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CHAPTER 22

A Model Approach to the Adaptation of Cardiac Structure by Mechanical Feedback in the Environment of the Cell

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ABSTRACT

The uniformity of the mechanical load of the cardiac fibers in the wall is maintained by continuous remodeling. In this proposed model the myocyte changes direction in optimizing systolic sarcomere shortening. Early systolic stretch and contractility increases the mass of contractile proteins. Cyclic strain of the myocardial tissue diminishes passive stiffness, resulting in the control of ventricular end–diastolic volume. Utilizing these rules of remodeling in our mathematical model yields that the natural helical pathways of the myocardial fibers in the wall are formed automatically.

INTRODUCTION

The contractile work of the myocardial fibers is converted into pump work during ejection of blood from the cardiac left ventricle (LV). Under normal loading conditions, all myocardial fibers contribute equally to the total pump function [1, 2]. It is, however, yet unclear how this uniformity is preserved, and under what circumstances. Clearly, chronic changes in hemodynamic load affect the structure and shape of the heart [3]. For instance, an increase in aortic pressure causes predominantly an increase in wall mass. An increase in stroke volume is followed by an increase of both wall mass and cavity volume. After return to the original load level, the adaptations are reversible to a large extent. The complicated helical organization of the muscle fibers [4, 5] is maintained throughout these changes of the cardiac mass.

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Here we discuss the mechanism of preservation of the cardiac structure. Obviously, the global cardiac structure may be maintained by a permanent comparison of the current structure with the structure as defined by a reference design. Adaptations of the global structure will be carried out if deviations from the reference are detected. However, such a hypothesis is not attractive, as no biological mechanism is known that senses the global structure of the heart and changes selected parts of the structure.

Alternatively, the mass and shape of the heart may be controlled as an entity by the summed action of many regional control units. Cells can sense mechanical signals. Within their small sphere of influence the various cells may respond by adapting their mass, shape and intra- and extra-cellular structure. The characteristics of the controlling units within the myocardium may be similar everywhere. The summation of controlling actions of the numerous cardiac cells should guarantee preservation of the macroscopic anatomical structure. An attractive aspect of this hypothesis is that the cell is likely to have the tools for such individual cellular controlling actions. Cells can respond to various physical stimuli related to mechanics. Cells have messengers that control the growth and formation of various intra- and extra-cellular structures according to a stored program determined by the type of the cell. The question remains to be solved if a multitude of regional controlling mechanisms can yield stable control of the global structure of the heart.

UNIFORMITY OF REGIONAL MECHANICAL LOAD

Evidence is growing that the systolic mechanical load of the healthy LV is evenly distributed over all myocytes in the heart. In investigating the relation between the mechanics of the LV and the coronary perfusion, mechanical stresses within the LV were estimated [6, 7]. In this mathematical model, the equatorial region was simulated by a thick-walled cylinder, having helical structures of myocardial fibers inside. Mechanical load of the myocardium was assumed to be uniformly distributed. Consequently the relation between the torsional motion and volume decrease of the LV was predicted to be unique. This predicted relation was found to be in close agreement with the data in the open chest dog [8] and in the closed chest dog under normal hemodynamic load [9].

More recently it was investigated whether this relation may also hold under a wide variety of hemodynamic load conditions. Radiopaque markers were attached to the LV free wall and septal wall in an open chest dog preparation [10]. Preload, afterload and contractility were varied over a wide range. The relation between torsion and the logarithm of cavity volume was almost linear in each experiment. The slope of this relation (-0.173 ± 0.028; mean $\pm$ sd; n = 38) was close to the model prediction, as based on the mechanics of a cylindrical LV wall segment (-0.194 ± 0.026).

The LV transmural differences in coronary perfusion, metabolic activity, and mechanical load are likely to be small [2]. The reported vulnerability of the subendocardial layers to coronary artery stenosis can be fully attributed to the fact that the decrease of coronary perfusion in the subendocardial layers is more prominent than in the subepicardial layers. In the normal LV, the differences in coronary perfusion are small between the subendocardial and subepicardial layers, as well as between different regions of the LV wall [11, 12]. Coronary flow may become more inhomogeneous on a smaller scale because of the fractal character of the flow distribution [13].

