Effects of activation pattern and active stress development on myocardial shear in a model with adaptive myofiber reorientation

Marieke Pluijmert,1,2 Peter H. M. Bovendeerd,2 Wilco Kroon,3 Frits W. Prinzen,1 and Tammo Delhaas1
1Cardiovascular Research Institute Maastricht, Departments of Biomedical Engineering/Physiology, Maastricht University, Maastricht, The Netherlands; 2Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; and 3Institute of Computational Science, University of Lugano, Lugano, Switzerland

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FE modeling results from our group indicate a strong relation between myofiber orientation and strain distribution in the LV wall, in particular shear strain. However, experimental data show that shear strain varies little in between healthy individuals (6), suggesting that variation of cardiac myofiber orientation in between individuals is low as well. Therefore, we hypothesized that myofiber orientation adapts to achieve a preferred mechanical loading state in the normal adult heart can be seen as the result of a successful adaptation process. This hypothesis has been pushed further in a computational model study in which myofiber orientation was allowed to change in response to mechanical load (18, 24). The myofiber orientation field predicted for a normal adult heart agreed favorably with experimental data. In addition, a significant increase in homogeneity of mechanical load was observed after reorientation, along with an increase in pump function. Finally, the level of shear strain was reduced to physiological levels, but differences remained between the patterns of predicted and measured shear strains.

We hypothesized that the differences between predicted and measured shear strains are caused by simplifications in the model of LV mechanics. The simplifications will not only have a direct effect on the deformation pattern of the myocardium but also an indirect effect, since they affect the process of shear-induced myofiber reorientation. For example, earlier studies that used a perfectly synchronous onset of active stress development (17) also showed synchronous onset of myofiber shortening. However, electrical activation in a healthy heart takes 50–70 ms and also onset of myofiber shortening has been shown to be asynchronous (3). This suggests that active stress development is asynchronous as well. Asynchronous shortening induces shearing deformation of the myocardium, and this in turn will affect the hypothesized myofiber reorientation mechanism.

Also, until now active stress was assumed to develop along the myofiber direction only. Experimentally it has been shown that a considerable component of active stress may be generated perpendicular to the myofiber direction (19). Extension from uniaxial to triaxial active stress development in models of cardiac mechanics was found to lead to a reduction of shear amplitudes, due to an increase of transmural mechanical coupling (6, 29, 30).

Therefore, the aim of the current study was to investigate the effects of a physiological, slightly asynchronous, timing of activation and the effects of triaxial active stress development on myofiber reorientation, on LV global pump and on local myofiber function, and on shear deformation, as computed in a...
cardiac mechanics model with shear-induced myofiber reorientation (18).

METHODS

Model of left ventricular mechanics. Tissue deformations during the cardiac cycle are calculated with a generic FE model of LV mechanics (Fig. 1). With respect to geometry, material properties, and the circulation in which the LV is embedded, this FE model is identical to the model presented in extenso in Bovendeerd et al. (6). Characteristics important for this article are repeated here for readability.

In the reference state, defined as the passive stress-free state, a thick-walled ellipsoidal geometry is assumed (Fig. 1A). During the cardiac cycle, myocardial tissue Cauchy stress \( \sigma \) is composed of an active component \( \sigma_f \) and a passive component \( \sigma_p \):

\[
\sigma = \sigma_0 + \beta(\varepsilon - \varepsilon_0) + \sigma_p
\]

with \( \varepsilon \), \( \varepsilon_0 \), and \( \varepsilon_0 \) the unit vectors in the current myofiber, sheet, and sheet-normal direction in the deformed tissue, respectively. Active stress \( \sigma_a \) is modeled through a series arrangement of a contractile and a series elastic element. The parameter \( \beta \) describes the level of active stress development in the cross-fiber direction. The magnitude of \( \sigma_a \) depends on time elapsed since activation, sarcomere length, and sarcomere shortening velocity (17). Active stress development is initiated with a cycle time of 800 ms. Passive material behavior is assumed nonlinearly elastic, transversely isotropic, and nearly incompressible (6).

In the model, the quasistatic equations of conservation of linear momentum are solved. At the base, essential boundary conditions are assumed nonlinearly elastic, transversely isotropic, and nearly incompressible (6).

