Relative systolic dysfunction in female spontaneously hypertensive rat myocardium

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Renna BF, MacDonnell SM, Reger PO, Crabbe DL, Houser SR, Libonati JR. Relative systolic dysfunction in female spontaneously hypertensive rat myocardium. J Appl Physiol 103: 353–358, 2007. First published April 12, 2007; doi:10.1152/japplphysiol.01416.2006—Hypertension and exercise independently induce left ventricular (LV) remodeling and alter LV function. The purpose of this study was to determine systolic and diastolic LV pressure-volume relationships (LV-PV) in spontaneously hypertensive rats (SHR) with and without LV hypertrophy, and to determine whether 6 mo of exercise training modified the LV-PV in SHR. Four-month-old female SHR (n = 20), were assigned to a sedentary (SHR-SED) or treadmill-trained (SHR-TRD) group (~60% peak O2 consumption, 5 days/wk, 6 mo), while age-matched female Wistar-Kyoto rats (WKY; n = 13) served as normotensive controls. The LV-PV was determined using a Langendorff isolated heart preparation at 4 (no hypertrophy: WKY, n = 5; SHR, n = 5) and 10 mo of age (hypertrophy: WKY, n = 8; SHR-SED, n = 8; SHR-TRD, n = 7). At 4 mo, the LV-PV in SHR was similar to that observed in WKY controls. However, at 10 mo of age, a rightward shift in the LV-PV occurred in SHR. Exercise training did not alter the extent of the shift in the LV-PV relative to SHR-SED. Relative systolic function, i.e., relative systolic elastance, was ~50% lower in SHR than WKY at 10 mo of age (P < 0.05). Doppler-derived LV filling parameters [early wave (E), atrial wave (A), and the E/A ratio] were similar between groups. LV capacitance was increased in SHR at 10 mo (P < 0.05), whereas LV diastolic chamber stiffness was similar between groups at 10 mo. Hypertrophic remodeling at 10 mo of age in female SHR is manifest with relative systolic decompensation and normal LV diastolic function. Exercise training did not alter the LV-PV in SHR.

Systolic performance with hypertension-induced hypertrophy (2, 6, 8, 17), one aim of the present paper was to examine indexes of systolic and diastolic cardiac function specifically in the female SHR model, at age intervals in which hypertension-induced hypertrophy is either absent (4 mo of age) or present (10 mo of age). The rationale for the use of female animals in our study was based on clinical data that suggest that female patients are more apt to exhibit congestive heart failure with preserved LV systolic function and LV diastolic dysfunction, than are male patients (16). Our study was also intended to complement already existing in vivo and in vitro data from Cingolani et al. (11).

It is well documented that exercise training favorably impacts the entire cardiovascular system and improves systolic and diastolic cardiac performance in human and experimental animal models (31). In normotensive animals, peak O2 consumption is well correlated to diastolic function (1, 5, 12, 20, 21, 25, 30, 40, 41), with training reported to decrease LV diastolic stiffness (43, 44) and induce a rightward shift in the pressure-volume relationship (23, 24, 26). Training has also been shown to enhance survival in rodent models of cardiomyopathy (19) and heart failure (14, 22). Thus we hypothesized that if LV diastolic dysfunction exists in the pressure-overloaded SHR myocardium, training would mitigate its severity. Few studies have specifically examined how cardiac performance is impacted when exercise training is superimposed on SHR, with no study to our knowledge specifically examining cardiac mechanics (28, 35, 36). Thus the second aim of the present study was to establish whether the intervention of exercise training altered the LV mechanical phenotype, i.e., the Frank-Starling relationship, in female SHR.

