Effects of Sildenafil Citrate (Viagra) Combined With Nitrate on the Heart

Fuminobu Ishikura, MD; Shintaro Beppu, MD; Toshiaki Hamada, BS; Bijoy K. Khandheria, MD; James B. Seward, MD; Ajay Nehra, MD

Background—Sildenafil citrate (Viagra) is indicated for the treatment of erectile dysfunction. Large and sudden decreases in systemic blood pressure were reported in a substantial number of patients taking sildenafil citrate combined with nitroglycerin. We studied the effect of sildenafil citrate on the relationship between changes in systemic blood pressure and coronary blood flow.

Methods and Results—Healthy male beagles were used to assess systemic blood pressure, pulmonary arterial pressure, and flow in the left circumflex artery (in which a critical stenosis was established) and left anterior descending coronary artery. After measurement of the hemodynamic variables, 2 mg/kg sildenafil citrate was administered via a nasogastric tube. Hemodynamic changes were monitored for 1 hour. Subsequently, the acute effect of nitrate combined with sildenafil citrate was studied by the bolus injection of 0.2 mg isosorbide dinitrate before and after sildenafil citrate. Systemic blood and pulmonary arterial pressures and circumflex flow did not change during this study; however, left anterior descending coronary arterial flow increased from 16.0±5.8 to 24.6±8.7 mL/min 1 hour after administration of sildenafil citrate. The prolongation of systemic blood pressure decrease and the circumflex flow decrement induced by isosorbide dinitrate after sildenafil citrate were significantly larger and longer than those before sildenafil citrate.

Conclusions—Sildenafil citrate had the effect of vasodilation in a normal coronary artery; however, a combined effect with nitrate resulted in large and protracted decreases in systemic blood pressure and coronary blood flow in vessels with critical stenosis. (Circulation. 2000;102:2516-2521.)

Key Words: blood flow | coronary disease | sildenafil citrate

Sildenafil citrate (Viagra) is a selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5) and is indicated for the treatment of erectile dysfunction.1 The physiological mechanism responsible for erection of the penis involves the release of NO in the corpus cavernosum in response to sexual stimulation. NO activates the enzyme guanylate cyclase, which results in locally increased levels of cGMP, thereby producing smooth muscle relaxation. By inhibiting PDE5, sildenafil citrate enhances the normal physiological action of NO and cGMP, thereby allowing patients to attain erection adequate for sexual intercourse.1-3

Sildenafil citrate was evaluated in numerous randomized placebo-controlled trials involving >3000 men with various degrees of impotence associated with diabetes, spinal cord injury, history of prostate surgery, and no identifiable organic cause of impotence. In all trials using a sexual function questionnaire and diaries of their sexual histories, men receiving sildenafil citrate reported success more often than did men receiving the placebo, and the rate of success increased with the dose.4 The recommended oral dose is 50 mg taken 1 hour before sexual activity. The most common side effects reported in clinical trials included headache, flushing, and indigestion, which occurred at a slightly higher rate in patients taking the drug than among those taking placebo. Some patients receiving sildenafil citrate (∼3%) also reported changes in vision, principally altered color perception.5,6

Sildenafil citrate is contraindicated in patients who may require organic nitrates, such as nitroglycerin patches or sublingual tablets, because the combination may lower blood pressure. Recently, there were 16 reported cases in which a fatal outcome was encountered with the concomitant use of sildenafil citrate. In some of these cases, the clinical data were incomplete, and there is no way to determine whether these drugs caused the reported reactions. Furthermore, a given reaction may actually have been due to an underlying disease process or to a coincidental factor.

The physiological mechanism of not combining this drug with nitrates was explained by data from several double-blind placebo-controlled interaction studies performed with either sublingual nitroglycerin or isosorbide mononitrate in which large and sudden decreases in systemic blood pressure oc-
curred in the majority of patients taking sildenafil citrate. However, there is no report about the effect of sildenafil citrate on the relationship between changes in systemic blood pressure and coronary blood flow.

**Methods**

**Animal Preparation**

Eight healthy beagles weighing 9.8 to 11 kg (mean±SD, 10.5±0.6 kg) were used to assess systemic blood pressure, pulmonary blood pressure, cardiac output, and coronary flow. The present study was approved by the Osaka University Medical School animal care and use committee and was in compliance with the Osaka University Medical School guidelines for the care and use of laboratory animals. Dogs were anesthetized with thiopental sodium (35 mg/kg), and continuous anesthesia (6 to 8 mg/kg per hour) was given during the experiment. They were intubated with a cuffed endotracheal tube and ventilated with a respirator (model SN-480-3, Shinano), supplementing room air. The animals received saline at ~1 mL/min during the surgical procedure. A pigtail catheter was inserted via the right femoral artery, and a Swan-Ganz catheter was inserted from the right femoral vein and placed at the pulmonary artery. A left thoracotomy was performed, and the heart was suspended in a pericardial cradle. The left anterior descending coronary (LAD), circumflex (LCx), and left common carotid arteries were dissected free from surrounding tissues, and ties were loosely placed. A perivascular flow probe (2SB1212 probe and T106 blood flowmeter, Transonic Systems Inc) was placed on the LAD to measure the coronary flow.

