Determinants of left ventricular shear strain

Peter H.M. Bovendeerd¹, Wilco Kroon¹,², Tammo Delhaas²

¹Department of Biomedical Engineering, Eindhoven University of Technology,
PO Box 513, NL-5600 MB Eindhoven, The Netherlands

²Cardiovascular Research Institute Maastricht, Maastricht University,
PO Box 616, NL-6200 MD Maastricht, The Netherlands

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correspondence: Peter Bovendeerd
Department of Biomedical Engineering
Eindhoven University of Technology
PO Box 513
5600 MB Eindhoven, The Netherlands
+31 40 2474087 (phone)
+31 40 2447355 (fax)
p.h.m.bovendeerd@tue.nl
Mathematical models of cardiac mechanics can potentially be used to relate abnormal cardiac deformation, as measured noninvasively by ultrasound strain rate imaging or Magnetic Resonance Tagging (MRT), to the underlying pathology. However, with current models correct prediction of wall shear strain has proven to be difficult, even for the normal healthy heart. Discrepancies between simulated and measured strains have been attributed to (1) inadequate modeling of passive tissue behavior, (2) neglecting active stress development perpendicular to the myofiber direction, or (3) neglecting cross-over of myofibers in between subendocardial and subepicardial layers.

In this study, we used a finite element model of left ventricular (LV) mechanics to investigate sensitivity of midwall circumferential-radial shear strain \( E_{cr} \) to settings of parameters determining passive shear stiffness, cross-fiber active stress development, and transmural cross-over of myofibers. Simulated time courses of midwall LV \( E_{cr} \) were compared to time courses obtained in three healthy volunteers using MRT. \( E_{cr} \) as measured in the volunteers during the cardiac cycle was characterized by an amplitude of about 0.1. In the simulations, a realistic amplitude of the \( E_{cr} \) signal could be obtained by tuning either of the three model components mentioned above. However, a realistic time course of \( E_{cr} \), with virtually no change of \( E_{cr} \) during isovolumic contraction and a correct base-to-apex gradient of \( E_{cr} \) during ejection, could only be obtained by including transmural cross-over of myofibers. Thus, accounting for this cross-over seems to be essential for a realistic model of LV wall mechanics.
Key words: magnetic resonance tagging, finite element model, cardiac mechanics, myofiber angle.
Introduction

Deformation of the cardiac wall can be assessed noninvasively using ultrasound strain rate imaging [11] or Magnetic Resonance Tagging (MRT) [4]. The deformation patterns acquired may deviate from normal in case of cardiac pathology, e.g. aortic stenosis, ischemia or conduction disorder [39, 40, 43]. Analysis of abnormal deformation patterns towards the underlying pathology is not straightforward: the relation between the change in deformation pattern and the pathology is complex and criteria for normal and abnormal strain patterns have not been defined yet. A mathematical model, capable of predicting the forward relation between pathology and deformation, could, if used in an inverse analysis, be a useful clinical tool, not only in diagnosis but also in intervention selection and planning, by simulating candidate interventions beforehand.

Several models describing deformation of the cardiac walls have been proposed [5, 6, 14, 19, 20, 28, 35, 41, 42, 45], but none of these models has already been used as a diagnostic tool. As a first step towards this application, one would require the models to be able to correctly predict deformation in the wall of the healthy heart. Most models are able to correctly predict circumferential, longitudinal and radial strain [5, 14, 28, 41, 42, 45]. However, correct prediction of shear strains, in particular circumferential-radial shear, has proven to be difficult [6, 14, 28, 42]. Discrepancies between simulated and measured circumferential-radial shear strain have been attributed to (1) inadequate modeling of passive tissue behavior [14], (2) neglecting active stress development perpendicular to the myofiber direction [42, 45], or (3) neglecting cross-over of myofibers in between subendocardial and subepicardial layers [41]. In a model study by Usyk et al., the change from a transversely isotropic to an orthotropic model of passive material properties yielded improved agreement between simulated and measured shear strains for end diastole, but not for end systole [42]. In the same model, introduction of active cross-
fiber stress affected end-systolic shear strains significantly, but agreement with experimental values was not obtained [42]. In a different model, we have shown that the pattern of myocardial deformation depends strongly on fiber orientation [6]. Reasonable agreement between circumferential-radial shear in model and experiment could be obtained by optimizing the transverse fiber angle, that describes the extent of cross-over of myofibers between the endocardial and epicardial layers [41]. Despite these results, it is difficult to draw conclusions on the role of passive tissue behavior, multiaxial active stress development and transmural cross-over of myofibers, since the studies were performed with different models.

Thus, the aim of this study was to investigate to what extent circumferential-radial shear strain, as measured in healthy subjects using MRT, could be reproduced in a single model of LV mechanics [19] by varying settings of passive shear stiffness, multi-axiality of active stress development, and the transmural cross-over of myofibers.

Methods

Assessment of LV wall strain using MR tagging

The protocol for the MRT measurements was described before [41]. In short, in three healthy subjects (age 28 to 33 years) deformation patterns of the heart were assessed noninvasively using MRT. The experiments were performed at the University Hospital Maastricht, in a 1.5 T scanner (Gyroscan NT, Philips Medical Systems, Best, The Netherlands), with imaging parameters set as follows: echo time 10 ms, inter-tag distance 6 mm, slice thickness 8 mm, tag-width 2.5 mm, field of view 250 mm and image size 256 x 256 pixels. Images were acquired using ECG-triggering on the R wave during breath hold for a period of about 20 s. Three parallel short-axis slices of the heart were imaged: the basal slice, the mid-ventricular slice and the apical slice, with a distance to the basal plane of one third, one half, and two
thirds of the base-to-apex distance, respectively. From the same slices two series of
line-tagged images were obtained, with time intervals of about 20 ms, using spatial
modulation of the magnetization [4]. One series contained vertical tags, the other
horizontal tags.

