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Viscoelastic properties of the papillary muscle: experimental and theoretical study

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It is well known that the structure of biological tissue is closely related to tissue functions and defines its viscoelastic properties. It is necessary to create a model combining structural organization of myocardium and its viscoelastic properties to develop a model of cardiac wall of intact or deceased heart. This paper is devoted to experimental and theoretical study of viscoelastic behavior of isolated myocardial samples. A three-dimensional structural-functional model of papillary muscle is presented. The model adequately describes nonlinear viscoelastic behavior of isolated papillary muscles under uniaxial strain both in static condition and under dynamic loading.

Key words: *viscoelastic properties, myocardium, collagen structure, modelling*

1. Introduction

It is well known that viscoelastic properties of cardiac tissues play a crucial role in the heart function maintenance. Passive tension is an important factor in cardiac muscle mechanics because it determines the extent of filling of the heart and its subsequent stroke volume [1]. It is also important in the contracting myocardium because it has been shown that shortening velocity of cardiomyocytes depends on the passive tension [2]. The main sources of passive tension in myocardium are extracellular connective tissue matrix (ECM) and cardiac myocytes [3]. Thus quantification of the contribution of myocytes and connective tissue matrix in myocardium viscoelastic properties is an important problem.

Like other biological tissues, myocardium exhibits a highly complex nonlinear mechanical behavior which includes active, quasi-incompressible, fibre-reinforced, viscoelastic and hyperelastic behavior [4]. Therefore, it should be assessed as composite anisotropic medium. The spatial organization of biological tissues largely determines the functions performed by these tissues, as well as their viscoelastic properties. Also it is important to consider modular structure of the tissue (modulus is the simple morphofunctional unit of the tissue) [5], [6]. Development of mathematical models relating to the structural organization of the cardiac wall tissue and its viscoelastic properties allows us to study transformations of the heart both in normal development and various diseases. To build such a model it is necessary to create a model of morphofunctional unit – fasciculum of the myocardium.

Although some mathematical models of cardiac muscle have been developed in recent years [7]–[10], there is no model that relates geometry changing and viscoelastic properties of the fascicle over the entire range of physiological strains. Thus the goal of our work is to experimentally study viscoelastic properties of isolated myocardial sample and develop and validate the mathematical model of myocardial fascicle taking the changes of structural organization under different strains into account. It should be noted that isolation of fascicle from the ventricular wall is a dif-

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ficult task due to inability to educe fascicle without damaging its structure. On the contrary the papillary muscle could easily be isolated. In papillary muscle as well as in fascicle cardiomyocytes are practically oriented in parallel direction [11]. Therefore we used rat papillary muscles in our study.

2. Materials and methods

2.1. Experimental protocol

Rat right ventricular papillary muscles of ~2500 μm in length, ~400 μm in diameter with practically cylindrical shape were used. Animals were treated according to the Principles of Laboratory Animal Care of the National Society for Medical Research and the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institute of Immunology and Physiology of Ural Branch of RAS Animal Ethics Committee. Before the experiment the animals were introduced with heparin (0.3 ml/kg) to prevent the formation of blood clots in the coronary vessels. Rats were instantaneously killed by cervical dislocation and hearts were quickly excised. Isolated hearts were placed in solution containing (in mM): NaCl 118.5, KCl 4.2, $MgSO_4 \cdot 7H_2O$ 1.2, $NaHCO_3$ 14.5, KH_2PO_4 1.2, $CaCl_2$ 2.5, glucose 11.1, buffered to pH = 7.35 and bubbled with O_2. 2,3-butanedione monoxime (BDM, 30 mM) was used to avoid myocardial damage when small muscle preparations were isolated from the hearts [12]. Papillary muscles were excised from the right ventricle after 5–10 minutes of BDM treatment and placed in temperature-controlled bath (25 °C). One end of the muscle strip was tied to the stock of the force transducer and the second end to the rod of the length servomotor. Before starting the experiment a papillary muscle had been electrically stimulated in normal solution within ~60 minutes until steady-state contractility was reached and BDM removed.

After establishing steady-state contractility we determined two control lengths: L_0 and L_{max}. Length L_0 corresponds to zero-level of passive tension of the papillary muscle. Length L_{max} corresponds to maximum active tension of the muscle. Then we assessed functional condition of the papillary muscle. It was stretched until L_{max} and released to so called "work" length that was approximately equal to 0.95 L_{max}. Subsequently we calculated relation between passive tension (F_p) and active tension (F_A) provided that $F_p/F_A \leq 0.10$. Higher value of the relation F_p/F_A suggested that the muscle was damaged and it was excluded from the analysis.

