Influence of gender on control of arterial tone in experimental hypertension

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1Department of Pharmacological Sciences, Medical School, University of Tampere, FIN-33101 Tampere, and Departments of 2Clinical Physiology, 3Clinical Chemistry, and 4Internal Medicine, Tampere University Hospital, FIN-33521 Tampere, Finland

Kähönen, Mika, Jari-Petteri Tolvanen, Kirsimarja Sallinen, Xiumin Wu, and Ilkka Pörsti. Influence of gender on control of arterial tone in experimental hypertension. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H15–H22, 1998.—Endothelial dysfunction has been found to be less severe in female than in male spontaneously hypertensive rats (SHR), which could contribute to the gender differences observed in the extent and rate of progression of hypertension in SHR. However, the influence of gender on the roles of different endothelium-derived mediators in the arterial responses in hypertension have not been evaluated in detail. Therefore, contractile and relaxation responses of mesenteric arterial rings in vitro were studied in female and male SHR, with normotensive female and male Wistar-Kyoto rats (WKY) serving as controls. In norepinephrine (NE)-precontracted arterial rings, endothelium-dependent relaxations to ACh as well as endothelium-independent dilations to sodium nitroprusside were more pronounced in female than in male SHR, whereas relaxations to the β-adrenoceptor agonist isoproterenol remained equally impaired in female and male SHR. The cytoxygenase inhibitor dicyfenac, which reduces the synthesis of dilating and constricting prostanooids, markedly enhanced the relaxations to ACh in male SHR but not in the other groups. The nitric oxide (NO) synthase inhibitor Nω-nitro-L-arginine methyl ester attenuated the relaxations to ACh more effectively in female SHR and WKY than in the male groups. However, when endothelium-dependent hyperpolarization was prevented by precontracting the preparations with KCl, no significant differences were found in relaxations to ACh among the study groups. In conclusion, release of cytoxygenase-derived constricting factors appeared to be more pronounced in male than in female SHR. In addition, the relative role of NO in endothelium-dependent arterial relaxation seemed to be higher in female than in male SHR, and relaxation induced by an NO donor also was more pronounced in female than in male SHR.

arterial smooth muscle; endothelium; spontaneously hypertensive rat; Wistar-Kyoto rat

Materials and Methods

Animals and experimental design. Female and male SHR (Okamoto-Aoki strain, n = 12 in each group) and WKY were obtained from Møllegaard’s Breeding Centre (Ejby, Denmark). The rats were housed in an experimental animal laboratory (illuminated from 0600 to 1800, temperature 22°C) with free access to water and chow (Ewos, Södertälje, Sweden). The systolic blood pressures of conscious animals were measured at 28°C using the tail-cuff method (model 129 Blood Pressure Meter; IITC, Woodland Hills, CA). At the age of 20 wk the rats were decapitated and exsanguinated. The hearts were removed and weighed, and the superior mesenteric arteries were excised. The experimental design was approved by the Animal Experimentation Committee of the University of Tampere (Tampere, Finland).
Mesenteric arterial responses in vitro. Five successive sections (3 mm in length) of the mesenteric artery from each animal were cut. In the three most distal rings, the endothelium was left intact, and vascular endothelium was gently removed from the first two pieces (2). The rings were placed between hooks (diameter 0.3 mm) and suspended in an organ bath chamber (volume 20 ml) in PSS (pH 7.4) of the following composition (in mM): 119.0 NaCl, 25.0 NaHCO3, 1.1 glucose, 1.6 CaCl2, 4.7 KCl, 1.2 KH2PO4, and 1.2 MgSO4, aerated with 95% O2-5% CO2. The rings were initially equilibrated for 1 h at 37°C with a resting force of 1.5 g. The force of contraction was measured with an isometric force-displacement transducer and registered on a polygraph (FT03 transducer and model 7E polygraph; Grass Instruments, Quincy, MA). Normally, the presence of intact endothelium is confirmed by an almost complete relaxation to 1 µM ACh in 1 µM norepinephrine (NE)-precontracted rings, whereas no relaxation is observed in endothelium-denuded rings (2). However, in the study reported here, the responses to ACh in the SHR groups hardly attained 50% relaxation. Therefore, no vascular preparations were excluded from the study.

