Structure and torsion in the normal and situs inversus totalis cardiac left ventricle. II. Modeling cardiac adaptation to mechanical load

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Departments of Pediatrics, Physiology, and Biophysics, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht; and Department of Biomedical Technology, Eindhoven University of Technology, Eindhoven, The Netherlands

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Kroon W, Delhaas T, Bovendeerd P, Arts T. Structure and torsion in the normal and situs inversus totalis cardiac left ventricle. II. Modeling cardiac adaptation to mechanical load. Am J Physiol Heart Circ Physiol 295: H202–H210, 2008. First published April 18, 2008; doi:10.1152/ajpheart.00877.2007.—Mathematical models provide a suitable platform to test hypotheses on the relation between local mechanical stimuli and responses to cardiac structure and geometry. In the present model study, we tested hypothesized mechanical stimuli and responses in cardiac adaptation to mechanical load on their ability to estimate a realistic myocardial structure of the normal and situs inversus totalis (SIT) left ventricle (LV). In a cylindrical model of the LV, 1) mass was adapted in response to myofiber strain at the beginning of ejection and to global contractility (average systolic pressure), 2) cavity volume was adapted in response to fiber strain during ejection, and 3) myofiber orientations were adapted in response to myofiber strain during ejection and local misalignment between neighboring tissue parts. The model was able to generate a realistic normal LV geometry and structure. In addition, the model was also able to simulate the instigating situation in the rare SIT LV with opposite torsion and transmural courses in myofiber direction between the apex and base [Delhaas et al. (6)]. These results substantiate the importance of mechanical load in the formation and maintenance of cardiac structure and geometry. Furthermore, in the model, adapted myocardial architecture was found to be insensitive to fiber misalignment in the transmural direction, i.e., myofiber strain during ejection was sufficient to generate a realistic transmural variation in myofiber orientation. In addition, the model estimates that, despite differences in structure, global pump work and the mass of the normal and SIT LV are similar.

Mathematical models provide a suitable platform to test hypotheses on the relation between local mechanical stimuli and responses to cardiac structure and geometry, such as changes in mass (18, 22), shape (23), and internal myofiber arrangement (2, 10, 17, 26). Model-based prediction of a realistic myocardial structure of the normal and SIT LV (6). Special focus was on the transition zone between the apex and base.

To be able to incorporate the apex-to-base changes in myofiber orientation as present in the SIT LV, the one-dimensional model by Arts et al. (2) was extended to include structural variations in the apex-to-base direction. Model-predicted LV structure and torsion were compared with experimental data reported by Delhaas et al. (6). In a sensitivity study, the effect of the degree of myofiber coupling in the transmural and apex-to-base directions on the final cardiac structure and function was determined.

METHODS

In a numerical model, we simulated adaptation of global LV geometry and myofiber architecture to local mechanical tissue load. Mechanical quantities computed at the beginning and end of ejection, using a model of LV mechanics, act as stimuli for adaptation of tissue mass, tissue shape (cavity volume), and myofiber orientations. Subsequently, the adapted myocardial structure and geometry are used in the end-diastolic state of the next cardiac cycle, thus completing an adaptation cycle. The process of adaptation was simulated as a sequence of adaptation cycles.

Model of LV Mechanics

Kinematics. The LV geometry is represented by a rotational symmetric cylinder. To allow for axial variation in mechanics and structure, the cylindrical model is divided in a number of ring-shaped wall segments (Nring) stacked from the apex to base (see Fig. 1). Deformation of such a segment is assumed to be a combination of axial stretch (λa), torsion (circumferential-axial shear strain) (τ), and contraction as quantified by the ejection volume (Vej).

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Balance laws. Within the wall, stresses are restricted by the balances of axial force, radial force, and axial momentum (e.g., Ref. 10). Assuming zero epicardial pressure,

\[
\int r_1^{r_0} \left[ \sigma_r - \frac{1}{2} (\sigma_r - \sigma_{\phi\phi}) \right] r dr = 0 \quad \text{Axial forces} \quad (5)
\]

\[
\int r_1^{r_0} \sigma_\phi r^2 dr = 0 \quad \text{Axial momentum} \quad (6)
\]

\[
\int r_1^{r_0} \left[ \frac{\sigma_{\phi\phi} - \sigma_{rr}}{r} \right] dr = p_c \quad \text{Radial forces} \quad (7)
\]

where \(p_c\) is the cavity pressure and \(r_1\) and \(r_0\) are the inner and outer radii of the ring, respectively. The components of the stress tensor \((\sigma_{rr}, \sigma_{\phi\phi}, \sigma_{zz}, \text{and } \sigma_{r\phi})\) are given by Eq. 2.

Numerical implementation. Kinematics, constitutive laws, and balance laws are applied to each ring. Thus, each ring is attributed a torsion \(\tau\) and an axial extension \(\lambda_e\). Ejection volume \(V_{ej}\) of each ring is prescribed by the total ejection volume \(V_{ej,tot}\) of the LV, i.e., \(V_{ej} = V_{ej,tot} N_{ring}\). The elastance \(C\) is constant throughout the wall, indicating synchronous mechanical activity. The contractility \(C\) is constant in each ring but may vary in the axial direction between ring segments.

