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COMPLEX SYSTEMS BIOPHYSICS

The Intracellular Calcium Kinetics and Action Potential in the Ventricular Myocardium of Spontaneously Hypertensive ISIAH Rats

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Abstract—Here, we show the dependence of intracellular calcium kinetics and the duration of the action potential of cardiomyocytes on an animal's age in multicellular preparations of the myocardium of the left and right ventricles of healthy control rats and rats with inherent arterial hypertension. In the myocardium samples from control or hypertensive rats the kinetics of the decline of free intracellular calcium slows with age and the differences between the groups become minimal. The short-term deceleration phase of intracellular calcium decline, which is clearly seen in the right ventricle of young hypertensive rats, is smoothed. The duration of the repolarization phase in cardiomyocytes of both ventricles of rats of the control and hypertensive groups shortens; however, it is always higher in the right ventricle samples of control rats with respect to that in the myocardium of hypertensive rats. Here we show the age-related changes in some features of the electromechanical coupling in the myocardium of rats with inherited arterial hypertension for the first time. These experimental data demonstrate the development of spontaneous hypertrophy probably induced by activation of the renin–angiotensin system.

Keywords: myocardium, age, hypertension, kinetics of free intracellular calcium, action potential@

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The long-term action of hypertension is one of main issues that lead to the development of heart hypertrophy and heart failure. There are several experimental models of the development of arterial hypertension and, as a rule, the mechanisms that initiate hypertension in most of them start immediately after treatment such as injections of active substances or various ligatures. Recently, rat strains with genetically predetermined gradually developing hypertension have been developed. One strain is a widely known strain of spontaneously hypertensive rats; a second strain with inherited stress-induced arterial hypertension (ISIAH) was bred in Russia [1, 2]. It is important to study changes in the biophysical features of the myocardium of ISIAH rats during the development of hypertension.

It is well known that hypertrophy is reflected in some modifications in the system of electromechanical coupling of excitation with myocardium contraction, particularly, in alterations of the duration of the action potential and the kinetics of free Ca^{2+} in myocytes [3]. Age also affects the Ca^{2+} kinetics and duration of the action potential [4]. Here, we studied 1.5- and 7-month-old male rats in order to compare data on the changes of the kinetics of cytosolic Ca^{2+} and the duration of the action potential during aging and gradual development of hypertrophy. Wistar albino Glaxo (WAG) rats were used as the control (normotensive) animals and ISIAH rats with genetically predetermined stress-induced arterial hypertension were used as experimental (hypertensive) animals. Electromechanical coupling has practically not been studied in the myocardium of ISIAH rats. Taking the fact into account that the interrelationship between the functions of the ventricles has been experimentally confirmed [5–8], it is possible to expect the development of hypertrophy in both cardiac regions. We studied isolated samples of the right and left ventricles of the heart.

MATERIALS AND METHODS

The experiments were performed on 1.5- and 7-month-old male rats. We studied cardiac muscle samples from normotensive WAG rats and hyperten-

Abbreviations: SHR, spontaneously hypertensive rats; ISIAH, inherited stress-induced arterial hypertension; WAG, Wistar albino Glaxo normotensive rats; WKY, Wistar-Kyoto normotensive rats; $[Ca^{2+}]_i$, free cytosolic calcium ions.

sive ISIAH rats. The data from these strains were compared to each other and to the literature data for SHR rats. Hypertension develops gradually in genetically modified rats; therefore, we used isolated papillary muscles and trabeculas of the right and left ventricles (RV and LV, respectively) sampled from hearts of WAG or ISIAH rats of the following age groups: ISIAH 1.5 months, $n = 14$; WAG 1.5 months, $n = 9$; ISIAH 7 months, $n = 8$; WAG 7 months, $n = 14$. Eight groups were formed according to the animal strain and age and heart region, specifically WAG(1.5)-RV, ISIAH(1.5)-RV, WAG(7)-RV, ISIAH(7)-RV, WAG(1.5)-LV, ISIAH(1.5)-LV, WAG(7)-LV, and ISIAH(7)-LV.

