Exercise Tolerance in Rats with Aortic Stenosis and Ventricular Diastolic and/or Systolic Dysfunction

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Abstract

Background: Physical stress tolerance (ST) is a measurement of cardiorespiratory fitness. Aerobic capacity is reduced in heart failure (HF) although there is no data available on this parameter in animals with ventricular dysfunction and no signs of HF.

Objective: Evaluate ST in rats with ventricular diastolic dysfunction isolated or associated with systolic dysfunction induced by ascending aortic stenosis (AoS).

Methods: Young male Wistar rats (20-30 days old), divided in: control group (CG, n=11) and AoS group, (n=12). Animals were assessed at 6 and 18 weeks after AoS surgery. Treadmill exercise test was until exhaustion and evaluated treadmill speed and lactate concentration [LAC] at lactate threshold, treadmill speed and [LAC] at exhaustion, and total testing time.

Results: Echocardiography data revealed remodeling of the left atrium and left ventricular concentric hypertrophy at 6 and 18 weeks. Endocardial fractional shortening was greater in AoS than CG at 6 and 18 weeks. Midwall fractional shortening was greater in AoS than in CG at 6 weeks. Cardiac index was similar in CG and AoS at 6 and 18 weeks and decreased between from 6 to 18 weeks in both groups. The E wave to A wave ratio was greater in CG than in AoS at both periods and did not change in both groups between week 6 and 18. Treadmill stress testing parameters were similar in both groups at 6 or 18 weeks.

Conclusion: Although AoS promotes isolated diastolic dysfunction or associated with systolic dysfunction at 6 or 18 weeks, it is not sufficient to modify physical stress tolerance. (Arq Bras Cardiol. 2013;100(1):44-51)

Keywords: Mice; Exercise; Aortic Valve Stenosis; Ventricular Dysfunction.

Introduction

The term cardiac remodeling (CR) has been widely used and can be defined as a modification in genome expression resulting in molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart following aggression.

CR is an important adaptive mechanism to chronic hemodynamic load that allows the heart to maintain its basic functions in response to increased load, but it is also a considerable risk factor for ventricular dysfunction and heart failure.

A variety of experimental models have been proposed to investigate pressure overload-induced CR. More recently, the model of ascending aortic stenosis (AoS) has been used to promote the gradual development of left ventricular hypertrophy in rats. In this model, animals develop cardiac remodeling that is associated, in the short term, with diastolic dysfunction and improved systolic function followed by depressed systolic performance and heart failure.

The physical stress test (ST), one of the most commonly used noninvasive methods for the evaluation of cardiovascular disease, can detect heart function abnormalities not observable at rest. Tolerance to ST, a normative measurement of cardiorespiratory fitness and aerobic capacity, is the ability to perform dynamic activities during physical stress. This ability is commonly reduced in patients and animals with heart failure (HF). However, information on patients and animals with ventricular dysfunction and no signs of HF was not found in the literature.

The purpose of this study was to test the hypothesis that tolerance to physical stress is impaired in the presence of ventricular diastolic dysfunction isolated or associated with systolic dysfunction and no heart failure induced by aortic stenosis.
Methods

All experiments and procedures were performed in agreement with Guide for the Care and Use of Laboratory Animals published by the National Research Council (1996) and were approved by the Animal Ethics Committee of the Botucatu Medical School, UNESP — Universidade Estadual Júlio Mesquita Filho on 10/19/2005 (protocol number 506/2005).

Animal

Twenty-three young male Wistar rats were randomly distributed in two groups: control (CG, n=11) and ascending aortic stenosis (AoSG, n=12). In AoSG, aortic stenosis was induced by placing a silver band on the aorta. CG underwent the same surgery without band placement. All animals were housed in individual cages in a room maintained at 23°C on a 12:12-h light-dark cycle and fed standard Purina® rat chow and water ad libitum.

Ascending aortic stenosis induction

Cardiac remodeling was induced by AoS according to the method used by several authors5-7,9. The animals, weighing 70-90 g, 20-30 days old, underwent median thoracotomy under anesthesia with intraperitoneal ketamine hydrochloride (60 mg/kg) and xylidine hydrochloride (10 mg / kg). The ascending aorta was disected and a 0.6-mm internal diameter silver band was placed at approximately 3 mm of the aortic root. CG animals underwent the same surgery, but without band placement.