The mechanical load appears to be maintained by adaptation of the cardiac structures. After a chronic increase of hemodynamic load, the mass of the myocardium increases. An increase in aortic pressure causes an increase in wall mass, while cavity volume remains practically the same (concentric hypertrophy) [14-16]. An increase in

aortic flow with constant systolic aortic pressure causes an increase of both wall mass and cavity volume (eccentric hypertrophy). Fiber stress (σ_f) and natural fiber shortening ($\varepsilon_f = \ln[l/l_{ref}]$) in the LV wall may be calculated from the LV pressure (P_{lv}), cavity volume (V_{lv}) and wall volume (V_{wall}) by the following relations [17]:

$$\sigma_f = P_{lv}(1 + 3V_{lv} / V_{wall}) \qquad \varepsilon_f = 1/3 \; \Delta\ln(1 + 3V_{lv} / V_{wall}) \qquad (1)$$

After chronic adaptation, the calculated peak fiber stress and systolic fiber shortening appear to be similar ($\approx$37 kPa and 0.15, respectively) for different states of the hemodynamic load. The adaptations to changes in hemodynamic load are reversible to a large extent [18]. Cardiac mass returns to about normal after surgical repair of cardiac valve defects [19, 20]. The complicated helical organization of the muscle fibers [4, 5] is maintained during these changes in cardiac mass.

HYPOTHESIS ON REGIONAL CONTROL OF MECHANICAL LOAD

It is commonly accepted that the mechanical load is similar in the various regions of the normal heart. Furthermore, adaptations to chronic changes in hemodynamic load are aimed to maintain this situation. The question is how this uniformity of load is maintained. Several conditions should be satisfied when formulating a hypothesis on the control mechanism. The proposed mechanism should have a physiological basis. Cells are the basis of the cardiac structure. After a change in hemodynamic load the structure of the heart adapts. This adaptation is the summed effect of many changes on the small scale of the individual cells. Each cell acquires signals from the regional sphere of influence. They process these signals, and take appropriate action, resulting in regional adaptations. The summed effect of these adaptations should result in a stable control of the structure of the whole heart.

Because the main function of the myocardium is mechanical, feedback is postulated to be mediated by mechanical parameters too. The cardiac myocyte perceives a cardiac contraction as a sequence of events and actions (Fig. 1). The myocyte is stretched in diastole. Electrical depolarization is the first signal of an upcoming contraction. The cell develops force. This phase is critical. If the myocyte is activated relatively late or is not contracting as strongly as the cells in the environment, the myocyte will be stretched before contraction [21]. The myocyte shortens during the ejection phase. Note that the amount of

filling/rest
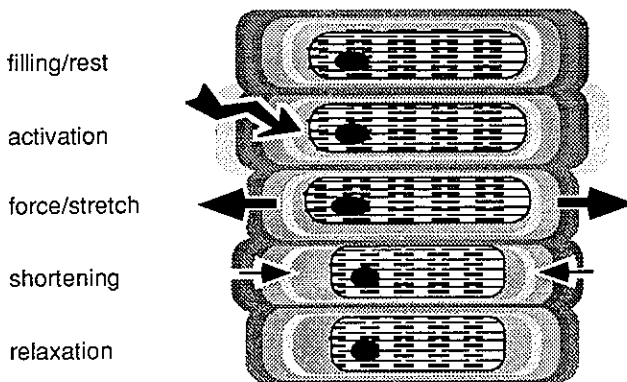
activation

force/stretch

shortening

relaxation

Figure 1. Sequence of events and actions as sensed by the cardiac myocyte.

shortening is mainly determined by the gross deformation of the tissue, because the force of a single cell is insufficient to significantly affect gross deformation of the tissue. During relaxation, force may decline asynchronously, causing transients in deformation. For instance, in the presence of ischemia, severe deformations may occur around the ischemic region.