Endothelium-independent relaxation and contraction to 5-hydroxytryptamine. The responses of endothelium-intact preparations to sodium nitroprusside (SNP) and isopropenol were cumulatively determined. The relaxations were elicited after precontraction with 1 µM NE, which resulted in ~60% of the maximal contraction in each group. The next drug concentration was added only after the previous level of relaxation was stable. Thereafter, the concentration-response curves for 5-hydroxytryptamine (5-HT) were cumulatively determined.

Responses to ACh after precontraction with NE. Responses to ACh were examined in endothelium-intact rings. The responses to ACh were repeated in the presence of 3 µM diclofenac, in the presence of diclofenac and 0.1 mM Nω-nitro-L-arginine methyl ester (L-NAME), and in the presence of diclofenac, L-NAME, and 1 µM apamin [inhibitors of cyclooxygenase, NO synthase, and Ca2+-activated K+ channels (KCa), respectively].

Arterial relaxations to ACh and ADP after precontraction with KCl. Relaxations to ACh and ADP were examined in endothelium-intact rings precontracted with 50 mM KCl. The responses to ACh and ADP were repeated in the presence of 3 µM diclofenac and in the presence of diclofenac and 0.1 mM L-NAME.

K+ relaxation. The endothelium-denuded ring was contracted with 125 mM KCl (reference response). When the maximal contraction was fully developed, the ring was rinsed with PSS to restore resting tension. After 30 min, the rings were exposed to K+-free solution (pH 7.4; KH2PO4 and KCl were substituted with NaH2PO4 and NaCl, respectively). The omission of K+ induced gradual contractions, and after the response had reached a plateau, 1 mM K+ was readded and the subsequent relaxation evaluating the activity of Na+–K+–ATPase was registered (2). The K+-free contractions and relaxations to K+ repletion were repeated in the presence of 1 mM ouabain.

Ca2+-contraction. Ca2+ was omitted from the buffer solution, and endothelium-denuded rings were contracted with 10 µM NE to empty the Ca2+ stores. The rings were challenged again with 1 µM Ca2+-free buffer, and Ca2+ was returned to the organ bath in increasing concentrations (0.05 to 2.5 mM). NaCl was replaced with KCl on an equimolar basis.

The contractions to 5-HT were expressed in grams, and the EC50 for 5-HT in each ring was calculated as the percentage of maximal response. The Ca2+-contraction responses were presented as the percentages of maximal responses. The relaxations in response to K+ repletion, ADP, ACh, isoproterenol, and SNP were presented as percentages of preexisting contractile force. The EC25 or EC50 values for the three latter relaxants were calculated as percentages of 1 µM NE-induced precontraction with the use of a computer program and were presented as the negative logarithm (pD25, pD50), which values were also used in the statistical analysis. The EC25 for ACh and isoproterenol were calculated because maximal relaxations of SHR groups to these agonists did not reach 50% relaxation in the present study.

Drugs. The following drugs were used: acetylcholine chloride (ACh), ADP, apamin, diclofenac, isoproterenol, Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME), and 5-HT (Sigma Chemical, St. Louis, MO); and L-norepinephrine hydrochloride (l-tartrate and SNP (Fluka Chemie, Buchs, Switzerland). The stock solutions were made by dissolving the compounds in distilled water. All solutions were freshly prepared before use and were protected from light.

Analysis of results. Statistical analysis was carried out by one-way ANOVA supported by the Bonferroni test for pairwise comparisons among the test groups. When appropriate, ANOVA for repeated measurements was applied for data consisting of repeated observations at successive time points. All results are expressed as means ± SE. Differences were considered significant when P < 0.05.

RESULTS

Blood pressure, heart weight, and body weight. The systolic blood pressures of male SHR were clearly higher than those observed in female SHR. Blood pressure levels were also slightly lower in female than male WKY. Absolute heart weights and heart-to-body weight ratios were higher in both SHR groups compared with those in the normotensive control groups. Female SHR and WKY gained less weight than male SHR and WKY (Table 1).

