Gender difference in flow-induced dilation and regulation of shear stress: role of estrogen and nitric oxide

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Gender difference in flow-induced dilation and regulation of shear stress: role of estrogen and nitric oxide. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1571–R1577, 1998.—Previous studies show that agonist-induced, nitric oxide (NO)-mediated arteriolar dilations are greater in female than in male rats. Thus we hypothesized that flow-dependent arteriolar dilation, which is in part mediated by NO, is also greater in females than in males. Gracilis muscle arterioles from 12-wk-old female and male Wistar rats were isolated, cannulated, and pressurized. At 80 mmHg of perfusion pressure, the active diameter and passive diameter (PD) of arterioles of female and male rats were 58.3 ± 3.4 and 53.2 ± 2.6 µm as well as 103.6 ± 4.0 and 115.3 ± 4.8 µm, respectively. Dilations to step increases in perfusate flow from 0 to 25 µl/min were significantly greater in arterioles of female rats and ovariectomized rats with estrogen replacement (OVE) than in male and ovariectomized female (OV) rats (98.6 ± 0.6 and 97.4 ± 1.1% vs. 72.6 ± 3.3 and 72.5 ± 3.6% of PD at 25 µl/min). Calculation of wall shear stress (WSS) revealed that the maintained WSS was significantly lower in arterioles of female than in those of male rats (−20 vs. −35 dyn/cm²). After indomethacin pretreatment, Nω-nitro-L-arginine methyl ester (L-NAME; 10−4 M) eliminated flow-dependent dilation in arterioles of male and OV rats but only attenuated (by ∼50%) the responses in arterioles of female and OVE rats. In vessels of these latter two groups of rats, the remaining flow-induced dilation was completely eliminated by administration of 10−5 M Hb or 10−3 M L-NAME. The greater flow/shear stress-induced dilation of arterioles of female rats indicates a gender difference in the regulation of WSS, which is likely to be due to the greater release of NO in female vessels requiring the chronic presence of estrogen. These findings suggest an important role for estrogen in the regulation of peripheral resistance in females.

Also shown that estrogen decreases coronary blood flow and dilates epicardial coronary arteries in humans (2). Furthermore, acute sublingual administration of 17β-estradiol significantly increased blood flow in forearm vessels in postmenopausal women (16), and intracoronary injection of 17β-estradiol in physiological concentrations enhanced acetylcholine-stimulated increases in coronary blood flow (15) and attenuated acetylcholine-induced constriction in coronary conduit arteries in postmenopausal women (14). Collectively, these studies indicate that both large vessels and microvessels are affected by the acute or chronic presence of estrogen in plasma. The possible underlying mechanisms for the acute effects of estrogen are still not elucidated, but a role for the endothelium in the long-term effects of estrogen has been suggested by several clinical and experimental studies (1, 3, 5, 10).

Previously, we have found a significantly greater dilation to substance P and an attenuated pressure-induced myogenic constriction in isolated arterioles of skeletal muscle of female compared with those of male rats, responses that are dependent on the greater release of nitric oxide (6), whereas the dilator effects of a nitric oxide donor were not different. In accordance with these observations, an increased expression of endothelial nitric oxide synthase by the chronic presence of estrogen has been documented (4, 17).

In vivo, an increase in flow/wall shear stress is perhaps the most effective stimulus for the release of nitric oxide (8, 9). There are as yet no studies extant that examined the possible effects of estrogen on endothelial regulation of shear stress, which would be especially important in microvessels in which increases in shear stress have already been shown to elicit great increases in diameter through nitric oxide release (8, 9). In this context, the significant increase in blood pressure elicited by systemic inhibition of nitric oxide synthase (13), in part, is likely to be caused by the lack of shear stress-induced release of nitric oxide in the peripheral circulation.

