The mechanics of the normal and ischemic left ventricle during the cardiac cycle : a numerical and experimental analysis

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The mechanics of the
normal and ischemic left ventricle
during the cardiac cycle

The mechanics of the normal and ischemic left ventricle during the cardiac cycle

– a numerical and experimental analysis –

Proefschrift

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aan de Rijksuniversiteit Limburg te Maastricht,
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volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
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door

Peter Hermanus Marie Bovendeerd

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Symbols, subscripts, superscripts, notation

Symbols

A	m^2	area
a_T	–	parameter in contraction model (2.2.4)
a_x	m^{-1}	parameter in contraction model (2.2.4)
a_1, a_2, a_3, a_4	–	parameters in strain-energy function (2.2.2)
b	$s \cdot m^{-1}$	parameter in contraction model (2.2.4)
$\mathbf{b}$	m^{-1}	discrete gradient operator (3.2)
C	m	focal length of ellipsoid (2.1.1)
C	Pa	parameter in strain-energy function (2.2.2)
C_{art}	$m^3 \cdot Pa^{-1}$	arterial compliance (2.3.3)
d_{eq}	m	equatorial wall thickness (5.1.1)
E_a	m^{-1}	parameter in contraction model (2.2.4)
$\mathbf{E}$	–	Green-Lagrange strain tensor (Appendix A)
e_1, e_2, e_3	–	orthogonal directions
e_3	–	fiber direction (2.2.2)
$\mathbf{F}$	–	deformation gradient tensor (Appendix A)
F	N	force
f	–	fractional height h/Z (2.1.1)
g	–	scalar weighting function (3.2)
h	m	truncation height (2.1.1)
$\mathbf{h}$	–	vectorial weighting function (3.2)
J	–	$\det(\mathbf{F})$ (Appendix A)
$\underline{K}$	–	stiffness matrix (3.2)
L	m	outer ventricular length
$\underline{L}$	m	column of contractile element lengths (3.2)
l	m	length
l_d	m	parameter in contraction model (2.2.4)
l_c	m	length of contractile element (2.2.4)
l_s	m	sarcomere length
l_x	m	parameter in contraction model (2.2.4)

Symbols (continued)

m_w	kg	mass of left ventricular wall
p	Pa	pressure
q	$\text{m}^3 \cdot \text{s}^{-1}$	flow
$\underline{R}$		column of residues (3.2)
R_{ao}	$\text{Pa} \cdot \text{s} \cdot \text{m}^{-3}$	characteristic aortic resistance (2.3.3)
R	m	short axis of ellipsoid (2.1.1)
R_{per}	$\text{Pa} \cdot \text{s} \cdot \text{m}^{-3}$	peripheral resistance (2.3.3)
S	Pa	second Piola-Kirchhoff stress tensor based on σ^d (Appendix A)
T	Pa	first Piola-Kirchhoff stress tensor based on σ^d (Appendix A)
T_a	Pa	active first Piola-Kirchhoff fiber stress
T_0	Pa	parameter in contraction model (2.2.4)
T_1	Pa	parameter in contraction model (2.2.4)
T_{max}	Pa	parameter in contraction model (2.2.4)
t	s	time
t_d	s	parameter in contraction model (2.2.4)
t_e	s	parameter in contraction model (2.2.4)
t_i	s	moment of initiation of activation (4.1.2)
t_r	s	parameter in contraction model (2.2.4)
t_s	s	time since onset of activation (2.2.4)
(u_1, u_2, u_3)	m, m, m	displacements in Cartesian coordinate system (4.1.1)
V_e	m^3	volume between epi- and endocardial ellipsoid (2.1.1)
V_i	m^3	volume within endocardial ellipsoid (2.1.1)
V_{lv}	m^3	volume of left ventricular cavity (2.1.1)
V_{pap}	m^3	volume of papillary muscles (2.1.1)
V_w	m^3	volume of left ventricular wall (2.1.1)
V_0	m^3	cavity volume at zero transmural pressure (2.1.1)
v_0	$\text{m} \cdot \text{s}^{-1}$	parameter in contraction model (2.2.4)
v_e	$\text{m} \cdot \text{s}^{-1}$	parameter in activation model (2.2.5)
W	Pa	strain-energy function (2.2.2)
W_{cycle}	J	global external work per cardiac cycle
w	$\text{J} \cdot \text{m}^{-3}$	local external work per cardiac cycle per unit of volume
$\underline{X}$		column of positions and pressures (3.2)
$\underline{x}$	m, m, m	position vector
(x_1, x_2, x_3)	m, m, m	Cartesian coordinates (2.1.2)
Z	m	long axis of ellipsoid (2.1.1)
α_i	—	ischemia parameter (6.1.1)
α_1	—	helix fiber angle (2.1.3)
α_{10}, α_{11}	—	parameters in fiber orientation model (2.1.3)
$\alpha_{12, en}, \alpha_{12, ep}$	—	parameters in fiber orientation model (2.1.3)
α_3	—	transverse fiber angle (2.1.3)
α_{31}, α_{32}	—	parameters in fiber orientation model (2.1.3)

Symbols (continued)

Δ	—	difference
δ	—	absolute convergence criterion (4.1.2)
δ	—	error in estimate (3.2)
ε	—	relative convergence criterion
ε	—	linear strain
η	—	column of isoparametric coordinates (3.3)
θ_A	—	parameter in activation model (2.2.5)
λ	—	stretch ratio
ξ	—	column of material coordinates (3.2)
(ξ, θ, ϕ)	—, —, —	ellipsoid coordinate system (2.1.2)
$(\tilde{\xi}, \tilde{\theta})$	—, —	local coordinate system (2.1.2)
ξ_1	—	parameter in fiber orientation model (2.1.3)
σ	Pa	Cauchy stress tensor
ϕ	—	interpolation function of pressure field (3.2)
ϕ_z	—	angle of rotation around long axis
ψ	—	interpolation function of position field (3.2)
I_E	—	first strain invariant (2.2.2)
II_E	—	second strain invariant (2.2.2)
III_E	—	third strain invariant (2.2.2)
I'_E	—	scalar combination of strain components (2.2.2)
II'_E	—	scalar combination of strain components (2.2.2)
∇	m^{-1}	gradient operator
∇_0	m^{-1}	gradient operator with respect to undeformed situation

Subscripts

<i>A</i>	area
<i>a</i>	active
<i>ao</i>	aortic
<i>ap</i>	apical
<i>art</i>	arterial
<i>b</i>	beginning
<i>ba</i>	basal
<i>bd</i>	beginning of diastole
<i>be</i>	beginning of ejection
<i>c</i>	cross-fiber
<i>e</i>	end, element, ejection
<i>ed</i>	end of diastole
<i>ee</i>	end of ejection
<i>en</i>	endocardial
<i>ep</i>	epicardial
<i>eq</i>	equatorial
<i>f</i>	fiber
<i>i</i>	inner, initial, in direction <i>i</i>
<i>lv</i>	left ventricle
<i>m</i>	midwall
<i>max</i>	maximum
<i>min</i>	minimum
<i>n</i>	in increment <i>n</i>
<i>o</i>	outer
<i>p</i>	passive
<i>pap</i>	papillary
<i>s</i>	sarcomere
<i>w</i>	wall
0	reference

Superscripts

<i>e</i>	element
<i>I</i>	in node <i>I</i>
<i>i</i>	in iteration <i>i</i>
$\sim$	estimate
—	mean

Notation

a	scalar
$\mathbf{a}$	vector
$\ \mathbf{a}\ $	length of $\mathbf{a}$
$\underline{a}$	column, matrix representation of $\mathbf{a}$
$\underline{a}^T$	transposed of $\underline{a}$
$\mathbf{A}$	second order tensor
$\mathbf{I}$	second order unit tensor
$\mathbf{A}^{-1}$	inverse of $\mathbf{A}$
$\mathbf{A}^c$	conjugate of $\mathbf{A}$
$\mathbf{A}^d$	deviatoric part of $\mathbf{A}$
$\det(\mathbf{A})$	determinant of $\mathbf{A}$
$\text{tr}(\mathbf{A})$	trace $\mathbf{A} = \mathbf{A} : \mathbf{I}$
$\underline{A}$	matrix representation of $\mathbf{A}$
$\underline{A}^T$	transposed of $\underline{A}$
$\mathbf{a}\mathbf{b}$	dyadic product of vectors $\mathbf{a}$ and $\mathbf{b}$
$\mathbf{a} \cdot \mathbf{b}$	dot product of vectors $\mathbf{a}$ and $\mathbf{b}$
$\mathbf{A} \cdot \mathbf{b}$	dot product of tensor $\mathbf{A}$ and vector $\mathbf{b}$
$\mathbf{A} \cdot \mathbf{B}$	dot product of tensors $\mathbf{A}$ and $\mathbf{B}$
$\mathbf{A} : \mathbf{B}$	$\text{tr}(\mathbf{A} \cdot \mathbf{B})$ double dot product of tensors $\mathbf{A}$ and $\mathbf{B}$

Introduction

The global mechanical performance of the left ventricle is the result of the cooperative action of the muscle cells in the ventricular wall. It can be characterized by experimentally assessable quantities such as ventricular pressure and aortic pressure and flow. The mechanical behavior at the level of the muscle cells can be characterized by the local state of stress and strain. Measurement of these quantities with sufficient accuracy and spatial resolution is difficult. Therefore, in this thesis a mathematical model for the analysis of the local mechanical behavior in the left ventricular wall under normal and pathological circumstances is presented.

In the first section of this chapter the aims of this study are formulated. In the second section relevant anatomical and physiological properties of the left ventricle are discussed. In the next section an overview is given of existing models describing left ventricular mechanics. Subsequently, a summary is given of the properties of the model developed in this study. The chapter is concluded with an overview of the contents of this thesis.

1.1 Aims

Investigations on the metabolic, electrophysiological and mechanical behavior of the heart under normal and pathological circumstances are major topics in cardiac research. Studies on the mechanical behavior focus mainly on the left ventricle. Important quantities for the description of the global mechanical performance of the left ventricle are ventricular pressure, aortic pressure and aortic flow. The global mechanical performance of the left ventricle is the result of the cooperative action of the muscle cells in the ventricular wall. Therefore, the mechanics at the level of the muscle cells should be known to understand the global mechanics of the ventricle. Important quantities for the description of local ventricular mechanics are deformation and stress.

Experimental investigation of the mechanics of the left ventricle involves measurement of left ventricular pressure, aortic pressure and flow, and local myocardial deformation and stress. The first three quantities, describing global ventricular mechanics, can be determined experimentally using conventional techniques. Several techniques are available for measurement of myocardial deformation. One-dimensional deformation can be determined by measurement of the length of a segment between ultrasonic transducers [29], strain gauges [49] or inductive coils [4]. Two-dimensional deformation can be determined by triangulation, using ultrasonic transducers [65], inductive coils [96] or optical markers [74,52]. Three-dimensional deformation can be assessed by following of radiopaque markers implanted in the wall [27,100]. Dependent on the spatial resolution of these techniques, an indication of the local state of deformation in the myocardial tissue is obtained. Reliable measurement of ventricular wall stresses [25] is difficult, because insertion of a force transducer damages the tissue [40]. One component of local wall stress is the pressure in the tissue. This intramyocardial pressure can be measured using a micropipette technique [35,77].

Because of the difficulties associated with the experimental analysis of local ventricular mechanics, in this study a mathematical model was developed to investigate the factors that govern the local mechanical behavior in the ventricular wall during the cardiac cycle. The model is based on the mechanical behavior of the individual muscle cells and the connective tissue that surrounds the cells. With the model a cardiac cycle can be simulated. The calculated change of left ventricular hemodynamics and deformation as a function of time is compared with experimental data. Subsequently, the changes in ventricular mechanics, as caused by the presence of an ischemic region in the ventricular wall, will be investigated.

1.2 Basic anatomy and physiology of the heart

1.2.1 Basic anatomy

The heart is a muscular organ that pumps blood through the vascular system. It consists of two pumps: the right pump maintaining the pulmonary circulation and the left pump maintaining the systemic circulation. Each pump consists of two chambers, the atrium and the ventricle. The actual pumping force is delivered by the right and left ventricles. The right and left atrium collect the blood returning from the systemic and pulmonary circulation, respectively. From the atria the ventricles are filled. The mitral valve separates the left atrium from the left ventricle. The right atrium is separated from the right ventricle by the tricuspid valve. These valves are supported by fibrous rings, the annuli fibrosi. A third annulus fibrosus supports the aortic valve, between left ventricle and aorta. The annuli fibrosi are connected together tightly, and form the base of the heart. The fourth cardiac valve, the pulmonary valve (between right ventricle and pulmonary artery), lies outside the base. The heart is connected to the surrounding tissue at the base by the large arteries and veins that enter and leave its chambers. The pericardium, a fibrous sac that surrounds the heart, is also connected to these vessels. The space between the pericardium and the outer surface of the heart, the epicardium, is filled with a thin lubricating layer of pericardial fluid.

The geometry of the left ventricle may be considered as a thick-walled truncated ellipsoid [89]. The relatively thin-walled right ventricle is connected to the subepicardial layers of the left ventricle and covers about half of the surface of the left ventricle. The intraventricular septum is the common wall of the ventricles. Anatomically, it belongs to the left ventricle. The epicardial free wall of the left ventricle is smooth. The endocardial wall is irregular, showing many invaginations protruding into the wall up to about 30% of its thickness. This portion of the wall is called the trabecular layer. In addition to these trabeculae, a number of papillary muscles originate from the endocardial wall. These papillary muscles support the leaflets of the mitral valve through fine fibers, the chordae tendinae.

The muscle fibers in the ventricular walls are distributed in an ordered pattern [1,86,87,88,89,91]. The epicardial fibers of the left ventricle run approximately in the axial direction (figure 1.1a). From the base the epicardial fibers spiral down into the apical vortex (figure 1.1b). They emerge again from this vortex in the endocardial layers in which they spiral towards the base. Near the basal plane the fibers cross over from the endocardial wall to the epicardial wall. In the midwall layers the fibers are oriented more circumferentially. In the basal part of the heart this circumferential layer is most profound, forming the bulbo-spiral muscle. The layers, described here, are not anatomically distinct: the orientation of the muscle fibers changes smoothly from epicardium to endocardium.

In a closer view the myocardial fibers consist of more or less parallel cardiac muscle cells (figure 1.1c). Adjacent muscle cells are interconnected by numerous

FIGURE 1.1: Basic anatomy of the left ventricle, showing (a) fiber structure of the left ventricular wall, (b) fibers spiralling into the apical vortex, (c) collagen fibers C connecting adjacent muscle cells M and (d) sarcomeres with length l_s consisting of thick myosine filaments M, and thin actine filaments A coupled at Z-lines Z.

bundles of short collagen fibers ('struts' [20]). It is expected that these struts prevent slipping of adjacent cells in both transverse and lateral directions. The collagen fibers also connect muscle cells to capillaries. Small groups of muscle cells are surrounded by a complex weave of collagen fibers. This weave is tightly connected to the cells which it surrounds. Its connections to other weaves are more loose: they are formed by relatively few long collagen fibers [20].

The contractile units, the sarcomeres, are located within the muscle cells (figure 1.1d). The sarcomeres consist of a parallel three-dimensional array of actine and myosine filaments. Sarcomeres are coupled in series through the Z-discs. These discs are connected to the cell membrane where they form the insertion places for the collagen struts that connect adjacent muscle cells [79]. Upon depolarization of the cell membrane, the actine filaments slide along the myosine filaments, causing shortening of the sarcomere. The details of the contraction process are not fully understood yet. However, it is clear that the force developed by the sarcomeres depends on the time after depolarization, the length of the sarcomeres, and their velocity of shortening.

1.2.2 Basic physiology: the left ventricular cycle

In a cardiac cycle four phases can be distinguished: the diastolic phase, the isovolumic contraction phase, the ejection phase and the isovolumic relaxation phase. The description of these phases will be focussed upon the left ventricle. Late in systole and during diastole the left atrium is passively filled from the pulmonary veins. As soon as the pressure in the relaxing left ventricle drops below left atrial pressure, the mitral valve opens and the ventricle is filled rapidly. Towards the end of the diastolic phase atrial contraction is initiated by a depolarization wave originating from the sinoatrial node. This atrial contraction contributes only to a limited extent of the filling of the ventricle. At the end of atrial contraction the depolarization wave has reached the endocardial apical part of the ventricle through a conducting system, the Purkinje network. From here the depolarization wave spreads across the myocardial wall, initiating contraction of the muscle cells. The increasing active stress is reflected by an increase of ventricular pressure that causes closure of the mitral valve.

This moment marks the beginning of the isovolumic contraction phase. During this phase ventricular volume remains constant because both the mitral valve and the aortic valve are closed. The increasing active stress in the ventricular wall causes a rapid increase of left ventricular pressure. As soon as ventricular pressure rises above aortic pressure the aortic valve opens and the ejection phase begins.

The first part of the ejection phase is marked by a rapid increase of aortic flow. After the flow has reached its maximum, it declines slowly. At the end of this phase aortic flow becomes slightly negative, causing complete closure of the aortic valve.

Now once again ventricular volume remains constant. During this isovolumic relaxation phase ventricular pressure falls because of the relaxation of the muscle cells in the ventricular wall. As soon as ventricular pressure drops below atrial pressure the diastolic phase starts again.

1.3 Existing models for description of ventricular mechanics

Based upon assumptions regarding geometry and material properties, mathematical models describing ventricular mechanics can be placed in one of the following categories:

- models with simple geometry and passive material
- models with realistic geometry and passive material
- models with simple geometry and contractile material
- models with both realistic geometry and contractile material

The following description of the models in the various categories is based partly upon review articles by Huisman *et al.* [39] and Yin [106].

1.3.1 Models with simple geometry and passive material

In the simplest models in this category it is assumed that the ventricular wall is thin as compared to the ventricular diameter. The geometry of the ventricle is approximated by a sphere, an ellipsoid or a cylinder [24,82]. In this case wall stress can be calculated from ventricular pressure and the dimensions of the geometry assumed. Predicted wall stress can be regarded as a first approximation of the average wall stress.

To evaluate transmural stress distribution, thickwalled models were developed. In these models the geometry of the left ventricle is approximated by a thick-walled sphere [55,56,57] or a thick-walled ellipsoid [31,54,104]. Usually, the myocardial tissue is assumed to be incompressible, isotropic and linearly elastic. In these models circumferential stress is found to decrease from the endocardium to the epicardium. However, the magnitude of this decrease is different for the various models. In the ellipsoid models longitudinal stress is found to decrease [31], to remain constant [104] or to increase [54] from endocardium to epicardium. In view of the different stress predictions of the various thick-walled models, Huisman *et al.* [39] concluded that the average wall stress predictions from the thin-walled ellipsoid model, designed by Falsetti *et al.* [24], are most suitable for clinical application.

1.3.2 Models with realistic geometry and passive material

A more realistic representation of the ventricular geometry can be obtained with the use of the finite element method. A short overview of the early models using the finite element method is given here. For a more detailed discussion the reader is referred to Yin [106]. Gould *et al.* [32] showed that the transmural stress distribution depends on local wall curvature. In a series of studies Janz *et al.* [45,46,47,48] showed the influence upon pressure-volume relationship and stress and strain distribution of 1) material anisotropy (to model the effect of the invaginations into the endocardial surface) [45], 2) regional heterogeneity of material properties [45,48], 3) material nonlinearity [46], and 4) the use of finite deformation theory instead of small deformation theory [47]. An axisymmetric geometry was used in these studies. Pao *et al.* [67,68] showed the effect of local wall curvature and varying wall thickness on stress distribution. In these models the material was assumed to be isotropic, homogeneous and linearly elastic. The influence of varying fiber orientation across the ventricular wall was investigated by Panda and Natarajan [66], who assumed a linearly elastic, anisotropic material. The transmural stress distribution was shown to vary with the degree of anisotropy assumed. Vinson *et al.* [99] examined the effect of different regional heterogeneities of material properties. The geometry of this model was nonsymmetric.

Yin [106] concludes that the models, discussed above, show that 'the finite element method can provide considerable insight into basic mechanical factors underlying function of the intact heart'. A related conclusion is that 'our ability to

optimally utilize this powerful method of analysis is currently limited by our inability to define very accurately the moment-to-moment three-dimensional geometry of the ventricle and our lack of data relative to the regional constitutive relations of myocardial tissue' [106]. To our view, these conclusions also apply to the finite element model presented in this thesis. Thus, the quantitative interpretation of the results obtained in our model must be done with care. However, in a qualitative respect, the model provides an increased understanding of mechanical behavior of the normal and ischemic left ventricle.

1.3.3 Models with simple geometry and contractile material

In the models in this category the geometry of the left ventricle is approximated by a thick-walled cylinder [2,3,4,7,21,26,92] or a thick-walled ellipsoid [10,11,12,13,93,94]. The shape of the thick-walled geometry assumed is preserved during the calculations. A variable fiber orientation is assumed across the ventricular wall. The myocardial material is represented as a fiber structure, embedded in an incompressible fluid. The most realistic models in this category are the model designed by Arts *et al.* [2,3,4,7] and the model designed by Beyer and Sideman [10,11,12,13].

The basis of the model designed by Arts *et al.* was presented in 1978 and 1979 [2,3]. In 1982 [4] minor modifications were introduced. Finally, in the 1989 model [7] a mitral valve papillary muscle system was incorporated. Since this last model yields results that are qualitatively and quantitatively in agreement with the simpler 1982 model, the 1982 model will be discussed. The model is meant to describe the mechanics of the equatorial region of the ventricular wall. This region is represented by a thick-walled cylinder composed of eight concentric cylindric shells. The myocardial tissue is modeled by a contractile fiber structure embedded in an incompressible fluid. In the passive state, stress in the fibers increases exponentially with strain. Contractile fiber stress depends on time, sarcomere length and velocity of sarcomere shortening. Material properties are homogeneous across the wall. Muscle fibers run parallel to the endo- and epicardial wall with different orientation for each cylindric shell. Fiber orientation in the outer four shells of the right half of the cylinder simulates the orientation in the right ventricular septum and free wall. Thus, it is different from the orientation in the corresponding shells in the left half, representing the left ventricular free wall. The aortic afterload is simulated by an inertia in series with a resistance and a parallel combination of a capacitance and a resistance. The cylinder can extend in axial and radial direction, and torsion around the cylinder axis is an allowed mode of deformation. The deformation is governed by conditions of axial and radial force equilibrium, and axial equilibrium of torques. With this model a complete cardiac cycle can be simulated.

During the ejection phase, homogeneous transmural distributions of fiber shortening and fiber stress are obtained in this model. This homogeneity can only be obtained if torsion around the cylinder axis is allowed. The calculated deformation of the cylinder is in agreement with the deformation as measured in animal

experiments [4].

The homogeneous distribution of fiber shortening and fiber stress is not found in the other models in this category. These models predict both maximum stress and shortening in the endocardial layers. In the model by Beyar and Sideman [12] ventricular torsion is introduced as a kinematic input variable. Although the twisting motion moderates stress and strain distributions, the latter model predicts that stress and strain remain higher in the subendocardium than in the subepicardium.

1.3.4 Models with realistic geometry and contractile material

Models in this category were designed by Huyghe [43] and the group of Perl [69] and Horowitz [37].

In the model by Perl and Horowitz the real irregular geometry of the left ventricle is considered, without rotation axis or symmetry planes. The myocardial material is composed of a bulk material, described by a Young's modulus and a Poisson's ratio of 0.45, in which fibers are embedded. Both the Young's modulus of the bulk material and the stiffness of the fibers increase with increasing strain. Varying fiber orientation across the wall is included. The simulation is based upon an experimentally determined time course of ventricular pressure and volume. In each time step, first the measured ventricular pressure is applied. Next active stresses in the fibers are chosen so that the calculated ventricular volume coincides with the experimentally determined volume. A good agreement is found between the computed geometry of the left ventricle and that measured experimentally. However, because of the way in which active stresses are implemented, the predictive value of this model is questionable.

In the model proposed by Huyghe [43] an axisymmetric geometry is assumed. Finite deformation including torsion around the axis of symmetry is considered. The myocardial tissue is represented as a spongy, anisotropic, viscoelastic material saturated with intracoronary blood. Both the solid material and the blood are incompressible. However, the volume of the ventricular wall can change since blood can be squeezed out of the wall. The constitutive behavior of the solid material is described by a quasi-linear viscoelastic law [28]. The elastic response of the viscoelastic law is nonlinear and anisotropic, while the relaxation behavior is isotropic. Active fiber stress depends on time, strain and strain rate. Transmural variation of muscle fiber orientation is included. It is shown that in subsequent cardiac cycles the transmural distribution of sarcomere stretch at end-diastole departs from the initially assumed distribution, due to the viscoelastic constitutive behavior. Calculated time course of ventricular pressure, aortic flow and epicardial deformation agrees fairly well with experimental data of Arts *et al.* [4]. During ejection, sarcomere shortening is larger and active fiber stress is lower in the midwall layers than in the subendo- and subepicardial layers. About 3 ml blood per 100 g myocardial tissue, which is equivalent to about 20% of the intramyocardial blood volume, is expelled from the myocardial tissue from the end of diastole to end of the ejection

phase. This value is rather high as compared to the total flow through the tissue which experimentally is found to be in the order of 1 ml per 100 g of myocardial tissue [84]. Subendocardial tissue pressure differs slightly from ventricular pressure. This result differs from the results obtained in models where the transverse passive stiffness of the solid is neglected. In the latter models subendocardial tissue pressure equals ventricular pressure.

1.4 Properties of the model

The model presented in this thesis has the following properties:

1. inertial forces and gravity forces are neglected
2. passive material behavior is three-dimensional, incompressible, anisotropic and nonlinearly elastic
3. active fiber stress depends on time, strain, and strain rate
4. transmural variation of muscle fiber orientation is included
5. a three-element aortic impedance is included
6. the initial left ventricular geometry is represented by a thick-walled truncated ellipsoid of revolution
7. during the simulation of a normal ventricular cycle rotational symmetry is maintained, as a result of rotationally symmetric input parameters
8. no rotational symmetry is assumed during the simulation of regional ischemia

The properties listed above are elucidated below:

1. assuming a characteristic radial dimension of the left ventricle of about 3 cm, gravity forces are important if ventricular pressure is in the order of 3 cm water pressure, or about 0.3 kPa. During systole, ventricular pressure is considerably higher than 0.3 kPa allowing the neglect of gravity forces. During diastole, effects of gravity are present. For simplicity, these effects are not taken into account. Moskowitz [58] has shown that the effect of inertia can also be neglected.
2. the viscoelastic constitutive law proposed by Huyghe [43] will not be used in the present model. In the first place, the concept of quasi-linear viscoelasticity [28] seems to be inadequate to describe the experimentally observed effects of viscoelasticity completely [43]. Secondly, evaluation of the parameter values in any viscoelastic law will be subject to large uncertainties, since experimental data on viscoelastic behavior of myocardial tissue are scarce. In the third place,

the incorporation of viscoelasticity implies that a number of consecutive beats must be simulated to obtain a steady-state solution. This is time consuming. Furthermore, the simple assumption of material incompressibility is preferred over the inclusion of intramyocardial blood flow.

3. the model for the description of the contractile properties of the myocardial tissue is similar to the model presented by Arts [4]. It differs from the latter model only through its slightly modified stress-strain rate dependency.
4. in the initial simulations, the muscle fibers are located in planes that are parallel to the endocardial and epicardial planes. Within these planes fiber orientation can vary. In later simulations the cross-over of muscle fibers between endocardium and epicardium is considered.
5. aortic impedance is modeled by a three-element Windkessel model, consisting of an aortic resistance in series with a parallel combination of an arterial compliance and a peripheral resistance.
6. a thick-walled truncated ellipsoid of revolution is a reasonable approximation of the major part of the left ventricular geometry [89]. A complete description of the geometry of the real ventricle is not available yet. Note that this model differs from the models described in section 1.3.4, since the deformed geometry is allowed to deviate from a truncated ellipsoidal geometry.
7. because limited information on the distribution of material properties and fiber orientation across the entire ventricular wall is available, no spatial variation of these properties is introduced in the model. Since the initial geometry of the ventricle is rotationally symmetric too, rotational symmetry is maintained during the entire cardiac cycle. Taking advantage of this symmetry for a regular cardiac cycle, computing time and cost can be reduced.
8. in the case of ischemia, material properties are no longer homogeneous and consequently no symmetry can be assumed anymore. Alterations in the deformation pattern caused by ischemia can be distinguished relatively easily from the rotationally symmetric regular deformation pattern.

In the model, the finite element method is used as a numerical solution method since it enables the introduction of the spatial variation of material properties. Thus, regional ischemia can be simulated. Moreover, using the finite element method, it is possible to simulate the complicated deformation pattern of the left ventricle, that is expected to occur in the case of ischemia.

1.5 Outline of the thesis

The design of the model of the left ventricle, starting from experimental physiological data, is described in chapter 2. Ventricular geometry, fiber orientation and boundary conditions are discussed. Constitutive equations are formulated, that describe the mechanical properties of the myocardial tissue, as observed in experiments on excised specimens.

In chapter 3 the constitutive equations are combined with the laws of conservation of mass, momentum, and moment of momentum. The resulting set of equations is transformed into a numerical formulation using the finite element method. A three-dimensional brickshaped element is developed to describe the deformation of a piece of myocardial tissue.

With these elements the geometry of the left ventricle is modelled in chapter 4. A reference simulation is made of the mechanical behavior of the normal ventricle during a cardiac cycle, in which the orientation of the fibers in the ventricular wall is estimated such, that fiber stress is distributed approximately homogeneously across the ventricular wall [4].

In chapter 5 the results of the simulation of the mechanics of the normal left ventricle during a cardiac cycle are compared with experimental data.

In chapter 6, the mechanical behavior of the ischemic left ventricle is simulated. Again, results of the simulation are compared with experimental results.

This thesis concludes with a general discussion on the validity and possible applications of the model.

Design of the model of the left ventricle

In section 1.2.1 a brief description has been given of the anatomy of the left ventricle. In section 2.1 of this chapter the anatomy is discussed more quantitatively. Based upon experimentally obtained anatomical data, in subsection 2.1.1 the geometry of the model of the left ventricle is defined. In subsection 2.1.2 the coordinate systems that are used in the model, are introduced. The implementation of the varying orientation of the muscle fibers across the ventricular wall is discussed in subsection 2.1.3. Subsection 2.1.4 deals with the distribution of sarcomere length across the ventricular wall.

The constituents of the myocardial tissue, such as the connective tissue, the muscle fibers, and the fluid matrix, contribute to the total stress in the tissue. In subsection 2.2.1 experimental data on the passive stress contribution of the connective tissue are presented. In subsection 2.2.2 for the passive myocardium a constitutive law is proposed, which approximates experimental observations reasonably well. Some experimental data on contractile properties of myocardial tissue are presented in subsection 2.2.3. A mathematical model of the relation between active stress, time, strain, and strain-rate in muscle fibers is presented in subsection 2.2.4. The activation sequence of the left ventricle is discussed in section 2.2.5. In section 2.3, the boundary conditions, that will be applied during the simulation of a cardiac cycle, are considered. Kinematic constraints, the loading of the endocardial and epicardial surface of the ventricle and the hemodynamic coupling of the ventricle to the aorta are discussed.

2.1 Geometry of the model of the left ventricle

2.1.1 Macroscopic geometry

The simulation of the cardiac cycle starts from a reference state, defined as the situation with zero transmural pressure. In this reference state, stresses and strains are assumed to be zero. Thus, residual stresses and strains [28,63] are neglected. The finite element method is capable of taking into account the complex geometry of the left ventricle. Because experimental data on this geometry are not complete, in the model a rather simple thickwalled geometry is assumed in which the endocardial and epicardial surfaces consist of truncated confocal ellipsoids. This geometry, which describes the major part of the real ventricular geometry reasonably well [87], is defined by only 4 parameters: the volume V_e , enclosed between the endocardial and epicardial ellipsoid, the volume V_i of the enclosed cavity, the height h above the equator at which the ellipsoids are truncated and the common focal length of the ellipsoids C . To quantify the volumes V_e and V_i from experimental data, additionally the left ventricular wall volume V_w and cavity volume V_{lv} , and the papillary muscle volume V_{pap} are defined. V_w represents the total volume of the left ventricular wall. V_{pap} is the volume of part of the ventricular wall lying within the endocardial ellipsoid, and is associated mainly with the papillary muscles. The blood in the ventricular cavity occupies a volume V_{lv} . The volumes are mutually related according to:

$$V_e = V_w - V_{pap} \quad (2.1)$$

$$V_i = V_{lv} + V_{pap} \quad (2.2)$$

In figure 2.1 the geometry of the left ventricle, as chosen in the model, is illustrated. The choice of the values of the parameters defining the geometry is based upon data presented in literature [80,87]. Streeter and Hanna [87] used experimental data on the dimensions of the left ventricle, presented by Ross *et al.* [80], to approximate the geometry by a set of nested, nonconfocal truncated ellipsoids of revolution. Focal length C and fractional height $f = h/Z$ above the equator were calculated in 5 hearts fixed at diastole and 5 hearts fixed at systole, for both the endocardial and epicardial ellipsoid. From these 20 values, the following average values were obtained: $C = 37.5 \pm 1.0$ mm and $f = h/Z = 0.475 \pm 0.029$. The 10 hearts had a left ventricular wall mass $m_w = 99.0 \pm 4.3$ g and a papillary muscle volume $V_{pap} = 2.6 \pm 0.6$ ml.