Arterial pressure was measured in rats using the plethysmographic method. Measurement was performed in anesthetized male 7-month-old ISIAH and WAG rats using a PowerLab 30 series complex (ADInstruments, United States) and LabChart 7 software (ADInstruments, United States). In groups of young rats pressure measurement was difficult due to the small size of the animals, which resulted in high variability of the data. Prior to measurement of arterial pressure the rats were injected intramuscularly with xylazine at a dose of 0.6–0.8 mL/kg and 10–15 min later with zoletil 50 at a dose of 0.06 mL/kg. This allowed light anesthetization and prevented problems associated with the effect of muscular activity on the recording using a pulse oximeter sensor in freely moving animals.

The animals were then euthanized by the cervical translocation method and the hearts were dissected and placed into a bath filled with Krebs–Henseleit solution consisting of (in mM): NaCl, 118; KCl, 4.7; $MaSO_4$, 1.2; $NaHCO_3$, 14.5; KH_2PO_4, 1.2; $CaCl_2$, 2.5; glucose, 11.1, pH 7.35, which was saturated with a mixture of 95% O_2 + 5% CO_2. To prevent damage of the samples during preparation 30 mM 2,3-butanedione monoxime was added to that solution. Thin papillary muscles and trabeculas were excised from the right ventricle and only papillary muscles were excised from the left ventricle. The samples were placed into an experimental bath with a flow of Krebs solution saturated with a mixture of 95% O_2 + 5% CO_2. All measurements were performed in samples with a length equal to 95% of the maximum length at 25°C, and the frequency of electrical stimulation of 0.33 Hz.

Fluorescence of free intracellular calcium ($[Ca^{2+}]_i$) was recorded in cardiomyocytes using the fura-2/AM calcium-binding fluorescent dye (Sigma-Aldrich, United States) at a concentration of 4 μM and 0.2% Pluronic F-127 (Sigma-Aldrich, United States), which is a special agent that facilitates the permeability of a fluorophore via the sarcoplasmic membrane. Perfusion with this solution continued for 1 h; it was then replaced by the standard Krebs solution without fluorophore. Measurements were started 30 min after washing. Optical recording of fluorescence in a multicellular sample was performed using a Muscle Research System for studies of muscular activity (Scientific Instruments GmbH, Germany), based on an Axiovert 200 inverted epifluorescent microscope (Carl Zeiss, Germany). A broad-band mercury lamp and a system of rotating narrow-band light filters with a transmission wavelength of 340 and 380 nm (Scientific Instruments GmbH, Germany) were used to excite the fura-2/AM fluorophore. The light flux of fluorophore emission was directed to a beam-splitting cube with a bandwidth of 510/590 nm (FilterSet #21HE, Carl Zeiss, Germany).

The membrane potential in cells of isolated cardiac muscle was recorded using floating glass microelectrodes connected to an Intracellular IE-210 Electrometer (Warner Instrument Corporation, United States). Microelectrodes were prepared using a KOPF needle/pipette puller, model 730 (David KOPF Instruments, United States) filled with 3 M KCl and attached to the remote unit of the measuring system's coordinator using a silver-chlorine wire inserted inside.

The measuring and control peripheral devices were connected to a personal computer via PCI-1716S ADC/DAC (AdLink Technology Inc., Taiwan) for recording signals with a time lapse of 0.1 ms. On-line measuring was performed using self-developed software that operated in the real-time HyperKernel interface (Arc Systems Ltd., Japan) integrated into OS Windows XP.

The experimental data were tested for the normality of the distribution using the Kolmogorov–Smirnov, Lilliefors, and Shapiro–Wilk's tests and were analyzed for asymmetry and kurtosis. Our data did not conform to a normal distribution. Thus, nonparametric methods were used to evaluate the statistical significance of differences between animal groups, including the Mann–Whitney *U*-test and the Kruskal–Wallis one-way analysis for multiple comparisons. The differences were considered statistically significant at $p < 0.05$.

