Cardiovascular Effects of Sildenafil During Exercise in Men With Known or Probable Coronary Artery Disease

A Randomized Crossover Trial

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Rectile Dysfunction Affects 30 million men in the United States1 and frequently coexists with coronary artery disease. Since the Food and Drug Administration approved the use of sildenafil citrate for the treatment of erectile dysfunction, millions of prescriptions have been issued.2 Reported adverse cardiovascular events associated with sildenafil use include acute myocardial infarction, ventricular tachycardia, hypotension, and death,3,4 raising concerns about the safety of this agent in patients with coronary artery disease.

Sildenafil is a cyclic guanosine monophosphate–specific type 5 phosphodiesterase inhibitor. Phosphodiesterase 5 is located not only in the corpus cavernosum, but also in other vascular tissue, including arteries and veins.5 Adverse cardiovascular events associated with sildenafil may be due to myocardial ischemia during sexual activity, with aggravation of ischemia by a vasodilator effect. Published guidelines regarding the management of cardiac patients with erectile dysfunction suggest that sildenafil may be hazardous in patients with ischemic heart disease and

For editorial comment see p 766.
that clinicians should use caution in prescribing this medication.2

However, it is also possible that the concern regarding adverse events associated with sildenafil may instead stem from the cardiovascular demands of sexual activity, the health of the population for whom sildenafil is prescribed, an adverse interaction with nitrates, or reporting bias. Hence, the purpose of this study was to assess the hemodynamic effects of sildenafil during exercise, including the effect on the onset, extent, and severity of electrophysiologic and echocardiographic evidence of ischemia in men with known coronary artery disease or high pretest probability of coronary artery disease.

METHODS

All study subjects were men older than 40 years with erectile dysfunction and either known coronary artery disease (≥50% diameter stenosis of a major epicardial vessel or one of its major branches, history of myocardial infarction, prior positive stress imaging test result, or prior coronary artery bypass surgery or angioplasty) or a high (>70%) pretest probability of coronary artery disease, according to the presence of typical angina pectoris.8 Subjects were recruited via posted advertisements, Mayo Clinic newsletter announcements, and physician referrals; in all cases, primary care physicians agreed to the subjects’ participation. All subjects had adequate resting echocardiographic images, were able to exercise, and agreed to participate in the study. No subject had asthma, severe aortic stenosis, hypertrophic obstructive cardiomyopathy, unstable angina, recent myocardial infarction (within 1 month), significant arrhythmia or atrial fibrillation, congestive heart failure, hepatic insufficiency, renal insufficiency, or a systolic blood pressure less than 90 mm Hg. No subjects were receiving therapy with dipyridamole, theophylline, erythromycin, or cimetidine, nor had they used sildenafil within the previous 24 hours. The use of long-acting nitrates was discontinued at least 72 hours before testing; the use of other cardioactive medications was continued. The sildenafil citrate dose was 50 mg, unless another dose was recommended by the man’s physician. The study was approved by the institutional review board of the Mayo Clinic, Rochester, Minn. Written informed consent was obtained from all subjects.

Exercise Echocardiography

All patients underwent 2 symptom-limited exercise echocardiograms separated by an interval of 1 to 3 days. Cardioactive medications were not changed between the 2 tests. Subjects were randomized in a double-blind crossover design to receive a single dose of sildenafil or placebo 1 hour before the exercise test. The order of administration was determined by a randomization schedule in blocks of 10, generated within the Section of Biostatistics, Mayo Clinic, so that half of the study population underwent the initial test after receiving sildenafil and half after receiving placebo. Sildenafil and placebo preparations, identical in appearance, were prepared in the institution’s pharmacy and labeled “first test” and “second test” for each study, according to the randomization schedule. Unblinding was performed only after the database was closed.

Baseline echocardiographic images (parasternal long-axis and short-axis views and apical 4-chamber and 2-chamber views) were obtained and repeated 1 hour after the administration of sildenafil or placebo. The exercise echocardiogram was performed with a supine bicycle (Medical Positioning, Kansas City, Mo) attached to a table tilted 30° to 45° to the left. Subjects began exercising at 25 W, with a 25-W increase in the resistance at 2-minute stages. Workload in metabolic equivalent tasks (METs) was calculated with a standard equation for ergometer exercise.9 Echocardiographic imaging was performed continuously during each stage of the exercise protocol by using an ultrasound system (Acuson Sequoia, Mountain View, Calif) with a 3-MHz transducer and harmonic imaging mode. The study was recorded on videotape, and representative cardiac cycles were acquired, digitized, and stored for each standard view at rest, 25 W, peak exercise, and immediate recovery. The criteria for test termination were development of symptoms, including fatigue, a systolic blood pressure decrease greater than 10 mm Hg, ventricular dilation or global reduction of systolic function, or significant arrhythmia.

