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Deficiency of Length-Dependent Activation of Contraction in the Cardiac Muscle of Rats with Heart Failure: Assessment of the Muscle Strip and Single Cell Levels

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Abstract—This paper reports on a comparison of the extent of length-dependent activation of contraction in the right ventricle myocardium in healthy rats and rats with monocrotaline-induced heart failure on two levels of heart-tissue organization, that is, muscle stripes and isolated cardiomyocytes, within the framework of a single study. It has been shown that a deficiency in the length-dependent increase in the contractile force produced by failing myocardium when expressed in quantitative terms is similar at both levels of organization of myocardial tissue. These findings indicate that the mechanisms of length-dependent regulation of myocardial contractility in the failing heart are suppressed mainly at the cellular level. In muscle strips, the deficiency of the length–tension relationship appears to be more pronounced, most likely because the spatial organization of myocytes affects the integral contractile response of the muscle.

Keywords: muscle, cardiomyocyte, length–tension relationship, heart failure, monocrotaline
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INTRODUCTION

In the adaptation of the heart pump function to exercise, a key role is played by the mechanisms of myocardial contractility regulation, which depend on the actual length of sarcomeres in cardiomyocytes [1–3]. The length-dependent mechanisms that regulate the contractile force of the cardiac muscle manifest themselves in the form of the Frank–Starling law, according to which the maximum pressure in the cardiac chamber is proportional to its end-diastolic volume (in the case of muscle strips, this phenomenon is referred to as the length–tension relationship). In failing myocardium, only a limited increase in the myocardial contractility following the change in the sarcomere length has been demonstrated [4–6], with some authors even reporting almost complete disappearance of this phenomenon, for instance, in a patient with terminal stage left-ventricle failure [7]. According to other works, the Frank–Starling mechanism remains partially functional in the heart of patients with pulmonary heart disease, as well as in dog and rat cardiomyocytes [8–10]. Finally, some data indicate that cardiomyocytes in the right ventricle of dogs with the severe whole ventricle failure retain their normal contractile function [11].

The significantly varying data on the degree of manifestation of the Frank–Starling phenomenon in failing myocardium may be accounted for by the differences in the level at which the study is carried out, as well as in the disease model that is used. Different experimental models of pulmonary heart disease in rats exist, including pulmonary artery ligation, use of animal lines with renal dysfunction, use of compounds that compromise normal renin–angiotensin–aldosterone system function with subsequent expression of endothelin and angiotensin. In our work we used a noninvasive experimental model involving the administration of a single dose of the monocrotaline (MCT) alkaloid, which induces the constriction of the pulmonary trunk with subsequent development of concentric hypertrophy of the right ventricle and pulmonary hypertension and heart failure.

The quantitative data on the extent of the deficit in the length-dependent tension increase were collected either using multicellular objects, or isolated cardiomyocytes, but no works exist that report an assessment performed simultaneously at the cellular and tissue levels. We have quantitatively assessed the extent of length-dependent activation of contraction in both muscle strips and isolated cardiomyocytes in rats with pulmonary heart disease and compared the results with the corresponding data obtained for rats with normal right ventricle myocardial function. This

Abbreviations: MCT, monocrotaline, L_{max}, the muscle length at which the maximum tension is produced.

approach to studying the specific features of the development of contractile dysfunction of the myocardium is fundamentally important, since it allows not only determination of the degree of contractile dysfunction in individual cardiomyocytes, but also comparison of the severity of the observed dysfunction with the contractile response deficiency in the multicellular heart tissue sample. Taking the complex geometry of the heart and the spatiotemporal heterogeneity of characteristics of its individual layers into account, it could have been expected that contractile function deficiency at the cellular level will not completely match the deficit in the function of the entire organ.