RESULTS

Arterial systolic pressure and morphometrical indices in the myocardium. Blood arterial systolic pressure in the tail artery was noninvasively measured and the morphometrical indices of animal hearts were analyzed to estimate hypertrophy of the heart. In the 7-month-old ISIAH rats the arterial pressure was significantly higher by 1.5 times compared to WAG rats of the same age (Table 1). One of the signs of hypertrophy is thickening of the ventricle walls and an increase in their weights [9, 10]. In 1.5-month-old ISIAH rats, the median heart weight was 0.68 g; it reached 1.1 g by 7 months of age, while in WAG rats, the median heart weight was 0.53 g and 0.8 g, respectively (the differences were significant between the age

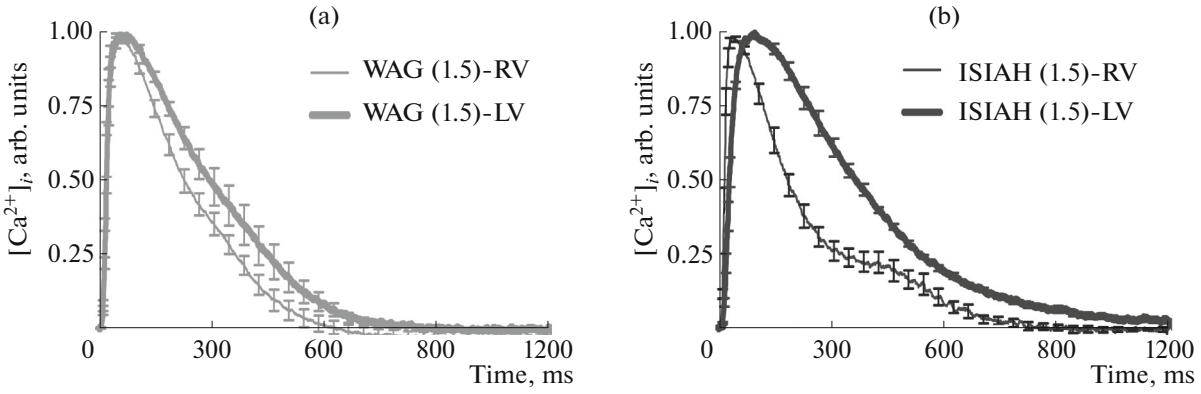

Fig. 1. Comparison of the kinetics curves of free cytosolic calcium ($[Ca^{2+}]_i$) in the myocardium samples of the right and left cardiac ventricles of 1.5-month-old rats: (a), normotensive WAG rats; (b), hypertensive ISIAH rats. The measurements were performed with the muscle length equal to 95% of the optimal length. The curves are normalized to their own maximum, and the diastolic level is subtracted. Data are presented as mean of all group samples ± standard error of the mean.

groups at $p < 0.05$). We found that the heart weight/body weight ratio was higher in 1.5-month-old ISIAH rats compared to same age WAG rats (0.0037 and 0.0034, respectively); this difference became even more substantial in 7-month-old animals (0.0028 and 0.0023, respectively; Table 1). Thus, the age-associated increase in the heart weight normalized to the body weight was higher in the group of spontaneously hypertensive rats compared to that in the control rats. This can be explained by the development of heart hypertrophy in the ISIAH rats. The heart weight/tibia length ratio was also higher in the ISIAH rats compared to control rats (0.0213 and 0.0192, respectively in 1.5-month-old rats); this difference also increased with age (0.0254 and 0.0212, respectively, in 7-month-old rats). This indicates progressing heart hypertrophy in spontaneously hypertensive rats in addition to the age-associated changes.

The kinetics of free intracellular calcium. The kinetics of free calcium were recorded in the cytosol of stimulated isometrically contracting isolated multicellular myocardium samples with 95% length of the maximum length. It is noteworthy that the absolute values of fluorescence intensity substantially depend on: 1, the geometric size of a sample; 2, the duration of sample staining with a fluorophore; and 3, the quality of sample staining with a fluorophore. To eliminate the effects of these factors we compared the curves of fura-2/AM fluorescence normalized to their maximum with subtraction of diastolic level for each sample. This allowed us to reveal specific features of $[Ca^{2+}]_i$ kinetics in the myocardium samples of different groups of animals.

