Estrogen improves acetylcholine-induced but not metabolic vasodilation in biological males

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New, Gishel, Stephen J. Duffy, Richard W. Harper, and Ian T. Meredith. Estrogen improves acetylcholine-induced but not metabolic vasodilation in biological males. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H2341–H2347, 1999.—We have previously shown that chronic estrogen therapy improves endothelium-dependent vasodilation in the conduit artery and functional hyperemic blood flow (exercise) in females (12). We have also shown that estrogen improves endothelium-dependent vasodilation in males (24). We now report data from 15 male-to-female transsexuals prescribed estrogen and in 14 age-matched males. Resting forearm blood flow (FBF), ACh-induced vasodilation, and functional hyperemic blood flow (exercise) were assessed before and after the inhibition of NO with Nω-monomethyl-l-arginine (L-NMMA) in 15 male-to-female transsexuals prescribed estrogen and in 14 age-matched males. Resting FBF was similar in the two groups and was similarly (P = 0.44) but significantly reduced by 48% after infusion of L-NMMA (P < 0.0001). The ACh dose-response relationship was shifted upward and to the left in the transsexual compared with the male group (P < 0.01). After the inhibition of NO, however, the difference in the ACh dose-response curve between the two groups was abolished (P = 0.15). Peak functional hyperemic blood flow was similar for the two groups (P = 0.94). L-NMMA produced a significant (P < 0.01) but similar (P = 0.64) reduction in peak hyperemia in the two groups. The volume of blood repaid to the forearm 1 and 5 min after exercise was also reduced by L-NMMA (P < 0.0001); however, there were no differences between the two groups. This suggests that ACh-mediated NO-dependent vasodilation may be more sensitive to the effects of chronic estrogen than exercise-induced vasodilation. Long-term estrogen does not appear to improve exercise-induced metabolic vasodilation in biological males, despite the fact that NO contributes to this process.

The effects of estrogen on vascular function are thought to be mediated at least in part through changes in endothelium-dependent NO-mediated vasodilation (38). Extensive work has verified that estrogen replacement therapy improves endothelial function in postmenopausal women (10, 11, 30), and recent work by Guetta et al. (12) has demonstrated a role for NO in this process. The potential importance of the effect of estrogen on endothelium-dependent NO-mediated vasodilation has been suggested clinically by the attenuation of exercise-induced coronary ischemia (34).

Some (4, 31) but not all studies (6) have shown that the acute administration of estrogen enhances ACh-dependent vasodilation in males. Although there is no evidence for a clinical benefit of estrogen in males at present, we have recently reported improvement in flow-mediated endothelium-dependent vasodilation (induced by reactive hyperemia) in the conduit artery and ACh-induced vasodilation in the resistance circulation of male-to-female transsexuals being prescribed long-term estrogen. Whether this improvement is NO mediated and whether long-term estrogen therapy actually improves metabolic vasodilation is unknown. The aims of this study therefore were to assess the contribution of NO to estrogen-augmented ACh-dependent vasodilation and to determine the effects of chronic estrogen on metabolic vasodilation in males. We chose to study a group of male-to-female transsexuals prescribed estrogen as part of their gender reassignment, as this group provides a unique opportunity to study the long-term effects of estrogen in biological males.

METHODS

Subjects. Fifteen male-to-female transsexuals and 14 age-matched healthy males between 22 and 60 yr were recruited (Table 1). The transsexuals were recruited from the Gender Dysphoria Clinic in the Department of Psychological Medicine at Monash Medical Centre. Most of the TX were involved in our previous studies (6, 25, 26). One transsexual smoked, four had a family history of coronary artery disease, and two had controlled hypertension. One transsexual had multiple coronary risk factors (hypercholesterolemia, non-insulin-dependent diabetes mellitus, and a family history of coronary artery disease), and one transsexual had stable coronary artery disease (previous coronary artery bypass grafting) as well as four coronary risk factors. Transsexuals prescribed vasoactive medications were required to cease taking them 2 days before the study.