METHODS

Experimental paradigm. Thirty-three, 4 mo-old, female Wistar-Kyoto rats (WKY; n = 13) and SHR (n = 20) were obtained from Charles River Laboratories (St.-Constant, Quebec, Canada). At 4 mo of age, 10 animals were killed (WKY; n = 5 and SHR; n = 5) to establish ex vivo LV performance when hypertension, but not compensated hypertension, is evident in SHR. The remaining 8 WKY served as the normotensive controls, while the remaining 15 SHR were further randomly subdivided into SHR sedentary (SHR-SED; n = 8) or SHR exercise-trained (SHR-TRD; n = 7) groups. As previously described (36), exercise training consisted of progressive low-intensity endurance training at speeds of 20–25 m/min, 0% grade, 60 min, 5 days/wk for 24 wk. All rats were housed three per cage, maintained on a 12:12-h light-dark cycle, and fed ad libitum (18%...
protein diet, Harlan Teklad Global Diets, Madison, WI). Blood pressures and heart rates were collected at 4 and 10 mo of age using a tail-cuff apparatus (model XBP 1000, Kent Scientific, Torrington, CT). Animals were acclimated to the tail cuff apparatus two times before blood pressure determination. At 10 mo of age, WKY and SHR animals underwent echocardiographic assessment of LV performance and on a separate day were killed for \textit{ex vivo} LV functional studies. All animals received humane care in compliance with Temple University Institutional Animal Care and Use Committee and the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

\textbf{Echocardiography.} Rats were studied using echocardiography as previously described (28, 36). Values were determined by averaging the measurements of three consecutive cardiac cycles. In accordance with the American Society of Echocardiography conventions, M-mode imaging of the parasternal short-axis view allowed for measurement of LV end-diastolic and end-systolic internal dimensions (LVEDD and LVESD, respectively) and anterior and posterior wall thicknesses. Pulsed wave Doppler was used to assess the early (E wave) and atrial (A wave) components of the LV diastolic filling period.

\textit{Langendorff experiments.} To characterize the effects of exercise on LV mechanical function, LV pressure-volume relationships were determined in isolated, isovolumic, buffer-perfused hearts. Rats were anesthetized with sodium pentobarbital (60 mg/kg ip) and heparinized (500 U iv). A thoracotomy was performed, and the heart was excised and retrogradely perfused in a Langendorff mode as previously described (28, 35, 36). During equilibration, all hearts were loaded with an initial balloon volume yielding an LV end-diastolic pressure (LVEDP) of 10 mmHg. LV systolic pressure (LVSP), LVEDP, and coronary perfusion pressure (CPP) were continuously recorded by means of a data acquisition system (Powerlab/8SP, ADI Instruments, \textit{Hemodynamics, animal characteristics, characteristics, citrate synthase activity, Doppler analysis, systolic elastance, and LV capacitance were compared with one-way ANOVA and least significant difference post hoc analysis. LV diastolic chamber stiffness was compared with ANOVA with normalized ranks and Bonferroni post hoc analysis. LV pressure-volume loops were compared with ANOVA for repeated measures followed by least significant difference post hoc analysis. All analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL). Statistical significance was set at an alpha level of \( P < 0.05 \). All data are reported as means \( \pm SE \).

\textbf{RESULTS}

\textit{Hemodynamic parameters.} Table 1 illustrates the systolic blood pressure (SBP), heart rate, and rate pressure product (RPP) in WKY and SHR at 4 and 10 mo of age. As expected, SBP was significantly lower in WKY compared with SHR at 4 mo (\( P < 0.01 \)). SBP in WKY was similar at 4 and 10 mo of age. SBP increased in both groups of SHR from 4 to 10 mo (\( P < 0.001 \)). At 10 mo of age, the SBP of WKY was lower than both groups of SHR (\( P < 0.001 \)). Both heart rate and RPP were also lower in WKY vs. SHR at 4 mo (\( P < 0.01 \)) and 10 mo of age (\( P < 0.001 \)). At 10 mo of age, SBP, heart rate, and RPP were similar between SHR-TRD and SHR-SED.

