Cardiovascular safety of PDE5 inhibitors

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Erectile dysfunction (ED) and cardiovascular disease share many of the same risk factors and have some common elements of pathophysiology. Clinically, they often coexist. Another link between the two conditions is that sildenafil, the first oral therapeutic agent effective in treating ED, has been shown to potentiate the hypotensive effects of nitrates, a potentially serious side effect. Nitrates are commonly used in the treatment of coronary artery disease. As such, sildenafil (and, likely, other new phosphodiesterase type 5 [PDE5] inhibitors) is contraindicated in men who use nitrate medications. This article will examine the risk of an acute coronary event during sexual activity, and review an algorithm for evaluating the cardiac risk of a patient with ED. The interaction between PDE5 inhibitors and cardiac medications will be discussed, along with guidelines for using sildenafil in men with cardiac disease.

Key Words: erectile dysfunction, cardiovascular, nitrates

Introduction

Cardiovascular diseases (CVD) are the most common cause of death among men in Canada, accounting for more than a quarter of all deaths.[1] Coronary artery disease (including angina and myocardial infarction [MI]), cerebrovascular disease (transient ischemic attacks and strokes), and peripheral vascular disease, between them contribute to an enormous burden of suffering, hospital care, health care costs, and death. The common nature of these diseases, and the common nature of erectile dysfunction (ED) as discussed in Dr. Pommerville's paper in this supplement, mean that the two conditions, CVD and ED, will often coexist – but they coexist much more often than can be accounted for by chance. One study of men hospitalized with acute MI found that 44% had ED before their coronary event.[2] Most of the risk factors for CVD are also risk factors for ED: age, diabetes, hypertension, smoking, and dyslipidemia. Atherosclerotic narrowing of small arteries, along

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with endothelial dysfunction, are central parts of the pathophysiology of both conditions. All of this means that the clinician treating a man with ED may have to consider the man's possible risk of CVD, be aware of associated risk factors, and consider objectively assessing the patient's risk of CVD. Before that, however, it is important to understand the effects of sexual activity on the heart and cardiovascular system.

Cardiovascular effects of sexual activity

In general, sexual activity has an effect similar to mild-to-moderate exercise in increasing heart rate, blood pressure, cardiac output, and respiratory rate.[3] The degree of change in these physiological parameters, however, is greater than expected, because of a disproportionate increase in sympathetic activation. This high degree of sympathetic activation, with elevated levels of plasma adrenaline and noradrenaline, can produce ventricular tachyarrhythmias in susceptible individuals with coronary artery disease.[3] However, most studies of the cardiovascular effects of sexual activity have shown wide individual variability with respect to physiologic responses to sexual activity.[3]

An early study that examined the cardiovascular effects of sexual activity was conducted with ten healthy, male, married volunteers.[4] The men were between 25 and 43 years old (mean 33.2 years), were free of known cardiac disease, and were taking no medications. In the laboratory, they were monitored while engaging in four different sexual activities: coitus with man on top, coitus with woman on top, noncoital stimulation by partner, and noncoital self-stimulation. All physiological parameters increased slightly during foreplay, more during stimulation, peaked during orgasm, then returned to baseline promptly. Figure 1[4,5] shows the average metabolic expenditures during stimulation and orgasm for each of the activities, expressed in METS (one MET is the metabolic equivalent of energy expenditure in the resting state, an oxygen consumption of roughly 3.5 mL/kg/min).[3] The figure includes, for comparison, the average metabolic expenditure of two common nonsexual activities.[5]

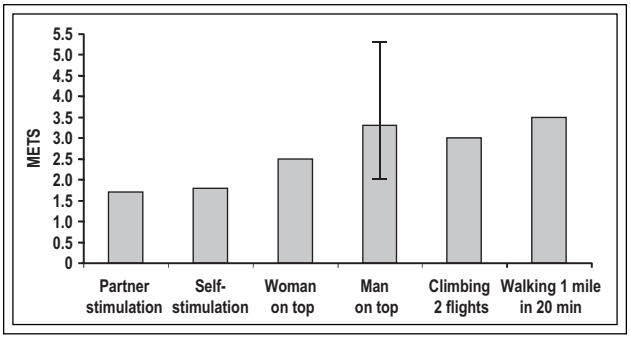

Figure 1. Cardiovascular effects of sexual activity in healthy volunteers.[4,5]

