Current perspectives

Sexual activity with and without the use of sildenafil: risk of cardiovascular events in patients with heart disease

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The data in the literature on the relationship between sexual activity, with and without the use of sildenafil, and the occurrence of cardiovascular events (ventricular arrhythmias, nonfatal myocardial infarction, stroke and death) have been reviewed in patients with heart disease.

To date, only patients with ischemic heart disease (IHD) have been investigated. The prevalence of premature ventricular beats during sexual intercourse is similar to that observed during other daily activities. Therefore, sexual activity does not seem to have a relevant arrhythmogenic effect. The incidence of sustained ventricular tachycardia during sexual intercourse in unknown. The relative risk of nonfatal myocardial infarction is 2.7 in males and 1.3 in females; however, the absolute risk appears extremely low and is similar in normal subjects and in patients with and without IHD. The risk appears to be restricted to the 2-hour time period after sexual intercourse. The incidence of stroke during sexual intercourse appears very low, but clear data are lacking. The incidence of death during sexual activity is unknown; the few available data suggest that it is very low. Extramarital sexual intercourse seems to increase the risk of death.

The incidence of cardiovascular events after sildenafil administration has been investigated in placebo-controlled studies in patients with IHD. The incidence of nonfatal myocardial infarction, stroke and death did not significantly differ between sildenafil-treated and placebo-treated patients; therefore, sildenafil does not appear contraindicated in subjects with IHD. However, the drug should be administered with caution in patients with recent myocardial infarction or stroke, in those with active coronary ischemia and in patients with episodes of heart failure. The drug is absolutely contraindicated in patients using nitrates.

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Sexual function is an important component of patients' quality of life and subjective well-being. Recent epidemiological data reveal that erectile dysfunction (ED) is widespread and adversely affects mood, well-being and interpersonal functioning[1]. ED is secondary to endothelial dysfunction, defined as a reduction in the availability of nitric oxide, and is associated with many of the common risk factors for cardiovascular disease. ED is an extremely common disorder (over 50% of men between 40 and 70 years old) and its incidence increases in relation to age and to cardiovascular disease. In particular, the problem of sexual dysfunction after myocardial infarction (MI) is quite common; in fact, it occurs in 50 to 75% of all patients and significantly alters their quality of life[2]. However, most cardiologists do not ask about ED and patients are often reluctant or embarrassed to discuss about it[2].

New pharmacological therapies such as sildenafil citrate (Viagra) are now available and effective. Because of the frequent association between ED and cardiovascular diseases, these drugs are often indicated in patients with known cardiovascular disease and this gave rise to uncertainties regarding the safety of "medicated" sexual activity.

In this review the risk of cardiovascular events during intercourse will be discussed separately in patients using and not using sildenafil. We reviewed the data in the literature on the relationship between sexual activity and the occurrence of cardiovascular events such as ventricular arrhythmias, nonfatal MI, stroke and death.

Sexual intercourse without the use of sildenafil

Heart rate (HR), metabolic expenditure and ventricular arrhythmias during sexual intercourse have been investigated in normal subjects[3-6]. The highest HRs were ob-

served during orgasm and the mean value ranged from 110 ± 24 to 129 ± 14 b/min; they were 60-70% of the predicted maximum HR. The highest blood pressure was observed during orgasm as well, and the mean value was 160/80 mmHg. The change in average oxygen consumption was investigated by Bohlen et al.[6], who reported an increase of about 1.0 l/kg/min above baseline. Using a conversion value of 1 MET to 3.5 l/kg/min of oxygen uptake, the average metabolic expenditures during stimulation and orgasm were only about 3 METs (range 2-5.4 METs). These results suggest that in normal subjects the metabolic expenditure during sexual activity is small and similar to that observed during a climb of two flights of stairs in 10 s[4]. Isolated premature ventricular beats (PVBs) were observed in about 5% of normal subjects during sexual intercourse.

