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Computational Modeling of Cardiac Growth in the Post-Natal Rat with a Strain-Based Growth Law

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Abstract

Introduction—The postnatal heart grows mostly in response to increased hemodynamic load. However, the specific biomechanical stimuli that stimulate cardiac growth as a reaction to increased hemodynamic load are still poorly understood. It has been shown that isolated neonatal rat cardiac myocytes normalize resting sarcomere length by adding sarcomeres in series when subjected to uniaxial static strain. Because there is experimental evidence that myocytes can distinguish the direction of stretch, it was postulated that myocytes also may normalize interfilament lattice spacing as a response to cross-fiber stretch.

Methods—A growth law was proposed in which fiber axial growth was stimulated by fiber strain deviating from zero and fiber radial growth by cross-fiber strain (parallel to the wall surface) deviating from zero. Fiber radial growth rate constant was 1/3 of the fiber axial growth rate constant. The growth law was implemented in a finite element model of the newborn Sprague-Dawley rat residually stressed left ventricle (LV). The LV was subjected to an end-diastolic pressure of 1 kPa and about 25 weeks of normal growth was simulated.

Results—Most cellular and chamber dimension changes in the model matched experimentally measured ones: LV cavity and wall volume increased from 2.3 and 54 μ liter, respectively in the newborn to 276 μ liter and 1.1 ml, respectively in the adult rat; LV shape became more spherical; internal LV radius increased faster than wall thickness; unloaded sarcomere lengths exhibited a transmural gradient. The major discrepancy with experiments included a reversed transmural gradient of cell length in the older rat.

Conclusion—A novel strain-based growth law has been presented that reproduced physiological postnatal growth in the rat LV.

Keywords

maturing; heart; residual stress; opening angle

Introduction

Cardiac growth is regulated by both intrinsic and extrinsic factors (Icardo, 1988; Zak, 1984). The growth of the embryonic heart (by hyperplasia and hypertrophy) is highly regulated by

intrinsic factors under normal conditions when hemodynamic load is very low: myocyte dimensions in normal embryonic hearts were not different from those grown *in oculo* (Bishop *et al.*, 1990). Growth in embryonic hearts is also susceptible to extrinsic factors because growth accelerates when hemodynamic load is increased (Sedmera *et al.*, 1999). The postnatal heart also grows – virtually only by hypertrophy a few days after birth – in response to increasing hemodynamic load (i.e. the left ventricle (LV) in the newborn enlarges rapidly after closure of the foramen ovale). Recently though, also an hypertrophic pathway of postnatal cardiac growth has been found, which is less dependent on hemodynamic load (Chen *et al.*, 2006).

The specific biomechanical stimuli that stimulate cardiac growth as a reaction to increased hemodynamic load however are still poorly understood (Ambrosi *et al.*, 2011; Holmes, 2004; Lorenz *et al.*, 2009; Omens, 1998). Growth at the organ level – by dilation and increase in wall thickness – finds its origin at the cell level by increases of cardiac myocyte length and diameter. It has been shown that isolated neonatal rat myocytes normalize resting sarcomere length by adding sarcomeres in series when subjected to uniaxial static strain (Mansour *et al.*, 2004). The cells grew axially by adding sarcomeres in the fiber direction (increasing the unloaded length of the cell) after a 10% stretch, restoring resting sarcomere length. Axial fiber growth at the cell level leads to eccentric hypertrophy (dilation) of the heart at the organ level and translates to a previously proposed hypothesis, that end-diastolic fiber strain could serve as a growth stimulus (Goktepe *et al.*, 2010; Holmes, 2004; Kroon *et al.*, 2009; Omens, 1998), such that a uniform transmural sarcomere length is maintained at end-diastole. It is thought that such an end-diastolic distribution – combined with the typical myocardial fiber architecture and residual stress/strain – facilitates a uniform fiber shortening during ejection.