The torsion \(\tau\) and axial extension \(\lambda_e\) for the rings are iteratively determined from the balance laws in Eqs. 5 and 6 by means of the conjugate gradient method for a given reference geometry and structure. To evaluate the integrals in Eqs. 5–7, each ring is radially divided into a number of shells \((N_{sh})\) that all have the same volume \((V_{sh})\) (see Fig. 1). Consequently, the wall mass of the ring \((M_w)\) is given by \(M_w = V_{sh} \times N_{sh}\). As a result, the continuous integrals over the radius \(r\) become summations over the discrete number of shells (for details, see Ref. 2). Myofiber stretch ratio \(\lambda_f\) may vary between all shells in the transmural direction as well as in the axial direction.

The cardiac cycle. Within the cardiac cycle, we discriminate between 1) the end of diastole, which acts as the reference (as denoted by subscript “0”); 2) the beginning of ejection (as denoted by subscript “be”); and 3) the end of ejection (as denoted by subscript “ee”). During the isovolumic contraction phase, the myofibers start to develop force as modeled by an increase in elastance \(E\) to 80 kPa at the beginning of ejection. Normalized contractility \(C\) is set to 1 in all rings. During the transition from the end of diastole to the beginning of ejection, the LV cavity volume remains constant by specifying \(V_{ej,tot} = 0\). To satisfy balance Eqs. 5 and 6, the individual rings will deform to their configuration at the beginning of ejection, exhibiting a torsion \(\tau_{be}\) and an axial extension \(\lambda_{e,be}\). At the new equilibrium, Eq. 7 gives the cavity pressures for each of the rings (denoted \(p_{cav,be}\)). During the ejection phase, the volume change of the total LV \((V_{ej,tot})\) is set to 80 ml whereas the elastance \(E\) in all rings remains at 80 kPa. Again, the balance laws in Eqs. 5 and 6 provide the torsion \(\tau_{ee}\) and axial extension \(\lambda_{e,ee}\), and Eq. 7 gives the cavity pressure \(p_{cav,ee}\) for all rings at the end of ejection.

Subsequently, the contractility \(C\) of the myofibers (Eq. 4) in each ring adapts so that a preferred cavity pressure \((p_{cav,pre})\) is reached. We relate the contractility to the mean of the LV cavity pressure at the beginning and end of ejection. Consequently, for ring \(j\), the contractility is given by the following:

\[
C_j = \frac{p_{cav,pre,j}}{p_{cav,be,j}} \quad \text{with } p_{cav,be,j} = \frac{p_{cav,ee,j} + p_{cav,be,j}}{2} \quad (8)
\]

Next, a new cardiac cycle is simulated with the new contractility values (\(C_j\)). The mechanical load quantities calculated at the beginning and end of ejection in this cycle are used as stimuli for adaptation.
Rules for Adaptation of Geometry and Myofiber Architecture

**Stimuli.** Wall mass, tissue shape (end-diastolic cavity volume), and myofiber orientations of each ring are locally adapted based on five load stimuli (s) during the cardiac cycle. At the beginning of ejection, we define the myofiber stretch stimulus (s_{be,i}) for shell $i$ in ring $j$ as follows:

$$s_{be,i} = \ln \left( \frac{\lambda_{be,i}}{\lambda_{be,pref}} \right)$$  \hspace{1cm} (9)

Similarly, we define stimuli due to deviations from preferred values of myofiber shortening during ejection ($s_{ej,i}$) and normalized contractility ($s_c$) as follows:

$$s_{ej,i,j} = \ln \left( \frac{\lambda_{ej,i,j}}{\lambda_{ej,pref,i,j}} \right) \quad \text{with} \quad \lambda_{ej,i,j} = \frac{\lambda_{be,i,j}}{\lambda_{be,pref}}$$  \hspace{1cm} (10)

$$s_{cj,j} = \ln(C_j) \quad \text{with} \quad C_j = \frac{p_{ej,j,pref}}{p_{ej,j}}$$  \hspace{1cm} (11)

In addition, we define stimuli at the beginning of ejection due to myofiber misalignment in the transmural (radial) direction ($s_r$) and the apex-to-base (axial) direction ($s_z$) as follows:

$$s_{r,i,j} = \left[ \frac{\alpha_{be,i,j} - \alpha_{be,i,j+1} + \alpha_{be,i,j-1}}{2}, \mod(180^\circ) \right]$$  \hspace{1cm} (12)

$$s_{z,i,j} = \left[ \frac{\alpha_{be,i,j} + \alpha_{be,i,j+1} + \alpha_{be,i,j-1}}{2}, \mod(180^\circ) \right]$$  \hspace{1cm} (13)

The modulus is added since angles at $+90^\circ$ and $-90^\circ$ essentially describe the same myofiber orientation.

It is noted that, during adaptation, sarcomere properties, as described by Eq. 4, are assumed to be unaffected.

**Tissue mass.** Local tissue mass was considered to change in response to myofiber stretch ratio at the beginning of ejection $\lambda_{be,i}$ and normalized contractility $C_j$ as follows:

$$g_{ij} = s_{be,i,j} + 0.1s_{ej,i,j}$$  \hspace{1cm} (14)

where $g_{ij}$ specifies the amount of growth. However, the calculation of mechanics requires a discrete number of shells with the same volume. Therefore, to implement growth, the shells were either duplicated and placed on the outside of the original shell (positive growth) or removed (negative growth). For this purpose, a probability function $G$ is computed from $g$ as follows:

$$G_{ij} = g_{ij} + \delta_g$$  \hspace{1cm} (15)

The value of $\delta_g$, randomly taken between $-\beta$ and $+\beta$ (flat histogram), is added to translate a change of wall mass (g) into a probability (G) of shell duplication or removal. To duplicate or remove the shell,

$$G_{ij} = \begin{cases} 
+\beta & \text{positive growth, shell duplication} \\
-\beta & \text{negative growth, shell removal}
\end{cases}$$  \hspace{1cm} (16)

We found that $\beta = 0.5$ yielded a sufficiently fast and stable growth response.

