Sympathetic Activation by Sildenafil

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Background—Sildenafil citrate is an effective and widely prescribed therapy for erectile dysfunction. Little is known about the effects of sildenafil on neural control of the circulation or about the effects of sildenafil on neurocirculatory stress responses.

Methods and Results—We studied 14 normal volunteers (age 32±7 years) who were randomized in a double-blind crossover fashion to receive a single oral dose of sildenafil 100 mg or placebo on 2 separate study days. Blood pressure, heart rate, forearm vascular resistance, muscle sympathetic nerve activity, and plasma catecholamines were measured at baseline and at 30 and 60 minutes after sildenafil and after placebo administration. The effects of sildenafil and placebo on neural and circulatory responses to stressful stimuli (sustained handgrip, maximal forearm ischemia, mental stress, and the cold pressor test) were also evaluated. Blood pressure, heart rate, and forearm vascular resistance after sildenafil and placebo were similar. However, muscle sympathetic nerve activity increased strikingly after sildenafil (by 141±26%, mean±SEM) compared with placebo (3±8%) (P=0.006); plasma norepinephrine levels also increased by 31±5% after sildenafil administration (P=0.004). Sympathetic nerve traffic during mental, physical, and cold stresses was 2- to 8-fold higher after sildenafil than with placebo (P<0.05).

Conclusions—Sildenafil causes a marked increase in sympathetic activation, evident both at rest and during stressful stimuli. Sympathetic activation by sildenafil may have implications for understanding cardiovascular events associated with sildenafil use. (Circulation. 2000;102:3068-3073.)

Key Words: sildenafil citrate • blood pressure • heart rate • nervous system, sympathetic • stress

Sildenafil citrate (Viagra) is an effective therapy for erectile dysfunction, a condition that affects ≈100 million men worldwide.1-3 It is prescribed in ≈50 countries and is also widely used as a recreational drug. Sildenafil is a selective vasodilator that prolongs the action of cGMP, the primary mediator of vasodilation in the corpus cavernosum of the penis, by selectively inhibiting cGMP-specific phosphodiesterase type 5 (PDE5) isozyme.4 Sildenafil is well tolerated and has a favorable side-effect profile, with most side effects related to vasodilation (eg, headache, flushing).5-7 After single therapeutic doses, there is a non-dose-dependent mild and transient decrease in blood pressure.8 No significant effects on heart rate have been noted.8

Recent concern and media coverage of temporally related cardiovascular events, including myocardial infarction, arrhythmias, and death, reported after the release of sildenafil onto the market raised questions regarding the safety of sildenafil in patients with cardiovascular disease.9 A clear link between sildenafil and cardiovascular sequelae is not apparent, because other important factors, including heart disease and other drug therapies, have been implicated in cardiovascular events during sexual activity.9-13 Nevertheless, it is clinically important to define clearly the cardiovascular effects of sildenafil.

Although there are some data on the hemodynamic effects of sildenafil, showing slight decreases in blood pressure and no change in heart rate, detailed studies of the neural circulatory effects of sildenafil are lacking. In particular, the effect of sildenafil on the sympathetic nervous system, a key contributor to cardiovascular events, is not known. Indeed, the recent American College of Cardiology/American Heart Association Expert Consensus Document on sildenafil highlighted the need for studying the effects of sildenafil on the central nervous system.14 Sympathetic neural effects of sildenafil would have direct relevance to understanding any interaction between sildenafil use and cardiovascular outcome. Using a randomized double-blind crossover trial, we therefore evaluated the effect of sildenafil on hemodynamics and sympathetic nerve traffic at rest and during stressful conditions.
Methods

Subjects
We prospectively studied 14 healthy male volunteers (age 32±7 years). Subjects weighed 79±11 kg, were 177±12 cm in height, and none were taking any medications. The studies were approved by the Institutional Review Board for Human Investigation, and written consent was obtained from all subjects. Only male subjects were studied, because sildenafil is currently not approved for use in women.

Protocol
Subjects were randomized in a double-blind crossover fashion to receive a single oral dose of sildenafil citrate (Viagra) 100 mg or placebo on 2 separate study days. Both sildenafil and placebo preparations were contained in identical capsules so that subjects and study investigators were not aware of which preparation was being administered. Subjects remained unaware of the nature of the drug administered on each study day throughout the study. On each study day, baseline measurements of heart rate, blood pressure, forearm blood flow (FFB), muscle sympathetic nerve activity (MSNA), and plasma catecholamines were obtained during 5 minutes of undisturbed supine rest in carefully standardized conditions. Identical measurements were then recorded over 5-minute periods at 30 and 60 minutes after sildenafil and placebo administration. Heart rate was measured continuously with an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). MSNA was recorded continuously by multiunit recordings of postganglionic sympathetic activity to muscle blood vessels, measured from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head as described previously.15 FBF was measured by venous occlusion plethysmography (EC4, Hokanson). Blood samples for catecholamines were obtained through an indwelling venous catheter at the end of each measurement period: at baseline and at 30 and 60 minutes after study drug administration.

