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HEMODYNAMIC EFFECTS OF SILDENAFIL IN MEN WITH SEVERE CORONARY ARTERY DISEASE

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ABSTRACT

Background The cardiovascular effects of sildenafil are important because of the frequent presence of underlying cardiac disease in men with erectile dysfunction and reports indicating serious cardiac events temporally associated with the use of this drug.

Methods We assessed the systemic, pulmonary, and coronary hemodynamic effects of oral sildenafil (100 mg) in 14 men (mean [±SD] age, 61±11 years) with severe stenosis of at least one coronary artery (stenosis of >70 percent of the vessel diameter) who were scheduled to undergo percutaneous coronary revascularization. Blood-flow velocity and flow reserve were assessed with a Doppler guidewire in 25 coronary arteries, including 13 severely diseased arteries (mean degree of stenosis, 78±7 percent) and 12 arteries without stenosis, used as a reference; maximal hyperemia was induced (to assess flow reserve) with the intracoronary administration of adenosine both before and after sildenafil.

Results Oral sildenafil produced only small decreases (<10 percent) in systemic arterial and pulmonary arterial pressures, and it had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. There were no significant changes in average peak coronary flow velocity, coronary-artery diameter, volumetric coronary blood flow, or coronary vascular resistance. Coronary flow reserve at base line was lower in the stenosed arteries (1.26±0.26) than in the reference arteries (2.19±0.44) and increased about 13 percent in both groups of arteries combined after the administration of sildenafil (from 1.70±0.59 to 1.92±0.72, P=0.003). The ratio of coronary flow reserve in coronary arteries with stenosis to that in the reference arteries (0.57±0.14) was not affected by sildenafil.

Conclusions No adverse cardiovascular effects of oral sildenafil were detected in men with severe coronary artery disease. (N Engl J Med 2000;342:1622-6.)

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ERECTILE dysfunction affects up to 30 million men in the United States¹ and may be particularly common in patients with heart disease, because of the presence of overlapping risk factors, including older age, diabetes mellitus, hypertension, and hypercholesterolemia.² Sildenafil (Viagra, Pfizer, New York) inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 in the corpus cavernosum and significantly improves erectile function and the rate of successful sexual intercourse in men with erectile dysfunction.³

Post-marketing surveillance data after approval of sildenafil by the Food and Drug Administration revealed a number of serious cardiovascular events, including myocardial infarction and sudden death from cardiac causes, temporally associated with the use of the drug.⁴ Although it has been suggested that these events were not unexpected given the characteristics of the population of men who were prescribed sildenafil,⁵ a few of the events occurred shortly after ingestion of sildenafil and before any attempt at sexual intercourse.⁶ It is not possible to determine whether these events were directly related to the use of sildenafil, the patient's underlying cardiovascular disease, or a combination of these and other factors. Since phosphodiesterase is also present in vascular smooth muscle,⁷ we hypothesized that if sildenafil had direct adverse cardiovascular effects, they could be detected by measuring the systemic and coronary hemodynamic effects of this drug in men with severe coronary artery disease.

METHODS

Study Subjects

We studied the effects of sildenafil in 14 men with a mean (±SD) age of 61±11 years. All the men had severe stenosis (of

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>70 percent of the vessel diameter) in at least one coronary artery, and had been referred for percutaneous revascularization. All study subjects provided written informed consent, and the protocol was approved by the institutional review board at the University of Pennsylvania.

Study Protocol

All the men had stable symptoms that permitted the discontinuation of nitrates at least 24 hours before the start of the study; other medications, including beta-blockers, aspirin, heparin, and angiotensin-converting-enzyme inhibitors, were continued as clinically indicated. The men were studied while in a supine position and while fasting after premedication with oral diphenhydramine and diazepam.