**Tissue shape.** In case the myocardial tissue is subjected to large deformations as induced by increased filling, the cavity pressure-volume relationship has been shown to shift to higher volumes (8). Increased filling logically translates into end-diastolic myofiber strain. However, due to an absence of the filling phase in our model, we used ejection myofiber strain as an estimate for end-diastolic strain. Consequently, to model the shift in the pressure-volume relation, we change the end-diastolic ring cavity volume ($V_{cav,ed}$) before adaptation to ($V_{cav,ed}^*$) after adaptation in response to the transmural average stimulus ($s_{t,e}$), as follows:

$$V_{cav,ed}^* = V_{cav,ed} \frac{1}{N_a} \sum_{i=1}^{N_a} \exp(s_{t,e,i,j})$$  \hspace{1cm} (17)

Each ring is assumed to contribute equally to the total end-diastolic cavity volume ($V_{cav,ed}$), i.e., $V_{cav,ed} = V_{cav,ed}^*/N_{ring}$. **Fiber Orientation.** The end-diastolic (reference) myocardial structure, defined by angles $\alpha_{be,i,j}$, adapts via reorientation of the myofibers. We hypothesize that myofibers reorient to achieve a shortening during ejection of 15% ($\lambda_{t,ej,pref} = 0.85$). In addition, we hypothesize that myofibers reorient to form straight pathways to relieve internal stresses arising in the extracellular matrix due to myofiber contraction.

Therefore, in the model, a local objective function ($O_{ij}$) was defined as follows:

$$O_{ij} = s_{ej,i,j}^2 + w_s s_{z,i,j}^2 + w_c s_{cj,j}^2$$  \hspace{1cm} (18)

The weight factors $w_s$ and $w_c$ scale contributions to $O_{ij}$ of the misalignment in the transmural (radial) and apex-to-base (axial) direction, respectively. Higher values of $w_s$ and $w_c$ indicate a higher degree of myofiber alignment imposed on the myocardial structure.

To determine a more preferred myocardial structure, in each adaptation cycle, proposed end-diastolic (reference) myofiber angles $\alpha_{ej,i,j}^r$ are determined by adding values $\delta_{ej,i}$, randomly selected between $-2.5^\circ$ and $+2.5^\circ$ to the existing myofiber angles $\alpha_{ej,i,j}^0$ as follows:

$$\alpha_{ej,i,j}^r = \alpha_{ej,i,j}^0 + \delta_{ej,i}$$  \hspace{1cm} (19)

Next, a cardiac cycle is simulated with the proposed myofiber angles $\alpha_{ej,i,j}^r$ and the values of objective function $O^*$ are determined. The proposed angles are accepted if the corresponding value of $O^*_{ij}$ is less than the original value of $O_{ij}$; if not, myofiber angles remain unaltered.

**Simulations Performed**

**Adaptation in the single-ring model of the LV.** A multiring model of the LV requires boundary conditions at the apex and base. To obtain these boundary conditions, we first performed a set of simulations with a single ring ($N_{ring} = 1$), starting with random myofiber orientations. Total ejection volume was set at $V_{ej} = 80$ ml. Initial cavity volume was arbitrarily set to $V_{cav,ed,init} = 90$ ml, and the wall initially consisted of $N_{sh,init} = 10$ shells of $V_{sh} = 1$ ml each. Imposed myofiber alignment within the ring in the transmural direction was given by $w_r = 1.0$. For a complete overview of the parameter values used in the model of cardiac mechanics and in the adaptation rules, see Table 1. Adaptation was simulated over 600 cycles.

In the simulations, after 600 cycles, either one of two stable myocardial structures was found (see Fig. 2A). In the NORM structure, myofiber angles gradually changed from positive at the endocardium to negative at the epicardium. The MIRROR structure was the mirror image of the NORM structure.

To assess the sensitivity of the final myocardial structure on $\lambda_{t,ej,pref}, \lambda_{t,ej,init}, E$, and $\lambda_{t,ed}$, a set of single-ring simulations was performed in which those parameters were individually increased and decreased. The resulting change of the myocardial structure was quantified by the root mean square (RMS) in the end-diastolic (reference) myofiber angle, as follows:

$$\text{RMS} = \frac{1}{N_a} \sum_{i=1}^{N_a} \left( \alpha_{ij} - \alpha_{ij}^0 \right)^2$$  \hspace{1cm} (20)

with $\alpha_{ij}$ as the angles that are obtained with the default value in Table 1, and $\alpha_{ij}^0$ as the myofiber angles resulting from the parameter change.

