Journal of Geriatric Cardiology (2020) 17: 169–172

Letter to the Editor · **Open Access** ·

Post-coital death in chronic sildenafil abuser

Stefano D'Errico[1,#], Diana Bonuccelli[2], Margherita Neri[3]

[1]*Department of Medicine, Surgery and Health, University of Trieste, Italy*
[2]*Department of Legal Medicine, Azienda USL Toscana Nordovest, Lucca, Italy*
[3]*Department of Morphology, Experimental Medicine and Surgery, Section of Legal Medicine and LTTA Centre, University of Ferrara, Ferrara, Italy*

J Geriatr Cardiol 2020; 17: 169–172. doi:10.11909/j.issn.1671-5411.2020.03.002

Keywords: Cardiovascular events; Sex; Sildenafil; Sudden death

Sex-related cardiovascular arrest is a rare event occurring typically among middle-aged men with cardiovascular risk.[1,2] The main etiologies of sex-related sudden cardiovascular arrest are acute coronary syndrome and subarachnoid hemorrhage and, to a lesser extent, chronic coronary artery disease and structural non-ischemic heart disease.[3] Coital angina that occurs during the minutes or hours after sexual activity represents < 5% of all anginal attacks and it is rare in patients who do not have angina during strenous physical exertion.[4] Moreover, sexual activity is the cause of < 1% of all acute myocardial infarctions.[5] Sudden death during sexual intercourse is reported with an incidence of 0.6%–1.7%.[6–8] The investigation of sudden death related to sexual activity may be difficult as it may be regarded as shameful or disgraceful to the family members and, especially to the remaining partner. Because of rarity of epidemiological data, considerable bias in the investigation of sudden death related to sexual activity has to be expected.[9–11] Extramarital sexual activity with younger partner and unfamiliar setting seems to represent risk factor as well as excessive food and alcohol consumption.[7]

We present the case of a 66 year man with no history of cardiac problems who suddenly collapsed during sexual intercourse with his spouse. The wife referred he used to take from 50–100 mg oral dose of sildenafil 30–60 min before sex from more than one year. She also referred that during sexual intercourse he complained onset of chest pain and fatigue and that few minutes after coitus collapsed. He was not using any other medicines regularly. A complete post mortem examination was performed the day after death. Pericardial tamponade was immediately recorded with 200 g clot and 200 mL of fluid blood in the pericardial sac. Cervico-thoracic organs were removed en bloc (Ghon) and fixed in 10% buffered formalin. Heart was normal in size (12 × 10.5 × 5.5 cm) with left ventricular hypertrophy (580 g weighed); coronary study according to Baroldi and Fineschi method was unremarkable for critical lumen obstruction. The ascending aorta was enlarged and mildly distended. The outer surface was smooth, glistening and dark brown. On opening, the aorta showed dissection involving ascending and descending portions. The false lumen between the intima and adventitia was filled with a large amount of blood and blood clots. The dissection also extended proximally toward the heart. An intimal tear in the lateral wall of the ascending aorta was recorded, 1.5 cm above the aortic valve. Adventitial rupture site was observed 3.5 cm above leaflets, approximately (Figure 1). White foam on the main bronchi and pulmonary oedema were recorded. Macroscopic examination of abdominal organs was unremarkable, stomach was empty. Cerebral haemorrhage were excluded. Samples of organs and aortic rupture were collected for a complete histopathological study. Microscopically, the dissecting hematoma spread along the laminar planes of the media between the middle and outer thirds, and elastic staining of an aortic wall specimen did not demonstrated cystic medial degeneration. Toxicological examination was performed with GC/MS and confirmed high concentration of sildenafil (7.5 ng/mL) (Figure 2). Acute onset of hemopericardium resulted in cardiac tamponade wich was the main cause of death for patient.