MATERIALS AND METHODS

All manipulations with experimental animals were performed in accordance with the international recommendations on animal experimentation and were approved by the Commission for the Control of Laboratory Animals of the Institute of Immunology and Physiology of the Ural Branch of the Russian Academy of Sciences. The experiments were performed using young male and female Wistar rats with normal hearts and with experimental pulmonary heart disease induced by the pyrrolizidine alkaloid monocrotaline [12, 13]. Rats at an age of 4 weeks (80–100 g in weight) were randomly distributed between the control group and MCT group. The animals in each group received a single intraperitoneal injection of physiological solution in the volume of 2 mL with the addition of 50 mg monocrotaline per kg of weight or without monocrotaline. Rats in the MCT group were sacrificed within the 7th or 8th week of life when they started to demonstrate the clinical signs of heart failure (weight loss and dyspnoea at rest). The rats in the control group were sacrificed at the same age. A muscle relaxant (Rometar, 1 mL/kg), an anesthetic (Zoletil, 0.02 mL/kg), and heparin (1000 U/kg) were administered intramuscularly to the animals 15–20 min prior to euthanasia. To assess the severity of the length-dependent contractility activation deficiency in the rats with heart failure at the muscle and cell levels, the animals were subdivided into the following subgroups: control groups ($n = 15$ for the study at the muscle level and $n = 7$ for the study at the cellular level, respectively) and MCT groups ($n = 23$ and $n = 9$, respectively).

The muscle level. After the animal was sacrificed, the heart was removed and placed into a dissecting dished filled with Krebs–Henseleit solution containing (mM) NaCl, 118; KCl, 4.7; $MgSO_4$, 1.2; $NaHCO_3$, 14.5; KH_2PO_4, 1.2; $CaCl_2$, 2.5; and glucose, 11.1 at pH 7.35 with 30 mM 2,3-butanedione monoxime. The thin trabecula was excised from the right ventricle and placed into an experimental chamber with circulating Krebs–Henseleit solution without 2,3-butanedione monoxime with constant delivery of the 95% O_2–5% CO_2 mixture. One end of the trabecula was attached to the stem of a strain gauge force-sensing device, while the other end of the trabecula was attached to the stem of the length servo-controlled motor. Biomechanical measurements were performed using the Muscle Research System (Scientific Instruments GmbH, Heidelberg, Germany) designed to study muscle activity in the near real-time mode (at 100 μs intervals) using a PCI-1716S DA/AD converter (AdLink Technology Inc., Taiwan) and a software package with the HyperKernel real-time platform (Arc Systems Ltd., Japan) integrated into the Windows XP OS. The measurements were performed at the electric stimulation frequency of 1 Hz and physiological solution temperature of 25°C.

To set the same relative extension (preload) in trabeculae with different initial lengths, the length at which it showed the maximum isometric-force amplitude was determined for each trabecula. This length was designated as L_{max} and the preload was further set as a percentage of this length. At each applied preload, the isometric contraction under steady-state was recorded for each trabecula. Isometric muscle tension was calculated as the ratio of the muscle force value to the muscle cross-section area value, which was determined according to the following formula:

$$S = \pi d^2/12,$$

where d is the unstretched muscle diameter.

The cellular level. After the animal was euthanized, the intact heart was excised and placed into modified Krebs–Henseleit solution precooled to 10°C for intact heart preparation (Table 1). The aorta was further attached to a cannula 1 mm in diameter; the cannula was then connected to the heart-perfusion system (Radnoti, AD Instruments, Australia) with aerated solution containing physiological calcium concentrations heated to 37°C (Table 1, step 1). Then, 15–20 min later, perfusion was continued with a nominally calcium-free solution (Table 1, step 2) for another 20 min to completely inhibit the contractile activity. The solution was replaced with a nominally calcium-free solution with added collagenase (Table 1, step 3) and the heart was perfused for 15–20 min. Upon completion of the perfusion process, the ventricles were cut off and placed into a nominally calcium-free solution without collagenase. In this solution, ventricles were carefully cut to obtain a suspension. The cardiomyocyte suspension upon filtration was allowed of sedimentation for 10 min, supernatant was removed, Tyrode's solution (Table 1, step 4) was added, and the calcium concentration was subsequently gradually increased to 100, 250, 400 μM and 1.25 mM (final calcium concentration). Cardiomyocytes with an intact membrane and clear cross striation that were not producing spontaneous contractions and were demonstrating a stable response to external electric stimulation were chosen for subsequent study.