Baseline blood pressure and heart rate were recorded before sildenafil or placebo administration and immediately before the exercise test. During exercise, blood pressure and pulse were recorded at the end of each stage, a 12-channel electrocardiogram was obtained each minute, and 3-channel monitoring of cardiac rhythm was performed continuously.10,11 After termination of exercise testing, subjects were monitored for 15 minutes. Oxygen via nasal cannula and intravenous esmolol hydrochloride were available for treatment of persistent symptoms and evidence of marked ischemia.

Stress Echocardiogram Interpretation

Interpretation of the echocardiographic studies was performed by a single experienced reviewer (P.A.P.) blinded to clinical information, subject identity, and results of the other stress echocardiogram. Each study was scored semiquantitatively with a 16-segment model.12 Each segment was analyzed individually and scored by motion and systolic thickening at rest, 1 hour after medication, and with exercise. Wall motion was scored according to a 5-point grading system (1 = normal or hyperdynamic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysm).10,11 The wall motion score index (WMSI) was calculated at rest and with exercise as the sum of the scores divided by the number of segments visualized. The normal response to exercise was an increase in contractility. Myocardial ischemia was diagnosed when the exercise echocardiographic images documented a new regional wall motion abnormality or worsening of preexisting wall motion.10,11 Resting wall motion abnormalities were classified as infarction. For assessment of the number of vascular regions with echocardiographic abnormalities, the anterior, an-
teroseptal, midinferoseptal, and apical segments were attributed to the left anterior descending coronary artery, the anterolateral and inferolateral segments to the circumflex, and the inferior and basal inferoseptal segments to the right coronary artery. The percentage of ischemic segments was determined at peak exercise. The heart rate at the onset of new or worsening wall motion abnormalities was recorded. Left ventricular ejection fraction and end systolic volume were assessed at baseline, 1 hour after administration of sildenafil or placebo, and at peak exercise by using the biplane Simpson method.13

Exercise electrocardiography results were considered positive for ischemia if there was horizontal or downsloping ST-segment depression of 1 mm or more at 80 milliseconds after the J point, nondiagnostic if the baseline ST segment was abnormal, or negative for ischemia in the absence of these criteria. The heart rate at which the electrocardiogram result became positive was recorded.

**Statistical Analysis**

Continuous variables were summarized as the mean (SD). Categorical variables were summarized as percentages. In the first step of the analysis, a test for residual carryover effects of sildenafil was conducted for each variable and none were significant (all P>0.05).14 For continuous variables, treatment effects were assessed by calculating the difference between first and second study data. These differences were then compared between the subjects randomized to receive placebo and then sildenafil vs sildenafil and then placebo by using the 2-sample test with corresponding 95% CIs.15 The matched-pairs paired t test was used to evaluate differences between premedication and postmedication data (ie, before vs after sildenafil administration and before vs after placebo administration). To evaluate differences in categorical data, variables were categorized as follows: −1, positive result in the first study and negative result in the second study; 0, positive result in both studies or negative result in both studies; and 1, negative result in the first study and positive result in the second study. The linear trends test for percentages was then used to assess significant treatment differences by comparing these categorizations between the subjects randomized to placebo and then sildenafil vs sildenafil and then placebo.16 Odds ratios and corresponding 95% CIs for these comparisons were estimated with the method of Gart17 and converted to relative risk estimates by using methods described by Zhang and Yu.18

The sample size for this study was based on detectable differences of exercise WMSI between the 2 treatments. Our initial estimate of the SD for exercise WMSI for this study was 0.6 and was based on treadmill stress echocardiographic studies conducted in men who were older than 40 years and had known or high pretest probability of coronary artery disease between January 1990 and September 1998. A conservative estimate of the SD of the paired difference in exercise WMSI between the 2 examinations would be approximately 0.85 (ie, √2 × 0.6), which is considered conservative because observations on the same subject under the different treatments will be positively correlated, thus reducing the SD of paired differences. Given the estimates, this study had approximately 80% power to detect a mean increase in exercise WMSI of 0.24 between the 2 treatments, assuming a 2-sided significance level of .05 with 100 subjects (analyses performed with SAS software version 6.12 [SAS Institute Inc, Cary, NC]). In at least 3 of the 16 segments, this increase corresponds to 1 or more levels on average per subject (eg, 3 or more segments that change from hypokinesis to akinesia).