Stress tests (sustained handgrip, maximal forearm ischemia, mental stress, and the cold pressor test) were conducted in a randomized fashion immediately after the 60-minute rest period. Isometric handgrip was performed with a dynamometer and by asking the subjects to sustain a handgrip of 30% of their maximum voluntary contraction for 2 minutes. Just before release of handgrip, an arm cuff was inflated to suprasystolic levels (220 mm Hg) for 2 minutes to trap exercise-related metabolites so as to evaluate the maximal forearm ischemic response.16 Mental stress involved asking the subjects to complete serial subtractions as fast as possible for 2 minutes. The cold pressor test required subjects to place one hand in ice water for 2 minutes. The cold pressor test was always performed by guest on April 20, 2017 http://circ.ahajournals.org/ Downloaded from measured during 5 minutes of undisturbed rest and during 5 minutes of lower-body negative pressure (LBNP) at −5 mm Hg.

Analyses
ECG, FBF, CVP, and MSNA were recorded simultaneously with a computerized data acquisition system (MacLab, AD Instruments Inc) and Macintosh Quadra 950 Computer (Apple Computer Inc). FBF was measured as mL · min⁻¹ · 100 mL forearm volume⁻¹, and forearm vascular resistance was calculated as mean arterial pressure divided by FBF and expressed in arbitrary units. Sympathetic bursts were identified by careful inspection of the voltage neurogram, with sympathetic activity expressed as bursts per 100 heartbeats and by the percent change from baseline in burst amplitude. For each variable (heart rate, blood pressure, forearm vascular resistance, CVP, MSNA), each period of data collection was averaged to a single value. Plasma norepinephrine levels were determined by high-performance liquid chromatography with electrochemical detection. The assay has interassay and intra-assay coefficients of variation of 3.4% and 3.1%, respectively, and a lower limit of detection of 25 pg/mL. Blinding was maintained until completion of analysis of data.

Effects of sildenafil on baseline and stress measurements were determined by use of a 2-way repeated-measures ANOVA with time as the within factor and group (sildenafil versus placebo) as the between factor. The key variable was the group-by-time interaction. Differences in hemodynamics (blood pressure, heart rate, CVP) and MSNA before open-label sildenafil administration and at 30 and 60 minutes after sildenafil administration were determined by repeated-measures ANOVA. Differences in hemodynamic (blood pressure, heart rate, CVP) and MSNA measurements at baseline and after LBNP and phenylephrine were determined by Student’s paired t test. Statistical significance was defined as P<0.05. Data are presented as mean±SEM.

Results

Sympathetic Activity and Hemodynamics at Rest
MSNA, measured either as burst frequency (bursts/100 heartbeats) or by the percent change in burst amplitude, was markedly increased after sildenafil compared with placebo (P=0.001 and P=0.006, respectively) (Figures 1 and 2). Plasma catecholamine levels were also higher after sildenafil than with placebo (P=0.004). Norepinephrine was 235±22 pg/mL at baseline before sildenafil, increasing to 265±26 pg/mL at 30 minutes after sildenafil and 305±31 pg/mL at 60 minutes after sildenafil. Norepinephrine levels remained relatively unchanged before (255±30 pg/mL) and at 30 (220±28 pg/mL) and 60 (266±45 pg/mL) minutes after placebo. Mean arterial pressure and heart rate were similar both after sildenafil and after placebo (P=0.23 and P=0.24, respectively) (Figure 2). Forearm vascular resistance was also not changed by either sildenafil or placebo (P=0.61).

Stress Responses
Blood pressure and heart rate responses were similar for sildenafil and placebo during mental stress (Figure 3), sustained handgrip and maximal forearm ischemia (Figure 4), and the cold pressor test (Figure 5). For all the stressful stimuli, however, MSNA was between 2- and 8-fold higher after sildenafil than with placebo (Figures 3, 4, and 5).