According to previous studies, animals start to develop ventricular diastolic dysfunction isolated or associated with systolic dysfunction at 6 and 18 weeks after surgery, respectively5,7,9. Thus, all animals were assessed at these time points: 6 weeks (diastolic dysfunction) and 18 weeks (diastolic dysfunction associated with systolic).

Echocardiography assessment

LV diastolic and systolic functions as well as heart structure were assessed by ECHO according to the method used in our laboratory16. The animals were anesthetized with intraperitoneal ketamine hydrochloride (50 mg/kg) and xylidine hydrochloride (1 mg/kg) for examination with a M-Mode echocardiograph (Philips®, model HDI 5000) equipped with a 12-MHz electronic transducer to measure the left atrium diameter (LA) and the following left ventricular parameters: diastolic and systolic diameter (LVDD and LVDs, respectively), diastolic and systolic posterior wall thickness (LVDWT and LVSWT, respectively), diastolic and systolic interventricular septal thickness (IVSDT and IVSST), and left ventricle mass (LV MASS). The left ventricular mass index (LVMI) was determined by normalizing LV mass for body weight (BW). LV wall relative thickness (LWWRT) was estimated dividing LVDWT by LVDD.

The LV systolic function was determined by the percent of endocardial shortening (ΔD endo) and the midwall fractional shortening (ΔD mid), and cardiac index (CI). The ΔD mid was calculated using the formula (\[\{(LVDD + \frac{1}{2} PWDT + \frac{1}{2} IVSDT) - (LVSD + \frac{1}{2} PWST + \frac{1}{2} IVSST)\}/(LVDD + \frac{1}{2} PWDT + \frac{1}{2} IVSDT))\). The ΔD endo was calculated by the formula (\[(LVDD − LVSD) / LV DD x 100\]).

The diastolic function was assessed by E-waves and A, ratio between E-waves and A-wave (E/A).

Assessment of physical stress tolerance

Physical stress testing

Stress testing was performed using a rodent treadmill constructed by the Technological Center of Clinical Engineering - Universidade Estadual Júlio Mesquita Filho UNESP/Botucatu, São Paulo, Brazil. The protocol used for multistage interval testing was adapted from that previously described by Carvalho et al17. Each animal was tested individually. The test consisted of an initial 5-min warm up at 5m/min. After 1 min of passive recuperation, the animal was submitted to interval exercise at a speed of 6m/min followed by 3m/min increases in speed every 3 minutes until exhaustion. Exhaustion was determined when the animal refused to run even after sound stimulation or was unable to coordinate steps. After each load increase, the animal was manually taken out of the treadmill for 1 min for blood collection16.

Experimental Protocol

A schematic representation of the test protocol is shown in Figure 1. All rats underwent a period of adaptation to become familiarized with the experiment protocol by daily walking 5 minutes at 5 m/min for one week before testing. Physical stress testing was performed 6 and 18 weeks after surgery in CG and AoSG, that is, by the diastolic dysfunction isolated or associated with systolic dysfunction, respectively.

Parameters assessed

Treadmill speed (SLT, m/min) and lactate concentration ([LAC]ₘₐₓ mmol/L) at lactate threshold