From the two series of tagged images, maps of horizontal and vertical
displacement were determined [40]. To relate timing of the tagged images to phases
in the cardiac cycle, for each moment in each slice the midwall radius was
determined. Using the interslice distance, the volume enclosed by the ventricular
midwall was estimated using Simpson’s rule. This volume was differentiated with
respect to time, yielding an estimation of mitral inflow and aortic outflow. Zero
crossings of this signal were used to define moments of transition between phases in
the cycle.

Next, the Green-Lagrange strain tensor $E$ was determined, referred to the
moment of begin ejection. Circumferential and circumferential-radial shear
components, $E_{cc}$ and $E_{cr}$, were determined with respect to a local righthanded
cylindrical coordinate system $\{\vec{c}_r, \vec{c}_\phi, \vec{c}_z\}$, with unit vectors in radial, circumferential
and apex-to-base direction, respectively (figure 6). This definition implies that shear
strain $E_{cr}$ is positive when rotation of subepicardial layers in circumferential direction
exceeds that of subendocardial layers. Strain components were averaged in the
transmural direction, with weight factors $w(\vec{r})$, defined as:

$$w(\vec{r}) = \frac{(1 - \vec{r}_i^2)^2}{\sum_{i=1}^N (1 - \vec{r}_i^2)^2} \quad (1)$$

where $\vec{r}_i$ is a normalized transmural coordinate, running from -1 at the endocardium
to +1 at the epicardium, and $N$ is the number of averaging points. Finally, these
transmurally averaged values were averaged in circumferential direction. Average 
circumferential strain $E_{cc}$ and circumferential-radial shear strain $E_{cr}$ were used for 
further analysis.

**Computation of LV wall strain using the finite element model**

The finite element (FE) model of LV mechanics is based on [19]. For the purpose of 
this study, it was slightly modified to allow variation of passive material properties and 
multiaxiality of axial stress development.

**Geometry and fiber orientation**

In the passive stress-free state, a thickwalled geometry is assumed, described by 
confocal endocardial and epicardial ellipsoids, truncated at the same height above 
the equator. In this state, wall and cavity volume equal 144 ml and 40 ml, 
respectively.

The helix angle $\alpha_h$ and transverse angle $\alpha_t$, illustrated in figure 1, are used 
to describe the base-to-apex component and the transmural component of the 
myofiber direction [6]. The helix angle spans the local circumferential direction and 
the projection of the myofiber orientation on the plane parallel to the wall. The 
transverse angle spans the local circumferential direction and the projection of the 
myofiber orientation on the plane perpendicular to the local longitudinal direction.

The spatial distribution of $\alpha_h$ and $\alpha_t$ is a function of normalized local 
coordinates $(u,v)$ [31]. The normalized longitudinal coordinate $u$ varies linearly with 
the distance from the equatorial plane, as measured along the meridional curve 
through the point of interest, from $u = +0.5$ in the basal plane, through $u = 0$ at the 
equator to $u = -1$ at the apex. The normalized coordinate $v$ varies linearly with the 
actual distances in the ventricular wall, from $v = -1$ at the endocardial surface to 
$v = +1$ at the epicardial surface. The fiber angles are described by:
\[ \alpha_4(u,v) = \left( h_{10} L_0(v) + h_{11} L_1(v) + h_{12} L_2(v) + h_{13} L_3(v) + h_{14} L_4(v) \right) \times \left( 1 + h_{22} L_2(u) + h_{24} L_4(u) \right) \]  

(2)

\[ \alpha_1(u,v) = \left( 1 + t_{11} L_1(v) + t_{12} L_2(v) \right) \times \left( 1 - v^2 \right) \times \left( t_{21} L_1(u) + t_{23} L_3(u) + t_{25} L_5(u) \right) \]  

(3)

where \( h_{22}, h_{24}, t_{11} \) and \( t_{12} \) are dimensionless parameters, and \( h_{10} \) through \( h_{14}, t_{21}, t_{23} \) and \( t_{25} \) are expressed in radians. The polynomials \( L_i(v) \) and \( L_j(u) \) are normalized Legendre polynomials of order \( i \). Values of the fiber angle parameters are listed in table 1, while transmural courses of the angles are shown in figure 1.

Material properties

Myocardial tissue Cauchy stress \( \sigma \) is composed of a passive component \( \sigma_p \) and an active component \( \sigma_a \):

\[ \sigma = \sigma_p + \sigma_a \left( \tilde{e}_f \tilde{e}_f + \beta \left( \tilde{e}_s \tilde{e}_s + \tilde{e}_a \tilde{e}_a \right) \right) \]  