\textit{Animal characteristics.} The physical characteristics of all groups are presented in Table 2. Before death, body weight in WKY was significantly greater than SHR at 4 mo (\( P < 0.05 \)) and significantly greater than both SHR groups at 10 mo of age (\( P < 0.001 \)). Heart weight was greater in WKY vs. SHR at 4 mo. However, heart weight-to-body weight ratio was similar between WKY and SHR at 4 mo. Heart weight and heart weight-to-body weight ratio were lower in WKY compared with both SHR groups at 10 mo of age (\( P < 0.001 \)). Heart weight and heart weight-to-body weight ratio also increased from 4 to 10 mo in both groups of SHR (\( P < 0.05 \)) but not WKY. In fact, heart weight-to-body weight ratio was reduced in WKY from 4 to 10 mo (\( P < 0.001 \)). At 10 mo of age, the physical characteristics of SHR-SED and SHR-TRD were similar. Soleus citrate synthase activity at 10 mo of age is also reported in Table 2. Citrate synthase activity was increased in SHR-TRD compared with both WKY and SHR-SED (\( P < 0.01 \) and \( P < 0.05 \), respectively).

\textit{Echocardiography.} Echocardiographic indexes at 10 mo of age are reported in Table 3. Anterior wall thickness during diastole was greater in SHR-TRD than WKY or SHR-SED (\( P < 0.05 \)). LV internal dimensions, peak E, A, E/A ratio, and LV fractional shortening between WKY and SHR at 10 mo of age were not statistically different between groups.

\textit{Langendorff Isolated Heart Performance.} Figure 1 illustrates the LVSP/V and LVEDP/V in WKY, SHR-SED, and SHR-TRD at 4 and 10 mo of age. At 4 mo of age both the LVSP/V and LVEDP/V were similar in WKY and SHR. From 4 to 10 mo of age the LVSP/V and LVEDP/V were also similar in WKY. However, in SHR at 10 mo of age, there was a decrease in LVSP/V and LVEDP/V and an increase in LVSP/V and LVEDP/V at 10 mo of age.

Table 1. \textit{Hemodynamics at 4 and 10 mo of age}

\begin{tabular}{lccc}
\hline
Group & SBP, mmHg & HR, beats/min & RPP \\
\hline
4 mo & & & \\
WKY (n = 5) & 141 & \( \pm 7 \) & 348 & \( \pm 16 \) & 49.389 & \( \pm 4.611 \) \\
SHR (n = 5) & 156 & \( \pm 4^* \) & 443 & \( \pm 18^* \) & 69.539 & \( \pm 4.636^* \) \\
10 mo & & & \\
WKY (n = 8) & 139 & \( \pm 2 \) & 380 & \( \pm 15 \) & 52.756 & \( \pm 2.516 \) \\
SHR-SED (n = 8) & 188 & \( \pm 2^†† \) & 504 & \( \pm 16^†† \) & 94.682 & \( 3.747^†† \) \\
SHR-TRD (n = 7) & 190 & \( \pm 2^†‡ \) & 486 & \( \pm 12^†‡ \) & 92.218 & \( 2.607^†‡ \) \\
\hline
\end{tabular}

Values are means \( \pm SE \), n, no. of animals. SBP, systolic blood pressure; HR, heart rate; RPP, rate-pressure product. \( ^* P < 0.01 \) WKY vs. SHR. \( ^† P < 0.05 \) SHR-TRD vs. SHR-SED and SHR-TRD. 3\( P < 0.001 \) WKY 10 vs. SHR-SED and SHR-TRD.