The cavity volume at zero transmural pressure is called the equilibrium volume V_0 . Spotnitz *et al.* [85] measured an equilibrium volume $V_0 = 12.5 \pm 0.9$ ml and a wall mass $m_w = 96.4 \pm 2.6$ g ($n = 27$). Assuming a tissue density of 1.05 g/ml this yields a ratio $V_0/V_w = 0.14$. Based upon data collected from several studies described in literature, Nikolić *et al.* [60] obtained the following values: $m_w = 90 \pm 27$ g and $V_0/m_w = 0.29$ ml·g⁻¹, ($n = 35$). From these data a ratio $V_0/V_w = 0.30$ is calculated. McCulloch *et al.* [53] measured the following values: $V_0 = 40 \pm 9$ ml, $m_w = 145 \pm 19$ g, ($n = 6$), from which a ratio $V_0/V_w = 0.29$ results.

FIGURE 2.1: Geometry of the model showing inner and outer short axis R_i and R_o , inner, midwall and outer long axis Z_i , Z_m and Z_o , height above the equator h , focal length C , volume between endo- and epicardial ellipsoid V_e , papillary muscle volume V_{pap} and ventricular volume V_{iv} .

In the model a value $V_w = 140$ ml is chosen, since this volume was approximately the mean of the ventricular wall volumes in the dogs used in our experiments (chapter 5). Assuming papillary muscle volume to be proportional to wall volume, and using the data presented by Streeter [87], a papillary muscle volume $V_{pap} = 4$ ml is found. Using the data from Nikolić *et al.* [60] and McCulloch *et al.* [53], the equilibrium volume V_0 is chosen to be 40 ml. The ratio $V_0/V_w = 0.14$, obtained by Spotnitz *et al.* [85], was neglected in this choice: this ratio is very small, as compared to the data obtained in the other studies described above, and may have been caused by ischemic contracture. The values for C and h are based upon above mentioned data obtained by Streeter [87]. Assuming the focal length C to be proportional to $\sqrt[3]{V_w}$, a value $C = 43$ mm is obtained. The fractional height above the equator of the midwall ellipsoid $f_m = h/Z_m$ is assumed to be 0.50. Using the values of V_w , V_{pap} , V_0 , C and f_m , the values of R_i , R_o , Z_i , Z_o and h , indicating the dimensions of the geometry of the left ventricle in the reference state, were calculated (table 2.1).

2.1.2 Coordinate systems used in the model

In the geometry of the left ventricle three coordinate systems are introduced:

- a global Cartesian coordinate system (x_1, x_2, x_3) ,
- a global ellipsoid coordinate system (ξ, θ, ϕ) , and
- a local normalized coordinate system $(\bar{\xi}, \bar{\theta})$.

The origin of the Cartesian coordinate system (x_1, x_2, x_3) is located in the common center of the endocardial and epicardial ellipsoids (figure 2.2a). The positive x_3 -axis is directed towards the base along the long axis of the ellipsoids. The positive x_1 -axis is directed towards the free wall of the left ventricle, while the negative x_1 -axis

TABLE 2.1: Values of the parameters describing the geometry of the left ventricle in the reference state; f_m represents the fractional height h/Z_m of the midwall ellipsoid.

input data			derived data		
parameter	value	unit	parameter	value	unit
V_w	140.	ml	R_i	16.3	mm
V_{pap}	4.	ml	R_o	31.3	mm
V_0	40.	ml	Z_i	46.0	mm
C	43.	mm	Z_o	53.2	mm
f_m	0.5	-	h	24.8	mm

points at the intraventricular septum. These Cartesian coordinates are used in the finite element program.

The origins of the global Cartesian and ellipsoid coordinate system (figure 2.2b) coincide. The transformation of the ellipsoid coordinates (ξ, θ, ϕ) to the global coordinates (x_1, x_2, x_3) is given by:

$$x_1 = C \sinh(\xi) \sin(\theta) \cos(\phi) \quad (2.3)$$

$$x_2 = C \sinh(\xi) \sin(\theta) \sin(\phi) \quad (2.4)$$

$$x_3 = C \cosh(\xi) \cos(\theta) \quad (2.5)$$

where C represents the common focal length of the ellipsoids. The circumferential ellipsoid coordinate ϕ is equal to $\arctan(x_2/x_1)$. At the endocardial and epicardial surfaces the radial ellipsoid coordinate ξ is constant and equals ξ_{en} and ξ_{ep} , respectively. In the reference geometry, defined in the previous subsection, $\xi_{en} = 0.37$ and $\xi_{ep} = 0.68$. The longitudinal ellipsoid coordinate θ ranges from 0 on the positive x_3 -axis to π on the negative x_3 -axis. Surfaces of constant θ intersect surfaces of constant ξ perpendicularly. Ellipsoid coordinates are used in section 2.2.5 to describe the activation pattern of the ventricular wall.

The local normalized coordinates $(\bar{\xi}, \bar{\theta})$ are defined in a plane of constant ϕ (figure 2.2c). Like the ellipsoid coordinates, they are chosen to describe the geometry of the ventricle in a simple way. In contrast to the ellipsoid coordinates, the normalized coordinates vary linearly with the actual distances in the ventricular wall. The origin of the normalized coordinate system is located at the equator on the midwall ellipsoid. The normalized radial coordinate $\bar{\xi}$ varies linearly from $\bar{\xi} = -1$ at the endocardial surface to $\bar{\xi} = +1$ at the epicardial surface. The normalized longitudinal coordinate $\bar{\theta}$ varies linearly with the distance from the equatorial plane. This distance is measured along the curve of constant ϕ and ξ , that passes through the point of interest. $\bar{\theta}$ is defined to vary from $\bar{\theta} = +0.5$ in the basal plane, through

FIGURE 2.2: Coordinate systems used: (a) global Cartesian coordinates (x_1, x_2, x_3) . (b) global ellipsoid coordinates (ξ, θ) in a plane of constant $\phi = \arctan(x_2/x_1)$; lines of constant θ (---) are indicated for clarity. (c) local coordinates $(\tilde{\xi}, \tilde{\theta})$ in a plane of constant ϕ .

$\tilde{\theta} = 0$ at the equator until $\tilde{\theta} = -1$ at the apex. In the next subsection, muscle fiber orientation will be modeled using the normalized coordinates.

2.1.3 Muscle fiber orientation

In subsection 1.2.1 a qualitative description of the structure of the left ventricular wall has been given. The orientation of muscle fibers in the ventricular wall can be quantified by the helix fiber angle α_1 and the transverse fiber angle α_3 , as shown in figure 2.3. The helix fiber angle is defined as the angle between the ϕ -direction and the projection of the fiber path on the (θ, ϕ) -plane. The transverse fiber angle is defined as the angle between the ϕ -direction and the projection of the fiber path on the (ξ, ϕ) -plane. This way of defining fiber orientation is consistent with Streeter [89]. Since muscle fibers run approximately parallel to the endo- and epicardial surface, measurements of fiber orientation have been focussed almost exclusively upon α_1 . Some of the results of such measurements are presented in figure 2.4 [33,81,86,89]. A monotonic increase of α_1 from epicardium to endocardium is measured. In the subepicardial layers measured values of α_1 range from about -80° to -50° . In the midwall region fibers run approximately circumferentially. In the subendocardial layers measured values of α_1 range from $+20^\circ$ to $+80^\circ$. The relatively large variation in the endocardial layers is partly caused by the irregular shape of the endocardium, making it difficult to define the endocardial surface. Ross *et al.* [81] and Streeter [89] use the point of farthest invagination of the endocardium into the wall in their

FIGURE 2.3: Quantification of muscle fiber orientation: (a) helix fiber angle α_1 (which is negative at the indicated epicardial site) and (b) transverse fiber angle α_3 at the base as viewed from the atrial side; indicated angle α_3 is positive.

procedure of normalizing the transmural coordinate. With the use of this definition a smaller variation of measured values of α_1 is found.

The transverse fiber angle α_3 describes how the fibers proceed between endocardium and epicardium. This 'cross-over' occurs mainly near the base and the apex [1,91]. Above the equator, α_3 has been measured to be positive. Below the equator, measured values of α_3 range from -30° to 0° , with an average value of $-8.4^\circ \pm 1.0^\circ$ [88]. In another study [89] the value of α_3 , averaged across the wall thickness, was found to be $-4.6^\circ \pm 0.8^\circ$ near the apex and $-3.5^\circ \pm 0.6^\circ$ halfway between equator and apex.

In the model, the spatial distribution of α_1 and α_3 is a function of the local coordinates $(\bar{\xi}, \bar{\theta})$ that were defined in subsection 2.1.2. It is assumed that the helix fiber angle α_1 is independent of the longitudinal coordinate $\bar{\theta}$. The transmural variation of α_1 is modelled as:

$$\alpha_1(\bar{\xi}) = \alpha_{10} + \alpha_{11}\bar{\xi} + \begin{cases} \alpha_{12,en} \left(\frac{\bar{\xi} + \bar{\xi}_1}{-1 + \bar{\xi}_1} \right)^2 & \bar{\xi} \leq -\bar{\xi}_1 \\ 0 & -\bar{\xi}_1 < \bar{\xi} < \bar{\xi}_1 \\ \alpha_{12,ep} \left(\frac{\bar{\xi} - \bar{\xi}_1}{1 - \bar{\xi}_1} \right)^2 & \bar{\xi} \geq \bar{\xi}_1 \end{cases} \quad (2.6)$$

This transmural course of α_1 is illustrated in figure 2.5a.

Experimental information on the spatial distribution of α_3 is limited. Since muscle fibers do not end at the endocardial and epicardial surfaces, α_3 was assumed to be zero at these surfaces. The following transmural course of α_3 satisfies this condition:

$$\alpha_3(\bar{\xi}, \bar{\theta}) = \alpha_3(\bar{\theta}) (1 - \bar{\xi}^2) \quad (2.7)$$

FIGURE 2.4: Transmural variation of the helix fiber angle α_1 : (a) Streeter et al. [86], ten dog hearts; (b) Greenbaum et al. [33], human heart. (c) Ross et al. [81], macaque heart; (d) Streeter [89], eight human hearts. In figures (c) and (d) $\bar{\xi}^* = 0$ indicates the point of deepest invagination of the endocardium into the wall while at the epicardial surface $\bar{\xi}^*$ equals +1.0. Measurements were performed approximately in basal (Δ), equatorial ($\circ$), equatorial/apical ($\square$) and apical (∇) region.

FIGURE 2.5: Illustration of muscle fiber orientation in the model as described by equations (2.6) through (2.8); (a) transmural variation of $\alpha_1(\bar{\xi})$ for initial (—) and reference (---) parameter values in table 2.2; (b) transmural variation of $\alpha_3(\bar{\xi}, \bar{\theta})$ at $\bar{\theta} = +0.5$ (—) and $\bar{\theta} = -1$ (---) for reference parameter values; (c) longitudinal variation of $\alpha_3(\bar{\xi}, \bar{\theta})$ at $\bar{\xi} = 0$ for reference parameter values.

Since α_3 is positive above, and negative below the equator [88] it is assumed that in the equatorial plane α_3 equals zero. This condition is satisfied by the following longitudinal course of α_3 :

$$\alpha_3(\bar{\theta}) = \begin{cases} \alpha_{31} \bar{\theta} & \bar{\theta} < 0 \\ \alpha_{31} \bar{\theta} + \alpha_{32} (2\bar{\theta})^2 & \bar{\theta} \geq 0 \end{cases} \quad (2.8)$$

The transmural and longitudinal variation of α_3 is illustrated in figure 2.5b and c. Because of the limited experimental information, in the initial calculations α_3 is set at 0. In later calculations, the influence of a different choice of α_3 will be investigated.

In table 2.2 parameter values determining fiber orientation for both the initial

TABLE 2.2: Values of the parameters describing muscle fiber orientation in the initial and reference calculations.

parameter	α_{10}	α_{11}	$\alpha_{12,en}$	$\alpha_{12,ep}$	$\bar{\xi}_1$	α_{31}	α_{32}
initial	0°	-30°	30°	-30°	0.5	0°	0°
reference	25°	-70°	-25°	-25°	0.5	10°	5°

FIGURE 2.6: Transmural variation of sarcomere length in the post-mortem left ventricle at various levels of ventricular pressure; (a) Spotnitz *et al.* [85]: 0.0 kPa (∇), 0.3 kPa ($\circ$), 0.7 kPa ($\square$), 1.0 kPa ($\diamond$), 1.3 kPa ($\triangle$) and 1.6 kPa ($+$); (b) Yoran *et al.* [108]: 0.3 kPa (∇), 0.8 kPa ($\circ$), 1.6 kPa ($\square$), 2.6 kPa ($\triangle$); (c) Grimm *et al.* [34]: 0.0 kPa (∇), 0.4 kPa ($\circ$), 0.8 kPa ($\square$), 1.6 kPa ($\diamond$), 3.2 kPa ($\triangle$), 6.3 kPa ($+$).

and the later defined (section 4.3) reference calculations are listed.

2.1.4 Transmural distribution of sarcomere length

Active stress developed by the muscle fibers depends on sarcomere length. Results of measurements of the transmural distribution of sarcomere length in the passive left ventricle are shown in figure 2.6. According to Spotnitz *et al.* [85] the longest sarcomeres are found in the subendocardial region (figure 2.6a). This agrees with the results of Yoran *et al.* [108], as far as the midwall and epicardial region is concerned. At pressures up to 1.6 kPa Yoran *et al.* found the shortest sarcomeres in the subendocardial layers (figure 2.6b). This finding agrees with the results of Grimm *et al.* [34]. However, the latter investigators measured an increase in sarcomere length from the endocardium up to three quarters of the wall thickness. In the subepicardial layers sarcomere length was shorter again (figure 2.6c).

Because of the large variation observed in these measurements, in the model a homogeneous spatial distribution of sarcomere length is chosen in the reference state. The length is set at $1.85 \mu\text{m}$, since passive stress is measured to be zero at this sarcomere length [90].

2.2 The constitutive behavior of myocardial tissue

In subsection 1.2.1 a qualitative description has been given of the constituents of myocardial tissue: connective tissue (mainly collagen fibers), muscle fibers and fluid matrix. Each constituent contributes to the total stress in the tissue in the following way:

$$\boldsymbol{\sigma} = -p\mathbf{I} + \boldsymbol{\sigma}_p + \sigma_a \mathbf{e}_3 \mathbf{e}_3 \quad (2.9)$$

In the fluid matrix only the hydrostatic pressure component $-p\mathbf{I}$ is present. Deformation of the cardiac tissue gives rise to a three-dimensional passive stress $\boldsymbol{\sigma}_p$ in the collagen fibers. Finally, a uniaxial active stress $\sigma_a \mathbf{e}_3 \mathbf{e}_3$ is generated in the muscle fibers, parallel to the fiber direction $\mathbf{e}_3$. In this section experimental results regarding passive and active stress in cardiac tissue will be presented. On the basis of these findings, the mechanical behavior of the tissue is described in terms of constitutive equations.

2.2.1 Passive constitutive behavior: experimental data

The mechanical properties of cardiac tissue in the passive state have been studied by several investigators [71,90,107]. Yin *et al.* [107] subjected thin (1-2 mm) slices of canine myocardium to a simultaneous equal stretch in fiber and cross-fiber direction. In both fiber and cross-fiber direction the force, needed to obtain a certain stretch, was measured. Strains were determined in the central part (1×1 cm) of the specimen, which measured about 4×4 cm. From these strain and force measurements, stress was calculated and plotted as a function of strain. A four-parameter strain-energy function, relating second Piola-Kirchhoff stress to Green-Lagrange strain (see appendix A for definitions of stress and strain) was introduced to describe the stress-strain plots mathematically. The parameters in the strain-energy function were determined from a fit to experimental data obtained from five specimens, that were subjected to strains up to about 14 %. Fiber and cross-fiber stresses, calculated from this strain-energy function for the case of an equibiaxial stretch test, are shown in figure 2.7a and b, respectively. In these experiments Green-Lagrange strain E is given by:

$$E = \frac{1}{2} \left(\left(\frac{l}{l_0} \right)^2 - 1 \right) \quad (2.10)$$

l and l_0 denote the actual and reference length of the specimen, respectively. For small strain values Green-Lagrange strain is approximately equal to linear strain $(l - l_0)/l_0$. In these experiments second Piola-Kirchhoff stress S is given by:

$$S = \left(\frac{l_0}{l} \right)^2 \sigma \quad (2.11)$$

FIGURE 2.7: Stress-strain relationship in canine cardiac tissue as derived from the strain-energy function proposed by Yin et al. [107] for the case of equal stretch in fiber and cross-fiber direction in five specimens: (a) second Piola-Kirchhoff fiber stress S_{ff} versus Green-Lagrange fiber strain E_{ff} ; (b) second Piola-Kirchhoff cross-fiber stress S_{cc} versus Green-Lagrange cross-fiber strain E_{cc} . Different specimens are indicated by different line types. Corresponding fiber and cross-fiber data are indicated by the same line type.

Cauchy stress σ is defined as force divided by actual area. For small strain values second Piola-Kirchhoff stress is approximately equal to Cauchy stress. The behavior of the five specimens varies significantly: at a Green-Lagrange fiber strain $E_{ff} = 0.15$ the second Piola-Kirchhoff stresses S_{ff} range from 5 kPa to 100 kPa. The cross-fiber stresses S_{cc} were observed to be proportional to the fiber stresses, with a ratio S_{ff}/S_{cc} of 1.10, 1.55, 1.67, 2.67 and 2.95, respectively, yielding a mean ratio of 1.99. The large variations in the observed mechanical behavior may be the result of specimen differences. They can also be caused by variations in the choice of the reference state to which the strains are referred. This reference state, the unloaded state, is not well-defined because of the very compliant behavior of the tissue under conditions of small stress, and because of viscoelastic effects. Furthermore, the excised specimens may have been subject to different degrees of ischemic contracture.

In the uniaxial experiments of Ter Keurs *et al.* both active and passive properties of rat trabeculae were measured [90]. After excision, the trabeculae were submerged in a fluid, that ensured a stable mechanical response during at least 6 hours. Using sarcomere length as a measure of tissue strain, the problems associated with the definition of a reference state were avoided. Stress was calculated by dividing the

FIGURE 2.8: Results of uniaxial stretch experiments in 20 rat trabeculae (Ter Keurs *et al.* [90]). Passive stress, calculated as applied force F divided by unloaded cross-sectional area A_0 , is plotted versus sarcomere length l_s . Sarcomere length in the unloaded state equals $1.85 \mu\text{m}$.

force, needed to extend the trabeculae, by the cross-sectional area of the unloaded trabeculae. Despite the mechanical stability of the trabeculae and the well-defined measure of strain, large variations in stress-strain behavior are observed in these experiments also, as is apparent from figure 2.8.

At present the data from the experiments, described above, are the most accurate data available. In these experiments, the tissue was subjected to normal stresses. Experiments in which the direction of mechanical loading was neither parallel nor perpendicular to the fiber direction, have not been published yet.

2.2.2 A constitutive law for the passive myocardium

As discussed in section 1.5, in this study the passive myocardium is assumed to be elastic. Its mechanical behavior may be characterized by a strain-energy function, relating stresses to strains. A suitable form of the strain-energy function can be found using a microstructural or a phenomenological approach.

The microstructural approach was followed by Horowitz *et al.* [38], who applied a theory proposed by Lanir [50]. In this theory the macroscopic behavior of the tissue is described in terms of the properties of the muscle fibers, the collagen fibers and the fluid matrix. Since the material parameters are associated with microstructural properties, this approach can provide insight into the origin of the observed macroscopic behavior. However, at present not all relevant material parameters have been evaluated experimentally, and consequently they have to be estimated. Moreover, the mathematical description is complicated.

The advantage of the phenomenological approach is its mathematical simplicity. However, no insight is provided into the mechanisms that are responsible for the macroscopically observed material behavior. Almost all constitutive laws, that have been proposed for the passive myocardium, belong to this category [41,42,43,71,107]. For various reasons, none of these constitutive models are used in the present study. The models presented by Pinto and Fung [71] and Yin *et al.* [107] do not describe the three-dimensional mechanical behavior of the tissue. Huyghe [43] assumes orthotropic behavior of the tissue. However, on the basis of the structure of myocardial tissue, transverse isotropy with respect to the fiber direction may be preferred. In the model presented by Humphrey and Yin [41,42] transverse isotropy is assumed. However, in this model stresses exist in the absence of strain. Application of this function to the model of the left ventricle, as proposed in subsection 2.1.1, would lead to the conclusion that residual stresses exist in the ventricle in the reference configuration. Generally, the ventricle would not be in mechanical equilibrium in this reference state.

In the present study a new strain-energy function has been used. This function $W(\mathbf{E})$ relates the second Piola-Kirchhoff stress tensor $\mathbf{S}$, based upon the deviatoric Cauchy stress tensor, to the Green-Lagrange strain tensor $\mathbf{E}$ according to:

$$\mathbf{S} = \partial W(\mathbf{E}) / \partial \mathbf{E} \quad (2.12)$$

The myocardial tissue is assumed to be transversely isotropic with respect to the fiber direction. With respect to an orthonormal coordinate system with direction $\mathbf{e}_3$ parallel to the fiber direction, and cross-fiber directions $\mathbf{e}_1$ and $\mathbf{e}_2$, the strain tensor $\mathbf{E}$ is written as the strain matrix E with components E_{ij} . The strain-energy function $W(E)$ for a material that is transversely isotropic with respect to $\mathbf{e}_3$, can be expressed as a single valued function of the following set of scalars [51]:

$$I_E = E_{11} + E_{22} + E_{33} \quad (2.13)$$

$$II_E = E_{12}^2 + E_{23}^2 + E_{31}^2 - E_{11}E_{22} - E_{22}E_{33} - E_{33}E_{11} \quad (2.14)$$

$$III_E = \det(E) \quad (2.15)$$

$$I'_E = E_{33} \quad (2.16)$$

$$II'_E = E_{31}^2 + E_{32}^2 \quad (2.17)$$

The functional form of $W(E)$ is chosen so that (1) W is zero in the unstrained state, (2) stress is an exponential function of strain and (3) no stresses are predicted in the undeformed situation. The following strain-energy function is consistent with these conditions:

$$W(E) = C \left[\exp(a_1 I_E^2 + a_2 II_E + a_3 E_{33}^2 + a_4 (E_{31}^2 + E_{32}^2)) - 1 \right] \quad (2.18)$$

Because of the additional condition of incompressibility of the cardiac tissue the scalar III_E is left out of this strain-energy function.

The values of the material parameters are estimated from fitting this function to experimentally obtained data. Firstly, according to the experimental findings of Yin

TABLE 2.3: Values of parameters in the strain-energy function describing passive material behavior: $W(\underline{E}) = C[\exp(a_1 I_E^2 + a_2 II_E + a_3 E_{33}^2 + a_4 (E_{31}^2 + E_{32}^2)) - 1]$.

parameter	C	a_1	a_2	a_3	a_4
value	0.7	5.0	10.0	5.0	0.0
unit	kPa	-	-	-	-

et al. [107], the ratio of second Piola-Kirchhoff fiber to cross-fiber stress is required to equal 2 under conditions of equal fiber and cross-fiber stretch. This condition is satisfied by setting:

$$a_1 = 2 a_2 = a_3 \quad (2.19)$$

Secondly, it is required that the uniaxial stress-strain data obtained by Ter Keurs *et al.* [90] are described reasonably well. Thirdly, a_4 is set at zero, because of the lack of experimental data on the mechanical behavior of cardiac tissue under conditions of shear stress. The resulting parameter values are listed in table 2.3.

2.2.3 Contractile constitutive behavior: experimental data

In experiments it has been found that active stress, generated by cardiac muscle cells, depends on time, sarcomere length and velocity of shortening of the sarcomeres [16,72,90,95]. Reviews on these investigations are given by Bergel and Hunter [9] and Fung [28]. As a representative example of these investigations, in this subsection the results of experiments performed on rat trabeculae by ter Keurs *et al.* [90] and van Heuningen *et al.* [95] are described. In figure 2.9a the time course of active force during a twitch, in which sarcomere length is held constant, is shown. Both maximum active force and duration of contraction increase with increasing sarcomere length. In figure 2.9b active force is shown to increase with increasing extracellular calcium concentrations as well. Finally, figure 2.9c shows how the velocity of sarcomere shortening decreases with increasing load: a load of 100% corresponds to the isometric contractions shown in figure 2.9a.

2.2.4 A mathematical model describing active material behavior

Commonly, contractile behavior is modeled by a three-element model [36]. This model consists of a passive parallel elastic element, in parallel to a series elastic element in series with a contractile element (figure 2.10a). The passive parallel elastic element represents the stress-strain behavior of the passive tissue, which has been described in the subsections 2.2.1-2.2.2. The active element is modeled according to Arts [2,4]. The first Piola-Kirchhoff stress T_a is used. This measure of

FIGURE 2.9: Results of experiments on rat trabeculae at 25°C: (a) twitch force as a function of time t at constant sarcomere length l_s of 1.65, 1.75, 1.85, 1.93, 2.11 and 2.28 μm , respectively; (b) relation between active first Piola Kirchhoff stress T_a (active force divided by cross-sectional area of the trabeculae in the situation with $l_s = 2.0 \mu\text{m}$) and sarcomere length l_s for two levels of extracellular calcium concentration: $[Ca^{++}] = 2.5 \text{ mM}$ (—) and 0.5 mM (---); (c) velocity of sarcomere shortening versus applied load. 100% load corresponds to zero sarcomere shortening. Data adapted from ter Keurs et al. [90] (figure b) and van Heuningen et al. [95] (figures a and c).

stress is easily obtainable in experiments, since it represents generated active force F_a per unit of cross-sectional area A_0 in a certain reference situation:

$$T_a = \frac{F_a}{A_0} \quad (2.20)$$

The stress generated by the contractile element is transmitted by the series elastic element. In the unstressed state, the length of this element is zero. In the active state it equals $l_s - l_c$, where l_c and l_s are the length of the contractile element and the sarcomere, respectively. The stress in the passive element is given by:

$$T_a = E_a T_{maz}(l_s - l_c) \quad (2.21)$$

The stiffness of the passive element is equal to $E_a T_{maz}$ where E_a is constant. T_{maz} depends on l_s , l_c , and the time t_s that has elapsed since the moment of onset of activation:

$$T_{maz} = T_1 A(l_c) B_r(t_s) B_d(t_s, l_s) \quad (2.22)$$

FIGURE 2.10: Active material behavior as assumed in the model: (a) three-element model with parallel elastic element PE, series elastic element SE, contractile element CE, sarcomere length l_s and contractile element length l_c ; (b) length-dependency of active stress; (c) time dependency of active stress at $l_s = 1.7, 1.9, 2.1$ and 2.3 μm; (d) force-velocity relationship ($v_c = dl_c/dt$).

The constant T_1 is associated with the level of maximum isometric stress. The factor $A(l_c)$ represents the length-dependency of the active stress development (figure 2.10b):

$$A(l_c) = 1 + a_x(l_c - l_x) - \sqrt{(a_x(l_c - l_x))^2 + 0.01} \quad (2.23)$$

At $l_c > l_x$ the active stress T_a levels off. The constant a_x is associated with the increase of active stress as a function of sarcomere length at small ($1/(2a_x) < l_c < l_x$) sarcomere lengths. The rise and decay of active stress as a function of time is described by the factors $B_r(t_s)$ and $B_d(t_s, l_s)$, respectively (figure 2.10c):

$$B_r(t_s) = 1 - \frac{1}{1 + (t_s/t_r)^4} \quad (2.24)$$

TABLE 2.4: Values of the parameters in the contraction model.

parameter	value	unit	parameter	value	unit
T_1	110.0	kPa	t_r	75.0	ms
T_0	55.0	kPa	t_d	75.0	ms
E_a	20.0	μm^{-1}	v_0	0.0075	$\mu\text{m}\cdot\text{ms}^{-1}$
a_x	1.3	μm^{-1}	b	150.0	$\text{ms}\cdot\mu\text{m}^{-1}$
l_x	2.0	μm	a_T	1.5	—
l_d	-0.4	μm			

$$B_d(t_s, l_s) = \begin{cases} 1 - \frac{1}{1 + \left(\frac{(t_e - t_s)}{t_d}\right)^4} & t_s \leq t_e \\ 0 & t_s > t_e \end{cases} \quad (2.25)$$

In this equation t_r and t_d are characteristic time intervals for the rise and decay of the active stress, respectively. t_e denotes the total duration of the contraction. This duration depends on l_s according to :

$$t_e = b(l_s - l_d) \quad (2.26)$$

The constant b governs the increase of the duration of the activation with increasing sarcomere length, and l_d denotes the extrapolated sarcomere length at which this duration equals zero. The time derivative of l_c is modeled as:

$$\frac{dl_c}{dt} = - \left(\frac{T_a - T_{max}}{T_a + T_0} \right) v_0 \quad T_a \leq T_{max} \quad (2.27)$$

$$\frac{dl_c}{dt} = - \left(\frac{T_a - T_{max}}{T_a + T_0} \right) v_0 \exp \left(a_T \left(\frac{T_a}{T_0} \right) \right) \quad T_a > T_{max} \quad (2.28)$$

Equation (2.28) describes a hyperbolic relationship [36] between dl_c/dt and T_a (figure 2.10d), with asymptote velocity v_0 and asymptote stress T_0 . Equation (2.28) represents a modification of Arts's model: it incorporates the experimentally observed sigmoid shape of the force-velocity curve in the high-force region [95][28, chapter 10].

Table 2.4 lists the values of the parameters in the contraction model. The values of E_a , a_x , l_x , t_r , t_d , v_0 and b were adopted from Arts [4]. Using the experimental data obtained by ter Keurs *et al.* [90], which are presented in figure 2.9b, T_1 was chosen equal to 110 kPa. The ratio T_1/T_0 corresponds to the ratio G_{act}/G_0 in the model presented by Arts [4], and, according to the latter model, it was set at 2.

FIGURE 2.11: Activation sequence of the left ventricle: (a) assumed path along which a point P in the wall is activated, (b) activation map, indicated by isochrones at intervals of 10 ms.

The choice $a_T = 1.5$ was made to obtain a force-velocity relation which is similar to the relation obtained by van Heuningen *et al.* [95]. Choosing $l_d = -0.4\mu\text{m}$, the duration of contraction in the present model and in the model presented by Arts [4] is equal. In subsection 3.4.4 the behavior of this model for the description of active stress will be illustrated by simulating an experiment in which a trabecula contracts against different loads.

2.2.5 Activation sequence of the left ventricle

Contraction of the sarcomeres in the myocardium is initiated by a depolarization wave that spreads across the ventricular wall. A review of the investigations concerning the sequence of activation of the left ventricle is given by Scher [83]. Regularly, activation starts in the endocardial region at the apex. From this region the depolarization wave travels in radial and longitudinal direction across the wall, until it reaches the epicardial basal region after approximately 50 ms. The interventricular septum is activated slightly earlier than the left ventricular free wall. In the subendocardium, the depolarization wave is conducted relatively fast by the Purkinje fibers. From the endocardium towards the epicardium, the conduction velocity decreases, because gradually less Purkinje fibers are present.

In the model the activation pattern is considered to be rotationally symmetric. The activation of a particular point P in the ventricular wall is assumed to proceed as follows (figure 2.11a):

- activation starts in point A located on the endocardium in the apical region;
- from this point, the depolarization wave travels along the endocardial surface with a speed v_e , until it reaches B after Δt_{AB} seconds; B is the point on the endocardial surface located closest to P ;
- from B , the depolarization wave travels into the wall with speed v_r , in a period

TABLE 2.5: Values of the parameters determining the activation sequence of the ventricle.

symbol	value	unit
v_e	1.5	m·s ⁻¹
θ_A	$2\pi/3$	—

of Δt_{BP} seconds.

The delays Δt_{AB} and Δt_{BP} are calculated using the global ellipsoid coordinates, defined in subsection 2.1.2. It can be shown that:

$$\Delta t_{AB} = \left| \int_{\theta_A}^{\theta_B} \frac{C}{v_e} \sqrt{\sinh^2 \xi_A + \sin^2 \theta} d\theta \right| \quad (2.29)$$

$$\Delta t_{BP} = \int_{\xi_B}^{\xi_P} \frac{C}{v_r(\bar{\xi})} \sqrt{\sinh^2 \xi + \sin^2 \theta_B} d\xi \quad (2.30)$$

in which the coordinates of A , B and P are given by (ξ_A, θ_A) , (ξ_B, θ_B) and (ξ_P, θ_P) , respectively. C denotes the focal distance of the ellipsoids. The longitudinal conduction velocity in the subendocardium v_e is assumed to be constant. The radial conduction velocity v_r is assumed to decrease from the endocardium into the wall. In the outer two thirds of the ventricular wall v_r is assumed to be constant. Mathematically, this behavior is written as a function of the linear transmural coordinate $\bar{\xi}$:

$$v_r(\bar{\xi}) = \begin{cases} -\bar{\xi} v_e & -1 \leq \bar{\xi} \leq -\frac{1}{3} \\ \frac{1}{3} v_e & -\frac{1}{3} < \bar{\xi} \leq 1 \end{cases} \quad (2.31)$$

The values of v_e and θ_A are listed in table 2.5 [8]. The resulting activation sequence is shown in figure 2.11b.

