

# Hypertension

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*Hypertension* 2008;52;514-521; originally published online Aug 11, 2008;

DOI: 10.1161/HYPERTENSIONAHA.108.114744

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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# Is Gender Crucial for Cardiovascular Adjustments Induced by Exercise Training in Female Spontaneously Hypertensive Rats?

Rosemeire Coimbra, Lylian S. Sanchez, Janaina M. Potenza, Luciana V. Rossoni, Sandra Lia Amaral, Lisete C. Michelini

**Abstract**—Evidence of mild hypertension in women and female rats and our preliminary observation showing that training is not effective to reduce pressure in female as it does in male spontaneously hypertensive rats (SHR) prompt us to investigate the effects of gender on hemodynamic pattern and microcirculatory changes induced by exercise training. Female SHR and normotensive controls (Wistar-Kyoto rats) were submitted to training (55%  $\text{VO}_2$  peak; 3 months) or kept sedentary and instrumented for pressure and hindlimb flow measurements at rest and during exercise. Heart, kidney, and skeletal muscles (locomotor/nonlocomotor) were processed for morphometric analysis of arterioles, capillaries, and venules. High pressure in female SHR was accompanied by an increased arteriolar wall:lumen ratio in the kidney (+30%;  $P < 0.01$ ) but an unchanged ratio in the skeletal muscles and myocardium. Female SHR submitted to training did not exhibit further changes on the arteriolar wall:lumen ratio and pressure, showing additionally increased hindlimb resistance at rest (+29%;  $P < 0.05$ ). On the other hand, female SHR submitted to training exhibited increased capillary and venular densities in locomotor muscles (+50% and 2.3-fold versus sedentary SHR, respectively) and normalized hindlimb flow during exercise hyperemia. Left ventricle pressure and weight were higher in SHR versus WKY rats, but heart performance (positive  $\text{dP}/\text{dt}_{\text{max}}$  and negative  $\text{dP}/\text{dt}_{\text{max}}$ ) was not changed by hypertension or training, suggesting a compensated heart function in female SHR. In conclusion, the absence of training-induced structural changes on skeletal muscle and myocardium arterioles differed from changes observed previously in male SHR, suggesting a gender effect. This effect might contribute to the lack of pressure fall in trained female SHRs. (*Hypertension*. 2008;52:514-521.)

**Key Words:** skeletal muscle ■ myocardium ■ kidney ■ arterioles ■ capillaries ■ venules ■ vascular resistance

Hypertension is the most important risk factor for cardiovascular disease in developed countries, affecting approximately one third of adults and elderly people of both sexes.<sup>1,2</sup> Although several clinical trials using different antihypertensive drugs showed significant reductions in pressure and cardiovascular morbidity and mortality,<sup>1</sup> the age-adjusted death rate from hypertension in men and women has been shown to increase in the United States in the last decade.<sup>1-3</sup> It is known that gender affects hypertension. High-pressure levels are less prevalent in young women (premenopause) compared with age-matched men<sup>1,3-5</sup> but of similar prevalence in elderly women.<sup>4,6</sup>

Regular aerobic exercise, other than several antihypertensive treatments available, was shown to be an important therapeutic tool, causing significant pressure fall in hypertensive patients and animals.<sup>1,5,7-9</sup> Exercise-induced reductions in vascular resistance,<sup>10,11</sup> cardiac output,<sup>12</sup> insulin resistance,<sup>13</sup> and sympathetic activity<sup>14,15</sup> have been associated with pressure fall. There is no clear information as to whether gender affects

training-induced pressure effects. Our preliminary results in female spontaneously hypertensive rats (SHR; the best-known animal model for essential hypertension) submitted to low-intensity training did not show any significant pressure fall.<sup>16</sup> This observation contrasted with our previous studies on age-matched male SHR submitted to a similar training protocol, in which we documented significant resistance and pressure fall<sup>11,17,18</sup> associated with wall:lumen ratio normalization of hypertrophied skeletal muscles and heart arterioles, without changes in the geometry of renal arterioles.<sup>11,17</sup> Although not specifically related to pressure changes, trained male SHR also exhibited high venule and capillary densities.<sup>17,18</sup> Based on these observations, we hypothesized that absence of pressure fall in exercised female SHR could be conditioned by different cardiovascular adjustments. Therefore, in the present study we investigated in female SHR (and age-matched normotensive controls) the effects of exercise training on hemodynamic parameters and heart performance, as well as on microcirculatory (arterioles, capillaries, and venules)

Received April 10, 2008; first decision April 27, 2008; revision accepted July 11, 2008.