**RESULTS**

**Study Group**

From March 4, 1999, through October 4, 2000, 110 men were randomized into the study (FIGURE). Of the 105 subjects with evaluable data, the mean (SD) age was 66 (9) years (range, 43-87 years). Ninety-three (89%) had known coronary artery disease and 29 (28%) had typical angina pectoris. Ninety-seven men (92%) received 50 mg of sildenafil citrate; 8 (7%) received 100 mg. The median interval between tests was 24 hours (range, 22-77 hours). The use of long-acting nitrates was discontinued in 21 subjects (20%) 72 hours before exercise testing. Subjects’ clinical characteristics are summarized in TABLE 1.

The baseline electrocardiogram result was abnormal in 59 patients (56%): 15 (14%) had previous Q-wave myocardial infarction, 42 (40%) had ST-segment abnormalities, 1 (1%) had left ventricular hypertrophy, 7 (7%) had right bundle-branch block, 1 (1%) had left bundle-branch block, and 13 (12%) had other conduction abnormalities.

Resting wall motion abnormalities were present in 60 patients (57%), whereas the mean (SD) resting WMSI was 1.2 (0.3). The mean (SD) resting ejection fraction was 56% (7%) (range, 39%-68%). A resting ejection fraction of less than 50% was present in 16 men (15%) and less than 40% in only 2 men (2%).

**Blood Pressure and Heart Rate**

Resting heart rate did not change significantly after sildenafil administration (mean difference, 1/min; 95% CI, −0.1 to 2.1; P=.80). Systolic blood pressure decreased significantly after sildenafil administration (mean [SD], 135 [19] mm Hg to 128 [17] mm Hg; mean

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difference, −7 mm Hg; 95% CI, −9 to −4 mm Hg; P < .001); this significant decrease was not observed with placebo (mean [SD], 135 [20] mm Hg to 133 [19] mm Hg; mean difference, −3 mm Hg; 95% CI, −6 to 0.3 mm Hg; P = .08). Diastolic blood pressure did not change significantly after sildenafil administration (mean difference, −2 mm Hg; 95% CI, −4 to 0.1 mm Hg; P = .16) or placebo. Exercise hemodynamic data are summarized in Table 2. After exercise, the rate of recovery for heart rate and systolic and diastolic blood pressure was similar for sildenafil and placebo. The average rate of decrease in heart rate from peak exercise was 3% (1%) per minute for both sildenafil and placebo (mean difference, 0%/min; 95% CI, −0.1% to 0.1%; P = .88). For systolic blood pressure, the rate of decrease was 3.6 (1.5) mm Hg/min with sildenafil and 3.3 (1.5) mm Hg/min with placebo (mean difference, −0.3 mm Hg/min; 95% CI, −0.5 to 0.02; P = .07). Diastolic blood pressure decreased 1.0 (0.8) mm Hg/min with sildenafil and 0.9 (0.8) mm Hg/min with placebo (mean difference, −0.1 mm Hg/min; 95% CI, −0.3 to 0.1; P = .30).

### Clinical, Electrocardiographic, and Echocardiographic Response

The resting WMSI did not change significantly after administration of sildenafil (mean difference, 0; 95% CI, −0.005 to 0.003; P = .53) or placebo (mean difference, 0; 95% CI, −0.005 to 0.005; P > .99). The resting ejection fraction did not change significantly (56% [7%] before and 57% [7%] after sildenafil; mean difference, 0.3%; 95% CI, −0.5% to 1.0%; P = .43) or placebo administration.

Symptoms of dyspnea or angina developed in 69 men taking sildenafil and in 70 men taking placebo (P = .89). Reasons for termination of exercise and electrocardiographic interpretations were similar with sildenafil and placebo (Table 3). One subject developed hypotension with exercise after taking 100 mg of sildenafil citrate. This subject's blood pressure decreased from 114/70 to 90/60 mm Hg at peak exercise. Blood pressure in recovery was 70/50 mm Hg. The subject was asymptomatic and was treated with a 500-mL intravenous bolus of isosorbide dinitrate solution. Hypotension persisted for 22 minutes. This subject was taking a calcium channel blocking agent, an α1-adrenergic receptor blocking agent, and aspirin.