A larger study examined the cardiovascular effects of sexual activity in 88 men with known coronary artery disease (most with previous MI, some with angina).[6] The average age of the subjects was 52 years. The men were given near-maximal bicycle stress tests, then underwent 24-hour Holter ECG monitoring, during which time they had intercourse at home. The mean peak heart rate during the exercise test was 138 beats/min; during intercourse, it was significantly lower, at 118 beats/min. However, patients with symptomatic or silent ischemia had similar heart rates during exercise and intercourse. The exercise test was strongly predictive of ischemia during intercourse. All men with ischemia during intercourse also had ischemia during exercise. Conversely, men who showed no ischemia during exercise were also free of ischemia during intercourse.[6] The study concluded that the pathogenic mechanisms involved in coital and exercise ischemia are similar.

Risk of MI during sexual activity

The absolute risk of sexual activity triggering an MI is low. Among men at low risk of cardiac disease, the risk of a cardiac event occurring is estimated at 1 in a million per hour (this is equivalent to a 1/114 risk of cardiac event over the course of a year).[5] During sexual activity and for the two hours following, that risk doubles to 2/million/h. Men with coronary artery disease or previous MI have a ten-fold higher risk, which means that during intercourse the probability of such a man having an MI is 20/million/h.[5]

Cardiac risk stratification

In managing the patient with ED who is thought to be at risk of potential cardiac complications, the crucial concept is risk stratification. A simple office evaluation can allow patients to be placed into one of three categories: those at low risk of cardiac events, for whom treatment with ED can proceed; those at high risk, who require specific cardiological evaluation and therapy before sexual activity or treatment for ED is safe; and those at intermediate risk, who require further assessment.[3] The risk factors

TABLE 1. **Major risk factors for cardiovascular disease in men.[3] Reprinted with permission from Excerpta Medica Inc.**

Age
Hypertension
Diabetes mellitus
Obesity
Smoking
Dyslipidemia
Sedentary lifestyle

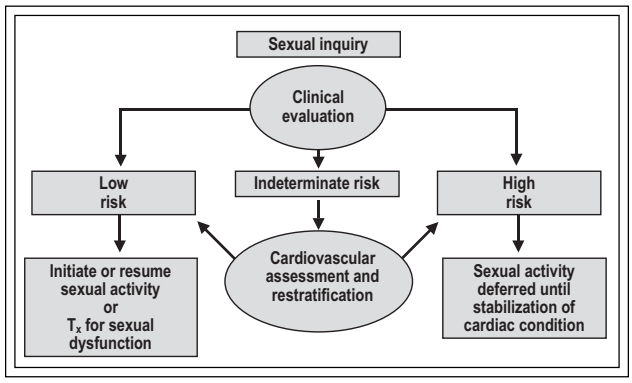

Figure 2. An algorithm for assessment of cardiac risk in men with ED.[3] Reprinted with permission from Excerpta Medica Inc.

that are used in this evaluation are listed in Table 1, while Figure 2 shows an algorithm for this process.[3]

The patient at low risk

The majority of patients with cardiac disease who are seen in the family physician's or urologist's office will fit into this group, men who can safely have intercourse, and safely be treated for ED. Low-risk males include those with two or fewer of the risk factors listed in Table 1: those with controlled hypertension, mild stable angina, previous coronary artery bypass or angioplasty, or uncomplicated previous MI (after six weeks); those with mild valvular disease; and those with mild heart failure who can manage ordinary physical activity without symptoms (New York Heart Association [NYHA] class I).[3] An important caveat for the men with mild stable angina concerns the interaction between sildenafil (and presumably other phosphodiesterase type 5 [PDE5] inhibitors) and nitrates, which are often used in the treatment of angina. This interaction will be discussed in more detail later in this article.