On the basis of the aforementioned, we hypothesized that the flow/shear stress-induced dilation of skeletal muscle arterioles is greater in females than in males and that this is because of the greater release of nitric oxide, for which the chronic presence of estrogen is necessary. To test this idea, arterioles of gracilis muscle of male and female rats, including ovariectomized rats (OV) and ovariectomized rats with estrogen replacement (OVE), were isolated and cannulated, and changes in diameter, as a function of perfusate flow/shear stress, were contrasted.

MATERIALS AND METHODS
Experimental animals. Twelve-week-old Wistar rats (Charles River Laboratories, Wilmington, MA) were divided

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into four groups: male, female, OV, and OVE. Ovariectomy was performed at 9 wk of age (6). Rats were anesthetized by inhaling methoxyflurane (Metofane). An incision of \(-1 \text{ cm}\) in length was made on both sides of the back to expose the ovaries retroperitoneally. Ovaries were removed by clamping and cutting between them and the uterus; the Fallopian tubes were then ligated, and the skin was closed with sutures. One week after the operation, rats were divided into two groups. One group received injection of 17\(\beta\)-estradiol benzoate (50 \(\mu\)g/kg, every 48 h) in sesame oil subcutaneously for 3 wk, and the other group received the vehicle only. The volume of each injection was 0.1 ml. The 17\(\beta\)-estradiol benzoate was dissolved in pure ethanol (5 mg/ml) with sesame oil as vehicle.

Isolation of arterioles. Experiments were conducted on isolated arterioles (\(\sim 55 \mu\)m ID) of rat gracilis muscle. Rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (Nembutal, 50 mg/kg). The isolation procedure of arterioles has been described previously (8). Briefly, the muscle was excised and placed into a refrigerated dissecting dish containing a cold (0–4°C) modified physiological salt (PS1) solution. The PS1 solution contained (in mM) 145 NaCl, 5 KCl, 2.0 CaCl\(_2\), 1.0 MgSO\(_4\), 1.0 NaH\(_2\)PO\(_4\), 5.0 dextrose, 2 pyruvate, 0.02 EDTA, and 3.0 MOPS to reach pH 7.4. The muscle was then split open as a flat sheet of tissue and pinned to the bottom of the silicone-lined base of a Petri dish. Rats were killed by an overdose of pentobarbital sodium injected to the bottom of the silicone-lined base of a Petri dish. Rats were killed by an overdose of pentobarbital sodium injected to the bottom of the silicone-lined base of a Petri dish.

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Perfusion system. As described previously (6), both the vessel chamber and final experiments were performed by assessing flow-dependent responses in the absence of inhibitors. Stable responses indicated that there was no time-related decline in arteriolar responsiveness to flow during the experiments (data not shown).

All drugs were added to the reservoir connected to the vessel chamber, and final experiments were performed by assessing flow-dependent responses in the absence of inhibitors. Stable responses indicated that there was no time-related decline in arteriolar responsiveness to flow during the experiments (data not shown).

Perfusion system. As described previously (6), both the proximal (inflow) and distal (outflow) glass micropipettes filled with a second physiological salt (PS2) solution at room temperature. The PS2 solution used for perfusion and perfusion of the vessels contained (in mM) 118 NaCl, 5 KCl, 2.5 CaCl\(_2\), 1.0 MgSO\(_4\), 1.0 K\(_2\)HPO\(_4\), 24 NaHCO\(_3\), 10 dextrose, and 0.02 EDTA and was equilibrated with a gas mixture of 21% O\(_2\), 5% CO\(_2\), and balanced with N\(_2\), at pH 7.4 (37°C). From a reservoir (50 ml), the vessel chamber (15 ml) was continuously supplied via tubing (35 ml) with PS2 solution at a rate of 40 ml/min. After the vessel was mounted on the proximal micropipette and secured, the perfusion pressure was raised to 20 mmHg to clear the dextran from the lumen, and the other end of the vessel was mounted on the distal micropipette. To flush the vessel and cannulas, the system was perfused for several minutes. The perfusion pressure was then slowly (~1 min) increased to 80 mmHg. At this time, the perfusion system was placed in manual mode in which the stable pressure value indicated that there was no leak in the system. The pressure-servo system was then set in the automatic mode at 80 mmHg, in a no-flow condition, with a double-antibody estradiol kit (Diagnostic Products, Los Angeles, CA). The minimal detectable concentration by this assay is \(\leq 2 \text{ pg/ml}\). Samples were assayed in duplicate, and means are reported. The data reported are means \(\pm\) SE. Only one vessel was studied from each animal. Flow-induced responses were expressed as change in diameter. Wall shear stress was calculated by the following formula: \(4\pi Q/R^2\), where \(R\) is the radius of the perfusate (0.007 P at 37°C), Q is the perfusate flow, and \(R\) is the vessel radius. The value of shear stress required to dilate arterioles maximally was also calculated. Statistical analyses were done by ANOVA, followed by Tukey’s post hoc test and regression analysis. A P value of \(< 0.05\) was considered significant.
RESULTS