There were no deaths, acute myocardial infarction, or ventricular fibrillation associated with exercise studies. Nasal oxygen was administered.

### Table 2. Exercise Test Hemodynamics (N = 105)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil First (n = 53)</th>
<th>Placebo First (n = 55)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest†</td>
<td>64 (11)</td>
<td>64 (11)</td>
<td>−0.19 (−1.6 to 1.2)</td>
<td>.78</td>
</tr>
<tr>
<td>Exercise</td>
<td>110 (18)</td>
<td>118 (18)</td>
<td>−0.42 (−2.5 to 1.7)</td>
<td>.69</td>
</tr>
<tr>
<td>Difference (exercise − rest)</td>
<td>46 (14)</td>
<td>45 (14)</td>
<td>−0.22 (−2.4 to 1.9)</td>
<td>.84</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest†</td>
<td>128 (17)</td>
<td>133 (19)</td>
<td>4.3 (0.9 to 7.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Exercise</td>
<td>174 (29)</td>
<td>176 (30)</td>
<td>−2.4 (−2.5 to 7.4)</td>
<td>.34</td>
</tr>
<tr>
<td>Difference (exercise − rest)</td>
<td>46 (24)</td>
<td>44 (26)</td>
<td>−1.9 (−6.8 to 3.0)</td>
<td>.45</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest†</td>
<td>76 (11)</td>
<td>79 (10)</td>
<td>3.7 (1.9 to 5.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Exercise</td>
<td>93 (15)</td>
<td>96 (16)</td>
<td>2.2 (−0.52 to 5.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Difference (exercise − rest)</td>
<td>17 (11)</td>
<td>16 (12)</td>
<td>−1.5 (−4.4 to 1.4)</td>
<td>.32</td>
</tr>
<tr>
<td>Double product†</td>
<td>19,294 (5317)</td>
<td>19,503 (5423)</td>
<td>209 (−589 to 1007)</td>
<td>.60</td>
</tr>
<tr>
<td>Exercise capacity, METs</td>
<td>4.5 (1.0)</td>
<td>4.6 (1.0)</td>
<td>0.07 (−0.06 to 0.19)</td>
<td>.29</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; METs, metabolic equivalent tasks.
†Rest was measured after medication receipt but before exercise testing.
‡Double product is the product of the heart rate and systolic blood pressure at peak exercise.
during the recovery period in 6 men (6%) taking sildenafil and 2 (2%) taking placebo (P=.16). No subjects required treatment with an intravenous β-blocker during recovery.

The interpretation of exercise echocardiograms was similar for sildenafil and placebo (P=.49). The overall summary of interpretations of exercise echocardiograms was as follows (Table 4): results were normal in 16 subjects (15%) taking sildenafil and 14 (13%) taking placebo, ischemia was present in 25 subjects (24%) taking sildenafil and 27 (26%) taking placebo, infarction was present in only 5 subjects (5%) taking each, and infarction with ischemia was present in 59 men (56%) taking sildenafil and placebo. In sildenafil and placebo groups, there was no difference in the numbers of subjects with any ischemia (84 and 86 subjects, respectively; P=.53) or multivessel ischemia (39 and 57 subjects, respectively; P=.62) or in WMSI during exercise, ejection fraction, or heart rate at onset of ischemia.

**COMMENT**

In this prospective, randomized, double-blind crossover study in men with erectile dysfunction and known or probable coronary artery disease, sildenafil administered 1 hour before maximal, symptom-limited exercise testing was well tolerated and did not change the onset, extent, or severity of ischemia, as assessed by exercise electrocardiography or echocardiography.

Risk factors for erectile dysfunction and coronary artery disease are similar and include age, diabetes mellitus, hypertension, and smoking. The coexistence of coronary artery disease and sexual dysfunction in middle-aged and older men is common. Phase 2/3 studies of sildenafil include predominantly patients without coronary artery disease and patients at low risk for coronary artery disease. In those studies, sildenafil improved erectile function and was well tolerated, and the incidence of severe adverse effects was low. However, in patients who have used sildenafil, 130 deaths have been reported to the Food and Drug Administration. Seventy-seven had cardiovascular events, including 41 with definite or suspected myocardial infarction, 27 with cardiac arrest, 6 with cardiac symptoms, and 3 with coronary artery disease. Accordingly, there has been concern regarding the safety of sildenafil in patients with ischemic heart disease. The men in our study are likely representative of many seeking treatment for erectile dysfunction.