2.3 Boundary conditions

2.3.1 Kinematic boundary conditions

To perform a finite element analysis of the dynamics of the left ventricle, rigid body motion of the ventricle should be suppressed. In the thorax the left ventricle is restrained by its connections to the right ventricle, the atria, the aorta, the pericardial sac and the lungs. Quantitative information on the kinematic boundary conditions imposed by these structures is not available. In the model the axial motion of the

FIGURE 2.12: Three-element model simulating aortic impedance with characteristic aortic resistance R_{ao} , arterial compliance C_{art} and peripheral resistance R_{per} . p_{lv} represents left ventricular pressure.

basal plane is suppressed. Circumferential motion of the endocardial ring in the basal plane is suppressed also.

2.3.2 Dynamic boundary conditions

In the real ventricle, the endocardial surface of the ventricular wall is subject to a pressure exerted by the blood in the ventricular cavity. This pressure depends on time and position. The spatial pressure distribution is complicated, and requires knowledge of the hemodynamics of the blood in the cavity [70]. The epicardial surface of the left ventricle is subject to three types of external loading: (1) a normal stress on the septum exerted by the blood in the right ventricle, (2) a stress that is transmitted through the attachment of the right ventricular wall, and (3) a normal stress that is imposed on the left ventricular free wall by the pericardial fluid.

For simplicity, in the model a uniform pressure is applied to the entire endocardial surface. Variation of this ventricular pressure with time is implemented differently for different phases in the cardiac cycle (section 4.1):

- during the diastolic filling phase pressure is prescribed,
- during the isovolumic contraction and relaxation phase, pressure is calculated to balance the passive and active forces in the ventricular wall in such a way, that ventricular volume is kept constant,
- during the ejection phase pressure is determined from the interaction between the contracting ventricle and the hemodynamic impedance of the aorta.

Epicardial pressure is assumed to be zero during the whole cardiac cycle.

2.3.3 Hemodynamic coupling

The left ventricle is coupled to the left atrium by the mitral valve. Although several studies have dealt with mitral valve dynamics [5,105], in the model the filling phase

TABLE 2.6: Values of the elements in the three-element model simulating aortic input impedance.

parameter	value-unit	
R_{ao}	$2.3 \cdot 10^7$	$\text{Pa} \cdot \text{s} \cdot \text{m}^{-3}$
R_{per}	$4.8 \cdot 10^8$	$\text{Pa} \cdot \text{s} \cdot \text{m}^{-3}$
C_{art}	$4.3 \cdot 10^{-9}$	$\text{m}^3 \cdot \text{Pa}^{-1}$

is simulated by prescribing ventricular pressure. In our analysis, this simplification is allowed, since we are interested primarily in the active phases of the cardiac cycle.

The hemodynamic coupling of the left ventricle to the aorta can be described mathematically by a three-element aortic input impedance [102]. This impedance consists of an aortic characteristic resistance R_c , placed in series with an arterial compliance C_{art} which is in parallel to a peripheral resistance R_{per} (figure 2.12). In experiments, in which a cat left ventricle was loaded with the real arterial system and a three-element model simulating the real system, similar time courses of ventricular and aortic pressure, and aortic flow were measured [23,103]. Burkhoff *et al.* [18] imposed real and best-fit three-element aortic input impedances on a model of the left ventricle. With the three-element model stroke volume, stroke work, and systolic and diastolic aortic pressures were predicted reasonably well. Peak aortic flow was underestimated by about 15% and the time course of aortic pressure and flow differed slightly from the time course calculated with the real aortic input impedance.

The values of components in the three-element model used in our simulations are based on data reported by Burkhoff *et al.* [18]. In five dogs with an average body weight of 23 kg, these investigators obtained the following values: $R_{ao} = 3.3 \cdot 10^7 \text{ Pa} \cdot \text{s} \cdot \text{m}^{-3}$, range $1.8 - 4.7 \cdot 10^7 \text{ Pa} \cdot \text{s} \cdot \text{m}^{-3}$; $R_{per} = 6.4 \cdot 10^8 \text{ Pa} \cdot \text{s} \cdot \text{m}^{-3}$, range $3.0 - 12.1 \cdot 10^8 \text{ Pa} \cdot \text{s} \cdot \text{m}^{-3}$; $C_{art} = 3.0 \cdot 10^{-9} \text{ m}^3 \cdot \text{Pa}^{-1}$, range $1.5 - 6.8 \cdot 10^{-9} \text{ m}^3 \cdot \text{Pa}^{-1}$. Physiologically, these values are closely related to the size of the left ventricle. Using a ratio of left ventricular weight to body weight of $4.5 \cdot 10^{-3}$ [19], the estimated ventricular weight in Burkhoff's experiments was 104 g. This is about 70% of the ventricular weight used in our model. Assuming a linear relationship between ventricular weight and aortic resistance, peripheral resistance, and the inverse of the arterial compliance, the values listed in table 2.6 were obtained.

Numerical description of cardiac tissue deformation

In this chapter the theory of continuum mechanics is used for the description and calculation of the deformation of the heart. Application of this theory is possible, because the size of the components forming cardiac tissue, such as muscle cells, collagen fibers, and fluid, is small as compared to the macroscopic dimensions of the heart muscle. In the first section of this chapter the basic equations governing the local deformation of cardiac tissue are presented. In the next section these equations are transformed into a set of matrix equations. Using the finite element method, a set of equations is derived, that describes the deformation of a brick-shaped piece of cardiac tissue. The resulting 20-node brick element is tested in the last section.

3.1 Description of tissue deformation

In this section the equations are presented, that govern the deformation of cardiac tissue. These equations are based on the theory of continuum mechanics, described briefly in appendix A. A more extensive treatment of this theory can be found in the textbook by Malvern [51].

Local deformation of a continuum can be described by the deformation gradient tensor $\mathbf{F}$. This tensor describes how an infinitesimal material vector $d\mathbf{x}_0$ in the undeformed reference situation is transformed into a vector $d\mathbf{x}$ in the deformed situation:

$$d\mathbf{x} = \mathbf{F} \cdot d\mathbf{x}_0 \quad ; \quad \mathbf{F} = (\nabla_0 \mathbf{x})^c \quad (3.1)$$

The local stress state in the material is given by the Cauchy stress tensor $\boldsymbol{\sigma}$. In an incompressible material only the deviatoric part $\boldsymbol{\sigma}^d$ of $\boldsymbol{\sigma}$ is related uniquely to the deformation of the material. In this case it is advantageous to write the Cauchy stress tensor as the sum of its deviatoric part and a hydrostatic pressure p :

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^d - p\mathbf{I} \quad (3.2)$$

The deformation of a continuum is governed by conservation of mass, conservation of momentum and conservation of moment of momentum. As cardiac tissue is assumed to be incompressible, conservation of mass is equivalent to conservation of volume, which is expressed by the relationship:

$$\det(\mathbf{F}) = 1 \quad (3.3)$$

Conservation of momentum is given by:

$$\nabla \cdot \boldsymbol{\sigma} = 0 \quad (3.4)$$

As described in section 1.4, inertial and gravity effects are neglected in this equation. Combination of (3.2) and (3.4) yields:

$$\nabla \cdot \boldsymbol{\sigma}^d - \nabla p = 0 \quad (3.5)$$

Conservation of moment of momentum is equivalent to the condition that the Cauchy stress tensor is symmetric:

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^c \quad (3.6)$$

The equilibrium equations (3.3) and (3.5) form the basis for the numerical solution procedure.

3.2 Transformation of the equilibrium equations

In this section the equilibrium equations are combined with the constitutive equations, presented in chapter 2. With the resulting set of equations the deformation of the cardiac tissue, as caused by externally applied forces or internally generated active forces, can be calculated.

Cardiac tissue can be regarded as a collection of material points. Each material point can be labeled uniquely by a set of three material coordinates ξ :

$$\xi^T = [\xi_1 \quad \xi_2 \quad \xi_3] \quad (3.7)$$

The state of stress and strain in the tissue is known, once the position $\mathbf{x}$, the hydrostatic pressure p and the contractile element length l_c (subsection 2.2.4) are known in every material point of the tissue. Since it is impossible to take into account all material points of the tissue, a finite number n_x material (nodal) points are chosen for calculation of position and contractile element length; in n_p of these n_x nodal points the pressure p is also calculated. Moreover only a finite number of moments in time are chosen at which these variables are calculated. This procedure of spatial and temporal discretization has been described before [15,43,64]. In this section a qualitative description of the procedure is given. A more detailed description is given in appendix B.

Let the position vector $\mathbf{x}^I$ of node I be given by its components (x_1^I, x_2^I, x_3^I) in an orthonormal coordinate system $(\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3)$. The contractile element length l_c and the hydrostatic pressure p in node I are denoted as $(l_c)^I$ and p^I , respectively. With the use of interpolation functions ψ and ϕ the position field, contractile element length field and pressure field are approximated by:

$$\begin{aligned} \mathbf{x}(\xi, t) &\approx \psi^I(\xi) \mathbf{x}^I(t) = \psi^I(\xi) x_j^I(t) \mathbf{e}_j & I &= 1, \dots, n_x \\ l_c(\xi, t) &\approx \psi^I(\xi) (l_c)^I(t) & j &= 1, 2, 3 \\ p(\xi, t) &\approx \phi^J(\xi) p^J(t) & J &= 1, \dots, n_p \end{aligned} \quad (3.8)$$

where the Einstein summation convention is used: a double superscripted capital index denotes summation over the nodal points, while a double subscripted index denotes summation over the three coordinate directions. The interpolation functions are dependent on the material coordinates ξ and chosen so that:

$$\psi^I(\xi^J) = \delta^{IJ} ; \quad \phi^I(\xi^J) = \delta^{IJ} \quad (3.9)$$

For convenience the nodal variables are stored in the columns X and L :

$$X^T = \begin{bmatrix} x_1^1 & x_2^1 & x_3^1 & p^1 & x_1^2 & \dots \end{bmatrix} \quad (3.10)$$

$$L^T = \begin{bmatrix} (l_c)^1 & (l_c)^2 & (l_c)^3 & (l_c)^4 & (l_c)^5 & \dots \end{bmatrix} \quad (3.11)$$

The state of deformation of the tissue at a certain instant t is determined completely by the columns $\underline{X}$ and $\underline{L}$ at that time. Suppose that $\underline{X}$ and $\underline{L}$ are known up to a certain time $t = t_n$. The next state $\underline{X}_{n+1}$, $\underline{L}_{n+1}$ at $t = t_{n+1}$ is calculated as follows. The time increment Δt_{n+1} is prescribed:

$$t_{n+1} = t_n + \Delta t_{n+1} \quad (3.12)$$

In the constitutive model for active stress the time derivative of l_c is given as an explicit function of l_c , l_s and t (subsection 2.2.4):

$$\frac{\partial l_c}{\partial t} = \frac{\partial l_c}{\partial t}(l_c, l_s, t) \quad (3.13)$$

which is equivalent to:

$$\frac{\partial \underline{L}}{\partial t} = \frac{\partial \underline{L}}{\partial t}(\underline{L}, \underline{X}, t) \quad (3.14)$$

The column $\underline{L}_{n+1}$ in the new state is estimated from the previous states up to $t = t_n$ by a numerical approximation:

$$\underline{L}_{n+1} = \underline{L}_{n+1}(\underline{X}_n, \underline{X}_{n-1}, \dots, \underline{L}_n, \underline{L}_{n-1}, \dots) \quad (3.15)$$

Next, $\underline{X}_{n+1}$ must be determined. The last nodal positions and pressures $\underline{X}_n$ are used as a first approximation of the new state $\hat{\underline{X}}_{n+1}$ at $t = t_{n+1}$. For the relationship between the estimated and actual state it holds:

$$\underline{X}_{n+1} = \hat{\underline{X}}_{n+1} + \delta \underline{X}_{n+1} \quad (3.16)$$

Because of the estimation error $\delta \underline{X}_{n+1}$ the equilibrium conditions in the nodal points will not be fulfilled. This violation of the equilibrium equations results in force imbalances and deviations from volume conservation in the nodal points, that can be stored in a column $\underline{R}_{n+1}$. An approximation $\delta \hat{\underline{X}}_{n+1}$ of the estimation error $\delta \underline{X}_{n+1}$ is given by:

$$\delta \hat{\underline{X}}_{n+1} = [\underline{X} \underline{K}_{n+1}]^{-1} \underline{R}_{n+1} \quad (3.17)$$

The stiffness matrix $\underline{X} \underline{K}_{n+1}$ describes how in the tissue forces and volume depend on nodal positions and pressures. A new estimate $\hat{\underline{X}}_{n+1}$ is obtained according to:

$$\hat{\underline{X}}_{n+1} := \hat{\underline{X}}_{n+1} + \delta \hat{\underline{X}}_{n+1} \quad (3.18)$$

With this new approximation a new error column $\underline{R}_{n+1}$ is calculated. If the deviations from force equilibrium and volume conservation are unacceptably large, a new iteration step (3.17) through (3.18) is performed. Finally, if the equilibrium equations are satisfied sufficiently accurately, the last estimate is accepted as the configuration at $t = t_{n+1}$:

$$\underline{X}_{n+1} = \hat{\underline{X}}_{n+1} \quad (3.19)$$

This configuration $\underline{X}_{n+1}$, $\underline{L}_{n+1}$ is now used as a first estimate for the configuration at the next instant in time $t = t_{n+2}$, and the procedure (3.12) through (3.19) is repeated.

FIGURE 3.1: The 20-node brick element: (a) pressure/displacement nodes • and displacement nodes o; (b) location of the 14 integration points in the element.

3.3 The 20-node brick element

In the calculation procedure described in the previous section usually a large number of nodes are involved. According to the finite element method these nodes are grouped in elements by choosing the interpolation functions ψ and ϕ so that an interpolation function belonging to a material point ξ^I can be non-zero only in those elements E to which this material point belongs:

$$\xi^I \notin E \implies \psi^I = \phi^I = 0 \quad \text{in } E \quad (3.20)$$

For the calculation of the deformation of the cardiac tissue the 20-node brick element shown in figure 3.1a is used. Within the element isoparametric coordinates η are defined:

$$\eta^T = [\eta_1 \quad \eta_2 \quad \eta_3] \quad ; \quad -1 \leq \eta_1, \eta_2, \eta_3 \leq 1 \quad (3.21)$$

Positions and displacements within the element are interpolations of the positions and displacements of the 20 nodes (3.8). The pressure field within the element is interpolated from the pressures in the eight corner nodes. The interpolation functions ϕ and ψ (3.16) are defined as a function of the isoparametric coordinates η :

$$\phi(\pm 1, \pm 1, \pm 1) = \frac{1}{8}(1 \pm \eta_1)(1 \pm \eta_2)(1 \pm \eta_3)(\pm \eta_1 \pm \eta_2 \pm \eta_3 - 2) \quad (3.22)$$

$$\phi(0, \pm 1, \pm 1) = \frac{1}{4}(1 - \eta_1^2)(1 \pm \eta_2)(1 \pm \eta_3) \quad (3.23)$$

$$\phi(\pm 1, 0, \pm 1) = \frac{1}{4}(1 - \eta_2^2)(1 \pm \eta_1)(1 \pm \eta_3) \quad (3.24)$$

$$\phi(\pm 1, \pm 1, 0) = \frac{1}{4}(1 - \eta_3^2)(1 \pm \eta_1)(1 \pm \eta_2) \quad (3.25)$$

$$\psi(\pm 1, \pm 1, \pm 1) = \frac{1}{8}(1 \pm \eta_1)(1 \pm \eta_2)(1 \pm \eta_3) \quad (3.26)$$

The stiffness matrix ${}^X K$ and the error column R , that were introduced in the previous section, are integrals over the volume of the object that is considered. These integrals are calculated as a sum of integrals over the volumina V_0^e of the n_e elements, out of which the object is composed:

$$\int_{V_0} f(x, y, z, p) dV_0 = \sum_{e=1}^{n_e} \int_{V_0^e} f(x, y, z, p) dV_0^e \quad (3.27)$$

After transforming the element integrals to the space of isoparametric coordinates it follows:

$$\int_{V_0^e} f(x, y, z, p) dV_0^e = \int_{-1}^1 \int_{-1}^1 \int_{-1}^1 f(x(\eta), y(\eta), z(\eta), p(\eta)) \det\left(\frac{\partial x}{\partial \eta}\right) d\eta_1 d\eta_2 d\eta_3 \quad (3.28)$$

The integrals are approximated numerically as a weighted sum over n_i integration points:

$$\int_{-1}^1 \int_{-1}^1 \int_{-1}^1 g(\eta) d\eta_1 d\eta_2 d\eta_3 \approx \sum_{i=1}^{n_i} w_i g_i \quad (3.29)$$

with weighting factor w_i and function value g_i at integration point i . Within the element, displacements are approximated by a quadratic function in each of the isoparametric coordinates. Usually, integration of a quadratic function is carried out numerically by a 3 point Gaussian integration rule. So, for the 20-node element usually $3 \times 3 \times 3$ Gaussian integration is applied. However, comparable accuracy can be obtained by a 14-point integration rule [44], which reduces computation time by almost 50 %:

$$\begin{aligned} \int_{-1}^1 \int_{-1}^1 \int_{-1}^1 g(\eta) d\eta_1 d\eta_2 d\eta_3 &\approx A\{g(\pm a, \pm a, \pm a)\} \\ &+ B\{g(\pm b, 0, 0) + g(0, \pm b, 0) + g(0, 0, \pm b)\} \end{aligned} \quad (3.30)$$

with:

$$\begin{aligned} A &= 0.335180055 & a &= 0.758786911 \\ B &= 0.886426593 & b &= 0.795822426 \end{aligned} \quad (3.31)$$

The location of the integration points is illustrated in figure 3.1b. Calculation of the surface integrals, occurring in appendix B, is carried out similarly using 3×3 Gaussian integration.

3.4 Testing the element

3.4.1 Introduction

In this section a number of deformation processes are simulated using the 20-node brick element. The stresses, calculated in the simulations, are compared to those obtained from analytical solutions. The material used in the tests is incompressible, nonlinearly elastic and transversely isotropic with respect to the $\mathbf{e}_3$ -direction. The material behavior is described by the strain-energy function presented in section 2.2.2. Assuming $a_1 = a_2/2 = a_3 = a$ and $a_4 = 0$ the strain-energy function can be written as:

$$W(\underline{E}) = C \exp \left[a(E_{11}^2 + E_{22}^2 + 2E_{33}^2) + a(E_{12}^2 + E_{21}^2 + E_{23}^2 + E_{32}^2 + E_{31}^2 + E_{13}^2) \right] \quad (3.32)$$

From this strain-energy function the following second Piola-Kirchhoff stress matrix $\underline{S}$ can be derived :

$$\underline{S} = \begin{bmatrix} E_{11} & E_{12} & E_{13} \\ E_{21} & E_{22} & E_{23} \\ E_{31} & E_{32} & 2E_{33} \end{bmatrix} 2aW(\underline{E}) \quad (3.33)$$

The material parameter values used in the tests are:

$$C = 0.5 \text{ kPa} \quad (3.34)$$

$$a = 3.0 \quad (3.35)$$

This choice corresponds to the 'adapted' passive material behavior, which is discussed in section 4.2.1.

3.4.2 Deformation of a rectangular block

Consider a solid rectangular block with dimensions l_{10} in $\mathbf{e}_1$ -direction, l_{20} in $\mathbf{e}_2$ -direction, and l_{30} in $\mathbf{e}_3$ -direction. The block is subdivided into 5 elements, as is shown in figure 3.2a. The block will be subjected to (1) uniaxial compression and stretch, (2) equibiaxial stretch and (3) shear.

Uniaxial compression and stretch

Consider a uniform compression or extension of the block in figure 3.2a in the $\mathbf{e}_3$ -direction. Its length changes from l_{30} to l_3 :

$$l_3 = \lambda l_{30} \quad (3.36)$$

For the matrix representation $\underline{F}$ of the deformation gradient tensor $\mathbf{F}$ it holds:

FIGURE 3.2: Deformation of a rectangular block: (a) division of the block into 5 elements; (b) finite extension and compression in e_3 -direction: analytical (—) and finite element solution: Cauchy stress σ_{33}^d (O) and pressure p (•) versus stretch ratio λ .

$$\underline{F} = \begin{bmatrix} \frac{1}{\sqrt{\lambda}} & 0 & 0 \\ 0 & \frac{1}{\sqrt{\lambda}} & 0 \\ 0 & 0 & \lambda \end{bmatrix} \quad (3.37)$$

Using the deformation gradient matrix $\underline{F}$, the Green-Lagrange strain matrix $\underline{E}$ and the second Piola-Kirchhoff stress matrix $\underline{S}$ can be calculated. Using $\underline{F}$ and $\underline{S}$, the deviatoric Cauchy stress matrix $\underline{\sigma}^d$ and the hydrostatic pressure p are obtained:

$$\underline{\sigma}^d = \begin{bmatrix} S_{11}/\lambda & 0 & 0 \\ 0 & S_{22}/\lambda & 0 \\ 0 & 0 & \lambda^2 S_{33} \end{bmatrix} ; \quad p = S_{11}/\lambda = S_{22}/\lambda \quad (3.38)$$

The analytical and the finite element solution are shown in figure 3.2b.

Equibiaxial stretch

In this case the block in figure 3.2a is subjected to an equibiaxial stretch in e_2 and e_3 -direction. The deformation matrix equals:

$$\underline{F} = \begin{bmatrix} \frac{1}{\lambda^2} & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix} \quad (3.39)$$

For the deviatoric Cauchy stress matrix $\underline{\sigma}^d$ and the hydrostatic pressure p it can be derived that:

FIGURE 3.3: Deformation of the rectangular block shown in figure 3.2a: (a) equibiaxial stretch in e_2 -direction and e_3 -direction: analytical (—) and finite element solution: Cauchy stresses σ_{22}^d ($\diamond$), σ_{33}^d (O) and pressure p ($\bullet$) versus stretch ratio λ ; (b) finite shear in the e_1 - e_3 -plane: analytical (—) and finite element solution: Cauchy stresses σ_{11}^d ($\square$), σ_{33}^d (O) and σ_{13}^d ($\triangle$) versus shear parameter γ .

$$\underline{\sigma}^d = \begin{bmatrix} S_{11}/\lambda^4 & 0 & 0 \\ 0 & \lambda^2 S_{22} & 0 \\ 0 & 0 & \lambda^2 S_{33} \end{bmatrix} ; \quad p = S_{11}/\lambda^4 \quad (3.40)$$

The analytical and the finite element solution are shown in figure 3.3a.

Shear

The top surface of the block in figure 3.2a is subjected to a translation u_3 in the e_3 direction, while the bottom surface is fixed. The deformation gradient matrix $\underline{F}$ for this process is:

$$\underline{F} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ \gamma & 0 & 1 \end{bmatrix} ; \quad \gamma = (u_3/l_{10}) \quad (3.41)$$

The components of the deviatoric Cauchy stress matrix $\underline{\sigma}^d$ and the hydrostatic pressure p can be shown to be:

$$\underline{\sigma}^d = \begin{bmatrix} S_{11} & 0 & S_{13} + \gamma S_{11} \\ 0 & 0 & 0 \\ S_{31} + \gamma S_{11} & 0 & 2\gamma S_{13} + \gamma^2 S_{11} \end{bmatrix} ; \quad p = 0 \quad (3.42)$$

The analytical and the finite element solution are shown in figure 3.3b.

FIGURE 3.4: Inflation of a thickwalled sphere: (a) finite element mesh; (b) cavity volume V_c relative to wall volume V_w versus cavity pressure p_{cav} ; analytical solution (—) and finite element solution (•).

3.4.3 Inflation of a thickwalled sphere

Consider a thickwalled sphere with inner radius $r_{i,0}$ and outer radius $r_{o,0}$. Assume isotropic material behavior by putting $a_3 = a_4 = 0$. Upon inflation this sphere deforms into a sphere with inner radius r_i and outer radius r_o according to:

$$r_i = \lambda_i r_{i,0} \quad (3.43)$$

$$r_o = \lambda_o r_{o,0} \quad (3.44)$$

The cavity pressure p_{cav} needed for this inflation is given by [61]:

$$p_{cav} = \int_{\lambda_i}^{\lambda_o} \frac{\partial W / \partial \lambda}{\lambda^3 - 1} d\lambda \quad (3.45)$$

Figure 3.4 shows the pressure-volume relationship of a sphere with $r_{i,0} = 3$ and $r_{o,0} = 5$.

3.4.4 Simulation of a papillary muscle experiment

The contractile properties of myocardial tissue can be investigated experimentally using papillary muscles. In a typical experiment [16], the papillary muscle is loaded with a preload T_{pl} , causing an increase in length of the muscle from l_0 to l_{pl} . Next, the muscle is stimulated. Muscle length is held constant until the stress, generated by the muscle cells, exceeds a certain level, the afterload T_{al} . From this moment on, the muscle is allowed to shorten against a constant afterload. After maximum shortening has occurred, the muscle lengthens again due to the decay of active stress. As soon as the muscle has regained its preload length l_{pl} , muscle length is held constant again and active stress decreases to zero.

In figure 3.5 the experimentally determined (a) and calculated (b) changes of active stress, sarcomere length, and velocity of shortening as a function of time are

FIGURE 3.5: Contraction of a papillary muscle against different afterloads: (a) experimental data adapted from Brutsaert et al. (1971); (b) data calculated using the model presented in section 2.2.4: sarcomere length in unloaded and preloaded state equals $1.9 \mu\text{m}$ and $2.1 \mu\text{m}$, respectively. Top panel: time course of active stress expressed as active force F_a divided by undeformed cross-sectional area A_0 . Middle panel: time course of muscle length l normalized by muscle length at preload level l_{pl} . Bottom panel: time course of velocity of shortening normalized by l_{pl} . Different line types indicate different afterloads.

shown. In comparison to the model calculations, in the papillary muscle experiment (1) maximum active stress is lower, (2) development of stress as a function of time is slower, (3) amount of shortening is similar, and (consequently) (4) velocity of shortening is lower. The low stress level in the experiment is probably caused by stretch of the noncontracting ends of the muscle. Calculated maximum active stress level agrees with data presented by ter Keurs *et al.* [90], which were discussed in subsection 2.2.3 and shown in figure 2.9b. The slow response can be attributed to the relatively low temperature (29°C) at which the experiments were performed. Brutsaert *et al.* [16] showed that, in a typical experiment, time from stimulus to maximum stress in an isometric contraction decreased from 360 ms at 29°C to 200 ms at 37°C. The calculated response agrees reasonably well with the latter value.

Simulation of the mechanics of the left ventricle

In this chapter results are presented of several simulations of the mechanical behavior of the left ventricle during a complete cardiac cycle. The definition of the phases in the cardiac cycle and the numerical procedure used to simulate these phases are described in section 4.1. In section 4.2, an initial simulation of a cardiac cycle is presented in which the values of the model parameters were chosen as described in chapter 2. Based upon a comparison of the numerical results with experimental data, the values of the parameters describing passive material behavior and muscle fiber orientation are adapted. The resulting simulation, presented in section 4.3, is used as a reference simulation. From this simulation a number of parameter variations are performed, concerning the activation sequence of the ventricle, the contractility of the muscle cells, and the preload and afterload conditions. The calculated results of these parameter variations are presented in section 4.4. In section 4.5 a summary is given of the conclusions drawn from the simulations presented in this chapter.

4.1 Introduction

4.1.1 Finite element mesh and boundary conditions

In the model, the initial geometry of the left ventricle is rotationally symmetric with respect to its long axis. In the simulation of the mechanical behavior of the normal left ventricle, no variation of material properties across the ventricular wall is assumed. As a consequence, rotational symmetry of the ventricle is maintained during the complete cardiac cycle. Using the property of rotational symmetry, in the simulation of a normal cardiac cycle computing time has been reduced by considering only a quarter section of the complete ventricle. This quarter section is composed of 27 elements with a total of 208 nodes, as shown in figure 4.1. The position of a node I in the reference and deformed situation is given by $\mathbf{x}_0^I$ and $\mathbf{x}^I$, respectively:

$$\mathbf{x}_0^I = x_{01}^I \mathbf{e}_1 + x_{02}^I \mathbf{e}_2 + x_{03}^I \mathbf{e}_3 \quad (4.1)$$

$$\mathbf{x}^I = x_1^I \mathbf{e}_1 + x_2^I \mathbf{e}_2 + x_3^I \mathbf{e}_3 \quad (4.2)$$

The displacement $\mathbf{u}^I$ of node I is given by:

$$\mathbf{u}^I = u_1^I \mathbf{e}_1 + u_2^I \mathbf{e}_2 + u_3^I \mathbf{e}_3 \quad (4.3)$$

$$u_1^I = x_1^I - x_{01}^I \quad (4.4)$$

$$u_2^I = x_2^I - x_{02}^I \quad (4.5)$$

$$u_3^I = x_3^I - x_{03}^I \quad (4.6)$$

To maintain rotational symmetry in the quarter ventricle, the displacement and pressure fields in the x_1 - x_3 -plane and the x_2 - x_3 -plane are coupled. When considering two corresponding nodes I and J in these planes with coordinates $(a, 0, b)$ and $(0, a, b)$, respectively, it holds:

$$u_1^J(0, a, b) = -u_2^I(a, 0, b) \quad (4.7)$$

$$u_2^J(0, a, b) = u_1^I(a, 0, b) \quad (4.8)$$

$$u_3^J(0, a, b) = u_3^I(a, 0, b) \quad (4.9)$$

$$p^J(0, a, b) = p^I(a, 0, b) \quad (4.10)$$

Additionally, the boundary conditions discussed in subsection 2.3.1 are applied:

$$u_3^I = 0 \quad \text{for all nodes } I \text{ in the basal plane} \quad (4.11)$$

$$u_2^A = 0 \quad \text{for node } A \text{ indicated in figure 4.1} \quad (4.12)$$

4.1.2 Phases in the cardiac cycle

In figure 4.2 a flow chart is given of the numerical calculations associated with the simulation of a cardiac cycle. A complete cardiac cycle is subdivided into a finite

FIGURE 4.1: Finite element mesh of the quarter of the left ventricle considered in the simulation of the mechanical behavior of the normal left ventricle.

number of time increments. Within each increment, two iteration loops are nested. In the inner loop (loop I in figure 4.2) the iterative procedure described in section 3.2 is used to fulfill the conditions of conservation of mass, momentum and moment of momentum. The conditions to be fulfilled in the outer loop (loop II in figure 4.2) concern the hemodynamic loading of the left ventricle, which depends on the actual phase in the cardiac cycle.

The diastolic phase

During the diastolic phase ventricular pressure p_{lv} is prescribed. It is raised from 0 kPa at $t = 0$ ms to an end-diastolic pressure p_{ed} at a prescribed time t_i . At this moment the depolarization wave is started in the apical endocardial part of the left ventricle from where it spreads across the ventricular wall (section 2.2.5). Generation of active stress is started immediately after depolarization. The mitral valve is assumed to close after 50 ms. This moment t_{ed} marks the end of the diastolic phase.

The isovolumic contraction phase

During the isovolumic contraction phase left ventricular volume is constant. In the outer iteration loop (loop II in figure 4.2) left ventricular pressure is adapted until the calculated cavity volume equals the end-diastolic volume V_{ed} . Assuming pressure and volume to be known up to the current time t_n , a first estimate of the ventricular pressure p_{n+1} at the next time $t_{n+1} = t_n + \Delta t_{n+1}$ is made using an explicit two-step Adams-Bashforth integration scheme [98]:

FIGURE 4.2: Flow chart of the calculations; the inner iteration loop within dashed box I has been described in section 3.2; the outer iteration loop, within dashed box II, is explained in section 4.1.2.

$$p_{n+1}^0 = p_n + \frac{1}{2} \left(3 \left(\frac{\partial p}{\partial t} \right)_n - \left(\frac{\partial p}{\partial t} \right)_{n-1} \right) \Delta t_{n+1} \quad (4.13)$$

with:

$$\left(\frac{\partial p}{\partial t} \right)_n = \frac{p_n - p_{n-1}}{\Delta t_n} \quad (4.14)$$

The superscript '0' denotes iteration 0. At the pressure p_{n+1}^0 , in the inner iteration loop the deformed state is calculated. Generally, the ventricular volume V_{n+1}^0 in this state will not be equal to V_{ed} . The volume error ΔV_{n+1}^0 is given by:

$$\Delta V_{n+1}^0 = V_{n+1}^0 - V_{ed} \quad (4.15)$$

Using an estimate of the ventricular stiffness $\left(\frac{\partial p}{\partial V} \right)$, a new pressure estimate p_{n+1}^1 is made:

$$p_{n+1}^1 = p_{n+1}^0 + \Delta p_{n+1}^1 \quad (4.16)$$

with:

$$\Delta p_{n+1}^1 = \left(\frac{\partial p}{\partial V} \right) \Delta V_{n+1}^0 \quad (4.17)$$

The estimated stiffness is adapted if in a time step n two combinations of ventricular pressure and volume, (p_n^i, V_n^i) and (p_n^j, V_n^j) , are available for which the conditions of conservation of momentum and volume are fulfilled:

$$\left(\frac{\partial p}{\partial V} \right) = \frac{p_n^i - p_n^j}{V_n^i - V_n^j} \quad (4.18)$$

After executing the inner iteration loop with the improved estimate p_{n+1}^1 a new ventricular volume results. This iterative procedure is repeated until, in iteration i , the volume error ΔV_{n+1}^i is less than a preset value δ_V . If at time t_n , the calculated pressure p_n exceeds a preset minimal ventricular pressure at the beginning of the ejection phase $p_{be,min}$, the ejection phase starts with the following initializations:

$$p_{be} = p_n \quad (4.19)$$

$$t_{be} = t_n \quad (4.20)$$

FIGURE 4.3: Three-element Windkessel model simulating aortic impedance.