Table 1. The compositions of the solutions used in the protocol for the preparation of isolated cardiomyocytes from the ventricles of rats

Intended use	Intact heart preparation	Intact heart perfusion (step 1)	Intact heart perfusion (step 2)	Intact heart perfusion (step 3)	Manipulations with isolated cardiomyocytes (step 4)
component	modified Krebs–Henseleit solution (pH 7.4, aeration with 95% O_2 + 5% CO_2, titration with NaOH)				Tyrode's solution (pH 7.3, titration with NaOH)
Working temperature, °C	~ 5–10	37	37	37	25
NaCl, mM	118	118	118	118	118
KCl, mM	4.7	4.7	4.7	4.7	4.7
$MgSO_4$, mM	1.2	1.2	1.2	1.2	1
KH_2PO_4, mM	1.2	1.2	1.2	1.2	–
$NaHCO_3$, mM	25.0	25.0	25.0	25.0	–
HEPES, mM	10.0	10.0	10.0	10.0	10.0
Glucose, mM	11.1	11.1	11.1	11.1	11.1
$CaCl_2$ dehydrated, mM	1.25	1.25	0.025	0.025	1.25
Sodium heparin, MU/mL	20	–	–	–	–
Collagenase, mg/mL	–	–	–	1	–
Albumine, mg/mL	–	–	–	–	1

All reagents were purchased from Sigma-Aldrich (United States); the only exception was for collagenase (Collagenase Type 2, Worthington Biochemical Corporation, United States).

The carbon-fiber technique was utilized to record the mechanical activity of the isolated cardiomyocyte, as well as to control the degree of the stretch of the cardiomyocyte [14, 15]. According to this technique, a cardiomyocyte was mechanically attached to carbon fibers, which are highly adhesive to the cell surface. Carbon fibers 7 μm thick (Tsukuba Materials Information Laboratory Ltd., Japan) were mounted in specially-designed glass holders of an intricate shape fabricated by the authors using a needle pipette puller (model 730, David Kopf Instruments, United States, or ME-4, USSR). Two reflection symmetric holders with carbon fibers were mounted independently to precision micromanipulators that used the MP285 system for the control of the micropositioning devices (Sutter Instruments, United States).

Prior to attaching cardiomyocytes to carbon fibers, a thin coverslip covered with polyHEMA was placed on the bottom of the solution-filled experimental chamber to prevent cardiomyocytes from adhering to the bottom. A pair of carbon fibers was carefully forced against the opposite ends of a cardiomyocyte and the cardiomyocyte was then lifted slightly off the bottom surface of the chamber. Cardiomyocyte shortening was recorded directly by the degree of carbon fiber bending, while the produced force was calculated based on the carbon fiber bending value and the preliminarily calculated carbon-fiber stiffness. To determine the bending stiffness coefficient of the carbon fiber, a precision force-sensing device with a sensitivity in the 0–5 mN range and a discrimination power of 0.2 μN (model KG-7, Scientific Instruments GmbH, Heidelberg, Germany) was used and carbon fibers were pressed against the tip of the sensor. To determine the contractile force of the cardiomyocyte, the average value for the bending stiffness coefficients for a certain pair of carbon fibers was used.

The mechanical activity of a repeatedly stimulated isolated cardiomyocyte was measured using the LSM 710 laser confocal scanning microscopy system and Zen 2010 software (Carl Zeiss, Germany). In the course of measurement, a single image frame encompassing the entire cardiomyocyte was first obtained; a narrow (two pixel high) area horizontally oriented along the long axis in the center of cardiomyocyte was then chosen so that it included the positions of both carbon fibers, even if the cardiomyocyte was in a highly stretched state (Fig. 1a). The continuous scanning mode was then switched on for the chosen area to obtain an image-intensity profile. Carbon fibers have the minimum intensity. For this reason, they are shown as intensity gaps in the horizontal image-intensity profile (Fig. 1b). The scanning area size and scanning rate were set so that they allowed a recording frequency of no less than 300 frames per second. The length of the quiescent (or non-excited) unstretched myocyte (end-diastolic length, EDL_0) was defined as the length between the carbon fibers without stretch-