The patient at high risk

High-risk patients have unstable or serious heart disease, such that sexual activity poses a significant risk of ischemia, arrhythmia, or sudden death. In these patients, sexual activity and treatment of ED must be deferred until the cardiac disease is stabilized. Patients in the high-risk group have unstable or refractory angina; uncontrolled hypertension; congestive heart failure with symptoms at rest or with minimal exertion (NYHA class III or IV); recent MI (within two weeks); high-risk (particularly ventricular) arrhythmias; hypertrophic obstructive or other cardiomyopathies; or moderate-to-severe valvular disease.[3]

The patient at intermediate or indeterminant risk

Patients in this risk group generally require further assessment by the family physician or cardiologist, in order to definitively assign them to either a low-risk or high-risk group. The assessment might include exercise stress testing, or other cardiac evaluation. These men might also benefit from cardiac rehabilitation, to improve their functional status and exercise capacity. Patients in this group include those with three or more risk factors; moderate but stable angina; MI between two and six weeks previously; heart failure with slight limitations (NYHA class II) or left ventricular ejection fraction < 40%; and noncardiac atherosclerotic disease (stroke, or peripheral vascular disease).[3]

Phosphodiesterase 5 inhibitors and the heart

The widespread use of PDE5 inhibitors in men with coexistent ED and coronary artery disease (CAD) has allowed the accumulation of a large amount of data. The interaction between PDE5 inhibitors and nitrates will be discussed in a later section of this article: in this section, the focus will be on the hemodynamic effects of sildenafil and the other PDE5 inhibitors, and studies of the use of sildenafil in men with CAD.

Hemodynamic effects of PDE5 inhibitors

Sildenafil, in healthy volunteers, has little effect on hemodynamic parameters. One study of 16 men found modest reductions in blood pressure following doses of up to 200 mg of sildenafil.[7] After a dose of 100 mg, the mean maximum systolic/diastolic decrease was 10.2/6.8 mm Hg roughly an hour after oral intake of the medication, with blood pressure returning to normal after four hours.[7] No significant changes in heart rate were seen. Other studies found no changes in cardiac index,[8] and no change in coronary blood flow, coronary vascular resistance, or coronary flow reserve.[9]

Sildenafil in men with CAD

A randomized, double-blind, crossover study examined the effects of sildenafil in 105 men with ED and with known or suspected CAD (previous MI, bypass or angioplasty, or typical angina).[10] The men were studied with exercise echocardiography one hour after receiving either sildenafil or placebo, then again one to three days later after receiving the other agent. Compared with placebo, sildenafil caused a mean reduction in resting systolic blood pressure by 4.3 mm Hg ($p = 0.01$), and in resting diastolic pressure by 3.7 mm Hg ($p < 0.001$). However, no significant differences were seen with sildenafil compared with placebo in heart rate at rest or with exercise, blood pressure with exercise, double product (heart rate X systolic blood pressure at peak exercise), exercise capacity, or exercise echocardiographic parameters.[10] Patients who received sildenafil showed a small but statistically significant improvement in resting ejection fraction (1.08%, $p = 0.01$). Overall, these authors commented that sildenafil was well tolerated and did not change the onset, extent, or severity of ischemia as assessed with exercise electrocardiography or echocardiography.

Another source of information about the PDE5 inhibitor sildenafil and CAD comes from phase II and III studies conducted for FDA approval. In these trials, while men taking nitrates were excluded, men with stable CAD, hypertension, and diabetes were included. The rate of MI in over 5700 patient-years was 1.7/100 patient-years in the sildenafil group and 1.4/100 patient-years in the placebo group: the rate of death was 0.53/100 patient-years on sildenafil and 0.57/100 patient-years in men taking placebo.[8] A more recent paper looked at the incidence in MI in 53 clinical trials of sildenafil, comparing rates of MI and death with sildenafil and placebo Table 2.[11] These data, taken together, strongly suggest that sildenafil does not cause an increase in coronary events in men with ED.

PDE5 inhibitors and nitrates

The profound interaction between PDE5 inhibitors and nitrates is mediated through their synergistic effects on cyclic guanosine monophosphate (cGMP), a potent vasodilator. Nitric oxide is the neurotransmitter that controls erection by increasing levels of cGMP: cGMP is broken down by PDE5, so inhibition of PDE5 allows sustained increased levels of cGMP. Nitric oxide donors include all of the nitrates used in the management of CAD, from short-acting sublingual nitroglycerin, to long-acting isosorbide dinitrate, and nitroglycerin patches.