**Adaptation in the multi-ring model of the LV.** Subsequently, adaptation is simulated with a model consisting of 30 axially stacked rings (the multiring model). Boundary conditions at the base and apex determined whether a normal LV or a SIT LV is simulated. For the normal LV, the NORM structure was used at the apical boundary as...
Table 1. Input parameters for the model of cardiac mechanics and adaptation rules in the simulation of cardiac adaptation to mechanical load

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial total end-diastolic cavity volume, ml</td>
<td>V_{cav,ed, tot, init}</td>
<td>90*</td>
</tr>
<tr>
<td>Initial number of shells per ring</td>
<td>N_{sh}</td>
<td>10*</td>
</tr>
<tr>
<td>Shell volume, ml</td>
<td>V_{sh}</td>
<td>1* or 1/30†</td>
</tr>
<tr>
<td>Total ejection volume, ml</td>
<td>V_{ej, tot}</td>
<td>80</td>
</tr>
<tr>
<td>Number of rings</td>
<td>N_{ring}</td>
<td>1* or 30†</td>
</tr>
<tr>
<td>Systolic myocardial elastance, kPa</td>
<td>E</td>
<td>80</td>
</tr>
<tr>
<td>Myofiber stretch at zero stress</td>
<td>\lambda_{zs}</td>
<td>0.5</td>
</tr>
<tr>
<td>Preferred average systolic cavity pressure, kPa</td>
<td>p_{cav,ej, pref}</td>
<td>13</td>
</tr>
<tr>
<td>Preferred myofiber stretch during ejection</td>
<td>\lambda_{be, pref}</td>
<td>0.85</td>
</tr>
<tr>
<td>Preferred myofiber stretch at begin ejection</td>
<td>\lambda_{be, pref}</td>
<td>1.0</td>
</tr>
<tr>
<td>Apex-to-base alignment factor in myofiber reorientation</td>
<td>w_{z}</td>
<td>1.0†</td>
</tr>
<tr>
<td>Transmural alignment factor in myofiber reorientation</td>
<td>w_{z}</td>
<td>1.0†</td>
</tr>
</tbody>
</table>

*Single-ring simulation; †multiring simulation.

Table 1. Input parameters for the model of cardiac mechanics and adaptation rules in the simulation of cardiac adaptation to mechanical load

well as the basal boundary. For the SIT LV, the NORM structure was used at the apical boundary, whereas the MIRROR structure was taken at the basal boundary. Boundary structures remained unaltered during the adaptation process.

Between the apex and base, myofiber orientations, end-diastolic cavity volume, and wall volume were adapted. At the start, myofibers were randomly orientated while the end-diastolic cavity volumes for each ring were obtained by normalizing the resulting volumes in the single-ring simulation with respect to the number of rings. Shell volume was also normalized (equal to 1/N_{ring}; in ml).

The imposed alignment between myofibers in the transmural and axial direction was specified by \( w_z = 1.0 \) and \( w_z = 1.0 \), respectively. The sensitivity of the final SIT structure on values of \( w_z \) and \( w_z \) was determined via simulations using combinations of threefold increased or threefold decreased values of \( w_z \) and \( w_z \).

RESULTS

Adaptation in the Single-Ring Model of the LV

Figure 2 shows the resulting transmural course of end-diastolic (reference) myofiber angle \( \alpha_0 \) and the mechanical loads \( \lambda_{be} \) and \( \lambda_{ej} \) for the single-ring simulations.

In the NORM structure, the myofiber angle shows a gradual decrease from +60° at the subendocardium to about −30° at 92% of wall thickness, at which a large gradient occurs toward −90° at the subepicardium (Fig. 2A). The MIRROR structure shows the mirrored transmural course from −60° at the subendocardium to about −90° at the subepicardium. Associated stretch ratios of the myofibers at the beginning and end of ejection for the NORM simulation as well as the MIRROR simulation have obtained their reference values in the major part of the wall except for a 2% deviation in shortening near 92% of the wall thickness. This is the transmural location where the large gradient in the myofiber angle occurs (Fig. 2B).

Figure 2, C–E, shows the evolution of average ejection pressure \( p_{cav,ej} \), wall volume \( V_w \), and end-diastolic cavity volume \( V_{cav, ed} \) during the adaptation process, respectively. Table 2 shows that the global parameters in the single-ring LV have converged to stable values after 600 adaptation cycles. The obtained pressure value \( p_{cav,ej} \) is at the preferred level \( p_{cav,ej, pref} \) of 13 kPa, indicating that the increase in wall mass has fully compensated for the initial low ejection pressure (see Fig. 2, C and D). Except for the sign of torsion at end of ejection, the adapted global parameters were not significantly different between the NORM and MIRROR simulations.

Table 3 shows the RMS of the myofiber angles in response to changes in preferred myofiber stretch during ejection \( \lambda_{ej, pref} \), preferred ejection pressure \( p_{cav,ej, pref} \), myofiber elastance \( E \), and myofiber stretch at zero stress \( \lambda_{zs} \).

Adaptation in the Multiring Model of the LV

After 1,000 adaptation cycles, myofiber orientations in the multiring models of the normal and SIT LV have converged. For the multiring model of the normal LV, the resulting cavity volume, wall volume, torsion, and fiber orientations were very similar to those obtained with the single-ring model in the NORM simulation (see Table 2 and Figs. 2 and 3). Hence, for the analysis and discussion of the multiring simulations, we will focus on the SIT LV only.