A similar mechanism may exist for cardiac myocyte radial growth, which on the whole heart level leads to thickening of the myocardial walls. When isolated cardiac myocytes are subjected to strain perpendicular to the fiber direction, immunofluorescent labeling of hypertrophic marker atrial natriuretic factor is increased, phosphorylation of FAK is increased and contractile protein synthesis is up regulated (Gopalan *et al.*, 2003; Russell *et al.*; Simpson *et al.*, 1999). Russell and investigators (Russell *et al.*, 2010) have suggested a possible mechanical cross-fiber strain sensor located at the Z-disc. Therefore, whereas myocytes appear to regulate resting sarcomere length, they may also regulate interfibrillar lattice spacing. It is postulated in the present study that 1) cardiac myocytes aim to maintain normal interfibrillar lattice spacing by adding sarcomeres in parallel in response to altered crossfiber stretch and that 2) in combination with normalization of resting sarcomere length, these stimuli can serve to evolve physiological postnatal growth. These postulates were tested in a finite element model of the postnatal rat LV, and model results on cell and chamber level were compared with experimental literature.

Methods

A. Geometrical and Material Model Properties

The initially unloaded stress-free newborn rat LV was represented by a thickwalled truncated ellipsoid (Table 1 and Fig. 1), referred to as model LVINT1 (intact LV). The focal distance C was obtained from a measured LV long to short axis ratio of 1.61 (Lee *et al.*, 1975) and an internal radius of 0.8 mm (Omens *et al.*, 1998) in young rats. The LV dimensions given in table 1 yield a cavity and wall volume of 2.8 and 25.2 microliters, respectively. Fiber orientation was quantified by the fiber angle α with a linear distribution from endocardium to epicardium and was taken from previously performed measurements in the rat (Omens *et al.*, 1993). The material properties of the newborn model consisted of

passive properties only. The strain-energy law W was assumed to be transversely isotropic (Guccione *et al.*, 1991) and slightly compressible (Doll, Schweizerhof, 2000):

$$W = 1/2 C_{\text{pas}} \cdot (e^Q - 1) + C_{\text{comp}} (\det(\mathbf{F}) - 1) \ln(\det(\mathbf{F}))/2 \quad (1)$$

where $\mathbf{F}$ is the deformation gradient tensor and

$$Q = b_f E_{\text{ff}}^2 + b_c (E_{\text{cc}}^2 + E_{\text{rr}}^2 + 2E_{\text{cr}}^2) + b_{\text{fr}} (2E_{\text{fc}}^2 + 2E_{\text{fr}}^2) \quad (2)$$

E_{ff} is strain in the fiber direction, E_{rr} is transmural radial strain transverse to the fiber, E_{cc} is cross-fiber strain perpendicular to the former two, and the remaining are associated shear strains. C_{pas} , C_{comp} , b_f , b_c , and b_{fr} are material parameters, which were also obtained from (Omens *et al.*, 1993) (Table 1).

B. Growth Law

Volumetric growth was modeled by deforming the stress-free tissue configuration B_0 to a grown configuration B_g , which is not necessarily stress-free (Goktepe *et al.*, 2010; Kroon *et al.*, 2009; Rodriguez *et al.*, 1994). The growth model is based on a multiplicative decomposition of the deformation gradient $\mathbf{F}$ (Rodriguez *et al.*, 1994):

$$\mathbf{F} = \mathbf{F}_e \cdot \mathbf{F}_g \quad (3)$$

The growth deformation gradient $\mathbf{F}_g$ applies between B_0 and an intermediate fictitious configuration B'_g . The latter is a stress-free growth state where local kinematic compatibility conditions are not imposed. The deformation gradient $\mathbf{F}_e$ describes the deformation between B'_g and B_g and the Cauchy stress $\boldsymbol{\sigma}(\mathbf{F}_e)$ in the tissue only depends on this elastic deformation ($\mathbf{F}_g$ describes a plastic deformation).