The concept of outliers in regard to blood pressure drop is important when examining the interaction of PDE5 inhibitors and nitrates. As with any biological phenomenon that is being measured, the majority of observations (in this case, of blood pressure) will cluster around the mean. Some, however, will be outliers – in this context, men whose blood pressure drops much more than the average when the two medications are taken concurrently are defined as outliers. Men whose blood pressure response would be classified as outliers are at much greater risk of a symptomatic effect. Unfortunately, the extent of reaction for any man (i.e., whether he will be an outlier) cannot be predicted, which is part of what makes the concurrent use of a PDE5 inhibitor and organic nitrate a clinical risk for patients.

The extent of the interaction between sildenafil and nitrates was shown in a study of 12 healthy volunteers given sildenafil 25 mg tid for four days, then another 25 mg tablet on day 5.[12] The men were then given 0.5 mg sublingual nitroglycerin. Systolic blood pressure dropped significantly, 26 mm Hg to 51 mm Hg, and the subjects reported symptoms such as dizziness and headache.[12] The same investigators found a similar effect in a study of 31 men with stable angina who took 50 mg sildenafil while taking either

TABLE 2. **Incidence of myocardial infarction and death in 53 clinical trials of sildenafil.[11] Reprinted with permission from the American College of Cardiology Foundation**

Treatment group (patient-years)	Incidence (95%CI) of MI per 100 patient-years	Incidence (95% CI) of death per 100 patient-years
Placebo (543)	1.11 (0.41 to 2.40)	0.74 (0.20 to 1.89)
Sildenafil double-blind trials (964)	1.45 (0.79 to 2.44)	0.83 (0.36 to 1.64)
Sildenafil open-label (5920)	0.69 (0.50 to 0.94)	0.35 (0.22 to 0.54)
Sildenafil total (6884)	0.80 (0.60 to 1.04)	0.42 (0.28 to 0.61)

isosorbide mononitrate 20 mg twice daily, or a single dose of 0.5 mg sublingual nitroglycerin an hour before the sildenafil.[13] After taking sildenafil, standing systolic blood pressure dropped significantly more than after placebo (52 mm Hg in men taking isosorbide mononitrate, compared with 25 mm Hg for placebo, $p < 0.001$).[13]

The interaction between tadalafil or sildenafil and nitrates was examined in a double-blind, randomized, three-way crossover trial involving 49 healthy volunteers over 55 years of age.[14] The subjects were given sublingual nitroglycerin after doses of sildenafil (50 mg), tadalafil (10 mg), or placebo. The mean maximal change in standing systolic blood pressure was a statistically significant 3 mm Hg greater for sildenafil than for placebo; no difference was found between the tadalafil and placebo groups. The number of outliers (subjects with standing blood pressure less than 85 mm Hg) was 12 with placebo, 23 with tadalafil, and 23 with sildenafil.[14] This study underscored the concern regarding the hypotensive effects seen with the combination of nitrates and PDE5 inhibitors.

Consensus statement on sildenafil in patients with cardiovascular disease

Concerns about the safety of sildenafil in men with cardiovascular disease led the American College of Cardiology (ACC) and the American Heart Association (AHA) to establish a consensus group to examine the issue.[8] Their report, published in 1999, presented one clear contraindication to the use of sildenafil: concurrent use of nitrates. This contraindication includes the use of sildenafil in a man taking ongoing nitrates for ischemic heart disease, the use of recreational nitrates (amyl nitrate poppers) when sildenafil has been or will be used, and the therapeutic use of nitrates to relieve angina at any time up to 24 hours after sildenafil has been taken.[8]

The consensus group also listed clinical situations in which the use of sildenafil might be hazardous: active ischemia not requiring ongoing nitrates; heart failure with borderline low blood pressure and fluid volume; complicated, multidrug antihypertensive regimens; and the use of drugs that prolong the half-life of sildenafil.[8] Although the consensus group mentioned "a theoretical concern in a patient receiving multiple medications that include antihypertensive therapy and an inhibitor of the metabolic pathway (cytochrome P4503A4) of sildenafil," this concern was not based on clinical trials. Current clinical practice suggests that there is no concern in combining sildenafil with multiple antihypertensive agents.