Sildenafil, CVP, and MSNA
In the 6 subjects who returned for the third study, which examined the effect of sildenafil on CVP, CVP was 8.9±1 mm Hg at baseline, 8.1±1 mm Hg 30 minutes after sildenafil,
and $7.5 \pm 1$ mm Hg 60 minutes after sildenafil administration ($P=0.63$). In these 6 subjects, mean arterial pressure was $84 \pm 2$ mm Hg at baseline before sildenafil and $81 \pm 1$ mm Hg at 30 minutes and $82 \pm 2$ mm Hg at 60 minutes after sildenafil ($P=0.44$). Heart rate was $65 \pm 3$ bpm at baseline and $67 \pm 2$ bpm at 30 minutes and $66 \pm 2$ bpm at 60 minutes after sildenafil ($P=0.73$). Sympathetic activity was $32 \pm 5$ bursts/100 heartbeats at baseline before sildenafil, increasing to $51 \pm 6$ bursts/100 heartbeats at 30 minutes after sildenafil and $57 \pm 6$ bursts/100 heartbeats 60 minutes after sildenafil ($P=0.01$). At 30 and 60 minutes after sildenafil, MSNA amplitude increased by $98 \pm 25\%$ (when CVP had fallen by $0.8$ mm Hg) and $154 \pm 36\%$ (when CVP had fallen by $1.6$ mm Hg), respectively ($P=0.003$). In 4 subjects, phenylephrine administration resulted in an increase in CVP of $1.3 \pm 0.4$ mm Hg and an increase in mean arterial pressure of $3.4 \pm 1.5$ mm Hg over baseline measures before sildenafil administration; despite the higher blood pressure and CVP after phenylephrine administration, sildenafil still induced an increase in sympathetic burst frequency to $62 \pm 9$ bursts/100 heartbeats ($P=0.02$) and an increase in MSNA amplitude by $87 \pm 23\%$ ($P=0.005$) compared with baseline.

**LBNP, CVP, and MSNA**

LBNP decreased CVP by $2.0 \pm 0.2$ mm Hg from a baseline of $8.7 \pm 1$ mm Hg to $6.7 \pm 1$ mm Hg ($P=0.001$). Mean arterial pressure was $84 \pm 3$ mm Hg at baseline and $83 \pm 2$ mm Hg during LBNP ($P=0.21$). Heart rate was $61 \pm 2$ bpm at baseline and $60 \pm 3$ bpm during LBNP ($P=0.26$). Sympathetic burst activity was $40 \pm 5$ bursts/100 heartbeats at baseline and increased to $45 \pm 5$ bursts/100 heartbeats after LBNP; MSNA amplitude increased by $29 \pm 10\%$ (both $P=0.03$). Therefore, at 30 minutes after sildenafil, MSNA increased by almost 100%, whereas CVP fell insignificantly, by $0.8$ mm Hg. By contrast, the $2.0$ mm Hg fall in CVP induced by LBNP increased MSNA by only $29\%$; hence, changes in CVP alone did not appear to explain the increase in sympathetic activity after sildenafil.

**Discussion**

The important and novel findings of this study are that sildenafil elicits a marked increase in sympathetic nerve activity, as measured by intraneural recordings of MSNA and by plasma catecholamine levels. The sympathetic activation is selective for vascular sympathetic drive, because heart rate did not change. The very slight changes in blood pressure, heart rate, or CVP suggests that arterial and cardiopulmonary baroreflex responses alone do not explain the sympathetic excitation. First, it is improbable that arterial baroreflexes would change sympathetic drive by $>2$-fold in the absence of any change in heart rate. Second, even after administration of phenylephrine to maintain blood pressure and CVP higher than baseline, sildenafil still induced clear and significant increases in sympathetic traffic. Third, changes in CVP...
during lower-body negative pressure, even though in excess of CVP changes observed after sildenafil, elicit only a fraction of the sympathetic activation seen after sildenafil administration. Thus, these data suggest the intriguing possibility of an interaction between nitric oxide modulation and sympathetic activation. It is conceivable that sildenafil may have direct central effects on sympathetic outflow. This potential mechanism is supported, in part, by evidence that sildenafil crosses the blood-brain barrier and that PDE5 is present in the brain.\(^{17,18}\)

Our data on the hemodynamic effects of sildenafil are consistent with a recent study in patients with severe coronary artery disease. In these patients, sildenafil induced only small changes in blood pressure and no change in heart rate, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output.\(^{19}\)