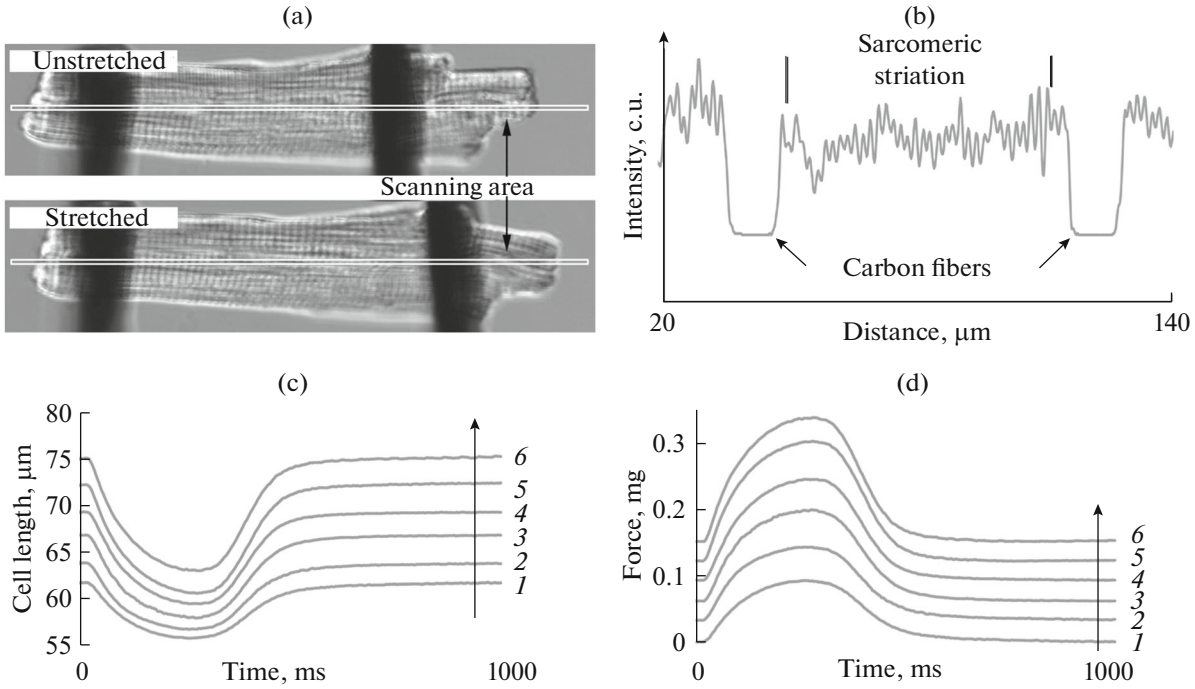

Fig. 1. Notes to the carbon fiber technique used to detect auxotonic contractions of the isolated cardiomyocyte. (a), An isolated cardiomyocyte to which ends carbon fibers are attached in the unstretched and stretched state; arrows indicate the scanning area. (b), An image-intensity profile for the scanning area; the arrows point to the intensity gaps that correspond to the sites of carbon-fiber attachment, the intensity oscillations between the gaps correspond to sarcomeric striation. (c), Series of auxotonic shortenings of the cariomyocyte at different stretch extent. (d), Series of auxotonic forces calculated on the basis of the shortening trajectories and average bending stiffness values for the certain carbon fiber pair. The arrows in panels (c) and (d) indicate the direction of the signal shift following cardiomycyte stretching; the numbers indicate the stretch extent (1), unstretched; (2–5(, gradual increase in stretch extent; (6) maximally stretched).

ing. The cardiomyocyte stretch extent was changed by moving one of the two carbon fibers using a micromanipulator. For each stretch extent, 10–15 cardiomyocyte contractions were recorded. As part of each stretching protocol, four to seven subsequent stretching events were set, which allowed us to obtain series of auxotonic shortenings of the cardiomyocyte at different stretch extent (Fig. 1c) within the 100–130% EDL_0 range. The measurement of the mechanical activity of isolated cardiomyocytes was performed at the electric stimulation frequency of 1 Hz and a solution temperature of 25°C.

The EqapA116 software was specifically designed by the authors to process and analyze the obtained stretching protocols. This software was used to assess the contractile activity of cardiomyocytes by converting auxotonic shortening into auxotonic force using the bending-stiffness coefficient of the carbon fiber (Fig. 1d). To convert the measured contraction force into mechanical tension, the cross-sectional area of a cardiomyocyte (considered as being elliptical in shape) was calculated according to the formula $\pi d^2/12$, where d is the broad side of the cardiomyocyte. This approach allowed quantitative comparison of the measurements made for individual cardiomyocytes possible. The method of Discrete Fourier Transform of the signal recorded in the intensity profile region between the carbon fiber sites was used to determine the average sarcomere length in a cardiomyocyte that was subjected to gradual stretching (Fig. 1b).

