# Growth and remodeling of the heart

# Growth and remodeling of the heart

Liesbeth Ossevoort

WFW-report 98.008

# Contents

# Chapter 1

# Introduction

Everybody knows that muscle tissue is able to adapt its structure and geometry to varying loading conditions. The cardiac muscle is no exception when it comes to adapt its structure and geometry: The overloaded heart is characterized by a thickened heart wall. It's common sense that the forces (stresses, strains and energy demands) that are applied to the muscle tissue, for instance during an athlete's training, are responsible for the growth of the muscle. This also holds for growth of the cardiac muscle. The translation of this intuitive knowledge into a sound biomechanical description of growth and remodeling of cardiac tissue is subject of this study.

We hypothesize that the geometry of the ventricular wall and its structure have been designed such that the mechanical load is similar for all muscle cells. In order to maintain this situation, geometry and structure of the cardiac muscle are adapted to long lasting changes in mechanical load of the heart wall. The exact mechanism that is responsible for these adaptations is not yet known. Several lines of evidence indicate that myocyte stretch and shortening are responsible for the adaptation process to start. We assume that the stimuli for adaptation act on the cellular level. The geometry and structure of the heart as an entity are then controlled by the summed action of many regional controlling units for fiber stretch and shortening. This hypothesis will be tested using an numerical model and accompanying validation experiments.

# Chapter 2

# The cardiac muscle

## 2.1 Basic anatomy

The heart is a three-dimensional, hollow muscular organ (figure 2.1). Its function is to maintain the circulation by pumping blood into the vascular system. The right heart half collects deoxygenised blood from the body and pumps it to the lungs, whereas the left heart half collects the oxygen-rich blood that returns from the lungs and pumps it into the rest of the body. Both these pumps consist of two chambers: the atrium in which blood is collected and the ventricle that delivers the actual pumping force. The atria are separated from the

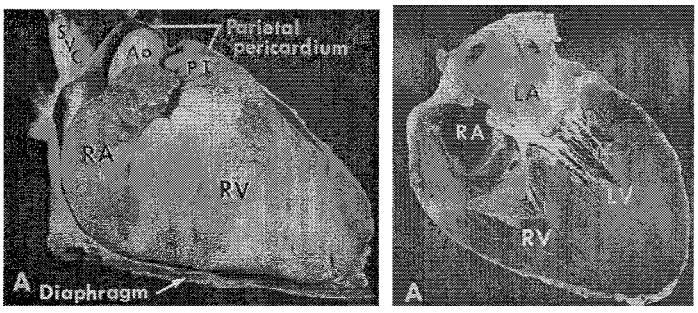


Figure 2.1: Anatomy of the human heart. A) Whole heart surrounded by pericardium. The great arteries can be seen to leave the heart. B) Long-axis view of a cross-section of the heart. SVC=Superior vena cava, Ao=Aorta, PT=Pulmonary trunk RA=Right atrium, LA=Left atrium, RV=Right ventricle and LV=left ventricle [9].

ventricles by valves: The left atrium and the left ventricle by the mitral valve, the right atrium and the right ventricle by the tricuspid valve. The valves are supported by fibrous rings, the annuli fibrosi. A third annulus fibrosus supports the aortic valve, between the left ventricle and the aorta. The annuli fibrosi are closely tied together. This results in a mechanically stiff and electrically isolating structure that forms the base of the heart. The fourth valve, the pulmonary valve that separates the right ventricle from the pulmonary artery, lies outside the base. The heart is attached to the surrounding tissue by the large arteries and veins that enter and leave its chambers. It is surrounded by and tightly contained in a membranous sack, the pericardium. Fluid secreted by the pericardium reduces the amount of friction between the beating heart and the surrounding stationary tissues. The strongly non-elastic

nature of the pericardium prevents the heart from becoming overfilled by blood and therefore overstretched. The pericardium is also attached to the diaphragm and firmly anchors the heart in position.

The left ventricular wall is the most dominant structure of the heart, being about three times as thick as the right ventricular wall due to the high cavity pressures that must be generated. The geometry of the left ventricle may be considered to be a thick-walled truncated ellipsoid. The relatively thin-walled right ventricle is positioned around the left ventricle, giving the right ventricular cavity a crescent shape when viewed in short-axis view. The intraventricular septum is the common wall of the ventricles, but anatomically it belongs to the left ventricle (figure 2.2). The epicardial free wall of the left ventricle is smooth, whereas

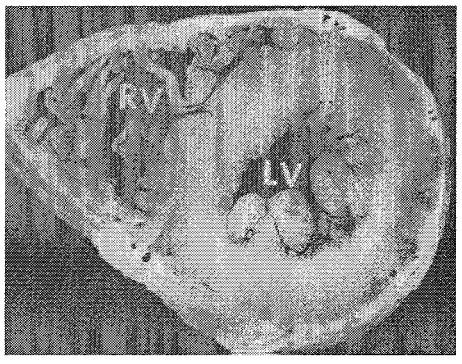


Figure 2.2: Anatomy of the human heart. The left ventricle is the dominant structure of the heart. The right ventricle is wrapped around the left ventricle. RV=Right ventricle and LV=left ventricle [9].

the endocardial wall is irregular. Many invaginations protrude into the wall up to about 30% of its thickness. This portion of the wall is called the trabecular layer. From the trabecular layer the papillary muscles originate. These muscles support the leaflets of the mitral valves through fine fibers, the chordae tendinae.