Here, volumetric growth was linearly related to biomechanical stimuli, which are derived from an imbalance in fiber and cross-fiber strain with set point values. The deformation gradient tensors were defined with respect to the local fiber orientation (with component F_{ff} in the fiber direction, component F_{cc} in cross-fiber direction parallel to the wall and F_{rr} the radial component, perpendicular to the two former), which allows for the definition of a transversely isotropic (diagonal) growth tensor. The cumulative growth deformation gradient tensor F_g^n was updated each growth step with the incremental growth deformation gradient tensor $F_{g,i}$ (Kroon *et al.*, 2009):

$$F_g^n = \prod_{i=1}^n F_{g,i} \quad (4)$$

$$F_{g,i,\text{ff}} = (\beta_f (E_{\text{ff}} - E_{\text{ff,set}}) \Delta t + 1) \quad (5)$$

$$F_{g,i,\text{cc}} = (\beta_c (E_{\text{cc}} - E_{\text{cc,set}}) \Delta t + 1)^{1/2} \quad (6)$$

$$F_{g,i,\text{rr}} = F_{g,\text{cc}} \quad (7)$$

Here, $F_{g,i,ff}$ describes incremental growth in the fiber direction due to the addition of sarcomeres in series, whereas for $F_{g,i,cc}$ and $F_{g,i,rr}$ it is assumed that sarcomeres are added equally in parallel in both cross-fiber directions. Because the cellular cross-sectional area increases due to a thickening stimulus, the square root is taken of the growth stretch ratio in cross-fiber directions such that the volumetric growth remains linearly related to the stimulus. β_f and β_c are growth rate constants in fiber and crossfiber direction, respectively and Δt is the time step. The homeostatic set points for fiber and cross-fiber strain ($E_{ff,set}$, $E_{cc,set}$) were chosen to be 0. These set point values are based on 1) hemodynamic load is low in the pre-natal rat heart, which would lead to approximately zero average strains with respect to an unloaded reference state and 2) isolated postnatal rat myocytes normalize resting sarcomere length. Deviation from cross-fiber strain E_{cc} (parallel to the wall) was chosen as a stimulus for cross-fiber growth – and not radial E_{rr} – because of the experimental finding that contractile protein synthesis is up regulated (Gopalan et al., 2003; Russell et al.; Simpson et al., 1999) with passive stretch in crossfiber direction (cross-fiber strain E_{cc} increases in diastole, whereas radial strain E_{rr} decreases).

C. Solution Procedure

1a) The starting state of the rat model was at birth. In the real heart, residual stress is already substantially present in the newborn rat LV: the myocardial opening angle after cutting equatorial slices at birth is about 90° and decreases as the rat ages (Omens *et al.*, 1998). Therefore, in order to obtain a residually stressed starting state, residual stress and strain were introduced in the unloaded, unstressed newborn rat LV (model LV1) by inducing growth in cross-fiber directions throughout the LV by 50% ($F_{g,ff}=1$, $F_{g,cc}=1.5$, $F_{g,rr}=1.5$) in 1000 growth steps, creating model LVINT2. The compatible growth theory proposed by (Rodriguez et al., 1994) predicts that a transmural uniform thickening – as performed here – in a thick-walled cylinder or ellipsoid leads to a positive opening angle with a longitudinal cut in the wall (see step 1c). This also led to a wall thickness and internal radius at the equator of 1.77 and 0.61 mm, which is consistent with extrapolation of measured rat LV dimensions from a 2-week-old rat to a newborn (Omens et al., 1998). Cavity and wall volume were 2.3 and 54 μ liter, respectively. The LV long to short axis ratio was 3.1. In this model – of the residually-stressed newborn LV – values of 7.6 μ m and 21.7 μ m were assigned homogeneously to fiber diameters and lengths, taken from measurements for a 1-day old rat (Anversa et al., 1980). Grown fiber diameters and lengths were obtained by multiplying the initial fiber diameters and lengths with the cumulative growth deformation tensor components $F_{g,cc}$ and $F_{g,ff}$, respectively. The number of sarcomeres in fiber and cross-fiber direction can be obtained by dividing cell length and diameter by unloaded sarcomere length (1.84 μ m)(Rodriguez *et al.*, 1993) and interthick filament spacing (~51 nm)(Irving *et al.*, 2000), respectively.