The SIT LV developed a transition zone in between the normal orientations at the apex and the mirrored orientations at the base. In this transition zone, especially in the endocardial layers, more myofibers appear to have adopted an orientation parallel to the apex-to-base axis. Figure 3, C and D, shows that the myofiber stretch ratio at the beginning of ejection is homogeneously distributed over the wall. However, within the

![Figure 2](http://ajpheart.physiology.org/)

Figure 2. Results of adaptation in a single-ring for the NORM (broken line) and MIRROR simulation (solid line). A: end-diastolic fiber angle (\( \alpha_0 \)). B: fiber stretch ratio at the beginning of ejection (\( \lambda_{be} \)) and during ejection (\( \lambda_{ej} \)). C: average systolic cavity pressure (\( p_{cav,ej} \)). D: wall volume (\( V_w \)). E: end-diastolic cavity volume (\( V_{cav, ed} \)). A and B show results for the last 100 adaptation cycles in increments of 10 cycles.
transition zone, the myofiber stretch ratio during ejection is heterogeneously distributed, ranging from 0.75 to 0.95.

After adaptation reached a stable result, cavity pressures within all rings of the SIT LV obtained a value of 13 kPa. Cavity and wall volume for the SIT LV were 118.1 ± 0.3 and 177.7 ± 0.3, respectively. Torsion values at different levels between the apex and base are shown in Fig. 3F. In the SIT LV, torsion generally changed sign over the transition zone from +0.136 rad at the base to −0.135 rad at the apex.

Figure 4 shows the sensitivity of myofiber stretch ratios during ejection and torsion at end of ejection to different values of \( w_z \) and \( w_r \) for the SIT LV. With increasing axial coupling factor \( w_z \), the transition zone widened, as reflected by the widening of the zone in which the myofiber stretch ratio during ejection is distributed inhomogeneously. Furthermore, torsion at the end of ejection changed more gradually from the apex to base. Decreasing \( w_z \) showed opposite results in myofiber shortening and torsion. Alterations in imposed myofiber coupling in the transmural direction by changing \( w_r \) did not significantly affect the myofiber stretch ratio and torsion patterns. Parameter \( w_r \) could be reduced to zero without a significant change in myofiber stretch ratio and torsion patterns.

**DISCUSSION**

In the present study, we investigate whether, based on adaptation to mechanical loading, we could estimate the myocardial torsion and structure of the SIT LV (6). We followed the approach as adopted by Arts et al. (2) in which, in a model of cardiac mechanics, parameters of shape, mass, and internal myocardial architecture are simultaneously adapted based on mechanical stimuli. Stimuli were linked to adaptation responses of the tissue using adaptation rules that phenomenologically describe results from in vivo and in vitro experiments.

**Model Results Compared With Experimental Data**

First, similar to Arts et al. (2), adaptation was simulated in a circumferentially symmetric model, representing a LV with no apex-to-base variation in myocardial structure (the single-ring model in the present study). As a result of adaptation, a random initial architecture converged to either one of two stable architectures that were mirror imaged with respect to one another (the NORM and MIRROR myofiber angle distributions in Fig. 2A). Geometrical parameters in both populations were identical (see Table 2 and Fig. 2, C–E). End-diastolic volumes, ejection fractions, and wall mass were realistic at ~125 ml, 64%, and 178 ml, respectively. Myofiber shortening during ejection was homogeneous across the wall.

As shown in Fig. 5, myofiber orientation in the NORM structure is within the range of experimental data of the normal LV. In addition, the torsion value of −0.135 rad at the end of ejection was in the range of experimental observations of the normal LV (6). The single-ring simulations typically show a large gradient in myofiber angle near the epicardium (see Fig. 2).

As shown in Fig. 5 and as also reported by Arts et al. (2), experimental data have shown a similar increase in transmural gradient in myofiber angle near the epicardium (2, 9, 21, 16). An explanation for this increased gradient has been provided previously (1). In short, near the epicardium, the myofiber direction is similar to the principle direction of tissue shortening (3). Consequently, the amount of shortening near the epicardium becomes relatively insensitive to the myofiber direction. Conversely, from the argument that the myofiber orientation adapts to achieve a certain amount of shortening, a wide range of myofiber directions are possible near the epicardium. Apparently, to achieve a balance of forces in our model, this local degree of freedom in myofiber orientation results in a steep gradient to more axial orientations.

Our model suggests that the mirror image of the normal structure is stable as well. However, to the best of our knowledge, a LV with a completely mirrored structure has never been reported. Instead, the SIT LV was found to have a dualistic myocardial structure in which a normal structure at the apex appears to transit into a mirrored structure at the base (6) (Fig. 3). To allow for the axial variation in the SIT myocardial structure, a multiring model was created. Preliminary simulations with the multiring model showed that when all ring were allowed to adapt, eventually the structure exhibited no transition zone, i.e., the structure became either fully normal (and equal to the results obtained with the single-ring model) or fully mirrored. Therefore, to enforce a transition zone, we fixed the ring at the basal boundary in the mirrored structure and the ring at the apical boundary in the normal structure as obtained after convergence in the single-ring model (Fig. 2). Starting with a random intermediate structure,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NORM</th>
<th>Mirror</th>
<th>Normal LV</th>
<th>SIT LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic cavity volume, ml</td>
<td>125.2±0.3</td>
<td>125.0±0.3</td>
<td>124.6±0.4</td>
<td>118.1±0.3</td>
</tr>
<tr>
<td>Wall volume, ml</td>
<td>178.3±0.6</td>
<td>178.0±0.7</td>
<td>177.9±0.3</td>
<td>177.7±0.3</td>
</tr>
<tr>
<td>Torsion at end of ejection, ml</td>
<td>−0.135±0.002</td>
<td>+0.136±0.002</td>
<td>See Fig. 3F</td>
<td>See Fig. 3F</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.7</td>
<td>63.8</td>
<td>64.2</td>
<td>69.4</td>
</tr>
</tbody>
</table>

Simulation results are expressed as means ± SD of the results of the last 100 adaptation cycles. LV, left ventricle; SIT, situs inversus totalis.