Patients with heart disease. With regard to patients with heart disease, to date HR, metabolic expenditure and ventricular arrhythmias have been investigated during sexual intercourse only in subjects with ischemic heart disease (IHD), mainly post-MI patients. HR and the other variables taken during sexual intercourse are reported in table I[3,4,7-14]. The mean age of the patients was about 50 years and almost all were in NYHA class I-II. As in normal subjects, the highest HR was observed during orgasm and even the mean values were similar (110-120 b/min). However, the range was wide since HR varied from 70-80 to 170-185 b/min; therefore, the behavior of HR during sexual intercourse varies significantly between subjects. The metabolic expenditure was investigated by Hellerstein and Friedman[7] and appeared rather small (mean value 4.5 METs). It is highly probable that the hemodynamic changes associated with sexual activity are greater with an unfamiliar partner and after excessive eating and drinking[15]; however, the hemodynamic findings in these situations have never been investigated.

Ventricular arrhythmias. The prevalence of PVBs during sexual intercourse is reported in table I[4,7,9-13]. It was low in the study by Garcia-Barreto et al.[12] (5%), but in the others it ranged from 21 to 58%. These data are not easy to interpret since we are mainly dealing with patients with previous MI in whom PVBs are present (rare or frequent) in about 90% of cases during 24-hour Holter recording[16]. For this reason, the prevalence of PVBs during sexual intercourse should be compared with that observed during daily activities or during exercise testing. Some authors[6,16] have compared the prevalence of PVBs during sexual activity with that observed during activities requiring moderate psychophysical effort (walking quickly, bike riding, manual labor, driving). The prevalence of PVBs was lower during sexual activity than during other daily activities (Table II)[7,10,13]. Drory et al.[13] compared the prevalence of PVBs during sexual intercourse and near-maximal exercise testing; PVBs were found during sexual intercourse in 56% of patients, compared to 38% at exercise. However, the occurrence or exacerbation of ectopic activity was the dominant pattern in patients with arrhythmia at exercise testing (89%), but the exacerbation was found only in 11% of patients during intercourse. Complex PVBs were detected in 13% of patients during sexual activity and in 9% during effort testing. These data show that in most patients with IHD, PVBs are not exacerbated during sexual intercourse

Table I. Variables determined during sexual activity in patients with ischemic heart disease.

	No./sex	Age (years)	HR (b/min)		SBP (mmHg)	VO_2 (ml/kg/min)	PVBs (% pts)
			Mean	Range			
Hellerstein and Friedman[7], 1970	14 M post-AMI	47	117	90-144		16 (4.5 METs)	21
Jackson[9], 1978	14 M angina	–	122	–			–
Johnston and Fletcher[10], 1979	9 M post-AMI	50	108	86-150			24
Johnston and Fletcher[10], 1979	12 M, 3 F post-revascularization	48	118	92-156			53
Larson et al.[4], 1980	8 M	50	115	–	144		–
Paolillo et al.[11], 1981	71 M post-AMI	49	106	70-170			58
Garcia-Barreto et al.[12], 1986	13 M, 10 F post-AMI	49	110	93-150			5
Drory et al.[13], 1996	88 M IHD	52	118	80-185			56

AMI = acute myocardial infarction; HR = heart rate; IHD = ischemic heart disease; PVBs = premature ventricular beats; SBP = systolic blood pressure; VO_2 = oxygen consumption.

Table II. Prevalence of premature ventricular beats during sexual activity and during other daily activities in patients with ischemic heart disease.

	Sexual activity (% pts)	Other daily activities (% pts)
Hellerstein and Friedman[7], 1970	21	33
Johnston and Fletcher[10], 1979	24	44
Johnston and Fletcher[10], 1979	53	73
Drory et al.[13], 1996	56	43 (effort test)

and ectopic activity is not higher than during other daily activities.

Recently, a case report dealing with a 66-year-old man with previous MI, who underwent cardioverter-defibrillator implantation for ventricular tachycardia has been published; he received appropriate shock therapy from his cardioverter-defibrillator for ventricular tachycardia triggered by sexual intercourse with an extramarital partner[17]. Apart from this case report, we do not have any data on the incidence of ventricular tachycardia during sexual activity.

