Mechanics of the pulmonary valve in the aortic position

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Abstract

Mathematical models can provide valuable information to assess and evaluate the mechanical behavior and remodeling of native tissue. A relevant example when studying collagen remodeling is the Ross procedure because it involves placing the pulmonary autograft in the more demanding aortic valve mechanical environment. The objective of this study was therefore to assess and evaluate the mechanical differences between the aortic valve and pulmonary valve and the remodeling that may occur in the pulmonary valve when placed in the aortic position. The results from biaxial tensile tests of pairs of human aortic and pulmonary valves were compared and used to determine the parameters of a structurally based constitutive model. Finite element analyzes were then performed to simulate the mechanical response of both valves to the aortic diastolic load. Additionally, remodeling laws were applied to assess the remodeling of the pulmonary valve leaflet to the new environment. The pulmonary valve showed to be more extensible and less anisotropic than the aortic valve. When exposed to aortic pressure, the pulmonary leaflet appeared to remodel by increasing its thickness and reorganizing its collagen fibers, rotating them toward the circumferential direction.

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1. Introduction

The mechanical function of cardiovascular tissue is mainly determined by the extracellular matrix (ECM) composition and structure. The matrix defines the response of the tissue to mechanical load and can also remodel in response to changes in its environment. Thus, an improved understanding of the adaptation capabilities of cardiac valve ECM is essential for understanding both valve pathology and physiology and for designing materials for valve repair or replacement. Yet, the events and mechanisms by which the matrix remodels and adapts are largely unknown since the collagen architecture and the local mechanical loading condition within the tissue are highly coupled. Mathematical models can give insight in this interaction and in predicting the tissue’s response and adaptation.

One particular case of a tissue undergoing a strong change in mechanical environment is the so called Ross procedure. The operation consists of replacing the aortic valve (AV) by the pulmonary autograft and the use of a homograft valve instead

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of the pulmonary valve (PV) (Ross, 1967). This procedure is particularly attractive for children, athletes and women of childbearing age because it eliminates the need for anticoagulation therapy and has the potential for somatic growth.

Usage of a pulmonary autograft has several advantages, in particular its ability to grow and its improved hemodynamics and durability (Elkins et al., 1994; Chambers et al., 1997; Santini et al., 1997). There are, however, potential disadvantages. In adults, the AV and PV are known to differ in morphology and structure, (Stradins et al., 2004; Vesely et al., 2000; Azadani et al., 2012; Hokken et al., 1997) and after pulmonary autograft replacement of the AV, the autograft is subjected to higher pressures. This mechanically more demanding environment may cause remodeling of the autograft. The valve explants show thickened leaflets and severe aneurysmal degeneration of the wall, which was characterized by intimal thickening, medial elastin fragmentation, and adventitial fibrosis (Schoof et al., 2006; Mookhoek et al., 2010). Concern exists, that these structural and functional changes in the implanted autograft lead to progressive aortic root dilatation and neoaortic regurgitation.

Another limitation of the technique is the lack of long term results (Phillips, 2003; Kouchoukos, 2011). Some midterm studies however, reported freedom from autograft reoperation between 93% and 98.6% at 10 years (Rabkin-Aikawa et al., 2004; Favalaro et al., 2008; Elkins et al., 2008; Takkenberg et al., 2009). This range of values may be dependent on the technique employed, the surgeon and the patient group selected. Therefore uncertainty remains regarding the suitability of the autograft to potentially become a viable permanent replacement.

The objective of this study was therefore to assess and evaluate the mechanical differences between the AV and PV leaflets and the remodeling that may occur in the PV leaflets when placed in the aortic position. The mechanical properties of sets of PVs and AVs leaflets from the same donor were assessed and evaluated. Next, a structurally based model for the aortic valve was applied to describe the mechanical behavior of the leaflets and severe aneurysmal degeneration of the wall, which was characterized by intimal thickening, medial elastin fragmentation, and adventitial fibrosis (Schoof et al., 2006; Mookhoek et al., 2010). Concern exists, that these structural and functional changes in the implanted autograft lead to progressive aortic root dilatation and neoaortic regurgitation.