(4)

where the material bound coordinate system \( \{ \tilde{e}_f, \tilde{e}_s, \tilde{e}_a \} \), is composed of unit vectors in fiber, sheet and sheet-normal direction, respectively. The 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 cross-fiber direction. The magnitude of the active stress \( \sigma_a \) depends on time \( t_a \) elapsed since activation, sarcomere length \( l_s \) and contractile element length \( l_c \) according to [19]:
\[ \sigma_a = \frac{l_s}{l_{s0}} f_{iso}(l_c) f_{\text{switch}}(t_a, l_s) E_a (l_s - l_c) \] (5)

where \( l_{s0} \) represents the sarcomere length in the stress-free state and \( E_a \) is the stiffness of the series elastic element. The length and time dependence are modeled as:

\[ f_{iso}(l_c) = \begin{cases} T_0 \tanh^2(a_t(l_c - l_{c0})) & l_c \geq l_{c0} \\ 0 & l_c < l_{c0} \end{cases} \] (6)

\[ f_{\text{switch}}(l_c) = \begin{cases} \tanh^2 \left( \frac{t_a}{\tau_r} \right) \tanh^2 \left( \frac{t_{max} - t_a}{\tau_d} \right) & 0 \leq t_a \leq t_{max} \\ 0 & t_a > t_{max} \end{cases} \] (7)

\[ t_{max} = b(l_s - l_d) \] (8)

The time course of the length \( l_c \) of the contractile element is described by:

\[ \frac{dl_c}{dt} = (E_a (l_s - l_c) - 1)v_0 \] (9)

The functional forms and the parameter values (table 1) were chosen such that experimental data on contraction could be reproduced [17]. Following [19], development of active stress was initiated simultaneously throughout the LV wall, at a cycle time of 800 ms.

Passive material behavior is assumed nonlinearly elastic, transversely isotropic and nearly incompressible. Passive Cauchy stress is related to a strain energy density function \( W \) by:

...
with deformation gradient tensor $F$ and Green-Lagrange strain tensor $E$. The strain energy density function $W$ is composed of a part $W_s$ related to shape change of the tissue, and a part $W_v$, related to volume change:

$$W = W_s + W_v$$

The shape part $W_s$ was based on [5], but slightly adapted to fit into the general formulation used in [14]. Formulated in terms of components of the Green-Lagrange strain tensor $E$ with respect to the material bound coordinate system $\{\tilde{e}_f, \tilde{e}_s, \tilde{e}_n\}$, it reads:

$$W_s = a_0 \left( \exp(Q) - 1 \right)$$

$$Q = a_1 \left( E_{ff}^2 + E_{ss}^2 + E_{nn}^2 \right) + \frac{1}{2} a_2 \left( E_{ss}^2 + E_{nn}^2 \right) + a_3 E_{ff}^2 + \frac{1}{2} \left( a_2 + a_4 \right) \left( E_{fs}^2 + E_{fn}^2 + E_{nf}^2 \right)$$

The volume part $W_v$ was taken from [19, 30]:

$$W_v = a_3 \left( \det(F^T \cdot F) - 1 \right)^2$$

**Governing equations and boundary conditions**

In the model, the equations of conservation of momentum are solved:
Essential boundary conditions are defined at the base to suppress rigid body motion. The epicardial surface is traction free while the endocardial surface is subject to a uniform left ventricular pressure \( p_{lv} \). During the isovolumic contraction and relaxation phase in the cycle, \( p_{lv} \) is determined such that mechanical equilibrium of the myocardial tissue is obtained at a constant end-diastolic or end-systolic left ventricular volume \( V_{lv} \), respectively. During the filling and ejection phase, \( p_{lv} \) is computed from the interaction of the LV with the circulation. This interaction is modeled by incorporating the LV model in a lumped parameter model (figure 1). The aortic and mitral valve are modeled as an ideal diode. Vessels are modeled with constant resistances \( R \) and capacitances \( C \). The pressure drop \( \Delta p \) across each of these components is given by

\[
\Delta p_C = \frac{V - V_0}{C} \quad (15)
\]

\[
\Delta p_R = Rq \quad (16)
\]

with \( V \) the volume in the capacitance and \( q \) the flow through the resistance. The pressure-volume relation of the capacitance represents a linearization around the physiologic working point, \( V_0 \), representing the volume at zero pressure. The sum of the blood volumes in the LV cavity and the arterial and venous capacitances is set equal to the total blood volume \( V_{blood} \).

The equilibrium equations (14) are solved numerically with a Galerkin type finite element method, using 27-noded hexahedral elements with a tri-quadratic interpolation of the displacement field. The LV wall is represented by 108 elements.
Simulations and postprocessing

First, an initial simulation INIT was performed, in which the helix angle $\alpha_h$ was
chosen according to [31], while the transverse angle $\alpha_t$ was set to zero (equation 3).
Active stress development was assumed uniaxial, by setting $\beta$ to zero (equation 4).
Initial model parameter settings are listed in table 1.

The range of shear strains in the INIT simulation was found to exceed the
range found in the experiment. Therefore, in three subsequent simulations the
mechanical coupling between the endocardial and epicardial layers was increased
such that the ranges in model and experiment became similar. In simulation PAS,
this situation was obtained by increasing the shear stiffness in the planes spanned by
the fiber and cross-fiber directions, by raising $a_4$ from 0 to 24 (equation 12). In
simulation ACT, active stress development perpendicular to the myofibers was
introduced by increasing $\beta$ from 0 to 0.25 (equation 4). Finally, in simulation FIB the
transverse fiber angle $\alpha_t$ was modeled according to the optimal setting in [41].

In each simulation, 8 cardiac cycles were computed, at the end which a cyclic
steady state was obtained. Results are presented for the last cycle. Computed
Green-Lagrange strains were referred to the moment of begin ejection, and
transmurally averaged in the same way as in the experiment.