This is the first report, to our knowledge, to describe exercise testing with sildenafil monitored by both electrocardiography and an imaging technique.

Exercise echocardiography is a well-validated, noninvasive technique to evaluate patients with known or suspected coronary artery disease. It is safe, sensitive, and specific, with an overall accuracy similar to that observed with other imaging techniques and higher than that of exercise electrocardiography. In our study, bicycle exercise echocardiography allowed continuous echocardiographic imaging throughout exercise, which enhanced the safety of the study. It also permitted assessment of the heart rate at which new wall motion abnormalities, indicative of ischemia, first developed.

### Table 3. Exercise Test Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
<th>Relative Risk (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reason for termination of exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (59)</td>
<td>0.82 (0.28 to 1.35)</td>
<td>.57</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26 (25)</td>
<td>1.00 (0.18 to 2.81)</td>
<td>.99</td>
</tr>
<tr>
<td>Leg distress</td>
<td>16 (15)</td>
<td>3.42 (0.32 to 8.91)</td>
<td>.16</td>
</tr>
<tr>
<td>Angina</td>
<td>0 (1)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (2)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>51 (49)</td>
<td>0.74 (0.27 to 1.39)</td>
<td>.48</td>
</tr>
<tr>
<td>Supraventricular ectopy</td>
<td>36 (34)</td>
<td>0.35 (0.09 to 1.09)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Exercise ECG interpretation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>85 (81)</td>
<td>0.05 (0.001 to 1.15)</td>
<td>.00†</td>
</tr>
<tr>
<td>Positive</td>
<td>12 (11)</td>
<td>1.90 (0.99 to 3.67)</td>
<td>.01</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>8 (8)</td>
<td>1.61 (0.41 to 1.26)</td>
<td>.16</td>
</tr>
<tr>
<td><strong>Mean (SD) heart rate at onset of ECG positivity, beats/min</strong></td>
<td>111 (21)</td>
<td>114 (22)</td>
<td>.52</td>
</tr>
</tbody>
</table>

†NE indicates not estimable because of the small number of events; ECG, electrocardiogram.

Table 4. Exercise Echocardiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil</th>
<th>Placebo</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMSI</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>-0.005 (−0.02 to 0.005)</td>
<td>.30</td>
</tr>
<tr>
<td><strong>Ejection fraction, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56 (7)</td>
<td>55 (7)</td>
<td>-1.08 (−1.90 to −0.26)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Exercise echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMSI</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.01 (−0.01 to 0.03)</td>
<td>.40</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>60 (10)</td>
<td>60 (9)</td>
<td>0.38 (−0.74 to 1.49)</td>
<td>.50</td>
</tr>
<tr>
<td>Ejection fraction difference, % †</td>
<td>4.0 (8.1)</td>
<td>4.4 (8.4)</td>
<td>0.33 (−0.79 to 1.45)</td>
<td>.56</td>
</tr>
<tr>
<td>LV end systolic volume, mL †</td>
<td>−7 (14)</td>
<td>−8 (12)</td>
<td>0.61 (−2.33 to 3.55)</td>
<td>.68</td>
</tr>
<tr>
<td>Percentage of ischemic segments</td>
<td>19 (17)</td>
<td>20 (17)</td>
<td>0.01 (−0.01 to 0.02)</td>
<td>.51</td>
</tr>
<tr>
<td>Heart rate at onset of new wall motion abnormalities, beats/min</td>
<td>96 (14)</td>
<td>96 (16)</td>
<td>−0.32 (−2.36 to 1.73)</td>
<td>.76</td>
</tr>
</tbody>
</table>

| tying difference and rest measurements. |         |         |                         |         |
In most of our subjects, exercise echocardiography demonstrated exercise-induced myocardial ischemia. However, exercise was no more likely to induce ischemia after sildenafil use than after placebo use. The extent and severity of ischemia and the heart rate at which it developed were similar. In this study group of 105 men, despite frequent ischemia after either placebo or sildenafil use, there were no clinically significant events. However, the study was powered only to assess the impact of sildenafil on extent and severity of ischemia. Larger numbers would be needed to assess any potential impact on clinical events.