Model of adaptive myofiber orientation. As opposed to myofiber orientation in the current loaded state, denoted by \( \varepsilon_f \), myofiber orientation in the mechanically unloaded state is denoted by \( \varepsilon_{f,0} \). In this unloaded state, myofiber orientation is defined with respect to a local cardiac coordinate system \( (l, t, \Phi) \) (Fig. 1B). The transmural direction \( l \) is defined as the outer normal to the cardiac surfaces. The longitudinal direction \( t \) is defined perpendicular to \( l \) from apex to base. To obtain a right-handed coordinate system, the circumferential direction \( \Phi \) is defined in clockwise direction when viewing the LV in apex-to-base direction.

In the local cardiac coordinate system, myofiber orientation is quantified by two angles. The helix angle \( \alpha_f \) is defined as the angle between \( l \) and the projection of \( \varepsilon_{f,0} \) on the circumferential-longitudinal plane \( (l, \Phi) \). The transverse angle \( \alpha_c \) is defined as the angle between \( \varepsilon_{f,0} \) and the projection of \( \varepsilon_{f,0} \) on the circumferential-transmural plane \( (l, \Phi) \).

Myofiber orientation in the unloaded state is subject to remodeling, causing a structural reorientation of the myofiber that is quantified by a change in \( \varepsilon_{f,0} \), and, consequently, a change in \( \alpha_f \) and \( \alpha_c \). The reorientation process is simulated with the model by Kroon et al. (18).

In this model, it was assumed that structural changes in myofiber orientation occur due to damage and repair of the connections between extracellular matrix and myofibers (Fig. 2). The conceptual model was translated into a mathematical model in which the myofiber orientation in the unloaded state \( \varepsilon_{f,0} \) will evolve towards the myofiber orientation in the loaded state corrected for rigid body rotation \( \varepsilon_f^* \):

\[
\frac{\partial \varepsilon_{f,0}}{\partial t} = \frac{1}{\kappa} \left( \varepsilon_f^* - \varepsilon_{f,0} \right)
\]

with \( \kappa \) the adaptation time constant, which is set to 3,200 ms. The \( \varepsilon_f^* \) was derived from the actual myofiber orientation in the deformed tissue \( \varepsilon_f \) as follows:

\[
\varepsilon_f = \frac{F \cdot \varepsilon_{f,0}}{\lambda_f} = R \cdot U \cdot \varepsilon_f = R \cdot \varepsilon_f^*; \quad \lambda_f = \left| U \cdot \varepsilon_{f,0} \right|
\]

with \( \lambda_f \) the myofiber stretch ratio and \( F \) the deformation tensor that consists of the actual deformation \( U \) and rigid body rotation \( R \). Since rigid body rotations are not sensed by the tissue, they are considered irrelevant to adaptation. At the endo- and epicardium, the adapted fiber orientation was forced to be parallel with the endo- and epicardial surfaces, respectively, to ensure myofibers do not stick out of these surfaces.

Fig. 1. Finite element (FE) model of left ventricular (LV) mechanics. A: ellipsoidally shaped FE mesh of the LV consists of 30 elements and is incorporated in a lumped parameter model of the circulation. AV, aortic valve; Cven, venous compliance; MV, mitral valve; \( R_{art} \), arterial resistance; \( R_{per} \), peripheral resistance; \( R_{ven} \), venous resistance. B: description of myofiber orientation vector in the unloaded state \( \varepsilon_{f,0} \) by helix angle \( \alpha_{f,0} \) and transverse angle \( \alpha_c \) using a local cardiac coordinate system \( (l, t, \Phi) \). C: mechanical activation pattern as simulated in uniaxial stress development (UNI) + physiological pattern (PHYS) and triaxial active stress development (TRI) + PHYS. The pattern is based on measurements from Durrer et al. (12). Black dots indicate 4 of the 10 locations of the beads from the experiments of Ashikaga et al. (3).
Fig. 2. Conceptual model on the hypothesis of myofiber reorientation adapted from Kroon et al. (18) and expressed in Eq. 2. In the unloaded configuration, the myofiber orientation vector is denoted by $\vec{e}_f$. During a cardiac cycle, tissue deformations take place (A). The myofiber orientation vector in the deformed configuration is denoted by $\vec{e}_f$. Shear forces as a result of these deformations are assumed to damage the connections between extracellular matrix (ECM, raster) and myofibers (thick black lines). Rigid body rotations are not sensed by the tissue and therefore considered irrelevant to adaptation (B). Here, myofiber orientation is denoted by $\vec{e}_f$. Due to tissue turnover, new connections between the ECM and the myofibers are formed continuously (C). When a connection is made, myofibers tend to be fixed within the tissue (D). This results in an adapted myofiber orientation in the unloaded state.

