Effect of sildenafil on coronary active and reactive hyperemia

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Chen, Yingjie, Ruisheng Du, Jay H. Traverse, and Robert J. Bache. Effect of sildenafil on coronary active and reactive hyperemia. Am J Physiol Heart Circ Physiol 279: H2319–H2325, 2000.—Sildenafil, a selective inhibitor of phosphodiesterase type 5, produces relaxation of isolated epicardial coronary artery segments by causing accumulation of cGMP. Because shear-induced nitric oxide-dependent vasodilation is mediated by GMP, this study was performed to determine whether sildenafil would augment the coronary resistance vessel dilation that occurs during the high-flow states of exercise or reactive hyperemia. In chronically instrumented dogs, sildenafil (2 mg/kg per os) augmented the vasodilator response to acetylcholine, with a leftward shift of the dose-response curve relating coronary flow to acetylcholine dose. Sildenafil caused a 6.7 ± 2.1 mmHg decrease of mean aortic pressure, which was similar at rest and during treadmill exercise (P < 0.05), with no change of heart rate, left ventricular (LV) systolic pressure, or LV maximal first time derivative of LV pressure. Sildenafil tended to increase myocardial blood flow at rest and during exercise (mean increase = 14 ± 3%; P < 0.05 by ANOVA), but this was associated with a significant decrease in hemoglobin, so that the relationship between myocardial oxygen consumption and oxygen delivery to the myocardium (myocardial blood flow × arterial O2 content) was unchanged. Furthermore, sildenafil did not alter coronary venous Po2, indicating that the coupling between myocardial blood flow and myocardial oxygen demands was not altered. In addition, sildenafil did not alter the peak coronary flow rate, debt repayment, or duration of reactive hyperemia that followed a 10-s coronary occlusion. The findings suggest that cGMP-mediated resistance vessel dilation contributes little to the increase in myocardial flow that occurs during exercise or reactive hyperemia.

phosphodiesterase; guanosine 3′,5′-cyclic monophosphate; myocardial oxygen consumption; blood flow

ENDOTHELIUM-DERIVED NITRIC OXIDE (NO) causes activation of soluble guanylyl cyclase in vascular smooth muscle. The resultant increase in cGMP and cGMP-dependent protein kinases causes vasodilation through modulation of calcium channels and by decreasing the calcium sensitivity of the vascular smooth muscle contractile proteins (24). The response to activation of phosphodiesterase: guanosine 3′,5′-cyclic monophosphate; myocardial oxygen consumption; blood flow
thoracic artery and advanced into the ascending aorta. A similar catheter was introduced into the left ventricle through the apex and secured in place. A solid-state micromanometer (model P5, Konigsberg Instruments, Pasadena, CA) was also introduced into the left ventricle at the apex. A final catheter was introduced into the right atrial appendage, manipulated into the coronary sinus ostium, and advanced into the great cardiac vein until the catheter tip could be palpitated within 1 cm of the interventricular sulcus. This method allowed selective sampling of coronary venous blood draining the myocardium perfused by the left anterior descending coronary artery (LAD). Approximately 1.5 cm of the proximal LAD was dissected free, and a Doppler velocity probe (Craig Hartley, Houston, TX) was positioned around the artery. Immediately distal to the velocity probe, a hydraulic occluder was placed around the vessel. A silicone catheter (0.3 mm ID) bonded to a larger silicone catheter (1.6 mm ID) was introduced into the LAD immediately distal to the hydraulic occluder. The pericardium was then loosely closed, and the catheters and electrical leads were tunneled subcutaneously to exit at the base of the neck. The chest was closed in layers, and the pneumothorax was evacuated. Catheters were flushed daily with heparinized saline. The catheters, electrical leads, and occluder tubing were protected with a nylon vest. Postoperative analgesia was provided with the use of butorphanol 0.4 mg/kg every 4–6 h.