**Table 3. Effect of a decrease and an increase of \( \lambda_{fzj, pref} \), \( p_{cav,j, pref} \), \( E \), and \( \lambda_{fzj} \) on final myofiber angles**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \lambda_{fzj, pref} )</th>
<th>( p_{cav,j, pref} )</th>
<th>( E )</th>
<th>( \lambda_{fzj} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root mean square value, &quot; ( \Delta )&quot;</td>
<td>0.94</td>
<td>0.68</td>
<td>1.28</td>
<td>0.97</td>
</tr>
</tbody>
</table>
the local adaptation resulted in a stable geometry and structure (see Table 2 and Fig. 3). The final myocardial architecture exhibited a small transition zone between the apex and base with predominantly axially and circumferentially oriented myofibers (see Fig. 3B). Myofiber shortening during ejection was locally heterogeneous (see Fig. 3D). Currently, the experimental data presented or referred to by Ref. 6 are all that is available on SIT hearts. Quantification of the SIT myocardial structure with magnetic resonance diffusion tensor imaging (MR-DTI) could be used to assess in more detail whether the structure estimated by the model is realistic. However, existing SIT heart specimens have been preserved in formalin or ethanol-glycerine for a long time, which makes them unsuitable for MR-DTI. Still, qualitatively, the model-estimated myofiber orientations shown in Fig. 3B are similar to the experimental data shown in Fig. 3A. Furthermore, the transmural course in

![Image](image_url)

**Fig. 3.** Real and model-predicted fiber structure for the normal and situs inversus totalis (SIT) LV. Model results were obtained after 1,000 adaptation cycles in a multiring model with 30 axially stacked ring segments. The figures show results interpolated to 18 rings consisting of 10 shells each. A: vector plots of experimentally determined myofiber orientations as adopted from Ref. 15. Myofiber orientations at several transmural depths were obtained by peeling off layers of the myocardium. Numbers indicate the depth with respect to the outer layer. RV, right ventricle; endo, endocardium; epi, epicardium. B: vector plots of model-determined myofiber orientations. Boundary conditions were adopted in the shaded rings. For each level from the apex to base, myofibers were visualized at transmural depths that increase along the circumference. C: angle plots of fiber orientation. Note that fiber angles $\alpha = -90^\circ$ and $\alpha = +90^\circ$ both refer to axially oriented fibers. D: fiber shortening during ejection ($\lambda_{f,\text{ej}}$). E: fiber shortening at the beginning of ejection ($\lambda_{f,\text{ee}}$). F: torsion at the end of ejection ($\tau_{ee}$). Solid lines are the model-determined torsion for the last 100 adaptation cycles in increments of 10. Dashed lines are experimental data from Ref. 6 for the hearts indicated by the asterisks.

![Image](image_url)

**Fig. 4.** Resulting fiber stretch ratio during ejection ($\lambda_{f,\text{ej}}$) and torsion values at the end of ejection ($\tau_{ee}$) for different values of scale factors in adaption ($w_r$ and $w_z$). A: dependence on the amount of imposed fiber alignment in the transmural direction ($w_r$). B: dependence on the amount of imposed fiber alignment in the apex-to-base direction ($w_z$).
myofiber angle is reflected by the torsion. Although there is some spread in the data, the experiments show a reversal in sign of torsion from the apex to base, where absolute values of apical and basal torsion are about the same. The torsion as estimated by the model exhibits the same characteristics (see Fig. 3F).

The model estimates some differences between the normal and SIT LV. Estimated end-diastolic cavity volume is slightly decreased by 5% with respect to that of the normal LV. Since stroke volume was used as a fixed input in the model, ejection fraction is somewhat elevated by 4% (see Table 2). However, these differences are small. In addition, wall mass and ejection pressures were similar to those in the normal LV. This indicates that for both hearts, the globally generated external work (area pressure-volume loop) per unit of mass is equal, despite local heterogeneity in SIT myofiber shortening.

Sensitivity Analysis

In the model, we used a preferred myofiber shortening and average cavity pressure during ejection as target values for the adaptation. Quantification of normal LV deformation with magnetic resonance tagging revealed myofiber shortening during ejection in the real normal LV to be \( \sim 15\% \) (14). In addition, cavity pressure during ejection is roughly 13 kPa. Apparently, in reality, the normal LV geometry and structure have adapted to achieve \( \sim 15\% \) myofiber shortening during ejection at an average pressure of 13 kPa. To investigate the sensitivity of the myocardial structure on the preferred values of myofiber shortening or ejection pressure, we performed a parameter variation in the single-ring model (see Table 3). The simulations revealed that the RMS value in the end-diastolic myofiber angle was no more than 2°, indicating that changes in the myocardial structure were minor. Cavity volume, wall mass, and deformation (torsion and axial shortening) appeared to have adapted in such a way that the preferred fiber shortening was achieved with the same myocardial structure.