Simulations performed. Four simulations of LV wall mechanics and myofiber reorientation were performed (Table 1). Simulation UNI + SYNC is the reference simulation with uniaxial stress development ($\beta = 0$) and synchronous development of active stress throughout the LV wall. In simulation TRI + SYNC, $\beta$ in Eq. 1 is set to 0.15, which indicates triaxial active stress development. The level of active stress in cross-fiber direction is equal to 15% of the level in myofiber direction. In simulation UNI + PHYS, active stress development was uniaxial, but the moment of onset of active stress development was not synchronous. Instead, a delay in transmural direction from endocardium to epicardium and a delay in longitudinal direction from apex to base of both 25 ms were introduced, resulting in a more physiological pattern of activation with a total activation time of 50 ms for the total LV (Fig. 1C). The combination of including triaxial active stress development and physiological onset of active stress development was simulated in TRI + PHYS.

In all simulations, the initial distribution of the helix angle $\alpha_{h,0}$ is described by the parameterized distribution in (6). It varies nonlinearly with the transmural position from endocardium to epicardium (Fig. 3, left). The initial condition for transmural distribution of $\alpha_{h,0}$ is set to zero.

The first 10 consecutive cardiac cycles were used to reach a hemodynamic steady state, and myofiber reorientation was disabled. In subsequent cycles myofiber orientation was adapted per node and the parameterized description of fiber orientation was abandoned. A total of 10 adaptation cycles was simulated, which corresponds with 40 cardiac cycles. The new LV structure was analyzed in terms of the adapted values of $\alpha_{h,0}$ and $\alpha_{l,0}$. LV global function was quantified through maximum LV pressure $p_{lv, max}$, stroke volume SV, and stroke work $W_{stroke}$. Since these global function parameters depend on LV filling pressure, and filling pressure after adaptation differed in between simulations, these parameters were determined from a new simulation at a constant preload of $p_{ven} = 1.8$ kPa. LV local function was quantified by local myofiber function, expressed through maximum myofiber stress $\tau_{m, max}$, and natural myofiber strain during ejection $\varepsilon_{f, ej}$, during isovolumic contraction (IC) $\varepsilon_{f, ic}$, and during isovolumic relaxation (IR) $\varepsilon_{f, ir}$.

Evaluation of the models was performed by comparing predicted fiber orientation and shear strain with experimental data. We used circumferential-radial shear strain data from our own group (6) ($n = 3$), extended with data from the original experiment (10) ($n = 9$). As heart rate varies between subjects, we corrected for differences in duration of the ejection and the filling phase. For determination of the Green-Lagrange strain tensor component $E_{cr}$ from MRT measurements, we refer to Bovendeerd et al. (6). Computed $E_{cr}$ in the final state (after 10 adaptation cycles) was compared with the experimental average $E_{cr}$. In addition, we compared predicted strain with data from other experimental studies (20, 31).

RESULTS

Figure 3 shows the structural changes after 10 adaptation cycles in simulations UNI + SYNC, UNI + PHYS, TRI + SYNC, and TRI + PHYS. In all simulations, major characteristics of the transmural distribution of the helix angle $\alpha_{h,0}$ remained. The transverse angle $\alpha_{l,0}$ developed a distribution with negative values at the apex and positive values at the base. The pattern is similar in all simulations, but angles are larger with uniaxial (UNI + SYNC and UNI + PHYS) than with triaxial (TRI + SYNC and TRI + PHYS) active stress development, especially towards the endocardial apex.

In all simulations, global LV function improved significantly during reorientation as indicated by the increase in maximum left ventricular pressure $p_{lv, max}$, stroke volume SV, and stroke work $W_{stroke}$ (Table 2). After 10 adaptation cycles, all these parameters are largest in UNI + SYNC (17.2 kPa, 65.6 ml, and 1.01 J, respectively), but differences between simulations are small.