Hemodynamic measurements included arterial blood pressure, recorded from a 7-French guide catheter in the coronary orifice; pulmonary-artery pressure and pulmonary-capillary wedge pressure, measured from the distal port of a 7-French Swan-Ganz catheter; and right atrial pressure, measured from the proximal port of the Swan-Ganz catheter. Heart rate and cardiac output determined by thermodilution were also recorded. A Doppler steerable guidewire (0.036 cm [0.014 in.] in diameter) (Flowire, Endosonics, Rancho Cordoba, Calif.) was then advanced into the coronary artery and coupled to a real-time spectrum analyzer and videocassette recorder. Angiography was performed with a nonionic contrast medium. The average peak velocity and coronary flow reserve at base line were measured before and after the administration of intracoronary adenosine (12 μ g in the right coronary artery and 18 μ g in the left coronary artery).⁸ After base-line measurements were obtained, 100 mg of sildenafil was administered orally, and all measurements were repeated, starting 45 minutes later (mean time between measurements, approximately 60 minutes).

A previous study has demonstrated a peak serum concentration of sildenafil 0.8 to 0.9 hour after a 100-mg oral dose.⁹ The hemodynamic and coronary flow measurements reported were the average of 10 beats and the average of three observations, respectively. Quantitative coronary angiographic assessments of the severity of stenosis and coronary diameter at the tip of the Doppler wire were made with digital electronic calipers and methods that have been previously validated.^{10,11} Percutaneous coronary revascularization was performed at the conclusion of the study.

Calculations

Standard hemodynamic formulas were used to calculate systemic and pulmonary vascular resistance and their indexes. Coronary flow reserve was measured in real time as the ratio of peak hyperemic velocity after the administration of adenosine to average peak velocity at base line. Measurements from 13 of 14 target vessels that underwent revascularization were analyzed. Measurements obtained in the proximal portion of a bypassed left anterior descending artery, which was the target vessel for intervention in one man, were discarded because of interference with the profile of flow velocity from retrograde coronary flow. Measurements were also obtained in the branch of the left coronary artery without stenosis (reference artery) in 12 men (measurements were not obtained in 2 men who underwent right-coronary-artery intervention). Thus, a total of 25 coronary arteries in the 14 men were studied, including 13 severely diseased arteries and 12 reference arteries.

Coronary blood flow was calculated as follows: (the average peak velocity \div 2) \times the cross-sectional area of the coronary artery, calculated as $\pi \times (\text{diameter of the artery} \div 2)^2$, which assumes a time-averaged parabolic velocity profile and a cylindrical coronary artery.⁸ Coronary vascular resistance (in millimeters of mercury per milliliter per minute) was calculated for the reference vessels as the mean arterial pressure divided by the coronary blood flow. Relative coronary flow velocity reserve in 11 men who had flow measurements in both a stenosed target vessel and a reference vessel was calculated as the ratio of the coronary flow reserve of the target vessel to the coronary flow reserve of the reference vessel.¹²

Statistical Analysis

The hemodynamic variables are shown as mean values \pm SD. For individual variables, values after the administration of sildenafil were compared with base-line values by paired t-test. Differences were considered significant when P values were less than 0.05. All data were analyzed with SPSS statistical software (SPSS, Chicago).

RESULTS

Clinical Characteristics

The study subjects were 14 men with stable angina and at least one severely stenosed coronary artery (mean degree of stenosis, 78 ± 7 percent) who had been referred for percutaneous coronary revascularization. Among these men, there were high rates of hypertension (57 percent), diabetes mellitus (43 percent), and smoking (57 percent) (Table 1).

Systemic and Pulmonary Hemodynamic Effects

The systemic and pulmonary hemodynamic effects of oral sildenafil are shown in Table 2. There were small but significant decreases (all less than 10 percent) in arterial blood pressure (systolic, diastolic, and mean pressure) and pulmonary pressure (systolic and mean pressure). The slightly smaller reductions in calculated systemic vascular resistance and pulmonary vascular resistance, and in the indexes of these measures, which are normalized for body-surface area, did not reach statistical significance. There were no significant changes in pulmonary-capillary wedge pressure, right atrial pressure, heart rate, cardiac output, or cardiac index. The heart rate times the systolic blood pressure (the double product) fell significantly, from 9435 ± 1739 mm Hg per minute to 8641 ± 1722 mm Hg per minute ($P=0.02$).