For the assessment of SLT and [LAC]ₘₐₓ, it was necessary to determine lactate threshold (LT), defined as the exercise intensity at which lactate concentration starts to substantially increase in the bloodstream during incremental exercise18. Blood samples (25 μl) were drawn from the tail of animals at rest and after every load increase. Collection was carried out using 25x75x1mm glass microscope slides (Sigma Chemical Company® – USA, model Techware S 8902) and 20-200 μl digital micropipettes (Nichiryo Co.® – Japan, model Nichipet NPX 200) with disposable tips that were changed after each collection. The blood collected was immediately stored in 1.5-ml Eppendorf tubes with lid containing 50 μl of 1% fluoride, anticoagulant and enolase enzyme inhibitor to suppress glycolytic activity. Blood samples were refrigerated during collection and then kept in a freezer until use. Lactate concentration was determined by the electroenzymatic method using a lactimeter (Yellow Springs Instruments®, 1500 Sport – USA) owned by the Exercise Physiology Laboratory.
of the Department of Physiological Sciences – Universidade Federal São Carlos, São Paulo, Brazil. The device was calibrated according to the instructions of the manufacturer. Lactate concentrations were plotted against stage speed. LT was considered as the point where lactate levels started to rise as a function of speed as detected by visual inspection. The speed and lactate concentration found at this point were considered as speed and lactate concentration at lactate threshold (SLT and [LAC]_{LT}, respectively). The graphs were analyzed by two experienced investigators with an inter-observer agreement of 96 %. When disagreement regarding LT occurred, the mean of the values indicated by each observer was used. The graph plotting results for one of the animals are shown in Figure 2.

Treadmill speed (SEx, m/min) and lactate concentration ([LAC]_{EX}, mmol/L) at exhaustion

These parameters were determined as described above, but at exhaustion.

Total testing time (TTT, sec)

TTT was the sum of all stage times up to exhaustion. Intervals between stages were not taken into consideration.

Body and heart morphological characteristics

By the end of the experiment, the animals were anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg) and decapitated. The following variables were assessed: final body weight (BW), LV weight, RV weight, atrial (left + right) weight (A), LV/BW, RV/BW, A/BW. Fragments of liver (LIVER_{w/d}) and lung (LUNG_{w/d}) were weighed before and after they were placed in an oven at 60°C for 48 h to obtain the wet-to-dry ratio.

Statistical Analysis

Results are reported as position and variability measurements according to data distribution. Morphological parameters were analyzed using the Student’s t-test, when the variable has shown adherence to the normal probability distribution, and using the Mann-Whitney test, when this characteristic was absent. Comparisons between groups were performed using two-way repeated measures ANOVA with one-factor repetition followed by Bonferroni’s multiple comparison procedure. For non-parametric parameters, Anova on ranks and Friedman test was used. Significance level for all tests was set at 5% (p<0.05). Statistical calculations were performed using SigmaStat 3.5 for Windows version (Copyright© 2006, Systat Software Inc.).

Results

Table 1 summarizes morphological data. Body weight was similar in control group (CG) and ascending aortic stenosis group (AoSG). The LV/body weight, RV/body weight and A/body weight were increased in AoSG in relation of CG. There was no difference in LIVER_{w/d} and LUNG_{w/d} fragments.

Table 2 shows serial echocardiographic data of structural and functional parameters at 6 and 18 weeks in CG and
AoSG. Left ventricular mass index decreased between week 6 and week 18 in CG and remained unchanged in AoSG; this parameter was higher in AoSG than CG at 6 and 18 weeks. Left ventricular wall relative thickness did not change in CG, but increased between week 6 and week 18 in AoSG; this variable was higher in AoSG than in CG at 6 and 18 weeks. LA/BW decreased in both groups at week 18 when compared to week 6; it was higher in AoSG than in CG at both evaluated times. Endocardial (ΔD endo) and midwall (ΔD mid) fractional shortening did not change with time in CG, but both decreased between 6 and 18 weeks in the AoSG; ΔD endo was higher in AoSG than in CG at 6 and 18 weeks; ΔD mid was higher in AoSG than in CG at week 6 and similar in both groups at week 18. Cardiac index decreased in both groups between 6 and 18 weeks; it was similar between both groups in the two evaluated times. E/A was similar in both groups between weeks 6 and 18; however, it was higher in CG than in AoSG in both moments.

Table 3 shows the results of physical stress tolerance assessment. There was no significant difference in speed at exhaustion, total testing time, speed at lactate threshold, lactate concentrations at SLT and at SEx between 6 and 18 weeks in both groups. These parameters were similar between CG and AoSG in both moments.