In 1.5-month-old WAG rats it was found that the durations of the increment phase of calcium transitions ($[Ca^{2+}]_i$) in right and left ventricular myocardium samples were similar (Fig. 1a). However, in the ISIAH rats the $[Ca^{2+}]_i$ increase phase in the left ventricle myocardium was more than two times longer compared to the right ventricle myocardium. In 1.5-month-old rats of both strains the decrease in the duration of $[Ca^{2+}]_i$ from the peak to the level of <5% $[Ca^{2+}]_i$ amplitude in the left ventricle myocardium was significantly higher compared to the right ventricle myocardium. This increase in the duration of the $[Ca^{2+}]_i$ decrease or decrease in slowing was more expressed in the myocardium of the ISIAH rats. Moreover, the difference in the $[Ca^{2+}]_i$ decrease patterns between the myocardium samples of the right and left ventricles was more prominent in the ISIAH rats than in the WAG rats (Figs. 1a, 1b). The decline of the calcium transition in the myocardium of the left ventricle is monotonous, while in the myocardium of the right ventricle it has a pronounced phase of short-term deceleration, forming a characteristic knee-shaped course of decline (the so-called "bump" phase" [11, 12]).

During aging the kinetics of the $[Ca^{2+}]_i$ decrease in the samples of the myocardium of the right ventricle was slowing in both strains of rats (Fig. 2). Interestingly, the pattern of the decrease remained unchanged in the WAG rats (Fig. 2a). However, in the ISIAH rats the phase of the short-term slowing of the $[Ca^{2+}]_i$ decrease became less expressed with age due to significant deceleration of the initial stage of the decrease (Fig. 2b).

Comparison of changes in the kinetics of $[Ca^{2+}]_i$ transitions in the samples of the myocardium of the right ventricle in the 1.5-month-old WAG and ISIAH rats revealed that it was substantially non-monotonic only in ISIAH rats, so that in the initial phase the decline was faster than in normotensive rats, but slowed in the later phase, while it occurred later than in normotensive rats (Fig. 3a). This also means that the total duration of the calcium transition in the right ventricle myocardium of 1.5-month-old ISIAH rats

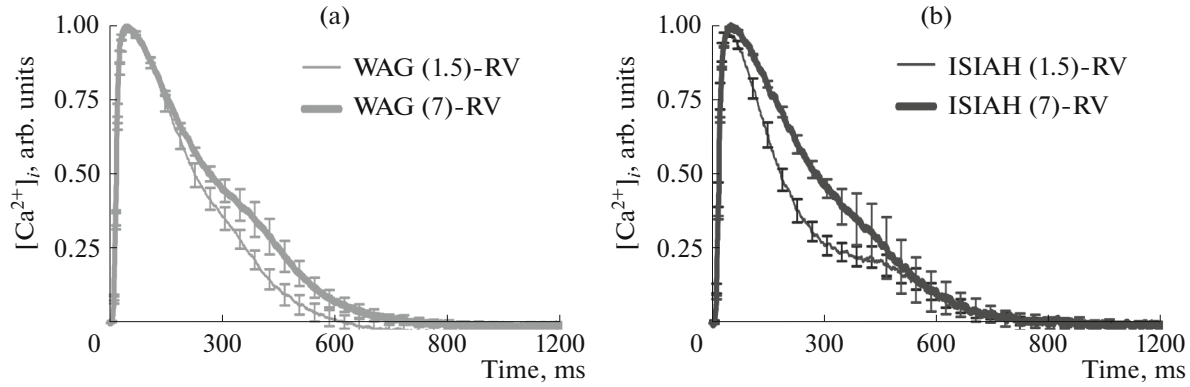

Fig. 2. Comparison of kinetics curves of free cytosolic calcium ($[Ca^{2+}]_i$) in the myocardium samples of the right cardiac ventricles of 1.5- and 7-month-old rats: (a), normotensive WAG rats; (b), hypertensive ISIAH rats. The measurements were performed with the muscle length equal to 95% of the optimal length. The curves are normalized to their own maximum, and the diastolic level is subtracted. Data are presented as mean of all group samples ± standard error of the mean.

was ~25% longer than in control rats of the same age. In the samples of the left ventricle myocardium of 1.5-month-old WAG and ISIAH rats, inherited arterial hypertension was associated with the slower decline of $[Ca^{2+}]_i$ regardless of the level of this decline (initial or advanced; Fig. 3b). Interestingly, in 7-month-old WAG and ISIAH rats no differences in the $[Ca^{2+}]_i$ increase or decrease kinetics were observed in the samples of the right ventricle myocardium (data not shown).