The objective of this study was therefore to assess and evaluate the mechanical differences between the AV and PV leaflets and the remodeling that may occur in the PV leaflets when placed in the aortic position. The mechanical properties of sets of PVs and AVs leaflets from the same donor were assessed and evaluated. Next, a structurally based model for collagenous cardiovascular tissues (Driessen et al., 2005) was applied to describe the mechanical behavior of the leaflets. Finite element analyzes (FEA) were performed to simulate the mechanical response of both leaflets to a transvalvular aortic pressure load. Last, the previous model extended with remodeling equations for the collagen angular fiber distribution (Driessen et al., 2008) was applied to study the remodeling of the PV leaflets when subjected to the aortic valve diastolic load.

2. Materials and methods

2.1. Tissue preparation

Five sets of human aortic and pulmonary heart valves from patients 11 to 51 years (mean 31.8±16.1 years) of age were obtained from Dutch postmortem donors, giving permission for research. The valves, which were assessed to be unif for implantation, were obtained from the Heart Valve Bank (Erasmus University Medical Center, Rotterdam, The Netherlands). All valves were structurally and mechanically unaffected. Previous studies suggest that the study of tissue (mechanical) properties can be done in cryopreserved heart valves since the structural integrity of collagen and elastin (Gerson et al., 2009) and mechanical properties (Virues Delgadillo et al., 2010) are not affected by the applied cryopreservation protocol. Furthermore, valvular disease or conditions known to precede valvular disease were not related to the cause of dead of the donors.

The cryopreserved valves were stored at −80°C. Prior to the ECM analysis and mechanical testing, the valves were thawed according to the guidelines of the Dutch Heart Valve Bank. Briefly, the package containing the cryopreserved homograft was gently agitated in warm saline (±40°C) to dissolve ice-crystals and soften the graft. After thawing, the package containing the valve was opened and deposited in phosphate buffered saline (PBS; Sigma-Aldrich, St. Louis, USA) to allow dimethyl sulfoxide (DMSO) to dilute from the tissue into the solution. Immediately after thawing, the cusps were carefully excised from the intact heart valves, using a scalpel. The specimens were cut in a square shape, using parallel razor blades (n=21 for the AV leaflets and n=26 for the PV leaflets, with n being the sample size). Each specimen had a dimension of 6 × 6 mm and its edges were aligned with the circumferential and radial axes. Mechanical testing was performed within 48 h after thawing. The leaflet specimen thickness distribution was obtained using a SensoFar Plu 2300 optical imaging profiler (SensoFAR-Tech, Barcelona, Spain) and the average thickness of each sample was measured.

2.2. Experimental protocol

The specimens were placed in aluminium foil and kept hydrated. The specimens were then mounted in a Bio-Tester 5000 test device (CellScale, Canada) using a BioRakes mounting system with pins with 0.7 mm tine space. These BioRakes had neglecting values of force due to pin deflection for stretches lower than 200%. To produce visual surface texture, the tissue was sprinkled with graphite particles. The samples were then tested while submersed in phosphate buffered saline (PBS) to mimic natural conditions.

The samples were biaxially tested to peak values ε_{CC} and ε_{RR}, where subscripts C and R correspond to the circumferential and radial directions, respectively. The complete biaxial testing regime consisted of 6 groups of 5 protocols. The first group of protocols of strain ratios was defined as ε_{CC} : ε_{RR} = 0 : 60, 11.5 : 55, 23 : 23, 24 : 11.5, 25 : 0(%). The strains were then sequentially increased during the next 5 group of protocols in steps of 5% or 10% until the last group ε_{CC} : ε_{RR} = 0 : 110, 49 : 105, 78 : 78, 79 : 49, 80 : 0(%) was performed. Preliminary studies showed that this particular biaxial stretch ratio could capture the nonlinear mechanical behavior of the heart valve leaflets without damaging the tissue and taking into account inter patient variability. The samples were left to recover for 1 min between protocols. Due to their viscoelastic properties (Lee et al., 1984), the specimens were preconditioned, before each group of protocols, for 10 contiguous cycles first to the maximum ε_{CC} and then to the maximum ε_{RR} of the group. The strain rate in the radial and circumferential direction was defined as l_0/min, with l_0 being the sample edge length. As the specimens were stretched, images were captured using a 1280 × 960 pixel charge-coupled device (CCD) camera at a sampling frequency of 5 Hz. The group of protocols that more closely achieved the valve working tension...
was chosen for analysis. This was estimated to be approximately 60 N/m for AV leaflets and 30 N/m for the PV (Mayne et al., 1989; Billiar and Sacks, 2000).