**Endothelium-dependent vasodilation.** In six dogs the effect of sildenafil on endothelium-dependent NO-mediated vasodilation was examined. Hemodynamic measurements and coronary blood flow were obtained with the dogs standing quietly in a sling. The increases in coronary blood flow produced by intracoronary infusion of acetylcholine (3.75 to 75 µg/min) was observed. After completion of these measurements, we administered sildenafil as an oral dose of 2 mg/kg. Thirty minutes after drug administration, coronary blood flow responses to intracoronary infusions of acetylcholine (3.75 to 75 µg/min) were repeated.

**Hemodynamic measurements.** Aortic pressure was measured with a fluid-filled pressure transducer positioned at midchest level. LV pressure was measured with the micromanometer calibrated with the fluid-filled LV catheter. The first time derivative of LV pressure (dP/dt) was obtained via electrical differentiation of the LV pressure signal. Coronary blood velocity was measured with a Doppler flowmeter system (Craig Hartley). Data were recorded on an eight-channel direct-writing oscillograph (Coulbourn Instruments, Lehigh Valley, PA), calibrated using an injection of 15-µm diameter microspheres labeled with 141Ce, 51Cr, or 95Nb (NEM, Boston, MA). Hemoglobin content was determined by the cyanmethemoglobin method. Hemoglobin oxygen saturation was calculated from the blood PO2, pH, and temperature by use of the oxygen dissociation curve for canine blood. Blood oxygen content was computed as (hemoglobin x 1.34 x % O2 saturation) + (0.0031 x PO2). Oxygen consumption in the region of myocardium perfused by the LAD was calculated as the product of myocardial blood flow and the difference in oxygen content between aortic and coronary venous blood.

**Myocardial oxygen consumption.** The blood specimens were maintained in iced syringes until the dogs completed each exercise trial. Measurements of PO2, PCO2, and pH were then immediately performed with a blood gas analyzer (model 113, Instrumentation Laboratory, Lexington, MA). Hemo- globin content was determined by the cyanmethemoglobin method. Hemoglobin oxygen saturation was calculated from the blood PO2, pH, and temperature by use of the oxygen dissociation curve for canine blood. Oxygen consumption in the region of myocardium perfused by the LAD was calculated as the product of myocardial blood flow and the difference in oxygen content between aortic and coronary venous blood.

**Data analysis.** Heart rate, LV and aortic pressures, and coronary velocity were measured from the strip-chart recordings. In five of the dogs, the coronary Doppler velocity was calibrated using an injection of 15-µm diameter microspheres labeled with 141Ce, 51Cr, or 95Nb (NEM, Boston, MA), while the coronary Doppler signal was simultaneously recorded. At the conclusion of the study, duplicate myocardial specimens were obtained from the region of LV perfused by the anterior descending coronary artery for radioactive counting and determination of blood flow per gram of myocardium as previously described (15). A calibration factor calculated as blood flow per gram of myocardium determined with microspheres per coronary Doppler shift was then used to convert the coronary velocity to blood flow per gram of myocardium throughout the study. In the remaining two dogs, coronary blood flow (Q) was computed from the Doppler shift using the equation \[ Q = \frac{\pi r^2 d f}{6} \] where \( f \) is the Doppler shift (kHz) and \( d \) is the diameter of the coronary artery (3). In these dogs, the mass of myocardium perfused by the LAD was obtained by multiplying LV weight \( \times 0.43 \) which has been reported to represent the average fraction of LV perfused by the LAD (31). Blood flow per gram of myocardium was then determined as LAD coronary artery flow per LAD perfused myocardium. Total LAD blood flow during reactive hyperemia was determined by electrical integration of the Doppler velocity tracing. Reactive hyperemia flows were calculated as follows: blood flow debt (ml) = control blood flow rate (ml/s) \( \times \) duration of occlusion (s); excess reactive hyperemia flow (ml) = total flow during reactive hyperemia (ml) – [control blood flow rate (ml/s) \( \times \) duration of reactive hyperemia (s)]; blood flow debt repaid during reactive hyperemia = excess reactive hyperemia flow (ml)/blood flow debt (ml). The duration of reactive hyperemia was taken...
SILDENAFIL AND CORONARY HYPEREMIA