Nonfatal myocardial infarction. Anecdotal case reports suggest that sexual activity may trigger MI, but the relative risk of MI during sexual intercourse has been investigated only recently, in the Onset study[18]. The relative risks and effect modification have been calculated using the case-crossover method, a new epidemiological technique designed to quantify the transient change in risk following exposure to a potential trigger. In this design, each person served as his or her own control. Data were obtained from 858 sexually active patients, admitted to hospital for MI, who were interviewed in 45 hospitals throughout the United States. Of the 858 patients, 79 (9%) reported sexual activity during the 24 hours preceding MI, and 27 (3%) during the 2 hours preceding the onset of symptoms of MI. The estimate of the relative risk of MI after sexual intercourse was 2.5 (2.7 in males and 1.3 in females). Therefore, the odds that a MI would occur after sexual intercourse was increased 2.5 fold over baseline. This increased risk appeared to be restricted to the 2-hour time period after sexual intercourse. Beyond that time-window, there was no increased risk of MI. Surprisingly, the risk after sexual intercourse was not higher in patients with IHD. In fact, among patients with a prior MI, the relative risk was 2.9, which was similar to that among subjects without such a history (2.5). Among patients with a history of angina, the relative risk that sexual activity triggered MI was 2.1 and was similar to the risk observed among subjects without angina (2.6).

The fact that sexual activity appears to increase the relative risk of MI makes it a biologically plausible cause of this event. However, what is important to the individual person is the absolute increase in the risk of MI due to sexual activity (the risk due to sexual activity minus the risk at all other times). Data from the Framingham Heart Study indicated that the baseline risk that a 50-year-old, nonsmoking, nondiabetic male will experience a MI is approximately 1% per year or approximately 1 chance in 1 million per hour[19,20]. Since the relative risk of MI is approximately doubled by sexual intercourse, by engaging in sexual activity such an individual would only increase his hourly risk to 2 in 1 million, and only for a 2-hour period. Although sexual activity doubles the risk of MI, the effect of this activity on the annual risk is negligible because the absolute risk difference is small, the risk is transient, and the activity is relatively infrequent. For example, for the individual free of cardiac disease described herein, weekly sexual activity would only increase his annual risk of MI from 1 to 1.01%. Even in a person with prior MI and an annual risk of reinfarction or death of 10%, weekly sexual activity would increase his annual risk to only 10.1%[18].

Stroke. Stroke is thought to be very rare during sexual activity but, to our knowledge, no study investigating the incidence of this event has been carried out.

Death. Data on sexual activity provoking death are extremely limited. Ueno[21], a forensic pathologist from Japan, reported that 34 of 5559 cases of sudden death (0.6%) occurred during sexual intercourse and that 18 of these 34 cases had heart disease at autopsy. He also reported that 27 of the 34 cases (79%) were noted to have occurred during extramarital sexual activity. This study suggests a very low incidence of sexual intercourse as a trigger event for sudden death.

A more recent study has been carried out by Parzeller et al.[22]; the epidemiological, retrospective mortality survey was based on the data gathered in the department of forensic medicine in Frankfurt. Over a period of 21 years (1972-1992), roughly 21 000 forensic autopsies revealed 39 cases (0.19%) of natural deaths occurring during sexual activity. Except for 2 women, all of these cases were male patients with an average age of 61 years. The history of 12 of the deceased showed a previous MI. Most of the deaths occurred during or just after sexual intercourse. In most cases (82%), sudden death occurred during extramarital sexual activity. The annual incidence of death during sexual intercourse was estimated to be 0.2/100 000 men. The risk for women was lower by a factor of 12. Both the above-mentioned studies were carried out in selected populations and, at present, the real incidence of death during sexual activity is unknown; however, it appears very low. It must be stressed that most of the deaths occurred during extramarital sexual intercourse. Of interest, with respect to this point, is the possibility of an enhanced sympathetic activity during sexual activity with an extramarital partner. With regard to this, Cantwell[23] noted a higher HR in a single patient, en-

rolled in a cardiac rehabilitation program, during sexual intercourse with an extramarital partner than during sexual intercourse with his spouse. The patient's HR rose form 96 to 150 b/min during intercourse with his girlfriend compared to an increase from 72 to 92 b/min with his wife.