Animals. Table 1 shows the changes in body weight, uterus weight, and uterus weight-to-body weight ratio in three groups of female rats. The uterus weight of OV females was significantly lower than that of normal females or OVE females (P < 0.01). In contrast, the body weight of OV females was significantly greater than that of normal females or OVE females (P < 0.05). As a result, uterus weight-to-body weight ratio was significantly less in OV females than in normal females or OVE females (P < 0.01). Also shown is the concentration of estradiol in male, normal female, OV female, and OVE female rats. The concentration of estradiol in males or OV females was significantly lower than in normal females or OVE females (P < 0.05), whereas in normal females and OVE females it was comparable.

Pressure-induced arteriolar tone. The active, passive, and normalized diameters (expressed as the percent of passive diameter) of arterioles of males, females, OV females, and OVE females obtained in the presence of constant intravascular pressure (80 mmHg, with no perfusate flow) are summarized in Table 2. Normalized diameters in males and OV females were significantly less compared with those of females and OVE females, indicating that the pressure-induced basal tone of arterioles of males and OV females is significantly greater than that of females and OVE females (P < 0.05). Addition of L-NAME (10^{-4} M) with or without Hb (10^{-5} M) or L-NAME (10^{-3} M) into the chamber solution (in the presence of indomethacin) significantly reduced both the basal and normalized diameters of arterioles of females and OVE females, indicating that inhibition of nitric oxide synthesis elicits significantly greater changes in diameter of vessels isolated from females and OVE females than in those from males and OV females.

Flow-induced responses. Summary data of the changes in diameter of arterioles of four groups of rats in response to step increases in perfusate flow in control conditions (without indomethacin) are depicted in Fig. 1. From 5 µl/min perfusate flow, the diameters of arterioles of females and OVE females started to deviate significantly from those of males and OV females, and at 25 µl/min flow, they were ~28% greater than those of males or OV females. Analyzing the slopes (see Fig. 1) of the flow-diameter curves revealed a significant difference between groups, those with and without estrogen.

Table 1. Effect of ovariectomy without and with estrogen replacement on body weight, uterus weight, UW/BW, and serum estradiol concentrations of rats

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>BW (g)</th>
<th>UW (g)</th>
<th>UW/BW</th>
<th>ES (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>9</td>
<td>2686±39</td>
<td>0.54±0.07</td>
<td>0.202±0.023</td>
<td>144.7±14.3</td>
</tr>
<tr>
<td>OV female</td>
<td>6</td>
<td>3128.8±8.9*</td>
<td>0.14±0.01</td>
<td>0.045±0.002*</td>
<td>5.3±1.2*</td>
</tr>
<tr>
<td>OVE female</td>
<td>6</td>
<td>2505.8±2.2</td>
<td>0.495±0.02</td>
<td>0.199±0.01</td>
<td>115.9±10.1</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>8.65±1.3*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. OV, ovariectomy; OVE, ovariectomy with estrogen replacement; BW, body weight; UW, uterus weight; ES, serum estradiol. *Significant difference from female and OVE female rats (P < 0.05).