- 1b) A model (LVCUT1) was created with the same dimensions as in Table 1 in which LV elements were separated along a meridian by adding extra nodes, leading to a “cut” LV. Also in this model, diameters of fibers were grown by 50% (model LVCUT2). Because of the cut and the requirement of compatible deformation, the mesh opened up and opening angle could be determined.
- 2) Model LVINT2, created in step 1a, was inflated in 50 incremental load steps from unloaded to a typical end-diastolic cavity pressure of 1 kPa, uniformly imposed on the endocardium, with the growth law not yet in effect.
- 3) While keeping pressure constant, the growth law was initiated with parameter values listed in Table 2 and the simulation was run for 1620 growth steps, which encompasses approximately the first 25 weeks of a Sprague-Dawley rat.

- 4) For every 15th growth step, the unloaded geometry was obtained by deflating the LV back to zero pressure, with the growth law turned off.
- 5) To obtain the opening angle for the adult LV, the growth deformation gradient tensor solved in step 3 above (for the 1620th growth step), was introduced in the newborn cut model LVCUT2, creating the adult cut model LVCUT3.

D. Numerical Implementation

The axisymmetric LV used for the simulation of maturation consisted of 15 finite elements (5 longitudinal, 3 transmural and 1 circumferential) with cubic Hermite basis functions for all prolate spheroidal coordinates in the transmural (λ) and longitudinal (μ) directions and linear ones for all coordinates in circumferential direction (ϕ). The LV used for the simulation of determination of the opening angle was represented in Cartesian coordinates with the long axis oriented along x and consisted of 60 elements (5 longitudinal, 3 transmural and 4 circumferential) with cubic basis functions for all coordinates. The models were solved with Continuity 6.4b (<http://www.continuity.ucsd.edu>). All simulations were solved on an eight-core Mac Pro with 2.26 GHz 64 bit Intel cores.

The nonlinear finite element models were solved with a modified Newton-Raphson iteration scheme. Integration was performed with $3 \times 3 \times 3$ Gaussian quadrature points. Convergence was reached when both the sum of incremental displacements and the sum of the residuals were lower than 10^{-5} mm and 10^{-8} N, respectively. The Jacobian was calculated and factorized in the first iteration of a new time step and when the solution was diverging. The system of linear equations was solved with Super LU (Li, Demmel, 2003).

Boundary conditions in the intact LV's (prolate spheroidal models) were such that the apex was only allowed to move along the LV long axis, the base was constrained in longitudinal direction, and the epicardium of the base was constrained in circumferential direction. Boundary conditions in the cut LV's (Cartesian models) were such that the base was constrained in longitudinal direction. One of the faces of the cut was constrained in displacement normal to the cut, whereas the epicardium of that face was constrained transmurally.

E. Comparison with experiments

Model validation was performed at two instances in time, at 11 days (t_1 , model LVINT3) and the adult (>25 weeks, t_2 , model LVINT4) and was based on heart and LV weight. To obtain these time instances, first the heart weights m_H of a Sprague-Dawley rat were obtained from (Omens et al., 1998) ($m_H(t_1)=0.2$ g; $m_H(t_2)=1.7$ g). Taking LV to heart weight ratios of 0.67 and 0.75 at t_1 and t_2 , respectively (Lee et al., 1975), LV weights were $m_{LV}=0.13$ g for a 11 days old heart and $m_{LV}=1.27$ g for an adult heart at 25 weeks. The model ventricles with the latter weights are then compared with published experimental results.

F. Summary of LV geometries

A total of 7 rat LV models were either created or solved for. They were:

LVINT1: intact unloaded stress-free newborn LV (Table 1);

LVINT2: intact unloaded residually-stressed newborn LV (with increased wall thickness);

LVINT3: intact loaded residually-stressed LV at 11 days of age;

LVINT4: intact loaded residually-stressed adult LV (25 weeks of age);

LVCUT1: cut unloaded stress-free newborn LV;

LVCUT2: cut unloaded mostly stress-free newborn LV (with increased wall thickness);

LVCUT3: cut unloaded mostly stress-free adult LV (25 weeks of age).

Results

Opening angle

The introduction of 50% homogeneous growth of fiber diameters in the newborn rat LV led to an average opening angle of about 75° . There are no measured opening angles available in the literature in the newborn rat, but the average opening angle in the model is at least within the range of rat opening angles measured in 2-week-old rats (Omens et al., 1998) (Fig. 2A and B). In the adult heart, the opening angle was 21° at the midwall equator, which is about half lower than the average reported measured angles (Fig. 2C and D) (Omens et al., 1998). The model of the adult LV exhibited a longitudinal gradient in opening angle.