Despite the randomized, double-blind design of the study, subjects may have been able to determine when they received sildenafil. However, the paramedical staff members who administered the test were not told which drug the subject had received. The physician who interpreted the tests was not present during the performance of the tests. Therefore, it is unlikely that nonblinding could have affected the results of this study.

In our study subjects, there was a slight decrease in blood pressure at rest after sildenafil administration, without changes in heart rate. A discrete blood pressure reduction at rest after sildenafil administration has been attributed to vasodilation and described both in healthy subjects and patients with stable angina.27,28 The peak plasma concentration following an oral dose occurs approximately 1 hour after sildenafil administration.29 The maximum decrease in blood pressure occurs at this time.27,28 Therefore, to maximize any potential adverse effects of the drug, stress testing was performed 1 hour after administration of the drug.

Exercise, including sexual activity, may trigger acute coronary events in patients with coronary artery disease.30,32 In our subjects, the exercise-induced increments in blood pressure and heart rate with exercise were similar with and without sildenafil use. During sexual intercourse, heart rate and blood pressure increase as with other forms of exertion.33,34 Hellerstein and Friedman35 monitored middle-aged men with known or suspected coronary artery disease during sexual intercourse with their spouses at home and observed a mean peak heart rate of 117/min. The mean (SD) peak exercise heart rate of patients in our study was slightly less (110 [18]/min). Our observations suggest that myocardial ischemia during sexual activity may be common in men with stable coronary artery disease.

The typical maximum workload during coitus is approximately 3.3 to 3.4 METs for less than 30 seconds.34,35 Guidelines from the American College of Cardiology and the American Heart Association suggest that if a patient can exercise more than 5 to 6 METs without demonstrating ischemia on exercise electrocardiography testing, the risk of ischemia during sexual intercourse is probably low.7 In our study, which included only men who could exercise, the mean (SD) exercise capacity was not affected by sildenafil use (4.5 [1.0] METs with sildenafil and 4.6 [1.0] METs with placebo, P = .29).

In this study, men were not taking nitrates or had discontinued the use of nitrates 72 hours before exercise testing. Both nitrates and sildenafil promote increased cyclic guanosine monophosphate levels. An interaction during concomitant administration of sildenafil and nitrates promotes marked reductions in blood pressure because of vasodilation in both animal models and humans.35,36 Of the cardiovascular deaths reported to the Food and Drug Administration, some involved a possible interaction between sildenafil and nitrates.7,23 Therefore, the coadministration of nitrates and sildenafil was accidentally avoided in our study.

Oral sildenafil increases coronary flow reserve in severely stenotic coronary arteries to an extent comparable to the increase in normal coronary arteries, thus preserving the ratio of flow reserve in stenotic and normal vessels.37 In another study37 of patients with chronic heart failure, oral sildenafil increased epithelium-dependent, flow-mediated vasodilation when compared with placebo. These studies, albeit in small numbers of patients, support our conclusions that oral sildenafil does not have an adverse effect on stress-induced myocardial ischemia in patients with ischemic heart disease.

The number of men with left ventricular dysfunction included in our study was limited. Although a variety of medications were taken by the subjects in this study, numbers were too small to permit subgroup analysis. Significant hypotension developed in a single subject who had taken 100 mg of sildenafil citrate. Numbers of men receiving the 100-mg dose were too small for conclusions to be drawn about the safety of this dose in this population.

Patients with known or suspected coronary artery disease and erectile dysfunction should have an individualized assessment before sildenafil prescriptions are issued. Exercise testing can be performed after sildenafil administration and may be indicated for risk stratification of some patients. Patients with stable coronary artery disease who are able to exercise to 4.5 METs without angina or hypotension and with a negative or mildly positive stress test result can probably safely take sildenafil. Further research will be needed, though, to clarify what levels of functional capacity and severity of ischemia can be considered truly safe for men with coronary disease who wish to use sildenafil.

CONCLUSIONS

In men who had known or probable coronary artery disease and were able to exercise, sildenafil had no effect on the presence or extent of exercise-induced regional wall motion abnormalities, symptoms, exercise duration, or arrhythmias. In patients who have stable coronary artery disease and are not taking nitrates, sildenafil did not potentiate myocardial ischemia.

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