Table 2. Effects of L-NAME and Hb on arteriolar diameter of rats

<table>
<thead>
<tr>
<th></th>
<th>Male (n - 6)</th>
<th>Female (n - 9)</th>
<th>OV (n - 6)</th>
<th>OVE (n - 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-NAME (10^{-4} M)</td>
<td>AD, µm 52.6±3.1</td>
<td>48.5±3.3*</td>
<td>47.8±3.9</td>
<td>50.8±2.7*</td>
</tr>
<tr>
<td>AD/PD, %</td>
<td>45.5±1.2</td>
<td>46.6±2.0*</td>
<td>44.5±2.5</td>
<td>46.8±2.0*</td>
</tr>
<tr>
<td>L-NAME (10^{-4} M)</td>
<td>AD, µm 50.6±5.4</td>
<td>46.3±3.7*</td>
<td>48.0±3.9</td>
<td>49.0±3.0*</td>
</tr>
<tr>
<td>AD/PD, %</td>
<td>41.4±3.0</td>
<td>44.8±2.5*</td>
<td>44.9±2.8</td>
<td>45.1±2.3*</td>
</tr>
<tr>
<td>L-NAME (10^{-3} M)</td>
<td>AD, µm 49.2±2.1†</td>
<td>46.6±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD/PD, %</td>
<td>46.6±1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. Control responses were obtained in presence of 10^{-5} M indomethacin. L-NAME, N-nitro-l-arginine methyl ester; AD, active diameter; PD, passive diameter; OV, ovariectomy; OVE, ovariectomy with estrogen replacement. *Significant difference between male and all groups of female rats. †Significant difference in females and OVE females vs. males and OV females. ‡Significant difference from control (P < 0.05).

These results indicate that arterioles of female and OVE female rats dilate to a greater extent in response to step increases in perfusate flow than arterioles of male and OV female rats, a function that correlates with the level of estrogen in plasma.

Calculated wall shear stress vs. diameter. From the flow and diameter data obtained, wall shear stress was calculated and plotted against the changes in arteriolar diameter. Figure 2 shows that after reaching a threshold value (~18–20 dyn/cm²), a given step increase in wall shear stress elicits a significantly greater increase in diameter of arterioles of female and OVE female rats.
compared with those of male and OV female rats. This results in a significant leftward shift of the upward portion of the shear stress-diameter curve of female and OVE female arterioles, revealing that the main-
tained arteriolar shear stress values are
35 dyn/cm$^2$ in males and
45 dyn/cm$^2$ in OV females, whereas they are
20 dyn/cm$^2$ in females and OVE females. Comparison of the shear stress required to dilate arterioles maximally indicates that this value is significantly less in arterioles of females (28.4 ± 3.3 dyn/cm$^2$) and OVE females (27.2 ± 5.1 dyn/cm$^2$) than in those of male (44.2 ± 5.3 dyn/cm$^2$) and OV female rats (69.9 ± 7.0 dyn/cm$^2$) (P < 0.05).