The ejection phase

During the ejection phase the left ventricle pumps blood into the aorta. The aorta is mathematically described by the three-element Windkessel model (section 2.1.4) shown in figure 4.3. For the aortic flow q_{ao} it holds:

$$q_{ao} = \frac{p_{lv} - p_{art}}{R_{ao}} \quad (4.21)$$

$$= \frac{p_{art}}{R_{per}} + C_{art} \frac{\partial p_{art}}{\partial t} \quad (4.22)$$

This flow q_{ao} should be equal to the rate of change of left ventricular volume q_v :

$$q_{lv} = -\frac{\partial V_{lv}}{\partial t} \quad (4.23)$$

In the model q_{ao} is discretized such that $q_{ao,n}$ represents the mean flow during the interval $t_{n-1} \leq t \leq t_n$. Assuming q_{ao} is known up to the interval $t_{n-1} \leq t \leq t_n$ an initial estimate $q_{ao,n+1}^0$ of $q_{ao,n+1}$ is made:

$$q_{ao,n+1}^0 = q_{ao,n} + \frac{1}{2} \left(3 \left(\frac{\partial q_{ao}}{\partial t} \right)_n - \left(\frac{\partial q_{ao}}{\partial t} \right)_{n-1} \right) \Delta t_{n+1} \quad (4.24)$$

with:

$$\left(\frac{\partial q_{ao}}{\partial t} \right)_n = \frac{q_{ao,n} - q_{ao,n-1}}{\Delta t_n} \quad (4.25)$$

Using a discretized form of equations (4.22) and (4.22) estimates for $p_{lv,n+1}$ and $p_{art,n+1}$ are calculated:

$$p_{art,n+1}^0 = \frac{q_{ao,n+1}^0 + \left(\frac{C_{art}}{\Delta t_{n+1}} - \frac{1}{2R_{per}} \right) p_{art,n}}{\frac{1}{2R_{per}} + \frac{C_{art}}{\Delta t_{n+1}}} \quad (4.26)$$

$$p_{lv,n+1}^0 = p_{art,n+1}^0 + p_{art,n} - p_{lv,n} + 2R_{ao}q_{ao,n+1}^0 \quad (4.27)$$

Using the latter ventricular pressure the inner iteration loop is executed, yielding a ventricular volume V_{n+1}^0 and a ventricular outflow:

TABLE 4.1: Prescribed values of characteristic quantities in the simulation of the cardiac cycle.

parameter	value	unit	meaning
p_{ed}	1	kPa	end-diastolic left ventricular pressure
$p_{be,min}$	10	kPa	minimal p_{lv} at the beginning of the ejection phase
t_i	150	ms	moment of initiation of the depolarization wave
t_{ed}	200	ms	end of the diastolic phase
t_{cycle}	600	ms	end of the simulation

$$q_{lv,n+1}^0 = -\frac{V_{n+1}^0 - V_n}{\Delta t_n} \quad (4.28)$$

In general, $q_{lv,n+1}^0$ will not be equal to $q_{ao,n+1}^0$. The difference in flow, Δq_{n+1}^0 , is given by:

$$\Delta q_{n+1}^0 = q_{ao,n+1}^0 - q_{lv,n+1}^0 \quad (4.29)$$

A new estimate $q_{ao,n+1}^1$ for $q_{ao,n+1}$ is made according to:

$$q_{ao,n+1}^1 = q_{ao,n+1}^0 + \frac{\Delta q_{n+1}^0}{\left(\frac{\partial q_{lv}}{\partial q_{ao}}\right) - 1} \quad (4.30)$$

The coefficient $\left(\frac{\partial q_{lv}}{\partial q_{ao}}\right)$ is an estimate of the change in q_{lv} due to a change in q_{ao} . It is adapted analogously to (4.18). The procedure (4.27) through (4.30) is repeated until at iteration i the difference Δq_{n+1}^i is less than a preset value δ_q . The end of the ejection phase is reached if the calculated flow becomes negative. The isovolumic relaxation phase starts with the following initializations:

$$t_{ee} = t_n \quad (4.31)$$

$$V_{ee} = V_n \quad (4.32)$$

$$p_{ee} = p_n \quad (4.33)$$

The isovolumic relaxation phase

The isovolumic relaxation phase is simulated analogously to the isovolumic contraction phase, while keeping ventricular volume constant at V_{ee} . The calculation ends at a prescribed time t_{cycle} .

In the above described numerical procedures to simulate the phases in the cardiac cycle, only a few quantities are prescribed. These quantities are listed in table 4.1.

TABLE 4.2: Original and adapted values of the parameters in the strain-energy function describing passive material behavior:

$$W(\underline{E}) = C [\exp(a_1 I_E^2 + a_2 II_E + a_3 E_{33}^2 + a_4 (E_{31}^2 + E_{32}^2)) - 1].$$

parameter	C	a_1	a_2	a_3	a_4
original value	0.7	5.0	10.0	5.0	0.0
adapted value	0.5	3.0	6.0	3.0	0.0
unit	[kPa]	-	-	-	-

4.2 Preliminary calculations

4.2.1 The diastolic phase

Description of the simulation

To simulate left ventricular filling, the ventricle, as proposed in chapter 2, was passively inflated by increasing ventricular pressure. An 'original' and an 'adapted' set of values of passive material parameters, as listed in table 4.2, were used.

Description of the results

In figure 4.4a, left ventricular pressure p_{lv} is plotted as a function of left ventricular cavity volume V_{lv} , normalized to the ventricular wall volume V_w . With the original material properties the ventricle is stiffer than with the adapted material properties. At a pressure of 1 kPa, which is a normal end-diastolic pressure, the increase of ventricular volume is $0.09V_w$ (12 ml) in case of the original material properties. With the adapted material properties the increase in ventricular volume equals $0.24V_w$ (34 ml). The sarcomere length distribution at the equator, as calculated for the case of the adapted material properties, is shown in figure 4.4b. Starting from a uniform sarcomere length of $1.85 \mu\text{m}$ at $p_{lv} = 0$ kPa, endocardial sarcomere length increases to about $2.2 \mu\text{m}$ at a ventricular pressure of 1.0 kPa. At this pressure epicardial sarcomere length is still below $2.0 \mu\text{m}$.

Discussion

Figure 4.4a also shows experimentally obtained pV -curves. The data by Spotnitz *et al.* [85] and McCulloch *et al.* [53] were obtained in isolated dog hearts. Nikolić *et al.* [60] determined pV -curves in the intact dog heart. From figure 4.4a it is apparent that with the original passive material behavior the model left ventricle is too stiff.

FIGURE 4.4: Diastolic filling of the passive left ventricle: (a) pressure-volume relationship: O: Spotnitz et al. [85]; $\square$: McCulloch et al. [53]; —: Nikolić et al. [60]; ∇ : model solution with original passive material properties; $\triangle$: model solution with adapted passive material properties; (b) calculated transmural distribution of sarcomere length at 0 kPa (∇), 0.2 kPa (O), 0.4 kPa ($\square$), 0.6 kPa ($\diamond$), 0.8 kPa ($\triangle$) and 1.0 kPa (+). $\xi = -1$ and $\xi = +1$ correspond to the endocardial and epicardial surface, respectively.

The stiff behavior might be caused by (1) an unrealistic choice of the geometry of the left ventricle, or (2) a too stiff passive material behavior. The representation of the left ventricle by a truncated thickwalled ellipsoid with a smooth endocardial surface can be expected to yield a relatively stiff behavior. In the real ventricle, the endocardial surface shows many invaginations that run approximately in longitudinal direction. Thus, the stiffness in circumferential direction in the endocardial part of the ventricular wall will be lower and the ventricle will be more compliant than in the case of a smooth endocardium. The high stiffness of the model left ventricle can also be caused by a too stiff passive constitutive relationship. As described in section 2.2, the passive material parameter values were determined from experimental data obtained in excised cardiac tissue. However, it has been shown that stiffening occurs in excised cardiac tissue. For example, McCulloch *et al.* [53] determined passive pressure-volume curves in isolated dog hearts. At a ventricular pressure of 3.3 kPa, a decrease in ventricular volume of about 10% ($n = 5$) during a 9-minute interval was noticed. A similar stiffening may have been present in the experiments from which the passive material parameter values were estimated.

The passive pressure-volume relationship can be fitted within the range of exper-

imental data by several modifications of the model. Firstly, the endocardial surface may be reshaped to a more realistic geometry. Secondly, the trabecular subendocardial layer of cardiac tissue, which is partly filled with ventricular blood, may be described as a two-phase material. Thirdly, the stiffness of the subendocardial tissue may be reduced in directions perpendicular to the fiber direction. Fourthly, the stiffness of the tissue in all layers of the ventricular wall may be reduced. This last possibility was chosen since the first three possibilities involve an increase in model parameters. The adapted values of the material parameters are listed in table 4.2. With these parameter values, the calculated pV -relationship matches the experimental results obtained by Nikolić *et al.* [60] reasonably well (figure 4.4a).

Comparison of the calculated transmural distribution of sarcomere length presented in figure 4.4b with the experimental data [34,85,108] presented in figure 2.6 shows that (1) calculated sarcomere lengths are smaller than experimentally determined sarcomere lengths, and (2) the transmural variation of calculated sarcomere length is larger than the experimentally measured variation. To bring calculated sarcomere length in the range of experimental values, sarcomere length at $p_{lv} = 0$ kPa was set at $2.0 \mu\text{m}$. The transmural variation of sarcomere length will be discussed later.

4.2.2 Initial simulation of a complete cardiac cycle

Description of the simulation

A first simulation of a complete cardiac cycle was performed using the proposed data describing ventricular geometry (table 2.1), initial muscle fiber orientation (table 2.2), adapted passive material behavior (table 4.2), active material behavior (table 2.4), activation sequence (table 2.5) and aortic impedance (table 2.6). The transmural distribution of the helix fiber angle is shown in figure 4.5. The transverse fiber angle α_3 was assumed to be zero in this simulation. Generally, time steps of 5 ms were used. During the diastolic phase time steps were increased to 30 ms. Time steps were reduced to 2 ms around the transition from the isovolumic contraction phase to the ejection phase and the transition from the ejection phase to the isovolumic relaxation phase. The depolarization wave was initiated at $t = 150$ ms. The mitral valve was assumed to close at $t = 200$ ms.

Description of the results: global behavior

In figure 4.6a ventricular pressure, ventricular volume and aortic flow are shown as a function of time. In figure 4.6b, ventricular pressure is plotted as a function of ventricular volume. The area enclosed by the pressure-volume loop represents the external work W_{cycle} , generated by the ventricle during a cardiac cycle:

$$W_{\text{cycle}} = \oint_{\text{cycle}} p_{lv} dV_{lv} \quad (4.34)$$

FIGURE 4.5: Variation of helix fiber angle α_1 from the endocardial ($\bar{\xi} = -1$) to the epicardial ($\bar{\xi} = +1$) surface as assumed in the initial simulation (—) and measured approximately at the equator; (O) Streeter et al. [86]; (□) Greenbaum et al. [23]; (Δ) Ross et al. [81]; (◇) Streeter [89]. Data from Ross et al. [81] and Streeter [89] were plotted assuming that the transmural position $\bar{\xi}^* = -0.5$ coincides with $\bar{\xi} = -1.0$ (see also figure 2.4).

Characteristic hemodynamic data are presented in table 4.3.

During the diastolic phase, ventricular pressure is prescribed to increase from 0.0 kPa to 1.0 kPa. Ventricular volume increases from 40 ml to 75 ml. During the isovolumic contraction phase, active stress is generated by the muscle fibers in the ventricular wall. The increase of active stress is reflected by an increase of ventricular pressure. At $t = 268$ ms ventricular pressure exceeds 10 kPa and the aortic valve opens. During the ejection phase 28 ml of blood is pumped out into the aorta. Ejection stops at $t = 440$ ms. During the isovolumic relaxation phase, ventricular pressure declines, and finally the ventricle becomes completely passive again. Ventricular pressure at the end of the simulation equals 0.23 kPa. Because the final state of the simulation differs from the reference state, from which the simulation was started, the increase of ventricular volume during diastolic filling (35 ml) is not equal to the ejected volume (28 ml). If, starting from the final state, ventricular pressure would be increased to 1 kPa, ventricular volume would increase by 28 ml. Thus, in subsequent cycles mitral inflow volume and aortic outflow volume are equal.

In figure 4.7 the shape of the ventricle is shown at 8 moments during the cardiac cycle. During the diastolic phase ventricular length and diameter increase. During

FIGURE 4.6: Global hemodynamics in initial simulation of a cardiac cycle: (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

the isovolumic contraction phase the ventricle becomes longer, while its diameter decreases. The decrease of ventricular volume during the ejection phase is obtained mainly by a decrease of ventricular diameter. During the first part of the ejection phase ventricular length increases. Towards the end of this phase ventricular length decreases, but it is still larger at the end of the ejection phase than at its beginning. During the isovolumic relaxation phase, the ventricle regains its original shape.

Description of the results: local behavior

The description of the local behavior of the ventricle will be focussed on muscle fiber strain, active muscle fiber stress, work generated by the muscle fibers and angle of rotation of the nodal points around the long axis of the ventricle. These parameters are investigated at the nodal points, shown in figure 4.8.

To describe local strain in the ventricular wall, six strain components are needed. From a physiological point of view, strain in the muscle fiber direction is the most important component, since it is an important determinant of the level of active stress that is generated in the muscle cell. Muscle fiber strain can be expressed in terms of sarcomere length. In figure 4.9a sarcomere length l_s is plotted as a function of time. In figure 4.10a, the amount of sarcomere shortening during the ejection

TABLE 4.3: Hemodynamics in the initial simulation of a cardiac cycle: moment of beginning t_{be} and end t_{ee} of the ejection phase, duration of the ejection phase Δt_e , ventricular pressure at beginning p_{be} and end p_{ee} of the ejection phase, maximum ventricular pressure p_{max} , ventricular volume at beginning V_{be} and end V_{ee} of the ejection phase, ejected volume ΔV_e , ejection fraction $\Delta V_e/V_{be}$ and maximum aortic flow q_{max} .

t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
268	440	172	10.8	16.0	19.4	75.1	47.1	28.0	37	243

phase, $\Delta l_{s,e}$, is shown. At the beginning of the cycle, the length of all sarcomeres is set at $2.0 \mu\text{m}$. During the diastolic filling phase all sarcomeres lengthen: in the subendocardial layers BA1 through AP1 sarcomere length increases to about $2.3 \mu\text{m}$, while the subepicardial sarcomeres are stretched to about $2.15 \mu\text{m}$. Early in the isovolumic contraction phase, the sarcomeres in the early activated subendocardial regions BE1 through AP1 shorten quickly. This shortening levels off towards the end of this phase. In the later activated regions the sarcomeres shorten during the entire isovolumic contraction phase. A slight increase of sarcomere length is found in the latest activated regions BA5-BA7-BE7. During the ejection phase, the sarcomeres in the subendocardial layers BA1 through AP1 shorten by a relatively small amount. At the end of the ejection phase sarcomere length in these layers is greater than the final length at the end of the simulation. In the remaining layers sarcomeres shorten to below their final length. Towards the end of the ejection phase some lengthening occurs in the midwall regions EQ3 through AP3 and EQ5 through AP5. In the latest activated subepicardial region at the base, BA5-BA7-BE7, sarcomere shortening continues during the first part of the isovolumic relaxation phase. Finally, during the isovolumic relaxation phase all sarcomere lengths return to a level slightly above $2.0 \mu\text{m}$, in agreement with the ventricular volume that is slightly higher than the volume at the beginning of the simulation. During this transition from the active to the passive ventricle, the subendocardial sarcomeres are shortened, while the sarcomeres in the remaining part of the ventricular wall are stretched.

The local stress state in the ventricular wall can be described by a three-dimensional stress matrix having six components. From a physiological point of view, the most important component is the component in the muscle fiber direction. In figure 4.9b, the fiber stress component T_a is shown, which is associated with the active contraction mechanism. In figure 4.10b, mean active stress during the ejection phase $\bar{T}_{a,e}$ is plotted. Active muscle fiber stress T_a is zero during the diastolic phase. During the isovolumic contraction phase active fiber stress increases. A relatively strong increase is found in the subendocardial layers BA1 through AP1. In these layers a maximum stress of about 110 kPa occurs shortly after the beginning of the ejection

FIGURE 4.7: Initial simulation: r - z -plot, showing global deformation of the ventricle during the diastolic phase D, the isovolumic contraction phase IC, the ejection phase E and the isovolumic relaxation phase IR; times are indicated in ms.

phase. During the remaining part of the ejection phase active stress decreases to about 70 kPa in these layers. In the remaining midwall and subepicardial layers, active fiber stress is relatively constant during the ejection phase, ranging from 25 to 50 kPa. In the apical region AP3-AP5-AP7, active stress is slightly lower. During the isovolumic relaxation phase, active stress decreases rapidly.

In figure 4.9c, total fiber stress T_f is plotted as a function of the fiber extension ratio $\lambda_f = l_s/l_{s,0}$. The area w enclosed by the stress-strain loop represents the external work generated per unit of volume during a cardiac cycle:

$$\begin{aligned}
 w &= \frac{1}{V_s} \oint_{cycle} F_s dl_s \\
 &= \oint_{cycle} \frac{F_s}{A_{s,0}} d\left(\frac{l_s}{l_{s,0}}\right) \\
 &= \oint_{cycle} T_f d\lambda_f
 \end{aligned} \tag{4.35}$$

V_s represents the volume of a sarcomere, which is equal to its undeformed cross-sectional area $A_{s,0}$ times its undeformed length $l_{s,0}$. F_s represents the total force

FIGURE 4.8: Nodes where local mechanics is presented: longitudinal levels BA (base), BE (base-equator), EQ (equator), EA (equator-apex) and AP (apex); radial levels 1 ... 7.

in the sarcomere in the fiber direction. The spatial distribution of w is shown in figure 4.10c. In the subendocardial layer BA1 through AP1, the combination of relatively high stress and limited sarcomere shortening yields stress-strain loops that are high and narrow. In the relatively early activated regions EQ3-EQ5-EA3-EA5-EA7-AP3-AP5-AP7, limited sarcomere shortening during the isovolumic contraction phase causes the loops to be narrow too. In the remaining regions the loops are relatively wide.

Additional information about the deformation of the ventricle is given in figure 4.9d, where the angle of rotation around the long axis of the ventricle at the 20 points is shown. The mean angle of rotation during the ejection phase is given in figure 4.10d. Rotation of the endocardial point at the base BA1 is prohibited. In the remaining points, the angle of rotation is positive during the diastolic phase, i.e. the cross-section rotates in counter-clockwise direction when observing the ventricle from the base towards the apex. During the isovolumic relaxation phase, a strong increase of rotation is found. In the basal region BA, the subepicardial layers rotate more than the subendocardial layers. This pattern is reversed in the apical region AP. At the equatorial level EQ almost no transmural variation of rotation angle is found. During the ejection phase, a slight increase of rotation is found in the basal region BA. At the end of this phase, the rotation angle of the subepicardial region BA1 with respect to the subendocardial region BA7 is about 40° . In the equatorial region EQ almost no change in rotation is observed during the ejection phase. In the more apical regions EA and AP, a rotation in negative circumferential direction is observed during the ejection phase. In the apical region AP, the subendocardial angle of rotation is about 25° more positive than the subepicardial angle during the entire ejection phase. During the isovolumic relaxation phase a quick decrease of angle of rotation towards zero is observed.

FIGURE 4.9: Local mechanics in initial simulation at 20 points in the ventricular wall: 5 longitudinal positions (BA - BE - EQ - EA - AP) and 4 radial positions (1 - 3 - 5 - 7); (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t , (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.10: Local mechanics in initial simulation at 5 longitudinal positions (BA - BE - EQ - EA - AP) in the ventricular wall as a function of the normalized transmural coordinate $\bar{\xi}$: (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{z,e}$. $\bar{\xi} = -1$ and $\bar{\xi} = +1$ correspond to the endocardial and epicardial surface, respectively.

Discussion: the hypothesis on homogeneous spatial distribution of active muscle fiber stress

To check the validity of the results of the simulation presented in the previous subsection, they should be compared with experimental data.

At the global level, the calculated changes of ventricular pressure and aortic flow with time are quite realistic. However, measurements have shown that, in contrast to the results of the simulation, both ventricular length and diameter decrease during the ejection phase [78,62].

At the local level, the regional distribution of active muscle fiber stress will be discussed first: the other local parameters will be discussed in subsequent sections. Experimentally, the distribution of muscle fiber orientation was found to vary considerably [33,81,86,89] (figures 2.4 and 4.5). From simulations performed with various distributions of muscle fiber orientation within the wide range of the experimental data, it was found that the spatial distribution of active muscle fiber stress is highly dependent on the choice of the distribution of muscle fiber orientation. Therefore, the field of active muscle fiber stress in the ventricular wall cannot be predicted accurately in a straightforward analysis, starting from anatomical data. Particularly,

FIGURE 4.11: Transmural variation of helix fiber angle α_1 as assumed in the second simulation (—) and measured approximately at the equator; (O) Streeter et al. [86]; (□) Greenbaum et al. [23]; (△) Ross et al. [81]; (◇) Streeter [89]. (see also figure 4.5). Helix angle distribution in the initial simulation is indicated by the dashed line.

the result of the present simulation that subendocardial active fiber stress is two to three times as high as active fiber stress in the other parts of the ventricular wall, holds only for this particular distribution of muscle fiber orientation.

Experimental data on the spatial distribution of muscle fiber stress are not available. However, it has been noticed that biological tissue adapts to changes in mechanical loading. For example, in the case of a chronic increase of left ventricular pressure, the left ventricular wall becomes thicker, causing a relative reduction of wall stress. This process of adaptation might indicate the existence of a certain level of optimal mechanical loading of the muscle cells. Since no differences between muscle cells in different parts of the ventricular wall have been found [97], mechanical loading might be distributed homogeneously across the ventricular wall [4].

4.2.3 Simulation with adapted transmural distribution of the helix fiber angle

Description of the simulation

As discussed in the previous subsection, the mechanical behavior of the left ventricle, as simulated with the model, is found to be highly dependent on the spatial distribution of the helix fiber angle. However, a large variation is found in experimental

FIGURE 4.12: Global hemodynamics in simulation of a cardiac cycle with adapted helix fiber angle distribution (—) compared with results of initial simulation (- - -): (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

data on this distribution. To give a basis to the choice of the distribution of the helix fiber angle in the model, in this simulation the hypothesis is applied that in the real ventricle active muscle fiber stress is distributed homogeneously across the ventricular wall. Adaptation of the ventricle to the large subendocardial stress levels found in the previous simulation is obtained by a thickening of the subendocardial layers. As a consequence, the variation of the helix fiber angle α_1 with the transmural coordinate ξ becomes weaker in the subendocardial layers of the ventricular wall and stronger in the subepicardial layers. The layer in which the muscle fibers run in circumferential direction shifts towards the epicardium. On the basis of several trials, the helix fiber angle distribution as shown in figure 4.11 was chosen. This distribution is within the wide range of experimentally determined values. As in the previous simulations, the transverse fiber angle α_3 was assumed to be zero.

Description of the results: global behavior

The global hemodynamic behavior of the ventricle is shown in figure 4.12. Characteristic hemodynamic data are listed in table 4.4. Compared to the previous simulation, the ventricle is slightly more compliant: end-diastolic ventricular volume

TABLE 4.4: Hemodynamics in simulation of a cardiac cycle with adapted helix fiber angle distribution.

t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
258	444	186	10.1	17.0	20.9	78.8	43.5	35.3	45	280

equals 79 ml. The ejection phase starts earlier and lasts longer. Peak ventricular pressure, peak aortic flow and ejection fraction $\Delta V_e/V_{be}$ are higher.

The deformation of the ventricle is shown in figure 4.13. In contrast to the previous simulation, relative changes of ventricular diameter and length are more similar.

Description of the results: local behavior

The local behavior in the ventricular wall is shown in the figures 4.14 and 4.15. In the equatorial region BE-EQ-EA, the distribution of active muscle fiber stress across the ventricular wall has become quite homogeneous (figures 4.14b and 4.15b). In the basal region BA homogeneity is less pronounced than in the equatorial region, while in the apical region AP stress is slightly lower than in the other parts of the wall.

Variation of sarcomere length l_s with time t is also more similar in different parts of the ventricular wall (figures 4.14a and 4.15a). In the subendocardial layer BA1 through AP1, sarcomere stretch during the diastolic phase has decreased, while sarcomere shortening during the ejection phase has increased. Compared to the previous simulation, at the radial levels 3 and 7 the pattern of sarcomere strain has hardly changed. At radial level 5, changes in sarcomere strain are opposite to the changes in the subendocardial layers: diastolic sarcomere stretch has increased, while systolic shortening has decreased.

Despite the more homogeneous spatial distribution of sarcomere strain and active muscle fiber stress, the spatial distribution of external work per unit of volume per cycle w is still rather inhomogeneous (figures 4.14c and 4.15c).

The overall pattern of the angle of rotation around the long axis of the ventricle is similar to the pattern found in the previous simulation (figures 4.14d and 4.15d). Transmural differences in angle of rotation have decreased in the basal and apical parts of the ventricle.

Discussion: introduction of the transverse fiber angle

The global deformation of the ventricle in this simulation agrees better with experimental observations than the deformation calculated in the initial simulation

FIGURE 4.13: Global deformation (r - z -plot) of the left ventricle at 8 moments during the cardiac cycle as calculated in simulation with adapted helix fiber angle distribution.

[78,62].

Due to the adaptation of the transmural distribution of the helix fiber angle, active muscle fiber stress has become distributed rather homogeneously across the ventricular wall. The reduced level of active stress in the subendocardial layers is associated with the smaller sarcomere length and higher velocity of sarcomere shortening. As discussed in the previous subsection, the spatial homogeneity of stress may be expected on the basis of the adaptation mechanism of biological tissue. The spatial distribution of external work w will be discussed in the next section. The present discussion will focus on the spatial distribution of the angle of rotation around the long axis of the ventricle.

Using a magnetic resonance imaging technique, Buchalter *et al.* [17] measured the rotation of the endocardial and epicardial surface in eight normal humans. The difference in angle of rotation from end diastole to end systole $\Delta\phi_{z,ed,es}$ was found to increase with increasing distance from the base. In the basal plane the angle of rotation of the endocardial and epicardial surface was found to be equal. At the equatorial and apical levels, epicardial values of $\Delta\phi_{z,ed,es}$ were found to be $3.7 \pm 0.8^\circ$ and $11.2 \pm 1.3^\circ$, respectively. Endocardial values of $\Delta\phi_{z,ed,es}$ were about twice as high as epicardial values. Values of $\Delta\phi_{z,ed,es}$, as calculated in the model, are higher than measured values. Calculated transmural differences of $\Delta\phi_{z,ed,es}$ at the basal

FIGURE 4.14: Local mechanics in simulation with adapted helix fiber angle distribution (—) compared with results of the initial simulation (---): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t , (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.15: Local mechanics in simulation with adapted helix fiber angle distribution (—) compared with results of the initial simulation (---): (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{z,e}$.

and apical levels are higher than the measured transmural differences.

The large transmural differences in angle of rotation are likely to be due to the choice of the muscle fiber direction. Until now, in the simulations it was assumed that muscle fibers are located in surfaces parallel to the endocardium and epicardium. Because of the transmural variation of the helix fiber angle, shear stresses act between those parallel surfaces. In the model, these shear stresses can only be counteracted by the passive material. The stiffness of the passive material is low compared to the stiffness of the activated muscle fibers. Therefore, the shear stresses induced by the activated muscle fibers are counteracted by shear stresses in the passive material only at high shear strains, implying large gradients of angle of rotation. A possible mechanism to prevent these unphysiologically high transmural shears, may be the presence of the cross-over of the muscle fibers between the subendocardial and subepicardial layers. Such cross-over has been observed experimentally [88,89,91]. However, quantitative data on this cross-over, which is described in the model by the transverse fiber angle α_3 , are scarce.

4.3 The reference cardiac cycle

4.3.1 Description of the simulation

The simulation of a cardiac cycle presented in this section will be used as a reference simulation to evaluate the effects of the parameter variations described in the next section. It is based upon the data, presented in chapter 2, regarding ventricular geometry (table 2.1), active material behavior (table 2.4), activation sequence (table 2.5) and aortic impedance (table 2.6). For the description of the passive material behavior, the adapted values presented in table 4.2 are used. The boundary conditions at the base were changed slightly. Each point in the basal plane was assumed to move in a plane defined by the local ξ and ϕ direction. This change was made to approximate better the kinematic constraints imposed by the structures attached to the base, such as the annuli fibrosi and the valves.

Muscle fiber orientation was chosen so that (1) active muscle fiber stress is distributed approximately homogeneously across the left ventricular wall (subsection 4.2.2) and (2) transmural differences in angle of rotation around the long axis of the ventricle ϕ_z are less than 10° (subsection 4.2.3). The first condition was satisfied in the simulation described in subsection 4.2.3 by a suitable choice of the spatial distribution of the helix fiber angle α_1 . The second condition, which is based upon experimental data [17], is satisfied by a suitable choice of the spatial distribution of the transverse fiber angle α_3 . Since the introduction of non-zero values of α_3 was found to affect the spatial distribution of active muscle fiber stress, the helix fiber angle distribution was adapted slightly in comparison to the distribution in the previous simulation. The resulting muscle fiber orientation is shown in figure 4.16. To investigate the influence of the transverse fiber angle α_3 , two simulations were performed with zero and non-zero values of α_3 , respectively.

TABLE 4.5: Hemodynamics in the simulation of a cardiac cycle with non-zero (reference simulation) and zero transverse fiber angle α_3 .

	t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
	ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
$\alpha_3 \neq 0$	254	446	192	10.6	17.3	21.1	79.6	43.9	35.8	45	265
$\alpha_3 = 0$	260	446	186	10.5	17.0	20.7	80.2	47.8	32.4	40	262

FIGURE 4.16: (a) Transmural variation of helix fiber angle α_1 as assumed in the reference simulation (—) and measured approximately at the equator; (O) Streeter et al. [86]; ($\square$) Greenbaum et al. [23]; ($\triangle$) Ross et al. [81]; ($\diamond$) Streeter [89] (see also figure 4.5); variation of the helix fiber angle in the previous simulation is indicated by a dashed line; (b) transmural variation of transverse fiber angle α_3 at the base (—), the equator (---) and the apex (- · -).

4.3.2 Description of the results

Global behavior

The global hemodynamic behavior of the ventricle is shown in figure 4.17 and table 4.5. Ejection fraction $\Delta V_e/V_{be}$ is higher with non-zero than with zero transverse angle. The global deformation pattern of the ventricle is shown in figure 4.18. In contrast to the situation in the previous simulations, no uniform wall thickening is found during the ejection phase. In the basal region, the ventricular wall becomes relatively thin as compared with the equatorial region.

Local behavior

The mechanical behavior at a local level in the ventricular wall is shown in the figures 4.19 and 4.20. Sarcomere length, as shown in figure 4.19a, varies with time rather similarly in all parts of the ventricular wall. During diastole, subepicardial sarcomeres are stretched slightly less than the sarcomeres in the other parts of the wall. During the isovolumic contraction phase, all sarcomeres shorten, except for the sarcomeres in the late activated regions in the basal epicardial part of the

FIGURE 4.17: Global hemodynamics in simulation of a cardiac cycle with non-zero (—) (reference simulation) and zero (---) transverse fiber angle distribution: (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

ventricle. In those regions, sarcomere length is constant or increases. During the ejection phase, the sarcomeres in the levels BE and EQ shorten to their initial length approximately. In the more apical levels EA and AP sarcomeres shorten to below their initial length. Towards the end of the ejection phase these sarcomeres lengthen already. In the basal region, no consistent pattern of sarcomere shortening is found. During the isovolumic relaxation phase sarcomere length returns to a level slightly above the initial length of $2.0 \mu\text{m}$. Setting the transverse fiber angle at zero causes minor changes in the pattern of changes of sarcomere length.

In figure 4.19b active muscle fiber stress is plotted as a function of time. At the levels BE-EQ-EA active fiber stress is distributed approximately homogeneously across the ventricular wall. In the apical and subendocardial basal region, active stress is slightly lower. The distribution of active muscle fiber stress is altered slightly if the transverse fiber angle is set at zero.

From figure 4.19c and figure 4.20c it is apparent that the spatial distribution of external work, generated per unit of volume during a cardiac cycle, is still quite inhomogeneous in both simulations. The amount of generated external work seems to be related to the activation pattern of the ventricular wall: the later a region is

FIGURE 4.18: Global deformation (r - z -plot) of the left ventricle at 8 moments during the cardiac cycle as calculated in the reference simulation.

activated, the more external work is generated.