Table 1. Overview of the four simulations performed characterized by two settings of active stress development, uniaxial or triaxial, and two settings of timing of onset of active stress development, synchronous or physiological

<table>
<thead>
<tr>
<th>Onset Active Stress Development</th>
<th>Active Stress Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronous</td>
<td>UNI + SYNC, TRI + SYNC</td>
</tr>
<tr>
<td>Physiological</td>
<td>UNI + PHYS, TRI + PHYS</td>
</tr>
</tbody>
</table>

UNI, uniaxial; TRI, triaxial; SYNC, synchronous; PHYS, physiological.
Local LV function also improved during reorientation as indicated by the absolute increase of maximum myofiber stress $f_{\text{max}}$ and myofiber strain during ejection $f_{\text{ej}}$ (Table 3). Simulation UNI SYNC not only showed largest values for global parameters but also for local parameters $f_{\text{max}}$ (42.1 ± 5.2 kPa) and $f_{\text{ej}}$ (−0.164 ± 0.012).

Absolute values of myofiber strains during the isovolumic phases, $f_{\text{ic}}$ and $f_{\text{ir}}$, decreased significantly as a result of reorientation (Table 3). In simulations with physiological onset of active stress development (UNI PHYS and TRI PHYS), absolute myofiber strain during IC $f_{\text{ic}}$ was larger and less homogeneous, and absolute myofiber strain during ejection $f_{\text{ej}}$ was smaller and less homogeneous than in simulations with synchronous onset of active stress development UNI SYNC and TRI SYNC. Myofiber strain during IR $f_{\text{ir}}$ was smallest with triaxial active stress development and synchronous timing of activation (TRI SYNC). Standard deviations were also smallest in simulation TRI SYNC. Introducing physiological onset of active stress development induced inhomogeneity as reflected by the increased standard deviation in simulation TRI PHYS.

The results of $E_{\text{cr}}$ are presented in Fig. 4. Simulation results are presented in the four graphs in Fig. 4, left. In Fig. 4, top right, averaged $E_{\text{cr}}$ (means ± SD) of nine healthy subjects is shown. Both simulated and experimental strains are computed with respect to begin ejection and averaged per MR slice in circumferential and radial direction. In the cross-section in Fig. 4, bottom right, MR slices relative to the model geometry are shown. $E_{\text{cr}}$ amplitudes were smaller with triaxial (TRI SYNC and TRI PHYS) than with uniaxial (UNI SYNC and UNI PHYS) active stress development. When including physiological onset of active stress development (UNI PHYS and TRI PHYS), $E_{\text{cr}}$ amplitudes increased. In addition, the simulations with triaxial active stress development showed a more realistic base-to-apex gradient of $E_{\text{cr}}$ during ejection. With uniaxial active stress development, the base-to-apex gradient of $E_{\text{cr}}$ only resembled experimental results at end ejection. Amplitudes of $E_{\text{cr}}$ exceeded experimental amplitudes with uniaxial active stress development (UNI SYNC and UNI PHYS). The combination of triaxial active stress and physiological activation pattern (TRI PHYS) brought values and base-to-apex gradient of $E_{\text{cr}}$ in more agreement with experimental results.

To further test the match between computed and experimental strains, we collected strain data from MRT (20, 31) and biplane radiography (2, 4) studies in Table 4. In both

Table 2. Values of global pump parameters maximum LV pressure, stroke volume, and stroke work before and after 10 adaptation cycles

<table>
<thead>
<tr>
<th>Simulation</th>
<th>$p_{\text{lv,max}}, \text{kPa}$</th>
<th>SV, ml</th>
<th>$W_{\text{stroke}}, \text{J}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>UNI + SYNC</td>
<td>15.6</td>
<td>17.2</td>
<td>57.8</td>
</tr>
<tr>
<td>TRI + SYNC</td>
<td>15.6</td>
<td>16.8</td>
<td>57.8</td>
</tr>
<tr>
<td>UNI + PHYS</td>
<td>15.4</td>
<td>16.9</td>
<td>57.2</td>
</tr>
<tr>
<td>TRI + PHYS</td>
<td>15.9</td>
<td>16.8</td>
<td>58.6</td>
</tr>
</tbody>
</table>

Pump parameters were determined in a simulation where myofiber reorientation was not allowed and with a constant preload of 1.8 kPa. $p_{\text{lv,max}}$, left ventricular pressure; SV, stroke volume; $W_{\text{stroke}}$, stroke work; initial and final, before and after 10 adaptation cycles.
simulations and measurements, values of normal strains were larger than shear strains. Also, variation of normal strains in between simulations was far less than variation of shear strains. In general, the normal strains lay well within the experimental range. Only radial strain $E_{rr}$ was larger in the simulations. Near the equator (eq), shear strains also fell within the experimental range. In the apical region (apex), only shear strain values in simulation UNI + PHYS deviated from experimental values. When including triaxial active stress development (TRI + PHYS), shear strain values lay in the experimental range.