In the multiring model, alignment of myofibers was imposed by coupling neighboring myofibers in the transmural and apex-to-base direction. To assess the influence of the degree of myofiber coupling on the final myofiber architecture, a parameter sensitivity analysis was conducted. A change in transmural myofiber coupling (factor \( w_z \)) from the reference value did not significantly alter final ejectional shortening and torsion (see Fig. 4A). In fact, even in the absence of coupling (\( w_z = 0 \)), shortening and torsion did not change significantly. Since myofiber shortening is very sensitive to myofiber orientations (5), it is likely that the final myocardial structure did not change significantly as well. In contrast, shortening and torsion changed significantly in response to a variation in parameter \( w_z \), controlling coupling between myofibers in the axial (apex-to-base) direction (see Fig. 4B). This indicates that myofiber orientations have changed as well. The size of the transition zone increased, as indicated by an increase of the zone in which myofiber shortening is heterogeneously distributed and by a more gradual change in torsion from the apical to basal value. Simulations with \( w_z < 0.3 \) showed that no transition zone developed between the apical and basal structure, i.e., the structure in the upper half of the LV was fully mirrored, whereas the structure in the bottom half of the LV was fully normal. In the case of \( w_z > 3.0 \), the transition zone extended to the apical and basal boundaries. In that case, the prescribed apical and basal boundary conditions, rather than the adaptation rules, dominated the architecture in the transition zone. Our model suggests that for the development and maintenance of the transmural variation in myofiber orientation, imposed myofiber coupling in the transmural direction is not required, i.e., the mechanical load (fiber shortening during ejection) sensed by each individual cell appears to be sufficient.

Assumptions and Limitations

Adaptation rules. The adaptation rules used in this study are based on the rules proposed by Arts et al. (2). We added an apex-to-base component in the adaptation rules to study adaptation in SIT. In our model, 1) increased diastolic myofiber stretch and increased contractility are linked to an increase in wall mass, 2) increased strain excursions induces cavity dilation, and 3) myofibers align with their environment, attempting to achieve a preferred amount of systolic shortening. These rules are substantiated by more recent in vitro and in vivo data and remain up to date. For instance, strain remains one of the primary correlates to changes in wall mass and cavity volume (7, 8, 11). Nonetheless, experiments have not yet ruled out other mechanical stimuli such as stress or strain rate (12, 22).

There is still some debate on whether increased contractility is a stimulus to hypertrophy. Cathecholamine release in response to low systemic pressure is known to induce an acute increase in contractility via adrenergic receptors, chronically leading to an increase in wall mass in vivo (4, 20). However, in an in vivo volume overload model, Holmes (11) did not find a high correlation between observed contractility [as quantified by a maximum rate of pressure increase (\( dp/dt_max \)) and the increase in wall mass.

It is noted that, in the adult heart, myofiber reorientation was never confirmed in vivo or ex vivo (9). Therefore, it may seem odd that we propose fiber reorientation as a means for the tissue to adapt to mechanical loading. However, the high sensitivity of load distribution to myofiber orientation (5) and the apparent absence of heterogeneities in loading in the real LV (25, 27) advocate for the existence of a myofiber orientation-controlling mechanism (2). In other words, mechanical load redistribution may be achieved by a very small amount of myofiber reorientation. This amount may well fall within the measurement accuracy of \( \pm 6\% \) for MR-DTI, which is currently one of the

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most accurate techniques to measure myofiber orientations (9, 19). Thus, the lack of in vivo or ex vivo confirmation of fiber reorientation does not exclude its existence.

In reality, adaptation is likely to be a continuous process. However, the time scale at which changes in geometry and structure occur are orders of magnitude larger than the time scale at which changes in mechanics occur during the cardiac cycle. We found that, provided the adaptation yielded a stable solution, this solution was insensitive to the rate at which the adaptation occurs (see also Ref. 2). Therefore, the time scale of the simulated adaptation becomes arbitrary. In our model, we have chosen to adapt the geometry and structure in a discrete fashion after each cardiac cycle to improve computational efficiency.

Mechanics model. The presented mechanics model provides a suitable initial step toward simulation of load-induced adaptation. In this mechanics model, the cardiac LV is represented by a rotationally symmetric cylinder. The real LV basal geometry is, by good approximation, cylindrical, whereas the apical geometry is rather spherical. Also, the internal myocardial structure is not entirely symmetric, exhibiting marked differences between the septum and free wall (e.g., Ref. 9). In addition, the right ventricle (RV) affects mechanics of the LV through direct mechanical coupling via the septum. Neglecting the contribution of the RV to LV mechanics may affect the adaptation and, as a result, the final geometry and structure of the LV. In future studies, finite element models may be used to include more complex asymmetries in cardiac geometry and structure to investigate the influence of the RV and a closed apex on the final structure.

Furthermore, the fluid-fiber model of the cardiac tissue behavior during ejection neglects contributions of the passive matrix as well as transmural components in the myofiber orientation. During systole, stresses passively induced due to matrix deformation are usually much smaller than the actively developed stress (13). Therefore, exclusion of passive stress is not likely to affect the model results on myocardial structure and torsion. Similarly, although a transmural component in myofiber orientation may affect the torsion (24), the torsion pattern from the apex to base is not likely to be significantly affected. In the SIT LV model, a dualistic pattern will still be seen.