The muscular stretching rate significantly affected the $[Ca^{2+}]_i$ decrease in its cells in the myocardium of the right cardiac ventricle of WAG and ISIAH rats independent on their age. The decrease of $[Ca^{2+}]_i$ is monotonic in the non-stretched muscle; however, elongation of the myocardium sample up to 95% of its maximum length followed by its relaxation resulted in the $[Ca^{2+}]_i$ decline with a specific phase of short-term deceleration. This phase was more expressed in the rats with inherited arterial hypertension. In is import-

Table 1. The morphometrical indices of hearts of normotensive (WAG) and hypertensive (ISIAH) rats of two age groups (1.5 and 7 months)

Indices	Groups			
	ISIAH, 1.5 months, $n = 14$	WAG, 1.5 months, $n = 9$	ISIAH, 7 months, $n = 8$	WAG, 7 months, $n = 14$
Body weight, g	187.5 (170.0; 196.0) * #	159.0 (154.0; 170.0) * ##	398.0 (374.0; 416.0) #	374.5 (358.0; 393.00) ##
L_{tibia}	31.25 (29.30; 31.80) * #	27.80 (26.95; 28.30) * ##	42.40 (41.45; 43.20) ** #	39.95 (38.70; 41.40) ** ##
Heart weight, g	0.6791 (0.5917; 0.7287) * #	0.5294 (0.5222; 0.5720) * ##	1.0967 (1.0547; 1.1672) ** #	0.8367 (0.7882; 0.9505) ** ##
Heart weight/body weight ratio, g/g	0.0037 (0.0033; 0.0040) * #	0.0034 (0.0033; 0.0034) * ##	0.0028 (0.0027; 0.0029) ** #	0.0023 (0.0022; 0.0024) ** ##
Heart weight/L_{tibia} ratio, g/mm	0.0213 (0.0189; 0.0241) #	0.0192 (0.0187; 0.0194) ##	0.0254 (0.0250; 0.0274) ** #	0.0212 (0.0208; 0.0233) ** ##
P_{syst}, mmHg	–	–	169.3 (142.7; 194.3) **	114.7 (104.3; 123.0) **

Data are presented as median (lower quartile, upper quartile). L_{tibia}, length of tibia; P_{syst}, systolic arterial pressure in the tail artery. The differences are significant at $p < 0.05$ between the groups: *, ISIAH 1.5 months and WAG 1.5 months; **, ISIAH 7 months and WAG 7 months; #, ISIAH 1.5 months and ISIAH 7 months; ## WAG 1.5 months and WAG 7 months.

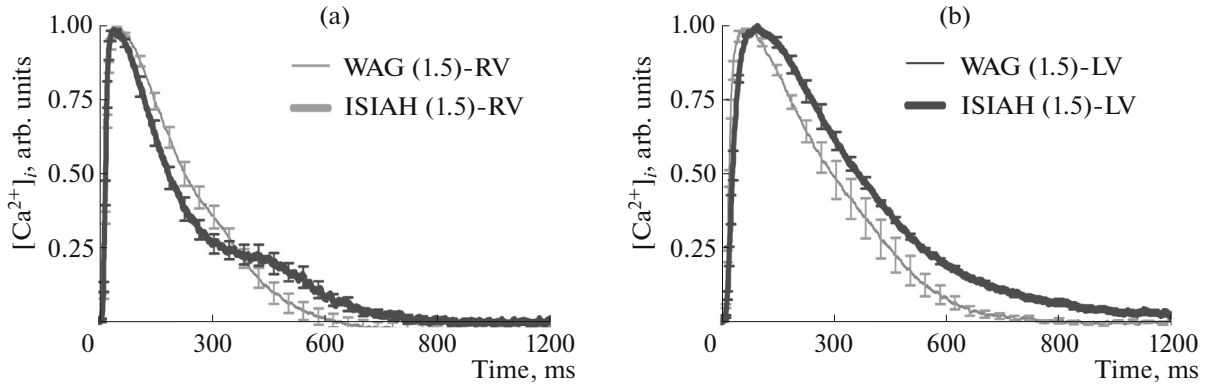

Fig. 3. Comparison of kinetics curves of free cytosolic calcium ($[Ca^{2+}]_i$) in the myocardium samples of the right and left cardiac ventricles of 1.5-month-old normotensive WAG rats and hypertensive ISIAH rats: (a), right ventricle; (b), left ventricle. The measurements were performed with the muscle length equal to 95% of the optimal length. The curves are normalized to their own maximum and the diastolic level is subtracted. Data are presented as the mean of all group samples ± standard error of the mean.