In Fig. 5, left, myofiber strain at four transmural locations (Fig. 1C) is shown for the simulations during a cardiac cycle after 10 adaptation cycles. With synchronous onset of active stress development, myofibers at the epicardium started to shorten while endocardial myofibers were initially stretched. When onset of active stress development is more physiological, endocardial fibers started to shorten first at the expense of

### Table 3. Values of local tissue loading parameters maximum myofiber stress $\sigma_{f,max}$, and natural myofiber strain during ejection, IC, and IR before and after 10 adaptation cycles

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Initial $\sigma_{f,max}$, kPa</th>
<th>Final $\sigma_{f,max}$, kPa</th>
<th>Initial $\varepsilon_{f,ic}$</th>
<th>Final $\varepsilon_{f,ic}$</th>
<th>Initial $\varepsilon_{f,ir}$</th>
<th>Final $\varepsilon_{f,ir}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNI + SYNC</td>
<td>35.6 ± 8.7</td>
<td>42.1 ± 5.2</td>
<td>-0.141 ± 0.014</td>
<td>-0.164 ± 0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRI + SYNC</td>
<td>36.5 ± 6.1</td>
<td>38.9 ± 4.7</td>
<td>-0.141 ± 0.012</td>
<td>-0.160 ± 0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNI + PHYS</td>
<td>33.6 ± 10.0</td>
<td>37.7 ± 7.9</td>
<td>-0.103 ± 0.038</td>
<td>-0.138 ± 0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRI + PHYS</td>
<td>33.8 ± 7.0</td>
<td>35.7 ± 7.1</td>
<td>-0.112 ± 0.035</td>
<td>-0.135 ± 0.038</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Local function parameters are presented by means ± SD calculated from the grey area in Fig 2, bottom right. $\sigma_{f,max}$, maximum myofiber stress; $\varepsilon_{f,ic}$ natural myofiber strain during ejection isovolumic contraction (IC); $\varepsilon_{f,ir}$ natural myofiber strain during ejection isovolumic relaxation (IR).

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**Fig. 4.** Results of circumferential-radial shear $E_{cr}$ after 10 adaptation cycles from the four simulations defined in Table 1 (left). IC, isovolumic contraction phase; EJECT, ejection phase; IR, isovolumic relaxation phase; FILL, filling phase. The location of the MR-slices relative to the model geometry at begin-ejection is shown at bottom right. At top right, average $E_{cr}$ from 9 healthy subjects as measured with MRT (10) are shown. Begin-ejection (BE, time = 0) is the reference state and $E_{cr}$ is averaged in circumferential and transmural direction.
stretching epicardial fibers. Results with physiological activation PHYS resembled experimental data from Ashikaga et al. (3) better (Fig. 5, right).

**DISCUSSION**

In this study, we investigated the effects of uniaxial vs. triaxial active stress development and of a synchronous vs. a physiological activation pattern on myofiber reorientation, LV function, and shear deformation in a combined model of LV mechanics with shear-induced myofiber reorientation. The effect on the developed pattern of the transverse fiber angle $\theta_{t,0}$ and the effect on global pump function are minor. Patterns of circumferential-radial shear $E_{cr}$ differ between the simulations. Triaxial active stress development decreases amplitudes of $E_{cr}$.