## 2.2 The cardiac cycle

The cardiac cycle is the sequence of events by which blood is pumped through the body. The pumping action of the heart consists of alternate contractions and relaxations. In the cardiac cycle four stages can be distinguished: diastole, isovolumic contraction, ejection and isovolumic relaxation. The description of these phases will be focused upon the left ventricle. In the diastolic phase the ventricle is filled with blood from the atrium. With the onset of ventricular contraction, the mitral valve closes while the aortic valve remains shut for some time. In this period the ventricle contracts isovolumetrically. When ventricular pressure equals that in the aorta, the aortic valve opens and blood is ejected rapidly. Aortic and ventricular pressures rise and fall together in the ejection period, following a trajectory dictated by the time course of muscle contraction and the systemic arterial input impedance. Eventually, ventricular pressure starts to fall sharply and the aortic valve immediately closes. An isovolumic relaxation period follows, with no change in volume until pressure in the ventricle falls below that in the atrium, whereupon the mitral valve opens again and diastole begins.

## 2.3 Muscle fiber architecture of the left ventricle

Each cardiac muscle fiber, like a voluntary muscle fiber, is surrounded by a sarcolemma. Abundant mitochondria are present, and capillaries in the muscle tissue provide a rich blood supply (figure 2.3). Cardiac muscle cells or myocytes are 80 to 100 $\mu$m in length and are

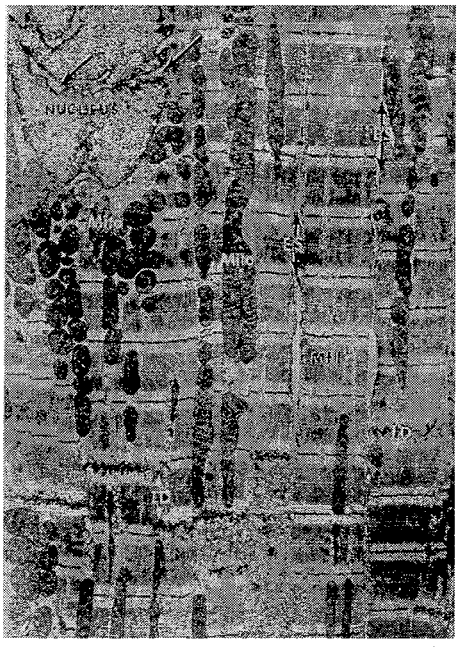


Figure 2.3: Electron micrograph of cardiac muscle cells in longitudinal section. The nucleus of one myocyte and the cytoplasmic regions of four myocytes are shown. The cytoplasm of these cells contains myofilaments (Mfl) in cross-striated arrays. Mitochondria (Mito) vary in size and shape and are closely applied to the surface of the myofilaments. The cells are separated by the extracellular space (ES) and connected to each other at the intercalated discs (ID) [4].

roughly cylindrical with cross-sectional dimensions of 10 to 20 $\mu$m. The cells are connected to each other by intercalated discs. These discs provide structural and electrical integrity of the myocardium. Individual cardiac myocytes are coupled end-to-end but also branch and connect to their immediate neighbors. In this way ordered three-dimensional arrays are formed in which the axes of adjacent cells are nearly parallel. Therefore it is possible to identify a mean myocyte direction, which is usually referred to as 'fiber orientation'.

The fiber orientation in the left ventricle is orderly structured. Streeter and coworkers [22] suggested that fibers are wound on imaginary approximately toroidal surfaces, with the pitch of winding depending on the depth in the wall. In the middle of the wall, at the equator, muscle fibers run purely circumferential. In any other toroidal surface, a fiber spirals down at the epicardial side of the torus, it crosses over to the endocardial side and spirals back up towards the base. Blunt anatomical dissections and DTI-experiments [36] indicate that fiber direction is likely to have a transmural component of a few degrees with the epicardial surface. Fiber orientation can thus be quantified by the helix and transverse angles. The helix angle is defined to be the angle between the circumferential direction and the projection of the fiber on the plane perpendicular to the local transmural direction. The transverse angle

is the angle between the circumferential direction and the projection of the fiber on the plane perpendicular to the local longitudinal direction. The orientation of the muscle fibers changes smoothly from epicardium to endocardium in a non-linear manner as shown in figure 2.4a.

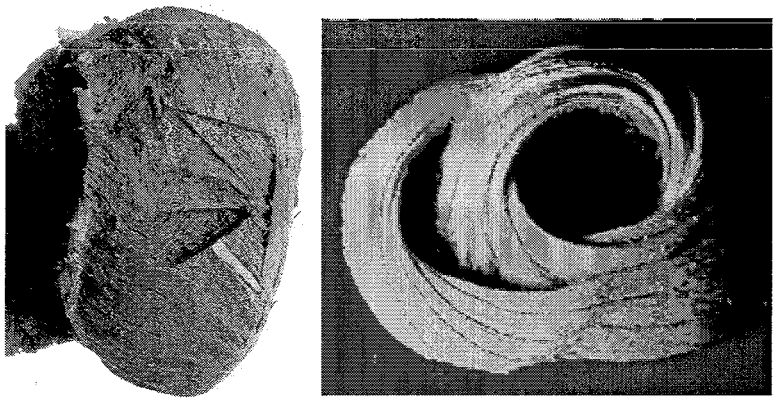

Figure 2.4: a) Left ventricular free wall, partially fenestrated to show the continuous turn of fiberorientation [39]. b) Apex-to-base view of muscle fibers of the ventricular wall spiraling down at the epicardial surface and crossing over at the apex [27].