Results

MRT experiments

From the tagging images, strains could be determined over a time span of about 650
ms. No strains were determined for the last part of the filling phase and the initial part
of the isovolumic contraction phase. Measured circumferential strain $E_{cc}$ and
circumferential-radial strain $E_{cr}$ are similar in all three hearts (figure 2). Typically, $E_{cc}$
decreases by about -0.15 during ejection, increases slightly during isovolumic relaxation, and increases to about -0.02 during early filling (figure 2).

The total amplitude of shear strain $E_{cr}$ is about 0.10. Shear strain decreases equally in all three slices until about one quarter of the ejection period, indicating that the subendocardial wall rotates in clockwise direction with respect to the subepicardial wall, when viewing the heart from the apex. Thereafter, $E_{cr}$ continues to decrease near the apex, remains about constant near the equator, and increases near the base. Throughout the isovolumic relaxation phase, $E_{cr}$ increases in all slices. During the first part of filling, mean $E_{cr}$ over all slices converges towards zero, leaving a maximum range of 0.04 at the end of the measurement. In the remaining part of the cycle, a gradual change of $E_{cr}$ towards zero at the beginning of the next ejection phase may be expected: in particular changes in $E_{cr}$ during isovolumic contraction may be expected to be small.

**FE simulations**

Time course of circumferential strain $E_{cc}$ is about equal for all four simulations and all three longitudinal levels (figure 3). $E_{cc}$ at end ejection is about -0.15. Variations between the three levels are largest in simulation INIT and smallest in simulation ACT.

Time course of circumferential-radial strain $E_{cr}$ differs significantly in between the four simulations (figure 4). In simulation INIT, during isovolumic contraction changes in $E_{cr}$ are 0.25, 0.13 and -0.02 at the apical, mid-ventricular and basel level, respectively. During ejection, $E_{cr}$ is positive at the apical and mid-ventricular level, and remains about zero at the basal level. $E_{cr}$ amplitude is maximal at the apical level, with a value of about 0.35. In the three subsequent simulations, the amplitude
of the $E_{cr}$ signal was reduced to about 0.1, similar to that in the experiment, by tuning either the passive shear stiffness (simulation PAS), or the cross-fiber active stress development (simulation ACT) or the transmural cross-over of the myofibers (simulation FIB). In simulations PAS and ACT, the time course of $E_{cr}$ is essentially unchanged as compared to that in simulation INIT, with the exception that in simulation ACT, in between the levels, differences in $E_{cr}$ during ejection are reduced.

A common finding in simulations INIT, PAS and ACT is that 1) during isovolumic contraction changes in $E_{cr}$ are large, 2) during ejection $E_{cr}$ is positive at the apical level, and decreases to zero or slightly negative values at the basal level and 3) during isovolumic relaxation $E_{cr}$ decreases at the mid-ventricular and apical level. In simulation FIB, findings are different: 1) during isovolumic contraction changes in are small, 2) during ejection $E_{cr}$ is slightly positive at the basal level, and becomes increasingly negative towards the apical level and 3) during isovolumic relaxation $E_{cr}$ increases at all levels. Thus, the pattern of $E_{cr}$ in simulation FIB agrees better with the experimental observations than the patterns found in simulations INIT, PAS and ACT.

Ventricular hemodynamic performance in the four simulations is shown in figure 5 and table 2. The INIT LV performs least in terms of stroke volume, ejection fraction, maximum LV pressure and stroke work. The PAS LV is slightly stiffer, resulting into a lower end-diastolic volume. Stroke volume is increased with respect to the INIT simulation. In the ACT LV, pressure during ejection is higher than in the INIT LV, but stroke volume is about the same. Finally, in the FIB LV, stroke volume, ejection fraction, maximum pressure stroke work are highest of all four simulations.
To identify determinants of LV shear strain, we compare strains simulated with our FE model to those measured with MR tagging. Thus it is important that the measured strains are realistic. Measured time course of circumferential strain $E_{cc}$ agrees well with that reported in literature, e.g. in [46]. This is not surprising since the time course of $E_{cc}$ is kinematically related to that of LV volume. LV volume is determined by the interaction of the LV as a whole with the vascular system, and overall LV pump function is fairly independent of details in constitutive and structural properties of the myocardium, as shown in figure 5. This explains why $E_{cc}$ is correctly predicted in most model studies of LV mechanics, including our model.