Next electrical stimulation was switched off and the length–force relationship of passive muscle was assessed. The muscles were stretched from slack length L_0 to L_{max} with a constant rate of 0.5 μm/s. Then the muscle returned to L_0 and we recorded the force relaxation in response to stepwise stretching with increment equal to 2% of L_0 (figure 1a). Each subsequent deformation was carried out by the length servomotor after disappearance of evident relaxation of passive tension in response to previous deformation. To avoid hypoxic contracture electrical stimulation was repeated from time to time during the whole experiment.

Tests were conducted initially in normal solution and then preparations were treated with 1% sodium dodecylsulfate solution (SDS) which can remove the cardiomyocytes for 60 minutes according to methods [13]. After SDS treatment the tests were repeated with the same experimental protocol to obtain viscoelastic properties of connective tissue sample.

We carried out a statistical analysis of experimental results: control group of $N = 15$ muscles, SDS-group of $N = 10$. Statistical significance was verified by a mean at a confidence interval of 95%. Significant differences were tested by Mann–Whitney's U-test.

2.2. Experimental results

Experimental data showed that the same increment of the strain at different lengths of the muscle can lead to difference in the magnitude of impact tension – instantaneous response to stepwise stretching, and difference in tension relaxation time. It is important to note that in the experiments we measured real forces (not tensions) developed by the muscles. Then, we normalized the forces to the initial cross-section area of the corresponding muscle. The value of cross-section area was calculated as $S = \pi d^2/4$, where d is the diameter of the muscle. That value of the cross-section area was also used in validating the model. The deformation was defined as $\varepsilon = (L - L_0)/L_0$, where L_0 is the muscle slack length (see experimental protocol), L is the current length of the muscle. We observed nonlinear dependencies both in the case of steady-state stress–strain relation and the dynamics of the viscoelastic properties of papillary muscles (figure 1b).

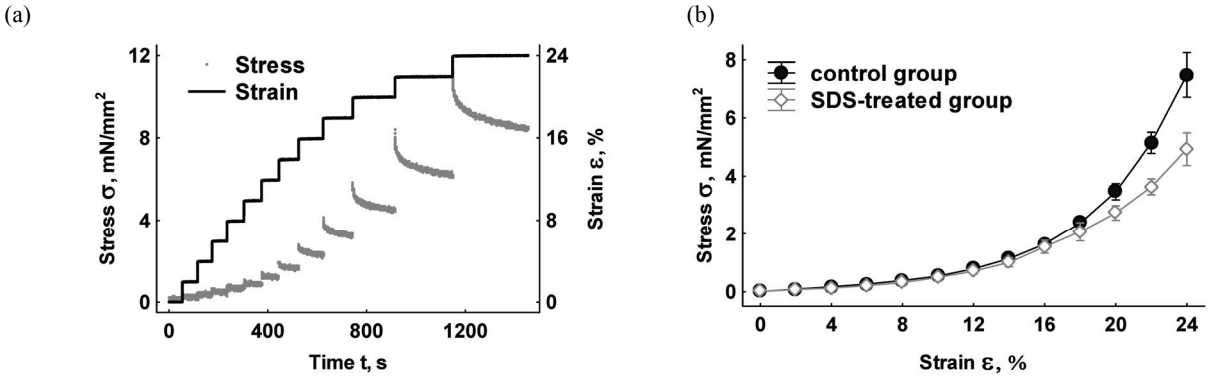

Fig. 1. (a) Representative example of stress relaxation data of rat papillary muscle in response to stepwise stretching with increment 2% of L_0. Grey circles – passive tension, left scale; solid black line – strain rate, right scale; (b) experimental stress–strain relation of papillary muscle: black circles – control group, grey diamonds – SDS treated group

We conclude that viscoelastic properties of papillary muscles of control group and muscles of SDS-group are quantitatively different. Nevertheless the form of nonlinearity is maintained in both groups. In SDS muscles the maximal decrease in elasticity was observed at 20% strain. In our experiments it has been shown that SDS treatment also leads to a decrease in viscosity all over the range of strains being analyzed.