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*Hypertension* is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.108.114744

**Table 1. Resting Values of Body and Hindlimb Weight, BP, HR, Absolute and Relative HLF, and Relative HLR in S and T Female SHR and WKY Rats**

Measured Parameters	WKY <sub>S</sub> (n=13)	WKY <sub>T</sub> (n=14)	SHR <sub>S</sub> (n=11)	SHR <sub>T</sub> (n=11)
Body weight, g	219±7	213±3	202±7	204±5
Hindlimb dry weight, g	2.16±0.07	2.26±0.09	2.12±0.08	2.33±0.15
Systolic pressure, mm Hg	132±3	146±4	180±5*	184±5*
Diastolic pressure, mm Hg	106±5	97±6	131±4*	132±4*
Mean pressure, mm Hg	113±4	118±4	153±5*	155±3*
Heart rate, beats · min <sup>-1</sup>	325±11	352±18	422±10*	388±6
Absolute HLF, mL · min <sup>-1</sup>	6.69±0.64	5.52±0.38	8.03±1.08	6.90±0.38
Relative HLF, mL · min <sup>-1</sup> · g of tissue	3.22±0.28	2.77±0.22	3.78±0.51	2.99±0.23†
Relative HLR, mm Hg · mL <sup>-1</sup> · min · g of tissue <sup>-1</sup>	38.71±3.08	47.23±3.46	42.41±4.30	54.59±3.95†

Values are means±SEMs.

\**P*<0.05 vs WKY.

†*P*<0.05 vs S.

structural changes induced by training on skeletal muscles, myocardium, and kidney. In addition, we examine the joint effects of gender and exercise training by comparing data collected on female SHR with our data published previously on male SHR.<sup>11,17,18</sup>

## Methods

An expanded Methods section can be found in an online supplement available at <http://hyper.ahajournals.org>.

### Animal Protocols

Animal procedures and protocols were followed in accordance with the ethical principles in animal research of the Brazilian College of Animal Experimentation and were approved by the institutional animal care and use committee. As described previously, only active female Wistar-Kyoto (WKY) rats and SHR aged 2 to 3 months were used in this study.<sup>11,17,18</sup> VO<sub>2</sub> max measurements (by means of expired gas analysis<sup>19</sup>) and maximal exercise tests were used to determine training intensity, to assign rats with equivalent capability to trained (T) or sedentary (S) groups, and to compare the efficacy of the training protocol between groups.<sup>11,17,18</sup> Progressive low-intensity training protocol (50% to 60% of VO<sub>2</sub> peak) was similar to that used before for age-matched male SHR and WKY rats.<sup>11,17,18</sup> During S and T protocols, body weight and tail pressure were measured weekly.<sup>11</sup>

### Hemodynamic Measurements

Hindlimb flow (HLF), arterial pressure (AP), and heart rate (HR) were recorded, and hindlimb resistance (HLR) was determined (instantaneous ratio between mean AP [MAP]:HLF) in conscious freely moving WKY<sub>S</sub>, WKY<sub>T</sub>, SHR<sub>S</sub>, and SHR<sub>T</sub> groups as described previously.<sup>11,18,20</sup> Heart dynamics during the cardiac cycle (left ventricle [LV] systolic pressure and LV diastolic pressure, positive dP/dt<sub>max</sub> and negative dP/dt<sub>max</sub>) were measured in other groups of anesthetized rats (ketamine/xylazine/acepromazine, 0.7/0.2/0.1 vol/vol/vol; 0.04 mL/kg, IM) with a catheter placed into the LV through the right carotid artery. AP and HR were also measured during anesthesia, after replacing the arterial catheter into the carotid artery. Two functional protocols were used: protocol 1, continuous recording of AP and HLF (pulsatile and mean values) and HR in conscious rats at rest (basal values: 40 to 50 minutes) and during dynamic exercise on the treadmill (0.4, 0.8, and 1.1 km/h for S groups and up to 1.4 km/h for T groups; 0% grade; 2 minutes each load), and protocol 2, evaluation of heart dynamics (high speed recordings of ≈150 cardiac cycles) in other anesthetized WKY<sub>S</sub>, WKY<sub>T</sub>, SHR<sub>S</sub>, and SHR<sub>T</sub> groups, followed by AP and HR measurements (≈10 minutes).

### Morphometric Evaluations

Rats were deeply anesthetized (sodium pentobarbital, 60 mg/kg, IP). Heart and hindlimb muscles (kept apart from bones and subcutaneous tissue) were excised immediately after the respiratory arrest for determination of LV, right ventricle, and skeletal muscle dry weight (48 hours, 50°C). Other groups of deeply anesthetized rats were perfused with 4% paraformaldehyde for harvesting and histological processing of locomotor (gracilis, red gastrocnemius) and nonlocomotor (temporalis) muscles, LV, and kidney, as described previously.<sup>11,17,18</sup> Morphometric analysis (Leica DML, ×200 magnification, Image ProPlus) included determination of arterioles ID/OD ( $D=2r$ , where  $r$  is the inner or outer radius) and the calculation of both wall thickness ( $\delta$ =outer  $r$  - inner  $r$ ) and wall:lumen ratio ( $\delta$ /inner  $D$ ). Capillary (vessels <12 μm, lined by a single layer of endothelial cells) and venule (larger vessels with endothelium surrounded by pericytes and a thin layer on muscular cells) densities were also analyzed on digitized images (10 to 15 fields per tissue chosen randomly) and expressed as the number of vessels per millimeter squared, as described previously.<sup>11,17,18</sup>