Numerous studies have examined the cardiovascular response to sexual arousal and intercourse, with most assessing male physiological responses during heterosexual vaginal intercourse.[2,12–15] During foreplay, systolic systemic arterial blood pressure and heart rate increase mildly (rarely exceed 170 mmHg and 130 beats/min, respectively), with more modest increases occurring transiently during sexual arousal. The greatest increases occur during the 10 to 15 s of orgasm, with a rapid return to baseline systemic blood pressure and heart rate thereafter. Although sexual activity

[#]**Correspondence to:** sderrico@ospedalesantandrea.it

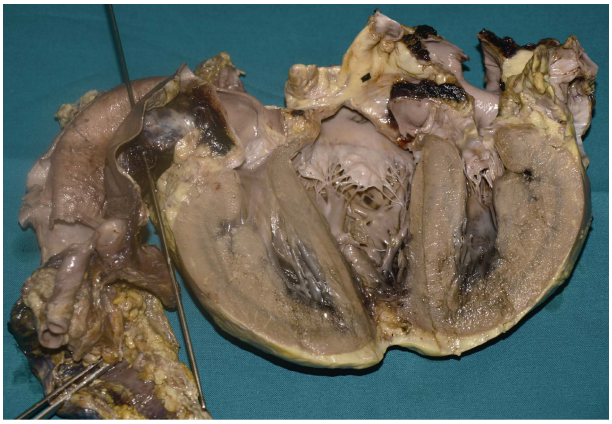

Figure 1. Left ventricular hypertrophy in fixed in formalin heart sectioned according to the "four chambers" method. Enlargement of ascending aorta with dissection involving thoracic aorta and intimal tear in the lateral wall of ascending aorta and adventitial rupture site 3.5 cm above leaflets of aortic valve.

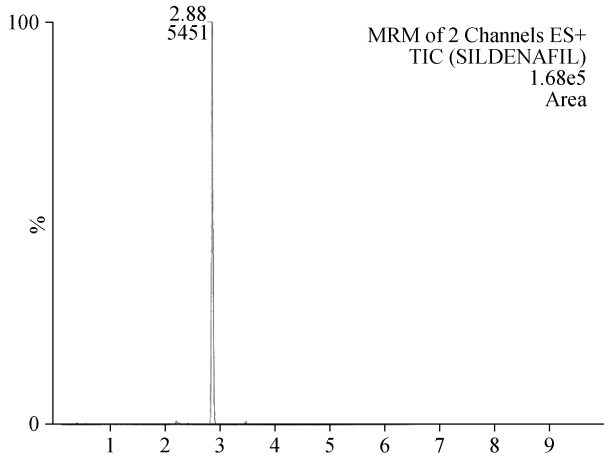

Figure 2. Determination in blood sample of sildenafil with GC-MS.

is associated with an increase risk of cardiovascular events, the absolute rate of events is miniscule because exposure to sexual activity is of short duration, anyway it can cause natural death in individuals with pre-existing illness.[13] Older people for example may have difficulty reaching an orgasm for medical or emotional reasons; in attempting to achieve climax, it is possible that such individuals may exert themselves to a greater degree of exhaustion with relatively greater demand on their cardiovascular system.[16] Natural deaths connected with sexual activity appear to be associated with male sex and preexisting cardiovascular disorders. The annual incidence of sudden cardiovascular death during sexual activity is estimated to be 1.9 per 1000 autopsies for men and 0.16 per 1000 autopsies for women.[3,6,15] Most cases recorded occurred with mistresses, prostitutes or during masturbation.

The main etiologies of sex-related sudden death are acute coronary syndrome and subarachnoid hemorrhage and, to a lesser extent, chronic coronary artery disease and structural non ischemic heart disease.[3]

Although transient hemodynamic changes associated with sexual activity seem to play some role in the pathogenesis of subarachnoid haemorrhage, the mechanism of physical activity induced subarachnoid haemorrhage is still not completely understood.[17–22] Aortic dissection during sexual intercourse has been described occasionally.[23]