The transsexuals had been taking estrogen [ethinyl estradiol (n = 7), conjugated equine estrogen (Premarin, n = 6), and estradiol valerate (n = 2)] for at least 6 mo (61 ± 71 mo, mean ± SD). Premarin doses were within the range for hormone-replacement therapy; however, doses of ethinyl estradiol were on average two to three times that of the oral contraceptive. All doses of estrogen prescribed were sufficient
to produce "medical orchidectomy" in the transsexuals, thereby reducing serum testosterone levels to within the normal female range. Six transsexuals had undergone surgical orchidectomy as part of their gender reassignment surgery. Three transsexuals were taking spironolactone, six were taking cyproterone acetate, and one transsexual was taking medroxyprogesterone acetate.

Healthy male controls were recruited by advertisement. They were excluded if they had any major illness or coronary risk factors (including a past history of smoking) and a total cholesterol or low-density lipoprotein (LDL-C) greater than the 75th percentile for their age and sex based on the Australian Risk Factor Prevalence Study (32). They had no known reproductive disorders and had never taken hormonal therapy. All had serum testosterone levels within the normal male range. The study was approved by the Human Research & Ethics Committee at Monash Medical Centre, and all procedures followed were in accordance with institutional guidelines. All subjects gave written informed consent.

Blood samples were taken in the sitting position after a 12-h overnight fast to measure plasma concentrations of lipids and glucose and serum concentrations of testosterone. Serum testosterone levels were used as an index of estrogen therapy in the transsexuals. This was measured by RIA. Serum estradiol levels were not reported, as ethinyl estradiol, conjugated equine estrogen, and estradiol valerate (the agents used by the transsexuals for feminization) have variable or no cross-reactivity with the RIA for estradiol and hence do not provide an accurate reflection of estrogen therapy in transsexuals. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations were measured enzymatically. LDL-C was calculated according to the Friedewald formula. If the TG levels were >4.5 mmol/l, LDL-C was not calculated. Lipoprotein (a) was measured via a modified Behring commercial latex-enhanced immunonephelometric method.

Study design. All subjects were studied after a light meal in the afternoon in a quiet temperature-controlled room. Subjects were asked to refrain from caffeine, alcohol, and smoking (1 TX) for 12 h before the study. Each subject had his forearm volume (nondominant arm) measured using the water displacement principle. ACh was delivered by varying the drug concentration in the solvent, while allowing the infusion rate to remain the same for all subjects. This enabled standardization of drug infusion doses to 100 ml of forearm tissue.

Forearm blood flow (FBF) was assessed bilaterally using the technique of venous occlusion plethysmography as previously described (15). The study protocol included five phases (Fig. 1). An infusion of isotonic glucose was continuously infused into the forearm at a rate of 0.4 ml/min except during infusion of ACh. After intra-arterial cannula insertion, a 30-min rest period was observed to establish a stable baseline FBF. FBF was recorded at baseline and for each dose of ACh (Iolab Pharmaceuticals, Sydney, Australia) at 2.7, 9.1, and 27.3 μg/min. Each dose of ACh was infused for 3 min at the same rate, and FBF was recorded for a subsequent 2 min during which the drug infusion was continued. After waiting between 10 and 30 min for flow to return to baseline, resting FBF was rerecorded.

Isotonic forearm exercise was performed for 2 min. This involved simple maximum wrist flexion and extension at 45 cycles/min paced by a metronome. Blood flow was recorded immediately after cessation of exercise and continued for 5 min to obtain peak hyperemic flow and the volume repaid at 1 and 5 min. After the 5 min of recording, another rest period of 10 min was observed for flow to return to baseline. This technique has been shown to be reproducible in our laboratory (7).

To assess the contribution of NO to basal flow, intra-arterial infusion of N5-monomethyl-L-arginine (L-NMMA) at 2 mg/min (Clinalfa) was then commenced. L-NMMA was infused for 10 min after which a new basal flow was recorded. Resting FBF, ACh responses, and exercise-induced vasodilation were assessed before and after the infusion of L-NMMA, as previously described (7).