A carotid-to-coronary bypass was established to permit controlled and isolated perfusion of the LCx. The flow through the bypass tube was measured with a calibrated electromagnetic flow probe (Nihon-Kohden). This also allowed coronary arterial pressure monitoring. The proximal end of the shunt was inserted into the carotid artery, the distal end was inserted into the LCx, and both ends were secured with preplaced ties. Thus, blood flow to the LCx was provided only from the shunt. The coronary arterial perfusion pressure was monitored via a fluid-filled pressure transducer.

**Establishment of a Critical Stenosis**

The LCx was cannulated and perfused with arterial blood withdrawn from the left carotid artery. This blood flow was controlled by a small vise placed around the bypass tube. A critical stenosis was made by constricting a small vise until mean coronary arterial perfusion pressure decreased to nearly 70% of mean systemic blood pressure.

We measured the flow of the aortocoronary bypass before and after the establishment of a critical stenosis. We also calculated the flow reserve of aortocoronary bypass by a 20-second occlusion, ie, the peak flow after occlusion divided by the flow before occlusion. A critical stenosis was confirmed by the minimum reactive hyperemia.

**Effects of Isosorbide Dinitrate Combined With Sildenafil Citrate**

After the baseline measurement of hemodynamic variables, coronary blood flow and cardiac output, 2 mg/kg sildenafil citrate was administrated via a nasogastric tube. These hemodynamic changes were monitored for 1 hour after oral administration. Subsequently, the acute effect of nitrate combined with sildenafil citrate was studied by a bolus injection of 0.2 mg isosorbide dinitrate before and after sildenafil citrate. During those procedures, mean systemic blood pressure and both coronary flows were monitored. We measured the pressure and flow recovery half-times to assess the prolongation of the vasodilating effect of isosorbide dinitrate.

**Plasma Concentration of Sildenafil Citrate**

Blood for the determination of the plasma concentration of sildenafil citrate was collected from the artery. Plasma concentration was measured by high-performance liquid chromatography. As a control,

**Results**

**Plasma Concentration of Sildenafil Citrate**

One hour after administration of 2 mg/kg sildenafil citrate, the plasma concentration of the drug was 55.6±25.8 ng/mL. In 5 unanesthetized dogs, the plasma concentration 1 hour after administration of 1 mg/kg of the drug was 155.7±56.0 ng/mL.

**Results of a Critical Stenosis**

Before a critical stenosis was formed, the coronary flow of the LCx increased from 21.9±9.4 to 39±15.7 mL/min after 20 seconds of occlusion. The coronary flow reserve was 1.80±0.15. After a critical stenosis was formed, the coronary flow in the LCx increased from 18.5±8.1 to 22.1±7.8 mL/min after 20 seconds of occlusion. The coronary flow reserve was 1.23±0.15. The coronary flow reserves before a critical stenosis were significantly higher than those after a critical stenosis was formed (P<0.0001). At that time, mean systemic blood pressure was 104.4±18.1 mm Hg, and mean coronary perfusion pressure was 72.1±17.8 mm Hg. The ratio of mean coronary perfusion pressure to mean systemic blood pressure was 68.9±10%.

**Changes in Systemic Blood and Pulmonary Arterial Pressure After Sildenafil Citrate Administration**

Systemic and diastolic blood pressure and pulmonary arterial pressure did not change during the protocol (Figure 1, Table 1).

**Changes in Coronary Perfusion Pressure and Flow of LAD and Bypass to LCx 1 Hour After Sildenafil Citrate Administration**

Systolic, diastolic, and mean circumflex coronary arterial perfusion pressure did not change during the protocol (Figure 1, Table 1).
The flow in the LAD 1 hour after sildenafil citrate administration significantly increased from $16.0 \pm 5.8$ to $24.6 \pm 8.7$ mL/min ($P < 0.0002$). The flow in the bypass to LCx 1 hour after sildenafil citrate administration did not change during the protocol.