The angle of rotation of the various points around the long axis of the ventricle is plotted in figure 4.19d. The introduction of the cross-over of the muscle fibers between the subendocardial and subepicardial layers results in a decrease of the magnitude of rotation across the entire ventricular wall. In the basal plane BA, rotation angles are less than 10° . At the BE and EQ levels, rotation angle decreases from endocardium to epicardium. At the more apical levels EA and AP, almost no transmural differences in angle of rotation are present. In the subepicardial layer BE7 through AP7, angles of rotation increase with increasing distance from the basal plane. In the subendocardial layer BE1 through AP1, the magnitude of rotation is more constant.

4.3.3 Discussion

Experimental physiological and biochemical data indicate that no major transmural differences in energy requirement exist under normal circumstances [97]. Assuming that the efficiency of conversion of chemical energy to external work is equal for all muscle fiber cells, it may be concluded that the amount of generated external work is similar for all muscle fiber cells too.

FIGURE 4.19: Local mechanics in the reference simulation (—) compared with results of simulation with zero transverse fiber angle distribution (---): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t ; (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.20: Local mechanics in the reference simulation (—) compared with results of simulation with zero transverse fiber angle distribution (- -): (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{z,e}$.

In the model, external work w , generated per unit of volume per cardiac cycle, is distributed across the ventricular wall quite inhomogeneously, despite the rather homogeneous distribution of fiber stress and sarcomere strain. From figure 4.19c it can be concluded, that w is related to changes in sarcomere strain during the isovolumic contraction phase. In early activated regions, sarcomeres shorten during this phase and the stress-strain loops shift towards the left and become narrow. In later activated regions, sarcomeres are stretched due to the active stress generated in the early activated regions. As a result stress-strain loops are relatively wide. A similar dependency of sarcomere shortening on moment of activation has been found experimentally under conditions of ventricular pacing [76]. To investigate the dependency of generated external work on the moment of activation, in subsection 4.4.1 the influence of a change in the timing of the activation of the ventricular wall is considered.

4.4 Variation of input parameter values

In sections 4.2 and 4.3 it has been shown that the local mechanical behavior of the left ventricle strongly depends on muscle fiber orientation. In this section the

influence of a change in such input parameters as (1) the activation sequence of the ventricle, (2) the active stress-strain relationship, (3) the preload of the ventricle and (4) the afterload of the ventricle will be investigated. The results of each simulation will be compared to the results of the reference simulation.

4.4.1 Simultaneous activation of the ventricle

Description of the simulation

The results of the reference simulation suggest a dependency of the locally generated external work on the activation sequence of the ventricular wall. To investigate this dependency, in this simulation the ventricle was activated virtually simultaneously by increasing the conduction velocity v_e (subsection 2.2.5) from 1.5 m/s to 1500 m/s. The moment of initiation of the activation wave, t_i , was shifted from 150 ms to 180 ms. Thus, timing of the global hemodynamic behavior in this simulation and the reference simulation was similar.

Description of the results: global behavior

The hemodynamic behavior is presented in figure 4.21 and table 4.6. Apart from a slight increase of the ejection fraction no significant changes are introduced by the change in activation pattern. The global deformation of the ventricle, shown in figure 4.22, is hardly affected either.

Description of the results: local behavior

The variation of sarcomere length with time has become more similar in different parts of the ventricle (figures 4.23a and 4.24a). During the isovolumic contraction phase, the relatively large sarcomere shortening in the early activated regions and the sarcomere stretch in the later activated regions have disappeared. Sarcomere length at the end of the ejection phase is smaller in the apical than in the basal part of the ventricle. During the isovolumic relaxation phase, sarcomeres obtain their final length monotonically. The distribution of active stress is similar to that found in the reference simulation (figures 4.23b and 4.24b). The more homogeneous pattern of

TABLE 4.6: Hemodynamics in simulation of a cardiac cycle in which the ventricle is activated simultaneously

t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
258	452	194	10.4	17.3	21.7	80.1	42.4	37.8	47	272

FIGURE 4.21: Global hemodynamics in simulation in which the ventricle is activated simultaneously (—) and the reference simulation (- -): (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

FIGURE 4.22: Global deformation (r - z -plot) of the left ventricle at 4 moments during the cardiac cycle as calculated in simulation in which the ventricle is activated simultaneously.

FIGURE 4.23: Local mechanics in simulation in which the ventricle is activated simultaneously (—) and reference simulation(---): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t ; (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.24: Local mechanics in simulation in which the ventricle is activated simultaneously (—) and reference simulation(---): (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{x,e}$.

sarcomere shortening results in a more homogeneous pattern of generated external work per unit of volume during the cardiac cycle (figures 4.22c and 4.23c). Except for the basal endocardial region, generated external work in the subendocardial layers is slightly higher than in the subepicardial layers. The magnitude of rotation has remained unchanged in the basal part BA and BE of the ventricle and has decreased in the remaining regions (figures 4.23d and 4.24d). During the isovolumic relaxation phase rotation angles decrease to zero monotonically.

Discussion

Experimental data on metabolism in the ventricular wall suggest a homogeneous spatial distribution of generated external work. In this simulation, this homogeneity is obtained by assuming a simultaneous activation of the ventricular wall. However, the real ventricle is not activated simultaneously. The cause of this discrepancy is not clear yet. Maybe in the real situation, sarcomeres may not stretch as easily during the early phase of activation as in the present model. Possibly, the constitutive equations describing the early phase of cardiac muscle contraction should be modified.

FIGURE 4.25: Relationship between active muscle fiber stress and sarcomere length in simulation with reduced contractility of the muscle cells (—) and reference simulation (- -).

4.4.2 Reduced contractility of the muscle fiber cells

Description of the simulation

In this simulation the active stress-length relationship was altered by setting $a_x = 0.85 \cdot 10^6 \text{ m}^{-1}$ and $l_x = 2.2 \mu\text{m}$. Compared to the original stress-length relationship the increase of active stress with sarcomere length is slower, while active stress levels off at $l_s > 2.2 \mu\text{m}$ (figure 4.25). This change simulates the effect of decreased contractility due to a reduced Ca^{++} concentration [90] (figure 2.8b).

Description of the results: global behavior

The reduced contractility results in a decrease of maximum ventricular pressure and ejection fraction, as can be seen in figure 4.26 and table 4.7. The global deformation pattern of the ventricle is similar to the pattern in the reference simulation (figure 4.27).

TABLE 4.7: Hemodynamics in simulation of a cardiac cycle with reduced contractility of the muscle cells.

t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
258	448	190	10.5	15.5	18.4	79.8	53.7	26.1	33	206

FIGURE 4.26: Global hemodynamics in simulation with reduced contractility of the muscle fiber cells (—) and reference simulation (- - -). (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

FIGURE 4.27: Global deformation (r - z -plot) of the left ventricle at 4 moments during the cardiac cycle as calculated in simulation with reduced contractility of the muscle fiber cells.

FIGURE 4.28: Local mechanics in simulation with reduced contractility of the muscle fiber cells (—) and reference simulation(---): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t ; (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.29: Local mechanics in simulation in with reduced contractility of the muscle fiber cells (—) reference simulation(---): (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{z,e}$.

Description of the results: local behavior

The pattern of variation of the local parameters with time is similar to that found in the reference simulation (figure 4.28). Both the amount of sarcomere shortening during the ejection phase and generated external work have decreased (figure 4.29). The level of active stress has also slightly decreased. Angles of rotation around the long axis are almost identical to those found in the reference simulation.

Discussion

Changes in contractility, for example caused by a change in Ca^{++} concentration, may easily occur in the ventricle. This simulation shows that the response of the ventricle to these changes is similar in all parts of the ventricular wall.

4.4.3 Variation of end-diastolic pressure

Description of the simulations

Simulations were performed with end-diastolic pressures of 0.5 kPa, 1.0 kPa (reference simulation) 1.5 kPa, respectively.

FIGURE 4.30: Global hemodynamics in simulations with end-diastolic pressures of 0.5 kPa (- - -), 1.0 kPa (- · - ·; reference simulation) and 1.5 kPa (—): (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; (b) pressure-volume loops.

Description of the results: global behavior

The global hemodynamic behavior is shown in figure 4.30 and table 4.8. Duration of the ejection phase Δt_e , ejection volume ΔV_e , maximum ventricular pressure p_{max} and maximum aortic flow q_{max} increase with increasing end diastolic pressure p_{ed} , while ejection fraction $\Delta V_e/V_{be}$ is virtually unaffected. In the simulation with $p_{ed} = 0.5$ kPa, ventricular volume at the end of the ejection phase is lower than the volume of the completely passive ventricle at zero ventricular pressure. Thus, ventricular

TABLE 4.8: Hemodynamics in simulations with two end-diastolic pressures p_{ed} .

p_{ed} kPa	t_{be} ms	t_{ee} ms	Δt_e ms	p_{be} kPa	p_{ee} kPa	p_{max} kPa	V_{be} ml	V_{ee} ml	ΔV_e ml	$\frac{\Delta V_e}{V_{be}}$ %	q_{max} ml·s ⁻¹
0.5	256	432	176	10.7	15.7	18.6	59.7	32.8	26.9	45	227
1.0	254	446	192	10.6	17.3	21.1	79.6	43.9	35.8	45	265
1.5	252	455	203	10.3	18.1	22.4	93.6	52.5	41.1	44	278

FIGURE 4.31: Global deformation (r - z -plot) of the left ventricle at 4 moments during the cardiac cycle in case of an end-diastolic pressure of (a) 0.5 kPa and (b) 1.5 kPa.

pressure at the end of the cycle becomes negative. Because of numerical instabilities, the simulation was terminated at $t = 525$ ms. At this moment, ventricular pressure equaled -0.2 kPa. The global deformation pattern of the ventricle is shown in figure 4.31. The increased ventricular volume in the simulation with high preload results in decreased ventricular wall thickness. However, the pattern of deformation, with basal wall thinning and equatorial wall thickening, is preserved.

Description of the results: local behavior

The pattern of variation of sarcomere length with time is similar in all three simulations, but the magnitude of this variation increases with increasing end-diastolic pressure (figures 4.32 and 4.33). Generated external work w increases also with increasing end-diastolic pressure, while the shape of the local stress-strain loops is preserved. Both the magnitude and the pattern of variation with time of active stress and angle of rotation are hardly affected.

Discussion

Changes in left ventricular end-diastolic pressure frequently occur. As a result of the change in preload of the ventricle, a change in mechanical load of the local muscle

FIGURE 4.32: Local behavior in simulation with end diastolic pressure of 0.5 kPa (---), 1.0 kPa (- - -) and 1.5 kPa (—): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t ; (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.33: Local mechanics in simulations with end-diastolic pressures of 0.5 kPa (---), 1.0 kPa (- · -) and 1.5 kPa (—): (a) sarcomere shortening during the ejection phase $\Delta l_{s,e}$; (b) mean active first Piola-Kirchhoff fiber stress during the ejection phase $\bar{T}_{a,e}$; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle during the ejection phase $\bar{\phi}_{z,e}$.

fibers, that is evenly distributed across the whole ventricular wall, is found.

4.4.4 Aortic occlusion

Description of the simulation

The influence of a change in afterload was investigated by preventing the aortic valve from opening. Thus, an isovolumic cardiac cycle results.

Description of the results: global behavior

The global hemodynamic behavior is shown in figure 4.34. Ventricular pressure rises to 28.2 kPa. The pressure-volume relation during rise and decay of ventricular pressure is identical, which indicates that no external work is generated. During the systolic phase, only minor changes in ventricular shape are calculated (figure 4.35).

FIGURE 4.34: Global hemodynamics in simulation with an aortic occlusion (—) and the reference simulation (---): (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{aao} as a function of time t ; the dotted line indicates the end of the diastolic phase; (b) pressure-volume loop; dot indicates the end of the diastolic phase.

FIGURE 4.35: Global deformation (r - z -plot) of the left ventricle at 4 moments during the cardiac cycle as calculated in simulation with an aortic occlusion.

FIGURE 4.36: Local mechanics in simulation of a cardiac cycle in case of an aortic occlusion (—) and reference simulation(---): (a) sarcomere length l_s versus time t ; (b) active first Piola-Kirchhoff fiber stress T_a versus time t ; (c) total first Piola-Kirchhoff fiber stress T_f versus fiber extension ratio $\lambda_f = l_s/l_{s,0}$; (d) angle of rotation around long axis of the ventricle ϕ_z versus time t .

FIGURE 4.37: Local mechanics in simulation of a cardiac cycle with an aortic occlusion (—) and reference simulation(---): (a) sarcomere shortening $\Delta l_{s,e}$ during period in which the ventricle would eject under normal circumstances; (b) mean active first Piola-Kirchhoff fiber stress $\bar{T}_{a,e}$ during the same period; (c) external work per unit of volume during one cardiac cycle w ; (d) mean angle of rotation around long axis of the ventricle $\bar{\phi}_{x,e}$ during period defined under (a).

Description of the results: local behavior

The local behavior is shown in the figures 4.36 and 4.37. The quantities in figure 4.37 are calculated over the period during which the ventricle would eject under normal circumstances. Sarcomere length is affected after the moment at which ejection starts in the reference cardiac cycle (figure 4.36a). In the period during which the ventricle would eject under normal circumstances, sarcomere length remains approximately constant. Thereafter, sarcomere length returns to the end-diastolic level. Like in the previous simulations, active muscle fiber stress remains approximately homogeneously distributed across the ventricular wall (figure 4.36b). Maximum stress levels are higher and the period of generation of active stress is prolonged. The amount of generated external work per unit of volume w decreases by about the same amount in all parts of the ventricular wall. Consequently, in the basal part BA-BE the ventricle w remains positive, while in the remaining part of the ventricle w becomes negative. In the latter regions, the local stress-strain loops are completed in a clock-wise direction. The pattern of rotation around the long axis of the ventricle is affected in the apical region mainly. In this region, angles of rotation are slightly higher than in the reference simulation.

Discussion

Maximum stress level is higher than the level in the reference simulation, because sarcomeres are longer and sarcomere shortening velocity is lower. The period of generation of active stress is prolonged, because sarcomere length is higher. The change of sign of the generated external work w suggests an exchange of energy between the basal and apical half of the ventricle. However, since the decrease in w is similar in all parts of the ventricular wall, the resulting distribution of w is largely determined by the distribution of w in the reference simulation. If in the reference simulation w would have been distributed homogeneously across the ventricular wall, as can be expected on the basis of experimental findings [97], then in this simulation w would have been approximately zero everywhere in the ventricular wall.

4.5 Conclusions

The mechanics of the left ventricle during a cardiac cycle was simulated for several values of the model parameters. From the results of these simulations the following can be concluded:

- The distribution of active muscle fiber stress across the left ventricular wall depends primarily on the transmural distribution of the helix fiber angle α_1 .
- The distribution of the differences in angle of rotation around the long axis of the ventricle depends primarily on the spatial distribution of the transverse fiber angle α_3 .
- The distribution across the ventricular wall of generated external work per unit of volume per cardiac cycle depends primarily on the activation sequence of the ventricular wall.
- The spatial distributions of (1) active muscle fiber stress, (2) angle of rotation around the long axis of the ventricle and (3) locally generated external work per unit of volume per cardiac cycle remain virtually unchanged in the case of (1) a change of active stress-strain relationship, (2) a change of end-diastolic pressure and (3) aortic occlusion.
- The spatial distributions of (1) active muscle fiber stress and (2) angle of rotation around the long axis of the ventricle remain virtually unchanged in the case of a change of the activation sequence of the ventricle.
- The changes of left ventricular pressure, aortic pressure and aortic flow as a function of time are hardly affected by (1) a change of the spatial distribution of the helix and transverse fiber angle and (2) a change of the activation sequence of the ventricle.

Comparison of cardiac deformation and hemodynamics in model and experiment

In this chapter the results of the simulations presented in the previous chapter are compared with results obtained in physiological experiments. In section 5.1 a comparison is made with experimental data derived from literature on global hemodynamical behavior, local three-dimensional deformation and rotation. In section 5.2 a comparison is made with data from our experiments, in which the two-dimensional deformation of part of the epicardial surface was determined.

5.1 Comparison with experimental data derived from literature

In this section calculated and experimentally determined data on global hemodynamic behavior, local three-dimensional deformation and rotation are compared.

5.1.1 Global left ventricular hemodynamics and deformation

Experimental data

Olsen *et al.* studied left ventricular minor and major axis diameters and equatorial wall thickness in the conscious dog with chronically implanted pulse-transit time ultrasonic dimension transducers [62]. Representative data on pressure, flow, and global deformation are shown in figure 5.1a. Global deformation of the ventricle is characterized by global circumferential strain ε_R , global axial strain ε_L and equatorial wall thickness strain ε_d , that are defined as:

$$\varepsilon_R = \frac{R_o - R_{o,ed}}{R_{o,ed}} \quad (5.1)$$

$$\varepsilon_L = \frac{L_o - L_{o,ed}}{L_{o,ed}} \quad (5.2)$$

$$\varepsilon_d = \frac{d_{eq} - d_{eq,ed}}{d_{eq,ed}} \quad (5.3)$$

R_o , L_o and d_{eq} denote outer equatorial ventricular radius, outer ventricular length and equatorial wall thickness, respectively. Using a geometric model, presented by Olsen *et al.*, and assuming papillary muscle volume to be 4% of the wall volume (subsection 2.1.1), the following volumina can be calculated from the deformation data: $V_{ed} = 55$ ml, $V_{ee} = 26$ ml, $V_w = 76$ ml. Thus end-diastolic volume is equal to 72% of the wall volume and the ejection fraction equals 53%.

Comparison of experimental and calculated data

The experimental data on pressure, flow and deformation are compared with the calculated data for the case of the reference simulation (figure 5.1b and section 4.3) and the case of simultaneous activation of the ventricle (figure 5.1c and subsection 4.4.1). In these simulations end-diastolic volume equals 57% of the wall volume and the ejection fraction equals about 46%.

The overall pattern of changes in pressure, flow and deformation with time is reasonably similar in model and experiment. In a closer view, the following differences are apparent. Experimentally determined maximum ventricular pressure is lower and occurs earlier than calculated maximum pressure. In the experiment, during the ejection phase global circumferential strain ε_R is about twice as high as global axial strain ε_L . In the simulations, ε_R and ε_L are approximately equal during the ejection phase. In the experiment, the ventricular length increases during the isovolumic contraction phase and decreases monotonically until the end of the ejection

FIGURE 5.1: Left ventricular hemodynamics and deformation; ventricular pressure p_{lv} , aortic flow q_{aa} , change of outer equatorial diameter ε_R , change of outer ventricular length ε_L , and change of equatorial wall thickness ε_d as a function of time t ; the dotted lines indicate the end of the diastolic phase and beginning and end of the ejection phase; (a) experimental data adapted from Olsen et al. [62]; (b) results of reference simulation; (c) results of simulation in which the ventricle is activated simultaneously.

phase. In the reference simulation, no ventricular lengthening is found during the isovolumic contraction phase, while ventricular length oscillates at the end of the ejection phase and the beginning of the isovolumic relaxation phase. The change of ventricular length with time, as calculated in the simulation with simultaneous activation, agrees better with the experimental observations.

Discussion

The difference between measured and calculated variations in ventricular pressure with time during the ejection phase may be caused by inaccuracies in the description of the afterload and the contractile material properties in the model. The difference between measured and calculated ratio of global circumferential and axial strain may be reduced by a minor modification of the transmural distribution of the helix fiber angle. In the simulations, the latter distribution was found to be an important determinant of the change of ventricular radius and length during the ejection phase (compare results in figures 4.7 and 4.13).

In the simulations, the change of ventricular length as a function of time is found to depend on the pattern of activation of the ventricular wall (figures 5.1b and c). The oscillatory change of ventricular length at the end of the ejection phase, as calculated in the reference simulation, is probably associated with the asynchronous distribution of sarcomere shortening across the ventricular wall. Thus, the descrip-

tion of the contractile properties of the myocardial tissue may have to be modified so that the asynchronous electrical activation of the ventricle is partly compensated for, resulting in a more synchronous contraction of the fibers in the entire ventricular wall. In subsection 4.4.1, the same conclusion was drawn on the basis of the hypothesis that locally generated external work is distributed homogeneously across the ventricular wall.

5.1.2 Local three-dimensional deformation

Experimental data

Local three-dimensional deformation of the ventricular wall was investigated by Waldman *et al.* [100,101]. Lead beads were implanted in the left ventricular wall at $67\% \pm 7\%$ of the distance from base to apex at a mutual distance of about 3 mm. Using high-speed biplane cineradiography, the three-dimensional coordinates of the beads were obtained as a function of time. From the marker coordinates three-dimensional Green-Lagrange strains were calculated with respect to the end-diastolic configuration. Strain components are expressed with respect to a coordinate system that is similar to the ellipsoid coordinate system shown in figure 2.2b. The directions of local longitudinal coordinate θ and the local circumferential coordinate ϕ ly in the epicardial tangent plane, while the third radial coordinate r is defined along the surface normal.

In figure 5.2a, the variation of left ventricular pressure with time is shown, as determined in one experiments. The variation with time of the six strain components is indicated by the dotted bands. The strain components were computed from the measured coordinates of four beads, forming a tetrahedron the centroid of which was located in the inner third of the ventricular wall. In figure 5.2c, the transmural variation of the six strain components, as measured at the same longitudinal site at the end of ejection phase is shown; the mean values and the standard deviation in the inner and outer half of the ventricular wall are plotted ($n = 7$).

Comparison of experimental and calculated data

Figure 5.2b shows the variation of left ventricular pressure and the six strain components with time, as calculated in the reference simulation. Calculated and experimentally determined circumferential strains $E_{\phi\phi}$ are similar. In the experiment, longitudinal strain $E_{\theta\theta}$ is zero, while in the model longitudinal strain varies similarly to circumferential strain. Calculated radial strain E_{rr} in the inner third of the ventricular wall is about twice as large as experimentally determined radial strain. During the ejection phase, the change of calculated shear strain components with time is opposite to the measured change.

In figure 5.2c, the solid lines represent the transmural variation of the six strain components at the end of the ejection phase, as calculated in the reference simulation. Measured data are given by the symbols and error bars. Calculated and

FIGURE 5.2: Local three-dimensional deformation of the ventricular wall; (a) experimental data adapted from Waldman et al. [100]; change of left ventricular pressure p_{lv} , circumferential strain $E_{\phi\phi}$, longitudinal strain $E_{\theta\theta}$, radial strain E_{rr} , and shear strains $E_{\phi\theta}$, $E_{\phi r}$ and $E_{\theta r}$ as a function of time t ; strains were measured at $67\% \pm 7\%$ of the distance from base to apex in the inner third of the ventricular wall; (b) change of ventricular pressure and strain components as a function of time t as calculated in the reference simulation in node EA2; (c) variation of strain components from endocardium ($\bar{\xi} = -1$) to epicardium ($\bar{\xi} = +1$) at the end of the ejection phase; dots (•) and error bars represent strains measured at $67\% \pm 7\%$ of the distance from base to apex (adapted from Waldman et al. [101]); solid lines (—) represent strains calculated in the reference simulation at longitudinal level EA.

measured transmural variations of normal strains agree reasonably well while calculated and measured transmural variations of shear strains are rather different.

Discussion

Calculated and measured changes of the normal strain components as a function of time and transmural position in the ventricular wall are reasonably similar. Calculated normal strain components are larger than measured ones, indicating that in the simulation the ejection fraction may be higher than in the experiment. The ratio $E_{\theta\theta}/E_{\phi\phi}$ of local longitudinal strain to local circumferential strain is closely related to the ratio $\varepsilon_L/\varepsilon_R$ of global axial strain to global circumferential strain (subsection 5.1.1). In the simulation, the ratios $E_{\theta\theta}/E_{\phi\phi}$ and $\varepsilon_L/\varepsilon_R$ are higher than those in the experiment. As discussed in the previous subsection 5.1.1, a minor modification of the transmural distribution of the helix fiber angle may yield a better agreement of calculated and measured strain ratios.

The differences between calculated and measured strain components may also be caused in part by difficulties associated with the experiment. Firstly, in an inhomogeneous strain field, the use of markers at a finite separation in a tetrahedral configuration may yield errors in the determination of maximum principal strain of up to 25% [22]. Secondly, the experimental determination of the orientation of the coordinate system is difficult. Minor errors in the orientation of the coordinate system may significantly affect the values of the strain components. Thirdly, determination of the location of the subendocardial boundary of the ventricular wall is difficult because of the presence of the trabecular layer. As a result, the estimate of the transmural position may be inaccurate. Since radial strain gradients are large, a relative small inaccuracy in transmural position may yield relatively large errors in the strain values obtained.

5.1.3 Rotation of the wall of the ventricle around the long axis

Experimental data

Buchalter *et al.* measured the angle of rotation ϕ_z of the endocardial and epicardial surface around the long axis of the ventricle using magnetic resonance imaging [17]. Rotation angles ϕ_z were measured in eight normal humans, at eight locations in the circumferential direction and at five longitudinal levels. Changes $\Delta\phi_{z,ee,ed}$ of the angle of rotation from the end of the diastolic phase to the end of the ejection phase are plotted in figure 5.3 for five axial levels. Data are averaged over the eight subjects and the eight circumferential locations. At the base, no transmural differences in angle of rotation are found. $\Delta\phi_{z,ee,ed}$ increases with increasing distance from the base, endocardial values being about twice as high as epicardial values.

FIGURE 5.3: Angle of rotation $\Delta\phi_{z,ee,ed}$ around long axis of the left ventricle from the end of the diastolic phase to the end of the ejection phase (a) at endocardial surface and (b) at epicardial surface; results from measurements by Buchalter et al. [17] (●), reference simulation (□) and simulation identical to reference simulation with transverse fiber angle set to zero (▽).

Comparison of experimental and numerical data

In figure 5.3 the values of $\Delta\phi_{z,ee,ed}$ as calculated with the use of the model at five longitudinal levels BA, BE, EQ, EA and AP are shown (see figure 4.8). Data were obtained in the reference simulation and a simulation that is identical to the reference simulation with the exception, that the transverse fiber angle is set at zero (section 4.3). In the reference simulation, the pattern of epicardial $\Delta\phi_{z,ee,ed}$ agrees reasonably well with the measured pattern. However, calculated and measured endocardial $\Delta\phi_{z,ee,ed}$ is quite different. If the transverse fiber angle is set at zero, the calculated pattern of $\Delta\phi_{z,ee,ed}$ changes considerably. In the latter case, agreement with the experimental data is better at the endocardium than at the epicardium.

Discussion

In the parameter $\Delta\phi_{z,ee,ed}$ contributions of both the isovolumic contraction phase and the ejection phase are combined. Thus, it is impossible to decide whether the discrepancy between measured and calculated values of $\Delta\phi_{z,ee,ed}$ is caused by an unrealistic transition from the passive diastolic phase to the active ejection phase or a poor description of the ejection phase itself. This aspect will be discussed further in the next subsection.

Since the spatial distribution of the transverse fiber angle α_3 appears to be an important determinant of the spatial distribution of $\Delta\phi_{z,ee,ed}$, adaptation of the spatial distribution of α_3 may yield a closer agreement between measured and calculated spatial distribution of $\Delta\phi_{z,ee,ed}$.

5.1.4 Torsion of the left ventricle

Torsion as calculated with the use of the model

Torsion of the left ventricle is associated with rotation of the apex with respect to the base around the long axis of the ventricle [6]. In the model, torsion was quantified by the parameter $\phi_{z,ba,ap}$, which was calculated as follows. The angle of rotation ϕ_z of the midwall nodes at five longitudinal levels BA, BE, EQ, EA, AP (see figure 4.8) was plotted versus the axial coordinate z of these nodes. In figure 5.4a this ϕ_z - z -plot is shown at the beginning of the ejection phase, for the case of the reference simulation. The slope of the best linear fit through these data was multiplied by the midwall base-to-apex distance. Thus the angle of rotation $\phi_{z,ba,ap}$ of the apex with respect to the base was calculated.

In figure 5.4b, $\phi_{z,ba,ap}$ is plotted versus ventricular volume V_{lv} , normalized by ventricular wall volume V_w . The results of three simulations are shown, in which end-diastolic pressure was equal to 0.5, 1.0 and 1.5 kPa, respectively (subsection 4.4.3). During the diastolic filling phase $\phi_{z,ba,ap}$ increases approximately linearly with normalized ventricular volume V_{lv}/V_w . During the isovolumic contraction phase, $\phi_{z,ba,ap}$ increases by about 12° in all three simulations. During the ejection phase, $\phi_{z,ba,ap}$ decreases with decreasing normalized ventricular volume, the decrease being more pronounced at smaller volumes. During the isovolumic relaxation phase, $\phi_{z,ba,ap}$ reaches its diastolic equilibrium value non-monotonically.

Experimental data on torsion

Beyar *et al.* [14] investigated torsion in four dogs with open chest and two dogs with closed chest. Using biplane cineradiography, the coordinates of 15-26 radiopaque markers implanted in the myocardial midwall were measured. Angles of rotation of the markers around the long axis with respect to the situation at the beginning of the ejection phase were plotted versus the axial coordinates of the markers. The slope of the linear regression line in this plot was defined to be ventricular twist. A change in cavity dimensions was quantified by normalization of the radial displacement of the markers to the total displacement during the ejection phase. Results are presented in terms of twist per unit of normalized radial shortening.

Twist, as defined by Beyar *et al.*, is expressed in $\text{rad}\cdot\text{m}^{-1}$. We prefer to express torsion in terms of a dimensionless quantity $\phi_{z,ba,ap}$, as defined above. In the study of Beyar *et al.*, a twist of $0.056 \text{ rad}\cdot\text{cm}^{-1}$ is mentioned to be equivalent to a base-to-apex rotation of 13.4° . On this basis, we have concluded that the average long axis length in Beyar's experiments was 42 mm. Using this length, twist is converted to base-to-apex rotation. Beyar *et al.* also estimated ventricular cavity volume V_{lv} on the basis of the measured coordinates of the markers using a cubic spline curve-fitting algorithm. The estimated ventricular cavity volume, normalized to total volume change during the ejection phase, was found to vary linearly with normalized radial shortening. Thus, the results of Beyar *et al.*, can be expressed in terms of

FIGURE 5.4: Torsion of the left ventricle: (a) calculated angle of rotation ϕ_z at the beginning of the ejection phase plotted versus axial coordinate z in 5 midwall nodal points; multiplication of the slope of the best linear fit (---) through the data points with the base-to-apex distance yields the base-to-apex rotation $\phi_{z,ba,ap}$; (b) base-to-apex rotation $\phi_{z,ba,ap}$ plotted versus ventricular volume V_{lv} divided by wall volume V_w , as calculated in simulations with an end-diastolic pressure of 0.5 kPa (---), 1.0 kPa (—) and 1.5 kPa (- · -), respectively; diastolic filling phase (D) and ejection phase (E) are indicated; (c) base-to-apex rotation $\phi_{z,ba,ap}$ plotted versus normalized ventricular volume $(V_{lv} - V_{ee})/\Delta V_e$, with ventricular volume at the end of the ejection phase V_{ee} and ejected volume ΔV_e ; the thick solid line (—) represents data derived from Beyar et al. [14]; the remaining three lines correspond to the calculated data, already shown in figure (b); (d) base-to-apex rotation $\phi_{z,ba,ap}$ plotted versus ventricular volume V_{lv} divided by wall volume V_w , as calculated in the reference simulation (---) and a simulation in which the ventricle is activated simultaneously (—).

base-to-apex rotation per unit of normalized ventricular volume.

In figure 5.4c, mean ($n = 6$) base-to-apex rotation $\phi_{z,ba,ap}$, as derived from Beyar's experimental data, is plotted versus normalized ventricular volume (solid line). During the ejection phase, $\phi_{z,ba,ap}$ varies linearly with normalized ventricular volume. The apex rotates over an angle of $13.4^\circ \pm 4.1^\circ$ with respect to the base in counter-clockwise direction, as viewed from the apex. During the isovolumic relaxation phase and the early part of the diastolic filling phase, up to the point where ventricular volume has increased with 15% of the stroke volume, a rotation in clockwise direction of $5.7^\circ \pm 4.3^\circ$ is measured. During the remaining part of the diastolic filling phase, counterwise direction is $6.2^\circ \pm 2.4^\circ$. During the latter period, rotation varies linearly with normalized volume. During the isovolumic contraction phase, no significant apical rotation is measured.

Comparison of calculated and experimental data

In addition to the experimental data on torsion, in figure 5.4c similarly defined measures of torsion are plotted for the three simulations. Ventricular volume is normalized to range from 0.0 to 1.0 and base-to-apex rotation $\phi_{z,ba,ap}$ is referred to the situation at the beginning of the ejection phase. Comparison of the calculated data in the figures 5.4b and 5.4c shows that the normalization with respect to ventricular volume, as applied by Beyar *et al.*, yields a less consistent picture of ventricular torsion, especially during the ejection phase.

In the simulation with an end-diastolic pressure of 0.5 kPa, calculated and measured rotation during the ejection phase agree quite well, but at higher preloads, calculated rotation during the ejection phase is less. In contrast with the experimental results, in the model $\phi_{z,ba,ap}$ does not vary linearly with normalized ventricular volume during the ejection phase. During the diastolic filling phase, calculated and measured apical rotation agree reasonably well. In contrast with the experimental results, during the isovolumic relaxation phase calculated apical rotation does not vary monotonically with time. During this phase, the net calculated apical rotation is opposite to the measured apical rotation. During the isovolumic contraction phase the discrepancy between calculated and measured apical rotation is largest: in the model, a large apical rotation is found, while in the experiment virtually no rotation is measured.