Since the time course of $E_{cr}$ is less restricted kinematically, a larger variability may be expected and $E_{cr}$ measured in our study may deviate more from that reported in other studies. Buchalter et al. used MRT to measure rotation of the endocardial and epicardial surface about the LV long axis, for five levels from base to apex [7]. As in our study, the angle of rotation was defined positive in counterclockwise direction when viewing the heart from the apex. The angle of rotation at end systole, measured with respect to end diastole, was found to be positive, to increase from base to apex, and to be about twice as large at the endocardial surface as at the epicardial surface. This observation implies that $E_{cr}$ at end systole is negative, and increases from base to apex, which is in agreement with our results. Comparison with other experimental data is complicated since strain is often expressed with respect to a wall bound system, in which the circumferential direction is identical to that in our cylindrical system, but the radial direction is perpendicular to the wall and the longitudinal direction is perpendicular to those two directions [3, 9, 27]. At the equator, the cylindrical and wall bound coordinate system coincide. Towards base and apex, the systems and the associated radial-
circumferential shear will deviate to an extent, governed by the curvature of the wall in the radial-longitudinal plane. Several studies have indicated a base-to-apex gradient of $E_{cr}$ in a wall-bound system that is similar to the gradient in our study, though a one-to-one comparison is not strictly valid. Moore et al. measured $E_{cr}$ in healthy volunteers using MRT in the septal, anterior, lateral and inferior wall [27]. Averaging over these four sectors, and correcting for differences in sign due to an opposite definition of the positive circumferential direction, they found end-systolic $E_{cr}$ to equal -0.025, -0.053 and -0.078 at the basal, equatorial and apical level, respectively. These data are comparable to our results in figure 2. Costa et al. measured myocardial strains in anesthetized open chest dogs using biplane radiography of lead beads, implanted in the LV wall [9]. They computed strains with respect to end diastole. Correcting for differences in sign due to an opposite definition of the positive circumferential direction, the base-to-apex gradient of end-systolic $E_{cr}$ in their measurements is consistent with our experimental findings. With the same method as used by Costa et al., at a longitudinal position corresponding to our apical slice Ashikaga et al. obtained end-systolic $E_{cr}$ values of -0.051±0.016 and -0.075±0.020 at the epicardium and endocardium, respectively [3]. These data are comparable to our transmurally averaged values of $E_{cr}$, as presented in figure 2. We thus conclude that our experimental data on $E_{cr}$ are in line with reports in literature, and can be used to assess the quality of the various model simulations.

Patterns of circumferential-radial shear strain $E_{cr}$ vary strongly between experiments and the four simulations. To understand the differences we look at the mechanism underlying the generation of $E_{cr}$ in a geometrically simplified model of the LV, shown in figure 6. $E_{cr}$ originates from the shear load that is imposed on the myocardial tissue by the contracting oblique fibers in the subendocardial and
subepicardial layers. In the INIT simulation, the shear stiffness of the passive tissue is so low, that the shear load is counteracted only at large shear strains, with a range that is about four times as large as that measured in the experiment. In simulation PAS, the range of $E_{cr}$ is reduced to realistic values by increasing the shear stiffness (figure 4). However, the apex-to-base gradient of $E_{cr}$ in the model remains opposite to that in the experiment.

The extreme shear deformation in simulation INIT can also be reduced by reducing the shear load. This is done in simulation ACT by making active force development multiaxial. By setting active cross-fiber stress to 25% of active fiber stress, the amplitude of $E_{cr}$ is reduced to the level found in the experiment. Still, the apex-to-base gradient of $E_{cr}$ in the model remains opposite to that in the experiment.

Finally, in simulation FIB, the shear load imposed on the tissue is not only born by the passive tissue, but also by the active fibers that cross over between the subendocardial and subepicardial layers, as modeled by a non-zero transverse angle $\alpha$. As in simulations PAS and ACT, the amplitude of $E_{cr}$ is reduced to physiological levels. Agreement between measured and simulated pattern of $E_{cr}$ is larger for simulation FIB than for simulations PAS or ACT: the base-to-apex gradient of $E_{cr}$ has the same sign and changes in $E_{cr}$ during isovolumic contraction are small. The latter observation indicates that the transition of passive to active tissue involves small changes in shape, suggesting that the passive and active ventricular architecture are matched to each other. Interestingly, in a model of cardiac remodeling, the assumption that myofibers reorient to minimize shear deformation during the cardiac cycle was found to lead to a cross-over of myofibers between the subendocardium and the subendocardium, that was similar to that used in simulation FIB [22].
In simulations PAS, ACT and FIB, we simulated the effect of passive stiffness, multi-
axial active stress and transmural cross-over separately. While the FIB results match
the experimental results best, the agreement is not complete. We did investigate how
the FIB results changed by adding the effects of the PAS and ACT simulation. As
shown in figure 7, in simulation PAS+FIB the amplitude of the $E_{cr}$-signal reduced
slightly, and the oscillations at the basal level decreased. In simulation ACT+FIB, the
amplitude of the $E_{cr}$-signal became unphysiologically low during ejection, and
comparatively high during filling. In simulation PAS+ACT+FIB, $E_{cr}$ during ejection
was again more physiological, but the large differences in $E_{cr}$ during filling remained.
Agreement between model and experiment might be improved by carefully tuning the
contribution of the three effects, using a method similar to that proposed by Stevens
et al. to investigate sensitivity of diastolic ventricular mechanics to settings of passive
material properties [36]. We considered such an optimization inappropriate, since in
doing so we would compensate for other model simplifications, discussed below.

Our results are obtained from a parameter variation around the INIT
simulation. The INIT model adopts the common assumptions in many FE models of
LV mechanics that development of active myofiber stress is uniaxial, and that
transmural cross-over of myfibers is absent. Passive material behavior is identical to
that in [5], except for the value of $a_0$, which was reduced from 0.5 kPa to 0.4 kPa. In
the model, cardiac tissue was considered transversely isotropic. The part $W_s$ in (12)
was originally formulated in terms of the invariants of the Green-Lagrange strain $\mathbf{E}$
for transverse isotropy, with the parameters $a_3$ and $a_4$ governing the deviation from
isotropy [26]. Meanwhile, experimental data have become available, that allow for a
more detailed, orthotropic characterization of the tissue [12]. Schmid et al. [33, 34]
concluded that these data could be described best by the orthotropic material law
proposed by Costa et al. [10]. Using the notation in [33], this law reads:
where we used the superscript 'C' to distinguish between this law and our law (equation 12). It was found that a transversely isotropic material law was not able to capture the response of myocardial tissue under simple shear deformation. However, fitting parameters to experimental data in [12] yielded no statistically significant differences between $b_{nn}$ and $b_{ss}$ and between $b_{fn}$, $b_{fs}$ and $b_{ns}$, which supports our use of a transversely isotropic law (12) for a computational model that also does not capture myocardial sheets.