### Table 4. End-ejection strain values computed from the simulation results after 10 adaptation cycles

<table>
<thead>
<tr>
<th>Sim + Exp → Strain</th>
<th>UNI + SYNC</th>
<th>TRI + SYNC</th>
<th>UNI + PHYS</th>
<th>TRI + PHYS</th>
<th>Moore et al. (20)</th>
<th>Young (31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{eq}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eq</td>
<td>$-0.15$</td>
<td>$-0.16$</td>
<td>$-0.16$</td>
<td>$-0.16$</td>
<td>$-0.22 (0.03)$</td>
<td>$-0.21 (0.02)$</td>
</tr>
<tr>
<td>apex</td>
<td>$-0.15$</td>
<td>$-0.15$</td>
<td>$-0.18$</td>
<td>$-0.14$</td>
<td>$-0.24 (0.04)$</td>
<td>$-0.22 (0.02)$</td>
</tr>
<tr>
<td>$E_{ap}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eq</td>
<td>$0.54$</td>
<td>$0.44$</td>
<td>$0.59$</td>
<td>$0.46$</td>
<td>$0.38 (0.18)$</td>
<td>$0.21 (0.10)$</td>
</tr>
<tr>
<td>apex</td>
<td>$0.51$</td>
<td>$0.43$</td>
<td>$0.46$</td>
<td>$0.37$</td>
<td>$0.49 (0.29)$</td>
<td>$0.10 (0.06)$</td>
</tr>
<tr>
<td>Shear strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{cr}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eq</td>
<td>$0.08$</td>
<td>$0.01$</td>
<td>$0.08$</td>
<td>$-0.02$</td>
<td>$0.05 (0.06)$</td>
<td>$-0.03 (0.02)$</td>
</tr>
<tr>
<td>apex</td>
<td>$0.13$</td>
<td>$0.03$</td>
<td>$0.19$</td>
<td>$0.03$</td>
<td>$0.05 (0.08)$</td>
<td>$-0.05 (0.03)$</td>
</tr>
<tr>
<td>$E_{cl}$</td>
<td>$0.03$</td>
<td>$0.01$</td>
<td>$0.08$</td>
<td>$0.04$</td>
<td>$0.07 (0.06)$</td>
<td>$0.02 (0.02)$</td>
</tr>
<tr>
<td>apex</td>
<td>$0.07$</td>
<td>$0.01$</td>
<td>$0.13$</td>
<td>$0.03$</td>
<td>$0.05 (0.08)$</td>
<td>$0.00 (0.04)$</td>
</tr>
<tr>
<td>$E_{cl}$</td>
<td>$0.03$</td>
<td>$0.03$</td>
<td>$0.08$</td>
<td>$0.08$</td>
<td>$0.03 (0.04)$</td>
<td>$-0.03 (0.01)$</td>
</tr>
<tr>
<td>apex</td>
<td>$0.06$</td>
<td>$-0.01$</td>
<td>$0.09$</td>
<td>$0.04$</td>
<td>$0.04 (0.03)$</td>
<td>$-0.01 (0.02)$</td>
</tr>
</tbody>
</table>

Experimental data in humans were taken from Moore et al. (20) and Young et al. (31) and are presented as mean (SD). Strains were taken near the mid-wall, at 55% (eq), and at 30% (apex) of the distance from the apex to the basal plane with the reference at begin-ejection.

In the experiment, fiber strains were measured at 10 locations between epi- and endocardium. Here, results are shown at 10% (solid), 40% (dashed), 60% (dashed-dotted), and 90% (dotted) of the measured wall depth. At left and right, fiber strains are computed with respect to the first moment of onset of myofiber shortening.

![Fig. 5.](http://ajpheart.physiology.org/)

Fig. 5. **Left**: fiber strain $E_f$ after 10 adaptation cycles in the 4 simulations. Linestyles refer to the location between the epicardial and endocardial surface (Fig. 1C), assumed to resemble 4 locations of the original experimental results of (3). **Right**: fiber strains that are measured using transmural bead markers in dogs in vivo [taken from Ashikaga et al. (3)]. In the experiment, fiber strains were measured at 10 locations between epi- and endocardium. Here, results are shown at 10% (solid), 40% (dashed), 60% (dashed-dotted), and 90% (dotted) of the measured wall depth. At left and right, fiber strains are computed with respect to the first moment of onset of myofiber shortening.
towards values that lie in the experimental range and results in a similar base-to-apex gradient during ejection in model computed and measured $E_{cr}$. The physiological pattern of mechanical activation resulted in better agreement between computed and measured myofiber strain, especially during isovolumic contraction phase and first half of ejection. Combining physiological sequence of activation and triaxial active stress development improves agreement between computed and measured $E_{cr}$ and myofiber strain.

In this study, we especially focused on $E_{cr}$ to make the comparison between computed and experimental results, because our own experimental data contain time courses of $E_{cr}$ in several levels between apex and base. This makes it possible to compare patterns and gradients during the cardiac cycle. According to Table 4, $E_{cr}$ values differed in between simulations, but all fell within the wide range of available experimental data. Figure 4 showed that the range of $E_{cr}$ during a cardiac cycle was too large in simulations with uniaxial active stress development when compared the experimental average.