Statistical processing. The two-tailed t-test for unequal samplings was utilized to evaluate the statistical significance of the differences in the average values for the morphometric and contractility indices, as well as in the mechanical tension values obtained for the control group and the MCT group at the same relative muscle length and diastolic sarcomere length. The observed effects were considered statistically significant at $P < 0.05$. The data are provided as the arithmetical mean ± the standard error of the mean.

RESULTS

Pulmonary hypertension and heart failure induced by monocrotaline in rats. Table 2 presents the morphometric indices of the intact heart and contractility indices of the unstretched muscle preparation from the myocardium of the right ventricle of healthy rats and rats after monocrotaline administration. From 3 to 4 weeks after the administration of a single dose of monocrotaline, rats showed the loss of approximately 20% of their initial weight (from 215 ± 13 g to 175 ±

Table 2. The morphometric indices (of the animal, heart, muscle preparation, and isolated cardiomyocyte) and contractility indices of the unstretched muscle preparation from the myocardium of the right ventricle of healthy rats and rats after monocrotaline administration

Morphometric indices	Control group ($n = 15$)	MCT group ($n = 23$)
Age at the time of euthanasia, weeks	7.7 ± 0.3	7.6 ± 0.1
Weight at the time of euthanasia, g	215 ± 13	175 ± 7*
Intact heart weight, g	0.69 ± 0.04	0.78 ± 0.02*
Left ventricle weight, g	0.35 ± 0.03	0.32 ± 0.01
Right ventricle weight, g	0.16 ± 0.01	0.33 ± 0.01*
Tibia length, mm	31.3 ± 0.8	31.2 ± 0.3
Average trabecula diameter, μm	258 ± 22	316 ± 23
Average cardiomyocyte length, μm	112.7 ± 1.3	107.2 ± 0.9*
Average cardiomyocyte crosswise size (width), μm	23.3 ± 0.3	24.6 ± 0.3*
Trabecula contractility indices	Control group ($n = 13$)	MCT group ($n = 15$)
Isometric tension amplitude, mN/mm^2	8.2 ± 1.2	3.3 ± 0.4*
Time to peak tension, ms	16.0 ± 2.0	141.0 ± 2.8*
Half-amplitude relaxation time, ms	66.7 ± 2.2	87.4 ± 3.6*

* The difference between the control group and MCT group is statistically significant as determined using the two-tailed t test for unequal samplings ($P < 0.05$).

7 g, the differences were statistically significant at $P < 0.05$) and a two-fold increase in the right ventricle weight (from 0.16 ± 0.01 g to 0.33 ± 0.01 g, the differences were significant at $P < 0.05$). The "tibia length" index, independent of the development of heart pathology, showed no difference between these groups. We also observed a statistical decrease in the length and an increase in the crosswise size (width) of the isolated cardiomyocytes from the animals in the MCT group. At the level of the isolated muscle preparation from the right ventricle, the analysis of the muscle-strip contractility in the unstretched state revealed a considerable drop in amplitude and overall slower development of the contractile response in the rats in the MCT group. As an example, the amplitude of the isometric tension decreased by more than two times, from 8.2 ± 1.2 to 3.3 ± 0.4 mN/mm^2 ($P < 0.05$), while the time of the maximum active tension and the half-relaxation time increased statistically. Thus, the morphometric indices of the intact heart and contractility indices of isolated muscle preparations provide evidence of the development of pronounced myocardial hypertrophy in the right ventricle and subsequent heart failure in rats induced by a single dose of mononcrotaline.