Role of nitric oxide in the mediation of flow-induced dilation. The effects of $10^{-4}$ M L-NAME (in the presence of indomethacin) on flow-induced responses in arterioles of four groups of rats are summarized in Fig. 3. This concentration of the L-arginine analog significantly reduced flow-induced arteriolar dilation in all groups, but to a different degree. At 25 µl/min flow, the dilation of arterioles of males and OV females was nearly completely eliminated by $10^{-4}$ M L-NAME (Fig. 3, A and C). In females and OVE females, however, there was only ~50% reduction in dilation (Fig. 3, B and D) after L-NAME administration. In an attempt to elucidate the mediation of the remaining flow-induced arteriolar dilation in female and OVE female rats, Hb (10$^{-5}$ M), known to interfere with the action of nitric oxide, was used. Figure 3 shows that additional administration of Hb (in the presence of indomethacin and $10^{-4}$ M L-NAME) did not further affect the flow-diameter curve of vessels of males and OV females, whereas it eliminated the remaining flow-induced dilation in arterioles of both females and OVE females. Based on the flow-diameter curves depicted in Fig. 3, values of the corresponding wall shear stress were calculated and plotted against the changes in arteriolar diameter in Fig. 4. Administration of L-NAME displaced the shear stress-diameter curve of vessels of female and OVE rats to the right. The additional administration of Hb, because it prevented the dilation in response to increases in flow, eliminated the regulation of shear stress in these vessels. In contrast, in vessels of male and OV rats, the administration of $10^{-4}$ M L-NAME alone proved to be sufficient to disrupt this regulation, and thus shear stress increased linearly with increases in flow. To ascertain further that in vessels of females the nonprostaglandin-mediated portion of the flow induced response is entirely nitric oxide dependent, a study was performed using a higher concentration of L-NAME (10$^{-3}$ M). Figure 5 shows the results of these experiments, demonstrating that $10^{-3}$ M
L-NAME eliminated flow-dependent dilation of arterioles of female rats.

**DISCUSSION**

The novel finding of this study is that because of the greater release of nitric oxide, flow-induced dilation of skeletal muscle arterioles of female rats is greater than that of male rats. This gender difference, due, in large part, to the presence of estrogen, may have important consequences for the regulation of arteriolar wall shear stress and peripheral resistance in males and females.

Previous studies demonstrated that estrogen replacement therapy increases blood flow to various tissues and that this response may be due to an enhanced synthesis of nitric oxide in vascular endothelium (3, 6, 15). In vivo, the primary stimulus for the release of nitric oxide is the presence of shear stress caused by the flowing blood (9, 13). In the present study, the possible role of estrogen in affecting flow-dependent dilation was studied in four groups of rats in which the serum estrogen concentrations were significantly different. Male and OV female rats had low levels of estrogen, whereas normal female and OVE female rats had significantly higher levels of estrogen (Table 1). Ovariectomy elicited a significant reduction of plasma estrogen levels and uterus weight and a marked increase in body weight, as described previously (6).

To avoid the interference of several mechanisms that participate in the regulation of arteriolar diameter, changes in diameter to increases in perfusate flow were investigated in isolated arterioles in the presence of a constant intravascular pressure. In agreement with previous findings (6), the pressure-induced endothelium-independent myogenic tone of arterioles of female rats was significantly less pronounced than that of male rats, due to the greater synthesis/release of nitric oxide (Table 2).

Role of estrogen in augmented flow-induced dilation. In response to increases in perfusate flow, arterioles of female rats exhibited a greater dilation than arterioles of male rats. Also, the arterioles of OV females without estrogen-replacement responded in a fashion similar to those of males, but arterioles of OVE rats showed a significantly greater dilation to flow than those of males and OV females (Fig. 1). These findings suggest that the presence of higher levels of estrogen in the plasma may account for the greater flow-induced arteriolar response in female rats.

Because the stimulus for vasodilation in response to increases in flow is the increase in wall shear stress (8, 9), we calculated wall shear stress and plotted it against changes in diameter (Fig. 2). We found that shear stress-induced increases in diameter were greater, whereas the threshold for dilation tended to be lower in arterioles from rats having high plasma estrogen con-
lower level of maintained shear stress values recorded significantly lesser inhibitory effect on the dilation to sub-female arterioles and L-NAME eliminated flow-induced dilation of arterioles wall shear stress-diameter curve, indicating the level of concentrations compared with rats with low plasma estrogen. Because of these differences, the upward portion of wall shear stress-diameter curve, indicating the level of maintained wall shear stress, was at ~20 dyn/cm² in female arterioles and ~35 dyn/cm² in male vessels. The lower level of maintained shear stress values recorded in vessels of males vs. those of OV rats (~45 dyn/cm²) could well be a result of a greater dilator reserve of arterioles of males due to their significantly greater passive diameter (Table 2). Extrapolating the above findings to in vivo conditions, one can speculate that resistance vessels of females (with normal plasma estrogen levels) are exposed to a lower shear stress than those of males, resulting in a lower power dissipation in the female cardiovascular system compared with that of males. If so, this could be one of the underlying mechanisms for the lower blood pressure before menopause and, perhaps, for the delayed appearance of hypertension in women compared with men.