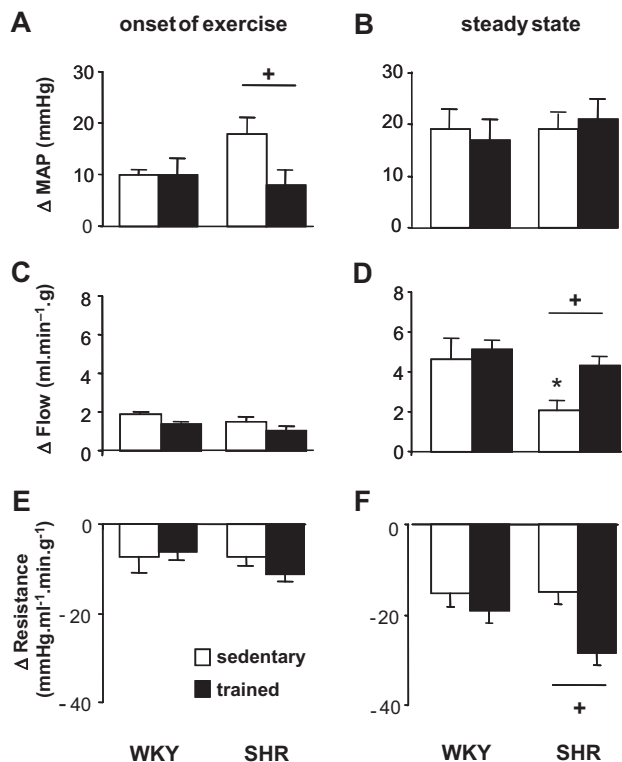
### Statistical Analysis

Data are reported as means±SEMs. Statistical significance (*P*<0.05) of hemodynamic parameters (MAP, HR, HLF, and HLR), heart dynamics (LV systolic pressure, end LV diastolic pressure, positive dP/dt<sub>max</sub>, and negative dP/dt<sub>max</sub>), and structural changes between groups (SHR and WKY rats) and conditions (T and S) was assessed by 2-way ANOVA. Responses during exercise were compared by 2-way ANOVA for repeated measurements. Tukey was used as the posthoc test.

## Results

### Tail Pressure and Efficacy of Training Protocol

Tail pressure was high in the SHR group since the first week of the experiment (168±4 versus 129±3 mm Hg for the WKY rats), with no increments during the entire 13-week period, indicating that female SHRs had established hypertension. In the SHR and WKY groups there were no significant pressure changes during the T and S protocols. At the end of the 3-month period, rats were 5 to 6 month old and exhibited similar body weight (Table 1). T was essential to maintain VO<sub>2</sub> max (80 to 90 mL of O<sub>2</sub> · kg<sup>-1</sup> · min) during the 3-month period in the WKY<sub>T</sub> and SHR<sub>T</sub> groups, whereas WKY<sub>S</sub> and SHR<sub>S</sub> groups presented significant reductions (63±4 and 76±5 mL of O<sub>2</sub> · kg<sup>-1</sup> · min, respectively; *P*<0.05). Therefore, at the end of protocols, T groups exhibited a 20%



**Figure 1.** Effects of training on mean AP (MAP; A and B), relative HLF ( $\Delta$  Flow; C and D), and relative HLR ( $\Delta$  Resistance; E and F) responses at onset (A, C, and E) and steady-state exercise (B, D, and F) in sedentary (S) and trained (T) female WKY rats and SHR. Significance:  $P < 0.05$  vs \*WKY and vs +S.

higher  $\text{VO}_2$  max compared with S controls. In addition, 3-month training was effective to improve performance on the treadmill compared with respective sedentary groups ( $1.25 \pm 0.09$  and  $1.88 \pm 0.08$  km/h for WKY<sub>T</sub> and SHR<sub>T</sub> groups versus  $0.85 \pm 0.05$  and  $0.96 \pm 0.11$  km/h for WKY<sub>S</sub> and SHR<sub>S</sub> groups, respectively).

### Hemodynamic Parameters at Rest and During Exercise

Hemodynamic data are depicted on Table 1. Female SHR<sub>S</sub> exhibited elevated pressure and tachycardia but similar HLF and HLR compared with WKY<sub>S</sub> rats. Exercise training did not change AP (systolic, diastolic, or mean), absolute HLF, and HR, but there was no resting tachycardia in the SHR<sub>T</sub> versus the SHR<sub>S</sub> group (8% reduction). Comparison of relative HLF between groups indicated a conditioning effect (T versus S;  $P < 0.05$ ), with a significant difference between the SHR<sub>T</sub> versus the SHR<sub>S</sub> group (decreased by 21%; Table 1). Unexpectedly, female SHRs exhibited a 29% increase in relative HLR after training ( $P < 0.01$  versus the SHR<sub>S</sub> group; Table 1). The slight hemodynamic changes induced by training in the WKY group did not attain significance.