Assessment of the length-dependent activation of contractility at the muscle-tissue level. We previously demonstrated a significant deficiency in the length-dependent increase in the isometric tension amplitude in the myocardium of rats with monocrotaline-induced pulmonary hypertension and heart failure [16, 17]. These results were obtained at the stimulation frequency of 0.33 Hz. In the current study at the muscle-tissue level, we show that this deficiency is also significant in the myocardium of rats in the MCT group at a higher stimulation frequency (1 Hz) and can be observed in the case of each muscle stretch extent in the 75% L_{max} to 100% L_{max} range (Fig. 2a). Within the indicated relative length range, trabeculae from the right ventricle of rats in the MCT group produced 40.5 ± 1.5% of the maximum isometric tension observed for the trabeculae of the control animals ($P < 0.05$). It should be noted that because of the nonlinearity of the isometric force–length relationship in the case of a multicellular preparation, we did not calculate the linear slope coefficient for each individual plot. In such a manner, a significant deficiency in the length-dependent increase in the heart-muscle contractile force in pulmonary hypertension and heart failure was clearly demonstrated at stimulation frequencies closer to physiological ones. In addition, our data indicate that within the physiological muscle-preparation length range (>90% L_{max}), the diastolic (passive) stiffness of the myocardium with pulmonary hypertension and heart failure is statistically higher than that of the normal myocardium (Fig. 2b). As an example, the diastolic tension at L_{max} was 13.1 ± 1.7 mN/mm^2 in the MCT group preparations versus 4.9 ± 0.7 mN/mm^2 in the normal myocardium preparations (more that 2.5 times higher, the differences were significant at $P < 0.05$).

Assessment of the length-dependent activation of contractility at the isolated single-cell level. Length-dependent activation of contraction at the single-cell level was assessed on the basis of the relationship between the active tension amplitude produced by the cardiomyocyte in the end-systolic phase and the dia-

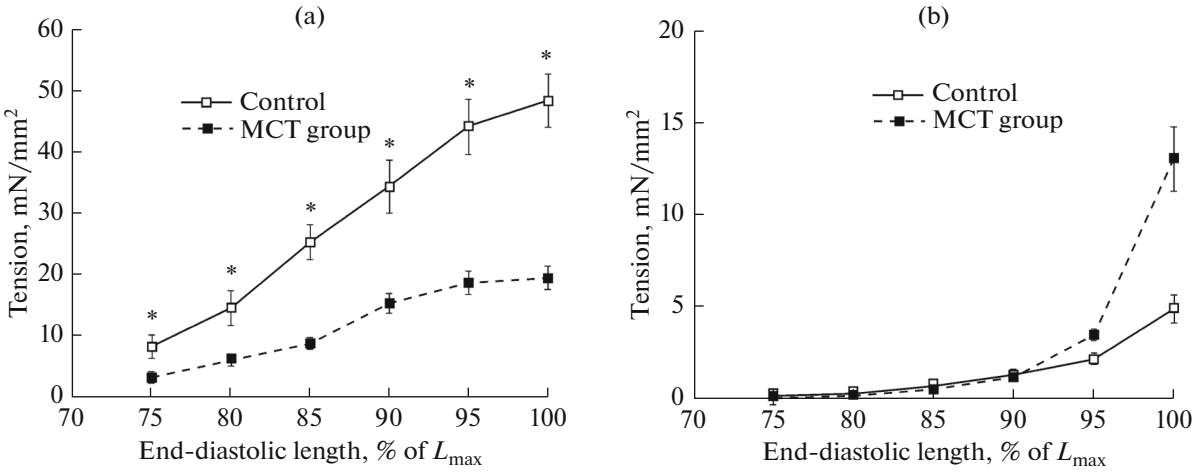

Fig. 2. The averaged isometric tension–end-diastolic length relationships for the active (a) and passive (b) tension components obtained for the multicellular right ventricle myocardium preparations from healthy rats (n = 13) and rats with monocrotaline-induced pulmonary hypertension and heart failure (n = 15). The relative length is provided as the percent of L_{max}. The tension values are provided as the mean ± standard error of the mean. *Differences between the control group and the MCT group at the given relative muscle length are statistically significant ($P < 0.05$).