The software provided with the BioTester (CellScale, Canada) was used to define a grid of 25 points on the interior portion of the specimen to track point motion. With the configuration of the grid in both undeformed and deformed situations, the 2D deformation tensor \( \mathbf{F} \) was determined for each grid point, using a second-order method to compute strains from the discrete set of displacements (Geers et al., 1996). The undeformed situation was defined as the first image of the protocol.

### 2.3. Constitutive equations

The native heart valve was modeled as an incompressible fiber-reinforced tissue (Lanir, 1983; Holzapfel et al., 2000). The total Cauchy stress \( \sigma \) consists of the hydrostatic pressure \( p \) and the extra stress \( \tau \):

\[
\sigma = -p \mathbf{I} + \tau.
\]

The extra stress was split into an isotropic matrix contribution and an anisotropic fiber contribution (van Oijen, 2003):

\[
\tau = \hat{\mathbf{t}} + \sum_{i=1}^{N} \phi_i (\psi_i - \mathbf{e}_i \cdot \mathbf{e}_i) \mathbf{e}_i \cdot \mathbf{e}_i,
\]

with \( \hat{\mathbf{t}} \) the isotropic matrix stress, \( \phi_i \) the fiber volume fraction, \( \psi_i \) the fiber stress, \( \mathbf{e}_i \) the current fiber direction and \( N \) the number of fiber directions.

The isotropic matrix stress was modeled as a Neo-Hookean material with a shear modulus \( C \). For the fibers, the following constitutive equation was used (Holzapfel et al., 2000):

\[
\psi_i = k_1 \lambda_i^2 [e^{k_2 (\lambda_i - 1)} - 1],
\]

where \( k_1 [N/mm^2] \) and \( k_2 [-] \) are material constants. The current fiber direction \( \mathbf{e}_i \) can be calculated from the fiber direction in the undeformed configuration \( \mathbf{e}_{i0} \) with the relation:

\[
\lambda_i \mathbf{e}_i = \mathbf{F} \cdot \mathbf{e}_{i0}
\]

with \( \lambda_i \) the fiber stretch \( \lambda_i = \sqrt{\mathbf{e}_{i0} \cdot \mathbf{C} \cdot \mathbf{e}_{i0}} \) and \( \mathbf{C} = \mathbf{F}^T \cdot \mathbf{F} \) the right Cauchy-Green deformation tensor.

The angular fiber distribution was incorporated into the constitutive model by specifying an appropriate set of fiber directions \( \mathbf{e}_{i0} \) and fiber contents \( \phi_i \). For that purpose, the fiber directions were defined as:

\[
\mathbf{e}_{i0}(\gamma_i) = \cos (\gamma_i) \mathbf{v}_1 + \sin (\gamma_i) \mathbf{v}_2
\]

where \( \gamma_i \) was defined with respect to \( \mathbf{v}_1 \) in the plane spanned by \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \) (Fig. 1). The vectors \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \) are defined in Section 2.7.

For the fiber volume fraction a periodic version of the normal probability distribution function was used (Gasser et al., 2006):

\[
\phi_i = A \exp \left( \frac{\cos [2(\gamma_i - \alpha)] + 1}{\beta} \right)
\]

with \( \alpha \) the main fiber angle and \( \beta \) the dispersity of the fiber distribution function. The scaling factor \( A \) was obtained by defining the total fiber content to be equal to \( \Phi_{tot} \):

\[
A = \frac{\phi_{tot}}{\sum_{i=1}^{N} \exp \left[ \frac{\cos [2(\gamma_i - \vert \alpha \vert)] + 1}{\beta} \right]}
\]

### 2.4. Collagen fiber remodeling

To model the fiber distribution, it was assumed that the preferred main fiber direction \( \alpha_p \) is situated in between \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \). Thus, stimulus functions \( g_1 \) and \( g_2 \) were introduced in the direction of \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \) (Driessen et al., 2008), and the value of \( \alpha_p \) was then defined as:

\[
\alpha_p = \arctan(g_2/g_1).
\]

Two preferred main fiber orientations, situated at \( \gamma = \pm \alpha_p \), were used to preserve material symmetry. The preferred value of fiber dispersity was given by

\[
\beta_p = \begin{cases} 
    k \cdot \frac{1}{|g_1/g_2| - 1} & \text{if } g_1 \geq g_2 \\
    k \cdot \frac{1}{|g_2/g_1| - 1} & \text{if } g_1 < g_2 
\end{cases}
\]

with \( k \) a scaling factor.