Figure 1 compares, in the SHR and WKY groups, the effects of training on MAP, HLF, and HLR responses during dynamic exercise. At the onset of exercise (4 seconds after starting running), pressure response was higher in the SHR<sub>S</sub> group ( $+18 \pm 3$ ;  $P < 0.05$  versus other groups; Figure 1A), but HLF and vasodilatation were similar among the 4 groups

(increments of  $+1.0$  up to  $+1.8$   $\text{mL} \cdot \text{min}^{-1} \cdot \text{g}$  of tissue and reductions of 6 to 11  $\text{mmHg} \cdot \text{mL}^{-1} \cdot \text{min} \cdot \text{g}$  of tissue<sup>-1</sup>; Figure 1C and 1E, respectively). When maximal responses at the steady-state exercise were considered, pressure drive was similar among groups (Figure 1B), and training improved hindlimb vasodilator response only in the SHR<sub>T</sub> group ( $-28.42 \pm 2.87$  versus  $-15.00 \pm 2.70$   $\text{mmHg} \cdot \text{mL}^{-1} \cdot \text{min} \cdot \text{g}$  of tissue<sup>-1</sup>;  $P < 0.05$  for SHR<sub>T</sub> versus SHR<sub>S</sub> group; Figure 1F), which exhibits larger resistance at rest. The larger vasodilatation in the SHR<sub>T</sub> group was able to normalize the reduced blood flow presented by the SHR<sub>S</sub> group at steady-state exercise ( $+4.32 \pm 0.43$  versus  $+2.97 \pm 0.50$   $\text{mL} \cdot \text{min}^{-1} \cdot \text{g}$  of tissue; SHR<sub>T</sub> versus SHR<sub>S</sub> group; Figure 1D).

### Cardiac Function and Heart Weight

To analyze the effects of hypertension and training on female heart dynamics, we measured LV pressure and ventricles weight in other WKY<sub>S</sub>, WKY<sub>T</sub>, SHR<sub>S</sub>, and SHR<sub>T</sub> groups. LV systolic pressure and end LV diastolic pressure (Table 2) were significantly higher in SHR versus WKY groups. On the other hand, positive  $dP/dt_{\text{max}}$  and negative  $dP/dt_{\text{max}}$ , as well as HR of anesthetized rats, did not differ among groups. Training did not significantly affect the heart dynamics of female SHR and WKY rats (Table 2). In these groups, direct measurement of AP (systolic/diastolic; Table 2) confirmed the persistence of hypertension, discarding possible valvular damage as a consequence of LV catheterization.

Absolute and relative weights of ventricles are also presented in Table 2. The LV, but not the right ventricle, was significantly heavier in female SHR versus WKY rats. Again, training did not change LV and right ventricle weights in both groups.

### Morphometric Responses of Skeletal Muscles, Myocardium, and Kidney

Figure 2 compares cross-sections of similar order arterioles of gracilis, temporalis, and kidney taken from female SHR<sub>S</sub> and SHR<sub>T</sub> groups. In the SHR<sub>S</sub> group, renal cortex arterioles exhibited a thicker wall and smaller lumen area than skeletal muscles arterioles; training seems not to change the arteriolar structure of any tissue. Quantitative data were taken from arterioles with an ID ranging from 10 to 20 up to 60 to 70  $\mu\text{m}$ . For all of the WKY<sub>S</sub> arterioles analyzed, mean wall thickness and average internal diameter were  $22 \pm 2$  and  $42 \pm 5$   $\mu\text{m}$  for the gracilis,  $17 \pm 4$  and  $28 \pm 6$   $\mu\text{m}$  for the gastrocnemius,  $10 \pm 2$  and  $18 \pm 4$   $\mu\text{m}$  for the temporalis,  $18 \pm 1$  and  $47 \pm 4$   $\mu\text{m}$  for the myocardium, and  $32 \pm 6$  and  $25 \pm 5$   $\mu\text{m}$  for the renal tissue, respectively. Therefore, the wall:lumen ratio of kidney arterioles was higher and that of myocardium arterioles (Figure 3) was slightly smaller than those of locomotor (gracilis, red gastrocnemius) and nonlocomotor (temporalis) muscles. Interestingly, in the female SHR, hypertension was not accompanied by significant changes on the wall:lumen ratio of myocardium and skeletal muscle arterioles (small increases did not attain significance) but by a marked increase on the wall:lumen ratio of kidney arterioles ( $+30\%$ ; SHR<sub>S</sub> versus WKY<sub>S</sub> group;  $P < 0.01$  for group factor; Figure 3). Training did not change the arteriolar wall:lumen ratio in any tissue ( $P > 0.05$  for condition factor for all tissues analyzed;

**Table 2. Comparison of LV Function and Heart Weights in S and T Anesthetized Female SHR and WKY Rats**

Measured Parameters	WKY <sub>S</sub> (n=18)	WKY <sub>T</sub> (n=21)	SHR <sub>S</sub> (n=24)	SHR <sub>T</sub> (n=25)
SP, mm Hg	101±3	101±2	132±5*	132±4*
DP, mm Hg	65±3	65±4	84±4*	88±3*
HR, beats · min <sup>-1</sup>	281±23	277±19	272±18	285±22
LVSP, mm Hg	99±4	101±4	126±4*	125±4*
End LVDP, mm Hg	2.7±1.0	0.8±0.8	5.1±0.9*	5.1±1.1*
dP/dt+, mm Hg · s <sup>-1</sup>	5426±563	5373±492	6023±257	5960±234
dP/dt-, mm Hg · s <sup>-1</sup>	-4120±406	-3828±318	-4776±203	-4835±149
Body weight, g	218±3	223±3	198±3	205±2
LV, mg	585±13	622±15	695±24*	701±18*
RV, mg	145±6	169±10	137±4	138±4
LV/BW, mg/g	2.75±0.08	2.81±0.07	3.52±0.13*	3.42±0.10*
RV/BW, mg/g	0.69±0.02	0.76±0.04	0.69±0.01	0.68±0.02

Values are means±SEMs. SP indicates systolic pressure; DP, diastolic pressure; LVSP, LV systolic pressure; end LVDP, end LV diastolic pressure; dP/dt+, ventricular pressure first positive time derivative; dP/dt-, ventricular pressure first negative time derivative; RV, right ventricle; BW, body weight.

