mmHg pressure) to 807.7kPa (systolic pressure *in vivo*) is shown in Figure 4. Stiffness at 0mmHg and 120mmHg is also shown (Figure 4). Within each bioprosthetic size, there were no significant differences in stiffness between the circumferential vs radial directions: 9.30±6.93MPa circumferential and 9.00±4.67MPa radial (p=0.37) in 21mm bioprosthesis; 7.40±2.21MPa circumferential and 7.86±1.77MPa radial (p=0.09) in 23mm bioprosthesis; and 9.63±3.81MPa circumferential and 9.87±4.26MPa (p=0.26) in 25mm bioprosthesis. Between different bioprosthetic sizes, there were no significant differences in leaflet stiffness between 0mmHg and systolic pressure in either circumferential or longitudinal directions between 21mm vs. 23mm bioprosthetic leaflets (circumferential, p=0.17 and radial, p=0.20); between 21mm vs 25mm leaflets (circumferential, p=0.48 and radial, p=0.41); and between 23mm vs 25mm leaflets (circumferential, p=0.10 and radial, p=0.16).

Similarly, at systolic pressure *in vivo*, within each bioprosthetic size, there were no significant differences in leaflet stiffness between circumferential and longitudinal directions, 43.73±18.93MPa circumferential and 44.02±21.48MPa radial, p=0.42 in 21mm bioprosthesis, 51.43±15.47MPa circumferential and 49.99±18.18MPa radial, p=0.21in 23mm bioprosthesis, and 53.00±25.19MPa circumferential and 52.59±23.47MPa radial, p=0.36 in 25mm bioproshesis. Also, between different bioprosthetic sizes, there were no significant differences in leaflet stiffness at systolic pressure in either circumferential or radial directions between 21mm and 23mm bioprostheses (circumferential, p=0.20 and radial, p=0.30); between 21 and 25mm bioprostheses (circumferential, p=0.275 and radial, p=0.29); and between 23mm and 25mm bioprostheses (circumferential, p=0.42 and radial, p=0.37).

Finally, at zero pressure, corresponding to *ex vivo* condition, within each size, there were again no significant differences in leaflet stiffness between the circumferential and radial directions, in the 21mm bioprosthesis (circumferential, 1.81±2.28MPa and radial, 1.32±1.21MPa, p=0.16); in the 23mm bioprosthesis (circumferential, 0.34±0.22MPa and radial 0.51±0.34MPa, p=0.09); and in the 25mm bioprosthesis (circumferential, 1.41±1.83MPa and 1.46±1.52MPa, p=0.42). On the other hand, *ex vivo* leaflet stiffness was significantly less in the 23mm than the 21mm bioprosthesis in both the circumferential (p=0.035) and radial (p=0.046) directions. *Ex vivo* leaflet stiffness of 23mm bioprosthesis was also significantly less than that of 25mm bioprosthesis in the circumferential (p=0.047) but not the radial direction (p=0.069). In contrast, our results showed no differences in *ex vivo* leaflet stiffness between 21 mm and 25 mm bioprostheses in circumferential (p=0.32) and radial (p=0.38) directions.

Discussion

Surgical bioprostheses have demonstrated excellent long-term durability for >20 years(2, 3, 12). Recently, *in vitro* accelerated wear-testing of the Carpentier-Edwards Magna Ease pericardial valve suggests a long-term durability of 25 years(13). However, durability of transcatheter aortic valves (TAVs), such as the Sapien, Sapien XT, or Sapien 3, is unknown. TAV durability has only been tested *in vitro* for 5 years of durability and assessed for up to 6 years clinically in patients >80 years old(14). The Sapien series of TAVs uses the same chemically processed, but thinner bovine pericardium as the Carpentier-Edwards Magna bioprostheses. Since durability is related to leaflet stress and thus leaflet mechanical properties, in this study, we determined leaflet mechanical properties of Carpentier-Edwards Magna pericardial bioprosthesis by biaxial stretching for better understanding of both surgical and TAV leaflets. Stiffness at *ex vivo* zero pressure, *in vivo* systolic pressure, and in the range between the two, was quantified and compared across different bioprosthetic sizes. Bioprosthetic bovine pericardial leaflets all demonstrated nonlinear hyperelastic behavior along the circumferential and radial directions, consistent with prior studies of bovine pericardium(5–9). No consistent differences in stiffness (Young's modulus) were found among leaflets from different sizes except at zero pressure. Furthermore, there was no significant difference in stiffness at systemic pressure or between zero and systemic pressure among different bioprosthetic sizes in either circumferential or radial directions. At zero pressure, however, 23mm bioprosthetic leaflets were more compliant than 21 mm or 25mm bioprosthetic leaflets in the circumferential direction.