Eqs. (8) and (9) imply that for \( g_1 \leq g_2 \) or \( g_2 \leq g_1 \), a uniaxial fiber distribution (i.e. \( \beta_p \rightarrow 0 \)) is obtained with the preferred fiber distribution closer to \( \mathbf{v}_1 \) (i.e. \( \alpha_p = 0 \)) or \( \mathbf{v}_2 \) (i.e. \( \alpha_p = 90^\circ \)), respectively. Finally when \( g_2 \geq g_1 \) a uniform or isotropic fiber distribution (i.e. \( \beta_p \rightarrow \infty \)) with the preferred fiber direction \( \alpha_p = 45^\circ \) is predicted (Fig. 2). The uniform and uniaxial fiber distribution refers to a distribution with a maximum and minimum dispersity value, respectively (still to be specified).

The evolution of the main fiber direction and dispersity of the fiber distribution function were modeled by a first order rate equation:

\[
\frac{d\alpha}{dt} = \frac{1}{\tau_a} (\alpha_p - \alpha)
\]

\[
\frac{d\beta}{dt} = \frac{1}{\tau_b} (\beta_p - \beta)
\]
in the collagen orientation in each time step that led to numerical stable solutions.

2.5. Stimulus function

For the stimulus functions \( g_i(i=1,2) \) a strain-based and a stress-based approach were adopted (Driessen et al., 2008). For the strain-based remodeling algorithm the stimulus functions were related to the stretch \( \lambda_i \) in the direction of \( v_i \):

\[
g_i = \begin{cases} \chi \lambda_i & \text{if } \lambda_i \geq 1 \\ 0 & \text{if } \lambda_i < 1 \end{cases}
\] (11)

where \( \chi \) is the power of alignment. For the stress-based approach the stimulus functions were set equal to the extra stresses \( \tau_i \) in the direction of \( v_i \):

\[
g_i = \begin{cases} \chi \tau_i & \text{if } \tau_i \geq 0 \\ 0 & \text{if } \tau_i < 0 \end{cases}
\] (12)

with \( \chi \) the power of alignment. The maximum and minimum values of the preferred dispersity were set to 1000 and 0.1, to prevent numerical problems with the expression of \( \beta_p \) in Eq. (10).

Eqs. (8), (9), (11) and (12) result in an alignment of all fibers with the major loading direction (\( \eta_p = 0, \beta_p = 0 \)) in case of uniaxial loading conditions (\( g_1 \neq 0 \) and \( g_2 = 0 \) or \( g_1 = 0 \) and \( g_2 \neq 0 \)). For biaxial loading conditions (\( g_1 \neq 0 \) and \( g_2 \neq 0 \)), the fibers are situated in between \( v_1 \) and \( v_2 \) with the ratio of the stimulus functions dictating the value of the main orientation and dispersity. In case of an equibiaxial loading condition (\( g_1 = g_2 \)), the fibers are uniformly distributed in the plane of \( v_1 \) and \( v_2 \) (Fig. 2).

2.6. Balance equations

FEA was performed to simulate the mechanical response of the native valve during pressurization. Considering incompressibility, the continuity equation reduces to:

\[
\frac{J}{C_0} = 0
\] (13)

where the volume factor \( J = \det(F) \) defines the ratio of the volumes in the deformed and undeformed configuration. The quasi-static balance of linear momentum, neglecting body forces and inertia was written as

\[
\ddot{v} \cdot \sigma = 0
\] (14)

The balance equations were solved using the finite element package SEPRAN (Segal, 1984). A mixed formulation was used to account for incompressibility and the set of interpolation functions for the displacement and pressure field had to satisfy the Babuska–Brezzi condition. A hexahedral Taylor–Hood element was used, with a linear (continuous) interpolation for the pressure field and a quadratic interpolation for the displacement field.

2.7. Geometry and boundary conditions

Due to symmetry, 1/6 of a valve was used for the finite element analysis (Fig. 3). The radius was set to 12 mm and the thickness was obtained from the experimental results (0.82 mm for the AV and 0.62 mm for the PV). At the symmetry surface the normal displacements were suppressed. The displacements at the bottom curve of the fixed edge were also suppressed (stented valve). At the free edge,
a contact surface was defined to model contact between the leaflets (i.e. coaptation). On the top surface, a translavular pressure was applied. The pressure value was chosen to represent the aortic valve pressure (12 kPa). To assure numerical stability a value of 5 kPa was added to the experimentally determined shear modulus $G$.