Macroscopic LV growth from newborn to adulthood

Cavity volume increased faster than wall volume: cavity volume increased 122-fold whereas wall volume increased by a factor of 21 (Fig. 3). The LV shape became more spherical: the LV cavity long to short axis ratio was 3.3 in the newborn, 1.41 at about 11 days and 1.16 in the adult. This ratio change in Wistar rats also decreases with age, albeit slower: the ratios are 1.61 ± 0.04 and 1.42 ± 0.07 in the 11–12 day and adult rat, respectively (Lee et al., 1975).

The faster increase in LV cavity volume compared with wall volume is also reflected in the faster increase in LV internal radius compared with wall thickness, which is in agreement with experiments (Fig. 4).

Microscopic LV growth from newborn to adulthood

Naturally, the macroscopic changes in LV dimensions are caused by microscopic changes that occur at the lower scales. The fibers throughout the myocardium were increasing in diameter and length, as they are trying to normalize the cross-fiber and fiber strain, imposed on them by the end-diastolic load. Overall, fiber diameter and length changes are also in good qualitative agreement with experiments, with the exception of the reversed transmural gradient in fiber length (Table 3). From newborn to adult, average fiber diameter and length increased 2.3 and 4.6 fold, respectively.

The residual strains caused a transmural gradient of unloaded sarcomere length, with lengths shorter than resting length at the endocardium, and longer lengths at the epicardium in older rats (Fig. 5). This gradient is also in qualitative agreement with measurements (Rodriguez et al., 1993) and ensured a transmural homogeneous distribution of fiber strain at end-diastole (Fig. 5). Cross-fiber strain also became more homogeneous.

Discussion

A novel growth law has been presented, which consists of two growth rules: one for growth in the fiber direction and one for transverse isotropic fiber growth. The growth model was applied in a passively loaded model of the postnatal residually stressed rat LV. Axial fiber growth was driven by an end-diastolic fiber strain stimulus, based on the experimental finding that cells normalize resting sarcomere length. The novelty of the model relates to transverse fiber growth being driven by an end-diastolic cross-fiber strain stimulus, based on the postulation that cells may normalize interfibrillar spacing. For the latter, a stress stimulus has been commonly assumed.

Model validation

The growing LV model reproduced (qualitatively) many experimental results on both the chamber and cellular level, which included increase in cavity and wall dimensions, cellular dimensions and transmural distribution of unloaded sarcomere length.

Whereas the transmural distribution of unloaded sarcomere length – due to residual strain – in the adult rat matched closely with measured distributions (Rodriguez et al., 1993), calculated unloaded sarcomere length in the subendocardium may be too low (1.51–1.66 μm vs. 1.78 μm (average) in model and experiment, respectively). There may be several explanations for this discrepancy, caused by both model assumptions and experimental difficulties. The transmural gradient in unloaded sarcomere length is caused by the homeostatic target value of homogeneous fiber strain at end-diastole, which is reached gradually by the fibers throughout the growth process. Subsequently unloading leads to fiber compression and extension on the endocardium and epicardium, respectively. Cardiac strains have been shown to be sensitive to fiber orientation (Bovendeerd et al., 1992) and since the fiber orientation in the model came from a different study than the study in which unloaded sarcomere lengths were measured, the used fiber orientation may be responsible for this discrepancy. A second model-related probable explanation is that the endocardium in the model is smooth, as opposed to the highly trabeculated endocardium in the real heart, which likely affects the (residual) stress distribution in the subendocardium. Related to the latter point, from the experimental side, it is hard to define the endocardium and thus not straightforward to measure unloaded sarcomere length in this part of the wall: the investigators of Ref. (Rodriguez et al., 1993) reported the largest variation in unloaded sarcomere length occurred near the edges of the specimens, with magnitudes as low as 1.40 μm .