Discussion

The comparison of calculated and measured data shows that ventricular torsion during the passive diastolic filling phase and the active ejection phase is described reasonably well by the model. However, during the isovolumic phases in which the transition between passive and active material takes place, calculated and measured torsion differ significantly. Ventricular torsion is an overall measure of local rotation of the ventricular wall around the long axis. As shown in chapter 4, the spatial

distribution of the local angle of rotation and the transverse fiber angle are closely related. Thus, ventricular torsion will also depend on the latter distribution.

Another important determinant of ventricular torsion can be derived from figure 5.4d, in which torsion as calculated in the reference simulation is compared to that found in the simulation in which the ventricle is activated simultaneously. It can be concluded that the large apical rotation during the isovolumic contraction phase, as calculated in the reference simulation, is associated with the asynchronous shortening of the sarcomeres in the ventricular wall. In the reference simulation, the non-linear change of apical rotation with normalized ventricular volume during the last part of the ejection phase, may also be associated with this asynchrony. Based on the present comparison of calculated and measured ventricular torsion, it may be concluded again that in the real ventricle sarcomeres shorten more synchronously than can be expected on the basis of the asynchrony in electrical activation.

The present findings suggest that the discrepancy between calculated and experimental results, as found in the previous subsection 4.1.3, may be attributed mainly to an unphysiological transition from the passive to the active state in the simulation.

5.2 Comparison with epicardial deformation obtained in dog experiments

5.2.1 Experimental setup

Experiments were performed on 4 mongrel dogs of either sex and unknown age, ranging in weight from 23 to 29 kg. The dogs were premedicated with Hypnorm (1 ml·kg⁻¹ IM; 1 ml Hypnorm contains 10 mg fluanisone and 0.2 mg fentanyl base). Anesthesia was induced with pentobarbital sodium (10 mg·kg⁻¹ IV) and, after endotracheal intubation, was maintained with O₂/N₂O and a continuous infusion of pentobarbital sodium (2 mg·kg⁻¹·min⁻¹). Ventilation was kept constant with a positive pressure respirator (Pulmomat, DRÄGER). The chest was opened through the left fifth intercostal space, the fifth rib was removed and the heart was suspended in a pericardial cradle. An epicardial bipolar platinum pacing electrode was placed on the right atrium.

Left ventricular and aortic pressure were measured with catheter-tip micromanometers (MILLAR PC-470) (figure 5.5a). The lumen of the cathetertip manometer in the ventricular cavity was connected to an external pressure transducer (ELECTROMEDICS MS20), which could be set to a reference level by switching a three-way cock. This reference level was the center level of the left ventricular cavity. Aortic volume flow was measured with an electromagnetic flow meter (SKALAR TRANSFLOW 601). Pressure and flow signals were recorded on tape (AMPEX PR2200), from which they were retrieved later at a sample frequency of 200 Hz.

To determine two-dimensional epicardial deformation approximately 40 white markers (diameter 1.5 mm) were attached to the epicardial surface of the left ven-

FIGURE 5.5: Measurement of hemodynamics and epicardial deformation in the left ventricle; (a) schematic view of the heart showing the left ventricle LV, the right ventricle RV, the left atrium LA, the aorta AO, the pulmonary artery PA, the circumflex branch LCC and anterior descending branch LADC of the left coronary artery, catheters for measurement of ventricular pressure p_{lv} and aortic pressure p_{ao} , electromagnetic flow probe for measurement of aortic flow q_{ao} , and dots on anterior wall of the left ventricle for determination of epicardial deformation; (b) subdivision of the area covered with markers into 5×5 subregions; deformation is determined in 4×4 overlapping regions, each region consisting of 2×2 regions in the 5×5 subdivision.

tricular anterior wall at mutual distances of 5-7 mm, as shown in figure 5.5a [74]. The area covered with markers was perfused by branches of the left anterior descending and coronary circumflex arteries and had a size of 15-20 cm². The motion of the markers was registered via a mirror by a video camera (SONY AVC 32500CE) with a 200 mm tele-objective positioned at a distance of 2.5 m and recorded on tape by a video recorder (SONY SL-C9ES). To enable synchronization of hemodynamical and deformation data, left ventricular pressure was recorded on the audio channel of the video recorder. Video frames were digitized, markers were detected and the position of their center of gravity was determined. The markers were automatically tracked from frame to frame. Marker trajectories were filtered using a singular value decomposition filtering technique [59]. A rectangular area with one side parallel to the long axis of the ventricle was chosen so that it contained all markers. This area was subdivided into 5×5 subregions (figure 5.5b). Local epicardial deformation was

TABLE 5.1: Hemodynamics in the four experiments and the reference simulation; duration of the isovolumic contraction phase Δt_{ic} and the ejection phase Δt_e ; ventricular pressure at end-diastole p_{ed} and beginning p_{be} and end p_{ee} of the ejection phase, maximum ventricular pressure p_{max} , maximum aortic flow q_{max} , ejected volume ΔV_e and ventricular wall volume V_w .

	Δt_{ic}	Δt_e	p_{ed}	p_{be}	p_{ee}	p_{max}	q_{max}	ΔV_e	V_w
	ms	ms	kPa	kPa	kPa	kPa	ml·s ⁻¹	ml	ml
exp. 1	80	170	1.0	11.0	12.4	15.8	236	24.9	158
exp. 2	70	165	0.8	8.5	9.5	12.3	189	19.7	123
exp. 3	65	185	0.9	8.6	9.4	13.0	182	21.0	148
exp. 4	70	180	1.2	10.7	8.7	14.5	224	27.7	118
ref. sim.	54	192	1.0	10.6	17.3	21.1	265	35.8	140

determined from the marker positions in 4×4 overlapping regions, each region consisting of 2×2 subregions in the 5×5 subdivision. Deformation data were available at a frequency of 50 Hz.

The measurements were recorded during normal sinus rhythm. In case of irregularities, atrial pacing was applied at a higher frequency.

5.2.2 Experimental results

In figure 5.6a representative experimental data on ventricular pressure, aortic flow and epicardial deformation are shown. The end of the diastolic phase was defined as the moment at which the rate of increase of ventricular pressure with time exceeded $0.67 \text{ kPa} \cdot \text{s}^{-1}$. The beginning of the ejection phase was defined as the moment at which the left ventricular pressure exceeded the end-diastolic aortic pressure level. Duration of the ejection phase was determined from the aortic flow signal. Hemodynamical data obtained in the four experiments are listed in table 5.1.

Deformation was calculated with respect to the situation at the beginning of the ejection phase. Epicardial deformation was expressed in terms of fiber strain ϵ_f and area strain ϵ_A :

$$\epsilon_f = \frac{l_f - l_{f,be}}{l_{f,be}} \tag{5.4}$$

$$\epsilon_L = \frac{A - A_{be}}{A_{be}} \tag{5.5}$$

l_f and A represent epicardial fiber length and surface area, respectively. The values of the deformation parameters ϵ_f and ϵ_A are independent of the choice of the

FIGURE 5.6: Hemodynamics and local epicardial deformation as measured in experiment 1 and calculated in the reference simulation: (a) measured change of ventricular pressure p_{lv} (—) and aortic flow q_{ao} (---) as a function of time t ; (b) measured epicardial fiber strain ϵ_f (—) and epicardial area strain ϵ_A (---) in 16 epicardial regions; (c) calculated hemodynamics; (d) calculated epicardial fiber strain ϵ_f and epicardial area strain ϵ_A .

TABLE 5.2: Epicardial deformation during the ejection phase as obtained in experiment 1. Changes in fiber strain $\Delta\epsilon_{f,e}$ and surface area $\Delta\epsilon_{A,e}$ during the ejection phase in the 16 epicardial regions.

$\Delta\epsilon_{f,e}$						
	1	2	3	4	mean	SD
A	-0.083	-0.089	-0.098	-0.106	-0.094	0.008
B	-0.088	-0.094	-0.094	-0.101	-0.094	0.005
C	-0.069	-0.072	-0.076	-0.086	-0.076	0.006
D	-0.075	-0.086	-0.091	-0.102	-0.088	0.010
mean	-0.079	-0.085	-0.090	-0.099		
SD	0.007	0.008	0.008	0.008		

$\Delta\epsilon_{A,e}$						
	1	2	3	4	mean	SD
A	-0.103	-0.098	-0.097	-0.104	-0.100	0.003
B	-0.106	-0.101	-0.094	-0.091	-0.098	0.006
C	-0.119	-0.099	-0.092	-0.073	-0.096	0.016
D	-0.133	-0.140	-0.114	-0.106	-0.123	0.014
mean	-0.115	-0.110	-0.099	-0.094		
SD	0.012	0.018	0.009	0.013		

coordinate system. In figure 5.6b, ϵ_f and ϵ_A in the 16 epicardial regions are shown as a function of time. During the isovolumic contraction phase, the decrease of fiber strain is small as compared to the decrease of area strain. The change of ϵ_f and ϵ_A during the ejection phase, as measured in experiment 1, is given in table 5.2. Decrease of fiber strain ranges from -0.069 to -0.106 . Decrease of area strain ranges from -0.073 to -0.140 . No clear overall gradients in fiber strain or area strain are found. In table 5.3 the deformation parameters in all four experiments are listed. Since no circumferential differences are considered in the model, within each experiment data were averaged over the four circumferential regions 1 through 4. Within each experiment, deformation during the ejection phase is rather homogeneous.

TABLE 5.3: Epicardial deformation during the ejection phase as measured in four experiments and calculated in the reference simulation. Changes in fiber strain $\Delta\epsilon_{f,e}$ and surface area $\Delta\epsilon_{A,e}$ during the ejection phase. Values at the longitudinal levels A through D are averaged over the circumferential levels 1 through 4.

		$\Delta\epsilon_{f,e}$				
		exp. 1	exp. 2	exp. 3	exp. 4	ref. sim.
A	mean	-0.094	-0.085	-0.104	-0.097	-0.078
	SD	0.008	0.024	0.008	0.005	
B	mean	-0.094	-0.106	-0.093	-0.098	-0.084
	SD	0.005	0.012	0.008	0.007	
C	mean	-0.076	-0.114	-0.105	-0.111	-0.085
	SD	0.006	0.019	0.011	0.004	
D	mean	-0.088	-0.086	-0.090	-0.105	-0.085
	SD	0.010	0.045	0.016	0.010	

		$\Delta\epsilon_{A,e}$				
		exp. 1	exp. 2	exp. 3	exp. 4	ref. sim.
A	mean	-0.100	-0.096	-0.127	-0.129	-0.119
	SD	0.003	0.042	0.018	0.009	
B	mean	-0.098	-0.141	-0.129	-0.137	-0.132
	SD	0.006	0.022	0.018	0.007	
C	mean	-0.096	-0.162	-0.144	-0.146	-0.121
	SD	0.016	0.026	0.022	0.004	
D	mean	-0.123	-0.162	-0.135	-0.134	-0.119
	SD	0.014	0.067	0.023	0.020	

5.2.3 Comparison of measured and calculated hemodynamics and epicardial deformation

In figure 5.6c, ventricular pressure and aortic flow, as calculated in the reference simulation, are shown. In table 5.1, hemodynamical data, as calculated in the reference simulation, are compared with experimental data. In the simulation, both the increase and the maximum level of ventricular pressure during the ejection phase are high as compared to the experimental data. Maximum aortic flow and the ratio of ejected volume ΔV_e to wall volume V_w are also relatively high in the simulation. The differences between measured and calculated hemodynamics may be caused by inaccuracies in the description of the afterload and the contractile material properties in the model.

Calculated local epicardial deformation is shown in figure 5.6d. The change of ϵ_f and ϵ_A during the ejection phase is listed in table 5.3. As in the experiment, fiber strain ϵ_f is rather constant during the isovolumic contraction phase, while area strain ϵ_A decreases. During the ejection phase, no significant longitudinal differences in decrease of fiber strain $\Delta\epsilon_{f,e}$ and area strain $\Delta\epsilon_{A,e}$ are found. Averaged over the four longitudinal levels, in the simulation the ratio $\Delta\epsilon_{f,e}/\Delta\epsilon_{A,e}$ equals 0.68. Averaged over the 16 regions in all four experiments, the mean ratio $\Delta\epsilon_{f,e}/\Delta\epsilon_{A,e}$ was found to be 0.73. Thus, calculated and measured epicardial deformation agree reasonably well.

5.3 Conclusions

From the comparison of calculated and experimental data on ventricular hemodynamics and deformation, it can be concluded that in the model the following quantities are described reasonably well:

- the change of left ventricular pressure, aortic flow and global deformation of the left ventricle as a function of time.
- the change of circumferential, longitudinal and radial strains in the subendocardium at two thirds of the distance from base to apex as a function of time.
- the transmural change of circumferential, longitudinal and radial strains at two thirds of the distance from base to apex at the end of the ejection phase.
- local two-dimensional epicardial deformation as a function of time, expressed in terms of fiber strain and area strain.

Discrepancies between experimental and numerical data are related primarily to shear deformations in the ventricular wall, especially during the isovolumic contraction and relaxation phases. The agreement between calculated and measured results may be improved by (1) adaptation of the spatial distribution of the transverse fiber angle and (2) modification of the description of the active material behavior, particularly during the initial generation of active stress. Moreover, the influence of (1) the spatial distribution of the helix fiber angle and (2) the shear behavior of the passive myocardial tissue on the pattern of deformation of the ventricular wall may have to be investigated further.

The mechanics of the ischemic left ventricle

In the previous chapters, the mechanics of the normal left ventricle has been considered. In this chapter, the effect of an occlusion of the distal part of the left anterior descending coronary artery on left ventricular mechanics is investigated. Distal to the site of occlusion, the ventricular wall becomes ischemic and no active stress can be generated anymore. In section 6.1, the model is used to simulate the mechanics of the ischemic left ventricle paying special attention to hemodynamics, global deformation and local stress and strain. In section 6.2, experimental results are presented on the mechanics of the ischemic left ventricle, as assessed in terms of hemodynamics and deformation of the anterior epicardial surface. Measured epicardial deformation is compared with that calculated in the simulation. In section 6.3, myocardial function in the ischemic border zone is discussed. In section 6.4, the conclusions of the numerical and experimental analysis of the mechanics of the ischemic left ventricle are summarized.

FIGURE 6.1: Finite element mesh of the left ventricle; for clarity, one quarter section is removed; septum S ($\phi = -\pi$), anterior wall A ($\phi = -\pi/2$), lateral free wall L ($\phi = 0$) and posterior wall P ($\phi = +\pi/2$) are indicated, as well as the basal BA, basal-equatorial BE, equatorial EQ, equatorial-apical EA and apical AP level.

6.1 Simulation of the mechanics of the ischemic left ventricle

6.1.1 Localization and material characterization of ischemia in the model

In the simulation of the mechanics of the normal left ventricle, because of the property of rotational symmetry only a quarter section of the complete left ventricle had to be considered. The region, which becomes ischemic due an occlusion of the distal part of the left anterior descending coronary artery, disturbs the rotational symmetry. Therefore, the geometry of the complete ventricle has to be considered. The geometry is defined by the position of 591 nodes forming 108 elements. In figure 6.1, the geometric configuration is shown. For clarity one quarter of the geometry is removed in the figure. In the model, the ischemic region $\mathcal{I}$ is situated symmetrically with respect to the anterior wall and extends from the endocardium to the epicardium. Its localization is formulated in terms of the circumferential coordinate ϕ , the normalized longitudinal coordinate $\bar{\theta}$, and the normalized transmural coordinate $\bar{\xi}$:

$$\mathbf{x}(\phi, \bar{\theta}, \bar{\xi}) \in \mathcal{I} \quad \text{if} \quad \begin{cases} \frac{\pi}{2}\bar{\theta} \leq \phi + \frac{\pi}{2} \leq -\frac{\pi}{2}\bar{\theta} \\ \bar{\theta} \leq 0.0 \\ -1.0 \leq \bar{\xi} \leq +1.0 \end{cases} \quad (6.1)$$

FIGURE 6.2: Ischemic region, indicated by the dotted area, as assumed in the model: posterior wall P, septum S, anterior wall A and lateral free wall L are indicated; in transmural direction, the ischemic region extends from the endocardial to the epicardial surface.

In figure 6.2, the ischemic region is indicated. Its volume represents about 12% of that of the whole left ventricular wall.

To simulate ischemia in terms of material properties, the model for the description of active stress was modified. In equation 2.22 (subsection 2.2.4) the ischemia parameter α_i is added:

$$T_{maz} = \alpha_i T_1 A(l_c) B_r(t_s) B_d(t_s) \quad (6.2)$$

The value of α_i is set at 0.0 in the integration points located in ischemic region and 1.0 in the integration points in the remaining part of the ventricular wall. Thus, at the level of the integration points, a sharp boundary is assumed between the ischemic region, where no active stress is generated, and the healthy region, where generation of active stress is normal. In the model, values of variables in the nodes are calculated as a weighted sum of the values of those variables in the integration points in all elements to which the node belongs. Therefore, at the nodal level, α_i may have values in between 0.0 and 1.0, and the width of the boundary zone between the ischemic and the non-ischemic region depends on the size of the elements used.

6.1.2 Boundary conditions

In the simulation of a cardiac cycle with the ischemic left ventricle, the following boundary conditions were applied: (1) axial motion of the nodes in the basal plane was suppressed, (2) the circular shape of the endocardial basal ring was maintained and (3) rotation of the endocardial basal ring was prevented. As a consequence of numerical instabilities during the isovolumic relaxation phase, the simulation

FIGURE 6.3: Global hemodynamics in the simulation of a cardiac cycle with an ischemic (—) and non-ischemic (---) left ventricle: (a) change of ventricular pressure p_{lv} , ventricular volume V_{lv} and aortic flow q_{ao} as a function of time t ; the dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase; (b) pressure-volume loop; dots indicate the end of the diastolic phase and the beginning and end of the ejection phase.

was terminated at $t = 510$ ms. For comparison, a simulation of a normal cardiac cycle was performed using the conditions of the reference simulation as presented in section 4.3, except for the above mentioned boundary conditions regarding the motion of the nodes in the basal plane.

6.1.3 Description of the results

Global hemodynamics and deformation

In figure 6.3 and table 6.1 it is shown that pressure, aortic flow and ejection fraction are lower in the ischemic than in the normal left ventricle. The global deformation of the ischemic ventricle at eight moments during the cardiac cycle is shown in figures 6.4 and 6.5. In the top row of these figures, x_2 - x_3 -coordinates of the nodes positioned in the posterior-anterior, P-A, long axis cross-section at the beginning of the simulation are plotted. In the second row, x_1 - x_3 coordinates of the nodes, originally positioned in the septal-lateral, S-L, cross-section are shown. In the next five rows, x_1 - x_2 -coordinates of the nodes at the basal, BA, basal-equatorial, BE, equatorial, EQ, equatorial-apical, EA and apical, AP, levels are shown.

In the P-A cross-section, the ischemic part of the anterior ventricular wall bulges

TABLE 6.1: Hemodynamics in the simulation of a cardiac cycle with an ischemic and a normal left ventricle.

	t_{be}	t_{ee}	Δt_e	p_{be}	p_{ee}	p_{max}	V_{be}	V_{ee}	ΔV_e	$\frac{\Delta V_e}{V_{be}}$	q_{max}
	ms	ms	ms	kPa	kPa	kPa	ml	ml	ml	%	ml·s ⁻¹
ischemic	264	444	180	10.1	15.5	18.7	80.3	51.1	29.3	36	225
normal	254	446	192	10.3	17.0	20.7	80.2	44.2	36.0	45	264

and becomes relatively thin. The apex moves from the original base-to-apex axis into the posterior direction. Although the ischemic region is defined symmetrically with respect to the S-L cross-section, the deformation of the latter cross-section is asymmetrical. The endocardial and epicardial boundaries of the five short axis cross-sections, remain approximately circular. The endocardial and epicardial boundaries of the BA and BE short axis cross-sections remain centered at the original long axis of the ventricle. During systole, the centers of the circular boundaries of the EQ, EA and AP cross-sections shift away from the original long axis of the ventricle in the anterior direction. In the latter cross-sections, the ischemic anterior wall becomes relatively thin as compared to the posterior wall. The pattern of deformation of the cross-section at the AP level looks quite distorted because, already in the reference situation, the cross-section is not in the plane of drawing.

The reversal of systolic circumferential-radial shear between the BA and BE cross-sections was also found in the reference simulation. Circumferential-radial shear in the EQ and EA cross-sections is less than in the BA and BE cross-sections.

Local mechanics

In the figures 6.6 through 6.11, the local mechanical behavior in the subendocardial, midwall and subepicardial layer is presented. Within each layer, sarcomere length, active stress, passive stress and angle of rotation around the long axis of the ventricle are shown as a function of time at 40 nodes. The nodes are located at eight circumferential and five longitudinal levels. The eight circumferential levels are chosen at mutual distances of $\pi/4$ rad, while the five longitudinal levels correspond to those shown in figure 6.1.

In figure 6.6, the change of sarcomere length l_s as a function of time t is shown as calculated in the ischemic and the normal left ventricle. In the nodes indicated by a filled square in the bottom left corner of the l_s - t -plot, the ischemia parameter α_i is less than 0.05. This region will be called the ischemic region. In the nodes, indicated by an open square in the bottom left corner of the l_s - t -plot, α_i equals 0.74. In the remaining nodes α_i is greater than 0.98. During the diastolic filling phase, changes of sarcomere length as a function of time in the normal and the

FIGURE 6.4: Calculated global deformation of the ischemic left ventricle during the diastolic phase D, the isovolumic contraction phase IC and the ejection phase E; locations of the long and short axis cross-sections are indicated in figure 6.1; times are indicated in ms; in the cross-sections at $t = 0$ ms, the shaded area indicates the ischemic region.

FIGURE 6.5: Calculated global deformation of the ischemic left ventricle during the ejection phase E and isovolumic relaxation phase IR; see also figure 6.4.

FIGURE 6.6: Calculated variation of sarcomere length l_s as a function of time t in the ischemic (—) and the normal (---) left ventricle at circumferential levels P-PS-S-SA-A-AL-L-LP-P and longitudinal levels BA-BE-EQ-EA-AP in (a) the subendocardial layer, (b) the midwall layer, and (c) the subepicardial layer; the vertical dotted lines indicate the end of the diastolic phase and the beginning and end of the ejection phase.

FIGURE 6.7: Calculated variation of active fiber stress T_a as a function of time t in the ischemic (—) and the normal (---) left ventricle at circumferential levels P-PS-S-SA-A-AL-L-LP-P and longitudinal levels BA-BE-EQ-EA-AP in (a) the subendocardial layer, (b) the midwall layer, and (c) the subepicardial layer.

ischemic ventricle are identical. During systole, in the ischemic region sarcomere length, which was set at $2.0 \mu\text{m}$ at the beginning of the simulation, increases to about $2.8 \mu\text{m}$. In the nodes which are not directly adjacent to the ischemic region, the pattern of sarcomere shortening is approximately normal. In the subendocardial layer, sarcomere shortening in the nodes AL-BA, AL-BE and AL-EQ is greater than normal. Because the helix fiber angle in this layer equals $+70^\circ$, the fibers in the region marked by these nodes are continuations of the fibers in the ischemic region. In the nodes A-BA and SA-BE, SA-EQ and SA-AP, located in the region where the fibers are parallel to the fibers in the ischemic region, sarcomere shortening is less than normal. In node SA-EA, where fibers are parallel to the fibers in the ischemic region, sarcomere shortening is less than in the corresponding nodes in the midwall and subepicardial layers. In the midwall layer, in the region outside the ischemic region changes in the pattern of sarcomere shortening with respect to that in the normal ventricle are less pronounced than in the subendocardial and subepicardial layers. In the subepicardial layer, during the isovolumic contraction phase the stretch of the sarcomeres in the upper half of the ventricle BA-BE-EQ has decreased, and consequently sarcomeres are shorter during the remaining part of the cycle. Apart from this overall effect, in this layer, where $\alpha_1 = -70^\circ$, sarcomere shortening is relatively high in the nodes SA-BE and SA-EQ, where fibers are in series with fibers in the ischemic region. In node SA-EA, fiber shortening is pronounced as compared to shortening in the corresponding nodes in the subendocardial and midwall layers. Sarcomere shortening is relatively small in the nodes AL-BE, AL-EQ, AL-EA and L-AP, where fibers are parallel to the fibers in the ischemic region.

In figure 6.7, the change of active muscle fiber stress T_a as a function of time t is shown. In the ischemic region no active stress is generated. Outside the ischemic region, active stress is relatively high in those nodes where sarcomere shortening is relatively small, and vice versa. In the remaining part of the ventricular wall, active stresses are approximately equal to the stresses in the normal ventricle.

In figure 6.8, the change of passive fiber stress T_p as a function of time t is shown. Passive fiber stress is approximately zero in the nonischemic part of the ventricle. In the ischemic endocardial region, the level of passive fiber stress is similar to that of the active fiber stress in the non-ischemic part of the wall, except for node A-EQ, where both active and passive fiber stress are approximately zero. From endocardium to epicardium, passive stress in the ischemic region decreases considerably.

In figure 6.9, total fiber stress T_f is plotted versus the fiber stretch ratio λ_f . The area enclosed by the T_f - λ_f -loop, representing external work w generated per unit of ventricular wall volume, is plotted in figure 6.10. In the ischemic region, external work is about zero since stress-strain loops approximately follow the passive stress-strain curve. In some nodes, the stress-strain loop is completed in clockwise direction and external work is negative. In the transition region from ischemic to nonischemic tissue, external work is lower than normal, because of either the relatively low fiber shortening in regions where fibers are parallel to those in the ischemic region, or the

FIGURE 6.8: Calculated variation of passive fiber stress T_p as a function of time t in the ischemic (—) and the normal (---) left ventricle at circumferential levels P-PS-S-SA-A-AL-L-LP-P and longitudinal levels BA-BE-EQ-EA-AP in (a) the subendocardial layer, (b) the midwall layer, and (c) the subepicardial layer.

FIGURE 6.9: Calculated total fiber stress T_f plotted versus calculated fiber stretch ratio $\lambda_f = l_s/l_{s,0}$ in the ischemic (—) and the normal (---) left ventricle at circumferential levels P-PS-S-SA-A-AL-L-LP-P and longitudinal levels BA-BE-EQ-EA-AP in (a) the subendocardial layer, (b) the midwall layer, and (c) the subepicardial layer.

FIGURE 6.10: Calculated change of local work w , indicated by the solid line (—), as a function of the circumferential (P-A-P) and longitudinal (BA-AP) position in the wall of the ischemic left ventricle: (a) in the subendocardial layer; (b) in the midwall layer; (c) in the subepicardial layer.

relatively low fiber stress in the regions where fibers are in series with those in the ischemic region.

In figure 6.11, the angle of rotation ϕ_z around the long axis of the ventricle is shown as a function of time. In the upper three longitudinal levels BA, BE and EQ, angles of rotation are virtually unchanged as compared to the reference simulation. At the lower two levels EA and AP, a slight increase of rotation is found in the subendocardial layer of the ischemic region. In the midwall and subepicardial layers, the angles of rotation are less than normal in the septal, S, and septal-anterior, SA, cross-sections. In the anterior, A, the anterior-lateral, AL, and the lateral, L, cross-sections, the midwall and subepicardial angles of rotation are higher than normal. This change in pattern of rotation is associated with a circumferential stretch of the ischemic region.

6.1.4 Discussion

In this simulation, the volume of the ischemic region is about 12% of total left ventricular wall volume. Maximum ventricular pressure during the ejection phase p_{max} is found to decrease proportionally to the decrease of the amount of normally contracting wall tissue. The decrease of ejected volume ΔV_e , which is about 20%,

FIGURE 6.11: Calculated variation of angle of rotation ϕ_z around the long axis of the ventricle as a function of time t in the ischemic (—) and the normal (---) left ventricle at circumferential levels P-PS-S-SA-A-AL-L-LP-P and longitudinal levels BA-BE-EQ-EA-AP in (a) the subendocardial layer, (b) the midwall layer, and (c) the subepicardial layer.

is more than proportional to the decrease of the amount of normally contracting ventricular wall tissue. In the real ventricle, cardiac output and aortic blood pressure will obtain normal values again in subsequent cycles through feedback mechanisms.

The global deformation pattern, as observed in the long axis cross-sections, is not symmetrical with respect to the ischemic region. This asymmetry is related to the fiber structure of the ventricular wall. The asymmetric deformation pattern may be important for the interpretation of echocardiographic images of ischemic ventricles. In the short axis cross-sections, the ischemic region can be distinguished from a decrease of wall thickness. Endocardial and epicardial boundaries remain approximately circular.

At the local level, the sarcomere lengths, as calculated in the ischemic region, are unphysiologically large. In papillary muscle experiments, maximum sarcomere length was found to be approximately $2.4 \mu\text{m}$ [90]. This finding indicates that, at large deformations, the passive material is stiffer in the real ventricle than in the model, provided that sarcomere lengths in papillary muscles are representative of those in the left ventricular wall. Consequently, deformation in the ischemic region may be higher in the simulation than in the real ventricle. In regions where fibers are in series with fibers in the ischemic region, sarcomeres experience a relatively low load of the ischemic region and consequently sarcomere shortening is relatively high. The low load and sarcomere length are associated with a relatively low active stress level. In regions where muscle fibers are parallel to the muscle fibers in the ischemic region, active fiber stress is relatively high to partly compensate for the absence of active fiber stress in the ischemic region. The relatively high active stress level is associated with relatively large sarcomere lengths.

The absence of active fiber stress in the ischemic region is also partly compensated for by the increase of passive fiber stress in the ischemic region itself. Since the stiffness of the passive tissue is low as compared to that of the active tissue, deformation of the ischemic region will be larger than that of the remaining part of the ventricular wall. The ischemic region can be regarded as a part of an inflated thickwalled passive ellipsoid, in which strains decrease from the endocardium to the epicardium. Consequently, passive fiber stress also decreases from the endocardium to the epicardium. Thus, the stress distribution in the ischemic region resembles that as found in the early models describing ventricular mechanics, in which the myocardial tissue was assumed to be isotropic.

The change in the pattern of rotation around the long axis can be explained by the relatively low stiffness of the passive ischemic tissue as compared to the stiffness of the active tissue. The stretch of the ischemic region in circumferential direction is reflected in a decreased and increased rotation on the septal and lateral side of the ischemic region, respectively.

FIGURE 6.12: Example of the ischemic region (shaded area), resulting from the occlusion (bar) of the distal part of the left anterior descending coronary artery LADC; left ventricle LV, right ventricle RV, circumflex branch of the left coronary artery LCC, and dots for determination of epicardial deformation of the anterior left ventricular wall are shown.

6.2 Epicardial deformation in model and experiment

6.2.1 Experimental protocol

In section 5.2, experiments on four mongrel dogs were described, in which global hemodynamics and local epicardial deformation were measured under normal circumstances. Subsequently, in the same four dogs ventricular mechanics during ventricular pacing and increased preload was investigated. At the end of the experiment, the distal part of the left anterior descending coronary artery was occluded (figure 6.12). During sinus rhythm, regional myocardial blood flow was measured as described by Prinzen *et al.* [73]. Radioactively labeled microspheres were injected into the left atrium, 15 minutes after the moment of occlusion. A reference blood sample was taken from the brachial artery. Next, the motion of the optical markers on the epicardial surface of the left ventricle was recorded on video as described in section 5.2. After the experiment, the animals were killed and the heart was excised. The epicardial half of the left ventricular wall was dissected into blocks of tissue of about 0.5-1 g in weight. The blocks of tissue and the blood samples were weighed and subsequently radioactivity was quantified with a gammacounter. Myocardial blood flow q_m was calculated in $\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$.

FIGURE 6.13: Change of ventricular pressure p_{lv} (—) and aortic flow q_{a0} (---) as a function of time t as measured in the ischemic left ventricle; tracings in experiments 1 through 4 are plotted in panels (a) through (d).

6.2.2 Experimental results

In figure 6.13, ventricular pressure p_{lv} and aortic flow q_{a0} , as measured in the four experiments, are shown as a function of time. Hemodynamic data obtained in the experiments are listed in table 6.2. Comparison of the hemodynamics in the ischemic ventricle, as listed in table 6.2, with that in the normal ventricle, as listed in table 5.1, is subject to uncertainties because circulatory volume was increased in between the measurements in the normal situation and in case of ischemia. As a result, in the ischemic ventricle end-diastolic pressure and ejected volume are higher than in the normal ventricle.

TABLE 6.2: Hemodynamics in the ischemic left ventricle, as measured in four experiments and as calculated with the use of the model; duration of the isovolumic contraction phase Δt_{ic} and the ejection phase Δt_e ; ventricular pressure at end-diastole p_{ed} , and beginning p_{be} and end p_{ee} of the ejection phase, maximum ventricular pressure p_{max} , maximum aortic flow q_{max} , ejected volume ΔV_e and ventricular wall volume V_w .