The relation between tissue stress and strain is obtained from differentiating the strain energy density with respect to strain (10). The shear components of the Cauchy stress tensor $\sigma$ are dominated by the shear components of the second Piola-Kirchhoff stress tensor $S$, defined as:

$$S_{fn} = \frac{\partial W_s}{\partial E_{fn}}, \quad S_{fs} = \frac{\partial W_s}{\partial E_{fs}}, \quad S_{ns} = \frac{\partial W_s}{\partial E_{ns}}$$

(17)

Evaluation of these expressions for both the Costa law (17) and our constitutive law (11) yields:

$$S_{fn}^C = ab_{fn} \exp(Q^C)E_{fn}; \quad S_{fs}^C = a_0(a_2 + a_4)\exp(Q)E_{fs}$$

(18)

$$S_{ns}^C = ab_{ns} \exp(Q^C)E_{ns}; \quad S_{ns}^C = a_0 a_2 \exp(Q)E_{ns}$$
To obtain an indication of shear stiffness, we consider small strains for which \( \exp(Q^C) = \exp(Q) \approx 1 \). Then the relation between stress and strain becomes linear, with the ratio between stress and strain representing the stiffness. In the Costa model, shear stiffness in the \( fn \)-plane, the \( fs \)-plane and the \( ns \)-plane is governed by the value of \( ab_{fs} \) (3.1 kPa), \( ab_{fs} \) (3.1 kPa), and \( ab_{nr} \) (2.8 kPa), respectively, where the numerical values were obtained from [33]. In our model, corresponding stiffnesses are governed by \( a_0(a_2 + a_4) \), \( a_0(a_2 + a_4) \), and \( a_0a_2 \), respectively. In the INIT, ACT and FIB simulation, these three stiffnesses equal 2.4 kPa. Thus shear stiffness in these simulations is comparable to that in [33], and the increase of \( fn \) and \( fs \) shear stiffnesses to 12 kPa, needed in simulation PAS to obtain a realistic range of \( E_{cr} \), seems not physiological. The volumetric part in the strain energy density function (13) satisfies the convexity requirements formulated in [16], that \( W_v = 0 \), \( \frac{dW_v}{dJ} = 0 \) and \( \frac{d^2W_v}{dJ^2} > 0 \) at preservation of volume, i.e. for \( J = \text{det}(\mathbf{F}) = 1 \). It does not satisfy the requirements that \( W_v \to \infty \) and \( \frac{dW_v}{dJ} \to -\infty \) for \( J \to 0 \). However, this limitation did not affect our simulations where \( J \) always remained close to 1.

In the ACT model, active stress in cross-fiber direction had to be set to 25\% of active stress along the fiber direction, to obtain a realistic range of \( E_{cr} \). This fraction compares favorably with the 30\% cross-fiber active stress development, proposed before [42]. However, our analysis suggests a match between simulated and measured patterns of \( E_{cr} \) cannot be obtained by merely tuning cross-fiber stress development.

A transmural component of fiber orientation seems to have been included in models of cardiac mechanics from our group exclusively. We first included the transverse angle \( \alpha_i \) to better approximate experimental data on transmural differences in
rotation [6], making use of limited histological data presented by Streeter et al. [37, 38]. In a subsequent study, a similar spatial distribution of $\alpha_i$ emerged from optimization of myofiber strain for homogeneity during ejection [31], even though to transmural differences in rotation were not a criterion in the optimization process. In the latter study, Legendre polynomials were chosen to parameterize the fiber angle field since their property of orthogonality was advantageous in the optimization procedure [21]. A better approximation of measured $E_{cr}$ was found when the $\alpha_i$ obtained in [31] was increased by 25% [41]. It is this distribution of $\alpha_i$ that was used in the FIB simulation. Meanwhile, more recent experimental investigations have confirmed the earlier observations by Streeter and colleagues that myofiber orientation in the LV wall has a component in transmural direction [1, 13, 18, 23, 24, 25, 32]. Accurate quantification of the $\alpha_i$ has proven to be difficult, among others because unique definition of a wall-bound coordinate system to which the fiber orientation can be referred to is difficult [13]. Yet, the main experimental findings are that $\alpha_i$ is positive in the basal part and negative in the apical part of the LV wall [13, 18, 32], that $\alpha_i$ reaches its extremum closer to the endocardial than the epicardial surface [24], and that $\alpha_i$ is small ($<5^\circ$) in the bulk of the myocardium, but certainly not small near the apex and base [23], with some studies reporting that the magnitude of $\alpha_i$ may increase up to $40^\circ$ [25, 32]. The distribution of $\alpha_i$ in the FIB simulation agrees with these experimental findings.