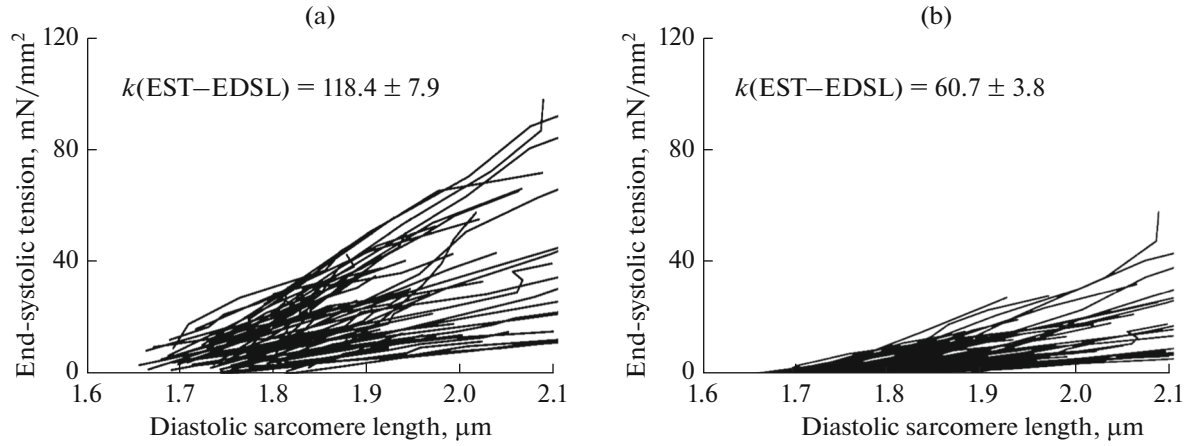

Fig. 3. Individual diastolic sarcomere length–end-systolic tension (a) and diastolic sarcomere length–end-diastolic tension (b) relationships obtained for the isolated right ventricle cardiomyocytes of healthy rats (n = 70 cells from N = 7 animals). The mean slope coefficient values ± the standard error of the mean are indicated on the plots.

stolic sarcomere stretch extent. Using the carbon-fiber technique (see the Materials and Methods section) we could set the cardiomyocyte stretch extent in a range such that it corresponded to the diastolic sarcomere lengths in the ~1.7 to ~2.1 μm range. Within the indicated sarcomere-length range, the diastolic sarcomere length–end-systolic tension and diastolic sarcomere length–end-diastolic tension relationships were linear, which made it possible to calculate the linear slope coefficients for these relationships and to compare them between the animal groups.

Figures 3a and 4a show individual end-systolic tension–diastolic sarcomere-length dependence curves obtained for the cardiomyocyte pool from the rats of the control group (n = 70 cells from N = 7 animals) and the MCT group rats (n = 84 from N = 9 animals). For each individual curve, we calculated the slope coefficient using a linear approximation. The average coefficients were 118.4 ± 7.9 and 85.4 ± 4.9 (mN/mm2)/μm for the control group and MCT group, respectively (the differences were statistically significant at P < 0.05). In such a manner we revealed a significant deficiency in the length-dependent increase in the contraction force in the MCT group rats.

In the same manner, we constructed and analyzed the end-diastolic tension–diastolic sarcomere length dependence plots for the cardiomyocyte pools from the rats of the control and MCT groups (Figs. 3b and 4b). At the isolated cardiomyocyte level, within

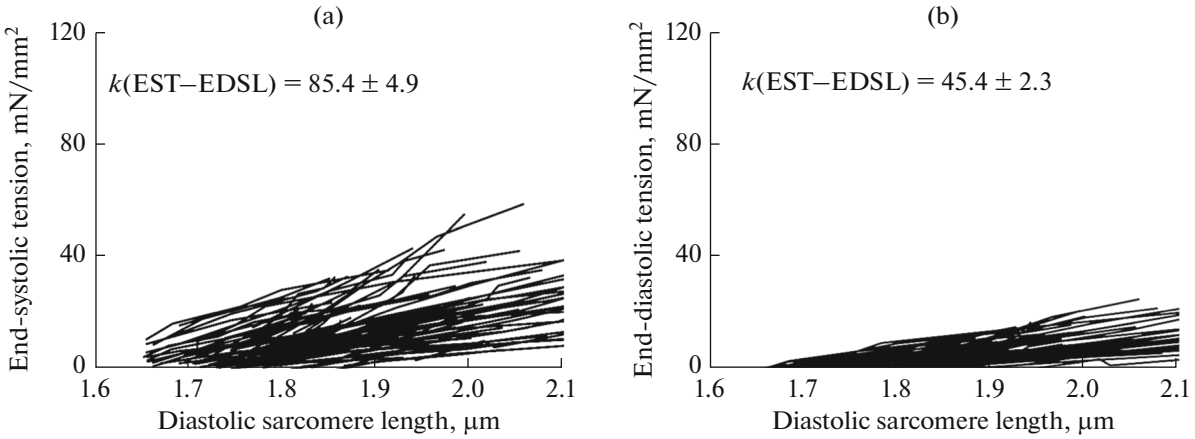

Fig. 4. Individual diastolic sarcomere length–end-systolic tension (a) and diastolic sarcomere length–end-diastolic tension (b) relationships obtained for the isolated right ventricle cardiomyocytes of rats with monocrotaline-induced pulmonary hypertension and heart failure (n = 84 cells from N = 9 animals). The mean slope coefficient values ± the standard error of the mean are indicated on the plots.