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rightward shift in the LVSP/V and LVEDP/V relationships relative to SHR at 4 mo, the magnitude of which was similar between SHR-SED and SHR-TRD. The rightward shift in the LV pressure-volume relationship at 10 mo of age did not, however, deleteriously alter absolute peak LV developed pressure between groups (WKY, 197 ± 5 mmHg; SHR-SED, 191 ± 11 mmHg; SHR-TRD, 186 ± 13 mmHg; P = not significant), nor did it alter the slope of the absolute LVSP/V relationship, i.e., E\(0\)/heart weight, between groups (Fig. 1). However, with hypertension-induced hypertrophy at 10 mo of age, peak LV developed pressure normalized to heart weight was decreased in both groups of SHR compared with WKY (WKY, 184 ± 5 mmHg/g; SHR-SED, 149 ± 10 mmHg/g; SHR-TRD, 143 ± 12 mmHg/g; P < 0.05). Similarly, as Fig. 2 illustrates, the relative slope of the LVSP/V, i.e., E\(0\)/heart weight relationship, was blunted in SHR hearts at 10 mo of age compared with WKY hearts at 10 mo of age (P < 0.05). The E\(0\)/heart weight relationship was not different in WKY from 4 to 10 mo, but declined in SHR hearts from 4 to 10 mo of age. As Table 4 illustrates, LV capacitance (i.e., \(V_{20}\)) at 4 mo of age, was similar between WKY and SHR (P = not significant). \(V_{20}\) did not significantly change from 4 to 10 mo of age in WKY. However, \(V_{20}\) at 10 mo of age was significantly greater in both SHR groups relative to SHR at 4 mo of age (P < 0.05). The \(V_{20}\) was also increased in SHR-TRD compared with WKY at 10 mo (P < 0.01). LV diastolic chamber stiffness was similar between WKY and both groups of SHR at both 4 and 10 mo of age of mo of age (Table 4). We also examined LVEDP/V relationship normalized to heart weight (Figure 3). As Fig. 3 illustrates, when normalizing the LVEDP/V relationship to heart weight, the rightward shift in the LVEDP/V was mitigated in SHR. We also evaluated the CPP at an LVEDP of 10 mmHg as a marker of coronary resistance. At 4 mo of age, the CPP was greater in SHR relative to WKY (WKY: 100 ± 11 mmHg vs SHR: 139 ± 17 mmHg; P < 0.05) and tended to remain elevated level in SHR through 10 mo of age (WKY: 104 ± 5 mmHg, SHR-SED: 123 ± 10 mmHg, SHR-TRD: 134 ± 15 mmHg; P = not significant).

**DISCUSSION**

Our results indicate that before the development of pressure-induced-hypertrophy in SHR, i.e., 4 mo of age, the LVSP/V and LVEDP/V relationships were similar to that observed in WKY controls. However, concomitant with pressure-induced

**Table 2. Animal characteristics at 4 and 10 mo of age**

<table>
<thead>
<tr>
<th>Group</th>
<th>BW, g</th>
<th>HW, g</th>
<th>Tibial Length, cm</th>
<th>HW/BW, mg/g</th>
<th>HW/TL, g/cm</th>
<th>CS, (\mu)mol·ml(^{-1})·min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mo</td>
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<td></td>
</tr>
<tr>
<td>WKY (n = 5)</td>
<td>208 ± 2</td>
<td>1.05 ± 0.02</td>
<td>3.56 ± 0.06</td>
<td>5.06 ± 0.15</td>
<td>0.30 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>SHR (n = 5)</td>
<td>185 ± 3*</td>
<td>0.97 ± 0.02*</td>
<td>3.32 ± 0.04*</td>
<td>5.25 ± 0.15</td>
<td>0.29 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>10 mo</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY (n = 8)</td>
<td>253 ± 3*</td>
<td>1.07 ± 0.02</td>
<td>3.61 ± 0.03</td>
<td>4.23 ± 0.05b</td>
<td>0.30 ± 0.01</td>
<td>14.2 ± 2.3</td>
</tr>
<tr>
<td>SHR-SED (n = 8)</td>
<td>230 ± 2*</td>
<td>1.29 ± 0.02*</td>
<td>3.59 ± 0.04e</td>
<td>5.61 ± 0.11c,d</td>
<td>0.36 ± 0.01c,d</td>
<td>19.8 ± 1.5</td>
</tr>
<tr>
<td>SHR-TRD (n = 7)</td>
<td>232 ± 2*</td>
<td>1.31 ± 0.02*</td>
<td>3.66 ± 0.05e</td>
<td>5.65 ± 0.08c,d</td>
<td>0.36 ± 0.01c,d</td>
<td>30.8 ± 3.9g</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of animals. BW, body weight; HW, heart weight; CS, citrate synthase; *P < 0.05 WKY vs. SHR, bP < 0.05 SHR-SED vs. WKY, cP < 0.05 SHR-TRD vs. WKY, dP < 0.05 SHR-SED vs. SHR-TRD, eP < 0.05 SHR-SED vs. WKY and SHR-TRD.