### Changes in Other Hemodynamic Variables 1 Hour After Sildenafil Citrate Administration

Heart rate increased from $131 \pm 24$ to $156 \pm 18$ bpm 1 hour after sildenafil citrate administration (Table 1). Cardiac output increased from $2.65 \pm 0.78$ to $3.18 \pm 0.9$ L/min. However, stroke volume did not change after sildenafil citrate administration.

### Changes in Mean Systemic Pressure

Before sildenafil citrate administration, mean systemic blood pressure decreased from $108.9 \pm 12.8$ to $69.9 \pm 8.6$ mm Hg by the bolus injection of 0.2 mg isosorbide dinitrate (Figure 2, Table 2). The recovery time was $42.0 \pm 19.0$ seconds.

After sildenafil citrate administration, mean systemic blood pressure decreased from $99.6 \pm 18.8$ to $53.8 \pm 11.5$ mm Hg by the injection of isosorbide dinitrate (Figure 2, Table 2). The pressure recovery half-time after sildenafil citrate was $124.0 \pm 45.7$ seconds, which was significantly longer than that before sildenafil citrate.

### Hemodynamic Changes Induced by Isosorbide Dinitrate

#### Changes in Mean Systemic Pressure

Before sildenafil citrate administration, mean systemic blood pressure decreased from $108.9 \pm 12.8$ to $69.9 \pm 8.6$ mm Hg by the bolus injection of 0.2 mg isosorbide dinitrate (Figure 2, Table 2). The recovery time was $42.0 \pm 19.0$ seconds.

After sildenafil citrate administration, mean systemic blood pressure decreased from $99.6 \pm 18.8$ to $53.8 \pm 11.5$ mm Hg by the injection of isosorbide dinitrate (Figure 2, Table 2). The pressure recovery half-time after sildenafil citrate was $124.0 \pm 45.7$ seconds, which was significantly longer than that before sildenafil citrate.

### Table 1. Serial Hemodynamic Changes After Sildenafil Citrate Administration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre*</th>
<th>20 min†</th>
<th>40 min†</th>
<th>60 min†</th>
<th>$P$ (Pre* vs 60 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>129.9±20.4</td>
<td>133.3±21.3</td>
<td>132.9±22.3</td>
<td>137.5±24.0</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>88.1±16.4</td>
<td>86.3±18.0</td>
<td>82.6±15.9</td>
<td>82.8±16.1</td>
<td></td>
</tr>
<tr>
<td>mSBP, mm Hg</td>
<td>102.2±17.3</td>
<td>102.7±18.2</td>
<td>99.9±16.3</td>
<td>101.6±17.6</td>
<td></td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>31.0±7.4</td>
<td>31.1±5.1</td>
<td>30.6±4.3</td>
<td>31.4±4.9</td>
<td></td>
</tr>
<tr>
<td>DPAP, mm Hg</td>
<td>15.5±7.0</td>
<td>14.6±5.8</td>
<td>13.1±4.6</td>
<td>13.6±4.8</td>
<td></td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>20.9±7.6</td>
<td>20.2±5.9</td>
<td>19.0±5.5</td>
<td>19.4±5.5</td>
<td></td>
</tr>
<tr>
<td>SCPP, mm Hg</td>
<td>93.0±17.7</td>
<td>91.8±20.2</td>
<td>94.0±19.7</td>
<td>93.1±17.9</td>
<td></td>
</tr>
<tr>
<td>DPAP, mm Hg</td>
<td>58.1±14.6</td>
<td>53.5±14.6</td>
<td>53.8±16.8</td>
<td>51.4±14.7</td>
<td></td>
</tr>
<tr>
<td>mCPP, mm Hg</td>
<td>70.4±15.6</td>
<td>68.3±16.0</td>
<td>67.9±17.1</td>
<td>66.0±15.2</td>
<td></td>
</tr>
<tr>
<td>LAD, mL/min</td>
<td>16.0±5.8</td>
<td>19.3±5.6</td>
<td>22.4±9.1</td>
<td>24.6±8.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>CX, mL/min</td>
<td>20.0±6.1</td>
<td>20.1±6.3</td>
<td>21.1±5.9</td>
<td>21.0±5.7</td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>130.8±24.4</td>
<td>141.5±22.9</td>
<td>147.1±18.8</td>
<td>156.3±17.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.65±0.78</td>
<td>...</td>
<td>...</td>
<td>3.18±0.9</td>
<td>0.0045</td>
</tr>
<tr>
<td>SV, mL</td>
<td>21±6</td>
<td>...</td>
<td>...</td>
<td>21±7</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; mSBP, mean systemic blood pressure; SPAP, systolic pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; SCPP, systolic coronary perfusion pressure; DCPP, diastolic coronary perfusion pressure; mCPP, mean coronary perfusion pressure; LAD, flow in LAD; CX, flow in LCx; HR, heart rate; CO, cardiac output; and SV, stroke volume.