In conclusion, the above-mentioned data on the relationship between sexual intercourse and cardiovascular events allow us to make some practical considerations:

• in patients with IHD the energy requirement of sexual intercourse is quite low (about 4 METs during the orgasmic stage). However, HR, blood pressure and, consequently, oxygen consumption may differ widely among individuals. For this reason, exercise training and beta-blockers reduce oxygen consumption during sexual activity[8,9] and may be prescribed in symptomatic subjects;

• in patients with IHD, the prevalence of PVBs during sexual intercourse is similar to or lower than that observed during other daily activities (walking quickly, bike riding, manual labor). Therefore, from the clinical point of view, sexual activity does not seem to have a relevant arrhythmogenic effect. The incidence of sustained ventricular tachycardia during sexual intercourse is unknown. At present, data on the incidence of PVBs and other ventricular arrhythmias in patients with non-IHD are lacking;

• the relative risk of nonfatal MI during sexual activity is higher in men than in women (2.7 vs 1.3); however, the absolute risk appears extremely low and is similar in normal subjects and in patients with IHD;

• stroke during sexual activity is thought to be very rare, but clear data are lacking;

• the real incidence of death during sexual intercourse is unknown; it appears higher in men than in women; the few available data suggest that it is very low. Extramarital sexual activity seems to increase the risk of death.

Sexual intercourse with the use of sildenafil

Sildenafil, the first of a new class of orally active agents effective for the treatment of ED, is a selective inhibitor of cyclic guanosine monophosphate, a specific type 5 phosphodiesterase, resulting in smooth muscle relaxation, vasodilation and enhanced penile erection[24]; it was originally investigated as an antianginal medication. From the hemodynamic point of view, in normal subjects sildenafil produces a transient modest reduction in systolic (8-10 mmHg) and diastolic (5-6 mmHg) blood pressure, with peak effects evident at 1 hour after the dose and returning to baseline values within 4 hours[25]. No significant effects are observed on HR. Manfroi et al.[26] investigated the hemodynamic effects of sildenafil in 12 patients (age 53 ± 7 years) with chronic stable angina. There were no significant changes in systemic or pulmonary arterial pressures, left ventricular end-diastolic pressure, cardiac output, and systemic or pulmonary vascular resistance. Similar results were reported by Herrmann et al.[27] who investigated the hemodynamic effects of sildenafil on 14 men (age 61 ± 11 years) with severe IHD. The drug produced only a mild decrease (< 10%) in systemic and pulmonary arterial pressures, and it had no effect on pulmonary capillary wedge pressure, right atrial pressure, HR, and cardiac output. There were no significant changes in the average peak coronary flow velocity, coronary artery diameter, and coronary blood flow. The coronary flow reserve was significantly increased by sildenafil ($p < 0.05$). The effects of sildenafil have been investigated also during exercise testing in patients with IHD[28,29]. Arruda-Olson et al.[28], in a randomized, double-blind, placebo-controlled crossover trial including 105 ambulatory patients (age 66 ± 9 years) with ED and IHD, did not observe any significant effects of the drug on symptoms, exercise duration and the presence or extent of exercise-induced ischemia, as assessed at exercise echocardiography. Similar results were reported by Patrizi et al.[29] who investigated, using exercise testing, the effects of sildenafil upon myocardial ischemia in 14 patients (age 52 ± 11 years) with chronic stable angina and on therapy with beta-blockers. These data show that sildenafil does not have any adverse hemodynamic effects with the patient in the supine position and during exercise in subjects with IHD.