Table 1. Systemic and coronary hemodynamic data at rest and during graded treadmill exercise

<table>
<thead>
<tr>
<th>Stage</th>
<th>Control</th>
<th>Sildenafil</th>
<th>Control</th>
<th>Sildenafil</th>
<th>Control</th>
<th>Sildenafil</th>
<th>Control</th>
<th>Sildenafil</th>
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</thead>
<tbody>
<tr>
<td>Rest</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>115 ± 7.2</td>
<td>114 ± 6.6</td>
<td>117 ± 9.0*</td>
<td>170 ± 9.4*</td>
<td>181 ± 8.4*</td>
<td>186 ± 12.3*</td>
<td>228 ± 10.8*</td>
<td>229 ± 11.1*</td>
</tr>
<tr>
<td>Mean aortic pressure, mmHg</td>
<td>122 ± 6.3</td>
<td>116 ± 8.0†</td>
<td>124 ± 6.7</td>
<td>113 ± 6.1†</td>
<td>124 ± 5.8</td>
<td>116 ± 6.0†</td>
<td>132 ± 3.8*</td>
<td>127 ± 2.3†</td>
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<tr>
<td>LV systolic pressure, mmHg</td>
<td>136 ± 6.0</td>
<td>133 ± 6.9</td>
<td>147 ± 7.9*</td>
<td>141 ± 5.4*</td>
<td>147 ± 6.9*</td>
<td>143 ± 4.5*</td>
<td>167 ± 4.6*</td>
<td>166 ± 6.4*</td>
</tr>
<tr>
<td>LV dP/dt, mmHg</td>
<td>2,551 ± 200</td>
<td>2,471 ± 196</td>
<td>3,635 ± 258*</td>
<td>3,657 ± 256*</td>
<td>4,169 ± 327*</td>
<td>4,220 ± 382*</td>
<td>4,270 ± 342*</td>
<td>3,631 ± 357*</td>
</tr>
<tr>
<td>MBF, ml·min⁻¹·g⁻¹</td>
<td>1.19 ± 0.03</td>
<td>1.35 ± 0.09†</td>
<td>1.67 ± 0.08*</td>
<td>1.88 ± 0.14†</td>
<td>1.76 ± 0.09*</td>
<td>2.04 ± 0.16†‡</td>
<td>2.39 ± 0.18*</td>
<td>2.69 ± 0.28*‡‡</td>
</tr>
<tr>
<td>CS-Po2, mmHg</td>
<td>20.4 ± 0.19</td>
<td>17.7 ± 1.0</td>
<td>15.4 ± 0.9</td>
<td>15.9 ± 0.9</td>
<td>13.9 ± 1.0</td>
<td>14.8 ± 0.8</td>
<td>13.4 ± 1.2*</td>
<td>13.7 ± 1.1*</td>
</tr>
<tr>
<td>MVO2, ml·min⁻¹·g⁻¹</td>
<td>0.15 ± 0.01</td>
<td>0.17 ± 0.02</td>
<td>0.25 ± 0.02*</td>
<td>0.26 ± 0.02*</td>
<td>0.27 ± 0.01*</td>
<td>0.28 ± 0.02*</td>
<td>0.37 ± 0.03*</td>
<td>0.41 ± 0.04*</td>
</tr>
</tbody>
</table>

All values are means ± SE (n = 7). LV, left ventricular; dP/dt, first derivative of LV pressure; MBF, myocardial blood flow; CS-Po2, coronary venous oxygen tension; MVO2, myocardial oxygen consumption; *P < 0.05 vs. rest; †P < 0.05 vs. control conditions by two-way ANOVA; ‡P < 0.05 vs. the corresponding control condition.

as the time from release of the coronary occlusion to the point at which flow returned to within 5% of control.

Statistical analysis was performed using two-way (exercise level and treatment) ANOVA for repeated measures. When a significant effect of exercise was observed, comparisons within treatment groups were made using one-way ANOVA followed by Scheffé’s post hoc test. When a significant difference between treatments was observed, comparisons between groups were made with the Student’s t-test with the Bonferroni correction. The effects of treatment on the relationship between two variables were analyzed by ANOVA. Statistical significance was accepted at P < 0.05. All data are presented as means ± SE.