In addition, sarcomere elastance and myofiber stretch ratio at zero active stress did not change during adaptation. Experimental data are unclear as to whether sarcomere properties change during adaptation or not (22). The stress-strain relation, as given by Eq. 4, was obtained from data presented by Donker et al. (7). They found that during ejection, the stress-strain relation is approximately linear. Although variation of sarcomere elastance and myofiber stretch ratio at zero active stress resulted in a change in wall mass, cavity volume, and cavity pressure, they did not yield significant changes in myofiber orientation (see table 3).

Summary and Conclusions

In the present model study, we tested hypothesized mechanical stimuli and responses in cardiac adaptation to mechanical load on their ability to estimate a realistic myocardial structure of the normal and SIT LV. Local changes in tissue altered cavity volume, wall mass, and myocardial architecture at the organ level. The model was able to generate a realistic LV geometry and structure. In addition, the model was also able to simulate the instigating situation in the rare SIT LV with mirrored movements and transmural courses in myofiber direction between the apex and base (6). These results substantiate the importance of mechanical load in the formation and maintenance of cardiac structure and geometry. Furthermore, adapted myocardial architecture was found to be insensitive to fiber misalignment in the transmural direction, i.e., myofiber strain during ejection was sufficient to generate a realistic transmural variation in myofiber orientation. In addition, the model estimates that the normal and SIT LV have similar global pump work and mass, despite differences in structure.

APPENDIX

During deformation, the material point displaces from cylindrical coordinates (r_0,\theta_0,z_0) to coordinates (r,\theta,z). Globally, the deformation is parameterized by ejection volume V_{ej}, axial stretch \lambda_z, and torsion \tau. Assuming the tissue to be incompressible,

$$r^2 \equiv \frac{r^2_0}{\lambda_z} - \left( \frac{r^2_0}{\lambda_z} - r^2 \right)$$  \hspace{1cm} (A1)

where \(r_0\) and \(r_0\) are the inner radius of the cylinder in the deformed and reference configuration, respectively. The ejection fraction related \(r_0\) and \(r_{f,0}\) as follows:

$$\frac{V_{ej}}{V_{cav,0}} = \frac{V_{cav,0} - V_{cav}}{V_{cav,0}} = 1 - \frac{r_f^2 h}{r_{f,0}^2}$$  \hspace{1cm} (A2)

where \(V_{cav,0}\) is the cavity volume enclosed by the cylinder. Rewriting Eq. A2 gives the following:

$$\left( \frac{r_{f,0}^2}{\lambda_z} - r_f^2 \right) \equiv \frac{r_{f,0}^2}{\lambda_z} \frac{V_{ej}}{V_{cav,0}}$$  \hspace{1cm} (A3)

The combination of Eqs. A1 and A3 results in the following:

$$r = \sqrt{r_0^2 - \frac{r_{f,0}^2}{\lambda_z} \frac{V_{ej}}{V_{cav,0}}}$$  \hspace{1cm} (A4)

$$r = f(r_0,r_{f,0},V_{cav,0},V_{ej},\lambda_z)$$  \hspace{1cm} (A5)

From continuum mechanics, the deformation field is described by the deformation gradient tensor \(F\). Tensor components with respect to the cylindrical coordinate base are stored in matrix \(E\), which is given by:

$$E = \begin{bmatrix} \lambda_z & 0 & 0 \\ 0 & \lambda_\theta & \lambda_z \\ 0 & 0 & \lambda_\tau \end{bmatrix}$$  \hspace{1cm} (A6)

with

$$\lambda_z = \frac{\partial z}{\partial z}; \quad \lambda_\theta = \frac{\partial \phi}{\partial \theta_0}; \quad \lambda_\tau = \frac{\partial \phi}{\partial z} = \frac{r_f^2 h}{r_{f,0}^2 \lambda_z}$$

According to Eq. 3 for the components of reference myofiber direction \(\varepsilon_{f,0}\)

$$\varepsilon_{f,0} = [0 \cos(\alpha_0), \sin(\alpha_0)]^T$$  \hspace{1cm} (A7)

where \(\alpha_0\) is the myofiber angle defined in the reference configuration. The components of deformed myofiber direction \(\varepsilon_f\) is given by the following:

$$\varepsilon_f = E \varepsilon_f \lambda_f$$  \hspace{1cm} (A8)

with myofiber stretch ratio \(\lambda_f\).
\[ \lambda_i = \frac{\epsilon_{i0} E}{E_{i0}} \]  

The combination of Eqs. A6, A7, and A9 results in the following:

\[ \lambda_i = \frac{\left(\cos(\alpha_i) \lambda_{bc} + \sin(\alpha_i) \lambda_{ac}\right)^2 + \sin(\alpha_i) \lambda_{bc}^2}{\cos(\alpha_i) \lambda_{bc} + \sin(\alpha_i) \lambda_{ac}} \]  

Furthermore, fiber angle \( \alpha \) in the deformed configuration is given by the following:

\[ \alpha = \arctan \left( \frac{\sin(\alpha_i) \lambda_{bc}}{\cos(\alpha_i) \lambda_{bc} + \sin(\alpha_i) \lambda_{ac}} \right) \]  

REFERENCES