In the leaflets, the directions $\vec{v}_1$ and $\vec{v}_2$ were obtained from the stress based principal loading directions with isotropic mechanical properties (Driessen et al., 2008) (Fig. 4). The direction $\vec{v}_1$ was chosen to coincide with the major principal loading direction. The direction $\vec{v}_2$ is constructed perpendicular to the direction $\vec{v}_1$ and to the normal to the plane of the leaflet ($\vec{n}$). When using the isotropic material response, the resulting $\vec{v}_1$ and $\vec{v}_2$ generally coincide with the circumferential and radial direction, respectively. Furthermore, $\vec{v}_3$ enters the fixed edge radially, consistent with observations from the literature that collagen fibers enter the aortic root perpendicular for an optimal transfer of loads into the wall (Sauren, 1981).

### 2.8. Parameter estimation

Based on values in the literature for native heart valves (Bashey et al., 1967; Li et al., 2001) the total fiber volume fraction $\phi_{\text{tot}}$ was set to 0.5. The results of a group of 5 protocols of independent biaxial tensile tests (defined in Section 2.2) were fitted simultaneously to estimate the material parameters ($G$, $k_1$, $k_2$, $\alpha$ and $\beta$) by minimizing the stress based nonlinear error function:

$$\text{Error} = w_c \sum_{i=1}^{n_c} (\sigma_{c}^{\exp} - \sigma_{c}^{\text{num}})^2 + w_r \sum_{i=1}^{n_r} (\sigma_{r}^{\exp} - \sigma_{r}^{\text{num}})^2$$

where $\sigma$ denotes the sample stress, $w$ is a weighting factor and $n$ is the number of data points. The subscripts $c$ and $r$ indicate the circumferential and radial directions, respectively, whereas the superscripts $\text{exp}$ and $\text{num}$ refer to experimental data and the values predicted by the constitutive model. The matrix parameter $G$ was fit to the initial part of the curve while the remaining parameters to the complete curve. Per specimen all parameters were obtained and the averaged parameters of all specimens were used for analysis. A nonlinear least-squares solver is used from the software package MATLAB (The MathWorks, Inc., Natick, MA), to fit the numerical parameters to the experimental data.

### 2.9. Statistical analysis

All data were presented as means and standard error of the mean. The data was assumed to follow a normal distribution and therefore, a t-test was performed to check for significance in difference between the AV and the PV parameters. Statistical significance was assumed for a $P<0.05$.

### 3. Results

#### 3.1. Mechanical properties

The constitutive model fitted the experimental data well (Fig. 5 and Fig. 6). The stress–stretch curves and the estimated values for the model parameters indicated that the AV leaflets were less extensible than the pulmonary tissues (Table 1). Results also showed that the AV leaflets were more anisotropic than the PV leaflets. These differences were due to structural and morphological variations between the AV and PV.

Structurally, the leaflets showed a collagen distribution with a significantly different dispersity $\beta$ ($P<0.05$). A larger or smaller value for $\beta$ implies that the fibers are distributed more or less uniformly and, consequently, the mechanical responses in the circumferential and radial directions are more or less similar, respectively.

The matrix properties also differed for the leaflets, which had a significantly different $G$ modulus ($P<0.05$). This parameter dictates the slope of the initial part of the curve. Morphologically, the leaflets of the AV were significantly thicker when compared to the PV ($P<0.01$).

#### 3.2. Mechanical behavior

The simulated stress–stretch curves of a node in the belly region of the AV and PV leaflets after aortic pressurization are shown in Fig. 7. It is noticeable that both valves responded similarly to the aortic diastolic pressure. Yet, the PV leaflets behaved less anisotropic than the AV leaflets, which was a result of the large dispersity of the PV collagen distribution compared to the AV. A larger value for the dispersity implies that the fibers are distributed more uniformly and, consequently, the mechanical responses in both directions are more similar. Furthermore, the PV leaflets appeared to be more extensible and reach higher stresses than the AV leaflet.

The simulated evolution of the leaflets’ symmetry line (Fig. 3) during pressure application is shown in Fig. 8. Due to the collagen organization, the PV leaflets deflected more in the radial direction than the AV leaflets. As a result, the deformed configuration of the PV leaflets showed a smaller coaptation surface than the AV leaflets.