	Δt_{ic}	Δt_e	p_{ed}	p_{be}	p_{ee}	p_{max}	q_{max}	ΔV_e	V_w
	ms	ms	kPa	kPa	kPa	kPa	ml·s ⁻¹	ml	ml
exp. 1	110	210	1.5	10.5	11.6	14.6	232	31.5	158
exp. 2	65	205	1.2	6.4	6.2	9.1	148	18.5	123
exp. 3	60	260	1.8	6.9	9.5	11.6	183	26.1	148
exp. 4	65	220	1.7	8.4	8.5	12.0	196	30.0	118
simulation	64	180	1.0	10.1	15.5	18.7	225	29.3	140

TABLE 6.3: Subepicardial perfusion, as measured in the four ischemic left ventricles in the 16 regions where deformation was measured; local perfusion q_m is compared to perfusion q_r in a non-ischemic subepicardial part of the ventricular wall; if $q_m/q_r < 0.50$, the region is defined to be ischemic and perfusion ratio is printed in italics; in experiment 1 through 4, q_r was equal to 1.04, 1.11, 1.08 and 0.64 ml·min⁻¹·g⁻¹, respectively; row A and column 1 are approximately parallel to the circumflex branch and the anterior descending branch of the left coronary artery, respectively (see also figure 6.12).

q_m/q_r								
	exp. 1				exp. 2			
	1	2	3	4	1	2	3	4
A	0.54	0.73	1.07	1.05	<i>0.10</i>	<i>0.44</i>	0.63	1.13
B	<i>0.48</i>	0.82	0.75	0.69	<i>0.05</i>	<i>0.07</i>	<i>0.14</i>	<i>0.36</i>
C	<i>0.49</i>	0.63	0.71	0.83	<i>0.05</i>	<i>0.03</i>	<i>0.05</i>	<i>0.04</i>
D	<i>0.38</i>	<i>0.29</i>	0.54	0.70	<i>0.05</i>	<i>0.03</i>	<i>0.05</i>	<i>0.02</i>
	exp. 3				exp. 4			
	1	2	3	4	1	2	3	4
A	0.63	0.75	0.81	1.02	1.17	1.02	1.03	1.11
B	<i>0.36</i>	<i>0.31</i>	<i>0.39</i>	0.56	1.05	0.97	1.00	1.23
C	<i>0.24</i>	<i>0.22</i>	<i>0.31</i>	<i>0.33</i>	<i>0.25</i>	<i>0.28</i>	<i>0.47</i>	0.70
D	<i>0.29</i>	<i>0.24</i>	<i>0.25</i>	<i>0.29</i>	<i>0.17</i>	<i>0.16</i>	<i>0.27</i>	<i>0.42</i>

In the four ventricles, myocardial perfusion q_m in the epicardial half of the ventricular wall was measured in the 16 regions where epicardial deformation was determined. The latter perfusions were compared with a reference perfusion q_r , as assessed in a non-ischemic subepicardial region of the ventricular wall. Ratios q_m/q_r are listed in table 6.3. A region was defined to be ischemic, if the ratio q_m/q_r was less than 0.50.

Epicardial deformation, as measured in the four experiments, is shown in figure 6.14. As discussed in section 5.2, epicardial deformation is expressed in terms of fiber strain ε_f and area strain ε_A . Ischemic regions are indicated by a filled square in the bottom left corner of the local deformation plot. The epicardial deformation pattern was characterized by the change of epicardial fiber strain ε_f and area strain ε_A during the isovolumic contraction phase ($\Delta\varepsilon_{f,ic}$ and $\Delta\varepsilon_{A,ic}$) and during the ejection phase ($\Delta\varepsilon_{f,e}$ and $\Delta\varepsilon_{A,e}$). Because in the first three experiments large parts of the border zone between the ischemic and the non-ischemic region were

FIGURE 6.14: Epicardial deformation of the ischemic left ventricle; change of epicardial fiber strain ϵ_f (—) and epicardial area strain ϵ_A (---) as a function of time t as measured in 16 epicardial regions; measurements in experiments 1 through 4 are plotted in panels (a) through (d).

FIGURE 6.15: Epicardial deformation in the normal and ischemic left ventricle; change of fiber strain during the isovolumic contraction phase $\Delta\epsilon_{f,ic}$ and the ejection phase $\Delta\epsilon_{f,e}$; change of area strain during those phases $\Delta\epsilon_{A,ic}$ and $\Delta\epsilon_{A,e}$; values are averaged over epicardial regions in the normal ventricle N, non-ischemic epicardial regions in the ischemic ventricle IN, and ischemic epicardial regions in the ischemic ventricle II; measured values (filled dots •) and calculated values (open dots o) are plotted.

located near the edge of the region where deformation was measured, comparison of epicardial deformation in the ischemic and non-ischemic regions within each of these experiments is difficult. Therefore, the deformation parameters $\Delta\epsilon_{f,ic}$, $\Delta\epsilon_{A,ic}$, $\Delta\epsilon_{f,e}$ and $\Delta\epsilon_{A,e}$ were averaged over the 36 ischemic and 28 non-ischemic regions in the four ischemic ventricles. For comparison, the deformation parameters were also determined in the four normal ventricles, where averaging was performed over the 64 epicardial regions. Resulting values of the deformation parameters are shown in figure 6.15 (filled dots) and table 6.4.

During the isovolumic contraction phase, epicardial fiber and area strain are negative in the epicardial regions N in the normal ventricle (figures 6.15a and c). In the ischemic ventricle, fiber and area strain are approximately zero in the non-ischemic regions of the ischemic ventricle IN, and positive in the ischemic regions II. During the ejection phase, area strain and fiber strain are in the order of -0.10 in the normal ventricle. Both strains are less negative in the non-ischemic regions NI of the ischemic ventricle, and approximately zero in the ischemic regions II.

6.2.3 Comparison of epicardial deformation in the ischemic ventricle in model and experiment

In table 6.1 characteristic hemodynamic quantities, as calculated in the simulation of a cardiac cycle with an ischemic ventricle, are listed. In the simulation, end-diastolic pressure is rather low as compared to that in the experiment, because preload had

TABLE 6.4: Epicardial deformation, as measured in the normal and ischemic left ventricle; change of fiber strain during the isovolumic contraction phase $\Delta\epsilon_{f,ic}$ and the ejection phase $\Delta\epsilon_{f,e}$; change of area strain during those phases $\Delta\epsilon_{A,ic}$ and $\Delta\epsilon_{A,e}$; values are averaged over 64 regions in the normal ventricle N, 28 non-ischemic regions in the ischemic ventricle IN, and 36 ischemic regions in the ischemic ventricle II.

	$\Delta\epsilon_{f,ic}$			$\Delta\epsilon_{f,e}$		
	N	IN	II	N	IN	II
mean	-0.023	0.006	0.016	-0.097	-0.072	-0.023
SD	0.022	0.012	0.011	0.019	0.016	0.023
	$\Delta\epsilon_{A,ic}$			$\Delta\epsilon_{A,e}$		
	N	IN	II	N	IN	II
mean	-0.055	0.020	0.029	-0.129	-0.071	-0.012
SD	0.031	0.024	0.015	0.033	0.017	0.032

been increased in the experiment. Calculated ventricular pressure during the ejection phase is rather high as compared to measured pressure. This may be caused by a low contractility of the ischemic hearts in the experiment, and inaccuracies in the description of the afterload and the contractile material properties in the model.

In figure 6.16, epicardial deformation, as calculated in the simulation in 16 epicardial points, is shown. Twelve of the 16 epicardial points correspond to nodes in the finite element model. In the remaining four points (A2, A4, C2 and C4), located in the middle of an epicardial element face, deformation was calculated as the average of the deformation in the eight nodes on the edges of the face. Values of the ischemia parameter α_i are listed in table 6.5. In figure 6.16a, in the region where deformation is presented, the ischemic region is indicated by the shaded area.

As in the experiment, local deformation was characterized by the parameters $\Delta\epsilon_{f,ic}$, $\Delta\epsilon_{f,e}$, $\Delta\epsilon_{A,ic}$ and $\Delta\epsilon_{A,e}$. The values of these parameters are listed in table 6.6 and plotted in figure 6.15 (open circles). During the isovolumic contraction phase, measured and calculated epicardial deformation in the normal ventricle (N) and the non-ischemic region of the ischemic ventricle (IN) agree reasonably well (figure 6.15). In the ischemic region of the ischemic ventricle (II), the calculated increase of area strain and epicardial fiber strain is high as compared to values obtained in the experiments. The latter finding, and the rather high standard deviation in the calculations are associated with the low stiffness of the ischemic region in the model. During the ejection phase, calculated and measured epicardial deformation agree reasonably well.

Calculated and measured deformation in the non-ischemic region of the ischemic

FIGURE 6.16: Epicardial deformation as calculated in the simulation of the mechanics of the ischemic left ventricle; (a) location of the 16 regions on the epicardial surface; the shaded area indicates the ischemic region; (b) change of epicardial fiber strain ϵ_f (—) and epicardial area strain ϵ_A (- · -) as a function of time t in the 16 epicardial regions.

ventricle can also be compared in more detail. During the ejection phase, calculated area decrease exceeds fiber shortening in the non-ischemic region on the lateral basal side of the ischemic region (upper right in figure 6.16), whereas calculated area decrease and fiber shortening are more similar in the non-ischemic region on the anterior basal side of the ischemic region (upper left in figure 6.16). During the ejection phase, measured area decrease is equal to or exceeds measured fiber shortening on the lateral basal side of the ischemic region (figure 6.14), whereas measured area decrease is less than or equal to measured fiber shortening in the non-ischemic region on the anterior basal side of the ischemic region. Thus, in the model as well as in the experiment, in the non-ischemic region during the ejection phase the ratio of area decrease to fiber shortening $\|\Delta\epsilon_{A,e}/\Delta\epsilon_{f,e}\|$ tends to be higher at the lateral basal side than at the anterior basal side of the ischemic region. As discussed in subsection 6.1.4, in the transition zone fiber shortening is related to the relative orientation of the fibers with respect to the ischemic region.

TABLE 6.5: Ischemia parameter α_i in the 16 epicardial regions where deformation is presented; if $\alpha_i < 0.50$, the region is defined to be ischemic.

	α_i			
	1	2	3	4
A	0.51	0.75	0.99	1.00
B	0.04	0.51	0.99	1.00
C	0.02	0.44	0.99	0.96
D	0.01	0.25	0.74	0.99

6.3 Discussion: myocardial function in the ischemic border zone

Some investigations of myocardial function in the border zone of the ischemic region have been presented in literature [30,75]. With the same techniques, as used in our experiments, Prinzen *et al.* [75] measured myocardial perfusion, epicardial fiber strain and area strain during the ejection phase in the border zone of an ischemic region. The absolute values of these parameters were normalized to range from 0% in the central ischemic region to 100% in the non-ischemic region. It was shown that the borders of perfusion and deformation, defined as the 50% contour lines of these variables, grossly coincide. The width of the transition zone of a variable was defined as the distance between the 20% and 80% contourlines of that variable. The widths of the transition zones of fiber strain, area strain and subepicardial blood flow were found to be 15.0 (12.9 – 18.5) mm, 20.5 (11.9 – 23.5) mm and 9.5 (6.7 – 14.3) mm, respectively. Thus the transition zone for deformation was found to be approximately twice as wide as that for subepicardial blood flow.

In the equatorial region of the finite element mesh used in the simulation of the mechanics of the ischemic left ventricle, the distance between two adjacent nodes in longitudinal and circumferential direction is about 8 mm and 14 mm, respectively. Moreover, in the model values of variables in the nodes are calculated as a weighted sum of the values of those variables in the integration points in all elements to which the node belongs. Therefore, values of variables in adjacent nodes are not independent. Thus, the present finite element mesh is too coarse to determine the width of the above mentioned transition zones reliably.

Nevertheless, a qualitative indication of the width of the transition zones for the ischemia parameter α_i , which can be related to myocardial perfusion, and epicardial fiber strain, can be derived from figure 6.6c. In this figure, the ischemia parameter α_i varies from 0.0 to 1.0 in adjacent nodes at the border of the ischemic region. Thus, half of the distance between these nodes can be considered a characteristic

Summary, conclusions and recommendations

In section 7.1 the study presented in this thesis is summarized. In section 7.2, the conclusions are formulated as derived from the simulations of the mechanics of the normal and ischemic left ventricle. In section 7.3 recommendations are given for the possible improvement of the model, based upon a comparison of calculated and measured ventricular mechanics, and suggestions are formulated for extensions of the present model.

Summary, conclusions and recommendations

In section 7.1 the study presented in this thesis is summarized. In section 7.2, the conclusions are formulated as derived from the simulations of the mechanics of the normal and ischemic left ventricle. In section 7.3 recommendations are given for the possible improvement of the model, based upon a comparison of calculated and measured ventricular mechanics, and suggestions are formulated for extensions of the present model.

7.1 Summary

In the left ventricle, numerous muscle cells work together to generate the pressure and ventricular outflow needed to maintain the circulation of the blood through the vascular system. The contribution of the individual muscle cells to the performance of the left ventricle as a whole is unknown since stress and external work generated at the level of the individual muscle cells cannot be assessed experimentally in the intact left ventricular wall.

In this study, a mathematical model of the mechanics of the left ventricle was developed to obtain insight into the factors that govern the individual contribution of the muscle fiber cells to the global ventricular pumping work. The model is composed of several submodels, describing ventricular geometry, muscle fiber orientation and activation sequence in the ventricular wall, active and passive material properties, and aortic hemodynamic input impedance. The values of the parameters in the submodels were estimated from experimental data presented in literature. An accurate choice of the values of the model parameters was often hampered by the large variation in the experimental data.

The deformation of the left ventricle during the cardiac cycle is governed by the laws of conservation of mass, momentum and moment of momentum. These laws were transformed into a set of matrix equations that was solved numerically. Using the finite element method, a three-dimensional 20-node brick-shaped element was formulated to describe the deformation of a piece of myocardial tissue. In assembling the left ventricle, 108 elements were used.

In the simulations of the mechanics of the normal left ventricle, special attention was paid to the influence of changes in muscle fiber orientation, activation sequence of the ventricular wall, active stress-length relationship, and ventricular preload and afterload on the mechanics of the normal left ventricle. The results of the simulations were compared with experimental data on ventricular deformation and hemodynamics. It was concluded that, concerning the latter variables, the model describes the actual mechanical behavior of the left ventricle reasonably well.

The influence of an occlusion of the distal part of the left anterior descending coronary artery on ventricular mechanics was investigated both numerically and experimentally. The calculated deformation of the epicardial surface in the ischemic region, the boundary zone and the non-ischemic region, was found to agree reasonably well with experimentally determined epicardial deformation.

In conclusion, the present model of left ventricular mechanics considers (1) three-dimensional deformation of the left ventricle, (2) varying muscle fiber orientation across the ventricular wall, including the cross-over of the muscle fibers between the subendocardial and subepicardial layers, (3) nonlinear anisotropic three-dimensional passive material properties, (4) active stress generation dependent on time, sarcomere length and sarcomere shortening velocity, and (5) hemodynamic loading with an aortic input impedance. To the author's best knowledge, the combination of the properties listed above is not found in any other model describing left ventricular

mechanics. The aspect of the cross-over of the muscle fibers between the inner and outer layers of the ventricular wall, which can be clearly observed at the base and the apex [89,91], has not been considered in any other model. In the present model, a radial spiralling angle of a few degrees was found to have a profound effect on the transmural distribution of deformation in the ventricular wall.

7.2 Conclusions

7.2.1 Conclusions with respect to the mechanics of the normal left ventricle on the basis of the simulations

From the simulations of the mechanics of the normal left ventricle with several settings of the values of the model parameters the following can be concluded.

- The distribution of active muscle fiber stress across the left ventricular wall depends primarily on the transmural distribution of the helix fiber angle.
- Circumferential-radial and circumferential-longitudinal shear strains in the left ventricular wall depend primarily on the spatial distribution of the transverse fiber angle, which describes the cross-over of the muscle fibers between the subendocardial and subepicardial layers of the ventricular wall.
- The activation sequence of the ventricular wall is a primary determinant of the distribution of generated external work per unit of volume across the ventricular wall.
- The spatial distributions of (1) active muscle fiber stress, (2) angle of rotation around the long axis of the ventricle and (3) locally generated external work per unit of volume remain virtually unchanged in the case of (1) a change of the active stress-strain relationship, (2) a change of end-diastolic pressure and (3) induction of aortic occlusion.
- The spatial distributions of (1) active muscle fiber stress and (2) angle of rotation around the long axis of the ventricle remain virtually unchanged when changing the velocity of the electrical depolarization wave across the ventricular wall from a physiological value to an extremely high value which results in virtually synchronous activation.
- The change of left ventricular pressure, aortic pressure and aortic flow with time is hardly affected by (1) a change of the spatial distribution of the helix and transverse fiber angle and (2) a change of the velocity of depolarization of the left ventricular wall.
- In modeling left ventricular mechanics, the large variation in experimental data is a major problem in estimating the values of the model parameters. Especially, more accurate data on muscle fiber orientation in the left ventricular wall and the mechanical properties of passive myocardial tissue are needed.
- In view of the lack of accurate data on the transmural distribution of the helix fiber angle across the left ventricular wall, the latter distribution can be estimated using the hypothesis of homogeneous spatial distribution of active muscle

fiber stress, as formulated by Arts *et al.* [4]. Application of this hypothesis in the present model yielded a transmural distribution of the helix fiber angle that was within the range of experimentally obtained distributions.

7.2.2 Conclusions with respect to the mechanics of the ischemic left ventricle on the basis of the simulations

From the simulation of the mechanics of the left ventricle with an ischemic apical anterior wall, the following can be concluded.

- In the ischemic region the ventricular wall becomes relatively thin as compared to the wall in non-ischemic regions.
- In the transition region between the ischemic and the non-ischemic region, sarcomere shortening is relatively large and active fiber stress is relatively low, if fibers are in series with those in the ischemic region.
- In the transition region between the ischemic and the non-ischemic region, sarcomere shortening is relatively small and active fiber stress is relatively high, if fibers are parallel to those in the ischemic region,
- Major changes in local ventricular mechanics in the non-ischemic region, as caused by the presence of the ischemic region, extend over about one eighth of the circumference of the ventricular wall.
- In the ischemic region, during systole passive fiber stress in the subendocardial layers reaches the level of active fiber stress in the non-ischemic region. Towards the epicardium, this passive stress component decreases considerably.

7.2.3 Conclusions on the basis of the comparison of left ventricular mechanics in model and experiment

From the comparison of calculated and experimental data on hemodynamics and deformation in the normal and ischemic left ventricle, the following can be concluded.

- In the normal left ventricle, the model describes the change of left ventricular pressure, aortic flow and global deformation as a function of time reasonably well.
- In the normal left ventricle, the model describes the change of circumferential, longitudinal and radial strains in the subendocardium at two thirds of the distance from base to apex as a function of time reasonably well.
- At the end of the ejection phase, the model describes the transmural change of circumferential, longitudinal and radial strains at two thirds of the distance from base to apex in the normal left ventricle reasonably well.
- In the normal left ventricle, the model describes the epicardial deformation of the anterior equatorial-apical part of the left ventricular wall as a function of time, expressed in terms of fiber strain and area strain, reasonably well.
- In the ischemic left ventricle, the model describes the epicardial deformation of the anterior equatorial-apical part of the left ventricular wall as a function

of time, expressed in terms of fiber strain and area strain, reasonably well in a qualitative respect.

- Discrepancies between experimental and numerical data are related primarily to circumferential-radial and longitudinal-radial shear deformations in the ventricular wall, especially during the isovolumic contraction and relaxation phases.

7.3 Recommendations

7.3.1 Recommendations for improvement of the present model

- On the basis of comparison of (1) calculated spatial distribution of external work generated by the muscle fiber cells, (2) calculated global deformation of the ventricle and (3) calculated torsion of the ventricle with experimental data, it is concluded that the model for the description of active muscle fiber stress should be modified, probably with respect to the early systolic response of active fiber stress to fiber extension.
- On the basis of comparison of calculated circumferential-radial and longitudinal-radial shear strains in the ventricular wall with experimental data it is concluded that the spatial distribution of the transverse fiber angle, which describes the cross-over of the muscle fibers between the subendocardial and subepicardial layers, should be adapted.
- On the basis of comparison of sarcomere length, as calculated in the ischemic region of the ventricle, with sarcomere length, as measured in papillary muscle experiments, it is concluded that, at sarcomere lengths above $2.3\ \mu\text{m}$, the stiffness of the passive tissue should be higher than described by the present model.
- Because calculated deformation in the basal region of the left ventricle deviates from that in the remaining part of the ventricle, it is concluded that the boundary conditions applied to the base may have to be modified, so that the kinematic constraints imposed to the base by the annuli fibrosi and the valves are described more accurately.

7.3.2 Recommendations for extensions of the model

- The mechanics of the left ventricle in which the pattern of electrical activation is abnormal, due to disturbances in the conduction of the depolarization wave or to stimulation by a ventricular pacemaker, may be simulated by incorporating a more realistic description of the electrical activation of the ventricular wall.
- Mechanical effects of intramyocardial blood flow may be simulated by considering the myocardial tissue as a two-phase material [43].

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Basic continuum mechanics

In this appendix some aspects of the theory of continuum mechanics are presented. A more elaborate treatment of this theory can be found for instance in the textbook by Malvern [51].

A.1 Deformation and strain

Consider a three-dimensional body. Every material point of this body can be labeled uniquely by a set of three material coordinates ξ :

$$\xi^T = [\xi_1 \quad \xi_2 \quad \xi_3] \quad (\text{A.1})$$

During deformation the position vector $\mathbf{x}$ of a material point changes. In general $\mathbf{x}$ will be a function of ξ and t :

$$\mathbf{x} = \mathbf{x}(\xi, t) \quad (\text{A.2})$$

Local deformation of a body can be described by the deformation gradient tensor $\mathbf{F}$. This tensor describes how an infinitesimal material vector $d\mathbf{x}_0$ in the reference situation is transformed into a vector $d\mathbf{x}$ in the deformed situation:

$$d\mathbf{x} = \mathbf{F} \cdot d\mathbf{x}_0; \quad \mathbf{F} = (\nabla_0 \mathbf{x})^c \quad (\text{A.3})$$

$\mathbf{F}$ contains information on the change of both orientation and shape of the body. Stresses in the body are related to change in shape, and not to change in orientation. Therefore, a measure of strain is defined that describes only the shape change component of the deformation process, the Green-Lagrange strain tensor $\mathbf{E}$:

$$\mathbf{E} = \frac{1}{2}(\mathbf{F}^c \cdot \mathbf{F} - \mathbf{I}) \quad (\text{A.4})$$

The relative change in length $\lambda(\mathbf{e}_0)$ of the material vector $d\mathbf{x}_0$ can be expressed as:

$$\lambda(\mathbf{e}_0) = \frac{\|d\mathbf{x}\|}{\|d\mathbf{x}_0\|} = (d\mathbf{x}_0 \cdot (2\mathbf{E} + \mathbf{I}) \cdot d\mathbf{x}_0)^{1/2} \quad (\text{A.5})$$

Consider two material vectors $d\mathbf{x}_{01}$ and $d\mathbf{x}_{02}$, that are transformed into $d\mathbf{x}_1$ and $d\mathbf{x}_2$, respectively. The angle between the elements equals γ_0 and γ in the undeformed and deformed situation, respectively, with:

$$\gamma_0 = \arccos \left(\frac{d\mathbf{x}_{01} \cdot d\mathbf{x}_{02}}{\|d\mathbf{x}_{01}\| \|d\mathbf{x}_{02}\|} \right) \quad (\text{A.6})$$

$$\gamma = \arccos \left(\frac{d\mathbf{x}_1 \cdot d\mathbf{x}_2}{\|d\mathbf{x}_1\| \|d\mathbf{x}_2\|} \right) \quad (\text{A.7})$$

$$= \arccos \left(\frac{d\mathbf{x}_{10} \cdot (2\mathbf{E} + \mathbf{I}) \cdot d\mathbf{x}_{20}}{(d\mathbf{x}_{01} \cdot (2\mathbf{E} + \mathbf{I}) \cdot d\mathbf{x}_{01})^{1/2} (d\mathbf{x}_{02} \cdot (2\mathbf{E} + \mathbf{I}) \cdot d\mathbf{x}_{02})^{1/2}} \right) \quad (\text{A.8})$$

The volumes dV and dV_0 of a material element in the deformed and undeformed situation, respectively, are mutually related according to:

$$dV = \det(\mathbf{F}) dV_0 \quad (\text{A.9})$$

A.2 Stress

Consider an infinitesimal surface with normal vector $\mathbf{n}_0$ and area dA_0 . Upon application of a force $d\mathbf{f}$, this surface deforms according to a deformation gradient tensor $\mathbf{F}$. The deformed surface has a normal vector $\mathbf{n}$ and an area dA . The local stress state in the material is given by the Cauchy stress tensor $\boldsymbol{\sigma}$. This tensor relates the applied force to the deformed surface:

$$d\mathbf{f} = \boldsymbol{\sigma}^c \cdot \mathbf{n} dA \quad (\text{A.10})$$

In experiments to determine the stress-strain behavior of materials, applied force is related to the undeformed area usually:

$$d\mathbf{f} = \mathbf{T}^c \cdot \mathbf{n}_0 dA_0 \quad (\text{A.11})$$

The tensor $\mathbf{T}$ is called the first Piola-Kirchhoff stress tensor. $\boldsymbol{\sigma}$ and $\mathbf{T}$ are related according to:

$$\boldsymbol{\sigma} = \det(\mathbf{F}) \mathbf{F} \cdot \mathbf{T} \quad (\text{A.12})$$

The mechanical behavior of an elastic material is described by a constitutive equation, relating some measure of stress to some measure of strain. For the case of large deformations, the Green-Lagrange strain tensor $\mathbf{E}$ is an appropriate measure of strain. The condition that the constitutive equation must be independent of rigid body motion, leads to the conclusion that in this equation $\mathbf{E}$ must be coupled to the second Piola-Kirchhoff stress tensor $\mathbf{P}$, which is defined as:

$$\mathbf{P} = \det(\mathbf{F}) \mathbf{F}^{-1} \cdot \boldsymbol{\sigma}^c \cdot \mathbf{F}^{-c} \quad (\text{A.13})$$

In an incompressible material only the deviatoric part $\boldsymbol{\sigma}^d$ of $\boldsymbol{\sigma}$ is uniquely related to the deformation of the material. In this case it is advantageous to write the Cauchy stress tensor as the sum of its deviatoric part and a hydrostatic pressure p :

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^d - p\mathbf{I} \quad (\text{A.14})$$

The second Piola-Kirchhoff stress tensor $\mathbf{S}$, related to the deviatoric Cauchy stress tensor, is defined as:

$$\mathbf{S} = \det(\mathbf{F}) \mathbf{F}^{-1} \cdot (\boldsymbol{\sigma}^d)^c \cdot \mathbf{F}^{-c} \quad (\text{A.15})$$

Transformation of the equilibrium equations

In this appendix a description is given of the procedure of transforming the equilibrium equations, presented in section 3.1, into a set of linear equations that can be solved numerically.

B.1 The weighted residual formulation

The deformation of a continuum is governed by conservation of mass, conservation of momentum and conservation of moment of momentum:

$$\det(\mathbf{F}) = 1 \quad (\text{B.1})$$

$$\nabla \cdot \boldsymbol{\sigma}^d - \nabla p = 0 \quad (\text{B.2})$$

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^c \quad (\text{B.3})$$

The momentum equation (B.2) is equivalent to:

$$\int_V \mathbf{h} \cdot (\nabla \cdot \boldsymbol{\sigma}^d - \nabla p) dV = 0 \quad (\text{B.4})$$

where V is the actual volume of the continuum, and $\mathbf{h}$ an arbitrary vector function defined in V . Equation (B.4) can be transformed into:

$$\int_V (\boldsymbol{\sigma}^d : (\nabla \mathbf{h})^c - p (\nabla \cdot \mathbf{h})) dV = \int_A \mathbf{h} \cdot (\boldsymbol{\sigma}^d \cdot \mathbf{n} - p \mathbf{n}) dA \quad (\text{B.5})$$

where $\mathbf{n}$ is the normal on A , the surface of V . The term $(\boldsymbol{\sigma}^d \cdot \mathbf{n} - p \mathbf{n})$ corresponds to the external pressure $-p_{ext}$ applied to the surface A :

$$(\boldsymbol{\sigma}^d \cdot \mathbf{n} - p \mathbf{n}) = -p_{ext} \mathbf{n} \quad (\text{B.6})$$

Transformation to the undeformed configuration yields :

$$\begin{aligned} \int_{V_0} (\boldsymbol{\sigma}^d : (\mathbf{F}^{-c} \cdot \nabla_0 \mathbf{h})^c - p (\mathbf{F}^{-c} \cdot \nabla_0 \cdot \mathbf{h})) J dV_0 = \\ - \int_{A_0} p_{ext} J \mathbf{h} \cdot (\mathbf{F}^{-c} \cdot \mathbf{n}_0) dA_0 \end{aligned} \quad (\text{B.7})$$

where $J = \det(\mathbf{F})$ and $\mathbf{n}_0$ represents the normal vector on the surface A_0 of the volume V_0 in the undeformed configuration. This equation can be written as:

$$\begin{aligned} \int_{V_0} ((\nabla_0 \mathbf{h})^c : (\mathbf{S} \cdot \mathbf{F}^c) - p J (\nabla_0 \mathbf{h}) : \mathbf{F}^{-c}) dV_0 = \\ - \int_{A_0} p_{ext} J \mathbf{h} \cdot (\mathbf{F}^{-c} \cdot \mathbf{n}_0) dA_0 \end{aligned} \quad (\text{B.8})$$

The second Piola-Kirchhoff stress tensor $\mathbf{S}$ is related to the deviatoric Cauchy stress according to:

$$\mathbf{S} = \det(\mathbf{F}) \cdot \mathbf{F}^{-1} \cdot \boldsymbol{\sigma}^d \cdot \mathbf{F}^{-c} \quad (\text{B.9})$$

Now suppose that at a certain time estimates are available of (1) the positions $\mathbf{x}$ of all material points of the continuum, (2) the stresses in the continuum and (3) the hydrostatic pressure in the continuum. The estimated quantities are marked by a '^' and the differences between estimated and the actual situation by 'δ':

$$\mathbf{x} = \hat{\mathbf{x}} + \delta \mathbf{x} \quad ; \quad p = \hat{p} + \delta p \quad ; \quad \mathbf{S} = \hat{\mathbf{S}} + \delta \mathbf{S} \quad ; \quad \mathbf{F} = \hat{\mathbf{F}} + \delta \mathbf{F} \quad (\text{B.10})$$

Then, with the use of:

$$\begin{aligned} \hat{\mathbf{F}} &= (\nabla_0 \hat{\mathbf{x}})^c \quad ; \quad \mathbf{F}^{-1} \approx (\mathbf{I} - \hat{\mathbf{F}}^{-1} \cdot \delta \mathbf{F}) \cdot \hat{\mathbf{F}}^{-1} \\ \delta \mathbf{F} &= (\nabla_0 \delta \mathbf{x})^c \quad ; \quad \det(\mathbf{F}) = \det(\hat{\mathbf{F}})(1 + \hat{\mathbf{F}}^{-1} : \delta \mathbf{F}) \end{aligned} \quad (\text{B.11})$$

and rearranging terms, equation (B.8) is transformed into:

$$\begin{aligned} & \int_{V_0} (\nabla_0 \mathbf{h})^c : (\hat{\mathbf{S}} \cdot \delta \mathbf{F}^c + \delta \mathbf{S} \cdot \hat{\mathbf{F}}^c) dV_0 + \\ & - \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(\delta p \hat{J} \hat{\mathbf{F}}^{-1} + \hat{p} \delta J \hat{\mathbf{F}}^{-1} - \hat{p} \hat{J} \hat{\mathbf{F}}^{-1} \cdot \delta \mathbf{F} \cdot \hat{\mathbf{F}}^{-1} \right) dV_0 + \\ & - \int_{A_0} p_{ext} \mathbf{h} \cdot \left(\delta \mathbf{F}^{-c} \cdot \mathbf{n}_0 \hat{J} + \hat{\mathbf{F}}^{-c} \cdot \mathbf{n}_0 \delta J \right) dA_0 + \\ & \text{higher order terms} = \end{aligned} \quad (\text{B.12})$$

$$\begin{aligned} & \int_{V_0} \left((\nabla_0 \mathbf{h})^c : (-\hat{\mathbf{S}} \cdot \hat{\mathbf{F}}^c) + \hat{p} \hat{J} \hat{\mathbf{F}}^{-1} \right) dV_0 + \\ & - \int_{A_0} p_{ext} \mathbf{h} \cdot (\hat{\mathbf{F}}^{-c} \cdot \mathbf{n}_0) \hat{J} dA_0 \end{aligned}$$

Stresses in cardiac tissue are composed of a passive part $\mathbf{S}_p$ and an active part $\mathbf{S}_a$. The passive component is assumed to be purely elastic (subsection 2.2.2), whereas the active component depends on time, sarcomere length l_s and the contractile element length l_c (subsection 2.2.4):

$$\mathbf{S} = \mathbf{S}_p(\mathbf{E}) + \mathbf{S}_a(l_s, l_c, t) \quad (\text{B.13})$$

The error $\delta \mathbf{S}$ in the estimate of stress can be written as:

$$\delta \mathbf{S} = \frac{\partial \mathbf{S}_p}{\partial \mathbf{E}} : \delta \mathbf{E} + \frac{\partial \mathbf{S}_a}{\partial l_s} \frac{\partial l_s}{\partial \mathbf{E}} : \delta \mathbf{E} + \frac{\partial \mathbf{S}_a}{\partial l_c} \delta l_c + \frac{\partial \mathbf{S}_a}{\partial t} \delta t \quad (\text{B.14})$$

This expression is substituted in (B.13). Furthermore the lefthandside (LHS) of (B.13) is linearized, and the surface terms in the LHS are neglected. The resulting equation is:

$$\begin{aligned}
 & \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(\hat{\mathbf{S}}_p \cdot \delta \hat{\mathbf{F}}^c + \left(\frac{\partial \mathbf{S}_p}{\partial \mathbf{E}} : (\hat{\mathbf{F}}^c \cdot \delta \mathbf{F}) \right) \cdot \hat{\mathbf{F}}^c \right) dV_0 + \\
 & \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(\hat{\mathbf{S}}_a \cdot \delta \hat{\mathbf{F}}^c + \left(\frac{\partial \mathbf{S}_a}{\partial l_s} \frac{\partial l_s}{\partial \mathbf{E}} : (\hat{\mathbf{F}}^c \cdot \delta \mathbf{F}) \right) \cdot \hat{\mathbf{F}}^c \right) dV_0 + \\
 & \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(\left(\frac{\partial \mathbf{S}_a}{\partial l_c} \delta l_c + \frac{\partial \mathbf{S}_a}{\partial t} \delta t \right) \cdot \hat{\mathbf{F}}^c \right) dV_0 \quad (B.15) \\
 & - \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(\delta p \hat{J} \hat{\mathbf{F}}^{-1} + \hat{p} \delta J \hat{\mathbf{F}}^{-1} - \hat{p} \hat{J} \hat{\mathbf{F}}^{-1} \cdot \delta \mathbf{F} \cdot \hat{\mathbf{F}}^{-1} \right) dV_0 = \\
 & \int_{V_0} (\nabla_0 \mathbf{h})^c : \left(-\hat{\mathbf{S}}_p \cdot \hat{\mathbf{F}}^c - \hat{\mathbf{S}}_a \cdot \hat{\mathbf{F}}^c + \hat{p} \hat{J} \hat{\mathbf{F}}^{-1} \right) dV_0 \\
 & - \int_{A_0} p_{ext} \mathbf{h} \cdot (\hat{\mathbf{F}}^{-c} \cdot \mathbf{n}_0) \hat{J} dA_0
 \end{aligned}$$

The righthandside (RHS) of this equation represents the difference between the internal and external forces due to the error in the estimated positions $\hat{\mathbf{x}}$ and pressures $\hat{p}$. This RHS can be used to improve iteratively the estimations $\hat{\mathbf{x}}$ and $\hat{p}$, or equivalently reduce the differences $\delta \mathbf{x}$ and δp . It is important to note that no approximations have been made in the RHS of (B.15). Thus, in the procedure of iteratively adapting $\hat{\mathbf{x}}$ and $\hat{p}$, convergence will occur towards the exact solution.