Anisotropy

Our results indicated that leaflet stiffness was not significantly different between the circumferential and radial directions at *ex vivo* zero pressure or *in vivo,* up to and including at systemic pressure; in other words, bioprosthetic leaflets were isotropic. Interestingly, bovine pericardium itself can be anisotropic, where tissue stiffness shows directional dependence in the circumferential vs longitudinal directions(6, 7). In Sacks' studies, samples of maximum uniformity were stretched along the preferred collagen fiber and cross-fiber directions. They evaluated anisotropy using peak stress and maximum tangent modulus along and across the collagen fiber direction at maximal equibiaxial strain state. Our findings showed no directional dependence in leaflet stiffness at zero or even systolic pressure when leaflets were stretched in the circumferential and radial directions based on orientation within the bioprosthesis itself. Notably, this suggests that the manufacturers do not take into account collagen fiber orientation when choosing or creating their leaflets.

Gluteraldehyde fixation process of bovine pericardium to create leaflets, results in inter-fiber collagen crosslinks, which has been shown to increase flexural stiffness(6). Collagen fiber orientation has been demonstrated to impact flexural properties of pericardial leaflet and its cyclic fatigue response(8). Interestingly, even though collagen fiber orientation might be optimized to improve bioprosthetic durability, orientation has not been taken into account in the manufacturing of bioprosthetic valves, and yet, current durability of surgical bioprostheses is very long-term. If TAVs prove in the future to be less durable, perhaps such optimization of collagen fiber orientation may be required of TAV leaflets.

Anisotropy has also been seen in other studies of mechanical properties of porcine aortic valves, with directional dependence seen in both natural and glutaraldehyde-treated porcine aortic valve leaflets(15, 16). These data demonstrate that bioprostheses which utilize porcine leaflets, glutaraldehyde fixed for implantation in humans, will have valves that maintain the normal anisotropic material properties of aortic valve leaflets. On the other hand, bioprostheses utilizing bovine pericardium would not, unless directional dependence is tested and that orientation maintained during creation of bovine pericardial valves.

Our results showing lack of directional difference in leaflet stiffness is further supported by others who stretched bovine pericardium randomly without collagen fiber orientation and those isotropic material models have been used in computational valve simulations(9). In one study of Edwards bovine pericardial valves, two valves were used for computational simulations(17). Six leaflets underwent biaxial stretch testing and showed variability in leaflet properties when stretched based on leaflet orientation within the valve. Unfortunately, bioprosthetic model and sizes were not reported. Such variability in mechanical properties has been noted by others as well(7, 18). Even when individual leaflets may demonstrate anisotropy, overall, our results also demonstrate significant variability in leaflet material properties such that the average does not reflect directional differences. Because of the variability in material properties of bioprosthetic leaflets, we reported both median and averaged material properties, where the median reflected material properties that the majority of valves clustered around, while the average, based upon averaging the coefficients, took into account outliers on both ends of the spectrum.

Comparison with Porcine and Human Aortic Bioprostheses

Mechanical properties have been studied of St Jude Epic bioprostheses, which consist of fixed porcine aortic valve leaflets rather than pericardium(19). Compared to our results, greater stiffness (Young's modulus) was reported circumferentially for Epic (101.99±58.24MPa) at 1.0MPa stress level vs. ours for Magna (50.16±20.88 MPa) at peak physiologic stress (807.7kPa). In the radial direction, Epic had stiffness of 9.18±1.81MPa at 0.1MPa. We examined Magna stiffness at 0kPa (1.05±1.23 MPa) and between 0–807.7kPa (8.92±4.00 Mpa), but not specifically at 0.1MPa, so the results were not directly comparable in radial direction.

In contrast, normal human aortic valves are compliant and have lower Young's modulus than that of bovine pericardial bioprostheses in our study *in vivo* at 807.69kPa in both circumferential (15.34±3.84MPa vs. 50.16±20.88MPa, respectively) and radial (1.98±0.15MPa vs. 49.78±21.66MPa, respectively) directions(20). Such greater stiffness in bovine pericardial bioprostheses is not unexpected and has been documented previously, particularly since glutaraldehyde fixation results in collagen cross-linking(21).