2.3. Mathematical simulations

As described above papillary muscles demonstrate nonlinear viscoelastic properties. As shown by other authors these properties cannot be described using only linear combinations of Hook's springs and Newton's damping elements with constant coefficients of elasticity and viscosity [4], [14], [15]. Nevertheless, it is known that during deformation of living tissue its geometry transforms. Namely, the cross-section area decreases upon stretching and increases upon shortening. In an earlier study of our coworkers it was shown that linear elastic and viscous units combined in specific geometry might possess nonlinear response to strain at geometry changing [16]. That concept became the basis of our model of myocardial fascicle. The model is a centrally symmetrical construction consisting of longitudinal and transverse elastic elements, inclined viscoelastic elements and incompressible butt elements connected pivotally without friction. The masses of the elements are not taken into account. The geometry of the model is similar to the geometry of papillary muscle. Experimentally measured slack length and diameter of papillary muscle were used as initial geometrical parameters to verify the model.

Lengths of each element of the model can be found from equilibrium condition of elastic and viscous forces at the model junctions (see figure 3).

$$\vec{F}_1 + \vec{F}_2 + \vec{F}_3 + \vec{F}_4 = 0\,. \tag{1}$$

Equation (1) in X, Y, Z components is shown below:

$$\begin{aligned} &Ox: F_2 - F_1 \cdot \cos\alpha = 0, \\ &Oy: F_1 \cdot \sin\alpha \cdot \cos\beta - F_3 = 0, \\ &Oz: F_1 \cdot \sin\alpha \cdot \sin\beta - F_4 = 0. \end{aligned} \tag{2}$$

where F_1, F_2, F_3, F_4 are the modules of the corresponding forces.

A relation between the lengths of each element of the model and the whole length of the model is expressed by the equation below:

$$(l_3 - h_3)^2 + (l_4 - h_4)^2 + (L - l_2)^2 = 4 \cdot l_1^2\,. \tag{3}$$

From equations (2) and (3) it follows that:

$$\begin{aligned} \cos\alpha &= \frac{L - l_2}{2 \cdot l_1}, \\ \sin\alpha &= \frac{\sqrt{(l_3 - h_3)^2 + (l_4 - h_4)^2}}{2 \cdot l_1}, \\ \cos\beta &= \frac{l_3 - h_3}{\sqrt{(l_3 - h_3)^2 + (l_4 - h_4)^2}}, \\ \sin\beta &= \frac{l_4 - h_4}{\sqrt{(l_3 - h_3)^2 + (l_4 - h_4)^2}}. \end{aligned} \tag{4}$$

Using equations (2), (3), (4) we get the system of equations that describes viscoelastic behavior of the model:

$$\begin{cases} 2\cdot l_1\cdot F_2-(L-l_2)\cdot F_1=0, \\ 2\cdot l_1\cdot F_3-(l_3-h_3)\cdot F_1=0, \\ 2\cdot l_1\cdot F_4-(l_4-h_4)\cdot F_1=0, \\ (l_3-h_3)^2+(l_4-h_4)^2+(L-l_2)^2=4\cdot l_1^2, \end{cases}$$

$$F_1=k_1\cdot(l_1-l_{10})+\eta_1\frac{d}{dt}l_1,$$

$$\text{where}\quad \begin{aligned} F_2&=k_2\cdot(l_2-l_{20}), \\ F_3&=k_3\cdot(l_{30}-l_3), \\ F_4&=k_4\cdot(l_{40}-l_4). \end{aligned} \qquad (5)$$

It is well known that protein titin is the main source of passive tension of cardiac myocytes [17]. Therefore it is reasonable to include a structure simulating titin in our model of morphofunctional unit of the myocardium. Elastic behavior of titin molecule is described by a worm-like chain (WLC) model [18]–[20]. The "WLC-model" sets the force–strain relation of a single titin molecule by the equation:

$$f_{\mathrm{WLC}}=\frac{kT}{A}\cdot\left[\frac{1}{4\cdot\left(1-\frac{z}{L}\right)^2}-\frac{1}{4}+\frac{z}{L}\right] \qquad (6)$$

where:

k – Boltzmann constant,
T – absolute temperature,
A – the persistence length,
z – end-to-end length,
L – chain contour length.

"WLC-model" is a spring providing elastic force under strain according to equation (6).