\* $P<0.05$  vs WKY.

Figure 3), although a tendency for increase could be observed in the kidney and exercised muscles. On the other hand, training increased capillary growth in locomotor muscles of female SHR and WKY rats (expressed as capillary density and capillary: fiber ratio; Table 3), even after anatomic rarefaction induced by hypertension. Capillary growth after training was not evident in nonlocomotor muscle and myocardium. Training also caused venular growth (measured in venules with ID  $\leq 50$  to  $55 \mu\text{m}$ ) in the gracilis muscle, but only in the SHR group ( $P<0.05$ ; for SHR<sub>T</sub> versus SHR<sub>S</sub> groups; Table 3), with no changes in the temporalis muscle and myocardium of SHR and WKY rats.

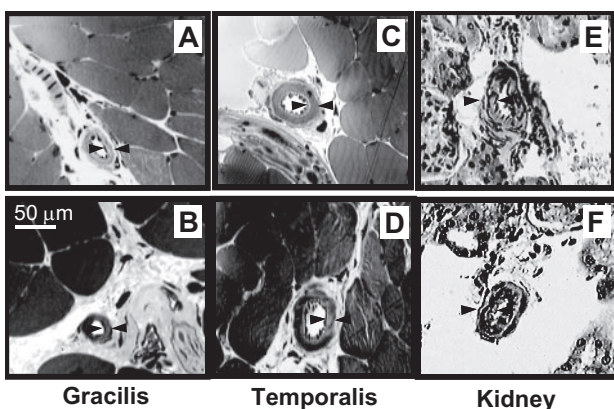
### Comparison of Training Effects Between Female and Male SHR

To clarify the gender specificity on training adjustments observed in hypertensive rats, the present results on female SHR were compared with those obtained previously in age-matched male SHR submitted to a similar low-intensity

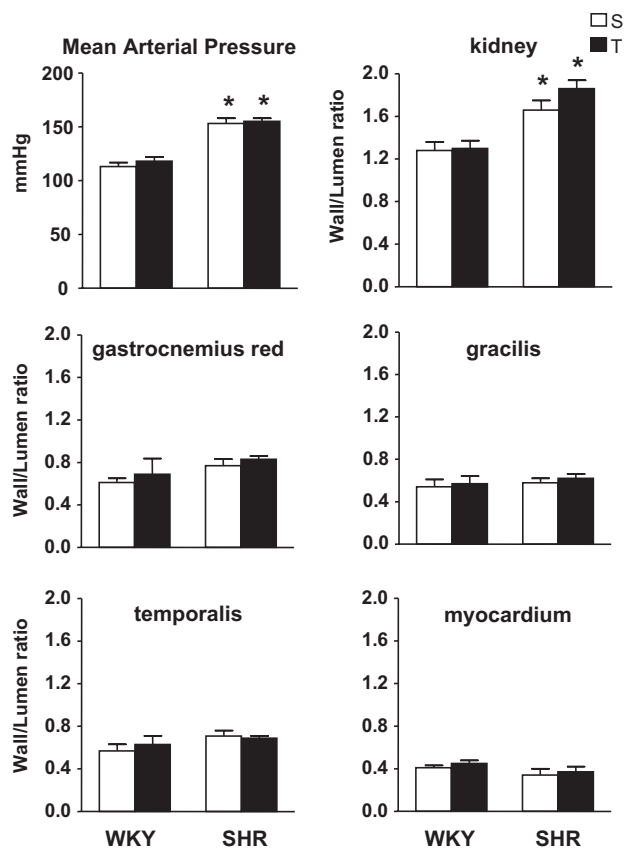
training protocol (original data in References 11, 17, and 18). As depicted in Figure 4, training-induced pressure-lowering effects ( $-11\%$ ) simultaneous to significant HLR fall ( $-18\%$ ) are specific adjustments for male SHR that exhibited higher values of pressure and HLR compared with female SHR. These changes are accompanied by marked training-induced reduction of the skeletal muscle arteriolar wall:lumen ratio in male SHR (Figure 5). On the other hand, skeletal muscle arterioles of female SHR (with similar geometry as the WKY group) did not show any change after training (Figures 3 and 5), the absence of hypotrophic remodeling being consistent with either the absence of HLR fall (indeed, relative HLR was increased by training, as shown in Table 1; Figure 4), the smaller HLF at rest and the lack of pressure fall after training (Table 1 and Figure 4). In addition, the wall:lumen ratio of renal arterioles (a tissue undergoing vasoconstriction, not vasodilatation during repeated exercise) was much larger in female than respective male SHR groups (Figure 5), thus contributing proportionally more to the total peripheral resistance at rest and to the maintenance of elevated blood pressure in female SHR after training. Of interest was the observation that training-induced enlargement of vascular capacity in the skeletal muscle (as represented by the capillary: fiber ratio and venule density in the gracilis muscle; Figure 6) was not gender specific but similar in female and male SHR.