Models of LV wall mechanics indicate that the distributions of fiber stress and strain over the LV wall are sensitive to the distribution of muscle fiber orientation, even if the latter is chosen within the range of anatomical findings [5], [20]. It has been shown that the introduction of a small transmural component of the fiber orientation has significant effects on the amount of radial-circumferential shear deformation that occurs in the left ventricular wall [6], whereas the helix angle distribution strongly influences the homogeneity of stresses and strains during ejection [36]. Several studies suggest that the distribution of fiber angles has been designed for maximal homogeneity of stresses and strains during ejection [6] [36].

The ventricular myocardium should not be viewed as a uniformly continuous structure. As can be seen in figure 2.5, adjacent myocytes are organized in layers or sheets [7] [25]. Branching between adjacent layers is relatively sparse, and the distance between two such branches can be $1 - 2$ mm. Layers consist of tightly packed groups of cardiac myocytes aligned such that the cell axis is parallel to the cut-edge of the layer. Typically, there are four myocytes across the thickness of a layer, whereas branches between adjacent layers are generally one or two myocytes thick. There is a clear transmural variation in the extent of coupling between adjacent layers, with a progressive reduction in the estimated density of branching between muscle layers from the subepicardium through to the deep midwall. The layers appear to be oriented predominantly in planes spanned by the myocyte axes and the radial direction.

The functional role of the laminar structure of the heart has been subject of discussion. It is possible that the laminar architecture of the myocardium and the transmural variation of coupling between layers provide a framework that enables muscle fiber extension and wall stress to be appropriately distributed through the ventricular wall. Cleavage planes may be oriented along planes where maximum shear stresses occur [25].

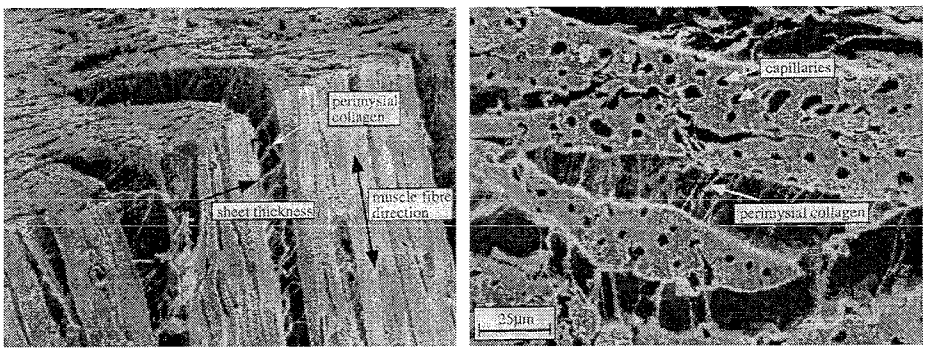


Figure 2.5: a) Scanning electron micrograph showing two orthogonal surfaces of an midwall specimen. The laminar structure of the heart can be seen. b) Transverse midwall specimen. Capillaries are running inside the sheets. [19]

## 2.4 The connective tissue matrix.

When a passive muscle is stretched it develops passive tension. Passive tension opposes the stretch and restores the original length of the muscle after release. Passive tension is an important factor in cardiac muscle because it is part of the diastolic wall tension that determines the extent of filling of the heart and its subsequent stroke volume. The passive material properties of cardiac tissue are largely determined by the composition and structure of the connective tissue matrix. Cardiac myocytes are embedded in a complex extracellular matrix which consists of collagen, elastin, glycoaminoglycans and glycoproteins. The extracellular matrix however is not the only contributor to the passive tension development. Even if isolated muscle cells are regarded, passive tension is developed. The recent discovery of titin molecules within the sarcomeres provides the molecular explanation of this phenomenon.

It was found that over the working range of sarcomere lengths in the heart (lengths $1.9 - 2.2\mu$m), collagen and titin are the most important contributors to passive tension with titin dominating at the shorter end of the working range and collagen at longer lengths [13]. Therefore, the organization of the collagen network and the titin properties will be discussed here in more detail.

Collagen contributes to passive tension over the whole working range of sarcomeres in the heart. The contribution is small at short lengths but increases greatly at lengths longer than about $2.10\mu$m. Collagen forms a very extensive network in which three subdivisions can be seen [7]. There are numerous bundles of collagen fibers that extend from one myocyte to adjacent myocytes. They are present circumferentially providing interconnections with all contiguous myocytes. The second regionalization of the collagen struts consists of myocyte to capillary connections. These struts are consistently longer than the intermyocyte connections. Both these types of collagen have also been called endomysium. The third regionalization of collagen consists of planes of collagen bundles in the form of a complex weave and is distributed throughout the left ventricle. The thin collagen layers encircle sheets of myocytes, thus contributing to the laminar structure of ventricular myocardium. This collagen type is also called perimysium.