It should be noted that WLC-model is a microscopic model but we simulated macroscopic object like papillary muscle. Therefore we used a certain analog of "WLC-model". We have taken into account the fact that myocytes in the papillary muscle are oriented mainly in one direction. Thus microscopic "WLC-models" could be connected serially and parallel. Given serial connection of equal elements the strain of the whole system increases in proportion to the number of elements and the force remains constant. And given parallel connection of equal elements the force of the whole system increases in proportion to the number of elements and the strain remains constant. In our case, the force made by our "WLC-model" was calculated as follows: $F_{\mathrm{WLC}} = \mu \cdot f_{\mathrm{WLC}}$, where μ is the index distinguishing the number of titin molecules and f_{WLC} is the force of single titin molecule. Index μ was estimated as the ratio of cross-section area of the papillary muscle and cross-section area of the sarcomere. Based on the data from previous works we assumed that myocytes occupy ~80% of papillary muscle volume and sarcomeres occupy approximately a half of the cross-section area of the myocytes [21], [22]. Taking into account cross-section area of the papillary muscle, the number of thick filaments per cross-section-area unit and that each myosin filament is connected with *Z*-disks by six titin molecules we calculated the number of titin molecules [23].

The next problem was how to include "WLC-model" into the structure of our model. In our experiments, it has been shown that papillary muscle possessed nonlinear viscoelastic properties both in the case of control muscle and SDS-treated muscle. Notably connective tissue matrix added its own nonlinear viscoelastic properties to viscoelastic properties of titin in the muscle. Thus there was a superposition of viscoelastic properties of different morphological structures. Consequently, the inclusion of "WLC-model" across the model of fascicule between the incompressible butt elements would be functionally incorrect as in this case "WLC-block" would not affect structural viscosity of the whole model. Taking into account that myocytes in papillary muscle are practically oriented in the same direction and correspondingly molecules of titin are located similarly, it was reasonable to include "WLC-blocks" across the longitudinal elements of the fascicule model.

In this case, viscoelastic behavior of the model is defined by the system of equations below:

$$\begin{cases} 2\cdot l_1\cdot(F_2+F_{\mathrm{WLC}})-(L-l_2)\cdot F_1=0, \\ 2\cdot l_1\cdot F_3-(l_3-h_3)\cdot F_1=0, \\ 2\cdot l_1\cdot F_4-(l_4-h_4)\cdot F_1=0, \\ (l_3-h_3)^2+(l_4-h_4)^2+(L-l_2)^2=4\cdot l_1^2, \end{cases} \qquad (7)$$

where:

F_{WLC} – force developed by titin "WLC-blocks",
l_{10}, l_{20}, l_{30}, l_{40} – initial lengths of model elements,
l_1, l_2, l_3, l_4 – current lengths of the elements,
k_1, k_2, k_3, k_4 – elastic coefficients,
η_1 – viscous coefficient,
F_1, F_2, F_3, F_4 – forces developed by corresponding elements,
h_3, h_4 – dimensions of incompressible butt element,
L – length of the whole model.

The force developed by the whole model is calculated by the equation:

$$F=4\cdot F_2. \qquad (8)$$

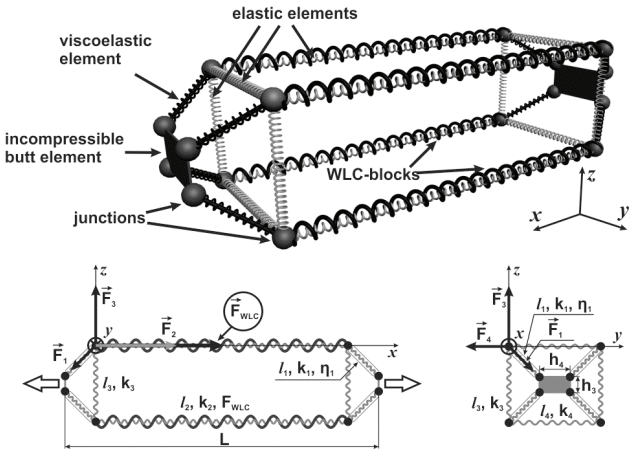

Fig. 2. Three-dimensional structural model of myocardial fascicle with WLC-units. Large empty arrows show the direction of deformation of the model

The final set of equations (7) was solved by the common fourth-order Runge–Kutta method. The fitting of the parameters of elasticity and viscosity was carried out by Levenberg–Marquardt algorithm.

Including "WLC-blocks" in the model allowed us to compare viscoelastic behavior of the model both with "WLC-block" and without it. This is equivalent to the comparison of experimental data of the viscoelastic properties of control papillary muscle and SDS-treated muscle. Thereby it is to conclude that the model adequately describes experimental data of the viscoelastic properties of papillary muscle. The coefficients of elasticity and viscosity of structural elements of the model remain constant all over the range of analyzed strains. The nonlinearity of viscoelastic properties occurs due to the variation of the angles between the model structural elements.