In the adult heart model, the fibers exhibited a transmural gradient in length that was opposite of reported measured values (McCrossan et al., 2004). The model assumption was that in the newborn fiber lengths are distributed homogeneously. In modeling the prenatal LV, Taber and Chabert (Taber, Chabert, 2002) prescribed time-varying growth rate constants and also allowed these to be different between the inner and outer half of the wall. Especially under pressure-overload conditions, fibers in the outer wall grow faster. Differing growth rates and the combination of hypertrophic and hyperplastic before birth may therefore lead to a transmural gradient with longer fiber lengths at the epicardium at birth. Furthermore, the growth rates in the current model were kept constant throughout the simulation, whereas in reality they may vary too over time.

In addition, the model underestimated endocardial and epicardial fiber lengths and diameters at the adult stage compared with the experiments of McCrossan et al (2004), but the average fiber diameter and length from the model were much closer to the average measured ones (Korecky and Rakusan, 1978). The latter experiments used Sprague-Dawley rats, which is what the rat model was based on, whereas McCrossan et al used Wistar rats. Hence there is also a difference between rat types (average diameter 22 micron in Sprague-Dawley vs. 32–33 micron in Wistar, whereas fiber length to diameter also differed between these rat types).

Parameter variation

Emphasis on comparing model results with literature was based on LV weight, thus “filtering out” the effects of time. Therefore, the value for the growth rate constant in the fiber direction (Table 1) was chosen arbitrarily. The value for the growth rate constant in the cross-fiber direction on the other hand was set to be one third of the one in the fiber direction, obtained after a parameter variation of the cross-fiber growth rate constant: this slower fiber thickening led to the result of wall radius exceeding wall thickness at a little

over 2 mm. When both growth ratios were of equal magnitude, the wall radius did not exceed wall thickness. The experimental data on measured LV radius and wall thickness showed some variation, such that wall radius exceeding wall thickness could occur anywhere between about 2 and 2.8 mm. This allows for a faster cross-fiber growth rate constant. A cross-fiber growth rate constant that was 2 times lower than the one in fiber direction, resulted in an average fiber diameter (18.5 micron) that was closer to the experimental value, but the radius exceeding the wall thickness in that case occurred at a little over 3 mm.

It is still unclear, how exactly residual stress is initiated in the newborn LV. In the model, residual stress/strain was introduced by a homogeneous transmural 50% thickening of fibers (which led to a 75° opening angle), but there are multiple means of introducing residual stress/strain. In another simulation, in which residual stress was introduced in the newborn LV by 25% of pure circumferential resorption of tissue however, the structure at the adult stage (diameter and length of fibers, unloaded sarcomere length) were very similar to the presented results. The method in which residual stress was introduced in the newborn rat LV may also explain the underestimation of subsequent LV long to short axis ratios. Another – more physiological – approach to introducing residual stress in a future study, would be to include the prenatal growth of the LV, as Taber and Chabert (2002) carried out.

Model limitations

In the current model implementation, growth will continue indefinitely: the fiber and cross-fiber strains are not able to reach their zero setpoints, because of the constant 1 kPa pressure that is prescribed. Fixed zero set point values were assumed for fiber and crossfiber strain, but likely, in the adult heart, these set points are non-zero (Kroon et al., 2009; Taber, Chabert, 2002). In another simulation, the set points of fiber and crossfiber strain were gradually increased to 0.23 and 0.7, respectively, at the desired maximum LV weight, which halted growth. These non-zero set-points led to slower growth with the same growth rate constants. One can also expect a large interaction between growth rate constants and non-zero set-points, affecting the actual growth rate. A more detailed study though is needed to investigate this and can be used to “tune” the model to experiments: an improved simulation would also include a systolic phase with preload increasing over time (Taber, Chabert, 2002).

It has been shown that myocardial collagen concentration increases with age (Omens et al., 1998). This likely results in an increase of tissue stiffness and thus – with no other changes – would slow down growth with increasing age. The tissue properties of the model were taken from those measured in adult rat (Omens et al., 1993), hence model tissue stiffness in the newborn was likely to be too high. Indeed, in another simulation, in which the passive stress scaling factor C_{pas} (Table 1) was increased over time from 0.367 to 1.1 kPa growth slowed and the magnitude of internal radius passed wall thickness at a higher LV weight value. Using a more microstructural material model would be an interesting future study to investigate more thoroughly remodeling and how it interacts with growth.