#### 3.3. Remodeling

Both the observed increase in thickness of valve explants and the importance of the collagen architecture in the leaflets mechanical properties were taken into account. Therefore, when investigating the potential remodeling of the PV leaflets subjected to diastolic aortic pressure, 3 remodeling responses were investigated:

Case 1 The thickness parameter $T$ was increased while maintaining the total collagen volume fraction constant ($\phi_{\text{tot}} = 0.5$).
Case 2 The thickness parameter $T$ was increased while keeping the absolute collagen content value constant (decreasing $\phi_{\text{tot}}$ proportionally).

Case 3 The remodeling of the PV's collagen distribution parameters $\alpha$ and $\beta$ was investigated.

The valve explants show thickened leaflets (Schoof et al., 2006; Mookhoek et al., 2010) An overview of the parameter variations performed in Cases 1 and 2 is given in Table 2. Utilizing these parameters, the stress–stretch curves of the AV and PV leaflets were obtained and are shown in Figs. 9.
Table 1 – Fitted parameters of the numerical model for the aortic valve and pulmonary valve leaflets. The data is presented as means and the standard error of the mean, t-test.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>G (kPa)</th>
<th>α (deg)</th>
<th>β (-)</th>
<th>k1 (kPa)</th>
<th>k2 (-)</th>
<th>T (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV</td>
<td>1.50 ± 0.30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.85 ± 1.86</td>
<td>0.21 ± 0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.16 ± 0.06</td>
<td>15.18 ± 5.42</td>
<td>0.90 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PV</td>
<td>0.92 ± 0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.62 ± 3.36</td>
<td>0.30 ± 0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06 ± 0.04</td>
<td>13.82 ± 1.07</td>
<td>0.62 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.05.  
<sup>b</sup> P < 0.01.

Fig. 7 – Simulated stress–stretch curves in the circumferential and radial directions for a node in the belly region of the aortic valve leaflets (black) and the pulmonary valve leaflet (grey).

and 10, respectively. The stress–stretch curves were taken from a node in the AV and PV leaflets belly region during pressurization. For the AV the experimentally obtained thickness was considered while for the PV the influence of an increased thickness was investigated. Fig. 9 shows that when the thickness of the PV increased, the nodal maximum valve leaflet stress was decreased in the stiffness of the curves.

For Case 3, the remodeling parameter \( \chi \) that better describe the fitted collagen distribution parameters of the AV leaflets was first estimated for both the strain and stress dependent algorithms (Eqs. (11) and (12), respectively). Numerical simulations of the leaflet pressurization were performed and the collagen architecture parameters \( a \) and \( \beta \) were left to remodel until stable values were obtained. To start with an isotropic fiber distribution, the initial \( a \) and \( \beta \) were set to 14.85° and 100, respectively. For the strain dependent algorithm \( \chi = 0.1 \) was obtained and for the stress dependent algorithm \( \chi = 1.0 \) respectively. The acquired collagen remodeling parameters \( a \) and \( \beta \) are summarized in Table 3. The values obtained with the stress dependent algorithm approximated better the fitted collagen architecture parameters. This was also observed when comparing the stretch-stress curve of a node in the belly region (Fig. 11). Results showed that the stress–stretch curves obtained with this algorithm (blue curve in Fig. 11) approximated better the AV leaflet stress–stretch curves (black curve in Fig. 11). Higher values for the same parameters were obtained when a strain dependent algorithm was applied. This was characteristic of

4. Discussion

In the present study, a structure-based numerical model was applied to assess and evaluate the mechanical properties of pairs of human aortic and pulmonary donor valves. The model was employed to evaluate and demonstrate valvular behavior in the Ross procedure. Furthermore, numerical remodeling laws were applied to assess the change in properties of the PV leaflet in the aortic position. The results from biaxial tensile tests were used to determine the model parameters. Comparing the results from both valves it was observed that the PV leaflet was more extensible than the AV tissues. The PV leaflets was also less anisotropic than the AV leaflets. Results also showed that the AV leaflets were thicker than the PV leaflets. When subjected to the aortic diastolic pressure, the simulated stresses in the PV leaflets tissue were also higher and the simulated coaptation area was smaller than in the AV leaflets. Furthermore, our study suggested that the PV leaflets appear to remodel by increasing its thickness and rotating its fibers toward the circumferential direction. However, these changes were not sufficient for the complete remodel of the PV leaflet toward an AV structure.