Coronary Hemodynamic Effects

The effects of oral sildenafil on the diameter of coronary arteries and on flow velocity before and af-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY POPULATION.*

CHARACTERISTIC	VALUE
No. of men	14
Age — yr	61 \pm 11
Current smoking — no. (%)	8 (57)
Hypertension — no. (%)	8 (57)
Previous myocardial infarction — no. (%)	5 (36)
Diabetes mellitus — no. (%)	6 (43)
Target vessel	
Left anterior descending artery — no. (%)	6 (43)
Left circumflex artery — no. (%)	6 (43)
Right coronary artery — no. (%)	2 (14)
Stenosis — %	78 \pm 7

*Plus-minus values are means \pm SD.

TABLE 2. HEMODYNAMIC VARIABLES AT BASE LINE AND AFTER ORAL SILDENAFIL.*

VARIABLE	BASE LINE	AFTER SILDENAFIL	P VALUE
Aortic pressure (mm Hg)			
Systolic	141.6±22.5	132.1±25.4	0.01
Diastolic	75.8±9.6	71.4±10.3	0.01
Mean	100.6±10.6	95.1±12.2	0.01
Pulmonary-capillary wedge pressure (mm Hg)	9.5±2.5	8.9±1.8	0.24
Pulmonary-artery pressure (mm Hg)			
Systolic	26.3±4.8	23.9±3.8	0.03
Diastolic	12.6±3.2	11.5±2.6	0.12
Mean	18.1±3.8	16.5±2.6	0.03
Right atrial pressure (mm Hg)	9.2±2.6	9.5±3.0	0.39
Heart rate (beats/min)	66.6±8.3	65.9±9.8	0.63
Cardiac index (liters/min/m ²)	2.6±0.5	2.6±0.5	0.74
Systemic-vascular-resistance index (dyn·sec·cm ⁻⁵ /m ²)	707.6±278.7	684.9±311.6	0.39
Pulmonary-vascular-resistance index (Wood units/m ²)	0.8±0.3	0.8±0.4	0.63
Heart rate×systolic blood pressure (mm Hg/min)	9435±1739	8641±1722	0.02

*Plus-minus values are means ±SD.

ter adenosine administration were measured in 25 arteries in 14 men, including 13 severely diseased arteries and 12 reference arteries in the same men. The mean results for all the men are shown in Table 3.

The average peak velocities at base line were 17.9±12.5 cm per second in the stenosed arteries and 29.4±13.3 cm per second in the reference arteries. The mean base-line coronary blood flow and coronary vascular resistance were calculated as 33.01±23.32 ml per minute and 3.34±1.49 mm Hg per milliliter per minute, respectively. Coronary flow reserve, assessed after intracoronary administration of adenosine, was lower in the severely stenosed arteries than in the reference arteries (1.26±0.26 vs. 2.19±0.44, P<0.05).

Sildenafil caused no significant changes in the average peak velocity at base line (Fig. 1), coronary-artery diameter, coronary blood flow, or coronary vascular resistance. However, the hyperemic average peak velocity and coronary flow reserve increased 13 percent after the administration of sildenafil (Fig. 2). These effects were consistently observed in reference arteries as well as severely stenosed arteries.

Finally, relative coronary flow reserve was assessed in 11 men in whom measurements were made in both a severely stenosed artery and a reference vessel. The relative coronary flow reserve, calculated as the ratio of coronary flow reserve in diseased vessels to that in reference vessels, was unchanged by sildenafil (base line, 0.57±0.14; after sildenafil, 0.57±0.15; P=0.90).

TABLE 3. CORONARY HEMODYNAMIC EFFECTS OF ORAL SILDENAFIL.*

VARIABLE	STENOSED ARTERIES (N=13)	REFERENCE ARTERIES (N=12)	ALL ARTERIES (N=25)
Average peak velocity (cm/sec)			
Base line	17.9±12.5	29.4±13.3	22.7±14.5
Sildenafil	16.6±10.9	26.5±13.6	21.4±13.0
Coronary flow reserve			
Base line	1.26±0.26	2.19±0.44	1.70±0.59
Sildenafil	1.41±0.38†	2.46±0.58†	1.92±0.72†
Coronary-artery diameter (mm)			
Base line	2.56±0.42	2.28±0.31	2.42±0.39
Sildenafil	2.61±0.44	2.30±0.25	2.46±0.39
Coronary blood flow (ml/min)			
Base line	30.85±28.89	34.58±13.40	33.01±23.32
Sildenafil	29.76±25.44	33.18±18.43	31.25±21.93
Coronary vascular resistance (mm Hg/ml/min)			
Base line	—	3.34±1.49	—
Sildenafil	—	3.60±1.84	—
Relative coronary flow reserve‡			
Base line	—	—	0.57±0.14
Sildenafil	—	—	0.57±0.15