Role of nitric oxide-mediated augmentation of flow-dependent dilation. Although in gracilis muscle arterioles both nitric oxide and prostaglandins contribute to the mediation of flow-induced dilation, in a proportion of ~55 and ~45%, respectively (9), previous studies in these arterioles suggested that it is the nitric oxide mediation that is affected by estrogen (6). Thus, to assess solely the role of nitric oxide in flow-dependent responses of arterioles of female rats, vessels were pretreated with indomethacin to block prostaglandin synthesis. In this condition, inhibition by 10⁻⁴ M L-NAME eliminated flow-induced dilation of arterioles of male and OV female rats, indicating a complete block of nitric oxide synthase. In contrast, arterioles of female and OVE female rats still dilated to flow in the presence of 10⁻⁴ M L-NAME (Fig. 3). We hypothesized that the remaining portion of flow-induced responses in females is due to the incomplete block of nitric oxide synthase. To confirm our hypothesis, we have used Hb, known to scavenge nitric oxide by forming nitrosyl-Hb in the extracellular space. Because nitric oxide readily crosses cell membranes, Hb provides an additional means for reducing the level of nitric oxide before it reaches arteriolar smooth muscle. In arterioles of female and OVE rats, additional administration of Hb (10⁻⁵ M) eliminated flow-induced responses, indicating that the dilation, still present after 10⁻⁴ M L-NAME and indomethacin, is also due to nitric oxide.

This suggestion is further supported by our previous finding that arterioles of female and OVE female rats exhibit a significantly greater dilation to substance P, a nitric oxide- and endothelium-dependent dilator agent, than those of male and OV females (6). On the other hand, dilator responses to sodium nitroprusside, an endothelium-independent dilator agent, were similar in the vessels of all four groups of rats studied, suggesting that the enhanced response of vessels in the presence of estrogen is due to a specific increase in the production rather than the activity of nitric oxide. Furthermore, N^-nitro-L-arginine (10⁻⁴ M) had a significantly lesser inhibitory effect on the dilation to substance P if estrogen was present in the plasma of rats (6).

To gain further support for the primary role for nitric oxide in female rats, in a separate experiment a higher concentration of L-NAME (10⁻³ M) was used, which completely eliminated the non-prostaglandin-mediated portion of the dilation, suggesting that the greater flow-induced dilation is due to a greater release of nitric oxide. This reasoning is supported further by reports of an upregulation of nitric oxide synthase by estrogen in vascular tissues (4, 17). A greater availability of L-arginine, the substrate of nitric oxide synthase, may also play a role in the greater nitric oxide-mediated flow-induced dilation in the presence of estrogen.

An age-dependent decline in the dilation of the brachial artery during reactive hyperemia was reported to be delayed by a decade in women relative to men (1). This response is also thought to be activated, at least in part, by the increase in shear stress upon release of a vascular occlusion, suggesting that estrogen may protect endothelial function in women by preserving and/or enhancing the release of nitric oxide to shear stress. Such beneficial effects of estrogen are further underscored by the report demonstrating that estrogen supplementation augments endothelium-dependent flow-mediated vasodilation in the brachial artery in postmenopausal women (10).

In conclusion, the present study indicates that increases in flow/shear stress elicit greater dilations in skeletal muscle arterioles of female than of male rats, a difference which is due to an estrogen-stimulated enhanced capacity of endothelial cells of arterioles from females to produce nitric oxide in response to increases in shear stress. These findings suggest that the presence of estrogen may play an important role in the regulation of wall shear stress and peripheral vascular resistance by enhancing endothelial nitric oxide release and that this may constitute the basis for the beneficial effects of estrogen on the cardiovascular system.

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