In recent discussions about potency-enhancing drugs such as sildenafil, health hazards associated with sexual activity have attracted increased attention. [24–26] Sildenafil citrate is a useful tool for the treatment of erectile dysfunction because it selectively inhibits phosphodiesterase type 5 (PDE-5), wich inactivates cyclic guanine monophosphate (cGMP), the mediator of smooth muscle relaxation in the corpus cavernosum.[27] By selectively inhibiting cGMP catabolism in cavernosal smooth cells, sildenafil citrate can restore the natural erectile response to sexual stimulation without causing erections in the absence of such stimulation. Sildenafil is relatively short acting, maximal plasma concentrations occurr within 1 h after oral administration and with half-life of approximately 3–5 h. Concern about adverse cardiovascular effects of sildenafil are related tovasodilatative effect inducing hypotension in patients with cardiovascular disease. It has been demonstrated that a single oral dose of sildenafil citrate had no significant hemodynamic effects in supine patients with stable angina.[28]

Several studies examining the effects of sildenafil on mortality have been published during recent years. Despite occasional anectodal case reports linking sildenafil to cardiac events, large trials and meta-analyses suggest that sildenafil is not an extra risk factor for serious cardiovascular events or sudden cardiac death.[29]

Typically, the adverse effects reported in patients from clinical trials of sildenafil have been mild to moderate and commonly include nausea, flushing and dyspepsia in addition to transient visual disturbances.[30,31]

Studies have reported the increased to misuse of un-prescribed sildenafil for enhancing sexual performance among college going males, night clubbers and illicit drug users. Due its extensive use by the club going people as a recreational agent, it has also earned itself the dubious status of a club drug. It is used along with different recreational agents like cocaine, amphetamine, marijuana, steroids etc, which

only further increases the risk of side effects. Increasing access to these drugs via the internet may facilitate such misuse. Misuse of sildenafil can have many adverse consequences. There have been case reports of aortic dissection resulting from sildenafil misuse. One case report described a type B dissection after the use of cocaine and sildenafil and an other type A aortic dissection in a patient who was using sildenafil without any prescriptions and with pre-existing heart disease.[32–35] Tyryakioglu, *et al*.[33] highlight that sildenafil abuse, independent of changes in the aorta pressure, can trigger an aortic dissection. A sildenafil-related decreasing effect on aortic stiffness in humans was postulated triggering intimal tearing on the base on the results of *in vitro* study on pulmonary aorta of rats with an antiproliferative effect on vascular smooths cells.[36,37]

Finally, a significant body of evidence now indicates that sildenafil generally has a good safety profile in men with erectile dysfunction and cardiovascular disease. Sildenafil therapy does not appear to be associated with ischemic events and it does not interact in a potentially hazardous way with antihypertensive or antianginal therapy, with the exception of nitrates.[38,39] It may be speculated though that chronic sildenafil use induces some changes in the aortic wall that ultimately makes dissection a possibility, nevertheless, until more evidence is accumulated, it appears the role of sildenafil in the causation of aortic dissection shall remain speculative.[40]

In the presented case, pathophysiology of the dissection during coitus was probably related to the well-recognized increases in blood pressure seen during vigorous exercise. Autopsy was important to exclude other cause of death and histopathological abnormalities of aortic wall. Cardiac concentric hypertrophy of the left ventricle was also documented as possibly related to aortic dissection. Despite dissection occurs in the peak plasma concentration time of sildenafil, its role as a trigger for the dissection was excluded.

References

1 Marijon E, Uy-Evanado A, Reinier K, *et al*. Sudden cardiac arrest during sports activity in middle age. *Circulation* 2015; 131: 1384–1391.

2 Levine GN, Steinke EE, Bakaeen FG, *et al*. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2012; 125: 1058–1072.

3 Parzeller M, Bux R, Raschka C, *et al*. Sudden cardiovascular death associated with sexual activity: a forensic autopsy study (1972–2004). *Forensic Sci Med Pathol* 2006; 2: 109–114.

4 DeBusk RF. Sexual activity in patients with angina. *JAMA* 2003; 290: 3129–3132.

5 Muller JE, Mittleman MA, Maclure M, *et al*. Determinants of myocardial infarction by sexual activity: low absolute risk and prevention by regular physical exertion. *JAMA* 1996; 275: 1405–1409.

6 Parzeller M, Raschka C, Bratzke H. Sudden cardiovascular death during sexual intercourse. Results of a legal medicine autopsy study. *Z Cardiol* 1999; 88: 44–48.

