THE INCIDENCE of cardiovascular disease in women is negligible before natural or surgically induced menopause (34) and increases after menopause. This protective effect seems to be due to the beneficial effect of ovarian hormones, in particular 17β-estradiol. Moreover, estrogen replacement therapy reduces the incidence of coronary artery disease and the progression of coronary artery lesions (3, 19, 20, 30). The spectrum of mechanisms that contribute to the cardiovascular protection of estrogen therapy in postmenopausal women includes favorable changes in plasma lipid profile, carbohydrate metabolism, and atheroma formation (8). Other potential protective mechanisms of estrogen action that relate to vascular function include calcium antagonism (4) and hormone-induced release of endothelium-derived relaxing factors and inhibition of contracting factors (17, 30).

Elastic properties of the aorta represent an important determinant of left ventricular function and coronary blood flow (1). The aorta is a dynamic organ, capable of almost instantaneous changes in size, compliance, and elasticity via a complex regulatory system influenced by hemodynamic factors, systemic and local reflexes, and neurohumoral activation. Furthermore, the manifestations and physiological implications of wave reflections in the vascular system are of considerable interest, inasmuch as they give us useful information about large artery function and systemic vascular vasomotion (2, 14, 16). The aorta is a potential target for an estrogen effect, inasmuch as estrogen receptors have been demonstrated in aortic tissue of several species (11, 12). Furthermore, postmenopausal women receiving estrogen therapy demonstrate an increase in thoracic aortic size within 3 mo (6).

Recently, we described an accurate technique to quantify the aortic pressure-diameter relation (21, 25, 26, 28). Using this highly sensitive method, we studied the acute effects of estrogen compared with placebo on aortic function and we examined the reflection properties in the systemic vasculature of postmenopausal women with and without coronary artery disease.

METHODS

Study Population

Subjects were postmenopausal women (59–68 yr of age) who presented for evaluation of chest pain and were referred for diagnostic coronary angiography. All subjects had their last menses > 2 yr before enrollment and were not receiving hormone replacement therapy. Patients with primary valvular heart disease, myocardial infarction, unstable angina, prior interventional revascularization, uncorrected hypokalemia, serum creatinine > 2.0 mg/dl, or diabetes mellitus and those requiring continuous vasoactive therapy were excluded.

On the basis of these criteria, 20 patients were selected and divided into two groups according to the presence of coronary artery disease: 10 patients without coronary artery disease (< 20% stenosis; group 1) and 10 patients with coronary artery disease (group 2). Coronary artery disease was considered present if left main coronary artery disease was present or at least one major coronary artery system (left anterior descending, circumflex, and right coronary artery) had a stenosis of > 50% diameter. The protocol was approved by our Institutional Ethics Committee; all patients gave written informed consent before participating in the study.

Study Protocol

All patients discontinued medications, if any, for at least five half-lives before the study. Patients arrived in the catheterization laboratory in the fasting state and underwent diagnostic left heart catheterization and coronary angiography by a standard percutaneous femoral approach.

After diagnostic catheterization, all patients were allowed to relax in the supine position. Baseline hemodynamic measurements were obtained 30 min after the last infusion of contrast medium. Thereafter, normal saline was infused at 2
ml/min iv for 2 min. Measurements were continuously monitored and recorded at baseline and repeatedly thereafter (at 5, 10, 15, 20, 25, 30, and 35 min). The effects of estrogen on the elastic properties of the aorta were then evaluated after intravenous administration of 17β-estradiol (10 μg in 2 ml over 2 min) and after repeated measurements of hemodynamic variables at 5, 10, 15, 20, 25, 30, and 35 min.

Aortic diameters and pressures were measured as previously described (21, 25, 26, 28). Aortic elastic indexes, i.e., aortic strain (23, 24, 29), distensibility (23, 24, 29), pressure-diameter relation, and aortic stiffness constant (21), were calculated before and after estradiol and normal saline administration in all women. Wave reflections were evaluated by measuring the augmentation index (10, 15).

17β-Estradiol Measurements

Serum 17β-estradiol levels were determined using a standard microparticle enzyme immunoassay (IMx, Abbott). Intra- and interassay variabilities of this technique are 4 and 5%, respectively. Blood samples were taken at baseline and repeatedly thereafter (at 5, 10, 15, 20, 25, 30, and 35 min).

Statistical Analyses

Values are means ± SD. For comparisons of patient characteristics between the two groups, the unpaired t-test was used. Changes over time within each group were assessed using ANOVA. Data of peak response to 17β-estradiol administration were compared with baseline by use of Student's paired t-test. Qualitative data were compared by use of the χ² test. P < 0.05 was considered significant.

RESULTS

Patient Characteristics

There were no significant differences between the groups with respect to age, number of years since menopause, body mass index, heart rate, systolic and diastolic blood pressures, and basal estradiol level (Table 1). In group 2 there were six patients with one-vessel coronary artery disease and four patients with two-vessel coronary artery disease.

