Tibolone Improves Myocardial Perfusion in Postmenopausal Women With Ischemic Heart Disease

An Open-Label Exploratory Pilot Study

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OBJECTIVES
We sought to determine the effect of tibolone on myocardial perfusion in postmenopausal women with ischemic heart disease.

BACKGROUND
Tibolone is a steroid that relieves climacteric symptoms and prevents osteoporosis. Recent studies have suggested a cardioprotective effect of this compound. However, its role on myocardial perfusion remains uncertain.

METHODS
Single-photon emission computed tomography myocardial perfusion imaging was performed in 26 postmenopausal women. Patients were randomly assigned to tibolone for six months (treatment group) or to usual care (control group). All women underwent cardiac imaging at baseline and at six months.

RESULTS
Mean stress perfusion defect (summed stress score) was moderate and did not differ between the two groups (8 ± 3 vs. 9 ± 4; p = NS). Summed difference score also was similar for both groups (7 ± 3 vs. 8 ± 3; p = NS). The six-month study revealed that summed stress and summed difference scores significantly improved in the treatment group (to 3 ± 3 and to 2 ± 2; p < 0.001) whereas it remained unchanged for control patients (to 10 ± 4 and to 8 ± 2; p = NS).

CONCLUSIONS
In postmenopausal women with ischemic heart disease, six months of therapy with tibolone significantly improved stress myocardial perfusion and the “amount of ischemia.” (J Am Coll Cardiol 2006;47:559–64) © 2006 by the American College of Cardiology Foundation

Specific-activity steroids have the beneficial effects of estrogen on bone and brain without the known increased risk for breast cancer and endometrial hyperplasia observed in long-term users of estrogen. Tibolone, a specific-activity steroid, is a synthetic compound that relieves climacteric symptoms and prevents osteoporosis (1).

Recent studies have reported that tibolone therapy might be of benefit in the prevention of cardiovascular disease. In healthy postmenopausal women, tibolone tends toward increased fibrinolysis and improves endothelial function (2,3). Interestingly, in women with coronary artery disease (CAD), it has been suggested that tibolone might attenuate the ischemic burden (4). However, its role in modulating myocardial perfusion remains uncertain. In this open-label pilot study, the objective was therefore to evaluate the effects of tibolone on myocardial perfusion in postmenopausal women with ischemic heart disease (IHD) as assessed by single-photon emission computed tomography (SPECT).

METHODS
Study population and design. Twenty-six postmenopausal women not on hormone-replacement therapy referred for a clinically indicated SPECT myocardial perfusion study with stress-induced perfusion defects were enrolled. All had cessation of menses of one year or longer, a normal mammogram, breast and pelvic examinations, and pap test within six months of the study. Patients with recent history of myocardial infarction (<1 month), severe aortic stenosis (as assessed by echocardiography), known or suspected cancer, or undiagnosed abnormal vaginal bleeding were excluded.

This study is a prospective randomized open-label study. Randomization was performed using a table with random numbers. After their baseline SPECT scans, all patients were assigned randomly to usual care (control group) or to tibolone (Paraclim, ELEA Pharmaceuticals, Buenos Aires, Argentina) at 1.25 mg/day for six months (treatment group). Vaginal ultrasound was performed on the subjects the day before they started tibolone therapy and then at six months. All women underwent SPECT imaging at baseline and at six months. Beta-blockers and calcium antagonists were stopped four days before each scan and caffeine 24 h before the test in all patients.

Patients performed a symptom-limited exercise stress test on both sessions. Dipyridamole was infused in one patient of each group (because of poor exercise tolerance in one and the development of left bundle branch block at peak exercise in the other patient). In all but one patient (because of a physical inability to exercise) the stress testing modality was maintained for the second SPECT scan. Rate-pressure product (RPP) was calculated in the patients that underwent exercise stress testing.

Coronary angiography was performed within 6 ± 4 months of the baseline scan. Significant CAD was defined as ≥50% diameter narrowing of a major coronary artery or...
Abbreviations and Acronyms

- CAD = coronary artery disease
- IHD = ischemic heart disease
- NO = nitric oxide
- RPP = rate-pressure product
- SDS = summed difference score
- SPECT = single-photon emission computed tomography
- SRS = summed rest score
- SSS = summed stress score

RESULTS

Study subjects. After randomization, 11 women were enrolled in the treatment group and 15 in the control group.