*All values are means ±SD.

†P<0.05 for the comparison between base-line values and values after the administration of sildenafil.

‡Relative coronary flow reserve was measured in 11 patients.

Adverse Effects

There were no adverse effects attributable to the research procedures that were performed in this study. Subacute stent thrombosis developed in one man shortly after intervention, necessitating urgent repeated revascularization. None of the men had hypotension, chest pain, or any other side effect that could be attributed to sildenafil.

DISCUSSION

Sildenafil is now frequently prescribed for men with erectile dysfunction. The relaxation of vascular smooth muscle in the corpus cavernosum that is necessary for penile erection is mediated by nitric oxide, which activates guanylate cyclase to produce cGMP. Sildenafil is a highly selective inhibitor of phosphodiesterase type 5, which degrades cGMP.¹³

Knowledge of the cardiovascular effects of sildenafil is important for a number of reasons. First, many men with erectile dysfunction may have cardiovascular disease. Risk factors for erectile dysfunction as well as for cardiovascular disease include older age, atherosclerosis, diabetes, hypertension, hyperlipidemia, and smoking.² Second, serious cardiovascular events, including myocardial infarction and sudden death due to cardiac causes, have been reported in temporal as-

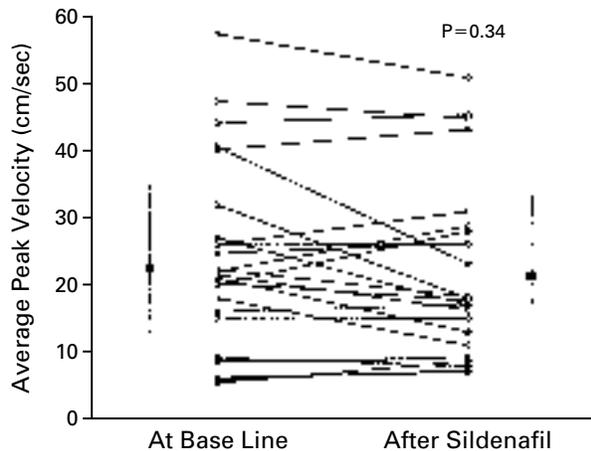


Figure 1. Individual and Mean (\pm SD) Values for Average Peak Coronary Blood Velocity at Base Line and after the Administration of Sildenafil in All 25 Coronary Arteries.

Results are shown for 13 severely diseased arteries (solid circles) and 12 reference vessels (open circles).

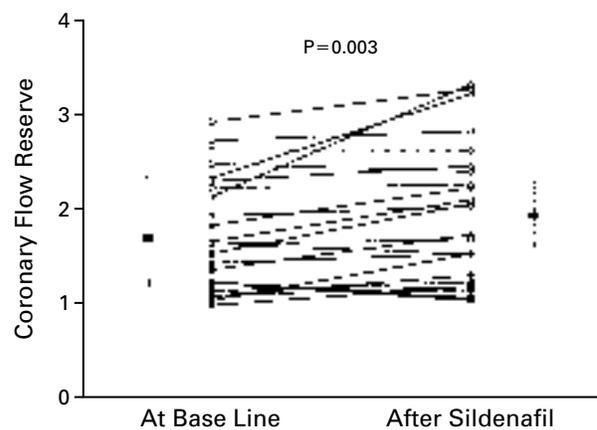


Figure 2. Individual and Mean (\pm SD) Values for Coronary Flow Reserve.