In addition, introduction of triaxial stress development reduced the amplitudes of $E_{cr}$ during IC to $<0.10$ (Fig. 4). Data during IC are not available from MRT experiments (20, 31). MRT images are constructed over a series of cardiac cycles. To avoid blurring of the images because of variations in cycle length that predominantly occur as variations in the duration of diastole, the reference frame is generally made at begin-ejection. Because the MR signal decreases over time due to relaxation of the magnetization in the tissue, data on $E_{cr}$ during IC are not available. Nevertheless, the experimental results in Fig. 4 suggested that $E_{cr}$ was small during IC, because the signals went back to zero. Strain can also be measured by biplane radiography of lead beads implanted in the LV wall. In these experiments end-diastole is usually taken as the reference. The experiments of Ashikaga and colleagues (2, 4) show that deformation occurs during IC, but with amplitudes not statistically different from zero, as is suggested also by the MRT results (Fig. 4). Thus even the amplitude of $<0.10$ in simulations with triaxial tress development is too high.

The finding that triaxial active stress development decreases $E_{cr}$ amplitudes is in line with results from our previous study (6). It is explained by the fact that the LV wall is stiffer in cross-fiber direction during the active phase of the cardiac cycle. Less shearing deformation results in a smaller difference between the unloaded myofiber orientation $\vec{e}_{f,0}$ and the actual myofiber orientation corrected for rigid body rotation $\vec{e}_f$ in Eq. 2. Consequently, the amplitude of myofiber reorientation during the cardiac cycle is smaller and fiber reorientation due to long-term remodeling is reduced as well. This effect is reflected by the smaller values of the transverse angle $\alpha_{t,0}$ in simulations triaxial compared with uniaxial active stress development (Fig. 3).

Remarkably, triaxial active stress development was able to keep $E_{cr}$ values during ejection in the experimental range under physiological sequence of activation (Fig. 4), a condition known to create significant transmural strain differences especially during IC (3) (Fig. 5). The increased shearing deformation during IC with physiological activation pattern did not result in larger values of $\alpha_{t,0}$, because myofiber reorientation takes place during the whole cardiac cycle.

Comparison with experimental data (20, 31) on other (shear) strain components is performed in Table 4. In all simulations, radial strain $E_{rr}$ was larger compared with the experimental results. The experimental results showed a coefficient of variation on the order of 50%, which indicates that $E_{rr}$ cannot be measured as accurately as the other two normal strain components $E_{cc}$ and $E_{ll}$. The coefficients of variation of $E_{cc}$ and $E_{ll}$ varied between 10 and 30%. The small variation in between simulations of both normal strains and global function showed that normal strains are kinematically coupled to the cavity volume. The effects of triaxial active stress development and physiological activation pattern were hardly reflected in the normal strains.

In contrast, shear strain values differed more in between simulations. This indicates that shear strains are a more sensitive measure for evaluating model results. However, the small values and the large variation (coefficients of variation up to and over 100%) of shear strains make it more difficult to accurately measure them. Nevertheless, from Table 4 we concluded that a physiological activation pattern altered shear strains compared with a synchronous activation pattern. Including triaxial active stress development decreased shear strain values. Especially shear strain values in the apical region showed more agreement with experimental data when active stress development was triaxial.
In the present study, β was set to 0.15, which means that the amount of active stress in cross-fiber direction was set to equal 15% of the amount of active stress generated along the myofiber direction. In Bovendeerd et al. (6), it was shown that setting β to 0.25 and excluding a transverse component in myofiber orientation decreased $E_{cr}$ to realistic values compared with measured $E_{cr}$. However, a β of 0.25 in combination with a transverse component in myofiber orientation that is measured in experiments (13) led to unrealistically small values. We performed additional simulations in which β was varied between 0 and 0.2. A higher β led to lower amplitudes of $\alpha_{cr}$, in agreement with the trend observed when comparing simulations UNI and TRI in Fig. 3. In addition, the amplitudes of $E_{cr}$ got smaller when β was higher. Finally, we chose to set β to 0.15 in simulations TRI + SYNC and TRI + PHYS, because this resulted in $E_{cr}$ values that are in the experimental range. Experimental results that were obtained in steady-state barium contracture, indicate that the amount of active cross-fiber stress is in the range of 40% (19). However, it still remains unknown to what extent these results are representative for the situation in the normal beating heart since no further experimental studies have yet been performed.