Differences in hemodynamics between the four simulations are shown in figure 5 and table 2. In simulation PAS, apparently the increased shear stiffness increases the stiffness of the LV as a whole, leading to a reduced end-diastolic volume as compared to that in simulation INIT (figure 5). Yet, LV stroke volume is increased, suggesting a beneficial effect of release, during ejection, of the increased amount of elastic energy stored in the LV wall during filling. In simulation ACT maximum LV
pressure during ejection is increased by 0.4 kPa, as compared to simulation INIT, probably due to active stress development in cross-fiber direction in the plane of the wall. This increase in ejection pressure does lead to a small increase in stroke volume of 0.6 ml only. This is probably caused by the development of active stress in radial direction, which counteracts the wall thickening that must accompany the reduction of LV volume during ejection, because of incompressibility of the myocardial tissue. Hemodynamic performance is better in the FIB LV than in the PAS and ACT LV, since the mechanism to reduce $E_{cr}$ does not involve adverse effects such as diastolic stiffening (PAS LV) or hampered wall thickening during ejection (ACT LV). Interestingly, although total wall mass was kept the same, the change in structural organisation of the myocardium enabled an increase of external mechanical work of about 10-15% (table 2). The clinical significance of the hemodynamic differences remains unclear. In all simulations hemodynamics is in reasonable agreement with clinical data [15]. The maximum LV pressure of about 16 kPa (120 mmHg) is representative for a normal adult. However, the cardiac output of 4.5 l/min, which results from the stroke volume of about 60 ml at a heart rate of 75 beats per minute, is lower than the typical value of 5 to 5.5 l/min. The ejection fraction of about 55% is also lower than the typical value of 60% to 65%.

Limitations of the study are related to the simplifications introduced in the FE model. Obviously, the real cardiac geometry is more complex than the ellipsoidal geometry used in the model. Especially, adding the right ventricle might affect the shear load on the LV wall, and consequently LV $E_{cr}$. Also, we assumed simultaneous stress development in the myofibers, as suggested by Kerckhoffs et al. [19]. To investigate sensitivity of shear strain to moment of onset of active stress development, we adapted the INIT simulation such that the subendocardial layers were activated 40 ms before the epicardial layers and found that the pattern of $E_{cr}$ was hardly affected (results not shown). The effect of a 40 ms transmural...
difference in activation was more pronounced when we applied it to the
PAS+ACT+FIB simulation: the difference in $E_{cr}$ between the basal, mid-ventricular
and apical level increased during ejection, and decreased during filling (simulation
PAS+ACT+FIB+TIM in figure 7). Apparently, additional effects, such as that of the
activation sequence, become more important once the transition of the LV from the
passive to the active state is in the physiological range. In addition, we assumed
constitutive tissue properties to be spatially homogeneous. However, while collagen
volume fraction seems relatively constant across the wall, subepicardial structural
organization of collagen seems to differ from that in midwall and subendocardial
regions [29]. Though these differences might affect myocardial strain, it is still unclear
how they should be translated into material properties. The most obvious
inhomogeneity seems to be the transmural variation of the duration of the action
potential and the duration of active stress development [8]. We did not investigate the
effect of such inhomogeneity in our model. However, we expect the effect to be
similar to that of varying the timing of active stress development, which we found to
be minor.

Experimental limitations involve the restriction to the circumferential-radial shear
component only, thus neglecting the other two shear components. Circumferential-
longitudinal shear, also known as torsion, has been shown to depend strongly on the
transmural variation of the helix angle [2]. The determinants of the third component,
longitudinal-radial shear, are less clear. We could not assess this component from
our experiments, in which we acquired short axis images only. In literature, several
studies have reported end-systolic values of $E_{lr}$, referred to end diastole and
expressed with respect to a wall-bound coordinate system with the longitudinal axis
pointing in basal direction. Transmurally averaged values of $E_{lr}$ were found to be
about 0.01 at the basal level [9], 0.066±0.014 at the mid-ventricular level [3] and
about 0.00 [9] or about 0.04 [44] at the apical level. Using the same coordinate
system and moment in time as a reference, in our simulations we find transmurally
averaged values for end-systolic basal, mid-ventricular and apical $E_{tr}$ of -0.05, -0.10 and -0.16 for simulation INIT, -0.04, -0.08 and -0.13 for simulation PAS, 0.00, -0.03, -0.06 for simulation ACT, and 0.00, -0.04 and -0.06 for simulation FIB, respectively.

Thus, end-systolic values of $E_{tr}$ in our simulations have an opposite sign as compared to those in the experiments. Comparison between simulations suggests that passive shear stiffness is less important as a determinant of $E_{tr}$ than active cross-fiber stress development or transmural cross-over of myofibers. Obviously, the determinants of $E_{tr}$ need further investigation.

In conclusion, we found circumferential-radial shear strain $E_{cr}$ in the LV wall to be dependent on all three factors, proposed in literature, i.e. the shear stiffness of the passive tissue, the level of active stress development perpendicular to the fiber direction, and the transmural cross-over of myofibers between the subendocardial and subepicardial layers, quantified through the transverse angle. According to the present model study, a qualitative agreement between $E_{cr}$ in model and experiment can only be obtained if transmural cross-over of myofibers is included. Thus, accounting for this cross-over seems to be essential for a realistic model of LV wall mechanics.
References