**Discussion**

The aortic stenosis employed in this study promoted early left atrium and ventricular hypertrophy, which persisted up to the end of the experiment. It was observed by atrial
Table 2 - Echocardiographic data

<table>
<thead>
<tr>
<th>Groups</th>
<th>PERIOD OF ASSESSMENT</th>
<th>6 weeks</th>
<th>18 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>CG</td>
<td>311 ± 34</td>
<td>327 ± 66</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>327 ± 46</td>
<td>345 ± 48</td>
</tr>
<tr>
<td>LVMI, g/kg</td>
<td>CG</td>
<td>2.62 ± 0.36</td>
<td>2.14 ± 0.32#</td>
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<tr>
<td></td>
<td>AoSG</td>
<td>3.29 ± 0.66*</td>
<td>3.01 ± 0.96*</td>
</tr>
<tr>
<td>LVWRT</td>
<td>CG</td>
<td>0.17 ± 0.01</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>0.23 ± 0.04*</td>
<td>0.28 ± 0.06#*</td>
</tr>
<tr>
<td>LA/BW, mm/kg</td>
<td>CG</td>
<td>16.95 ± 2.29</td>
<td>11.83 ± 2.65#</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>20.40 ± 2.92*</td>
<td>14.43 ± 2.95*</td>
</tr>
<tr>
<td>∆D endo, %</td>
<td>CG</td>
<td>48.20 ± 4.17</td>
<td>50.35 ± 3.00</td>
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<tr>
<td></td>
<td>AoSG</td>
<td>61.05 ± 5.04*</td>
<td>55.65 ± 9.20#</td>
</tr>
<tr>
<td>∆D mid, %</td>
<td>CG</td>
<td>29.71 ± 3.51</td>
<td>31.41 ± 2.35</td>
</tr>
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<td>AoSG</td>
<td>37.07 ± 2.64*</td>
<td>31.60 ± 4.75#</td>
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<tr>
<td>CI, ml/min.g⁻¹</td>
<td>CG</td>
<td>0.47 ± 0.09</td>
<td>0.38 ± 0.07#</td>
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<tr>
<td></td>
<td>AoSG</td>
<td>0.45 ± 0.11</td>
<td>0.33 ± 0.09#</td>
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<tr>
<td>E/A</td>
<td>CG</td>
<td>1.76 ± 0.16</td>
<td>1.43 ± 0.36</td>
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<tr>
<td></td>
<td>AoSG</td>
<td>1.32 ± 0.30*</td>
<td>1.09 ± 0.54*</td>
</tr>
</tbody>
</table>

Values are means ± SD; CG : control group (n = 11); AoSG : ascending aortic stenosis group (n = 12); D : diastolic dysfunction; S : systolic dysfunction; HR : heart rate; LVMI : mass index left ventricle; LVWRT : wall relative thickness; LA : left atrium; ∆D endo and mid : endocardial and midwall fractional shortening; CI : cardiac index; E : peak velocity of early ventricular filling; A : peak velocity of transmitral flow during atrial contraction. *: AoSG vs. CG; #: 18 vs. 6 weeks; two-factor ANOVA for repeated measures followed by Bonferroni’s test, p < 0.05.

Table 3 — Physical stress tolerance

<table>
<thead>
<tr>
<th>PERIOD OF ASSESSMENT</th>
<th>6 weeks</th>
<th>18 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEx*, m/min</td>
<td>CG</td>
<td>15.0 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>15.0 ± 1.5</td>
</tr>
<tr>
<td>TTT, sec</td>
<td>CG</td>
<td>680 ± 151</td>
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<tr>
<td></td>
<td>AoSG</td>
<td>580 ± 107</td>
</tr>
<tr>
<td>SLT†, m/min</td>
<td>CG</td>
<td>9.0 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>9.0 ± 3.0</td>
</tr>
<tr>
<td>[LAC]LT, mmol/L</td>
<td>CG</td>
<td>1.59 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>1.43 ± 0.38</td>
</tr>
<tr>
<td>[LAC]EX, mmol/L</td>
<td>CG</td>
<td>3.74 ± 1.63</td>
</tr>
<tr>
<td></td>
<td>AoSG</td>
<td>4.27 ± 1.51</td>
</tr>
</tbody>
</table>