We used the simple first order Eq. 2 with time constant $\kappa$ in the order of seconds to model the reorientation process. The value we chose for $\kappa$ is much lower than the half life of extracellular matrix collagen or than the time myocytes need to replace the bulk of their internal proteins. However, we did not aim to realistically model the time course of remodeling. Instead, we lowered $\kappa$ to a value that significantly decreased simulation time but had no effect on the final remodeled state.

Maximum LV pressure $p_{lv, max}$, stroke volume $SV$, and stroke work $W_{stroke}$ were chosen to quantify global function. Because in a closed loop circulation model, these variables depend on the preload of the LV, we ran simulations with constant preload after adaptation to determine global function. The improvement of global function with respect to the initial configuration in all simulations (Table 2) shows that reorientation, in particular the development of a transverse component in myofiber orientation, is favorable for LV pump function. The small differences in global parameters between the four simulations in their final configuration (Table 2) indicate that global function was similar.

Restructuring of the LV wall was also favorable for local function, as indicated by the increased local function parameters in Table 3 with respect to the initial configuration. The decrease in myofiber shortening and lengthening during isovolumic phases indicates a reduction of shearing deformation and an improvement of local myofiber function. These strains do not contribute to changes in cavity volume as the cavity volume is constant in those phases of the cardiac cycle.

Reorientation led to an increase in homogeneity of local myofiber function as indicated by the decreased standard deviations after reorientation (Table 3). The development of a transverse component in myofiber direction increases mechanical coupling in the transverse direction, and therefore, the tissue becomes less anisotropic. Triaxial active stress development also increases mechanical coupling in the transverse direction, which is seen in the smaller standard deviations in simulations with TRI compared with UNI. Nevertheless, complete homogeneity is unrealistic because electrical activation induces inhomogeneities (Fig. 5).

Limitations and recommendations. The good match between myofiber strains from the experiment and myofiber strains computed with a physiological sequence of activation was especially present during IC and during the first half of the ejection phase (Fig. 5). Presumably, the match between simulation and experiment will improve by taking into account the experimental finding that relaxation in the endocardium is delayed (3).

The best way to evaluate the model is to compare myofiber orientations predicted by the model with myofiber orientations obtained from experiments. Unfortunately, the accuracy of current measurement techniques, such as magnetic resonance diffusion tensor imaging, is too low to prefer one model solution over the others (see Fig. 6). Regarding the strong relation between myofiber orientation and deformation, a next best option is to evaluate the model indirectly by comparing computed and measured modes of deformation.

The results of the shear-induced myofiber reorientation may have been influenced by the absence of sheets in the transversely isotropic constitutive model. The organization of myocytes in sheets (7) explains the more orthotropic behavior observed in simple shear experiments (11). Extension of the adaptation model by including sheets and reorientation thereof can be a next step.

Geometry and structure of the LV were assumed rotationally symmetric and the interaction of the LV with the right ventricle was not taken into account. The mechanical interaction will influence the deformation pattern of the myocardium. According to our hypothesis on myofiber reorientation, myofiber orientations will be influenced as well. Indeed, experimental results show differences in myofiber orientation between septum and LV free wall (14). Restructuring alone does not describe the complete adaptive performance of the heart. Other adaptation mechanisms, such as changes in wall mass and cavity volume in response to pressure and volume overload, respectively, are likely to be active as well.

Conclusion. In conclusion, circumferential-radial shear $E_{cr}$ and myofiber strain $E_{r}$, predicted from a combined model of LV mechanics and remodeling of fiber orientation, were found to become more physiologic by extending the mechanics model with physiological sequence of activation and triaxial active stress development. These extensions did hardly affect the pattern of the transverse component in myofiber orientation emerging during restructuring of the LV wall. The development of this transverse component in myofiber orientation is favorable for global pump and local myofiber function.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

M.P., P.H.M.B., and W.K. conception and design of research; M.P. analysis and interpretation of data; M.P., P.H.M.B., F.W.P., and T.D. drafted manuscript; M.P. prepared figures; M.P. drafted manuscript; P.H.M.B., W.K.,
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