Degeneration

Bioprosthetic degeneration results from calcification, tissue degeneration, or a combination of the two. Non-calcified leaflet degeneration has been documented as a result of microstructural deterioration and consequent mechanical property changes(22, 23). In addition, stress concentration and increased deformation are believed to trigger calcification

process(24, 25). Edwards TAVs, using similar bovine leaflets as surgical bioprostheses, are expected to degenerate by similar mechanisms. TAV durability, from perspective of leaflet degeneration, would be strongly correlated with leaflet mechanical property and stress and strain concentrations on the leaflet. For properly functioning leaflets, stiffness should be high enough during diastole to prevent aortic regurgitation yet low enough during onset of systole to avoid aortic stenosis. Surgical bioprosthetic leaflets have met those challenges with durability >20 years(2, 13).

Leaflet thickness was significantly different among different bioprosthetic sizes, yet there were no significant differences in stiffness at systemic pressure. TAV leaflets are manufactured to be thinner than surgical bioprosthetic leaflets (~0.2mm vs 0.43±0.06mm, respectively) which raised concern that TAVR leaflets would be less stiff and possibly less durable than surgical ones. We showed minimal difference in leaflet stiffness when thickness was reduced from 0.47±0.06mm to 0.39±0.04mm suggesting TAV leaflet material properties may inherently be comparable to those of surgical bioprostheses. However, drastic reduction in thickness to 0.2mm may still result in material property differences as suggested by others(5). Our results are nonetheless a good starting point for assessing durability of TAV and surgical valves using simulations to determine leaflet stress, where leaflet geometry, thickness, and material properties are all required. For TAVs, additional considerations required are leaflet crimping, degree of stent expansion and deployment geometry. Our coefficients describing leaflet material properties will allow future simulations of Edwards' surgical bioprostheses and TAVs.

Conclusions

We reported mechanical properties of bovine leaflets across different sizes of Carpentier-Edwards Perimount Magna pericardial aortic bioprostheses using biaxial tensile testing. Bovine leaflets demonstrated nonlinear hyperelastic behavior along circumferential and radial directions. Our results indicated that stiffness showed no directional dependency along circumferential and radial directions as oriented within the bioprostheses. No significant differences in stiffness at systemic pressure or between zero and systemic pressure were found among different sizes in either circumferential or radial directions. However, 23mm bioprosthetic leaflets were more compliant than 21mm or 25mm leaflets at systole in the circumferential direction.

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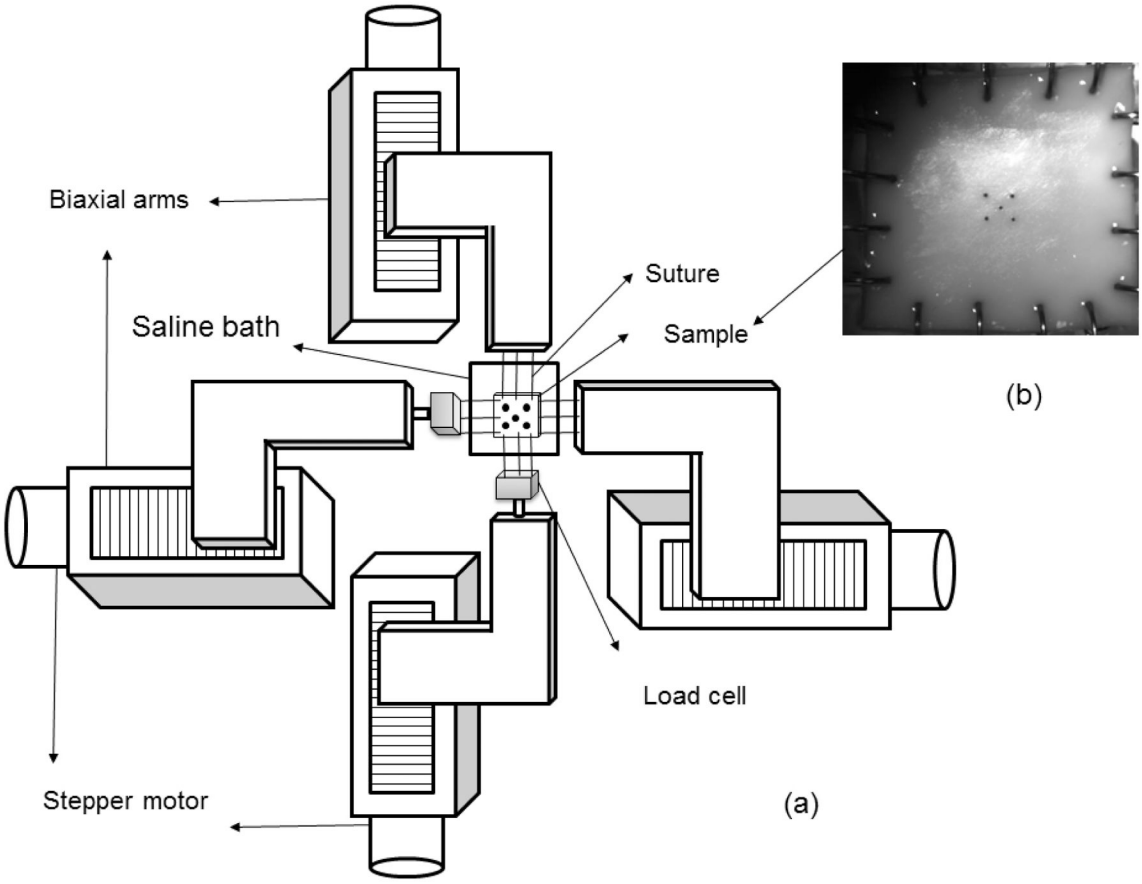