Mesenteric arterial responses. The relaxations induced by ACh in endothelium-intact NE-precontracted (1 µM) mesenteric arterial rings were markedly impaired in female and male SHR compared with those in the two WKY groups (Fig. 1). Interestingly, the responses to ACh were more pronounced in female than in male SHR. Cyclooxygenase inhibition with diclofenac (3 µM) clearly improved relaxations to ACh in male SHR but did not significantly affect the responses in the female SHR and the WKY groups. The NO

Table 1. Experimental group data at close of study

<table>
<thead>
<tr>
<th></th>
<th>MaleSHR</th>
<th>FemaleSHR</th>
<th>MaleWKY</th>
<th>FemaleWKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>369 ± 6</td>
<td>217 ± 6†</td>
<td>409 ± 6</td>
<td>229 ± 5†</td>
</tr>
<tr>
<td>Heart weight, mg</td>
<td>1,411 ± 78</td>
<td>970 ± 50</td>
<td>1,222 ± 20*</td>
<td>830 ± 30‡</td>
</tr>
<tr>
<td>Heart-to-body weight ratio, mg/g</td>
<td>3.8 ± 0.2</td>
<td>4.5 ± 0.1*</td>
<td>3.0 ± 0.1*</td>
<td>3.7 ± 0.2‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>358 ± 7</td>
<td>369 ± 6</td>
<td>330 ± 6‡</td>
<td>325 ± 9‡</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>149 ± 3</td>
<td>150 ± 3</td>
<td>114 ± 2‡</td>
<td>115 ± 2‡</td>
</tr>
<tr>
<td>Week 8</td>
<td>149 ± 3</td>
<td>188 ± 4*</td>
<td>144 ± 1‡</td>
<td>137 ± 3‡</td>
</tr>
<tr>
<td>Week 20</td>
<td>219 ± 4</td>
<td>—</td>
<td>219 ± 4</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10–12 rats for all groups. SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats. *P < 0.05 vs. male SHR; †P < 0.05 vs. female SHR; ‡P < 0.05 vs. male WKY; ††P < 0.05 vs. female WKY (Bonferroni test).
synthase inhibitor L-NAME (0.1 mM; in the presence of diclofenac) significantly diminished the relaxations of NE-precontracted rings to ACh in all groups (P < 0.001 in all groups), with the influence being more pronounced in female SHR and WKY groups than in their male control groups (Fig. 1). Apamin (1 µM), an inhibitor of KCa, slightly reduced the diclofenac- and L-NAME-resistant relaxations to ACh in both WKY groups (Fig. 1). When endothelium-mediated hyperpolarization of arterial smooth muscle was eliminated by precontraction induced by depolarization with 50 mM KCl, no differences were found among the study groups in the relaxation responses induced by ACh (Fig. 2) or another endothelium-dependent agonist, ADP (data not shown). In the presence of diclofenac, the responses to ACh were augmented in male SHR but not in the other groups. The addition of L-NAME almost completely abolished the relaxations to ACh in all study groups during KCl-induced precontractions (Fig. 2).

The responses to SNP, an agent that mediates arterial relaxation via the formation of exogenous NO and the subsequent accumulation of cGMP, were attenuated in male SHR compared with those in female SHR and the two WKY groups (Fig. 3 and Table 2). The vasorelaxations to the β-adrenoceptor agonist isoproterenol in endothelium-intact arterial rings were comparably impaired in both SHR groups compared with those in the WKY groups (Fig. 3, Table 2). The maximal contractions elicited by K⁺-free solution were not statistically different among the study groups (maximal forces in male SHR, female SHR, male WKY, and female WKY: 1.3 ± 0.2, 0.8 ± 0.2, 0.9 ± 0.2, and 0.9 ± 0.1 g, respectively), with the exception of the comparisons between male SHR and female WKY (P = 0.045) and between male SHR and female SHR (P = 0.031). After the return of K⁺ to the organ bath following the K⁺-free precontractions, the rate of the subsequent relaxation was faster in WKY than in SHR groups (Fig. 3). Furthermore, K⁺ relaxation was effectively inhibited by the Na⁺-K⁺-ATPase inhibitor ouabain in all groups (Fig. 3).