Titin (also known as connectin) is a giant filamentous, endo-sarcomeric elastic protein. It is connected to the Z-line of the sarcomere and the thick myosin filament (M-line). The

mechanism by which titin contributes to passive tension development has not yet been fully revealed. A generally accepted hypothesis however is that titin consists of two subsegments: an inelastic anchoring segment and an elastic passive tension segment. The anchoring segment, of about 100 nm long, is attached to the Z-line and runs parallel to the thin filament, whereas the elastic segment connects the anchoring segment to the thick filament. The elastic segment is in slack sarcomeres (sarcomere length 1.85$\mu$m) not straight, but highly folded. Upon sarcomere stretch this segment first straightens up to a sarcomere length of about 2.0$\mu$m and then stretches, developing passive tension in the process [12].

# Chapter 3

# Growth and remodeling of the cardiac muscle

## 3.1 Physiology of growth and remodeling

Growth and remodeling are fundamental processes both in the normal development of tissues and in various pathological conditions. Growth is generally defined as a change of mass, while remodeling involves changes in material properties. Growth can occur through cell division (hyperplasia), cell enlargement (hypertrophy), secretion of extracellular matrix, or accretion at external surfaces. Negative growth, generally referred to as atrophy, can occur through cell death, cell shrinkage or resorption. In most cases hyperplasia and hypertrophy are mutual exclusive processes. Remodeling may be brought about by alterations in modulus, internal structure, strength or density [11] [40].

Cardiac muscle is able to adapt its geometry and structure to changing loading conditions. The growth and remodeling processes involved are regarded as 'functional adaptation', since these processes result in normalization of mechanical load in the wall. The growth process of the mature heart is dominated by hypertrophy of the muscle cells. Structural changes in the cardiac muscle involve fiber and extracellular matrix reorientation. Two types of cardiac hypertrophy commonly occur (figure 3.1): pressure overload hypertrophy (also: concentric hypertrophy) and volume overload hypertrophy (also: eccentric hypertrophy). In pressure overload hypertrophy the cardiac muscle grows in order to be able to eject blood against an elevated aortic blood pressure. This results in an increased ventricular wall volume, while cavity size does not change. Volume overloading of the heart may be caused by a defect valve, resulting in a greater blood volume entering the ventricle during diastole. To accommodate this larger volume, the ventricular cavity enlarges while the wall thickness increases just enough to keep the ratio of radius to thickness approximately the same.

In both above described situations, the changes in mechanical load are similar all over the heartwall, resulting in a homogeneous adaptation pattern. This is however not always the case: Adaptation effects can also occur in response to direct local changes in mechanical loading of the left ventricular wall. In pacemaker stimulated cardiac muscle, the cells that are close to the pacing site are activated earlier than those at the opposite site of the heart. It has been demonstrated that fiber length at the onset of the ejection phase, fiber shortening and work during the ejection phase are reduced in early-activated regions and increased in late-activated regions. This indicates that mechanical load is lower in the early-activated regions,

Figure 3.1: Geometry of left ventricular hypertrophy. Left: Pressure overload hypertrophy produces an increase in wall thickness. Middle: Normal heart. Right: Non-compensated volume overload results in dilatation of the ventricle whitout a proportional increase of wall thickness [9].

resulting in a asymmetric adaptation pattern: wall thickness decreases in early-activated regions, whereas on the opposite sites (late-activated) wall thickness increases [35].

These findings indicate that a) local differences in mechanical load can be responsible for local differences in growth and other structural adaptations, and b) the adaptation that occurs tends to normalize mechanical load of the cardiac muscle. It is however still unclear which mechanical stimulus induces the adaptive growth process. Possible candidates are: stress, strain, strain-rate, sarcomere shortening or energy required.

Growth can be seen as a biochemical process, since tissues change and grow molecule by molecule. Mechanical factors however can play an important role in the growth process, as they are able to induce growth. In order for the tissue to respond to such a mechanical stimulus with alterations in their biology, it is essential that the mechanical stimulus is translated to the cell dialect, which is a biochemical signal. This translation of a mechanical signal into a biochemical signal is called mechanotransduction [43].

## 3.2 Mechanotransduction

The phenomenon of mechanotransduction is interesting in the study of cardiac growth and remodeling, since knowledge of the possible mechanotransduction pathways might give indications about which mechanical stimuli can be translated into biochemical signals. Basically two candidate pathways for mechanotransduction have been recognized [21] [43] [44]. These pathways are schematically depicted in figure 3.2.

- Mechanical deformation of the cell is directly transmitted from sites at which cells attach to the extracellular matrix. Transmembrane receptors such as integrins are good candidates for this mechanoreception. The signal is further transmitted along the cell cytoskeleton to the nucleus. Many of the enzymes and other substances that control protein synthesis, energy conversion and growth in the cell are physically immobilized on the cytoskeleton. For this reason, changing cytoskeletal geometry and mechanics could affect biochemical reactions and even alter genes that are activated.