Data acquisition and analysis. FBF was measured by venous occlusion plethysmography using calibrated mercury-in-Silastic strain gauges (D. E. Hokanson, Bellevue, WA). FBF was expressed as milliliters per minute per 100 milliliters of forearm tissue. Recordings were taken at each time point (see Fig. 1) for at least 2 min. An average of seven flows was used for analysis. Forearm vascular resistance (FVR: 

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transsexuals (n = 15)</th>
<th>Males (n = 14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>48 ± 7</td>
<td>45 ± 13</td>
<td>0.34</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7 ± 3.7</td>
<td>25.0 ± 3.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.73</td>
</tr>
<tr>
<td>Forearm volume, ml</td>
<td>1.079 ± 239</td>
<td>1.077 ± 98</td>
<td>0.99</td>
</tr>
<tr>
<td>Testosterone, nmol/l</td>
<td>0.7 ± 0.4</td>
<td>18.6 ± 5.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data expressed as means ± SD; n, no. of subjects. Normal range for testosterone is as follows: female = 1–3 nmol/l, male = 10–33 nmol/l.
expressed as mmHg·ml⁻¹·100 ml tissue⁻¹·min⁻¹) was calculated from mean arterial pressure (MAP) and FBF, whereas minimum resistance after exercise was calculated from MAP and peak functional hyperemic blood flow (FHBF). Peak hyperemic blood flow was determined in the first 10 s after completion of exercise. The volume of blood repaid in 1 and 5 min after exercise was calculated from the area under the time-decay curve.

Statistical analysis. Descriptive data are expressed as mean values ± SD. All results are expressed as mean values ± SE. Statistical significance was taken at a two-tailed value of P < 0.05. Paired observations of baseline characteristics and lipid profiles were made using the Student’s t-test. Logarithmic transformation was used for nonparametric baseline characteristics and results. The dose-response curves to the intra-arterial infusions of ACh were compared using a two-way repeated-measures ANOVA allowing for group times dose interaction. Comparisons of peak hyperemia, peak FVR, volume to be repaid at 1 and 5 min, and blood pressure responses were compared for the transsexual group versus males and for pre- and post-L-NMMA using the Student’s t-test and ANOVA. A Pearson’s correlation and a multivariate linear regression analysis were performed to determine the best predictors of responses to ACh and peak FHBF.

RESULTS

The clinical and morphometric characteristics of the subjects are described in Table 1. There were no significant differences in age, body mass index, waist-to-hip ratio, and forearm volume. Serum testosterone was at the lower level of the female range in the transsexuals and hence significantly lower than in the males (P < 0.0001).

Baseline FBF and resistance. Resting FBF was similar in the transsexual and male groups (3.57 ± 0.30 vs. 3.05 ± 0.36 ml·min⁻¹·100 ml forearm tissue⁻¹, mean ± SE for transsexuals and males, respectively, P = 0.51, Fig. 1). There was also no difference in baseline FVR between the two groups (27.28 ± 1.97 vs. 31.35 ± 3.6 units, P = 0.96, see Fig. 1). Although resting MAP was slightly higher in the transsexual compared with the male group, this difference did not reach significance (90 ± 4 vs. 82 ± 3 mmHg, P = 0.12). FBF did not change in the contralateral arm throughout each study.

Infusion of L-NMMA for 10 min reduced resting FBF by 48% from 3.84 ± 0.31 before L-NMMA to 2.01 ± 0.13 ml·min⁻¹·100 ml forearm tissue⁻¹ for the group as a whole (P < 0.0001). In the transsexual group, resting FBF decreased from 4.09 ± 0.55 to 2.11 ± 0.16 ml·min⁻¹·100 ml forearm tissue⁻¹ (P < 0.0005, Fig. 1) and in the male group from 3.60 ± 0.33 to 1.91 ± 0.20 ml·min⁻¹·100 ml forearm tissue⁻¹ (P < 0.0005, Fig. 1). There was no significant differences in the magnitude of the L-NMMA effect on resting FBF between the transsexual and male groups (P = 0.44). Commensurate with this, there was an overall 47% increase in FVR after L-NMMA from 26.32 ± 1.69 to 49.46 ± 2.93 units (P < 0.0001). There was no difference in the rise in FVR after L-NMMA between the transsexual and male groups (P = 0.96). Mean arterial blood pressure rose slightly but not significantly in the transsexual (P = 0.08) and male (P = 0.10) groups after the 10-min infusion of L-NMMA.