Aortic Geometry and Function at Baseline

Aortic strain (5.4 ± 1.6 and 3.2 ± 1.1% in groups 1 and 2, respectively, P < 0.001), aortic distensibility (1.7 ± 0.8 and 1.0 ± 0.7 cm²·dyn⁻¹·10⁻⁶ in groups 1 and 2, respectively, P < 0.05), and intercept (−772.6 ± 60.3 mmHg) were significantly lower in group 2 than in group 1. The aortic stiffness constant (0.4 ± 0.1 and 0.7 ± 0.1 mm⁻¹ in groups 1 and 2, respectively, P < 0.001) was significantly higher in group 2 than in group 1. Slope and augmentation index were similar in the two groups. In Fig. 1 the pressure-diameter relation is compared in a patient without coronary artery disease and a patient with coronary artery disease. This relationship lay in a different steeper hypothetical line of elasticity in the patient than in the control, indicating increased aortic stiffness in patients compared with controls.

Response to Placebo Administration

In both groups, no changes were observed in aortic diameters and blood pressure or aortic function indexes and augmentation index after placebo infusion.

Response to 17β-Estradiol Administration

17β-Estradiol plasma concentrations increased from 18 to 330 pg/ml in group 1 and from 21 to 362 pg/ml in group 2 (P < 0.001) after administration of intravenous 17β-estradiol. Concentrations peaked 20 min after drug infusion was completed (Fig. 2). No subjects reported any adverse effects after administration of 17β-estradiol or placebo. Peak response of all measured

Table 1. Subject characteristics

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
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<tr>
<td>Age, yr</td>
<td>59.4 ± 3.5</td>
<td>60.3 ± 3.6</td>
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<tr>
<td>Time since menopause, yr</td>
<td>7.3 ± 1.4</td>
<td>6.8 ± 2.3</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>26 ± 4</td>
<td>27 ± 5</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>75 ± 7</td>
<td>79 ± 8</td>
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<tr>
<td>BP, mmHg</td>
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<tr>
<td>Systolic</td>
<td>131.8 ± 12.7</td>
<td>133.5 ± 12.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84.3 ± 5.2</td>
<td>86.4 ± 6.0</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/s</td>
<td>411.8 ± 110.6</td>
<td>620.4 ± 132.8*</td>
</tr>
<tr>
<td>Basal estradiol level, pg/ml</td>
<td>18 ± 8</td>
<td>21 ± 10</td>
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</table>

Values are means ± SD for 10 women in each group. BP, blood pressure; dP/dtmax, maximum 1st derivative of pressure; group 1, controls; group 2, patients with coronary artery disease. * P < 0.05 vs. group 1.
parameters, as well as calculated aortic function indexes, to 17β-estradiol administration occurred 20 min after completion of drug infusion in both groups (Table 2).

17β-Estradiol administration did not induce significant alterations in heart rate, systolic and diastolic aortic pressures, and systolic and diastolic aortic diameters in either group.

Aortic function. Aortic strain increased in group 1 (P < 0.01, baseline vs. peak; P < 0.05 by ANOVA) and group 2 [P < 0.05, baseline vs. peak; not significant (NS) by ANOVA]

Administration of 17β-estradiol resulted in an improvement in pressure-diameter relation-derived elasticity indexes, which was associated with a downward and rightward shift of the pressure-diameter loops of both groups (Fig. 1). Distensibility increased significantly in group 1 (P < 0.05, baseline vs. peak; P < 0.05 by ANOVA) and group 2 (P < 0.05, baseline vs. peak; P < 0.05 by ANOVA). The slope of the loop became less steep in both groups (P < 0.05, baseline vs. peak; P = NS by ANOVA), the stiffness constant decreased in group 1 (P < 0.05, baseline vs. peak; P = NS by ANOVA for both), and the intercept increased in group 1 (P < 0.01, baseline vs. peak; P = NS by ANOVA) and group 2 (P < 0.05, baseline vs. peak; P = NS by ANOVA).

Wave reflection. The augmentation index decreased significantly in group 1 (P < 0.001, baseline vs. peak; P < 0.005 by ANOVA) and group 2 (P < 0.001, baseline vs. peak; P < 0.001 by ANOVA), indicating reduced wave reflection in the arterial periphery.

DISCUSSION

The present study, which is the first to demonstrate the behavior of the aortic pressure-diameter loop before and after estrogen administration, has two principal findings. First, the aorta of postmenopausal women with documented coronary artery disease is characterized by impaired elasticity compared with postmenopausal women without coronary artery disease. Second, intravenous 17β-estradiol improved the elastic properties of the aorta in menopausal women with and without coronary artery disease. Furthermore, 17β-estradiol led to reduced wave reflection in the arterial periphery.