RESULTS

Systemic hemodynamics. The hemodynamic responses to graded exercise during control conditions and after administration of sildenafil are shown in Table 1. During control conditions exercise caused significant increases in heart rate, LV systolic pressure, and LV dP/dtmax. Mean aortic pressure was significantly increased during exercise stage 3 compared with resting conditions. After administration of sildenafil, resting heart rate, LV systolic pressure, LV dP/dtmax and the rate-pressure product were unchanged. Two-way ANOVA testing for the effect of sildenafil considering rest and all three exercise stages simultaneously demonstrated that mean aortic pressure was significantly less after sildenafil treatment; however, this difference was not significant when rest and each exercise stage were tested individually (Table 1). After sildenafil exercise caused significant increases in heart rate, LV systolic pressure, LV dP/dtmax and the rate-pressure product that were not different from those during control conditions.

Coronary hemodynamics. Coronary responses to graded treadmill exercise during control conditions and with sildenafil are shown in Table 1 and Fig. 1. Exercise caused significant increases of myocardial blood flow and oxygen consumption and a significant decrease in coronary venous oxygen tension. During control conditions exercise caused a significant increase of hemoglobin from 13.1 ± 0.7 g/dl at rest to 14.6 ± 0.5 g/dl during the heaviest level of exercise (P < 0.05). Sildenafil caused a significant decrease of hemoglobin at rest and during exercise (P < 0.05 by two-way ANOVA), but did not interfere with the normal increase of hemoglobin from rest to exercise (hemoglobin after sildenafil increased from 12.5 ± 0.8 g/dl at rest to 13.9 ± 0.6 g/dl during the heaviest level of exercise; P < 0.05). Myocardial blood flow tended to be higher after sildenafil, and this achieved statistical significance when rest and all three exercise stages were considered simultaneously by using two-way ANOVA (mean increase = 0.26 ± 0.05 ml·min⁻¹·g⁻¹; P < 0.05). However, the slightly higher myocardial blood flow rates after sildenafil were almost exactly matched by the slightly lower hemoglobin, so that the relationship between coronary oxygen delivery (myocardial blood flow × arterial oxygen content) and myocardial oxygen consumption was unchanged by sildenafil (Fig. 2). Coronary venous oxygen tension was not significantly altered by sildenafil (Fig. 3).

Reactive hyperemia. During control conditions, a 10-s coronary occlusion was followed by a reactive hyperemia 40 ± 9.7 s in duration, during which a peak flow rate of 114 ± 9.7 ml/min was achieved, resulting in 424 ± 105% debt repayment. Sildenafil did not significantly alter debt repayment (361 ± 110%), the peak blood flow rate during reactive hyperemia (111 ± 9.6 ml/min), or the duration of reactive hyperemia (38 ± 9.8 s). In three dogs, in which reactive hyperemia after a 5-s coronary occlusion was examined on days...
when no exercise was performed, sildenafil also had no effect on the reactive hyperemia (control debt repayment = 322 ± 16%; debt repayment after sildenafil = 316 ± 24%). In three dogs, in which reactive hyperemia after a 10-s coronary occlusion was examined on days when no exercise was performed, sildenafil also had no effect on the reactive hyperemia (control debt repayment = 325 ± 19%; debt repayment after sildenafil = 307 ± 44%). In the three dogs in which 20-s coronary occlusions were performed, sildenafil did not alter the reactive hyperemia (control debt repayment = 305 ± 22%; debt repayment after sildenafil = 296 ± 18%).