ACh-induced endothelium-dependent vasodilation. ACh produced a dose-dependent increase in FBF in both groups. However, there was a significant upward and leftward shift in the FBF dose-response curve to ACh in the transsexual compared with the male group (P < 0.01, Fig. 2). FBF rose from a baseline of 3.57 ± 0.30 to a maximum of 20.23 ± 2.48 ml·min⁻¹·100 ml forearm tissue⁻¹ at the highest dose in the transsexual group and from 3.05 ± 0.36 to a maximum of 12.15 ± 2.09 ml·min⁻¹·100 ml forearm tissue⁻¹ with the highest dose in the male group. There were no differences between the two groups in MAP during infusion of ACh (P = 0.37).

After the infusion of L-NMMA, the difference in the FBF ACh dose-response curves between the transsexual and male groups was abolished (P = 0.15). FBF rose from 2.11 ± 0.16 to 14.18 ± 2.01 ml·min⁻¹·100 ml forearm tissue⁻¹ at the highest dose of ACh in the transsexual group and from 1.91 ± 0.20 to 9.15 ± 2.19 ml·min⁻¹·100 ml forearm tissue⁻¹ at the highest dose of ACh in the male group. MAP did not rise in either group during the ACh infusions after L-NMMA (P = 0.31).

Univariate analysis revealed that only the significant predictor of responses to ACh was the testosterone level (r² = 0.17, P < 0.05), which is our index of estrogen therapy. Multivariate analysis revealed that the best predictive model of responses to ACh was the combination of the testosterone level and age (r² = 0.27, P < 0.05).
Exercise-induced metabolic vasodilation. Isotonic exercise induced a similar increase in peak hyperemic blood flow in the transsexual and male groups (Table 2 and Fig. 3). There was no difference in minimum FVR achieved with exercise for the transsexual and male groups (Table 2 and Fig. 3). The total volume of blood repaid to the forearm after 1 (Table 2 and Fig. 4) and 5 (Table 2 and Fig. 4) min of exercise was also similar. MAP after exercise was also similar in the two groups (P = 0.18, Table 2).

Infusion of L-NMMA produced a 17% reduction in the peak hyperemic responses in both groups (Table 2 and Fig. 3). However, there were no differences in the magnitude of the reduction in peak FHBF responses with L-NMMA between transsexual and male groups (Table 2 and Fig. 3). Similarly, minimum FVR was significantly but similarly increased by 22% after L-NMMA in both groups (Table 2 and Fig. 3). The total volume of blood repaid to the forearm after 1 (Table 2 and Fig. 4) and 5 (Table 2 and Fig. 4) min of exercise was also similar. MAP after exercise was also similar in the two groups (P = 0.18, Table 2).

Effects of estrogen on resting blood flow. In keeping with our previous observations, this study confirms that estrogen does not affect resting skeletal muscle resistance; L-NMMA, G-monomethyl-L-arginine. *Pre- vs. post-L-NMMA for both groups combined.

<table>
<thead>
<tr>
<th>Exercise-induced metabolic vasodilation</th>
<th>Exercise</th>
<th>Exercise and L-NMMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Males P Value TX Males P Value TX Males P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak FHBF, ml·min⁻¹·100 ml⁻¹</td>
<td>21.09 ± 2.96</td>
<td>20.83 ± 1.99 0.94</td>
</tr>
<tr>
<td>Blood volume repaid in 1 min, ml/100 ml</td>
<td>14.35 ± 1.63</td>
<td>14.32 ± 1.63 0.71</td>
</tr>
<tr>
<td>Blood volume repaid in 5 min, ml/100 ml</td>
<td>42.75 ± 4.54 0.54</td>
<td>42.75 ± 4.54 0.54</td>
</tr>
<tr>
<td>Minimum FVR, units</td>
<td>5.93 ± 0.97</td>
<td>4.77 ± 0.54 0.31</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>95 ± 5</td>
<td>86 ± 3 0.18</td>
</tr>
</tbody>
</table>

Data expressed as means ± SE. TX, male-to-female transsexuals; FHBF, functional hyperemic blood flow; FVR, forearm vascular resistance; L-NMMA, N⁶-monomethyl-L-arginine. *Pre- vs. post-L-NMMA for both groups combined.