**Table 3. Echocardiographic indexes at 10 mo of age**

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHR-SED</th>
<th>SHR-TRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AW, (diastole)</td>
<td>1.61 ± 0.04</td>
<td>1.88 ± 0.11</td>
<td>2.22 ± 0.09*</td>
</tr>
<tr>
<td>PW, (diastole)</td>
<td>1.54 ± 0.03</td>
<td>1.70 ± 0.07</td>
<td>1.66 ± 0.11</td>
</tr>
<tr>
<td>LVEDD</td>
<td>5.70 ± 0.25</td>
<td>6.26 ± 0.17</td>
<td>6.06 ± 0.18</td>
</tr>
<tr>
<td>LVESD</td>
<td>2.51 ± 0.14</td>
<td>3.11 ± 0.18</td>
<td>2.94 ± 0.21</td>
</tr>
<tr>
<td>FS</td>
<td>0.56 ± 0.02</td>
<td>0.51 ± 0.02</td>
<td>0.52 ± 0.03</td>
</tr>
<tr>
<td>E wave</td>
<td>0.82 ± 0.05</td>
<td>0.86 ± 0.05</td>
<td>0.81 ± 0.07</td>
</tr>
<tr>
<td>A wave</td>
<td>0.46 ± 0.04</td>
<td>0.44 ± 0.02</td>
<td>0.42 ± 0.05</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.81 ± 0.15</td>
<td>1.97 ± 0.13</td>
<td>2.05 ± 0.27</td>
</tr>
</tbody>
</table>

Values are means ± SE. AW, Anterior wall; PW, posterior wall; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end systolic dimension; FS, fractional shortening; E wave, early wave; A wave, atrial wave; E/A ratio, E-wave-to-A-wave ratio. *P < 0.05 vs. WKY and SHR-SED.
Both groups of SHR had a lower $E_s/HW$ at 10 mo of age relative to WKY and reduced in SHR-SED at 10 mo of age compared with WKY at 10 mo of age. Values are mean ± SE. 

stress at 10 mo of age, a rightward shift in the LV pressure volume relationship was observed in SHR. Six months of exercise training in SHR did not mitigate hypertension nor the magnitude of the shift in the LV pressure volume relationship relative to SHR-SED animals. Absolute LV systolic function was well maintained in WKY from 4 to 10 mo of age. However, at 10 mo of age, systolic function in both SHR-SED and SHR-TRD showed signs of deterioration such that the absolute and relative systolic elastances were 30–50% lower, respectively, in SHR compared with WKY. Echocardiography-derived LV diastolic filling parameters, i.e., $E$, $A$, and $E/A$ ratio were similar among groups at 10 mo of age. LV capacitance was increased in SHR from 4 to 10 mo of age, consistent with pressure-induced ventricular remodeling, whereas LV diastolic chamber stiffness was similar between groups. Thus pressure-induced hypertrophic remodeling at 10 mo of age in the female SHR model is manifest with mild absolute and relative systolic decompensation with normal LV diastolic function.

The development of concentric hypertrophy has long been theorized to occur as an adaptational process necessary to normalize wall stress in the pressure-overloaded heart (37). However, recent reports have questioned whether pressure-induced hypertrophy is in fact a necessary compensation (15). Given that there appears to be both adaptive and maladaptive features of pressure-induced hypertrophy, we examined cardiac mechanics at ages in SHR in which hypertrophy was either absent or present. The SHR model is well established in this regard, with the recapitulation of a fetal cardiac phenotype and cardiomyocyte hypertrophy occurring relatively early on in the pathophysiological cascade, followed by the development of subsequent fibrosis later in the disease (3). These changes are hypothesized to lead to increased diastolic stiffness (11) and serve as the substrate for the development of overt heart failure (4).