Endothelium-dependent vasodilation. Intracoronary infusions of acetylcholine in doses of 3.75 to 75 μg/min had no effect on blood pressure (105 ± 6.0 mmHg) or heart rate (117 ± 5.5 beats/min). During control conditions coronary blood flow increased from 48.6 ± 4.4 ml/min at baseline to 130 ± 10.6 ml/min during infusion of acetylcholine at a dose of 75 μg/min (Fig. 4). Sildenafil did not significantly change heart rate or mean arterial pressure. However, the increase of coronary blood flow produced by intracoronary acetylcholine after sildenafil was significantly augmented (Fig. 4). Thus during control conditions an increase in coronary blood flow of 80 ml/min required a dose of acetylcholine of 61.2 μg/min, whereas after sildenafil an 80 ml/min increase in coronary blood flow was produced by a dose of acetylcholine of 11.3 μg/min.

Sildenafil plasma levels. Plasma sildenafil levels ranged from 383 to 789 nM (mean = 547 ± 77 nM). Because sildenafil is 84% bound to canine plasma protein (35), this represents a mean plasma-free sildenafil concentration of 87.5 ± 12.4 nM.

DISCUSSION

In this study, PDE5 inhibition with sildenafil augmented the endothelium-dependent coronary resistance vessel dilation produced by acetylcholine. After sildenafil, coronary blood flow was slightly higher at rest and during exercise, but this was associated with a slightly lower hemoglobin. Thus sildenafil produced no change in the relationship between myocardial oxygen availability and myocardial oxygen consumption, or in coronary venous oxygen tension. Furthermore, sildenafil did not augment the reactive hyperemia that followed a brief coronary artery occlusion. These findings indicate that inhibition of PDE5 augments coronary resistance vessel dilation produced by an endothelium-dependent NO-mediated agonist but does not augment the resistance vessel dilation that occurs during the increased endothelial shear associated with the high coronary blood flow rates of exercise or reactive hyperemia. The implications of these findings will be discussed below.

Effects of cGMP on coronary vasomotion. NO and sildenafil act on a common cGMP signaling pathway; one has the ability to increase cGMP synthesis and the other to elevate smooth muscle cGMP levels by selectively blocking cGMP degradation. As a result, the effect of PDE5 inhibition on coronary vessels might be expected to mimic the effect of NO donors. Therefore, it is of interest to review studies examining the effects of NO on the coronary circulation. Previous investigators have demonstrated that stimulation of endogenous coronary NO production (as with acetylcholine) (16, 20), intra-arterial infusion of authentic NO (8), or administration of NO donors (11) resulted in significant increases of coronary blood flow. Despite this evidence that NO can cause vasodilation of coronary resistance
vessels, NO synthase inhibition with N\(^{\text{G}}\)-nitro-L-arginine (\(l\)-NNA), N\(^{\text{G}}\)-monomethyl-L-arginine (\(l\)-NAME), or N\(^{\text{G}}\)-nitro-L-arginine methyl ester (\(l\)-NAME) did not decrease coronary blood flow in anesthetized (27) or awake (3, 4, 37) dogs, indicating that NO is not critical for maintaining coronary flow during basal conditions. This is in agreement with previous reports that coronary NO production is undetectable in vivo during resting conditions and that the cGMP content of unstimulated endothelial cells studied in vitro is very low. However, coronary NO production has been shown to increase during exercise, likely due to increased endothelial shear (4) and sympathetic nervous system activation of endothelial NO synthase (eNOS) by stimulation of endothelial \(\alpha\) and \(\beta\)-adrenoceptors (15). Nevertheless, blockade of NO production with NO synthase inhibitors did not impair the increase in coronary flow during treadmill exercise in normal dogs (3, 4). Furthermore, the relation between myocardial oxygen consumption and coronary flow was not altered by \(l\)-NAME, indicating that inhibition of NO production did not interfere with metabolic regulation of coronary vasomotor tone. Similarly, in the present study, blockade of cGMP degradation with sildenafil did not cause coronary resistance vessel dilation out of proportion to myocardial oxygen requirements. The apparent discrepancy between the demonstrated ability of NO to cause resistance vessel dilation in the heart and the failure of either decreasing coronary vascular cGMP levels by blocking NO synthesis or increasing cGMP levels by inhibiting PDE5 to alter coronary flow relative to myocardial oxygen demands may be explained by reciprocal vasomotor adjustments at several levels in the coronary microcirculation.