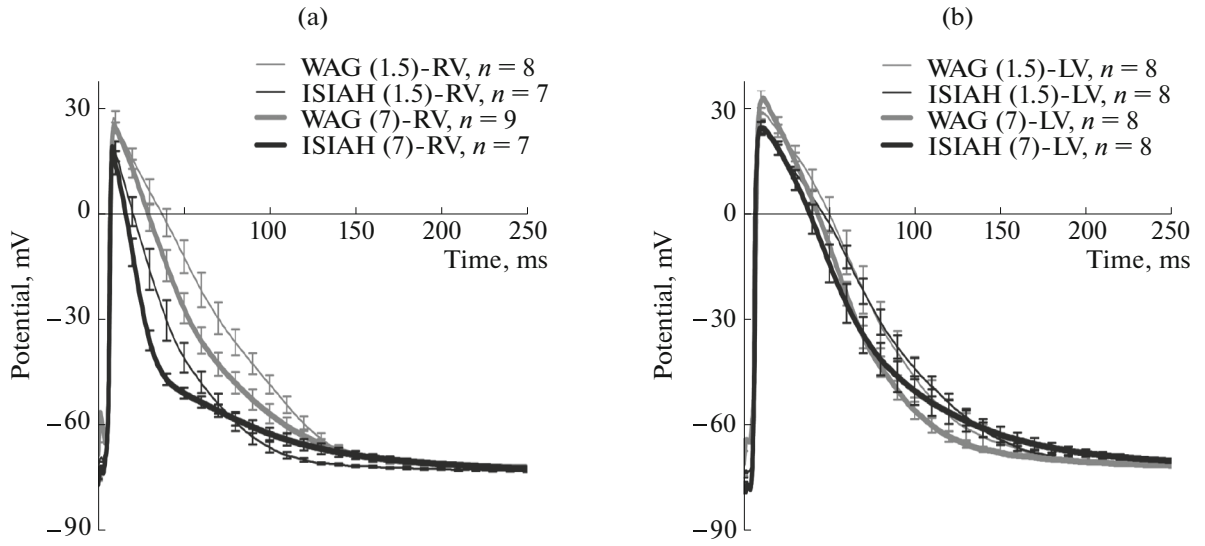

Fig. 4. Comparison of action potentials in the myocardium samples of the right and left cardiac ventricles of 1.5- and 7-month-old normotensive WAG rats and hypertensive ISIAH rats: (a), right ventricle; (b), left ventricle. The measurements were performed with the muscle length equal to 95% of the optimal length. Data are presented as mean of all group samples ± standard error of the mean.

ant that this effect was absent in the myocardium of the left ventricle.

The action potential. The action potentials in cardiomyocytes of 1.5- or 7-month-old WAG and ISIAH rats had typical appearance for myocardium in the samples of left and right ventricles (Fig. 4). Age-related differences were mostly expressed in the duration of the repolarization phase of the action potential in the samples of the right ventricle of the rats of both strains (Fig. 4a). The duration of the repolarization was significantly longer in the myocardium of the right ventricle of control rats compared to spontaneously hypertensive ISIAH rats. The duration of repolarization decreased with aging in the rats of both the experimental and control groups. Thus, in the myocardium of the right ventricle, the duration of repolarization of action potentials at the level of 50% amplitude and stimulation frequency of 0.33 Hz was 56.1 ± 3.8 and 43.1 ± 3.7 ms in 1.5- and 7-month-old WAG rats, respectively ($p = 0.0383$ according to Kruskal–Wallis test). In the myocardium of the right ventricle, the duration of repolarization of action potentials at the level of 50% amplitude was 30.7 ± 3.1 and 20.6 ± 1.1 ms in 1.5- and 7-month-old ISIAH rats, respectively ($p = 0.0086$ according to Kruskal–Wallis test). In papillary muscles of the left ventricle significant differences were observed between the groups of 1.5- and 7-month-old ISIAH rats in which the action potential durations at the level of 50% amplitude was 67.8 ± 3.9 and 54.6 ± 4.6 ms, respectively