In the present study, the directional rightward shift in the LV pressure-volume relationship and the increased ventricular capacitance in SHR, are consistent with the slight but statistically insignificant increase in LVEDD in 10-mo-old SHR hearts relative to age-matched WKY controls. Pfeffer et al. (32) showed nearly 3 decades ago that LV chamber dimensions were increased in SHR hearts relative to WKY up to 52 wk of age. Concomitant with increased LV remodeling in SHR hearts, Pfeffer et al. also reported a steady decline in in vivo peak pumping ability in SHR hearts up to 52 wk of age, an effect that became severely exacerbated by 90 wk of age. The rightward shift in the pressure-volume relationship in the present study did not impact LV diastolic chamber stiffness or the LV Doppler filling profile. Instead, perhaps the most interesting feature of our study is that while absolute systolic function was generally preserved in 10-mo-old SHR hearts, relative systolic function was impaired. In other words, our data in the SHR model can be interpreted in two very different ways: no LV systolic dysfunction as indexed by absolute markers, or relative systolic decompensation as indexed by the mismatch between heart mass and LV systolic pressure development. This is an important issue given the lack of consensus as to how hypertension impacts cardiac mechanics before the development of overt heart failure (11, 13, 18, 32). For instance, Kokubo et al. (18) showed echocardiographic evidence of both systolic and diastolic dysfunction in young (2–3 mo old), male SHR, whereas Cingolani et al. (11) reported that SHR hearts exhibited “hypersystolic” performance accompanied by delayed relaxation and increased diastolic stiffness relative to age matched, 10-mo-old WKY.

Clearly, differences in experimental models and paradigms may account for such discrepant findings. In the present study, we analyzed the Frank-Starling relationship in female SHR hearts by utilizing an isovolumic, Langendorff preparation. This model allowed us to precisely control coronary perfusion, preload, heart rate, and temperature while negating the confounding influences of pericardial restraint, the pulmonary and systemic circulation, ventilatory oscillations, and neural, hu-

### Table 4. Diastolic indexes

<table>
<thead>
<tr>
<th>Group</th>
<th>$V_{25}$, ul.</th>
<th>Slope, mmHg/ul</th>
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</thead>
<tbody>
<tr>
<td>4 mo</td>
<td></td>
<td></td>
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<tr>
<td>WKY ($n = 5$)</td>
<td>37±9</td>
<td>1.93±0.33</td>
</tr>
<tr>
<td>SHR ($n = 5$)</td>
<td>37±4</td>
<td>1.52±0.37</td>
</tr>
<tr>
<td>10 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY ($n = 8$)</td>
<td>62±4</td>
<td>1.00±0.13</td>
</tr>
<tr>
<td>SHR-SED ($n = 8$)</td>
<td>86±8*</td>
<td>0.83±0.11</td>
</tr>
<tr>
<td>SHR-TRD ($n = 7$)</td>
<td>103±19†</td>
<td>1.10±0.24</td>
</tr>
</tbody>
</table>

Values are means ± SE. $n$, no. of animals. $^*P < 0.05$ SHR4 vs. SHR-SED and SHR-TRD, $^†P < 0.01$ WKY10 vs. SHR-TRD. $V_{25}$, LV capacitance measured as LV volume that elicited an LVEDP of 25 mmHg.
moral and paracrine influences on cardiac function. Studies primarily utilizing in vivo methodologies are less likely to account for all of these extraneous variables. Moreover, variations in ex vivo experimental paradigms are also important to consider. For example, Cingolani et al. (11) obtained in vivo pressure-volume loops by a direct volume loading method, i.e., via intravenously infusing 0.9% NaCl and measuring subsequent cardiac performance, whereas they measured ex vivo LV pressure-volume relationships in KCl-arrested hearts. Although the KCl-arrested heart methodology is valuable for establishing passive LV diastolic properties, it negates important regulators of LV lusitropic performance, particularly Ca\(^{2+}\) balance, ATP turnover, and turgor (1).