3. Results

The first stage in the model verification consisted in fitting the elastic and viscous coefficients of the structural elements of the model. The fitting was carried out according to the experimental data of control muscle stress relaxation. Geometry of the model in unstrained condition corresponding to slack length L_0 and time stations of stepwise stretching were defined. The evolution of the response of our model was defined in real time. It is important to note that papillary muscles were in quasi steady-state condition at the time before stretching (i.e., stress relaxation continued but in what follows did not lead to significant changes in passive tension). This fact was taken into account during computational experiments. Stepwise stretching of the model was set at the same time stations as for papillary muscle during the experiment. Next model response was compared with experimental record of passive stress relaxation of the control muscle and then values of elasticity and viscosity of structural elements of the model were defined (figure 3a).

The next stage of verification was removal of "WLC-blocks" from the model structure without changing other parameters to simulate SDS treatment and comparison of the response of the model without "WLC-blocks" with experimental data of stress relaxation of the SDS-treated muscle. As shown in figure 5, using the set of elastic and viscous parameters selected for the control muscle resulted in significant discrepancy between the experimental curves of stress relaxation and the model response. Let us consider the factors affecting this phenomenon. These are: an error of estimation of proportionality coefficient μ defining the number of titin molecules; partial injury of connective tissue matrix with 1% SDS solution; contribution of cytoskeleton of cardiac myocytes to passive tension of the papillary muscle. It is quite difficult to estimate the proportionality coefficient μ defining the number of titin molecules in papillary muscle, because there is no way to accurately identify the muscle diameter and diameter of myocytes in each experiment.

We have seen that SDS treatment did not significantly affect the morphological structure of the connective tissue matrix. The geometry of the papillary muscle after SDS treatment was maintained. Histological study of SDS-treated muscles showed that connective tissue fibers remained intact. However, SDS treatment on molecular structure of connective tissue matrix cannot be excluded. SDS solution as detergent may affect connective tissue matrix at molecular level leading to changes in its viscoelastic properties. In this case, we cannot observe the changing of morphological structure.

We consider that the differences between experimental curves of stress relaxation of SDS-treated muscle and the model response may account for the presence of additional structures – cytoskeleton of cardiac myocytes that contribute to the passive tension of the papillary muscle. Therefore, we correct the values of elastic and viscous parameters of the structural elements of the model without "WLC-blocks".

In table 1, values of elasticity and viscosity of structural elements of the model are compared for the cases of control muscle and SDS-treated muscle.

As seen from table 1 to appropriately reproduce stress relaxation curves of SDS-treated muscle in the model together with "WLC-block" removing it is necessary to reduce the values of elastic and viscous

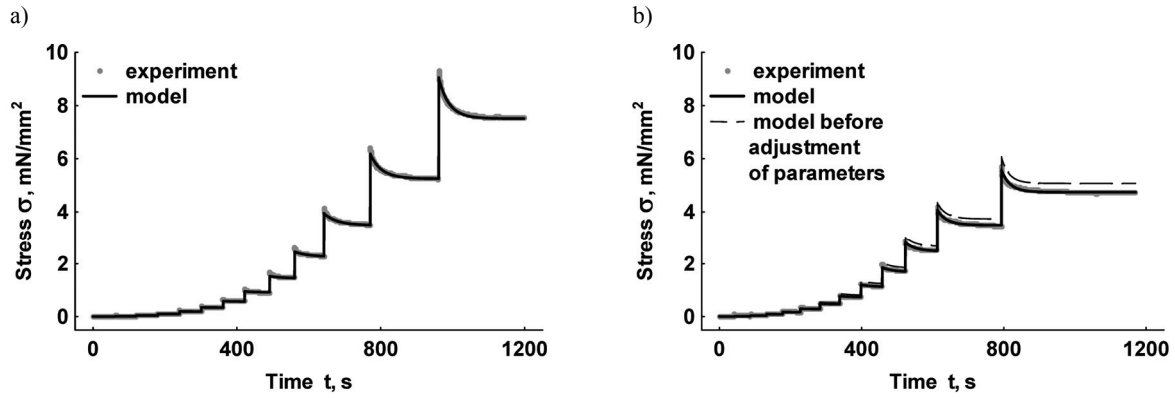

Fig. 3. Stress relaxation data: (a) experimental data of control papillary muscle – grey circles; simulation data (model with WLC-blocks) – solid black line; (b) experimental data of SDS-treated papillary muscle – grey circles; simulation data (model without WLC-blocks before adjustment of parameters) – dashed black line; simulation data (model without WLC-blocks after adjustment) – solid black line

parameters approximately by 10–15% in comparison with the values of these parameters in the case of control muscle.