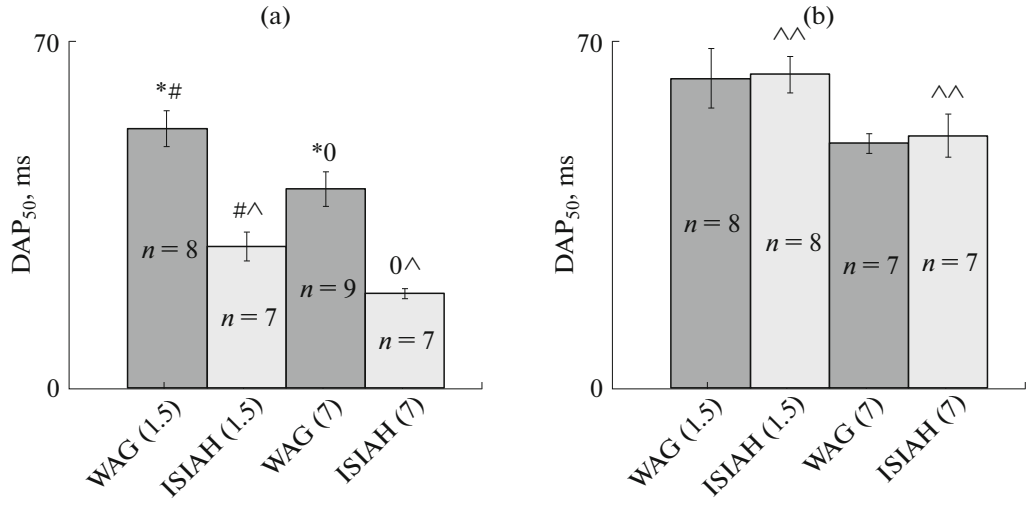

Fig. 5. The mean values of the duration of action potential at the level of 50% of the amplitude of action potential (DAP_{50}) in cardiomyocytes of papillary muscles of the right and left cardiac ventricles of 1.5- and 7-month-old normotensive WAG rats and-hypertensive ISIAH rats: (a), right ventricle; (b), left ventricle. The measurements were performed with the muscle length equal to 95% of the optimal length. Data are presented as mean of all group samples ± standard error of the mean. The differences are significant at $p < 0.05$ according to Kruskal–Wallis between *, WAG(1.5)-RV and WAG(7)-RV; ^, ISIAH(1.5)-RV and ISIAH(7)-RV; #, WAG(1.5)-RV and ISIAH(1.5)-RV; °, WAG(7)-RV and ISIAH(7)-RV; ^^, ISIAH(1.5)-LV and ISIAH(7)-LV.

($p = 0.0489$ according to Kruskal–Wallis test). The duration of action potentials at the level of 50% amplitude also decreased in both groups with aging (Fig. 4b).

A summary diagram of the duration of action potentials in the heart muscles of all the studied groups is provided in a more visual form in Fig. 5. An age-dependent decrease in the duration of action potentials in cardiac muscles of the left and right ventricles could be seen in both spontaneously hypertensive ISIAH and normotensive WAG rats. Samples of right ventricle myocardium differ from those of the left ventricle in that the duration of the action potentials at the level of 50% of the amplitude in ISIAH rats were shorter than in the WAG rats, regardless of age. In the left ventricle, the duration of the action potentials depends only on the ages of the normal and hypertensive rats.

DISCUSSION

The differences in the kinetics of calcium transitions ($[Ca^{2+}]_i$) found in the present study using isolated multicellular samples of ventricle myocardium from ISIAH rats with inherited arterial hypertension and myocardium of normotensive WAG rats are not in agreement with the literature data on the differences in the kinetics of free cytosolic calcium in the myocardium of spontaneously hypertensive SHR rats and normotensive Wistar-Kyoto (WKY) rats. Specifically, our experiments demonstrate that the duration of $[Ca^{2+}]_i$ fluorescence was longer, whereas its amplitude was lower in the ISIAH rats compared to those in myocardium of the normotensive WAG rats. Most studies in single ventricular cardiomyocytes of 1–6-month-old SHR and WKY rats show that the amplitude of $[Ca^{2+}]_i$ was higher in the hypertensive animals [3, 13, 14]. However, the duration of the $[Ca^{2+}]_i$ signal in the myocardium of hypertensive rats remained stable [13] or even increased [15], as we also showed. According to other studies, neither the amplitude nor the duration of the $[Ca^{2+}]_i$ signal change in spontaneously hypertensive rats [16].