- Upon mechanical deformation stretch receptors that are functionally integrated in the cell membrane evoke the production of growth-factors or serve as catalysts. The growth factors induce a great number of intracellular signals to be transmitted to the nucleus through a protein kinase cascade of phosphorylation. This cascade has been reported to play an important role in gene expression. The catalyst products can stimulate several cell-specific processes, like elevated ATP-production and changes in protein synthesis. Both these processes may induce cellular growth.

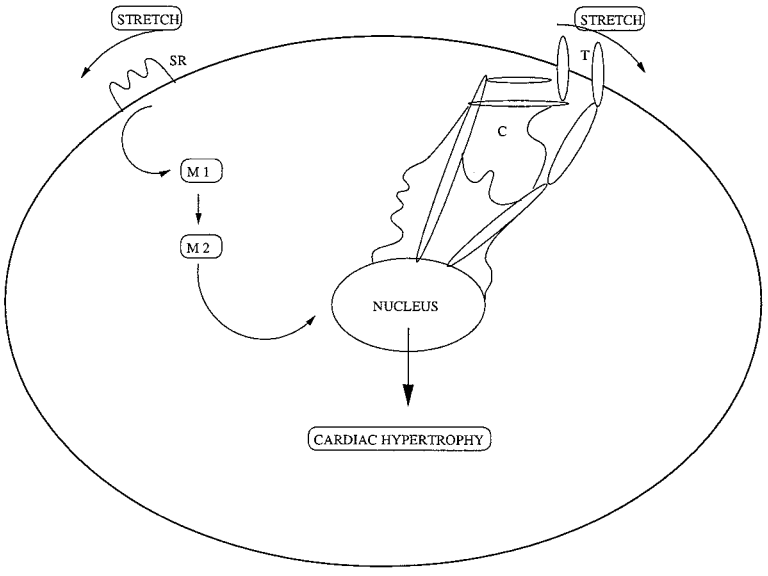


Figure 3.2: Two candidate mechanotransduction pathways. a) Deformation of the cell membrane is sensed by the stretch sensor (SR). This induces a number of intracellular growth signals that are transmitted to the nucleus (M1, M2), resulting in cardiac hypertrophy. b) A transmembrane molecule (T) transmits a mechanical deformation stimulus through the cell cytoskeleton (C) directly to the nucleus.

An other mechanotransduction mechanism that has been proposed is based upon the principles of stretch sensitive ion channels. The permeability of these channels for certain ions depends on the amount of stretch applied to the channel. Stretch sensitive ion channels however, are not likely to play a role in cardiac adaptation mechanisms, since channel inhibitors do not inhibit growth related processes, such as protein synthesis or gene expression, induced by stretch [29] [44].

In both candidate pathways, the mechanical stimulus that is translated into a biochemical signal is deformation. Although we cannot rule out the possibility of the existence of other mechanotransduction pathways, with stimuli such as energy consumption or stress, it is likely that deformation plays an important role in the adaptation process of the cardiac muscle.

# Chapter 4

# Cardiac modeling

## 4.1 Cardiac models

Several cardiac models have been developed to gain insight in function and disfunction of the heart in relation to its geometry, structure and mechanical properties. Most models regard left ventricular mechanics only, since the left ventricle is the motor of the entire systemic circulation and therefore the most burdened part of the heart. Cardiac models range from relatively simple cylindrical models with homogeneous (isotropic) material properties, to very sophisticated models in which a realistic geometry and an orthotropic material law are incorporated. Obviously, the more sophisticated the model, the more extensive computing times it requires.

### 4.1.1 Geometry

The most simplified geometry by which the mechanics of an equatorial ring of the left ventricle can be approximated is the cylinder. The cylinder is, because of its rotational symmetry, essentially a 1-dimensional object, a property which can be used to reduce computing times. Cylindrical models have extensively been used for parameter studies by Arts *et al.* [2, 1], Guccione *et al.* [15, 16], Nevo and Lanir [30, 31], Pietrabissa *et al.* [34], Taber [42] and Zinemanas *et al.* [45]. Extension of the results obtained on the cylindrical model to the whole left ventricle however is not a straightforward procedure. Therefore models have been developed in which the geometry of the left ventricle is described more realistic. A problem in these models is that the apex is always a singular point in the FEM analysis. This is caused by its position on the axis of rotational symmetry, where no fiber orientation is defined. Left ventricular geometry is idealized to be described by confocal truncated ellipsoids. This description incorporates a gradual decrease, from base/equator to apex, of the epicardial and endocardial diameters and the myocardial wall-thickness, as in the real heart geometry. The ellipsoidal model is rotationally symmetric, offering the possibility of 2-dimensional analysis. Truncated ellipsoidal models have been used by Azhari *et al.* [3] , Bovendeerd *et al.* [5, 6], Rijcken [36], Pietrabissa *et al.* [34] and Taber [42, 41]. They can be used for both parameter studies and more clinically oriented research.

An other approach that has been followed to describe the heart geometry is obtained by measuring the actual geometry of several hearts, averaging the results and incorporating these into a geometrical model. Allthough this procedure seems to yield the most realistic description of cardiac anatomy, the effects of biological variance are not taken into account.

Computing times for these kind of models will be elevated, since a full 3-dimensional evaluation is necessary. Models corresponding to a realistic geometry have been developed by Guccione *et al.* [14], Halmann *et al.* [17] and Hunter *et al.* [19].