*Before sildenafil citrate administration.
†After sildenafil citrate administration.
Ratios of systemic pressure decrease (before pressure—minimum pressure/before pressure) were significantly larger after sildenafil citrate administration than before sildenafil citrate administration (46.2±4.2% versus 35.3±9.1%, respectively; *P<0.01).

Changes in Flow of LAD
Before sildenafil citrate administration, the mean flow in the LAD decreased from 16.9±5.7 to 13.0±4.5 mL/min by the bolus injection of 0.2 mg isosorbide dinitrate. The recovery time was 17.1±17.7 seconds.

After sildenafil citrate administration, the mean flow in the LAD decreased from 27.3±10.7 to 19.6±6.6 mL/min by the injection of isosorbide dinitrate. The flow recovery half-time after sildenafil citrate was 72.0±86.3 seconds, which was not significantly longer than that before sildenafil citrate.

The flow-decrease ratios of the LAD (before flow—minimum flow/before flow) were not significantly larger after sildenafil citrate administration than before sildenafil citrate administration (26±13.4% versus 22.4±11.6%, respectively).

Changes in Flow of Bypass to LCx
Before sildenafil citrate administration, mean flow in the bypass to the LCx decreased from 17.7±6.2 to 12.6±5.1 mL/min by a bolus injection of 0.2 mg isosorbide dinitrate. The recovery time was 23.8±12.8 seconds.

After sildenafil citrate administration, mean flow in the bypass to the LCx decreased from 20.6±6.9 to 10.9±5.4 mL/min by an injection of isosorbide dinitrate. The flow recovery half-time after sildenafil citrate was 96.1±54.7 seconds, which was significantly longer than that before sildenafil citrate. The flow-decrease ratios of bypass (before flow—minimum flow/before flow) were significantly larger after sildenafil citrate administration than before sildenafil citrate administration (46.9±14.6% versus 30.1±8.8%, respectively; †P<0.05).

Discussion
After Furchgott and Zawadzki9 reported that endothelium-derived relaxing factor relaxed vascular smooth muscle, Palmer and colleagues10,11 and Ignarro et al12 showed that this factor is NO. Sildenafil citrate is a selective inhibitor of cGMP-specific PDE5 and enhances the normal physiological action of NO and cGMP. By inhibiting PDE5, sildenafil citrate might produce smooth muscle relaxation not only in the corpus cavernosum but also in systemic vascular smooth muscle. This is why it should not be used with organic nitrates such as nitroglycerin patches or sublingual tablets; the combination may lower blood pressure. There were many reports on sildenafil citrate in which there was a fatal outcome. In some of these cases, the reported clinical data were incomplete, and there is no way to determine whether these drugs caused the reported reactions. This is the first report on the effect of sildenafil citrate on the systemic and coronary circulation.

Plasma Concentration of Sildenafil Citrate
In the present study, we chose a dose of 2 mg/kg, which would be higher than the recommended clinical dose. Absorption of sildenafil citrate might deteriorate during anesthesia. In fact, 1 hour after 2 mg/kg of the drug was given orally to anesthetized dogs, its plasma concentration was significantly lower than after 1 mg/kg was given to unanesthetized dogs. A 2-mg/kg dose of sildenafil citrate for an anesthetized dog is not much higher than the clinical dose prescribed for patients.13

Effects of Sildenafil Citrate on Systemic Blood Pressure and Coronary Flow
Systemic blood pressure did not change after sildenafil citrate administration (2 mg/kg). So the drug in itself might not significantly influence systemic blood pressure. The blood flow in a normal coronary artery increased after sildenafil citrate administration. This effect is expected because of an increase in cGMP. In contrast, the blood flow in a coronary artery with critical stenosis did not change after sildenafil citrate administration, presumably because the flow reserve might be maximum before administration. We produced a critical but not flow-limiting stenosis that did not induce myocardial ischemia at rest. Sildenafil citrate also increased the flow in a normal coronary artery and did not decrease the flow in a coronary artery with a critical stenosis. If sildenafil citrate is administered alone, it cannot induce myocardial ischemia.