Consideration of Methods

Study of the pressure-diameter relation helps distinguish between active and passive changes in aortic elastic properties. The pressure-diameter relation for a given subject has a sigmoidal configuration. Movement of the pressure-diameter loop along this hypothetical sigmoidal line suggests changes in the elastic properties of the aorta due to changes in aortic pressure alone. In contrast, a right- or leftward shift of the pressure-diameter loop implies essential modification of the

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<th>Table 2. Mean aortic hemodynamic responses to intravenous 17β-estradiol in postmenopausal women without and with coronary artery disease</th>
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<td>BP, mmHg</td>
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<td>Pulse pressure, mmHg</td>
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<td>Aortic diameter, mm</td>
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<td>Strain, %</td>
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<td>Distensibility, cm² · dyn⁻¹ · m⁻²</td>
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<td>Stiffness constant, mm⁻¹</td>
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<td>Slope, mmHg/mm</td>
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<td>Intercept, mmHg</td>
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<td>Augmentation index, %</td>
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Values are means ± SD, with percent change in parentheses. *P < 0.05; †P < 0.01; ‡P < 0.001; §P < 0.005 vs. baseline.
intrinsic elastic properties of the aorta due to nonpassive factors (1).

Aortic Function in Postmenopausal Women and Response to 17β-Estradiol Administration

In the transfer of energy, pressure, and blood flow from the heart to the arterial tree, the aorta plays an important role in regulating left ventricular performance, myocardial perfusion, and interaction of the entire cardiovascular system. Previous studies from our laboratory have shown that aortic elastic properties are altered in several pathological conditions, such as coronary atherosclerosis and hypertension (23–26, 28, 29).

The present study demonstrated that the distensibility of the aorta was reduced in postmenopausal women with coronary artery disease compared with controls. Patients had a steeper pressure-diameter relation than controls associated with increased slope of the linear regression line. Decrease of the aortic distensibility could be attributed to the presence of atherosclerotic lesions (19, 20). Structural changes that may be responsible for aortic wall stiffening include smooth muscle cell proliferation, deposition of lipids, and accumulation of collagen, elastin, and proteoglycans (32).

An increase in the aortic distensibility was demonstrated after administration of 17β-estradiol in both groups. In contrast, no such change occurred after placebo administration. It has been reported that acute and chronic administration of estrogen affects the cardiovascular system (5, 13). Our findings regarding the thoracic aorta are in accordance with previous observations in postmenopausal women with established coronary artery disease, showing an enhancement of endothelium-dependent relaxation of coronary arteries by natural estrogen (33). Recently, it has been reported that estrogen therapy may decrease the stiffness of the aorta and large arteries in postmenopausal women (18).

The peak response to 17β-estradiol occurred at 20 min and with the maximum concentration of plasma 17β-estradiol. The plasma levels of estrogen achieved in this study are physiological and lie between the midcycle level found in premenopausal women and those found in pregnant women (9).

The pressure-diameter loop was shifted downward after 17β-estradiol administration along a different hypothetical sigmoidal line of elasticity. This movement suggests active changes in the elastic properties of the aorta, in contrast to movement along the same hypothetical sigmoidal line, which would suggest passive changes resulting merely from alteration of aortic pressure (1, 25, 26). Many mechanisms may be responsible for these active changes, including modulation of catecholamine release (19), endothelium-derived relaxing factor (17), and calcium channels (33). Estrogen has also been shown to result in cell membrane hyperpolarization mediated by an increase in potassium conductance of the vascular smooth muscle cell (22). Another possible mechanism of estrogen vascular action may involve stimulation of production of humoral substances such as the prostacyclin metabolite 6-ketoprostaglandin F1α, and endothelial production of nitric oxide, as demonstrated in rat aorta smooth muscle cell cultures and human umbilical vascular segments (31). The demonstrated beneficial effect of estrogen on the aorta, however, may be due to an indirect effect of estrogen on the vasa vasorum supplying blood to the aortic wall. A progressive decrease in the distensibility of the aorta after the removal of the vasa vasorum has been reported from our laboratory (22, 27).

Marked alterations in the properties of the vasculature, including a large reduction in the augmentation index, were found. Because decreased wave reflections indexed by the augmentation index represent vasodilation and increased arterial distensibility (14, 16), our findings suggest that the vasodilation of 17β-estradiol produces favorable effects on ventricular-vascular coupling. The mechanism for these effects has not been determined but may be a direct relaxing effect of estrogen on vascular myocytes, possibly involving calcium antagonism (4). Recently, we reported (21) that aortic function is improved in hypertensive and normotensive subjects after administration of diltiazem. In that study, diltiazem-induced changes in the pressure-diameter relation, as well as changes in the augmentation index, were similar to those observed with the administration of 17β-estradiol in the present study. A calcium antagonistic property of 17β-estradiol has been shown in isolated cardiac myocytes by inhibiting inward calcium current and thus reducing intracellular free calcium (33). An inhibitory effect of estrogen on endothelin-1-induced constriction might be possible and beneficial (4). It may also involve endothelium-dependent relaxation (13).

Specific Comments

The possible effect of constant contact by the arms of the diameter-measuring device on smooth muscle tone was investigated in previous studies (25, 26). It has been proved that there is no smooth muscle response to the prolonged contact of the aortic wall by the arms of the device. Furthermore, neither in this study nor in previous studies (25, 26) were any complications encountered, thus confirming the safety of the technique.

Conclusions

Aortic function is improved and wave reflections are decreased acutely with the administration of 17β-estradiol. This estrogen-induced alteration in the function of large arteries may contribute to the cardioprotective effects of pharmacological estrogen therapy in postmenopausal women.

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