Previous studies comparing the AV and PV leaflets mechanical properties showed minimal differences between these structures, both for human (Stradins et al., 2004) and porcine tissues (David et al., 1994). However, Joyce et al.
have shown that the AV and PV porcine leaflets have differences in functionality. In their study, the AV cusps in the unloaded configuration demonstrated substantial regional variations in fiber alignment, whereas the PV cusps were more uniform. Moreover, the AV leaflets demonstrated substantially larger changes in collagen fiber alignment with applied transvalvular pressure compared to the PV leaflets. Their results are in accordance with the differences in collagen architecture found in our study.

The simulated stress-stretch curves for the valves when subjected to the diastolic aortic pressure show a more isotropic behavior for the PV leaflets possibly due to the different collagen architecture. As a consequence, the stresses in the PV leaflet were higher than the AV leaflet and the tissue was less extensible in the radial direction, reducing the coaptation area. The differences in coaptation area might explain the suboptimal coaptation in the Ross procedure leaflets because the radial extensibility appears to be important to establish sufficient contact between the leaflets to prevent prolapse (Thubrikar et al., 1986; Schoen and Levy, 1999).

Regarding remodeling, with the stress based algorithm the collagen architecture of the AV leaflet remodeled to describe better the experimental results. In contrast, the strain based algorithm resulted in a more isotropic collagen orientation. The remodeling of the PV leaflet when subjected to diastolic aortic pressure was then assessed. The same remodeling parameter values obtained for the AV leaflet were applied. Results showed that this tissue remodeled by increasing its thickness and rotating the collagen fibers toward the circumferential direction. Yet, the remodeling was not sufficient for the complete remodel of the PV leaflet toward an AV leaflet. Moreover, the model also suggests that the increase in

<table>
<thead>
<tr>
<th>Case</th>
<th>Thickness (T)</th>
<th>Total volume fraction ($\phi_{tot}$)</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.71</td>
<td>–</td>
</tr>
<tr>
<td>1b</td>
<td>0.81</td>
<td>–</td>
</tr>
<tr>
<td>2a</td>
<td>0.71</td>
<td>0.43</td>
</tr>
<tr>
<td>2b</td>
<td>0.81</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Table 2 – Overview of the analysis performed for the pulmonary leaflet to study its remodeling in the aortic position (Cases 1 and 2). “–” indicates that the parameters are equal to their reference values.
collagen content appears not to be relevant for the valve survival in the new environment. Schoof et al. (2006) and Mookhoek et al. (2010) also observed increase in thickness of the leaflets and no changes in collagen content when analyzing valve explants from patients that went through the Ross procedure. It would be also expected that the PV leaflet collagen fibers would rotate to become more similar to the fiber architecture of the AV leaflet. When applying the remodeling law, this result was only obtained when a stress based stimulus was applied, suggesting that collagen remodeling is stress driven. Yet, further experiments with respect to the collagen architecture in Ross explants are necessary to support this finding.

When performing the biaxial tensile tests, the samples were held by metal pins that penetrated in the tissue. During the tensile test, the holes made by this pins increased in size damaging the tissue. This limitation of the method may have influenced our results by increasing the toe region of the stretch stress curve and decreasing the maximum stress. Furthermore, it was assumed that the initial configuration of the aortic valve is stress-free. However, the layers of the valve are pre-stressed by virtue of their attachment (Vesely, 1996; Amini et al., 2012; Rausch et al., 2012). Driessen et al. (2005) applied the model used here to studied the influence of residual stresses in the arterial wall and observed that the presence of residual stresses has a clear effect on the mechanical behavior by decreasing the arterial stiffness. These residual strains should be therefore, incorporated into the model to study their effect on the mechanical response of the leaflets. In the finite element simulations, homogenous properties were assumed for the entire leaflet. Yet, it is known that these material properties (including the tissue thickness) are heterogenous (Billiar and Sacks, 2000) and should thus be measured locally and incorporated into the model. In addition, when fitting the constitutive model to the experimental data, the shear modulus was obtained from the

Table 3 – Overview of the experimental and remodeled collagen architecture parameters of the AV and PV leaflets in the aortic position (Case 3).