The LV was approximated with a truncated ellipsoid and the RV was absent. The loading on the septum from the RV side affects fiber and crossfiber strain in the septum and thus may influence septal growth. Therefore, the results presented here would typically represent LV free wall growth. The quantitative difference between simulation and experiment of LV long to short axis ratio may partially be explained by geometrical simplification.

In this study, normal growth was assumed to be a function of preload only, whereas increased afterload typically leads to concentric hypertrophy (increase of wall thickness). The current approach kept computational demands low: each time step can be considered an

end-diastolic state for a cardiac cycle (in which one cardiac cycle would represent the average over several hours or days), hence it wasn't necessary to compute ~1600 cardiac cycles. From a physiological perspective, a fiber radial growth stimulus based on cross-fiber strain may still play an important role in normal cardiac growth, but may well be associated with other instances in the cardiac cycle.

Consequences for adult cardiac overload

Biomechanical stimuli and neurohumoral factors are the two main triggers of cardiac growth and remodeling (G&R) (Lorenz et al., 2009). Neurohumoral factors and their downstream signaling pathways that mediate cardiac hypertrophy are well known, but the specific biomechanical stimuli that stimulate different modes of ventricular hypertrophy are still poorly understood (Holmes, 2004; Lorenz et al., 2009; Omens, 1998). In ventricular pressure overload due to hypertension or aortic stenosis, concentric hypertrophy is characterized by thickening of the wall associated with cardiac myocyte thickening as sarcomeres are added in parallel (Gerdes, 1992). Following ventricular volume-overload – caused by mitral valve regurgitation or conduction block – eccentric hypertrophy ensues as cardiac myocytes grow axially by adding of sarcomeres in series (Gerdes, 1992) leading to ventricular cavity enlargement that is normally also accompanied by some wall thickening. In the literature, various stimuli have been proposed including those that depend on: fiber strains at different stages in the cardiac cycle (Bupha-Intr et al., 2007; Guterl et al., 2007; Kroon et al., 2009); wall stress (Goktepe et al., 2010; Grossman et al., 1975; Taber, Chabert, 2002); and regional strain-energy distributions (Vena et al., 2008). Of these, it has been shown that strain-based stimuli correlate better with growth than stress-based variables (Guterl et al., 2007; Omens, 1998), whereas Grossman's original hypothesis that hypertrophy is compensatory, maintaining normal cardiac function by normalizing wall stress (Grossman et al., 1975), has been challenged in the last decade (Opie et al., 2006). In cultured rat right ventricular papillary muscles for example, myocyte diameters increased independently of the level of stress with isometric contractions (Guterl et al., 2007). Russell and investigators have suggested a possible mechanical cross-fiber strain sensor located at the Z-disc (Russell et al., 2010). Therefore, it was postulated here that cardiac myocytes may normalize interfibrillar lattice spacing by adding sarcomeres in parallel in response to altered crossfiber stretch. In the current study, it has been shown that a cross-fiber strain stimulus can be used to drive wall thickening, but experiments are needed that will show that interfibrillar spacing changes in response to cross-fiber stretch. Arts et al presented a 0D model of the LV in which cavity enlargement was modulated by end-diastolic fiber strain and wall thickness by fiber shortening (Arts et al., 2005), which also led to physiological growth patterns. Testing a fiber and crossfiber strain-based growth law – as presented here – under different overload conditions in a 3D ventricular model would be an interesting future study.

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Fig. 1. Mesh of the unloaded stress-free newborn rat heart. The two dots indicate the nodes used to calculate internal radius and wall thickness.

Fig. 2. Side (A) and top view (B) of the model of the cut newborn rat LV and side (C) and top view (D) of the cut adult rat LV. In the newborn LV, fiber diameters were grown 50% homogeneously throughout the myocardium, which led to opening up of the wall due to the requirement of compatible deformation such that force equilibrium is satisfied (Rodriguez et al., 1994). LV models of newborn and adult are not shown to true scale.

Fig. 3. Longitudinal cross-sections of the growing rat LV, shown in proportion to each other. The cavity and wall volume increased from 2.3 and 54 μ liter, respectively in the newborn, to 276 μ liter and 1.1 ml, respectively in the adult 25-week-old rat.