The endothelium-intact vascular rings of both SHR groups showed higher sensitivity (i.e., pD50 values) to 5-HT compared with those of the corresponding WKY groups, whereas maximal contractile force generation to 5-HT was similar among the study groups. In addition, sensitivity to 5-HT was slightly higher in female than in male SHR (Table 2 and Fig. 4). The effect...
of organ bath Ca\(^{2+}\) concentration on NE-induced contractions, i.e., the Ca\(^{2+}\) sensitivity of the vascular rings during \(\alpha\)-adrenoceptor stimulation, was corresponding in the four study groups (Fig. 4).

**DISCUSSION**

Impaired endothelium-dependent relaxation has been repeatedly observed in experimental hypertension (12, 20, 23, 29), and in the present study the relaxations to ACh in NE-precontracted rings also were attenuated in both female and male SHR. Interestingly, the responses to ACh were more pronounced in female than in male SHR, in accordance with recent findings (23). One plausible explanation for the attenuated endothelium-mediated relaxations in hypertension is enhanced release of endothelium-derived contracting factor(s) (EDCF) (27), the formation of which, most likely prostaglandin H\(_2\) or thromboxane A\(_2\) (TxA\(_2\)), is increased by ACh in the mesenteric artery of male SHR (24). Previously, the endothelium-dependent vasoconstrictor responses in SHR have been shown to be blocked by cyclooxygenase inhibition (35), and treatment with a TxA\(_2\)-prostaglandin endoperoxide-receptor blocker has completely restored endothelium-dependent dilation in vivo in male SHR (37). In the present study, diclofenac clearly enhanced the relaxations to ACh in male SHR and abolished the difference between female and male SHR, suggesting that cyclooxygenase-derived constricting prostanoids were indeed involved in the responses of male SHR. However, diclofenac was without significant effect on the relaxations to ACh in the other groups, whereby products of the cyclooxygenase pathway did not seem to play a significant role in the responses to ACh in the female SHR and in the WKY groups. Therefore, the release of contractile factors from the endothelium appeared to be more pronounced in male SHR than in the other groups. On the other hand, testosterone has been reported to increase TxA\(_2\)-receptor density in cultured rat aortic smooth muscle cells (30), an effect that was more pronounced in the male than in the female study group (31). Thus another possibility for the present findings is that the sensitivity of arterial smooth muscle to the contractile factors was higher in male SHR.

In the present study, systolic blood pressures of male SHR were clearly higher than those in age-matched female SHR. In accordance, previous reports have shown that hypertension develops more rapidly and becomes more severe in male than in female SHR (17, 23). Interestingly, the production of EDCF has been shown to closely parallel the increase in blood pressure in SHR (18). Therefore, the lower blood pressure in female than in male SHR may be attributed to lower release of endothelial contractile factors in the female animals. Lower body weight in the female SHR provides another explanation for the lower blood pressures in these rats.

Inhibition of NO synthesis by \(L\)-NAME effectively diminished relaxations to ACh in both SHR groups, whereas the responses in the both WKY groups were slightly but significantly attenuated by \(L\)-NAME, in

![Graph](image_url)
accordance with previous findings (20, 25). Thus these findings indicate that there was a significant NO-mediated component in endothelium-mediated relaxations of mesenteric arterial rings in all groups studied. Interestingly, the inhibitory effect of L-NAME on ACh-induced relaxation was more pronounced in female SHR and WKY than in the corresponding male groups, thus suggesting that the relative role of NO in endothelium-mediated relaxation was higher in the female animals. Indeed, more pronounced endothelium-dependent vasodilation in normotensive female than in male experimental animals has been attributed to differences in the function of the L-arginine-NO pathway (11, 22). In addition, estrogen enhanced basal NO release in