A similar statement was published by the Heart and Stroke Foundation of Canada and the Canadian Cardiovascular Society.[15] This statement clarified that "sildenafil should not be used in patients on any form of nitrate therapy, or those patients with active myocardial ischemia who are likely to be prescribed nitrate therapy." As well, the statement suggested caution when prescribing sildenafil to men with left ventricular outflow tract obstruction or low blood volume.[15]

Although less information is available concerning the interaction between nitrates and the new PDE5 inhibitors tadalafil and vardenafil, the interaction can be assumed to be a class effect.

Conclusion

For most men with heart disease, sexual activity is still a desirable and pleasurable part of life – however, ED is more common in men with heart disease. The clinician treating ED in a man with cardiac disease is faced with a dilemma – is sexual activity, or treatment for ED, safe? Based on Canadian and American recommendations, the answer is usually yes. The clinician can often assess the man's risk of a cardiac event easily, based on history and risk factor analysis. For men at low risk of a cardiac event (the majority of men in most practices), oral therapy with PDE5 inhibitors is generally safe and effective. Men taking PDE5 inhibitors must be strongly cautioned to not use nitrates in any form, to avoid the risk of life-threatening hypotension. □

References

1. Statistics Canada. Selected leading causes of death by sex. [document online] 2002 Aug [accessed]. Available from: URL: *http://www.statcan.ca/english/Pgdb/People/Health/health36.htm.*
2. Wabrek AJ, Burchell RC. Male sexual dysfunction associated with coronary heart disease. *Arch Sex Behav* 1980;9:69-75.
3. DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. *Am J Cardiol* 2000;86:175-181.
4. Bohlen JG, Held JP, Sanderson MO, Patterson RP. Heart rate, rate-pressure product, and oxygen uptake during four sexual activities. *Arch Intern Med* 1984;144:1745-1748.
5. Jackson G. Sexual intercourse and stable angina pectoris. *Am J Cardiol* 2000;86(2A):35F-37F.
6. Drory Y, Shapira I, Fisman EZ, Pines A. Myocardial ischemia during sexual activity in patients with coronary artery disease. *Am J Cardiol* 1995;75:835-837.
7. Zusman RM, Morales A, Glasser DB, Osterloh IH. Overall cardiovascular profile of sildenafil citrate. *Am J Cardiol* 1999;83(5A):35C-44C.

8. Cheitlin MD, Hutter AM, Jr., Brindis RG, Ganz P, Kaul S, Russell RO, Jr., et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 1999;33:273-282.
9. Kloner RA. Sex and the patient with cardiovascular risk factors: focus on sildenafil. *Am J Med* 2000;109 Suppl 9A:13S-21S.
10. Arruda-Olson AM, Mahoney DW, Nehra A, Leckel M, Pellikka PA. Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA* 2002;287:719-725.
11. Mittleman MA, Glasser DB, Orazem J, Collins M. Incidence of myocardial infarction and death in 53 clinical trials of Viagra® (sildenafil citrate). *J Am Coll Cardiol* 2000;35(Suppl A):302A.
12. Webb DJ, Freestone S, Allen MJ, Muirhead GJ. Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist. *Am J Cardiol* 1999;83(5A):21C-28C.
13. Webb DJ, Muirhead GJ, Wulff M, Sutton JA, Levi R, Dinsmore WW. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000;36:25-31.
14. Herschorn S, Mitchell M, Bedding A, Emmick J. Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil. Presented at the 57th Annual Meeting of the Canadian Urological Association; 2002 Jun 23-26; St. John's, Canada.
15. A statement on the use of sildenafil in the management of sexual dysfunction in patients with cardiovascular disease. Heart and Stroke Foundation of Canada. Canadian Cardiovascular Society. *Can J Cardiol* 1999;15:396-399.