Effects of Nitrate Combined With Sildenafil Citrate
Murad et al14 reported that NO produced from nitroglycerin might relax vascular smooth muscle. Other organic nitrate esters, such as isosorbide dinitrate, also were reported to release NO.15–18

A bolus injection of 0.2 mg isosorbide dinitrate before sildenafil citrate administration temporarily decreased sys-
temic blood pressure and coronary blood flow. The decrease of systemic pressure and coronary blood flow with severe stenosis was significantly larger and persisted longer after sildenafil citrate administration than before administration. In our protocol, isosorbide dinitrate was given twice, which might produce a carryover effect. McNiff et al.\textsuperscript{19} reported that plasma nitroglycerin half-time was 3 minutes. There was a >1-hour difference between the first and second administration of isosorbide dinitrate.

The recovery curve of coronary blood flow with severe stenosis coincided well with that of systemic pressure. The decrease in coronary blood flow with severe stenosis by the bolus injection of 0.2 mg isosorbide dinitrate might strongly depend on the systemic pressure after sildenafil citrate administration. However, the decrease of normal coronary blood flow did not change significantly after sildenafil citrate administration compared with before sildenafil citrate administration. Changes in the blood flow of a normal coronary artery might be independent of changes in systemic blood pressure. The effect of isosorbide dinitrate may largely depend on volume. We did not measure the right and left ventricular filling pressure during the present study. We monitored pulmonary arterial pressure, which would reflect the left ventricular filling pressure. During the present study, there were no remarkable changes in the pulmonary arterial pressure. We used open-chest dogs for the present study. We administered an intravenous saline drip to prevent the excessive volume loss due to the open chest. We believe that there was no excessive volume loss because there was no significant systemic pressure drop after sildenafil citrate administration.

We could not document myocardial ischemia during isosorbide dinitrate administration, which temporarily decreased the systemic pressure and coronary flow. Recovery half-time of flow of the bypass to the LCx was <2 minutes, in which it is difficult to document myocardial ischemia.

We strongly suspected that a fatal outcome after sildenafil citrate combined with organic nitrates would be induced by a vicious circle in which lowering the coronary blood flow with severe stenosis causes a lowering of the blood pressure, thus resulting in cardiac ischemia, causing further lowering of blood pressure.

In the present study, we did not measure systemic and local cGMP and NO levels. However, several studies reported that PDE produced smooth muscle relaxation by locally increased levels of cGMP.\textsuperscript{20–22} Our results do not contradict the previous reports.

**Clinical Impacts**

Epidemiological reports have suggested an age-dependent relation of impotence probabilities to age, with the probability of complete impotence tripled, from 0.05 to 0.15, whereas the probability of moderate impotence doubled, from 0.17 to 0.34, between the ages of 40 and 70 years. In addition, several medical conditions, including diabetes, heart disease, and hypertension, were significantly associated with changes in the impotence probability pattern. A similar pattern was seen with respect to heart disease, with the addition of an exacerbating effect of current cigarette smoking. The probability of complete impotence was 39% in subjects who reported being treated for heart disease, among whom current cigarette smokers had a significantly higher rate (56%) than did nonsmokers (21%).\textsuperscript{23}

Certain medications, such as antidiabetic agents and anti-hypertensive vasodilators, were significantly associated with complete impotence. The impotence probability pattern in users of antidiabetic medication closely resembled that in subjects reporting treated diabetes. Likewise, men taking cardiac medications or antihypertensive drugs showed a pattern of impotence probabilities similar to that in men reporting treated heart disease or hypertension.

With approval of sildenafil citrate by the Food and Drug Administration, heightened public awareness, and recognizing the fact that impotence is usually multifactorial, this initial report demonstrates the cardiac-vasodilating effect of sildenafil citrate when used in conjunction with nitrates.

**Study Limitations**

Our intent was to determine the effect of sildenafil citrate on systemic and coronary circulation. We did not measure biochemical markers for ischemia and did not look for wall motion abnormalities or perfusion defects due to the reduction in coronary blood flow. The higher doses of sildenafil citrate used in the present study do not produce higher blood levels; hence, we do not believe that the conclusions of the study are affected by these doses.

**Conclusions**

Sildenafil citrate dilated a normal coronary artery; however, a combined effect with nitrate can result in large and prolonged decreases in systemic blood pressure and coronary blood flow in vessels with critical stenosis. These effects might potentially produce a fatal cardiac outcome.

**References**

6. Miska M. Viagra leads as rivals are moving up. JAMA 1998;280:119–120.
Effects of Sildenafil Citrate (Viagra) Combined With Nitrate on the Heart
Fuminobu Ishikura, Shintaro Beppu, Toshiaki Hamada, Bijoy K. Khandheria, James B. Seward and Ajay Nehra

Circulation. 2000;102:2516-2521
doi: 10.1161/01.CIR.102.20.2516

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/20/2516

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/