Chu et al. (9) found that blocking NO synthesis with \(l\)-NAME caused dose-related decreases in epicardial coronary artery diameter but had little effect on resting coronary blood flow in awake dogs. By using intravital microscopy, Jones and co-workers (19) reported that inhibition of NO synthesis with \(l\)-NMA caused constriction of small coronary arteries (\(>100\) \(\mu\)m), but this was counterbalanced by vasodilation of arterioles (\(<100\) \(\mu\)m), indicating that compensatory vasomotor adjustments in different segments of the coronary microvasculature occur to maintain coronary blood flow after inhibition of NO production. These findings suggest that cGMP-mediated vasodilation occurs principally at the level of the coronary arteries (including the resistance arteries) (9). In the present study, sildenafil augmented the vasodilator response to acetylcholine, in agreement with the concept that inhibition of PDE5 causes accumulation of cGMP during agonist-mediated NO production. The failure of sildenafil to similarly augment myocardial blood flow during exercise or reactive hyperemia suggests that the shear-mediated increase of endogenous NO production during the high flow rates of exercise or reactive hyperemia is insufficient to cause resistance vessel dilation. This is in agreement with our previous finding that coronary NO production in response to agonist is substantially greater than that which occurs during exercise (34).

Myocardial blood flow at rest and during exercise was slightly higher after sildenafil, but this was associated with a significant decrease of hemoglobin. In the dog, exercise is associated with an increase of hemoglobin resulting from \(\alpha\)-adrenergic-mediated splenic contraction that expresses erythrocyte-rich blood from the spleen into the systemic circulation (30). Nitroglycerin has been demonstrated to cause splenic dilation in dogs, suggesting that cGMP exerts a relaxing effect on splenic capsule smooth muscle (25). The decreased hemoglobin observed after sildenafil in the present study is compatible with splenic dilation and consequent trapping of circulating erythrocytes in the spleen. The resultant decreased blood oxygen-carrying capacity was associated with a reciprocal increase of coronary blood flow, so that oxygen delivery to the myocardium remained unchanged. These results indicate that sildenafil did not interfere with normal metabolic vasoregulation by which myocardial blood flow is maintained proportionate to myocardial oxygen needs. Because the human spleen is noncontractile, it is likely that the effect of sildenafil on hemoglobin would not occur in humans.

**PDE isoenzymes in vascular smooth muscle.** Previous studies using the PDE5 inhibitors zaprinast (23) or E4021 (29) demonstrated an increase in cGMP levels in isolated coronary artery segments and dose-dependent dilation of the large epicardial coronary arteries in awake pigs (1, 29). Similarly, Wallis and co-workers (36) reported that sildenafil resulted in a significant increase of cGMP concentration in isolated canine coronary artery segments in vitro. In the present study, PDE5 inhibition with sildenafil produced only a slight, although significant, augmentation of coronary resistance vessel dilation in response to exercise. Failure of sildenafil to produce a greater increase of myocardial blood flow may have been the result of alternate pathways for degradation of cGMP. In addition to PDE5, four other PDE enzymes have been identified in vascular smooth muscle (26, 36). Vascular smooth muscle cGMP-hydrolyzing activity is mainly due to PDE1, a calmodulin-dependent PDE, and PDE5, which is a calcium-calmodulin-independent cGMP-specific PDE (2). Of the total cGMP hydrolyzing activity, PDE1 constituted 73% in porcine and \(\approx80\)% in bovine coronary artery (2), suggesting that PDE1 would play an important role in regulating cGMP levels. Vinpocetine, a selective inhibitor of PDE1, has been shown to cause concentration-dependent relaxation of isolated arterial vessel segments (13). Increased levels of cAMP in vascular smooth muscle can also cause vasodilation. cAMP hydrolyzing activity is mainly due to PDE4, a cAMP-specific PDE, and PDE3, a cGMP-inhibited PDE (more abundant than PDE4). Selective PDE3 inhibitors have been shown to produce concentration-dependent relaxation of isolated canine coronary artery segments (14). Increased cGMP activity has the potential to enhance the effects of cAMP by inhibiting PDE3 activity. However, Wallis et al. (36) reported that the increase in cGMP in vascular smooth muscle caused by sildenafil did not produce a change in cAMP. PDE4, the cAMP-
specific PDE, is insensitive to cGMP. In contrast to PDE3, PDE4 inhibitors used alone caused only weak relaxation of blood vessels (21), suggesting that PDE4 is less important than PDE3 in regulating vasomotor tone under physiological conditions. PDE2 can hydrolyze both cAMP and cGMP but is present only in very small amounts in vascular smooth muscle. Sildenafil has a high affinity for PDE5 and a low affinity for the other PDE isoenzymes in vascular smooth muscle (36). Thus the IC50 for inhibition of human PDE1, PDE2, PDE3, PDE4, and PDE5 was (in nM) 280, 6,800, 16,200, 7,200, and 3.5, respectively, indicating that sildenafil is highly selective for PDE5 (36). The mean plasma-free sildenafil concentration of 87.5 ± 12.4 nM in the present study would have provided a high degree of blockade of PDE5 with relatively little inhibition of the other PDE isoenzymes. The modest effect of sildenafil on myocardial blood flow in the present study may have occurred because sildenafil inhibits principally PDE5, with much less effect on PDE1, which provides an alternate pathway for the degradation of cGMP.