The most relevant mechano–feedback signals are likely to be related to deformation (see also the contribution by Dr. Reneman in this Volume). In this respect, stress is likely to be of less importance [3]. Stretch is quantified by the maximum value of sarcomere length that occurs during the cardiac cycle. Stretch is likely to be involved in the control of cellular growth [22, 23]. Stretching of cardiac myocytes causes immediate expression of the proto–oncogene c–fos, the amount of which depends on the degree and duration of stretching [24]. Besides, other transcription factors, like c–jun and c–myc, are also induced rapidly [25]. The expression of proto–oncogenes may induce cell growth, as indicated by the finding that stretch enhances nuclear RNA labeling and translation of genes, such as skeletal α–actin, atrial natriuretic factor, and β–myosin heavy chain [25, 26]. Stretch induces ion transport through the cell membrane [27], but the role of this pathway in growth is subject to discussion [28]. Contractile activity also accelerates growth of cardiac myocytes [29], indicating that in addition to stretch, fiber shortening (strain) and/or contractility may also regulate cardiac growth. The fibroblast is also affected by stretch, causing enhancement of collagen expression [30]. The expression of collagen [31–34] and fibronectin [32, 35] is enhanced inn the early phase of adaptation to pressure overload.

Many indications can be found for the presence of control mechanisms acting in the cellular environment, in which mechanical load is involved. For instance, sarcomere length which is defined as the repetition length of the cross–striations of cardiac muscle, is controlled to approximately 1.95 μm for the unstressed LV [36, 37]. The regional character of adaptation of the cardiac tissue mass to mechanical load is also indicated during asynchronous electrical activation of the ventricle caused by pacing or conduction blockade of the left bundle branch, when regional differences in mechanical load and coronary perfusion are found [11, 38]. Tissue mass decreases selectively in those regions where load is relatively low [39].

DESIGN OF THE MODEL

The above mentioned cellular abilities for sensing of mechanical signals have been used to design a model for the regional feedback system (Fig. 2). The myocytes form the force generating structure. Orientation and mass of the myocytes are controlled by myocyte shortening, early systolic stretch, and more global signals related to contractility. The passive elastic structures are extremely important for the diastolic filling of the LV. The extra–cellular matrix of collagen fibers is formed and controlled by fibroblasts. The cooperation of both the active and the passive controlling structures is responsible for regional control of the mechanical structures. The input and output signals for control are active in the sphere of influence of the separate cardiac cells.

Fiber direction is controlled by the amount of sarcomere shortening during the ejection phase. In our model, the myocyte "looks" for an optimum shortening of 15% by trial and error. The frequency of trials for new directions increases the further the myocyte operates from the optimum. The mass of the myocyte is controlled by stretch and global contractility. Generally, stretch occurs in the early phase of systole. Large early systolic stretch is a strong stimulus for mass increase of the myocyte. Another stimulus to growth is related to contractility. If the mass of the LV is too low for a given stroke volume, blood
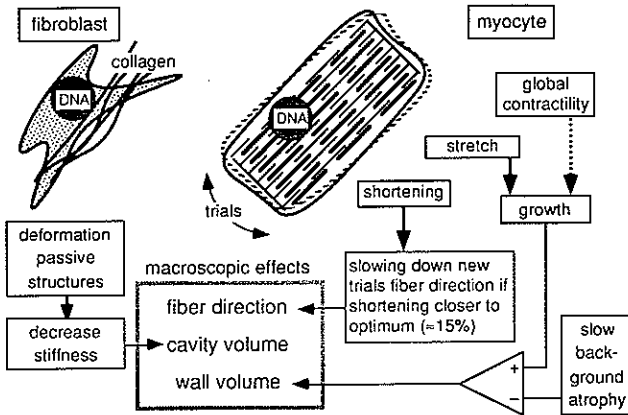
Figure 2. Model of the controlling system for adaptation of the mechanical structures to mechanical load, acting in the cellular sphere of influence. The myocyte controls mass and fiber direction on the basis of the input signals systolic sarcomere shortening, early systolic sarcomere stretch and global stimuli to increase contractility. The passive collagen structures are expected to become more compliant when the amount of cyclic deformation is above normal.

pressure is maintained by the control system for systemic blood pressure. The heart receives various physiological stimuli to increase work. Sympatic stimuli may increase the heart rate and contractility. Also, hormonal stimuli may be of importance. The point is that the heart is subjected to a chronic stimulus to increase its pump work. This stimulus is thought to have a relatively small but important mass increasing effect.