Recently, Geelen et al.[30], in 10 isolated guinea pig hearts, have demonstrated that sildenafil, at high plasma concentrations, exerts a direct electrophysiologic effect, similar to that of class III antiarrhythmic agents. In a subsequent study carried out on men with heart failure, sildenafil at the dosage of 50 mg caused no significant changes in the QT and QTc intervals and in QT dispersion[31]; these results suggest that sildenafil, at the dose usually taken for ED, has no direct effect on cardiac repolarization. The effects of sildenafil on the occurrence of cardiac arrhythmias have not been investigated; at present, we do not yet know whether in patients with IHD, the incidence of PVBs during sexual activity varies with or without sildenafil use.

Two cases of ventricular tachycardia occurring during sexual intercourse in males with previous MI and using sildenafil, have been reported in a letter to the Editor[32]; however, it is not possible to determine whether the ventricular tachycardia was facilitated by sildenafil or by the sexual activity *per se* or by both.

Following the approval of sildenafil, from April 1998 to November 1998 the Food and Drug Administration (FDA) included in its website spontaneous reports of death among men who had used the drug[33,34]. The FDA website recorded 130 deaths which were seized upon by the media. Of the 130 reports, 2 patients died as a result of homicide or drowning. The cause of death was unmentioned or unknown for 48 patients and

80 had cardiovascular or cerebrovascular events leading to death (41 a definite or suspected MI, 27 cardiac arrest, 9 cardiac symptoms, and 3 stroke). The age was provided for 104 individuals whose mean age was 64 years (range 29-87 years). Among the cases in which the dose was specified, 3 had taken the 25 mg dose, 46 the 50 mg dose, 9 the 100 mg dose, 2 were prescribed 50-100 mg, 1 took > 100 mg, and 1 took an overdose. Contrary to the recommendations of the drug leaflet, 16 men were either self-medicated or were administered a nitrate or a nitric oxide-donor drug. Three other men were found with nitroglycerin in their possession, but it was not known whether it had been taken.

The time from the use of sildenafil to the reported death was tabulated because sildenafil is taken periodically and the direct effect due to the drug may be limited to a finite period after drug administration. A total of 44 patients (34%) died or had the onset of symptoms leading to death within 4-5 hours of drug use. Six patients died or developed symptoms at least 6 hours after taking sildenafil; 8 patients died the day after, 5 died 2 days after, and 4 patients died 3-4 days after taking the drug. The time from drug ingestion to death or to the onset of symptoms leading to death was not stated or was unknown for 61 patients (48%).

During the observation period, > 6.4 million sildenafil prescriptions have been filled in the United States for > 3.5 million men, which corresponds to a cumulative exposure of approximately 25 million person-weeks since the drug was launched in April 1998. Do these numbers provide a signal that sildenafil is causing an increase in cardiovascular death? When looking at the FDA data, it is important to stress the strong limitations of the spontaneous reporting system, which does not offer any reliable epidemiological data. One might argue that because some of the deaths occurred temporally close to the use of sildenafil (4-5 hours), the drug was causative. However, it is likely that a certain number of these deaths would have occurred during this time, irrespective of the use of sildenafil or sexual activity. In the above mentioned Onset study[18], where the potential of sexual activity to trigger a MI was assessed, about 3% of MIs were associated with sexual activity. However, when a case-crossover technique that takes into account background noise was used, only 0.9% of MIs could be directly attributed to sexual intercourse. Thus, only a certain percentage of the deaths reported to occur during or just after sexual activity in sildenafil users were likely to be related to this activity or to the drug. With regard to this, Piccoli and De Santis[35] reported 2 patients using sildenafil, with no history of heart disease, who suffered from acute myocardial ischemia. However, one patient took the drug 48 hours before the symptoms and for the other, the time from drug ingestion was unknown; therefore, these is no evidence linking sildenafil use to the cardiovascular events.

The issue of whether sildenafil could have adverse effects on cardiovascular outcomes is best determined by placebo-controlled trials. In the phase II/III studies completed before FDA approval, > 3700 patients received sildenafil and almost 2000 received placebo in double-blind and open-label studies[25]. None were taking long-acting nitrates, although patients with IHD were not excluded. Approximately 25% of the patients had hypertension and were taking antihypertensive medications, and 17% were diabetic.