### 4.1.2 Material properties

Due to the complex tissue organization (see paragraphs 2.3 and 2.4), cardiac tissue behaves non-linear. The relationship between the stress and the strain in cardiac tissue can be defined by a constitutive law. The objective of this law is to express the experimentally observed relationship between stress and strain tensors as accurately as possible over the physiological range. From thermodynamics it can be proved that the constitutive behavior can be expressed in terms of a strain-energy function, according to:

$$W(\mathbf{E}) = f(\mathbf{E}) \tag{4.1}$$

$$\mathbf{S}_p = \frac{\partial W(\mathbf{E})}{\partial \mathbf{E}} \tag{4.2}$$

where $\mathbf{E}$ is the Green-Lagrange strain tensor and $\mathbf{S}_p$ is the $2^{nd}$ Piola-Kirchhoff stress tensor. This strain-energy function is an objective function, which means that it is invariant to rigid body motion, since $\mathbf{E}$ depends only on a material coordinate system.

In the formulation of a constitutive law, two approaches can be chosen: a phenomenological or a structural description of the material behavior can be derived. In both approaches the constitutive law is formulated according to equations 4.1, 4.2. The constitutive law must further meet requirements set by the type of isotropy of the material, i.e. it must fulfill the axiom of material invariance. For isotropic materials for instance, the strain-energy function is restricted to dependence on the invariants, $J_i$, of $\mathbf{E}$, since rotations of the material coordinate system then have no influence on $W(\mathbf{E})$. Also assumptions about material incompressibility should be taken into account in the strain-energy function. In general, material incompressibility is assured by choosing $detF = 1$, where $F$ is the deformation tensor [5], or by an additional term in the strain-energy function that provides a progressive increase in strain-energy at increasing volume-changes [36].

In a phenomenological approach the parameters of the constitutive law are fitted to match experimental results. Phenomenological models are widely used and have originally been developed by Fung [10]. A major objection to this black box approach is that the parameters of this model bear no direct relation to the underlying structure of the material.

In a structural approach, knowledge of the material structure is incorporated in the formulation of the material law and all parameters bear structural significance. This offers the possibility to study the influence of the amount and structure of individual components on mechanical behavior of the tissue. A full structural characterization of cardiac tissue however can currently not be derived: The structure is too complex to model in detail and our current knowledge of the mechanical properties of each component is limited.

As a compromise between a phenomenological and a structural approach several research groups have developed constitutive laws in which details of the micro-structure are included. Lanir [24] developed a model in which the strain energy function of an elastic tissue is considered as the sum of strain energies of all tissue components. The connective fibers are assumed to be wavy in the non-loaded case with non-uniform undulation. As the material is stretched, the fibers gradually straighten. Since only straight fibers are assumed to develop tension, this

model provides a gradual increase in passive tension. MacKenna *et al.* [28] developed a model in which the fibers are not gradually recruited, but gradually uncoiled. Individual ventricular collagen fibers were modeled as curved thin rods, subjected to bending and torsion using the Bernoulli-Euler beam theory. In this theory geometrical changes are responsible for the non-linear tissue behavior. Hunter *et al.* [18] recently developed a model that accounts for the laminar structure of the heart. In this model a different stress-strain relationship along the three microstructurally defined axes (the fiber-axis, the sheet-axis and the cross-sheet axis) is incorporated. Each of these stress-strain relationships has a different limit for an elastic response.

## 4.2 Special features

Cardiac tissue exhibits several features that have not been implemented into mechanical models yet. Since it may be valuable to account for these properties in future models, they are shortly discussed here.

Resting left ventricular myocardium contains residual stresses in the absence of any external loads [33, 23]. Sarcomeres in the outer wall are stretched by these stresses, whereas inner-wall sarcomeres are compressed [38]. This is indicated by a simple experiment: When a radial cut is made through an equatorial slice of the left ventricle, the ring opens up to an arc, showing the existence of residual stresses. The presence of residual strains may significantly influence mechanical function of the ventricle during the cardiac cycle, since it may provide a mechanism by which sarcomere lengths at the onset of ejection are optimized. Detailed 3-dimensional measurements of the residual strains present in cardiac tissue have recently been performed by Costa *et al.* [8].

Novak *et al.* [32] pointed out that the properties of passive myocardium are likely to be heterogeneous throughout the wall. Outer wall myocardium is stiffer than that in the underlying midwall, and may be stiffer than inner-wall myocardium as well. Because of the non-linear behavior of cardiac tissue, even slight differences in material properties, might have significant effects on the calculated regional mechanical load.