The collagen structure of the myocardial wall is subject to continuous deformation. If the span of cyclic deformation increases, the collagen structure is assumed to weaken. Thus, on the small scale of the cellular environment, the passive structures are thought to be more compliant in regions of large deformation like in the subendocardial layers. On the global scale, a large ejection fraction is a stimulus to make the ventricle more compliant. Given a fixed stroke volume, the resulting ventricular dilatation causes a decrease of the ejection fraction.

IMPLEMENTATION IN A MODEL OF CARDIAC MECHANICS

The myocardial elements defined in Fig. 2 were incorporated in a model of the mechanics of the equatorial region of the LV. This part of the LV was assumed to be cylindrical [1, 3]. The thick-walled cylinder was composed of 10–1500 concentric cylinders. Fiber orientation varied across the wall. Deformation was determined by equilibria of forces and torques acting on the short axis cross-section of the LV wall. Calculated deformation was converted to the input signals for regional load control. Mass and direction of the myocytes, and compliance of the passive structures, were adapted according to the proposed control mechanism. Deformation of the thus remodeled LV equatorial region has been calculated again, and a new calculation cycle has been performed.

Required LV pump load was defined by a given stroke volume and systolic cavity pressure. Initially, the transmural course of fiber orientation was simplified to two layers. The fibers in the subendocardial half were arranged according to a right handed helix with

a pitch angle of 40°. A left handed helix arrangement was used in the subepicardial half with the same, but opposite, pitch angle.

RESULTS

Using the model of LV remodeling, a natural [4] transmural course of fiber orientation automatically formed after about 200 calculation cycles (Fig. 3). The final solution appeared to be practically independent of the initially chosen distribution of fiber direction, as long as the primary helix structures could be recognized. Sarcomere shortening approached, but did not quite reach, the target value as set by the control mechanism related to myocyte direction. The solution oscillated around this value in a relatively narrow range. The variations in sarcomere length are followed by similar variations in fiber stress.
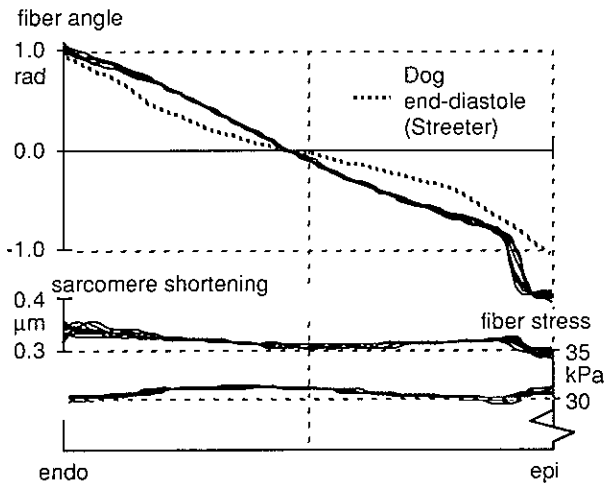

Figure 3. Transmural course of fiber direction, sarcomere shortening and fiber stress in a cylindrical model of LV mechanics. The distributions were obtained using the adaptation mechanism shown in Fig. 2. Changes in sarcomere length are to be referred to an end–diastolic length of 2.1 μm. The broken line indicates experimental results [4].