Table 1. Baseline Characteristics of the 21 Postmenopausal Women Completing the Study Protocol

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (n = 10)</th>
<th>Control Group (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63 ± 11</td>
<td>67 ± 7</td>
</tr>
<tr>
<td>Duration of menopause, yrs</td>
<td>17 ± 11</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.39 ± 3.29</td>
<td>26.66 ± 3.72</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>8 (80%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>2 (20%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n</td>
<td>3 (30%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Cigarette smoking, n</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Family history of CAD, n</td>
<td>6 (60%)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n</td>
<td>3 (30%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Previous coronary bypass surgery, n</td>
<td>0</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention, n</td>
<td>2 (20%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Coronary angiography, n</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>1 = vessel disease</td>
<td>3 (42%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>2 = vessel disease</td>
<td>2 (29%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>3 = vessel disease</td>
<td>2 (29%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Indications for SPECT imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain or dyspnea, n</td>
<td>8 (80%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Asymptomatic with known CAD, n</td>
<td>2 (20%)</td>
<td>2 (18%)</td>
</tr>
</tbody>
</table>

All p = NS between groups.

Table 2. Concomitant Medication Taken at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>6*</td>
<td>0</td>
</tr>
<tr>
<td>Statins</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Insulin</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*p = 0.011 vs. control patients.

ACE = angiotensin-converting enzyme.

One patient under tibolone was excluded because of vaginal bleeding. Thus, 10 patients comprised the treatment group. None of the women exhibited endometrial hyperplasia after tibolone treatment. Four women in the control group were excluded before the second scan (because of coronary revascularization in two and failure of subsequent follow-up in the other two participants). Thus, 11 women comprised the control group. Table 1 shows the baseline characteristics of the 21 women completing the study. Coronary angiography was obtained in 16 participants. Significant CAD was found in all patients. Two women in each group underwent SPECT imaging for diagnosis of CAD. Table 2 shows concomitant medications taken at baseline. They were not different at six months for both groups. None of the 21 patients were revascularized before the second scan.

Stress testing. In the treatment group, five patients exhibited chest pain and two exhibited ST-segment depression during stress. At six months, four women exhibited chest pain and one showed ST-segment depression during stress.

To address a scan interpretation bias, we also performed an automated quantitative analysis of the perfusion images using the Cedars method (5). A summed stress score (SSS), reflecting quantitative defect extent and severity, a summed rest score (SRS), and a summed difference score (SDS), reflecting “amount of ischemia” were calculated. Differences in summed perfusion scores from baseline to six-month perfusion study were rated as previously reported (3t o “improved,” >−3 to <3 = “no change,” “worse” (6). Resting images were gated and data were processed with QGS software (Cedars QGSTM program, Los Angeles, California) (7).

Consensus interpretation for myocardial perfusion data with visual over-reading by three readers was performed. Unblinded semiquantitative analysis was accomplished using the Cedars method (5). A summed stress score (SSS), reflecting quantitative defect extent and severity, a summed rest score (SRS), and a summed difference score (SDS), reflecting “amount of ischemia” were calculated. Differences in summed perfusion scores from baseline to six-month perfusion study were rated as previously reported (3t o “improved,” >−3 to <3 = “no change,” “worse” (6). Resting images were gated and data were processed with QGS software (Cedars QGSTM program, Los Angeles, California) (7).

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In the control group, 4 of the 11 patients exhibited chest pain and ST-segment depression during stress. At six months, 3 of the 11 patients exhibited chest pain and ST-segment depression (p = NS between the groups for both sessions). As shown in Table 3, exercise-induced comparable increases in heart rate, systolic blood pressure, and RPP in both groups at baseline and at six months.

**Single-photon emission computed tomography myocardial perfusion imaging.** Average baseline SSS was moderate for both groups (Table 4). In the treatment group, the six-month study exhibited a significant decline to a probably normal-average score. SSS showed a significant reduction in 9 of the 10 postmenopausal women and remained unchanged in 1 patient (Fig. 1, Table 4). The SRS was unchanged at six months in all women, but SDS was better for 9 of the 10 women receiving tibolone (Fig. 2). An example is shown in Figure 3.

**Table 3.** Results of the Exercise Stress Testing

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>82 ± 14</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>Exercise</td>
<td>144 ± 16*</td>
<td>135 ± 24*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>142 ± 18</td>
<td>141 ± 25</td>
</tr>
<tr>
<td>Exercise</td>
<td>181 ± 28*</td>
<td>177 ± 29*</td>
</tr>
<tr>
<td>Peak RPP, beats/min × mm Hg</td>
<td>27,561 ± 4,984</td>
<td>25,428 ± 6,046</td>
</tr>
<tr>
<td>% predicted heart rate</td>
<td>96 ± 16</td>
<td>93 ± 16</td>
</tr>
<tr>
<td>Exercise duration, min</td>
<td>6.14 ± 2.38</td>
<td>6.24 ± 2.32</td>
</tr>
<tr>
<td>Peak workload (METs)</td>
<td>6.23 ± 2.14</td>
<td>6.24 ± 1.92</td>
</tr>
</tbody>
</table>

* p < 0.0001 vs. rest. At six months, no variables were significantly different between either group.