Table 1. Values of viscosity and elasticity of structural elements of the model

	Control muscle	SDS-treated muscle
k_1, mN/mm^2	10.081	8.266
k_2, mN/mm^2	8.477	7.379
k_3, mN/mm^2	0.227	0.202
k_4, mN/mm^2	0.227	0.202
η_1, mN/mm^2·s	0.426	0.291
μ	113490	–

Computational model experiments showed that SDS treatment led to the removal of the structure simulating titin as well as diminishing the contribution of cytoskeleton of cardiac myocytes. This fact corresponds to the cytoskeleton of cardiac myocytes contributing to the passive tension of papillary muscles [24].

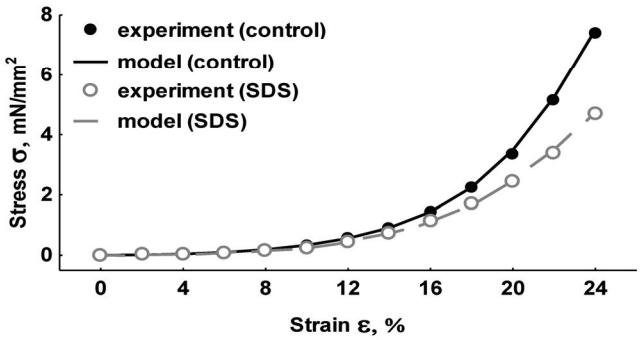

Fig. 4. Steady-state stress–strain relation. Experimental data of control papillary muscle – black circles; simulation data of control muscle – solid black line; experimental data of the same muscle after SDS treatment – grey empty circles; simulation data of SDS-treated muscle – grey dashed line

Having obtained the dynamics of response of the model to stepwise stretching with constant increment, using the values of elastic parameters $\mathbf{k}_1$, $\mathbf{k}_2$, $\mathbf{k}_3$, $\mathbf{k}_4$ of structural elements of the model and viscous parameter $\boldsymbol{\eta}_1$ tending to zero we obtained steady-state stress–strain relation both in the case of control muscle and SDS-treated muscle subject to correction of the parameters.

Figure 4 compares steady-state stress–strain relations of control papillary muscle and the same muscle after SDS treatment and steady-state response of the model of control muscle and SDS-treated muscle.

4. Discussion

We investigated static and dynamic viscoelastic properties of isolated rat papillary muscles and the same muscles after removing myocytes with SDS solution. We have developed a three-dimensional model of myocardial fascicle. The model adequately describes both viscoelastic behavior of control papillary muscle and behavior of SDS-treated muscle.

Our experiments have shown that a 1% SDS solution treatment of papillary muscle led to a significant decrease in stiffness and viscosity of the muscle. Nevertheless the form of nonlinearity of viscoelastic properties is preserved.

Our model reproduces the contribution of titin and connective tissue matrix that are the main sources of passive tension of the myocardium. The model experiments confirm that titin as the main source of passive tension of cardiac myocytes contributes significantly to viscoelastic properties of the papillary muscle. Removal of the structural elements of the

model simulating the titin leads to a significant decrease in stiffness and viscosity of the overall model. However it is well known that cytoskeleton of cardiomyocytes contributes to their viscoelastic properties besides titin [24]. This fact is represented in our model though initially the contribution of cytoskeleton was not taken into account in the structure of the model.

Resuming the results obtained we assume that viscoelastic properties of the papillary muscle are largely defined by organization of morphological structures composing myocardial tissue. Computational experiments with the use of the developed three-dimensional model of myocardial fascicle have shown that changing the geometry structure of linear elements of the model under strain leads to total nonlinear response of the model to strain. It is significant to note that values of elasticity and viscosity of the elements remained constant all over the range of analyzed strains.

Though it should be noted that the model presented does not take into account the volume changes of the preparation. It is well known that the volume of papillary muscle remains practically changeless at constant concentration of ions in the solution [25]. Preliminary calculations have shown that the model volume significantly changes under substantial strains. Therefore, additional experimental studies of the internal structure of papillary muscle under strain are required to obtain more certain information about structural organization of myocardial tissue and to modify the model structure for more sufficient description.

Based on the data regarding the substantial role of structural organization of morphofunctional units, similar models of biological tissue will allow us to obtain information about the contribution of topology of the tissue to its viscoelastic properties and to establish the relation between tissue structure and viscoelastic properties.

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