Values are means ± SD; CG : control group (n = 11); AoSG : ascending aortic stenosis group (n = 12); D : diastolic dysfunction; S : systolic dysfunction; Sex : speed of exhaustion; TTT : time total test; SLT : speed of lactate threshold; [LAC]LT : concentration of lactate on lactate threshold; [LAC]EX : concentration of lactate on exhaustion. Two-factor ANOVA for repeated measures followed by Bonferroni’s test, p<0.05; †: median ± half-amplitude, repeated measures analysis of variance (ANOVA) on ranks followed by Friedman test.

and ventricular mass at morphologic and echocardiography analysis. The increase of left ventricle wall relative thickness in stenosis group indicates concentric hypertrophy. The data are in agreement with previous studies that showed cardiac remodeling in this experimental model\(^5\)\(^,\)\(^9\)\(^,\)\(^11\)\(^,\)\(^20\). Remodeling of the left chamber is an adaptive response to ventricular pressure rise; the increase in wall thickness and cavity volume decrease parietal stress and, in consequence, LV function\(^1\)\(^,\)\(^21\).
No clinical or morphological signs of heart failure, i.e. tachypnea associated with edema, ascites, pleuropericardial effusion, LA thrombus or RV hypertrophy were observed. The isolated finding of an increase in RV/BW ratio does not indicate that AoSG rats developed heart failure; this was confirmed by the fact that LIVER\textsubscript{w/d} and LUNG\textsubscript{w/d} were similar in control and AoSG groups.

LV systolic function, as assessed by ΔD endo and ΔD mid, was increased in AoSG when compared with CG at week 6, and deteriorated during remodeling in the AoSG (Table 2). The ΔD endo observed at week 6 was similar to that reported by Bregagno et al\textsuperscript{24}, Ribeiro et al\textsuperscript{11} and Litwin et al\textsuperscript{9} who found an improved systolic function at this time. Furthermore, these authors also observed worsening after 18 or 21 weeks. The improved systolic function seen in AoSG, in comparison with CG at week 6 might be related to the development of concentric hypertrophy, wall systolic tension normalization, and maintenance of myocardial fiber oxygen consumption within its physiological range\textsuperscript{9}. The progressive loss of systolic function may be related with adverse remodeling of ventricular geometry, changes in myocardial composition, progressive contractility impairment or with all those factors combined\textsuperscript{22-24}.

Differently from systolic function, diastolic performance deteriorated early in AoSG in comparison with CG. At week 6, there was a reduction in E/A ratio which remained observable at week 18. AoSG E/A ratio, which was smaller than in CG, suggests the presence of diastolic dysfunction. Our results differ from author\textsuperscript{9} that observed no changes in E/A ratio 6 weeks after AoSG induction in rats and investigators who found an increase in E/A 12, 18 or 21 weeks after AoSG induction\textsuperscript{9,22}. Conflicting results may occur due to the different levels of left ventricular hypertrophy or technical difficulties in obtaining images adequate for the analysis of the Doppler effect; the high heart rate in rats fuse E and A waves making it difficult to measure diastolic function\textsuperscript{25}. Despite the inconsistent results found assessing diastolic function using E/A 6 weeks, an increased LA diameter observed in this study indicates LV diastolic dysfunction, since an improved systolic function was observed in the AoS group in comparison with controls. During ventricular diastole, LA is directly exposed to intraventricular pressures through the mitral valve. Eventual rises in ventricular diastolic pressure increase atrial pressure and thereby chamber remodeling. Experimental studies of AoS have associated myocardial stiffness with an increase in collagen fibers and changes in the proteins involved in intracellular calcium reuptake, particularly the sarcoplasmic reticulum calcium pump\textsuperscript{26}. Thus, the diastolic function depression observed 6 and 18 weeks after AoS may be related with changes in elastic properties and disturbances in calcium handling.