## 4.3 Growth and remodeling in mechanical models

Although much attention has been paid to bone remodeling, relatively little attempt has been made to model adaptive processes in cardiac tissue. As has long been recognized, mechanical quantities such as the stress and strain in the tissue can modulate its growth. Rodriguez *et al.* [37] developed a growth theory in which the shape change that occurs during growth of an unloaded body is regarded to be composed of two processes: (1) Material may be added or removed, changing the local stress-free reference state of the tissue; (2) An elastic deformation may be required to accommodate this change in tissue configuration and volume in order to make the total growth deformation compatible. Additionally, stress in a tissue may not only be caused or altered by growth, it may also affect growth itself. Thus, stress assumed to be the main stimulus for growth in this description. Lin and Taber adapted this model to describe growth in the developing (embryonic) heart [26]. An other approach has been followed by Arts *et al.* [1]. Based on observations of mechanotransduction pathways (see chapter 3.2), they concluded that stretch is likely to be involved in control of the heart shape and mass. Since stretch can be sensed on the cellular level, whereas no biological mechanism

is known that senses global structure of the heart, they assumed that growth is induced by summation of the action of many regional controlling units for fiber stretch and shortening. A model build on these assumptions has been showed to maintain the anatomical structure of a cylinder during changes in pressure and volume load.

# Bibliography


[1] T. Arts, F.W. Prinzen, L.H.E.H. Snoeckx, J.M. Rijcken, and R.S. Reneman. Adaptation of cadiac structure by mechanical feedback in the environment of the cell: A model study. *Biophysical journal*, 66:953–961, april 1994.

[2] T. Arts, P.C. Veenstra, and R.S. Reneman. Epicardial deformation and left ventricular wall mechanics during ejection in the dog. *American journal of physiology.*, 243:H379–H390, 1982.

[3] H. Azhari, M. Buchalter, S. Sideman, E. Shapiro, and R. Beyar. A conical model to describe the nonuniformity of the left ventricular twisting motion. *Annals of biomedical engineering*, 20:149–165, 1992.

[4] J.B. Bassingthwaighte. The myocardial cell. In E.R. Giuliani, V. Fuster, B.J. Gersh, M.D. McGoon, and D.C. McGoon., editors, *Cardiology — Fundamentals and practice. $2^{nd}$ edition*, chapter 5, pages 113–149. Mosby Year Book, 1991.

[5] P.H.M. Bovendeerd, T. Arts, J.M. Huyghe, D.H. van Campen, and R.S. Reneman. Dependence of local left ventricular wall mechanics on myocardial fiber orientation: A model study. *Journal of biomechanics*, 25(10):1129–1140, 1992.

[6] P.H.M. Bovendeerd, J.M. Huyghe, T. Arts, D.H. van Campen, and R.S. Reneman. Influence of endocardial-epicardial crossover of muscle fibers on left ventricular wall mechanics. *Journal of biomechanics*, 27(7):941–951, 1994.

[7] J.B. Caulfield and T.K. Borg. The collagen network of the heart. *Laboratory investigation*, 40(3):364–372, 1979.

[8] K.D. Costa, K. May-Newman, D. Farr, W. G. O'Dell, A.D. McCulloch, and J.H. Omens. Three-dimensional residual strain in midanterior canine left ventricle. *American journal of physiology*, 273:H1968–H1976, 1997.

[9] W.D. Edwards. Applied anatomy of the heart. In E.R. Giuliani, V. Fuster, B.J. Gersh, M.D. McGoon, and D.C. McGoon, editors, *Cardiology — Fundamentals and practice. $2^{nd}$ edition*, chapter 4, pages 47–112. Mosby Year Book, 1991.

[10] Y.C. Fung. Elasticity of soft tissues in simple elongation. *American journal of physiology*, 213:H1532–H1544, 1967.

[11] Y.C. Fung. *Biomechanics: motion, flow, stress, and growth.* Springer-Verlag New York Inc., 1990.

[12] H. Granzier, M. Helmes, and K. Trombitas. Nonuniform elasticity of titin in cardiac myocytes: A study using immunoelectron microscopy and cellular mechanics. *Biophysical journal*, 70:430–442, january 1996.

[13] H.L Granzier and T.C. Irving. Passive tension in cardiac muscle: Contribution of collagen, titin, microtubules, and intermediate filaments. *Biophysical journal*, 68:1027–1044, march 1995.

[14] J.M. Guccione, K.D. Costa, and A.D. McCulloch. Finite element stress analysis of left ventricular mechanics in the beating dog heart. *Journal of biomechanics*, 28(10):1167–1177, 1995.

[15] J.M. Guccione, A.D. McCulloch, and L.K. Waldman. Passive material properties of intact ventricular myocardium determined from a cylindrical model. *Journal of biomechanical engineering*, 113:42–55, february 1991.

[16] J.M. Guccione, L.K. Waldman, and A.D. McCulloch. Mechanics of active contraction in cardiac muscle: Part ii — cylindrical models of the systolic left ventricle. *Journal of biomechanical engineering*, 115:82–90, february 1993.

[17] M. Halmann, S. Sideman, J. Lessick, and R. Beyar. Relating coronary perfusion to myocardial function using three-dimensional reconstruction of heart and coronary arteries. *Medical & Biological Engineering & Computing*, 32:S144–S150, july 1994.

[18] P.J. Hunter, M.P. Nash, and G.B. Sands. Computational electromechanics of the heart. In A.V. Panfilov and A.V. Holden, editors, *Computational biology of the heart.*, chapter 12, pages 345–407. John Wiley and Sons, Ltd., 1997.

[19] P.J. Hunter, B.H. Smaill, P.M.F. Nielsen, and I.J. LeGrice. A mathematical model of cardiac anatomy. In A.V. Panfilov and A.V. Holden, editors, *Computational biology of the heart.*, chapter 6, pages 171–216. John Wiley and Sons, Ltd., 1997.