the 1.7 to 2.1 μms sarcomere diastolic length range we observed a decrease in the slope of the diastolic tension–sarcomere length dependence curve in the rats of the MCT group. As an example, the average values for the slope of the diastolic tension–sarcomere length dependence plot were 60.7 ± 3.8 and 45.4 ± 2.3 (mN/mm^2)/μm for the cell pools from the healthy rats and rats with pulmonary hypertrophy and heart failure, respectively (the differences were statistically significant at $P < 0.05$). It should be noted that for multicellular myocardium preparations a statistical increase in the diastolic tension in the myocardium of rats with monocrotaline-induced pulmonary hypertension and heart failure was demonstrated only at stretch equivalent to 95% L_{max} and 100% L_{max} (see Fig. 2b). At stretch extent less than 95% L_{max} no statistical differences were observed, with the average diastolic tensions being even lower than in the myocardium of the MCT group rats. This is in good correspondence with the results at the isolated cardiomyocyte level, since cells were stretched to sarcomere lengths not exceeding 2.1 μm, that is, to relative lengths shorter than 95% L_{max}.

CONCLUSIONS

Heart-muscle contractility is critical for the pumping function of healthy and pathologically changed hearts and depends on the activity of sarcomeres, while its strength is controlled by different intracellular systems and is modulated by the environmental conditions of the cardiomyocyte [1–3]. Within the framework of a single study, we compared length-dependent regulation of contraction in healthy and failing rat myocardium at two different levels of myocardial tissue organization, that is, in muscle strips and isolated cardiomyocytes. At the muscle-strip level, we observed a significant (by more than two times) deficiency in the increase of mechanical tension in response to the length increase in the myocardium of rats with monocrotaline-induced pulmonary heart disease and heart failure (in this work and [16, 17]). A deficiency in the length-dependent activation of contraction was observed in the isolated cardiomyocytes of rats in the same group that was less pronounced in quantitative terms, but was still statistically significant. A decrease in the slope of the length–tension dependence plot for the active contraction component was accompanied by an increase in the diastolic tension in the muscle preparation when stretched to lengths close to the maximum length. In the case of the isolated cardiomyocyte, we were not able to obtain stretch extent that correspond to the sarcomere length of ~2.3 μm. However, within the analyzed sarcomere-length range (from 1.7 μm to 2.1 μm), the behavior of the length–tension relationship for the diastolic-tension component is the same as that of the muscle strip.

It should be noted that although we carried out the study at two different levels of organization of the heart tissue, due to certain technical constraints we had to use different contraction modes for the two objects under study, that is, the isometric mode in the case of muscle strips, and the auxotonic mode in the case of isolated cells. Active cardiomyocyte shortening in the auxotonic mode gives rise to the phenomenon of shortening-induced length-dependent inactivation, which depends not only on the shortening amplitude, but also on the initial stretch extent of the cells [18–20], while the muscle strip produced tension at a quasi-constant sarcomere length. Because it has been demonstrated that the conditions of mechanical loading of cardiac cells directly influence the contractile behavior of a cell [21, 22] we did not compare the results that were obtained in the two different modes. In the current work, the attention is focused on the

existence of a significant decrease in the slope of the length–tension relationship plot in the failing myocardium irrespective of the contraction mode or myocardium organization level.

Thus, reduced length-dependent activation of contractility in myocardium with pulmonary hypertension and heart failure is to a large extent caused by a decrease in the sensitivity of the force-generation mechanisms to the change in the sarcomere length at the cellular level. At the tissue level, this pathological remodeling leads to quantitatively more-pronounced effects, which is most probably due to the spatial and temporal heterogeneity of the individual cardiomyocyte functions.

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