Fig. 4. Relationship between (A) internal radius, wall thickness and heart weight from experiments (Omens et al., 1998) and (B) internal radius, wall thickness and LV weight from the current model. The internal radius increased more pronounced compared with wall thickness, qualitatively in agreement with the experiment. In both cases, the internal radius passed wall thickness a little over 2 mm.

Fig. 5. Progression of transmurial distribution of unloaded sarcomere length (A), residual cross-fiber strain (B), fiber strain at end-diastole (C) and cross-fiber strain at end-diastole (D). The gradient in unloaded sarcomere length distribution is caused by residual fiber strain. The horizontal line at a sarcomere length of 1.84 μm in A) is the assumed value of unstressed resting sarcomere length (Rodriguez et al., 1993). Note that sarcomeres are stretched in the newborn rat LV and that most compressive strain is in the cross-fiber direction. The residual strains (A,B) ensure a homogeneous distribution of strains at end-diastole (C,D) in the adult rat.

Table 1

Geometrical and Material Properties of Unloaded Stress-Free Newborn Rat Heart (Model LV1)

Property	Description	Value
C (mm)	Prolate spheroid focal distance	1.0028
λ_{endo} (–)	Radial coordinate of the endocardium	0.7268
λ_{epi} (–)	Radial coordinate of the epicardium	1.4197
μ_{base} (°)	Longitudinal coordinate of the base	120
α_{endo} (°)	Fiber angle on endocardium	53
α_{epi} (°)	Fiber angle on epicardium	–52
C_{pas} (kPa)	Passive stress scaling constant	1.1
b_{f} (–)	Fiber strain coefficient	9.2
b_{c} (–)	Cross-fiber strain coefficient	2.0
b_{fr} (dimensionless)	Shear strain coefficient	3.7
C_{comp} (kPa)	Bulk modulus	350
ρ (g/ml)	Myocardial mass density	1.053

Table 2

Growth Properties

Property	Description	Value
β_f (timestep ⁻¹)	Growth rate constant in fiber direction	0.01
β_c (timestep ⁻¹)	Growth rate constant in cross-fiber direction	0.0033
$E_{ff, \text{set}}$ (–)	Fiber strain homeostatic setpoint	0
$E_{cc, \text{set}}$ (–)	Cross-fiber strain homeostatic setpoint	0

Table 3

Comparison of Cellular Dimensions with Experiments

	Sim $m_{LV}=0.13$ g (± 11 days Sprague-Dawley rat)	Exp 11–12 days	Sim $m_{LV}=1.27$ g (Adult Sprague- Dawley rat)	Exp Adult
Average Diameter (μm)	8.8	8.9* (Anversa <i>et al.</i> , 1980)	17.5	22.2 $\pm$ 0.3 (Korecky, Rakusan, 1978)#
Average Fiber Length (μm)	42	44.0 $\pm$ 3.3 (Anversa <i>et al.</i> , 1980)	103	119.9 $\pm$ 2.2 (Korecky, Rakusan, 1978)#
Fiber length to width ratio (–)	4.8	5.0 (Anversa <i>et al.</i> , 1980)	5.8	5.48 $\pm$ 0.10 (Korecky, Rakusan, 1978) #
Endocardial Fiber Length (μm)	50	-	130	133.0 $\pm$ 2.6 (McCrossan <i>et al.</i> , 2004)\$
Epicardial Fiber Length (μm)	38	-	82	144.1 $\pm$ 2.5 (McCrossan <i>et al.</i> , 2004)\$
Endocardial Fiber Diameter (μm)	9.4	-	21	33.0 $\pm$ 0.9 (McCrossan <i>et al.</i> , 2004)\$
Epicardial Fiber Diameter (μm)	8.3	-	15	31.9 $\pm$ 0.8 (McCrossan <i>et al.</i> , 2004)\$

* Diameter was obtained from cross-sectional area, assuming a circular cross-section; #Experiment with Sprague-Dawley rats; \$Experiment with Wistar rats. Sim = Simulation, Exp = Experiment, μm = micrometer