The inverse ratio of the duration of action potentials in the myocardium of normotensive and hypertensive rats shown in our work also contradicts most of the literature data on the ratio of the duration of action potentials in the normal and hypertrophied myocardium. Similar to most animal models of cardiac hypertrophy, the myocardium of SHR rats has an increased duration of action potentials [14]. This phenomenon was first reported in studies performed in multicellular samples [17]. A significant increase in the duration of action potentials has been shown in the myocardium of SHR rats compared to WKY rats. The durations of the action potentials at the level of 50% amplitude were 39.8 ± 18.9 and 10.0 ± 2.7 ms in SHR and WKY rats, respectively [3]. Prolongation of action potentials has been demonstrated in the cardiomyocytes of the left ventricle of 2- or 17-month-old spontaneously hypertensive SHR rats compared to normotensive WKY rats at the frequency of stimulation of 0.2 Hz and temperature of 35°C [18].

In the hypertrophied rat hearts prolongation of action potentials was caused by loss of density of the repolarizing potassium current I_{t0}. This phenomenon

is directly related to the duration of hypertension. The I_{t0} current plays a leading role during the repolarization phase of the action potential in the rat myocardium [19]. In these conditions, the density of the slow calcium current (I_{CaL}) was slightly modified in hypertrophied myocytes of SHR rats compared to control rats. The prolongation of action potentials has been demonstrated in single cardiomyocytes; therefore, the authors assumed that this may be related to changes only in membrane properties [18].

Here, we showed the age-related kinetics of intracellular calcium ($[Ca^{2+}]_i$) action potentials for the first time and the morphometrical parameters of the myocardium samples of the left and right cardiac ventricles of ISIAH rats.

A 1.5-fold increase in arterial pressure was found in 7-month-old ISIAH rats in comparison with their WAG age group, which indicates the development of severe arterial hypertension. The development of progressive heart hypertrophy was supported by the excessive heart weight, as well as indices of the ratio of the heart weight to the body weight, or to the length of the tibia in ISIAH rats in comparison with WAG rats, which increased with age. Significant differences are shown not only in the duration of the phases of the increase and decrease of the Ca^{2+} concentration, but also in the nature of the decline of the calcium transition in the right ventricle samples relative to the samples from the left ventricle of the hearts of rats of ISIAH rats, as well as of normotensive animals.

We found significant changes in the duration of action potentials in the right ventricle samples. The duration of action potentials at the level of 50% of the amplitude in the right ventricle samples of ISIAH rats is shorter than in WAG rats, regardless of age. In the left ventricle, the duration of action potentials depends only on the age of the animals of both normotensive and hypertensive groups. The presented results also confirm the development of heart hypertrophy in ISIAH rats because the shortening of action potentials observed in ischemia or suppression of metabolism are more pronounced in cells of hypertrophied ventricles than in healthy hearts [20].

According to modern data, one of the main mechanisms of the development of hypertrophy is triggered by the release and activation of angiotensin II [22]. We suggest that the mechanism of hypertension development in ISIAH rats is mediated by activation of angiotensin II. This is expressed in the shortening of the duration of action potentials compared to the control myocardium as was demonstrated after the activation of AT_1-receptors of angiotensin II [23].

CONCLUSIONS

Thus, taken together the presented morphometrical, biomechanical, electrophysiological, and calcium parameters indicate that although the hypertrophy development in the myocardium of the right and left ventricles spontaneously hypertensive male ISIAH rats differs to some extent from that in SHR rats, there are some common features. We must note that it is correct to compare the parameters of contractility in each of two strains only in respect to the initial strain of normotensive animals. According to our data and the data of other authors, myocardial hypertrophy, which develops in response to gradually increasing hypertension in the hearts of ISIAH rats or SHR rats, differs in the properties of electromechanical coupling from myocardial hypertrophy, which develops in response to a prolonged, but suddenly imposed load. In this respect, the hypertrophy of the heart of animals of these two strains is mostly similar to the myocardial hypertrophy in essential human hypertension.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

All experiments with animals were performed in accordance with international rules for the treatment of laboratory animals and approved by the Commission of the Institute of Immunology and Physiology, Ural Branch, Russian Academy of Sciences on the control on laboratory animals.

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