<table>
<thead>
<tr>
<th>Remodeling algorithm</th>
<th>AV</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>Not remodeled (Fitted)</td>
<td>–</td>
<td>14.85</td>
</tr>
<tr>
<td>Remodeled (Stress)</td>
<td>1.0</td>
<td>13.90</td>
</tr>
<tr>
<td>Remodeled (Strain)</td>
<td>0.1</td>
<td>25.20</td>
</tr>
</tbody>
</table>

Fig. 11 – Simulated stress–stretch curves in the circumferential and radial directions for a node in the belly region. The curves were obtained from the AV leaflets with the α and β found in Table 3. The values utilized were experimentally fitted (black), numerically estimated with a remodeling stress based algorithm (blue) and with a remodeling strain based algorithm (red). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

Fig. 12 – Simulated stress–stretch curves in the circumferential and radial directions for a node in the belly region. The curves were obtained from the AV and PV leaflets with the α and β found in Table 3. The values utilized were experimentally fitted from AV data (black), PV data (grey) and numerically estimated for the PV leaflet with a remodeling stress based algorithm (blue) and with a strain based algorithm (red). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

Fig. 13 – Representation of the principal strain (left) and stress (right) directions of the PV leaflet, obtained with the experimentally obtained α and β found in Table 3.
initial 20% of the curve only considering the isotropic part of the model. This methodology provided a more representative value for $G$ and a decrease in parameters when fitting to the experimental curve. For the FEA simulations, the value used for the shear modulus was the lowest value possible that led to stable solutions. Since the tissue mechanical behavior is mainly governed by the collagen fibers the increase in $G$ is not expected to affect our results. Furthermore, the instability may be localized and may have no influence in the overall behavior of the tissue. A Gaussian function was assumed for the fiber distribution based on measurements obtained from native porcine leaflets (Billiar and Sacks, 2000) and the main fiber angle $\alpha$ and standard deviation $\beta$ were estimated by the parameter fitting algorithm. Several techniques exist to determine the collagen architecture quantitatively and experiments on native tissues should be performed. Techniques such as small angle light scattering (Billiar and Sacks, 2000; Sacks, 2003), polarized light microscopy (Finlay et al., 1995; Canham et al., 1997), confocal (reflection) laser scanning microscopy and two-photon microscopy, using fluorescent probes to label collagen (Rubbens et al., 2009; Soares et al., 2011) can be used to assess the collagen architecture. It may then be possible to incorporate the measured fiber distribution directly into the model, thereby further reducing the number of model parameters. At larger strains, the experimentally measured mechanical responses tended to behave more linear than the exponential constitutive model for the fibers (Fig. 2). Models that account for fiber recruitment (Sacks, 2003) might be more appropriate to describe this phenomenon. Furthermore, stress and stretch remodeling stimuli are widely used in the literature and their predictions qualitatively agree with observations from the literature for native tissues (Rodriguez et al., 1994; Taber and Eggers, 1996; Lin et al., 1997), confocal (reflection) laser scanning microscopy and two-photon microscopy, using fluorescent probes to label collagen (Rubbens et al., 2009; Soares et al., 2011) can be used to assess the collagen architecture. Yet, the mechanism by which cells remodeled the collagen fibers is not fully understood. It is known that collagen fibrils align with cells in many native tissues suggesting that cells remodeled the extracellular matrix in such a way that the collagen fibers aligned with the preferred fiber directions. This may either be the result of cells contractile forces deforming the matrix by reorienting the collagen fibers (Friedrichs et al., 2007). Or the collagen fibers increased resistance against enzymatic degradation with increasing strain or stress (Bhole et al., 2009). Further experimental work has to be performed to further clarify the exact mechanisms of these processes and to determine their relative contributions to collagen reorganization. In addition, the current model focused mainly on the collagen thickness and fiber orientation however, the effect of remodeling on other collagen fibers properties such as cross-linking should also be addressed when studying the remodeling in native cardiovascular tissues. It is known that in response to environmental cues, collagen fibers can also increase in size and become crosslinked (Clark, 1996; Rubin and Farber, 1998).

Despite the limitations, our study revealed structural differences between the AV and PV. These variations resulted in a more extensible and less anisotropic behavior of the PV leaflet as compared to the AV leaflet. When exposed to aortic pressure, the PV leaflet appeared to remodel by increasing its thickness and reorganizing its collagen, rotating it toward the circumferential direction. Yet, this remodeling did not result in properties that are completely identical to the AV leaflet. Therefore, to fully elucidate the potential of the PV leaflet for the Ross procedure, the adaptive remodeling of other matrix components such as elastin should be taken into account. Also, a better understanding of the native tissue properties and their adaptation capabilities to different mechanical environments, as shown in this study, can be used to optimize mechanical conditioning protocols in heart valves TE.

**REFERENCES**