[20] J.M. Huyghe, T. Arts, D.H. van Campen, and R.S. Reneman. Porous medium finite element model of the beating left ventricle. *American journal of physiology*, 262:H1256–H1267, 1992.

[21] D.E. Ingber. The architecture of life. *Scientific American*, 278(1):30–39, january 1998.

[22] D.D. Streeter jr. *Gross morphology and fiber geometry of the heart. In: Handbook of physiology — The Cardiovascular system I.* American physiological society, 1979.

[23] T. Kang and F.C.P. Yin. The need to account for residual strains and composite nature of the heart wall in mechanical analyses. *American journal of physiology*, 271:H947–H961, 1996.

[24] Y. Lanir. Constitutive equations for fibrous connective tissues. *Journal of biomechanics*, 16:1–12, 1983.

[25] I.J. LeGrice, B.H. Smaill, L.Z. Chai, S.G. Edgar, J.B. Gravin, and P.J Hunter. Laminar structure of the heart: ventricular myocyte arrangement and connective tissue architecture in the dog. *American journal of physiology*, 269:H571–H582, 1995.

[26] I-E. Lin and L.A. Taber. A model for stress-induced growth in the developing heart. *Journal of biomechanical engineering*, 117:343–349, august 1995.

[27] P.P. Lunkenheimer, A. Lunkenheimer, and F. Torrent-Guasp. *Kardiodynamik: Wege zur strukturgerechten Analyse der Myokardfunktion.*, volume 33 of *Beitrage zur Kardiologie*, chapter Der Aufbau des Myokardkörpers zo einem Schleifenkontinuum nach *Torrent Guasp.*, pages 38–45. Perimed Fachbuch-Verlagsgesellschaft mbH, 1985.

[28] D.A. MacKenna, S.M Vaplon, and A.D. McCulloch. Microstructural model of perimysial collagen fibers for resting myocardial mechanics durng ventricular filling. *American journal of physiology*, 273:H1576–H1586, 1997.

[29] C. E. Morris. Mechanosensitive ion channels. *Journal of membrane biology*, 113:93–107, 1990.

[30] E. Nevo and Y. Lanir. Structural finite deformation model of the left ventricle during diastole and systole. *Journal of biomechanical engineering*, 111:342–349, november 1989.

[31] E. Nevo and Y. Lanir. The effect of residual strain on the diastolic function of the left ventricle as predicted by a structural model. *Journal of biomechanics*, 27(12):1433–1446, 1994.

[32] V.P. Novak, F.C.P. Yin, and J.D. Humphrey. Regional and mechanical porperties of passive myocardium. *Journal of biomechanics*, 27(4):403–412, 1994.

[33] J.H. Omens and Y.-C. Fung. Residual strain in rat left ventricle. *Circulation research*, 66:37–45, 1990.

[34] R. Pietrabissa, F.M. Montevecchi, and R. Fumero. *Ventricle mechanics based on sarcomere and fibre models.*, volume BED-9 of *Computational methods in engineering.* The American Society of Mechanical Engineers, 1998.

[35] F.W. Prinzen, E.C. Cheriex, T. Delhaas, M.F.M. van Oosterhout, T. Arts, H.J.J. Wellens, and R.S. Reneman. Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: A study in dogs with ventricular pacing and in patients with left bundle branch block. *American heart journal*, 130:1045–1053, 1995.

[36] J. Rijcken. *Optimization of left ventricular muscle fiber orientation.* PhD thesis, Maastricht University, september 1997.

[37] E.K. Rodriguez, A. Hoger, and A.D. McCulloch. Stress-dependent finite growth in soft elastic tissues. *Journal of biomechanics*, 27(4):455–467, 1994.

[38] E.K. Rodriguez, J.H. Omens, L.K. Waldman, and A.D. McCulloch. Effect of residual stress on transmural sarcomere length distributions in rat left ventricle. *American journal of physiology*, 264:H1048–H1056, 1993.

[39] P. Schmid, P. Niederer, P.P. Lunkenheimer, and F. Torrent-Guasp. The anisotropic structure of the human left and right ventricles. *Technology and health care*, 5(1,2):29–43, 1997.

[40] L.A. Taber. Biomechanics of growth, remodeling, and morphogenesis. *Applied mechanics review*, 48(8):487–545, 1995.

[41] L.A. Taber and W.W. Podszus. A laminated shell model for the infarcted left ventricle. *International journal of structures and solids.*, 34(2):223–241, 1997.

[42] L.A. Taber, M. Yang, and W.W. Podszus. Mechanics of ventricular torsion. *Journal of biomechanics*, 29(6):745–752, 1996.

[43] P.A. Watson. Function follows form: generation of intracellular signals by cell deformation. *FASEB journal*, 5:2013–2019, 1991.

[44] T. Yamazaki, I. Komuro, R. Nagai, and Y. Yazaki. Stretching the evidence in the case of cardiac growth. *Cardiovascular Research*, 31:493–498, 1996.

[45] D. Zinemanas, R. Beyar, and S. Sideman. An integrated model of lv muscle mechanics, coronary flow, and fluid and mass transport. *American journal of physiology*, 268:H633–H645, 1995.