Effect of sildenafil on reactive hyperemia. In the present study, sildenafil had no effect on the reactive hyperemia that followed a brief coronary occlusion. In contrast, in isolated guinea pig hearts (22), open-chest dogs (39), and awake dogs (3, 7), NO synthase inhibition with L-NNA (3), L-NMMA (39), or L-NAME (22) decreased total reactive hyperemia flow principally by attenuating the late phase of the hyperemia response. Despite this previous evidence that NO contributes to coronary reactive hyperemia, in the present study, sildenafil did not result in an increase of total reactive hyperemia flow, the peak flow rate, or the duration of reactive hyperemia. Failure of sildenafil to augment reactive hyperemia suggests that an alternate pathway, such as PDE 1, can effectively degrade cGMP after blockade of PDE 5 (36). Alternatively, it is possible that metabolic vasomotor adjustments at the arteriolar level are able to counter any increase in cGMP-mediated vasodilation of the coronary arteries.

Effect of NO and sildenafil on myocardial oxygen consumption. Several investigators have suggested that NO can contribute to regulation of myocardial oxygen consumption. Hintze and co-workers (4, 32) reported that blockade of NO production in vivo and in vitro (32) led to significant increases in myocardial and skeletal muscle oxygen consumption. Conversely, stimulating NO-endogenous production with bradykinin or ramiprilat, or administering an NO donor, resulted in decreases in oxygen consumption in primate myocardial tissue (12). However, studies from other laboratories have reported that blockade of NO synthesis resulted in a decrease (33) or no change (10, 28) in myocardial oxygen consumption. In the present study, sildenafil had no significant effect on myocardial oxygen consumption, or on the increase in oxygen consumption that occurred in response to exercise. Sildenafil had no effect on LV dP/dtmax, in agreement with a previous report demonstrating that sildenafil had no effect on contractility in isolated canine right ventricular trabecular muscle (36). These results suggest that this dose of sildenafil had negligible effects on the PDE isoenzymes that catabolize cAMP in myocardial myocytes. Sildenafil did cause a modest decrease of aortic pressure with no change in heart rate. Similarly, in normal men intravenous sildenafil (40–200 mg) produced transient decreases in systolic and diastolic blood pressures of 10 and 7 mmHg, respectively, with no change in heart rate (17, 40).

In conclusion, PDE5 inhibition with sildenafil augmented the coronary resistance vessel dilation produced by intra-arterial acetylcholine but did not alter the relationship between oxygen delivery to myocardium and myocardial oxygen consumption at rest or during exercise. The finding that inhibition of cGMP degradation did not increase coronary flow relative to myocardial oxygen requirements is in agreement with previous reports demonstrating that NO has little importance in mediating coronary resistance vessel dilation during exercise.

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