### Discussion

The present study in female SHR showed specific responses to hypertension and exercise training that differ from those described previously in age-matched male SHR submitted to a similar training protocol. Major findings are as follows: (1) hypertension in female rats was accompanied by marked hypertrophic remodeling of kidney arterioles but no significant change in the wall:lumen ratio of the skeletal muscle arterioles; (2) trained female SHR exhibited increased capillary and venule density in locomotor muscles and improved



**Figure 2.** Cross-sections taken from gracilis (A and B) and temporalis muscle arterioles (C and D) and from renal arterioles (E and F) of sedentary (A, C, and E) and trained (B, D, and F) female SHRs. Arrows indicate the thickness of vessel wall; bar=50  $\mu\text{m}$ .



**Figure 3.** Effects of hypertension and training on arteriolar wall:lumen ratio in the kidney, myocardium, locomotor (gastrocnemius red and gracilis), and nonlocomotor (temporalis) muscles of normotensive (WKY) and hypertensive (SHR) female rats. Mean values correspond with 20 to 30 arterioles in the myocardium and kidney and 5 to 15 arterioles in the skeletal muscles of 4 to 8 rats per group. For comparison, mean AP (MAP) values are shown in the top left panel. Significance: \* $P < 0.05$  vs WKY.

physical capacity but no change in the wall:lumen ratio of heart and skeletal muscle arterioles, with an unexpected additional increase in HLR; and (3) these adjustments on the skeletal muscle arterioles contrasted with those observed previously in age-matched trained male SHR and could contribute to the absence of resting pressure fall in trained female SHR.

Gender differences in hypertension have already been reported. Estrogen is known to decrease vascular tone either directly, via endothelium-derived relaxing factors,<sup>21</sup> or through changes in the renin-angiotensin system.<sup>22–24</sup> Indeed, a well-controlled, large population-based sample study has provided evidence that diastolic pressure and hypertension are linked to the angiotensin-converting enzyme locus in men but not in women.<sup>25</sup> Reckelhoff et al<sup>26</sup> also stated that gender differences on blood pressure control could be mediated by an androgenic effect on the renin-angiotensin system. All of these factors could contribute to mild and less prevalent hypertension in women<sup>1,4–7,25</sup> and rats, as shown in this and other studies.<sup>11,17,18,24</sup> In addition, we showed that heart dynamics was normal in female SHR (versus WKY<sub>s</sub> rats) aged 5 to 6 months. A comparison of LV/body weight between female (Table 2) and age-matched male SHR<sup>11</sup>

**Table 3.** Training-Induced Morphometric Changes in Capillaries and Venules of the Gracilis, Gastrocnemius Red and Temporalis Muscles, and in the Myocardium of S and T Female SHR and WKY Rats

Groups and Tissues	Capillary Density, n/mm <sup>2</sup>	Capillary: Fiber Ratio	Venule Density, n/mm <sup>2</sup>
WKY <sub>s</sub>			
Gracilis	1051 ± 68	2.4 ± 0.2	12.1 ± 3.3
Red gastrocnemius	779 ± 138	1.2 ± 0.1	
Temporalis	819 ± 35	2.0 ± 0.2	18.0 ± 4.7
Myocardium	2401 ± 320		23.0 ± 6.3
WKY <sub>t</sub>			
Gracilis	1301 ± 93†	2.9 ± 0.2†	18.7 ± 3.3
Red gastrocnemius	842 ± 23	1.6 ± 0.2†	
Temporalis	1017 ± 171	2.0 ± 0.2	11.3 ± 6.6
Myocardium	2778 ± 320		39.1 ± 2.1
SHR <sub>s</sub>			
Gracilis	471 ± 57*	1.2 ± 0.1*	9.8 ± 2.8
Red gastrocnemius	811 ± 94	1.2 ± 0.1	
Temporalis	880 ± 81	2.4 ± 0.4	13.9 ± 6.9
Myocardium	2431 ± 261		22.6 ± 6.1
SHR <sub>t</sub>			
Gracilis	809 ± 81†	1.8 ± 0.2†	23.1 ± 1.8†
Red gastrocnemius	964 ± 92	1.6 ± 0.08†	
Temporalis	998 ± 140	2.0 ± 0.3	11.0 ± 6.5
Myocardium	2422 ± 226		25.7 ± 5.6

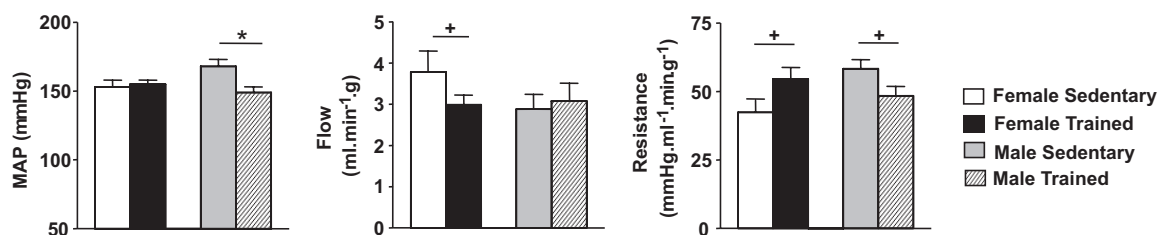
Values are means ± SEMs. Capillary density, venule density, and capillary: fiber ratio are average values of 20 to 40 transverse sections analyzed in 4 to 8 rats of each group.