While the echocardiographic data showed functional and structural changes at weeks 6 and 18, stress tolerance test did not detect change in functional capacity in both groups. In our knowledge, it’s the first research that evaluated exercise physical tolerance in rat with ascending aortic stenosis. The TTT was the only parameter to show a strong tendency toward decrease in animal with AoS (0.05<p<0.10). The similar stress response may be due to: 1) an inadequate protocol; 2) parameters insensitive to detect changes in functional capacity; and 3) ventricular dysfunction level. With regard to the first item, the physical stress testing used can be considered adequate for the following reasons: i) similar methods have been used in other experimental studies\textsuperscript{22,26}; ii) it allowed submitting the animals to an individualized physical stress program; iii) the gradual increase of load interrupted the linear pattern of the lactate concentration curve and allowed determining LT; iii) no deaths occurred during testing or immediately afterward, indicating that, despite being a maximal test, it can be used in the experimental AoS model. The parameters used were considered appropriate because: i) SLT and/or SEx have been successfully used in several experimental works in normal rats\textsuperscript{17,27,28}, in rats with abdominal aortic stenosis or myocardial infarction\textsuperscript{18,27}; ii) TTT has also been employed to assess functional capacity in infarcted and hypertensive animals\textsuperscript{26,29}. In asymptomatic AoS patients, it has been considered to be a good predictor of the onset of heart failure signs\textsuperscript{10}; iii) \([\text{LAC}]_{\text{i}}\) and \([\text{LAC}]_{\text{o}}\) have been used in experimental studies in humans as a marker of physical training intensity\textsuperscript{30}. In relation to item 3, the literature shows that stress testing has detected functional capacity reduction in animals with ventricular diastolic dysfunction induced by arterial hypertension\textsuperscript{9} or, more commonly, with heart failure induced by myocardial infarction\textsuperscript{31}. Moreover, the test is reported to be negative in rats with abdominal aortic stenosis and compensated ventricular hypertrophy\textsuperscript{26}, and in a rat model of hyperadrenalinemia induced by adrenalin tablet implantations. In this study, no signs of heart failure were observed, even though diastolic and systolic performances were depressed in AoSG during remodeling. Given that the literature shows that stress testing is significantly positive in animals with heart failure\textsuperscript{14,15}, the absence of changes observed here may be related to the level of ventricular dysfunction, which was probably moderate. The similar data of cardiac index indicates peripheral blood flow perfusion equivalent between groups. Another explanation about absence of difference between groups can be related of speed exhaustion of control rats. Physical stress test protocol showed small values of speed at exhaustion (15 m/min) and speed at lactate threshold (9.0m/min) in control rats. In accordance to literature it would be expected higher values of these parameters. Ferreira et al\textsuperscript{32} observed speed at exhaustion of 28 m/min and speed at lactate threshold of 15 m/min in untrained mice. Carvalho et al\textsuperscript{17} shown speed at exhaustion of 19.5 m/min and speed at lactate threshold of 14.9 m/min in untrained rats. Despite of controversy data, the lactate concentration at exhaustion observed by us were similar at 18 m/min of speed in the Ferreira et al\textsuperscript{17} study and in the speed of exhaustion (19.5 m/min) observed by Carvalho et al\textsuperscript{17}. Therefore, it means that our rats attained maximum or near of maximum effort during exercise testing.

The mechanisms responsible for the reduction in exercise capacity have not been completely elucidated. Some of the possible factors include inadequate flow to skeletal muscle secondary to systolic and diastolic dysfunction and changes in the metabolism of the peripheral musculature\textsuperscript{26}. Since the response to physical stress remained unchanged during interval testing, the factors mentioned above either were absent or of insufficient magnitude in the rats with AoS assessed in this study.

Some limitations about this research should be stated: 1) maximal physical exercise testing in rats with ventricular hypertrophy can be dangerous due to death risk; so our rats can perform sub maximal effort during test; 2) lacking of functional
parameters that estimate exercise intensity during physical testing (i.e. heart rate, arterial pressure, oxygen consumption); 3) lacking literature data about time, speed running, lactate in similar experimental conditions.

In conclusion, no changes in physical stress tolerance were observed in the presence of diastolic dysfunction isolated or associated with systolic dysfunction. The level of left ventricular dysfunction seems to be the major determinant on the results of this study. Further studies including animals with greater ventricular dysfunction or heart failure as well as the analysis of the mechanisms that might alter the cardiac remodeling/stress tolerance relationship are necessary.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This article is part of the master thesis submitted by Olga de Castro Mendes da Silva, from Faculdade de Medicina da Universidade Estadual Paulista Júlio de Mesquita Filho.

References