Table 2. Parameters of contractile and relaxation responses of isolated endothelium-intact arterial rings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male SHR</th>
<th>Female SHR</th>
<th>Male WKY</th>
<th>Female WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractions to 5-hydroxytryptamine</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>pD50</td>
<td>6.52 ± 0.05t</td>
<td>6.66 ± 0.03</td>
<td>6.32 ± 0.07*</td>
<td>6.42 ± 0.07t</td>
</tr>
<tr>
<td>Maximal force, g</td>
<td>2.0 ± 0.1</td>
<td>2.1 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Relaxation responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pD25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh</td>
<td>7.58 ± 0.14t</td>
<td>7.33 ± 0.23t</td>
<td>8.02 ± 0.11</td>
<td>7.69 ± 0.08t</td>
</tr>
<tr>
<td>Iso</td>
<td>4.58 ± 0.18</td>
<td>5.06 ± 0.31</td>
<td>5.72 ± 0.13*</td>
<td>5.59 ± 0.25*</td>
</tr>
<tr>
<td>pD50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>6.35 ± 0.11</td>
<td>7.01 ± 0.10*</td>
<td>7.21 ± 0.11*</td>
<td>7.45 ± 0.05*</td>
</tr>
<tr>
<td>Maximal relaxation (% of 1 µM NE-induced preconstriction)</td>
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</tr>
<tr>
<td>ACh</td>
<td>36.9 ± 9.6</td>
<td>53.3 ± 5.1*</td>
<td>99.3 ± 0.5*</td>
<td>91.7 ± 2.7*</td>
</tr>
<tr>
<td>Iso</td>
<td>41.8 ± 7.1</td>
<td>54.4 ± 7.2*</td>
<td>84.5 ± 2.0*</td>
<td>79.9 ± 4.1*</td>
</tr>
<tr>
<td>SNP</td>
<td>77.5 ± 5.7</td>
<td>90.2 ± 2.5*</td>
<td>96.3 ± 2.7*</td>
<td>94.3 ± 0.9*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10–12 rats in each group. EC25 and EC50 values are presented as negative logarithm (pD25 and pD50) of concentration of agonist. Iso, isoproterenol; SNP, sodium nitroprusside; NE, norepinephrine. *P < 0.05 vs. male SHR; †P < 0.05 vs. male WKY; ‡P < 0.05 vs. female SHR (Bonferroni test).
posed as a vasoactive autacoid of endothelial origin (9). EDHF has been described to be an endogenous K⁺-channel opener, but the nature of K⁺ channels opened by EDHF has not been fully characterized. Apamin, a blocker of K_{Ca}, has been found to reduce the \( L\)-NAME-insensitive relaxation in rat mesenteric artery, and apamin together with charybdotoxin completely abolishes these responses (38). In contrast, the ATP-sensitive K⁺-channel blocker glyburide was found to be ineffective (13, 32). These findings indicate that EDHF relaxes mesenteric arteries mainly by activating K_{Ca}. In the present study, apamin somewhat attenuated the \( L\)-NAME- and diclofenac-resistant relaxation to ACh in WKY groups, thus suggesting that this relaxation was mediated at least partially via arterial K_{Ca}.

The membrane depolarization induced by precontracting the arterial preparations with KCl has been reported to eliminate the action of EDHF (1). Interestingly, no significant differences were found among the present study groups in response to ACh and ADP when the precontractions were induced by KCl. The fact that the relaxations to ACh in KCl-precontracted rings were comparable among the study groups, whereas those induced in NE-precontracted rings were markedly reduced in hypertensive compared with normotensive rats, suggests that hyperpolarization induced by ACh was reduced in both SHR strains. In the presence of diclofenac, the relaxations to ACh and ADP were again augmented in male SHR but not in the other groups. Moreover, the relaxations to ACh and ADP in KCl-precontracted preparations of all groups were practically abolished by L-NAME, suggesting that NO and EDHF were indeed responsible for the observed dilator responses to these agonists.