\* $P < 0.05$  vs WKY.

† $P < 0.05$  vs S.

shows smaller hypertrophy in females, suggesting that their hearts are still compensated functionally, contributing to the maintenance of cardiac output at rest.

Experimental evidence had emphasized the efficacy of training to reduce pressure levels in hypertensive humans and animals.<sup>4,5,7–12,15,17,18,26–30</sup> Most of these studies, however, were conducted in men or male subjects,<sup>8–10,12,15,17,18,29,30</sup> with little and controversial information on hypertensive females. It has been shown that aerobic training reduces pressure in borderline<sup>28</sup> and essential hypertension,<sup>6</sup> with a smaller effect on older compared with young women<sup>5,7,31</sup> and in white versus black subjects.<sup>7</sup> Brown et al<sup>32</sup> reported that short-term training improved both insulin sensitivity and sodium excretion in black subjects, without pressure reduction. Compared with men, women also have low-renin hypertension<sup>27</sup> and reduced sympathetic variability to the heart.<sup>33</sup> It is important to note that the efficacy of training to reduce pressure in both human and animal models could be modified by the pathology and/or severity of hypertension; by ethnicity, genetic factors, and/or aging; by the presence or absence of body weight changes associated with chronic exercise; as well



**Figure 4.** Comparison of training effect on mean AP (MAP), relative HLF, and resistance in female and male SHR. Male SHR data were taken from References 11 and 17. Significance: + $P < 0.05$  vs S.

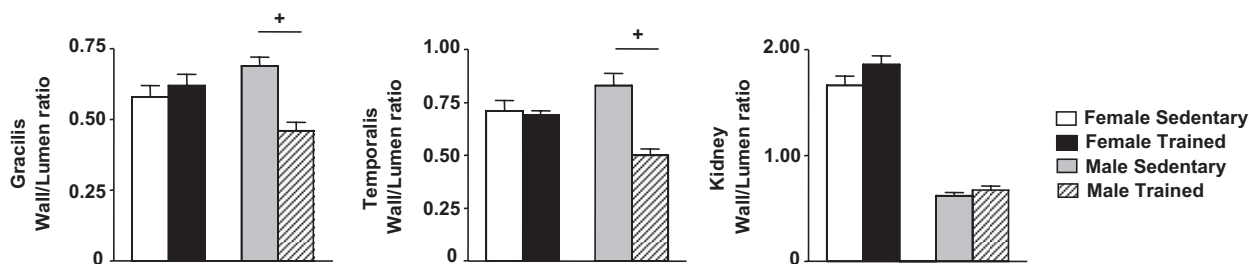
as by the intensity and duration of the exercise protocol.<sup>3–5,7,34</sup> By adjusting the data for all of the covariables, a long-term follow-up study showed that physical activity in hypertensive women, although reducing the risk of nonfatal cardiovascular and coronary heart disease, did not reduce pressure levels as it did in men.<sup>3</sup> Coherently, data of the present study confirmed that low-intensity training did not cause a pressure fall in female SHR (as indicated by tail and direct pressure measurements both in conscious and anesthetized rats), showing, in addition, no pressure reduction during steady-state exercise. The absence of pressure fall in trained female SHR was corroborated by 2 other responses to training that were opposite to those exhibited by age-matched male SHR submitted to a similar training protocol<sup>11,17,18</sup>: basal HLR was significantly increased, and there was no hypotrophic remodeling of skeletal muscle and myocardium arterioles (unchanged wall:lumen ratio after training).

It is important to note that, opposite to male SHR (marked hypertension-induced hypertrophic remodeling of arterioles in all of the tissues),<sup>11,17</sup> establishment of hypertension in female SHR was not accompanied by an increased wall:lumen ratio of the skeletal muscle and myocardium arterioles, but only of the kidney arterioles (present set of data). It was also shown that exercise training normalized both the myocardium and skeletal muscle arteriolar wall:lumen ratio in male SHR, which would be expected to cause a significant reduction in vascular resistance, likely contributing to the pressure fall.<sup>11,17</sup> Because in female SHR there was no significant hypertrophy of skeletal muscle arterioles, coherently training did not change it. Indeed, beneficial effects of training have been observed specifically in disease states, mostly in active tissues yielding to exercise hyperemia.<sup>2–12,17,18</sup> Opposite to active muscles, renal tissue responds to aerobic exercise with vasoconstriction and marked flow reduction in such a way that it is not prone to the beneficial effects of dynamic exercise. Therefore, training was not able to change

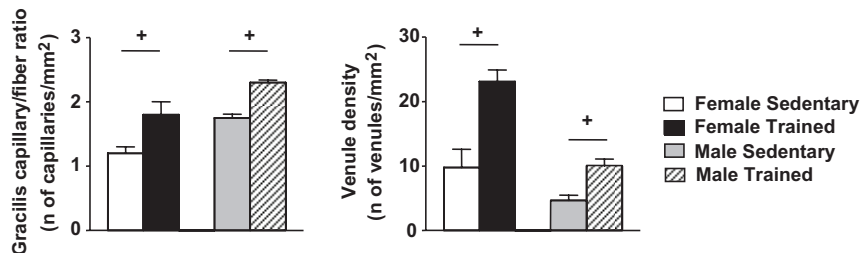
the structure of renal arterioles in both male<sup>17</sup> and female SHR (present set of data). On the other hand, differential responses of the skeletal muscle and myocardium arterioles to hypertension and training are gender specific and might contribute to both the mild hypertension in female SHR and the absence of a training-induced pressure fall. Specific neurohormonal mechanisms that modify these responses are now under investigation in our laboratory.