Adaptation to an Increase in Stroke Volume

Starting from the control state, stroke volume was doubled in the simulation (Fig. 4). The ejection fraction increased because the heart had to pump a larger stroke volume. The related larger deformation caused an immediate stimulus for dilatation of the cavity. Also, because of a mismatch of sarcomere shortening, more trials were performed to find a more optimal fiber direction. Contractility was above normal because the weight of the LV was low for the delivered stroke work. As a result, there was a stimulus to increase wall volume by growth. During this increase, part of the dilatation effect was reverted. Both weight and cavity volume were increased proportionally after stabilization to the new state.
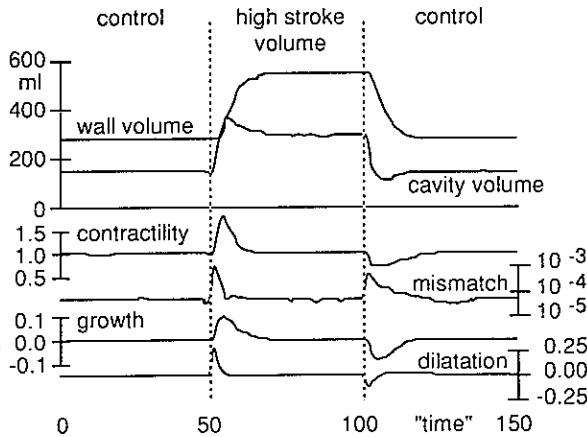
Figure 4. Time course of LV adaptation to an increase in volume load, followed by reversion to original loading condition. After the invoked change in stroke volume signals appear of dilatation and of increased mismatch with optimum shortening. Both stroke volume and contractility increase. Consequently wall mass increases steadily. After reversion of the load, most signal changes are approximately opposite.

DISCUSSION

The present study investigated whether the global structure of the heart could be controlled by a mechanism of distributed controlling actions. In a thick–walled cylinder, each shell represented such a control unit. The myocyte (Fig. 2) changed direction to optimize the amount of sarcomere shortening during the ejection phase. Early systolic stretch of the myocyte, and to a lesser extent stimuli for enhanced contractility, were assumed to increase the mass of the contractile proteins. Apart from the active myocytes, the passive elastic structures were also controlled by deformation signals. A large deformation was considered to weaken the strength of these structures.

Applying the program of regional control to the cylindrical shells in the model, a stable global fiber structure formed automatically. This rather complicated structure of helical fiber pathways is close to what is found in anatomical studies (Fig. 3). Furthermore, mass and geometry of the LV changed after a change in hemodynamic load. These changes were so that mechanical load of the myocytes was preserved in all regions. The observed changes of the geometry of the cavity and wall agreed with physiological findings on cardiac hypertrophy.

The proposed mechanism of control is attractive because several of its characteristics (Fig. 2) were indeed found to exist. The importance of stretch and contractility as stimuli to growth is consistent with molecular biological findings. So, stretch and contraction of cardiomyocytes are clearly involved in mechanical signaling and protein synthesis. The possibility to use trials as a tool to optimize fiber direction is indicated by a dispersion of myocyte direction of a few degrees. Furthermore, the limited length of the cardiac myocytes ($\approx$120 µm) allows the cell to change its direction. Such optimization of cellular orientation can also be understood as slowing down continuous search if conditions are more optimal. Statistically, each myocyte spends most time in the more optimal direction.

As suggested by Janicki [40], adaptation to an increase in the volume load involves a temporary phase of enhanced collagenase. This finding is consistent with our simulation

shown in Fig. 4. The increase of volume load is followed by a stimulus to decrease passive ventricular stiffness, as evident by the positive peak in the dilatation signal. This signal parallels collagenase. It represents the average decrease in stiffness, as shown in Fig. 2. After adaptation to the new loading state, the LV is scaled up to a larger size, while regional cyclic deformation is returned to normal. Because the mechanical properties of the tissue are mainly controlled by deformation, the tissue composition also returns to normal after reaching steady state. It has been reported [41] that the ventricular cavity becomes smaller during cardiac assist by volume unloading. According to the simulation in Fig. 4, the decrease of volume load is followed immediately by a decrease of end–diastolic cavity volume, before mass of the LV decreases significantly. This decrease is accompanied by a stimulus to increase ventricular passive stiffness. Using our hypothesis on remodeling, a cardiac assist procedure should preferably be directed to unload pressure rather than volume. Larger volume changes keep the ventricle more compliant. The end–diastolic pressure is then expected to stay at a lower level.