Arterial relaxations to the \( \beta \)-adrenoceptor agonist isoproterenol were comparably impaired in both SHR groups compared with those in the WKY groups. However, arterial relaxations elicited by SNP were more pronounced in female than in male SHR, suggesting that the sensitivity of arterial smooth muscle to NO was higher in the female group. Exogenous NO has been shown to hyperpolarize guinea pig uterine artery (36) and rat mesenteric artery (13), whereas the KCa blockers charybdotoxin and tetraethylammonium have been shown to decrease relaxation to NO in guinea pig pulmonary arterial and tracheal smooth muscle (4). Thus augmented function of K_{Ca} in smooth muscle could partially explain the enhanced relaxation to the SNP in female SHR in this study.

Taken together, inhibition of cyclooxygenase with diclofenac eliminated the difference in the ACh-induced relaxation between female and male SHR. Thus the release of cyclooxygenase-derived constricting factors appeared to be more pronounced in the male hypertensive animals. In addition, the inhibitory effect of \( L\)-NAME on ACh-induced relaxation was more pronounced in female SHR and WKY than in the corresponding male groups, suggesting that the relative role of NO in endothelial-mediated relaxation was higher in the female rats. Furthermore, prevention of hyperpolarization by precontractions induced by KCl eli-
nated the difference in the ACh-induced arterial relaxation among the study groups. Because NO has been proposed to directly activate \( K_{\text{Ca}} \) (5), the deviations in endothelium-mediated relaxation among the groups in this study may partially have resulted from differences in hyperpolarization of arterial smooth muscle. This conclusion is supported by the fact that the relaxations elicited by SNP were higher in female SHR and in both WKY groups compared with those in male SHR, indicating enhanced sensitivity of arterial smooth muscle to relaxation via NO. Interestingly, the mechanism of 17\( \beta \)-estradiol-induced endothelium-independent arterial dilation has been found to involve opening of \( K_{\text{Ca}} \) via cGMP-dependent phosphorylation (41). In addition, 17\( \beta \)-estradiol-induced elevation of basal NO release from endothelium has been suggested to activate \( K_{\text{Ca}} \) in coronary arterial smooth muscle (40). Thus the favorable influences of estrogens on NO-mediated smooth muscle hyperpolarization through \( K_{\text{Ca}} \) provide a possible mechanism by which gender affects arterial dilation in experimental hypertension.

Vascular Na\(^{+}\)-K\(^{+}\)-ATPase function was evaluated indirectly by K\(^{+}\) repletion in response to K\(^{+}\)-free medium-induced precontractions (2), because the return of K\(^{+}\) activates the Na\(^{+}\)-K\(^{+}\)-ATPase, which repolarizes the cell membrane and thus relaxes smooth muscle (6). The rate of K\(^{+}\) relaxation also reflects general smooth muscle relaxation mechanisms (e.g., contractile protein dephosphorylation, Ca\(^{2+}\) sequestration, and extrusion) (19), but previous results suggest that the K\(^{+}\) relaxation rate is indicative of Na\(^{+}\)-K\(^{+}\)-ATPase activity in the rat mesenteric artery (2). Previous studies on K\(^{+}\) relaxation have yielded conflicting results (2, 39). However, in the present study, the K\(^{+}\) relaxation rate was markedly slower in SHR than in WKY groups. The more pronounced K\(^{+}\) relaxation in WKY than in SHR groups suggests increased recovery rate of ionic gradients across the cell membrane, probably via differences in the function of Na\(^{+}\)-K\(^{+}\)-ATPase among the study groups. This conclusion is supported by the fact that K\(^{+}\) relaxation was effectively inhibited by the Na\(^{-}\)-K\(^{-}\)-ATPase inhibitor ouabain in all study groups. Enhanced function of Na\(^{-}\)-K\(^{-}\)-ATPase would also favor hyperpolarization of arterial smooth muscle in the normotensive groups.

In conclusion, the release of cyclooxygenase-derived constricting factors appeared to be more pronounced in male than in female SHR. In addition, the relative role of NO in endothelium-dependent arterial relaxation was higher in female than in male SHR, possibly via a hyperpolarization mechanism. Finally, endothelium-independent NO-mediated relaxation was also more pronounced in female than in male hypertensive rats. Taken together, the control of arterial tone was clearly affected by gender in the present model of genetic hypertension.

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