Heightened sympathetic drive was also evident during stressors directed at inducing emotional, physical, metabolic, and painful stimuli. After sildenafil, an 8-fold greater MSNA response to mental stress, a 4-fold greater MSNA response to isometric exercise, and a 2-fold greater MSNA response to cold stress were observed. The demands elicited by the stressors used in our study have considerable overlap with those experienced during sexual intercourse. Thus, it is reasonable to assume that the heightened resting sympathetic drive induced by sildenafil would be accompanied by increased levels of sympathetic activation during sexual intercourse. Activation of the sympathetic nervous system contributes importantly to the pathophysiology and the prognosis of cardiovascular diseases, including acute coronary syndromes, arrhythmias, congestive heart failure, and hypertension.\(^{20-24}\) This would be especially relevant when the heightened sympathetic drive occurs together with elevations in heart rate, blood pressure, and myocardial oxygen demand, such as is seen during stressful stimuli. Our findings do not exclude the use of sildenafil when indicated, but support the recommendation that it should be used with caution in patients with severe heart disease.

Recent reports of death and cardiovascular events temporally associated with sildenafil have caused many to question the safety of sildenafil in specific populations.\(^{9}\) However, no clear link between sildenafil administration and cardiovascular risk has been demonstrated. Furthermore, cardiovascular event rates after sildenafil administration are similar to those reported in patients with cardiovascular disease after coitus.\(^{25}\) Many of the reported cardiovascular events occurred in people with underlying cardiovascular disease who were taking other medications, primarily nitrates.\(^{9}\)

Our data suggest a mechanistic explanation for the link between nitrate use and sildenafil-induced cardiovascular events. Although the primary cause of the sildenafil-associated sympathetic activation is unclear, the increased sympathetic drive would be important in opposing the systemic vasodilator effects of sildenafil, thus maintaining blood pressure levels. Nitrates alone induce increased sympathetic drive.\(^{26}\) In the setting of an already high level of nitrate-induced sympathetic activation, there would be limited additional capacity for further sympathetic activation. Thus, in the setting of nitrate use, additional vasodilator effects of sild-
Sildenafil would not be able to be opposed by sympathetic activation, with consequent hypotension and impaired organ perfusion. Indeed, previous reports of sildenafil-associated cardiac events in the setting of nitrate use document marked hypotension. A similar concern regarding limitations in capacity to further increase sympathetic drive in the setting of preexisting sympathetic activation would apply to other cardiovascular diseases, including heart failure. Excessive sympathetic drive, even during rest, is a key pathophysiological feature of heart failure. Importantly, as with nitrates, hypotension in heart failure patients after sildenafil use also poses a significant and unresolved clinical problem.

A strength of our study is that subjects were studied in a randomized double-blind crossover design, thus limiting sources of bias. In addition, measurements of sympathetic nerve traffic included direct intraneural recordings of MSNA and plasma catecholamine levels. A limitation is that we studied relatively younger, healthy subjects. We cannot exclude the possibility that responses may differ in older subjects with underlying cardiovascular disease. A second limitation is that whereas our study invites speculation regarding an association between heightened sympathetic activity and the potential for detrimental outcomes in patients with cardiovascular disease, we show no link between sildenafil-induced sympathetic activation and cardiovascular risk. Nevertheless, it is reasonable to assume, first, that increased sympathetic drive may contribute to the initiation of cardiovascular events, and second, that cardiovascular events, particularly arrhythmias and myocardial infarction, that occur in the setting of a high level of sympathetic activation are likely to have poorer outcomes. Any accompanying hypotension is likely to contribute further to an adverse prognosis, especially in the setting of decreased cardiovascular reserve. Thus, even though cardiac events occurring in association with sildenafil use may be incidental and unrelated to sildenafil per se, the outcome of these events would probably be negatively affected by the heightened sympathetic drive induced by sildenafil.

In conclusion, our study shows that sildenafil induces heightened levels of sympathetic activity, both at rest and during physical, mental, and metabolic stress. Increased sympathetic traffic is not explained exclusively by the hemodynamic effects of sildenafil. Sympathetic excitation after sildenafil use may be implicated in any heightened cardiovascular risk in patients with severe cardiovascular disease.

Acknowledgments

These studies were supported by NIH grants HL-61560, HL-65176, HL-14388, and FIRCA R03-TW-01348 and by GCRC grant M01-RR-00585. Dr Phillips is a Sleep Academic Awardee of the NIH, and Dr Somers is an Established Investigator of the American Heart Association. Drs Narkiewicz and Winnicki are recipients of NIH Fogarty International Fellowships, and Dr Kato is a recipient of the Perkins Memorial Award from the American Physiological Society.

References

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Circulation. 2000;102:3068-3073
doi: 10.1161/01.CIR.102.25.3068

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