Interestingly, feedback through regionally sensed fiber stress is not a compelling condition. At a closer look, this is not surprising. No stress sensors are presently known. Generally, force or stress is detected by measuring deformation of a compliant structure. Another indication is given by the development of the chicken embryonic heart. The heart starts beating very early in the phase of development, and then LV systolic pressure is as low as a few mmHg [42], because the density of contractile proteins in the tissue is still very low. Evidently, cardiac structures are already forming in this phase. Deformation seems to be the most likely candidate for control of structure formation, because the level of cyclic deformation of this heart is already quite close to normal.

Indirectly, stress affects cardiac growth. For instance, if afterload increases, wall stress increases to above normal. Unless some precautions are taken, the stroke volume would diminish, causing systemic perfusion to be inadequate. As a result, systemic blood pressure control stimulates the heart to do more work. This physiological stimulus, or the related effects, are likely to be a factor in stimulating the synthesis of contractile proteins.

CONCLUSIONS

Adaptation of the tissue to mechanical load is postulated to be invoked by various deformation parameters. Using a thick–walled cylindrical model of LV mechanics yields that fiber direction changes to optimize sarcomere shortening. Early systolic stretch, and the physiological stimulus to increase cardiac work, increase cardiac mass. The stiffness of the passive structures diminishes with deformation. Beginning with a primitive design of the helical fiber structures in the LV, the distributed control system arranges the fibers automatically to a macroscopic structure, resembling the fiber structure of the true LV. Also, mechanical load is quite evenly distributed over the myocardial structures. The assumptions used for the properties of the regional mechano–feedback are in compliance with studies on mechano–transduction.

DISCUSSION

Dr. H.E.D.J. ter Keurs: When the heart and cardiac cells hypertrophy there are two different modalities: concentric hypertrophy and volumetric hypertrophy in response to volume overload. Various studies, including among others Cooper's group [Mann *et al. Circ Res.* 1989;64:1079–1090], have shown that you get two different kinds of responses of the cardiac myocyte. During concentric hypertrophy the myocytes show a large increase in cross sectional diameter and a much

smaller increase in length. This is in contrast to the eccentric hypertrophy where the cardiac cell adds more sarcomeres in series and thereby grows longer, leading to an increase of volume of the heart. It seems to me that in order to describe that you need the information so as to choose between adding more myofibrils in parallel or adding more sarcomeres in series within the myofibrils. I did not see how your model could do that.

Dr. T. Arts: We defined hypertrophy as an increase in wall mass. We did not distinguish between different kinds of hypertrophy. The findings of Cooper's group indicate that the design of the model needs more details. Maybe feedback signals should be introduced which can distinguish between elevated volume load and elevated pressure load. Such distinctions can be made locally. At increased volume load the cells are subject to more stretch and more shortening. At increased pressure load, shortening may diminish due to dilatation. So, the cell can locally obtain information about the type of external load.

Dr. H.E.D.J. ter Keurs: I would like to make a suggestion with respect to that, based on observations that we made. If you transplant a heart from one rat heterotopically into an identical recipient, which means that the heart now is not sensitive to hemodynamic conditions, and you test whether sympathetic drive causes hypertrophy, then you find that isoproterenol injections in the recipient of that transplant cause substantial hypertrophy in the recipient's heart but not in the donor heart. That means that calling the sympathetic system into action may be correct but may also be incorrect. An alternative hypothesis for what you have called contractility may be that the heart senses stress development by the contractile filaments and may use that to tell the local "factory" to build more myofilaments in parallel.

Dr. T. Arts: Maybe I did not emphasize clearly that stress itself is not a factor which induces hypertrophy. The present model is based on sensing deformation. I am not so sure if there is a stress sensor active in the heart. I do not know how it would be built. From the chicken embryo it is known that the heart starts beating when systolic pressure is only 2.5 mmHg, and remodeling seems to be already active. The structure of the chicken embryo heart is already present in a very early stage. In a later stage, the cells become more densely filled with myofilaments, causing the pressure to increase. I cannot easily understand how a stress sensor would change its sensitivity by a factor of 100. However, if deformation is sensed, this embryo development can be understood. Also, if we measure force or stress, we always convert stress to deformation, and we measure this deformation. So, deformation is more likely to be the primary sensed signal.