Low-intensity treadmill training did not change LV hypertrophy and heart dynamics in female SHR. In contrast, training-induced LV hypertrophy was observed in 2-kidney, 1-clip swimming-trained females<sup>35</sup> and in Sprague-Dawley female rats submitted to high-intensity treadmill running.<sup>36</sup> It is important to note that exercise-induced cardiac hypertrophy is greatly dependent on the exercise pattern; it is usually found in swimming but not in running protocols.<sup>37</sup>

One also observed that locomotor muscles of trained female SHR exhibited a marked increase on venule and capillary densities, whereas female WKY rats respond to exercise with an increased capillary supply only. Previous studies on trained age-matched males have also shown increased capillary density in WKY rats<sup>11,17,38</sup> and SHR<sup>11,17</sup> and neoformation of small venules in the skeletal muscle of SHR.<sup>17,18</sup> Increased capillary density contributes to improve the oxygen uptake by active tissues,<sup>11,38</sup> whereas a larger venular bed contributes actively and passively to the control of venous return and cardiac output, being, in addition, an important source for vasoactive endothelium-derived factors.<sup>39</sup> It was observed that an increased venular bed is correlated with larger HLF during exercise hyperemia in male SHR<sub>T</sub> group,<sup>18</sup> representing a beneficial adjustment for better control of skeletal muscle circulation during exercise. A training-induced increase in parallel conductance in the skeletal muscles of female SHR is a functional response to normalize HLF during steady-state exercise, which was markedly depressed on sedentary SHR (Figure 1). The presence of training-



**Figure 5.** Comparison of training effect on arteriole wall:lumen ratio in locomotor (gracilis) and nonlocomotor (temporalis) skeletal muscle and kidney in female and male SHR. Male SHR data were taken from References 11 and 17. Significance: + $P < 0.05$  vs S.



**Figure 6.** Comparison of training effect on capillary: fiber ratio and venule density of locomotor skeletal muscle circulation (gracilis muscle) in female and male SHR. Male SHR data were taken from References 17 and 18. Significance: + $P < 0.05$  vs S.

induced enlargement of the venular bed in both female (present data) and male SHR,<sup>17,18</sup> but not in normotensive groups, indicates that this adjustment is specific for hypertensive individuals but not gender specific. Other than the increased exercise hyperemia, female SHR<sub>T</sub> rats also exhibited reduced skeletal muscle flow at rest (versus SHR<sub>S</sub> group; Table 1). It should be stressed that resting flow, providing the necessary perfusion at basal condition, depends on the pressure gradient, vessel geometry (both unchanged after training), and active vasomotor tone (increased after training). Therefore, an elevated local resistance may overcome the increased conductance of the skeletal muscle circulation, thus maintaining a near-normal flow at rest. Additional experiments are necessary to investigate the mechanism(s) involved in these responses.

In conclusion, hypertension and training cause specific circulatory adjustments, some of which are gender specific. Different from the male SHR in which the arteriolar wall:lumen ratio is increased in all of the tissues, mild hypertension in female SHR is shown to occur simultaneously with a high wall:lumen ratio in the renal arterioles but normal vessel geometry in the skeletal muscle and myocardium. In opposition to male SHR, presenting significant training-induced pressure fall accompanied by a decreased wall:lumen ratio of skeletal muscle arterioles and reduced HLR, trained female SHR showed no geometric changes in skeletal muscle arterioles, a significant HLR increase, and no pressure fall. On the other hand, training-induced growth/proliferation of small venules and capillaries is not gender specific, because similar effects were observed in male and female SHR. Together these responses suggest that low-intensity training is specific to reverse adverse changes induced by hypertension in exercise-stimulated tissues.

### Perspectives

The present set of data, uncovering differential mechanisms on the whole body level that control AP and vascular responses to exercise in male and female hypertensive rats, improve our comprehension on the factors that contribute to hypertension in women. Data also help us to understand why exercise training in women, although preventing fatal and nonfatal cardiovascular events, is not as effective as in men to reduce pressure. The absence of pressure fall, however, does not mean the absence of effects in the trained hypertensive women (or female rat), because the beneficial effects on growth/proliferation of capillaries and small venules occur independent of the pressure response.

### Acknowledgments

We thank Natale Pinheiro Rolim for expert assistance on VO<sub>2</sub> measurements and Cleusa M.R. Pellegrini and Ana Lucia T.L. Mota for excellent technical support.

### Sources of Funding

This study was supported by Fundacao de Amparo a Pesquisa do Estado de Sao Paulo, Conselho Nacional de Desenvolvimento Cientifico e Tecnologico/Programa de Apoio a Nucleos de Excelência, and Coordenacao do Pessoal de Ensino Superior (fellowship to R.C.). L.C.M. and L.V.R. are research fellows from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico.

### Disclosures

None.

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