Figure 1.
Experimental setup for biaxial tensile testing and markers on the specimen.

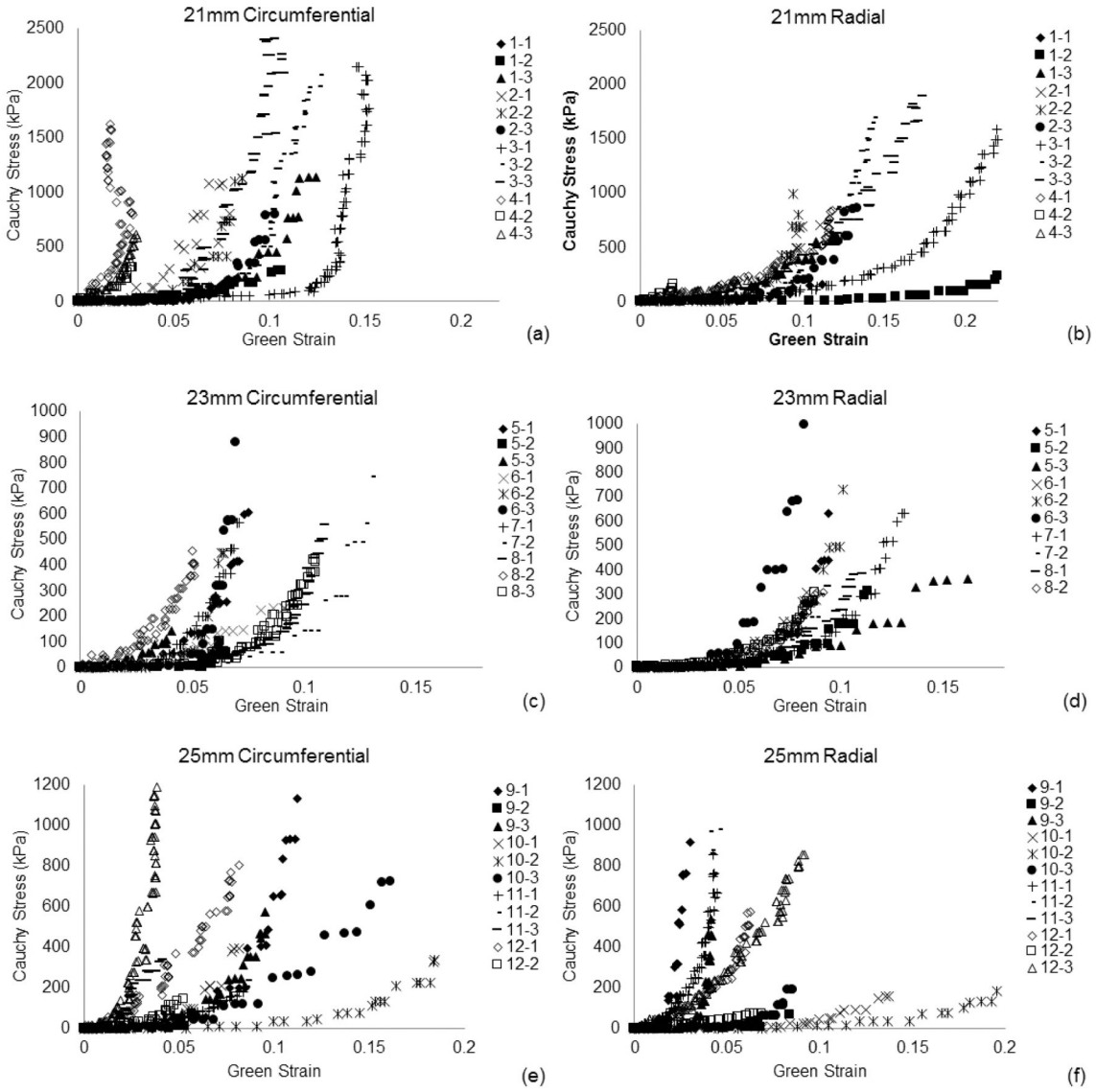

Figure 2.

Raw stress-strain data of all