DISCUSSION

This study confirms our previous findings (25) that long-term estrogen therapy improves endothelium-dependent vasodilation in the resistance circulation of transsexuals compared with age-matched males. The new finding in this present study is that the infusion of L-NMMA abolished the difference in ACh responses between the two groups. This observation suggests that the improvement in ACh-mediated vasodilation observed in transsexuals with estrogen therapy is due to augmented endothelium-dependent NO-mediated vasodilation. This study also sought to determine whether long-term estrogen improves exercise-induced metabolic vasodilation in the forearm of transsexuals compared with male subjects and to assess the contribution of NO to this effect. There were no appreciable differences in peak hyperemia and in the volume repaid after exercise between the two groups and no difference in the effects of L-NMMA. This indicates that, although NO contributes to exercise-induced functional hyperemia, chronic estrogen does not augment this in biological males.

Effects of estrogen on resting blood flow. In keeping with our previous observations, this study confirms that estrogen does not affect resting skeletal muscle...
Effects of estrogen on ACh-mediated increase in blood flow. ACh-induced increases in vessel diameter and blood flow have been shown in part to be endothelium dependent (29). Hence, responses to ACh have been frequently used as a measure of the integrity of endothelial function. Both the acute and chronic administration of estrogen have been shown to improve ACh-mediated vasodilation in postmenopausal females (6, 10, 11), suggesting that improvement in endothelial function may potentially be part of the cardioprotective effects of estrogen. Experimental studies have suggested that acute and chronic estrogen enhancement of endothelium-dependent vasodilation is mediated through the L-arginine-NO pathway (38). Guetta et al. (12) recently demonstrated the importance of NO in the augmentation of ACh-mediated vasodilation with acute estrogen in postmenopausal women. Studies on the effects of acute estrogen administration have not consistently demonstrated improvement in ACh-induced vasodilation in males (4, 6, 31). With regard to chronic estrogen administration in males, however, we have previously demonstrated enhanced ACh responses in both the conduit and resistance circulation (25). In the present study, we found that the differences in ACh-mediated blood flow responses between the transsexual and male groups are abolished after the infusion of L-NMMA. This suggests that the augmentation of ACh-mediated vasodilation by long-term estrogen in males is NO dependent.

Effects of estrogen on functional hyperemia. During exercise or stimuli that mimic exercise, such as cardiac pacing, blood vessels dilate and blood flow is increased in response to changing metabolic demand. This response is thought to be due to the release of local metabolites, such as adenosine, ions, and lactate (16). Endothelium-dependent vasodilators such as NO and prostaglandins also contribute to this process (9, 42). Although we were able to corroborate this, as evidenced by a reduction in peak FHBF and the volume of blood repaid to the forearm after exercise with L-NMMA, we did not observe any differences in the responses to L-NMMA between the two groups. This suggests that chronic estrogen administration does not affect metabolic vasodilation, at least in males.

These findings are consistent with some but not all studies in females. Anderson found that acute intracoronary Premarin did not increase coronary blood flow or coronary flow reserve after pacing in postmenopausal women (1). However, Rosano et al. (33) demonstrated an improvement in pacing-induced and exercise-induced coronary ischemia with acute sublingual estrogen. Similar discordance has been observed in preliminary reports with long-term estrogen therapy (27).

Despite demonstrating differences in ACh responses, we were unable to demonstrate a difference in functional hyperemia of the forearm with chronic estrogen in males. The lack of augmentation in vasodilation in the transsexual compared with the male group suggests that estrogen administration may not influence metabolic vasodilation as readily as it does ACh-induced vasodilation.

Discrepancy between ACh and metabolic responses. Improvement in ACh-mediated NO-dependent vasodilator responses by estrogen observed in our study may occur via a number of mechanisms. Estrogen may influence the upregulation of NO at several places in the L-arginine-NO metabolic pathway. Estrogen has been shown to control the production and bioavailability of NO.