The coronary flow reserve, defined as the ratio of hyperemic average peak velocity (after the intracoronary administration of adenosine) to the average peak velocity before adenosine, was measured for all 25 coronary arteries both before (base line) and after the administration of sildenafil. Results in 13 severely diseased arteries (solid circles) and 12 reference vessels (open circles) are shown.

sociation with sildenafil use.⁴⁻⁶ Finally, although sildenafil is highly selective for phosphodiesterase type 5, inhibition of this isozyme, which is present in platelets and vascular smooth muscle, as well as weak inhibition of other isozymes present in the heart, could potentially cause adverse cardiovascular effects.⁷

In this study of men with severe coronary artery disease, no adverse cardiovascular effects of oral sildenafil could be detected by measurement of systemic, pulmonary, or coronary hemodynamic variables. Previous studies of the hemodynamic effects of intravenous and oral sildenafil in normal men and men with stable ischemic heart disease have demonstrated a small but consistent decrease in systemic and pulmonary blood pressure after administration of the drug.⁹ The results of the present study confirm these findings in men with anatomically severe coronary disease. In addition, we investigated the effects of sildenafil on coronary hemodynamics.

Our data show that oral sildenafil does not adversely affect coronary blood flow, coronary vascular resistance, or coronary flow reserve. On the basis of the decrease in the heart rate–systolic blood pressure double product (a surrogate measure of myocardial oxygen demand), we might have expected a parallel decrease in coronary blood flow due to autoregulation. The absence of such a finding in our study may reflect the inaccuracy of the double product as a true measure of myocardial demand, variations in the calculated values for coronary blood flow and resistance, or a vasodilatory effect of sildenafil that blunts the expected reduction in coronary blood flow.

Interestingly, hyperemic coronary blood flow after the administration of adenosine, reflected as an increase in coronary flow reserve, increased in all the men treated with sildenafil. Adenosine dilates coronary resistance vessels by stimulating the production of cyclic AMP.¹⁴ It is possible that adenosine and sildenafil interact and that their interaction potentiates their individual effects on coronary resistance. The doses of adenosine used in our study have been shown to provide maximal coronary vasodilation,¹⁵ but our data suggest that further vasodilation is possible.

In this regard, a preliminary study demonstrated a slight increase in resting coronary blood flow and a more marked increase in coronary flow after exercise in dogs given sildenafil.¹⁶ Both the results of that study and our data in humans suggest that phosphodiesterase type 5 may play an important part in the regulation of coronary blood flow.

Our study did not address the mechanism for the previously reported adverse cardiovascular events after the use of sildenafil, but our results do suggest that this mechanism is not the result of an adverse effect on coronary hemodynamics. Others have speculated that cardiac events may be due to interactions with other drugs (particularly with nitrates¹⁷), to an increased risk of myocardial infarction due to an increase in myocardial oxygen demand resulting from sexual activity in a man with coronary disease, or to the shared risk factors for erectile dysfunction and coronary artery disease.^{5,18,19}

Our study has several limitations. The Doppler guidewire was carefully placed to optimize signal

strength and to ensure an accurate measurement of peak velocity. Nevertheless, this method assumes a time-averaged parabolic flow velocity, negates the effects of vessel tortuosity on alterations in pulsatility and the shape of the flow field, and assumes that the coronary artery is cylindrical and that the cross-sectional area can be accurately assessed by a single angiographic measurement.⁸ In addition, the measurements of coronary flow reserve incorporate both epicardial resistance and microvascular abnormalities. For this reason, we also measured relative coronary flow reserve, which is independent of microvascular flow, aortic pressure, and the rate–pressure double product.^{12,20} This measure confirmed the absence of an adverse effect of sildenafil on the coronary circulation. We cannot rule out the possibility that, because of variability among individual men, sildenafil could have an adverse effect in some patients or in those with other cardiovascular conditions and different hemodynamic status.

In conclusion, this study demonstrates that oral sildenafil has no direct adverse cardiovascular effects in men with severe coronary artery disease. In addition, a small positive effect on coronary blood-flow reserve was identified. Our data support the consensus position of the American College of Cardiology and the American Heart Association that sildenafil is safe for patients with stable coronary artery disease who are not taking medications containing nitrates.²¹

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