aortic bioprosthesis samples according to their size along the circumferential(A, C, E) and radial (B, D, F) directions.

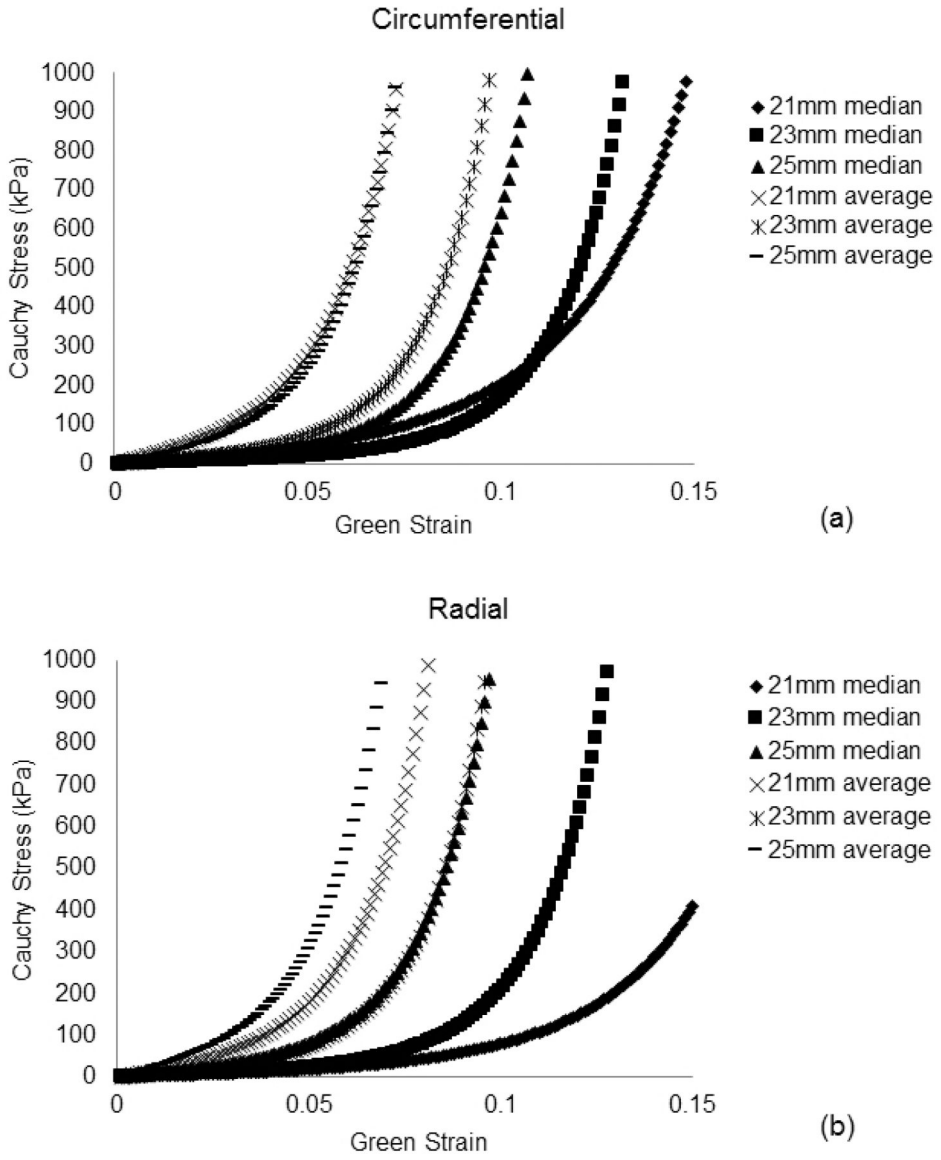

Figure 3.