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Figure 1: Model of the left ventricle and the circulation. Top: the ellipsoidally shaped model of left ventricular mechanics showing helix ($\alpha_h$) and transverse ($\alpha_t$) fiber angles. The fiber angles are defined from projection of the fiber direction $\vec{e}_f$ on planes spanned by the local transmural $\vec{e}_t$, circumferential $\vec{e}_c$ and longitudinal $\vec{e}_l$ direction. Middle: transmural course of the helix angle $\alpha_h$, used in all simulations, and the transverse angle $\alpha_t$, used in simulation FIB only. Bottom: lumped parameter model of the circulation with aortic valve AV, mitral valve MV, characteristic arterial impedance $R_{art}$, peripheral resistance $R_{per}$, venous resistance $R_{ven}$, arterial compliance $C_{art}$ with zero-pressure volume $V_{art,0}$, and venous compliance $C_{ven}$ with zero-pressure volume $V_{ven,0}$. 
Figure 2: Time courses of midwall circumferential strain $E_{cc}$ (left) and circumferential-radial shear strain $E_{cr}$ (right), as measured in three healthy subjects (top to bottom), in basal (— — —), midventricular (--) and apical (····) slice. Phases are indicated by ejec (ejection), ir (isovolumic relaxation), and fill (filling).
Figure 3: Time courses of midwall circumferential strain $E_{cc}$, as computed in simulations INIT (top left), PAS (top right), ACT (bottom left), and FIB (bottom right). Strains are shown at basal (−−−), midventricular (—) and apical (····) level.
Figure 4: Time courses of midwall circumferential-radial shear strain $E_{cr}$, as computed in simulations INIT (top left), PAS (top right), ACT (bottom left), and FIB (bottom right). Strains are shown at basal (---), midventricular (--), and apical (---) level. Horizontal dotted lines in simulation INIT (top left) indicate the range of the strain axis for the other three simulations and the experiment (figure 2).
Figure 5: Pressure-volume loops for simulations INIT (—) PAS (····), ACT (·····), and FIB (— —). Transitions between the phases in the cycle are indicated by ‘o’.
Figure 6: Illustration of the generation of transmural shear in a simplified cylindrical model of the LV. Shortening of oblique fibers in subendocardial and subepicardial layers (a) generates a clockwise apical rotation of the subendocardium (b) and a counterclockwise rotation of the subepicardium (c), in an apex-to-base view of LV. With respect to local right-handed cylindrical coordinate system $\{\vec{e}_r, \vec{e}_c, \vec{e}_z\}$, with $\vec{e}_z$ pointing from base to apex, this results in a positive circumferential-radial shear $E_{cr}$ (d).
Figure 7: Top and bottom left: combined effect of variations in PAS, ACT and FIB simulation on time courses of midwall circumferential-radial shear strain $E_{cr}$. Bottom right: additional effect of a transmural difference of activation time of 40 ms. Strains are shown at basal ($\cdots$), midventricular (—) and apical (− − −) level.
Table 1: Model parameter values. \(^a\)Non-zero transverse angle parameter values hold for simulation FIB only. \(^b\)Non-zero value of \(\beta\) holds for simulation ACT only. \(^c\)Non-zero value of \(a_4\) holds for simulation PAS only. For circulation parameters see figure 1.

<table>
<thead>
<tr>
<th>Fiber angles</th>
<th>Active material</th>
<th>Passive material</th>
<th>Circulation</th>
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<tr>
<td>(h_{10})</td>
<td>0.362 rad</td>
<td>(T_0) 160 kPa</td>
<td>(a_0) 0.4 kPa</td>
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<tr>
<td>(h_{11})</td>
<td>-1.16 rad</td>
<td>(E_a) 20 (\mu)m(^{-1})</td>
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<td>(h_{12})</td>
<td>-0.124 rad</td>
<td>(a_4) 2 (\mu)m(^{-1})</td>
<td>(a_2) 6 -</td>
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<tr>
<td>(h_{13})</td>
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<td>(l_{c0}) 1.5 (\mu)m</td>
<td>(a_3) 3 -</td>
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<tr>
<td>(h_{14})</td>
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<td>(l_{s0}) 1.9 (\mu)m</td>
<td>(a_4) 0 (24)(^c) -</td>
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<tr>
<td>(h_{22})</td>
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<td>(\tau_r) 75 ms</td>
<td>(a_5) 55 kPa</td>
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<td>(h_{24})</td>
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<td>(\tau_d) 150 ms</td>
<td>(V_{ven,0}) 3000 ml</td>
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<tr>
<td>(t_{11})</td>
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<td>(b) 160 ms·(\mu)m(^{-1})</td>
<td>(V_{blood}) 5000 ml</td>
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<tr>
<td>(t_{12})</td>
<td>0.502 -</td>
<td>(l_d) -0.5 (\mu)m</td>
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<tr>
<td>(t_{21})</td>
<td>0 (0.626)(^a) rad</td>
<td>(\beta) 0 (0.25)(^b) -</td>
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<tr>
<td>(t_{23})</td>
<td>0 (0.211)(^a) rad</td>
<td>| |</td>
<td></td>
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<tr>
<td>(t_{25})</td>
<td>0 (0.038)(^a) rad</td>
<td>| |</td>
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Table 2: Hemodynamics, expressed in LV cavity volume at begin ejection $V_{be}$, stroke volume $V_{stroke}$, ejection fraction $EF$, maximum LV pressure $p_{max}$ and stroke work $W_{stroke}$.

<table>
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<tr>
<th>simulation</th>
<th>$V_{be}$ [ml]</th>
<th>$V_{stroke}$ [ml]</th>
<th>$EF$ [%]</th>
<th>$p_{max}$ [kPa]</th>
<th>$W_{stroke}$ [kPa.ml]</th>
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<tbody>
<tr>
<td>INIT</td>
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<td>59.0</td>
<td>52.7</td>
<td>16.0</td>
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<tr>
<td>PAS</td>
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<td>64.0</td>
<td>57.8</td>
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<td>957</td>
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