Table 3. Lipid profiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transsexuals (n = 15)</th>
<th>Males (n = 14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.4 ± 0.3</td>
<td>4.9 ± 0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>2.8 ± 0.2</td>
<td>3.2 ± 0.1</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>1.46 ± 0.12</td>
<td>1.37 ± 0.06</td>
<td>0.55</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>2.3 ± 0.4</td>
<td>0.7 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipoprotein (a), mg/l</td>
<td>199 ± 78</td>
<td>253 ± 161</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Data expressed as means ± SE; n, no. of subjects. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
ity of endothelium-derived NO synthase (17, 20, 40), the enzyme responsible for converting L-arginine to NO. Estrogen may also effect the action of NO by influencing cofactors involved in NO production (40). The degradation of endothelium-derived NO synthase or NO has also been shown to be influenced by estrogen (2). The binding of estrogen to estrogen receptors on the vasculature may also play an important role in the regulation of NO production (13). The presence of estrogen receptors has been demonstrated on the endothelium and vascular smooth muscle (17). Whether these receptors are functionally important in either gender is unclear; however, a recent report of a male with a mutation of the estrogen receptor gene and premature atherosclerosis-impaired endothelium-dependent vasodilation and dyslipidemia suggests a role for the receptor in vascular protection (36). Furthermore, estrogen has also been shown to have an effect on other endothelium-derived substances such as prostaglandins, endothelin-1, histamine, and angiotensin II (41). Estrogen has also been shown to modulate the effects of adhesion molecules important in mediating endothelial responses to circulating lipoproteins (5). Hence the differences observed in response to ACh- and metabolically induced vasodilation may be explained perhaps by a greater dependence on NO by the former, possibly mediated via one of the above mechanisms. Metabolic vasodilation is regulated by a number of factors, including NO, prostaglandins, and adenosine, and NO inhibition may be quickly compensated for by other regulators should this pathway be impaired. L-Arginine administration similarly alters ACh-mediated vasodilation selectively without having an effect on metabolic vasodilation (14). Similarly, we have recently demonstrated that hypercholesterolemia impairs ACh-stimulated but not exercise-induced vasodilation, suggesting multiple compensatory mechanisms involved in regulation of metabolic vasodilation (unpublished results).

Effects on lipid profile. The only difference in the lipid profile observed in this study was in the TG level. An increase in TG levels with estrogen use has been reported in women prescribed estrogen (28), men prescribed estrogen for prostate cancer (24), and in our previous work in this group of subjects (25, 26). It is now recognized that hypertriglyceridemia is an independent risk factor in both men and women (35). Recent studies have also demonstrated an acute effect of hypertriglyceridemia on endothelial function (18). Hypertriglyceridemia is known to be associated with and a major determinant of LDL-C size (21). The size of the LDL-C particle has itself been shown to be an important determinant of endothelial function (8) and may play a major role in atherosclerosis (3). However, it has been argued that the rise in TG levels associated with estrogen therapy may not be detrimental to the endothelium. Unlike typical hypertriglyceridemia, which is characterized by increased very low-density lipoprotein (VLDL) from impaired catabolism, the increase in TG level seen with estrogen is due to increased production and increased clearance of VLDL. This decreases VLDL circulating time, reducing the opportunity for it to be converted into LDL-C (39). Our study also showed a reduction (albeit not significant) in LDL-C and lipoprotein (a) levels and an increase in HDL-C levels, findings known to be associated with the use of estrogen (28, 39).

Limitations of the study. As previously noted, we were unable to differentiate the direct effects of estrogen from the secondary effects of this hormone on androgen suppression. Comparisons with hypogonadal males should help resolve this problem.

This study is limited by its cross-sectional design. The effects of estrogen on metabolic vasodilation may be more readily appreciated in a longitudinal study. This study did not assess the effects of estrogen on other endothelium-derived substances such as prostaglandins and endothelium-derived hyperpolarizing factor. It is possible that estrogen may affect these substances differently.

This study has demonstrated that chronic estrogen therapy improves ACh-induced endothelium-dependent blood flow in the resistance vessels of the forearm of biological males. The improvement appears to be mediated via the L-arginine-NO pathway. We also demonstrated that chronic estrogen does not improve metabolic vasodilation, despite its partial dependence on NO. This may mean that, although NO contributes to metabolic vasodilation, other pathways that are not as readily influenced by chronic estrogen administration may play a more important role in the control of metabolic vasodilatory responses.

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