In these studies, the incidence of MI, stroke and death, evaluated during the entire period of treatment, was low and similar in the double-blind sildenafil group and the double-blind placebo group (Table III). In a retrospective analysis of data from all double-blind, placebo-controlled studies, the efficacy and safety of sildenafil were assessed in patients with ED and IHD who were not taking nitrates[36]. Two hundred and thirty-seven patients were on sildenafil and 120 on placebo. The most common serious cardiovascular events during the entire period of treatment were MI (sildenafil, 8 patients [3%]; placebo, 3 patients [3%]) and unstable angina (sildenafil, 5 patients [2%]; placebo, 3 patients [2%]). These results do not show any relationship between sildenafil use and cardiovascular events in patients with IHD.

The hemodynamic effects of sildenafil and those on exercise capacity have been investigated even in patients with heart failure[37,38], of whom about 70% complain of ED[39]. Katz et al.[37] have determined, in 48 men (age 55 ± 3 years) with chronic heart failure and most of whom had IHD, the effects of 25-50 mg of sildenafil on the flow-mediated vasodilation in the brachial artery. The drug increased the endothelium-dependent flow-mediated vasodilation to a greater extent than placebo. Bocchi et al.[38] have studied the effects of 50 mg of sildenafil in 23 patients (age 50 ± 10 years) with heart failure and ED and taking concomitant multiregimen drugs, in a double-blind, randomized, placebo-controlled study. In the first phase, the patients underwent a treadmill 6-min cardiopulmonary walking test followed by a maximal cardiopulmonary exercise test. In the second phase, patients received sildenafil. The drug was tolerated, effective for ED and improved exercise capacity. These data are encouraging, but not strong enough to define sildenafil as safe in patients with episodes of heart failure.

Despite the lack of definitive evidence linking sildenafil use to cardiovascular events, concern about the co-

Table III. Incidence of cardiovascular/cerebrovascular events during the entire period of treatment.

	Sildenafil (n = ~3700)	Placebo (n = ~2000)	p
AMI	1.7/100 patient-years	1.4/100 patient-years	NS
Stroke	0.4/100 patient-years	0.9/100 patient-years	NS
Mortality	0.5/100 patient-years	0.5/100 patient-years	NS

AMI = acute myocardial infarction.

administration of sildenafil in patients taking nitrates prompted the American College of Cardiology (ACC) and the American Heart Association (AHA) to issue an expert consensus document[25]. The document reiterates that sildenafil is absolutely contraindicated in patients who are taking any form of nitrate therapy because of the risk of potentially life-threatening hypotension. Animal studies suggest that the association of sildenafil and nitrates potentially facilitates even the onset of ventricular tachyarrhythmias[40]; nitrates must be stopped at least 24 hours before sildenafil intake. The ACC/AHA document also recommends that sildenafil should be used with caution in patients receiving complicated multidrug antihypertensive regimens, in patients with renal or hepatic dysfunction and in patients taking phosphodiesterase inhibitors or drugs affecting the metabolic clearance of sildenafil (erythromycin, rifampicin, amiodarone, diltiazem, verapamil, theophylline, dipyridamole, pentoxifylline, quinidine, nifedipine, atorvastatin, simvastatin, fluoxetine, imipramine, cimetidine, losartan).

Some patient groups were excluded from sildenafil trials, and no safety data exist on the drug in these groups. As a result, sildenafil should be used with caution in patients with unstable angina or heart failure, patients who have had MI, stroke or life-threatening arrhythmias within the last 6 months and patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/110 mmHg). Similar recommendations have been developed by the Princeton Consensus Panel for the clinical management of ED in patients with cardiovascular disease[41]. In our opinion, sildenafil should be used with caution even in patients with hypertrophic obstructive cardiomyopathy or with aortic stenosis, because of its vasodilatory effect.

In conclusion, because of the lack of any relationship between sildenafil use and cardiovascular events, the drug is not contraindicated in patients with IHD. However, sildenafil should be administered with caution in patients with recent MI or stroke, in those with unstable angina, and in patients with episodes of heart failure. The drug is absolutely contraindicated in patients using nitrates.

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