Dr. H.E.D.J. ter Keurs: Stressing cardiac muscle costs – ATP. So if you measure ATP fluxes you can convert that into a drive for hypertrophy [Meerson and Pomoinstsky. *J Mol Cell Cardiol.* 1972;4:571].

Dr. T. Arts: I agree.

Dr. P. Hunter: Your adapted fiber orientation had an interesting blip at the epicardial end, a sudden dive. I wonder whether that indicates that you should be putting into the model a distribution of more collagen content which adds an extra strengthening effect at the epicardial layer. A second question is: the fiber distribution in the septum is substantially different from the free wall and I think that your model is describing the behavior of the free wall. But it is an interesting study to explain why the septum develops as it does.

Dr. T. Arts: Both questions are strongly related. We have made a huge simplification in using a cylindrical model. The real heart is asymmetric due to the attachment of the right ventricle. This right ventricle normally counteracts torsion. Thus, the real deformation pattern is not rotational symmetric as it is in the model. The dip of the transmural course of the fiber angle just below the epicardium is caused by the presence of a forbidden zone, where optimum shortening cannot be reached. If you add more dispersion of the fiber angle or change values of the feedback parameters,

this dip may become less distinct or even disappear. I have to add that changing parameter values is not critical. The results may change somewhat, but not essentially. Stability of the structure is maintained even if you change the feedback parameter values over a range of a factor of 100.

Dr. Y. Lanir: Do you assume that the collagen becomes weaker when the LV expands?

Dr. T. Arts: In our opinion the LV undergoes a large cyclic deformation, if the range of strain is about 30%.

Dr. Y. Lanir: We have learned from Dr. Janicki that this is perhaps true in a short time scale, but after a while there is new synthesis of collagen which actually tends to increase the concentration of collagen. This may be a problem here.

Dr. T. Arts: No. In the case of volume hypertrophy there is no problem. If the heart is too light then it will adapt first. After stabilization the pressure is back to normal, and deformation is also back to normal. The remodeling signals are back to normal, and the structure may also be back to normal. Both the cavity and the wall volume are scaled up by the same factor. We should note, however, that this statement is not perfectly true. Back to normal should be interpreted to occur only approximately.

Dr. Y. Lanir: You had torsion in your model, so your model must distinguish between collagen that is parallel to the fibers and the one that is transverse to it. Do you include them as one compartment in your feedback mechanism, or do you distinguish between them?

Dr. T. Arts: We did not go into these details. If you really want to know the effects of cross deformation and stiffness, you should work with a model description in three dimensions. Then you also need big computational power.

Dr. J. Bassingthwaighte: I have a question on your modeling strategy. In your model you had reference points, and I know that there are no real reference points. You do not have feedback relative to some magic reference anywhere in the body. Those things do not exist. But you have reference points in your model.

Dr. T. Arts: I put in a reference setting of shortening of 12%, but it may not be correct.

Dr. J. Bassingthwaighte: So let me assume it is not correct. What will you do to replace that reference and what kind of strategy would you go about using to get rid of this obnoxious reference? Most reference points are more or less present in nature and they are defined by a multitude of nonlinear equations. They behave like reference, but not completely so. It is a cooperation of a complicated system which goes down to the cells. This would be a way to describe such a behavior macroscopically.

Dr. R. Beyar: When you have hypertrophy adapted to pressure overload, you have a thicker wall and you may need more twist to equilibrate between endocardium and epicardium strains. Do you get more twist in your model results? It has not been observed, to my knowledge, that hypertrophied hearts twist more. With MRI, we have looked at patients with hypertrophic cardiomyopathy. There was noise there but we could not say whether it increases, does not increase, or stays the same. That is one way to check the model experimentally and it might be that the heart can not adapt to an increase in the twist.

Dr. T. Arts: That might be true in a cardiomyopathic heart. In the hearts of different dogs under many different loading conditions we found a similar relation between torsion and normalized volume. We did not include hypertrophic hearts in our study. For those hearts there may be a difference.

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