The transformation of the equation describing conservation of volume is analogous to the transformation of the momentum equation. Equation (B.1) is equivalent to:

$$\int_V g dV = \int_{V_0} g dV_0, \quad \int_{V_0} g (det(\mathbf{F}) - 1) dV_0 = 0 \quad (B.16)$$

where g is an arbitrary scalar function in V and V_0 . Introduction of an estimation of the deformed situation and linearization yields:

$$\int_{V_0} g det(\hat{\mathbf{F}})(\hat{\mathbf{F}}^{-1} : \delta \mathbf{F}) dV_0 = - \int_{V_0} g (det(\hat{\mathbf{F}}) - 1) dV_0 \quad (B.17)$$

The equations (B.15) and (B.17), which are called the weighted residual equations, are the starting equations for the discretization process, described in the next section.

B.2 Discretization of the weighted residual equations

The equations (B.15) and (B.17) hold for all points in the continuum. To be able to solve these equations numerically, they have to be reduced to a finite number of linear equations involving a finite number of unknowns. This is accomplished by considering only a finite number of n_x material (nodal) points where the positions in the deformed configuration will be calculated. The pressure p will be calculated in n_p nodal points. From this point on the equations will be presented in a orthonormal coordinate system with unit vectors $\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3$. With the use of interpolation functions ψ and ϕ the position field and pressure field are approximated by:

$$\begin{aligned} \mathbf{x}(t) &\approx \psi^I(\xi) \mathbf{x}^I(t) = \psi^I(\xi) x_i^I(t) \mathbf{e}_i & I &= 1, \dots, n_x \\ & & i &= 1, 2, 3 \\ p(t) &\approx \phi^J(\xi) p^J(t) & J &= 1, \dots, n_p \end{aligned} \quad (\text{B.18})$$

where Einstein summation convention is used: a double superscripted capital index denotes summation over the nodal points, whereas a double subscripted index denotes summation over the three coordinate directions. x_i^I denotes component i of the position vector $\mathbf{x}^I$ of node I , and p^J represents the hydrostatic pressure at node J . The interpolation functions are dependent on the material coordinates ξ and chosen in such a way that:

$$\psi^I(\xi^J) = \delta^{IJ} \quad ; \quad \phi^I(\xi^J) = \delta^{IJ} \quad (\text{B.19})$$

With the help of the interpolation functions the contractile element length l_c can also be discretized:

$$l_c(t) \approx \psi^I(\xi) (l_c)^I(t) \quad I = 1, \dots, n_x \quad (\text{B.20})$$

Because of the approximation of p and $\mathbf{x}$, the equilibrium equations cannot be fulfilled for all g and $\mathbf{h}$. Following Galerkin's method, a finite set of weighting functions is chosen, equal to the set of interpolation functions:

$$\begin{aligned} \mathbf{h} &\rightarrow \mathbf{h}_i^I = \psi^I \mathbf{e}_i & I &= 1, \dots, n_x \\ & & i &= 1, 2, 3 \\ g &\rightarrow g^J = \phi^J & J &= 1, \dots, n_p \end{aligned} \quad (\text{B.21})$$

The discrete form of the gradient operator is defined as:

$$\mathbf{b}^I(\xi) = \nabla_0 \psi^I(\xi) \quad (\text{B.22})$$

from which it follows that:

$$\begin{aligned} \nabla_0 \delta \mathbf{x} &= \left(\nabla_0 (\psi^I \delta x^I) \right)_{ij} \mathbf{e}_i \mathbf{e}_j = b_i^I \delta x_j^I \mathbf{e}_i \mathbf{e}_j = \mathbf{b}^I \delta \mathbf{x}^I \\ \nabla_0 \mathbf{h}_i^I &= \nabla_0 (\psi^I \mathbf{e}_i) = (\nabla_0 \psi^I) \mathbf{e}_i = \mathbf{b}^I \mathbf{e}_i \end{aligned} \quad (\text{B.23})$$

After substituting these discrete forms into the equations (B.15) and (B.17) the following matrix equations result:

$$\sum_{k=1}^6 {}_k K_{ij}^{IJ} \delta x_j^J + {}_7 K_i^{IK} \delta p^K + {}_8 K_i^{IL} (\delta l_c)^L + {}_9 K_i^I \delta t = \sum_{k=1}^4 {}_k R_i^I \quad (\text{B.24})$$

$${}_7 K_j^{JJ} \delta x_j^J = {}_5 R^I \quad (\text{B.25})$$

with:

$${}_1 K_{ij}^{IJ} = \int_{V_0} \hat{\mathbf{S}}_p : \mathbf{b}^I \mathbf{e}_i \cdot \mathbf{b}^J \mathbf{e}_j dV_0 \quad (\text{B.26})$$

$${}_2 K_{ij}^{IJ} = \int_{V_0} \hat{\mathbf{S}}_a : \mathbf{b}^I \mathbf{e}_i \cdot \mathbf{b}^J \mathbf{e}_j dV_0 \quad (\text{B.27})$$

$${}_3 K_{ij}^{IJ} = \int_{V_0} (\hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I) : \frac{\partial \mathbf{S}_p}{\partial \mathbf{E}} : (\hat{\mathbf{F}}^c \cdot \mathbf{e}_j \mathbf{b}^J) dV_0 \quad (\text{B.28})$$

$${}_4 K_{ij}^{IJ} = \int_{V_0} (\hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I) : \left(\frac{\partial \mathbf{S}_a}{\partial l_s} \cdot \frac{\partial l_s}{\partial \mathbf{E}} \right) : (\hat{\mathbf{F}}^c \cdot \mathbf{e}_j \mathbf{b}^J) dV_0 \quad (\text{B.29})$$

$${}_5 K_{ij}^{IJ} = - \int_{V_0} (\hat{\mathbf{F}}^{-c} : \mathbf{b}^I \mathbf{e}_i) (\hat{\mathbf{F}}^{-c} : \mathbf{b}^J \mathbf{e}_j) \hat{p} \hat{J} dV_0 \quad (\text{B.30})$$

$${}_6 K_{ij}^{IJ} = \int_{V_0} (\hat{\mathbf{F}}^{-c} \cdot \mathbf{b}^I \mathbf{e}_i) : (\hat{\mathbf{F}}^{-c} \cdot \mathbf{b}^J \mathbf{e}_j) \hat{p} \hat{J} dV_0 \quad (\text{B.31})$$

$${}_7 K_i^{IJ} = - \int_{V_0} \hat{\mathbf{F}}^{-c} : \mathbf{b}^I \mathbf{e}_i \phi^J \hat{J} dV_0 \quad (\text{B.32})$$

$${}_8 K_i^{IJ} = \int_{V_0} \frac{\partial \mathbf{S}_a}{\partial l_c} : \hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I \psi^J dV_0 \quad (\text{B.33})$$

$${}_9 K_i^I = \int_{V_0} \frac{\partial \mathbf{S}_a}{\partial t} : \hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I \psi^J dV_0 \quad (\text{B.34})$$

$${}_1 R_i^I = - \int_{V_0} \mathbf{S}_p : \hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I dV_0 \quad (\text{B.35})$$

$${}_2 R_i^I = - \int_{V_0} \mathbf{S}_a : \hat{\mathbf{F}}^c \cdot \mathbf{e}_i \mathbf{b}^I dV_0 \quad (\text{B.36})$$

$${}_3 R_i^I = \int_{V_0} \hat{\mathbf{F}}^{-c} : \mathbf{b}^I \mathbf{e}_i \hat{p} \hat{J} dV_0 \quad (\text{B.37})$$

$${}_4 R_i^I = \int_{A_0} p_{ext} \psi^I \mathbf{e}_i \cdot \hat{\mathbf{F}}^{-c} \cdot \mathbf{n}_0 \hat{J} dA_0 \quad (\text{B.38})$$

$${}_5R^I = \int_{V_0} \psi^I (\hat{J} - 1) dV_0 \quad (\text{B.39})$$

Equation (B.25) can also be written in matrix notation:

$${}^X \underline{K} \cdot \delta \underline{X} + {}^L \underline{K} \cdot \delta \underline{L} + {}^t \underline{K} \delta t = \underline{R} \quad (\text{B.40})$$

where:

$${}^X \underline{K} = \begin{bmatrix} \sum_{i=1}^6 {}_i K_{11}^{11} & \sum_{i=1}^6 {}_i K_{12}^{11} & \sum_{i=1}^6 {}_i K_{13}^{11} & {}_7 K_1^{11} & \sum_{i=1}^6 {}_i K_{11}^{12} & \dots \\ \sum_{i=1}^6 {}_i K_{21}^{11} & \sum_{i=1}^6 {}_i K_{22}^{11} & \sum_{i=1}^6 {}_i K_{23}^{11} & {}_7 K_2^{11} & \sum_{i=1}^6 {}_i K_{21}^{12} & \dots \\ \sum_{i=1}^6 {}_i K_{31}^{11} & \sum_{i=1}^6 {}_i K_{32}^{11} & \sum_{i=1}^6 {}_i K_{33}^{11} & {}_7 K_3^{11} & \sum_{i=1}^6 {}_i K_{31}^{12} & \dots \\ {}_7 K_1^{11} & {}_7 K_2^{11} & {}_7 K_3^{11} & 0 & {}_7 K_1^{12} & \dots \\ \sum_{i=1}^6 {}_i K_{11}^{21} & \sum_{i=1}^6 {}_i K_{12}^{21} & \sum_{i=1}^6 {}_i K_{13}^{21} & {}_7 K_1^{21} & \sum_{i=1}^6 {}_i K_{11}^{22} & \dots \\ \dots & \dots & \dots & \dots & \dots & \dots \end{bmatrix} \quad (\text{B.41})$$

$$\delta \underline{X}^T = \begin{bmatrix} \delta x_1^1 & \delta x_2^1 & \delta x_3^1 & \delta p^1 & \delta x_1^2 & \dots \end{bmatrix} \quad (\text{B.42})$$

$${}^L \underline{K} = \begin{bmatrix} {}_8 K_1^{11} & {}_8 K_1^{12} & \dots \\ {}_8 K_2^{11} & {}_8 K_2^{12} & \dots \\ {}_8 K_3^{11} & {}_8 K_3^{12} & \dots \\ 0 & 0 & \dots \\ {}_8 K_1^{21} & {}_8 K_1^{22} & \dots \\ \dots & \dots & \dots \end{bmatrix} \quad (\text{B.43})$$

$$\delta \underline{L}^T = \begin{bmatrix} (\delta l_c)^1 & (\delta l_c)^2 & (\delta l_c)^3 & (\delta l_c)^4 & (\delta l_c)^5 & \dots \end{bmatrix} \quad (\text{B.44})$$

$${}^t \underline{K}^T = \begin{bmatrix} {}_9 K_1^1 & {}_9 K_2^1 & {}_9 K_3^1 & 0 & {}_9 K_1^2 & \dots \end{bmatrix} \quad (\text{B.45})$$

$$\underline{R}^T = \begin{bmatrix} \sum_{i=1}^4 {}_i R_1^1 & \sum_{i=1}^4 {}_i R_2^1 & \sum_{i=1}^4 {}_i R_3^1 & {}_5 R^1 & \sum_{i=1}^4 {}_i R_1^2 & \dots \end{bmatrix} \quad (\text{B.46})$$

Now suppose that at a certain time $t = t_n$ the deformed configuration of the cardiac tissue is known. The columns $\underline{X}$ and $\underline{L}$ at $t = t_n$ are written as $\underline{X}_n$ and $\underline{L}_n$, respectively. Furthermore, suppose that an estimation of the nodal positions and pressures at $t = t_{n+1}$ is available. This estimation is improved iteratively until the column $\underline{R}_{n+1}$, which represents the force imbalances and deviations from volume

conservation due to the error in X_{n+1} , is sufficiently small. The estimation at iteration step j will be denoted by a superscript ' j ':

$$t_{n+1} = \hat{t}_{n+1}^j + \delta t_{n+1}^j \quad (\text{B.47})$$

$$X_{n+1} = \hat{X}_{n+1}^j + \delta X_{n+1}^j \quad (\text{B.48})$$

$$L_{n+1} = \hat{L}_{n+1}^j + \delta L_{n+1}^j \quad (\text{B.49})$$

As a first estimation of quantities at $t = t_{n+1}$ the situation at $t = t_n$ is chosen:

$$\hat{t}_{n+1}^0 = t_n \quad (\text{B.50})$$

$$\hat{X}_{n+1}^0 = X_n \quad (\text{B.51})$$

$$\hat{L}_{n+1}^0 = L_n \quad (\text{B.52})$$

The time steps are prescribed according to:

$$t_{n+1} = t_n + \Delta t_{n+1} \quad (\text{B.53})$$

So it holds that:

$$\delta t_{n+1}^0 = \Delta t_{n+1} \quad (\text{B.54})$$

$$\delta t_{n+1}^j = 0 \quad \text{for } j > 0 \quad (\text{B.55})$$

In the constitutive model for active stress the time derivative of l_c is given as an explicit function of l_c , l_s and t :

$$\frac{\partial l_c}{\partial t} = \frac{\partial l_c}{\partial t}(l_c, l_s, t) \quad (\text{B.56})$$

or, equivalently:

$$\frac{\partial L}{\partial t} = \frac{\partial L}{\partial t}(L, X, t) \quad (\text{B.57})$$

It was found that L_{n+1} can be estimated from the situation up to $t = t_n$ with sufficient accuracy, using a second order Adams-Bashforth predictor followed by a second order Adams-Moulton corrector [98]:

$$\delta L_{n+1}^0 = \Delta L_{n+1} [L_n, L_{n-1}, X_n, X_{n-1}, t_n, t_{n-1}, \Delta t_{n+1}] \quad (\text{B.58})$$

$$L_{n+1} = L_n + \Delta L_{n+1} \quad (\text{B.59})$$

So it holds that:

$$\delta L_{n+1}^j = 0 \quad \text{for } j > 0 \quad (\text{B.60})$$

Since the differences δL and δt in equation (B.40) are known quantities now, a first estimate $\delta \hat{X}_{n+1}^1$ of the error δX_{n+1} can be derived from:

$${}^X K_{n+1}^0 \cdot \delta \hat{X}_{n+1}^1 = R_{n+1}^0 - {}^L K_{n+1}^0 \cdot \delta L_{n+1} - {}^t K_{n+1}^0 \Delta t_{n+1} \quad (\text{B.61})$$

A new estimate $\hat{X}_{n+1}^1$ is obtained according to:

$$\hat{X}_{n+1}^1 = \hat{X}_{n+1}^0 + \delta \hat{X}_{n+1}^1 \quad (\text{B.62})$$

Improvements on this estimate are obtained according to:

$${}^X K_{n+1}^j \cdot \delta \hat{X}_{n+1}^{j+1} = R_{n+1}^j \quad (\text{B.63})$$

After each iteration a new estimate for $\hat{X}_{n+1}$ is calculated:

$$\hat{X}_{n+1}^{j+1} = \hat{X}_{n+1}^j + \delta \hat{X}_{n+1}^{j+1} \quad (\text{B.64})$$

Using $\hat{X}_{n+1}^{j+1}$ the error in the momentum and volume balance R_{n+1}^{j+1} is calculated. If the maximum component of the column R_{n+1}^{j+1} is larger than a prescribed value ε_0 the iterative procedure (B.63) through (B.64) is repeated. If the maximum component of the column R_{n+1}^{j+1} is smaller than a certain value ε_0 it is assumed that the nodal positions and pressures have been estimated sufficiently accurately and a new time step can be performed.

Samenvatting:

de mechanica van de normale en ischemische linker ventrikel tijdens de hartcyclus

Inleiding

De cellen in het lichaam kunnen hun taak slechts verrichten wanneer zij in voldoende mate van bloed worden voorzien. Met het bloed worden voedingsstoffen en zuurstof aangevoerd, en afvalstoffen en koolzuur afgevoerd. De bloedvoorziening wordt in stand gehouden door het hart. Het hart bestaat uit een linker en een rechter pomp. Elke pomp bestaat uit twee holten, de boezem (atrium) en de kamer (ventrikel). In het rechter atrium wordt het bloed verzameld dat vanuit het lichaam naar het hart terugstroomt. Vanuit het rechter atrium wordt de rechter ventrikel gevuld, die vervolgens het bloed door de longen pompt. Het bloed dat terugkomt van de longen wordt opgevangen in het linker atrium. Van hieruit wordt de linker ventrikel gevuld, die tenslotte het bloed door het gehele lichaam pompt. We zullen ons nu verder concentreren op de linker ventrikel.

De geometrie van de linker ventrikel kan in goede benadering worden weergegeven door een dikwandige afgeknotte ellipsoïde (figuur 1a). In de wand van de linker ventrikel bevinden zich spiervezels, die in een geordend patroon gerangschikt zijn. In de buitenlagen van de wand lopen de vezels ongeveer in basis-apex richting. De hoek tussen de vezelrichting en de omtreksrichting wordt de helixhoek α_1 genoemd. Bij de basis steken de vezels over van de buiten- naar de binnenlagen onder een hoek α_3 , de transversale hoek (figuur 1b). In de binnenlagen lopen de vezels in de richting van de apex, waar zij weer oversteken naar de buitenlagen. In de lagen die meer in het midden van de wand gelegen zijn treffen we hetzelfde patroon aan, zij het dat de helixhoek α_1 kleiner is. In de middenlagen lopen de vezels min of meer in

FIGURE 1: (a) schematische weergave van de geometrie van de linker ventrikel met daarin aangegeven de vezelstructuur en de helixhoek α_1 ; (b) bovenaanzicht van de ventrikel met daarin aangegeven de transversale vezelhoek α_3 ; (c) samenstelling van een spiervezel met spiercellen S en bindweefsel B; (d) activatiepatroon van de ventrikelwand: de lijnen verbinden punten met een gelijk activatietijdstip, waarbij de getallen het activatietijdstip in milliseconden aangeven.

omtrekrichting. Een nadere beschouwing van de spiervezels laat zien dat zij bestaan uit een aaneenschakeling van langgerekte spiercellen, die onderling verbonden zijn door bindweefsel (figuur 1c).

Tijdens de hartcyclus kunnen vier fasen onderscheiden worden. Gedurende de diastolische vullingsfase wordt de linker ventrikel gevuld vanuit het linker atrium. Aan het eind van deze fase bereikt een depolarisatiegolf vanuit het atrium de cellen in de binnenwand van de ventrikel in de buurt van de apex. Van hieruit verspreidt deze golf zich in de loop van zo'n 40 milliseconden over de ventrikelwand (figuur 1d). Nadat de spiercellen in de wand door de depolarisatiegolf geactiveerd zijn, bouwen zij een mechanische spanning op. De druk in de ventrikelholte neemt hierdoor toe en de klep tussen atrium en ventrikel, de mitraalklep, sluit. In de nu volgende fase blijft het volume van de ventrikelholte constant, terwijl de druk snel toeneemt door de toenemende spanning in de spiercellen. Zodra de ventrikeldruk hoger wordt dan de aortadruk, gaat de aortaklep open en wordt bloed uitgepompt in de aorta. Tegen het eind van deze ejectiefase sluit de aortaklep weer door een lichte terugstroming

van bloed vanuit de aorta in de ventrikel. Tijdens de nu volgende fase blijft het holtevolume wederom constant. De ventrikeldruk neemt snel af doordat de spanning in de spiercellen afneemt. Zodra de ventrikeldruk lager wordt dan de atriumdruk gaat de mitraalklep open en begint de diastolische vullingsfase weer.

Het doel van dit onderzoek

Een eerste indruk van de hartfunctie kan worden verkregen uit een meting van de bloeddruk. Uit het luisteren naar het hart met behulp van een stethoscoop, het meten van een electrocardiogram (ECG), en het maken van ultrageluids- en röntgenopnamen van het hart kan nadere informatie over de hartfunctie verkregen worden.

Voor de interpretatie van de gegevens uit de bovengenoemde metingen is een goed inzicht in de werking van het hart noodzakelijk. Dit inzicht wordt onder andere verkregen uit dierexperimenten, waarin de werking van het hart onder uiteenlopende omstandigheden geanalyseerd wordt. Met name wordt daarbij gekeken naar de mechanische functie van de linker ventrikel. Metingen van de druk in de linker ventrikel en de aorta en de uitstroming in de aorta geven een indruk van de werking van de linker ventrikel als geheel. Deze globale werking van de linker ventrikel is het resultaat van de werking van een groot aantal spiercellen in de wand van de linker ventrikel: de druk in de ventrikel is het gevolg van de mechanische spanning die door de cellen geleverd wordt, en de arbeid die de ventrikel levert is de som van de arbeid die door alle spiercellen samen geleverd wordt. De bijdrage van de spiercellen afzonderlijk aan de functie van de linker ventrikel als geheel kan met de huidige meettechnieken nog niet voldoende gedetailleerd en nauwkeurig gemeten worden.

Om toch inzicht te krijgen in de factoren die van invloed zijn op het mechanisch gedrag op het niveau van de individuele spiercel, is in dit onderzoek een wiskundig model van de mechanica van de linker ventrikel ontwikkeld. In dit model is de geometrie van de linker ventrikel weergegeven door een dikwandige afgeknotte ellipsoïde. De vezelstructuur en het activatiepatroon van de ventrikelwand, de mechanische eigenschappen van de spiercellen en het bindweefsel, en de aorta zijn alle in rekening gebracht.

Resultaten van de berekeningen met het model

Uit de berekeningen bleek dat de verdeling van de mechanische spanningen in de wand van de ventrikel sterk afhangt van de keuze van grootte van de helixhoek α_1 . Helaas geven anatomische studies geen nauwkeurige informatie over de grootte van deze hoek α_1 . Op basis van de hypothese, dat biologisch weefsel zich aanpast aan de mechanische belasting en streeft naar een bepaalde optimale belasting, is in het model de grootte van α_1 daarom zodanig gekozen dat de mechanische spanningen in

elk punt van de ventrikelwand ongeveer even groot zijn. De op deze manier gevonden variatie van de hoek α_1 als functie van de positie in de ventrikelwand bleek niet in strijd met anatomische metingen.

Uit de eerste berekeningen bleek dat, met name bij de basis en de apex, de binnen- en buitenwand over een verschillende hoek om de lange as van de ventrikel roteerden. Het verschil in rotatiehoek liep op tot ongeveer 40° , hetgeen in tegenpraak is met experimentele gegevens. In deze berekeningen werd het oversteken van de spiervezels tussen binnen- en buitenwand verwaarloosd door de transversale hoek α_3 gelijk aan nul te stellen. Door het invoeren van een hoek α_3 van maximaal 15° konden, in overeenstemming met experimentele gegevens, de verschillen in rotatiehoek teruggebracht worden tot minder dan 10° . Voor zover bekend, is dit het eerste model waarin het oversteken van de spiervezels tussen de binnen- en buitenlagen van de ventrikelwand in rekening wordt gebracht.

Uit de berekeningen bleek verder dat de hoeveelheid arbeid, die de cellen in de verschillende delen van de ventrikelwand tijdens de hartcyclus verrichten, sterk afhangt van het patroon van elektrische activatie van de wand. De verrichte arbeid bleek het grootst te zijn in de gebieden die het laatst geactiveerd werden. De resultaten van dierexperimenten, waarin de linker ventrikel op verschillende posities elektrisch werd geactiveerd, wijzen ook op een dergelijke afhankelijkheid.

In de berekeningen werd ook de invloed onderzocht van veranderingen in werkomstandigheden van de linker ventrikel, zoals die normaal gesproken vaak optreden. Zo werd de vullingsgraad van de ventrikel gevarieerd om verschillen tussen rust en arbeid te simuleren. Verder werden de contractie-eigenschappen van de spiercellen gevarieerd, waarmee veranderingen in chemische werkomstandigheden nagebootst werden. Het bleek dat de gevolgen van deze ingrepen op het mechanisch gedrag van de ventrikel door alle spiercellen in de ventrikelwand in gelijke mate werden opgevangen.

Tenslotte zijn in de berekeningen de veranderingen in de mechanica van de linker ventrikel geanalyseerd, die optreden wanneer ten gevolge van de afsluiting van een kransslagader een infarctgebied (ischemie) ontstaat. Het ischemische gebied bleek sterker dan normaal op te rekken, waardoor ter plekke een lichte uitstulping van de hartspeer ontstond. De aard van de veranderingen in de mechanica in het gebied direct grenzend aan het ischemische gebied bleken sterk af te hangen van de lokale vezelrichting in relatie tot de vezelrichting in het ischemische gebied. In die gebieden waar de vezels de voortzetting vormden van de vezels in het ischemische gebied, bleek de vezelspanning lager en de vezelverkorting hoger dan normaal te zijn. In de gebieden waarin de vezels parallel liepen aan die in het ischemische gebied was de vezelspanning juist hoger en de vezelverkorting lager dan normaal.

Vergelijking van berekende en experimentele resultaten

Teneinde de juistheid van het model te toetsen zijn de berekende resultaten, voor zover mogelijk, vergeleken met resultaten uit dierexperimenten. In deze experimen-

ten werden de pompfunctie van de linker ventrikel als geheel en de vormverandering van een deel van het buitenoppervlak van de ventrikelwand gemeten. De metingen werden verricht onder normale omstandigheden en in het geval van ischemie van een deel van de ventrikelwand. De resultaten van de berekeningen bleken goed overeen te komen met die van de metingen. Ook bij de vergelijking van de berekende resultaten met experimentele resultaten, gepubliceerd in de literatuur, werd in het algemeen een redelijke overeenkomst gevonden.

Tot slot

In dit onderzoek is aangetoond dat de oriëntatie van de spiervezels in de ventrikelwand en het patroon van elektrische activatie van de spiercellen een grote invloed hebben op het lokale mechanische gedrag in de ventrikelwand. In het algemeen bleken berekende en experimentele resultaten goed met elkaar overeen te stemmen. De overeenstemming kan nog verder verbeterd worden door aanpassingen in de keuze van de transversale hoek α_3 , de beschrijving van de eerste fase in de opbouw van de actieve spanning in de spiercellen, en de mechanische eigenschappen van het passieve bindweefsel.

Tenslotte kan het huidige model nog verder uitgebreid worden. Door een meer realistische beschrijving van het proces van de elektrische activatie van de ventrikelwand zou het effect van een abnormaal activatiepatroon, veroorzaakt door een verstoorde elektrische geleiding of de elektrische stimulatie door een pacemaker, nader bestudeerd kunnen worden. Door het in rekening brengen van de doorbloeding van de hartspier, zou de relatie tussen lokale doorbloeding en lokale mechanische functie nader geanalyseerd kunnen worden.

Curriculum Vitae

- 30-06-1960 geboren te Sittard
- 1972-1978 Gymnasium B, St. Willibrord Gymnasium, Deurne
- 1978-1985 Technische Natuurkunde,
Technische Universiteit Eindhoven (met lof)
- 1985-1986 Philips I&E, Eindhoven
- 1986-1990 promotie-onderzoek vakgroep Biofysica,
Rijksuniversiteit Limburg,
in dienst van NWO en TUE

Het onderzoek, beschreven in dit proefschrift, is verricht in het kader van een projekt binnen de deelwerkgemeenschap Biomechanica van de Nederlandse organisatie voor Wetenschappelijk Onderzoek (NWO, Medigon). De praktische uitvoering vond plaats binnen de vakgroep Biofysica van de Rijksuniversiteit Limburg, in nauwe samenwerking met de vakgroepen Fysiologie van deze universiteit en Fundamentele Werktuigkunde van de Technische Universiteit Eindhoven. Een groot aantal mensen uit deze vakgroepen heeft bijgedragen aan het onderzoek en het tot stand komen van dit proefschrift.

Mijn direkte begeleider Theo Arts heeft mij wegwijs gemaakt in de hartspiermechanica en met tal van suggesties mede de richting van het onderzoek bepaald. Ook toen de toepassing van de elementenmethode niet zo recht-toe-recht-aan bleek te zijn als hij gedacht had bleef hij het onderzoek op stimulerende wijze begeleiden. Ook zijn zeer nauwgezette verwerking van voorlopige versies van het manuscript kan niet onvermeld blijven.

Jacques Huyghe stond steeds klaar om mijn vragen op het gebied van de elementenmethode en de continuümsmechanica te beantwoorden. Hij maakte mij wegwijs in de 'catacomben van NONSYS' en had met zijn altijd optimistische instelling een positieve invloed op het onderzoek.

Tammo Delhaas had de leiding tijdens de dierexperimenten en bleek achteraf uit de schier onoverzienbare hoeveelheid experimentele data precies die gegevens te kunnen destilleren waar ik om vroeg. Onze gesprekken op het gebied van de mechanica, de fysiologie, en de sociologie van de onderzoeksgroep waren wederzijds vaak zeer verhelderend.

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Rob Reneman was vooral in de afrondingsfase bij het werk betrokken. Zijn vragen dwongen mij het werk vanuit het perspectief van de fysioloog te bekijken en op te schrijven, hetgeen heeft bijgedragen tot de leesbaarheid van het proefschrift.

Hans Snijders was, op het moment dat het rekenen op de VAX door overbezetting praktisch onmogelijk werd, zonder aarzeling bereid zijn beperkte tijd op te offeren en te helpen bij de implementatie van de programmatuur op de SUN Sparc I.

Frits Prinzen leverde een bijdrage aan het slagen van de dierexperimenten en

bekeek verder de resultaten van de berekeningen vanuit het kritische standpunt van de fysioloog.

Bij de dierexperimenten was ook de bijdrage van Ruud Kruger, Theo van de Nagel, Jo Habets, Leo Hofstra en Jacques Lambrechts van groot belang.

Henk Grootenboer (TU Twente) droeg aan het onderzoek bij door het beschikbaar stellen van een verbeterde oplosroutine in het eindige elementen programma NONSYS.

Mijn kamergenoten, met name Peter de Jong en Joop Konings, zorgden voor een collegiale, prettige en ontspannende werkomgeving. Jan Corsel zorgde voor een gestage uitbreiding van rekenfaciliteiten op de VAX en Rosy Hanssen verschaftte secretariële ondersteuning. Daarnaast toonden deze personen een voortdurende belangstelling voor de voortgang van het onderzoek.

De leden van de beoordelingscommissie, Prof. Dr. A. Hasman, Prof. Dr. Ir. J.D. Janssen, Dr. Ir. C.W.J. Oomens, Prof. Dr. N. Westerhof en Prof. E.L. Yellin, PhD., hebben op kritische wijze het proefschrift doorgenomen.

Naast de bovenstaande personen wil ik alle niet met name genoemde personen, medewerkers van de vakgroepen Biofysica, Fysiologie, Fundamentele Werktuigkunde TUE, Medische Informatica en Statistiek, Bewegingswetenschappen en van het Rekencentrum van de RL bedanken voor de bijdrage die zij op enigerlei wijze geleverd hebben aan het tot stand komen van dit proefschrift.

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