Average and median stress-strain curves from Fung coefficients for bioprosthetic leaflets according to their size.

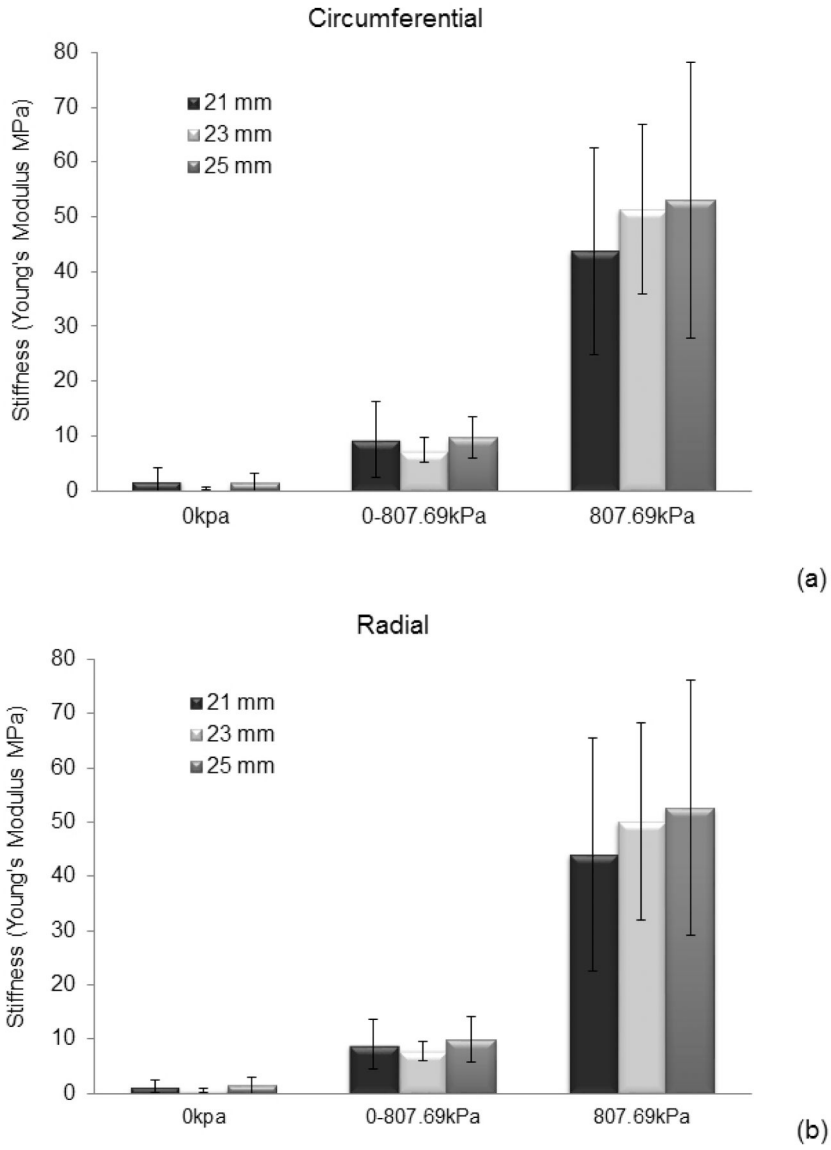

Figure 4.

Young's modulus at zero pressure *ex vivo*, between zero and systemic pressure, and at systemic pressure *in vivo* along circumferential (A) and longitudinal (B) directions, averaged within each size of prosthesis.

Table 1.

Thickness and dimension of aortic bioprostheses samples.

Bioprothesis Size	Thickness (mm)	Dimension (mm)
21 (mm)	0.39±0.04	9.60±0.67
23 (mm)	0.43±0.04	9.58±0.69
25 (mm)	0.47±0.06	9.95±0.33

Table 2.

Coefficients of Fung constitutive model.

Coefficients	21mm	23mm	25mm
c11	122.05±168.30	66.61±74.94	71.90±53.60
c12	54.04±85.30	67.06±63.43	77.38±112.33
c22	58.98±43.76	70.32±65.28	111.43±84.79
C	13.91±14.06	4.95±4.67	12.72±16.50