Given that exercise training in normal myocardium improves LV diastolic function (1, 5, 12, 20, 21, 25, 30, 40, 41), reduces LV stiffness (43, 44), and causes a rightward shift in the LV pressure-volume relationship (23, 24, 26), we hypothesized that exercise training superimposed on pressure overload in SHR would reduce LV diastolic chamber stiffness and improve the Frank-Starling systolic response. This hypothesis was based on our laboratory’s recent findings showing that training in SHR reduced pacing-induced LV diastolic stiffness (28), improved β-adrenergic signaling (28), and increased myocardial tolerance to acidosis (36). Clinically, this is an important question, because an increase in LV diastolic stiffness is a significant component of cardiovascular disease (1), particularly in women (16).

Similar to our laboratory’s previous reports, in the present study, exercise training did not reduce systolic blood pressure in SHR (28, 35, 36). Although exercise training increased LV anterior wall thickness relative to SHR-SED, LV remodeling appeared somewhat similar between SHR-SED and SHR-TRD. SHR-SED and SHR-TRD were similar in heart weight, the magnitude of the shift in the LV pressure-volume relationship, and ventricular capacitance. Moreover, training did not impact fractional shortening or the Doppler-derived LV diastolic filling profile. Although training is beneficial to the female SHR myocardium in many ways (28, 36), training did not alter LV diastolic chamber stiffness nor systolic elastance in our Langendorff studies. These data differ from previous reports from our laboratory using nonhypertensive (23, 26) and postinfarcted models (24), in which LV diastolic pressure-volume relationships were shifted rightward with training.

The SHR model was chosen for our research model because it well represents the clinical course of untreated hypertension in humans. We chose to study these animals at 10 mo of age because cardiac function is well maintained and fibrosis is minimal (13, 32). However, there are several design considerations that may affect the interpretability of the present study. First, our conclusions are limited to the Langendorff isovolumic model. Clearly, other experimental paradigms may provide alternative data. Second, we did not measure the Doppler profile in 4-mo-old animals, thus limiting our understanding of the in vivo time effect. Third, we acknowledge that the inclusion of a nonnormotensive exercise group would have expanded our understanding of the exercise-induced adaptation. However, this was not the direct purpose of the present study as we instead focused our efforts toward understanding how exercise training impacts the hypertensive myocardium. Fourth, we acknowledge that in some instances LV diastolic chamber stiffness may be reflected by expressing the LV stress-strain relationship. However, this method has limitations, because whole hearts have a three-dimensional stress-strain relationship that is not easily independently quantified in the Langendorff model (7). Lastly, our data are sex specific. Clearly there are significant sex differences in the SHR model which may impact the interpretability of this study. For example, female SHR have been reported to have greater sympathetic tone (9), decreased parasympathetic tone (9), increased resting heart rates (9), and similar (9) or decreased (29) blood pressure relative to male, age-matched controls. Female SHR have also been reported to have greater heart-to-body weight ratios compared with their male counterparts even at similar levels of systemic blood pressure (42). The impact of estrogen appears to be critical in this response, because neutering has been shown to diminish relative hypertrophy in females, whereas estrogen replacement concomitant with neutering brought heart-to-body weight ratio back closer to intact values (42). Our study is also limited in that we did not control for estrus cycle status in our animals. Sex-specific differences in the renin-angiotensin and endothelin systems (34), oxidation status (39), and Ca\(^{2+}\) signaling (27) are also important considerations.

Significance. While the present paper summarizes predominantly negative findings with respect to the impact of exercise training, perhaps the most important aspect of our paper is the finding that female SHR show signs of LV systolic deterioration somewhat early in the pathophysiological cascade of hypertension. These data might put into question whether pressure-induced hypertrophy is truly “compensatory” in nature.

GRANTS

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REFERENCES