**Table 4.** Single-Photon Emission Tomography Myocardial Perfusion Imaging and Left Ventricular Function for the 21 Postmenopausal Women

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Months</td>
<td>6 Months</td>
</tr>
<tr>
<td>Score perfusion analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>8 ± 3</td>
<td>3 ± 3*§</td>
</tr>
<tr>
<td>SRS</td>
<td>1 ± 2</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>SDS</td>
<td>7 ± 3</td>
<td>2 ± 2*§</td>
</tr>
<tr>
<td>Automated quantitative analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversibility (% LV)</td>
<td>16 ± 6</td>
<td>5 ± 5†§</td>
</tr>
<tr>
<td>Resting LV function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66 ± 8</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>68 ± 19</td>
<td>75 ± 21</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>24 ± 11</td>
<td>26 ± 12</td>
</tr>
</tbody>
</table>

*p ≤ 0.05 and †p < 0.01 vs. baseline; ‡p < 0.02 and §p < 0.005 treatment group vs. controls at six months.

The major finding of the current study is that six months of treatment with tibolone decreased the extent and severity of myocardial perfusion abnormalities during stress and the “amount of ischemia” in postmenopausal women with IHD.

To the best of our knowledge, this is the first report using SPECT imaging that assessed the effect of tibolone on myocardial perfusion in women with IHD.

Tibolone mainly is used for treating climacteric symptoms and for the prevention of osteoporosis. It displays estrogenic, progestogenic, or androgenic activity, depending primarily on the target tissue involved (9). Consequently, this compound is considered a drug with tissue-specific activity.

Experimental and clinical data have suggested that tibolone has beneficial effects on the cardiovascular system. For example, tibolone, unlike estrogen, possesses anti-inflammatory properties and tends toward increased fibrinolysis (2). Furthermore, in women with CAD, a single dose of 2.5 mg of tibolone improved the time to onset of ST-segment depression and angina symptoms during exercise (4). In our study, we did not observe such effect after six months of 1.25 mg/day of treatment. One possible explanation is that a lower dose of tibolone might be insufficient to detect a beneficial effect on these parameters. Because our patients were late postmenopausal women, we selected the lowest...
dose of tibolone with a proven clinical effect for treating climacteric symptoms (10). We observed a significant improvement in regional myocardial perfusion in women treated with this dose. Importantly, the heart rate and RPP achieved during stress were similar at baseline and after tibolone therapy. Thus, our findings cannot be attributed to differences in myocardial oxygen demand during exercise.

Estrogen withdrawal during menopause impairs coronary vascular function and is associated with lower nitric oxide (NO) levels than those measured in the general population, suggesting that endothelial dysfunction is involved (3). Consistently, recent studies using positron emission tomography have shown that postmenopausal women with risk factors have impaired endothelial function (11,12). Estrogen increases synthesis of NO by the vascular endothelium; however, estrogen administration did not reverse this abnormality as assessed by positron emission tomography (11). Animal studies have shown that tibolone activates the estrogen receptor and induces a similar percent increase in NO levels than estrogen in postmenopausal women (9). Tibolone may, therefore, have a favorable effect on the endothelium, which might suggest a cardioprotective effect (3). Despite the fact our study did not address the potential mechanism(s) by which tibolone improved myocardial perfusion, it has recently reported that nuclear cardiology methods can detect the effects of pharmacological interventions
Figure 3. Example of single-photon emission computed tomography images in a patient receiving treatment with tibolone. (A) At baseline, the short axis, horizontal long axis, and vertical long axis show an extensive and severe reversible perfusion defect in the inferior and lateral walls. (B) Six months after tibolone therapy, there is a significant improvement in the perfusion defects during stress.
targeting the vascular endothelium in individuals at risk for or with IHD (12).

**Study limitations.** We tested the possibility that our findings might have been attributed to a scan-interpretation bias. However, reanalyses of the studies without knowledge of their sequence and treatment allocation (data not shown) by semiquantitative and automated quantitative analysis confirmed our findings in both groups. In addition, vasoactive medications (beta-blockers and calcium antagonists) might have interfered with our findings. Because they were stopped for four days before each scan in both groups, it is unlikely that their effect could have been affected our results.

**Conclusions.** In postmenopausal women with IHD, six months of therapy with tibolone significantly improved stress myocardial perfusion defects and the “amount of ischemia” as assessed by SPECT imaging. However, clinical recommendations must wait until larger studies are performed.

**Acknowledgments**
The authors thank Gladys Dopta for performing the SPECT studies, the thoughtful comments of Dr. Enrique Gurfinkel, and ELEA pharmaceuticals for supplying tibolone for the study.

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**REFERENCES**