7 Lee S, Chae J, Cho Y. Causes of sudden death related to sexual activity: results of a medicolegal postmortem study from 2001 to 2005. *J Korean Med Sci* 2006; 21: 995–999.

8 Ueno M. The so-called coition death. *Jpn J Legal Med* 1963; 127: 333–340.

9 Sharifzadehgan A, Marijon E, Bougouin W, *et al*. Sudden cardiovascular arrest during sexual intercourse. *Circulation* 2018; 137: 1638–1640.

10 Aro AL, Rusinaru C, Uy-Evanado A, *et al*. Sexual activity as a trigger for sudden cardiac arrest. *J Am Coll Cardiol* 2017; 70: 2599–2600.

11 Lange L, Zedler B, Verhoff MA, *et al*. Love death—A retrospective and prospective follow up mortality study over 45 years. *J Sex Med* 2017; 14: 1226–1231.

12 Chen X, Zhang Q, Than X. Cardiovascular effects of sexual activity. *Indian J Med Res* 2009; 130: 681–688.

13 Exton MS, Bindert A, Kruger T, *et al*. Cardiovascular and endocrine alterations after masturbation-induced orgasm in women. *Psychosom Med* 1999; 61: 280–289.

14 Stein RA. Cardiovascular response to sexual activity. *Am J Cardiol* 2000; 86: 27F–29F.

15 Braun CT, Ricklin ME, Pauli A, *et al*. Death after sexual intercourse. *Case Rep Emerg Med* 2015; 2015: 646438.

16 Lindau ST, Schumm LP, Laumann EO, *et al*. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007; 357: 762–774.

17 Pfortmueller CA, Schankath AC, Mordasini P, *et al*. Radiological findings of sexual intercourse related emergency department admissions: a first overview. *PLoS One* 2014; 9: e104170.

18 Portunato F, Landolfa MC, Botto A, *et al*. Fatal subarachnoid hemorrhage during sexual activity: a case report. *Am J Forensic Med Pathol* 2012; 33: 90–92.

19 Valenca MM, Valenca LPAA, Bordini CA, *et al*. Cerebral vasospasm and headache during sexual intercourse and masturbatory orgasms. *Headache* 2004; 44: 244–248.

20 Reynolds MR, Willie JT, Zipfel GJ, *et al*. Sexual intercourse and cerebral aneurysmal rupture: potential mechanisms and precipitants. *J. Neurosurg* 2011; 114: 969–977.

21 Anderson C, Ni Mhurchu C, Scott D, *et al*. Triggers of subarachnoid hemorrhage: role of physical exertion, smoking and alcohol in the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke* 2003; 34: 1771–1776.

22 Gonsoulin M, Barnard JJ, Prahlow JA. Death resulting from ruptured cerebral artery aneurysm: 219 cases. *Am J Forensic Med Pathol* 2002; 23: 5–14.

23 Gansera L, Deutsch O, Szameitat L, *et al*. Aortic dissection type A during sexual intercourse in male patients: accident or

systematic coincidence? Examination of 365 patients with acute aortic dissection within 20 years. *Thorac Cardiovasc Surg* 2016; 64: 133–136.
24 Kontaras K, Varnavas V, Kyriakides ZS. Does sildenafil cause myocardial infarction or sudden cardiac death? *Am J Cardiovasc Drugs* 2008; 8:1–7.
25 Padma-Nathan H, Eardley I, Kloner RA, *et al*. A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; 60: 67–90.
26 Carson III CC. Sildenafil: a 4-years update in the treatment of 20 million erectile dysfunction patients. *Curr Urol Rep* 2003; 4: 488–496.
27 Goldstein I, Lue TF, Padma-Nathan H, *et al*. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *New Engl J Med* 1998; 338: 1397–1404.
28 Manfroi WC, Caramori PR, Zago AJ, *et al*. Hemodynamic effects of sildenafil in patients with stable ischemic heart disease. *Int J Cardiol* 2003; 90: 153–157.
29 Kloner RA. Cardiovascular risk and sildenafil. *Am J Cardiol* 2000; 86: 57F-61F.
30 Boshier A, Wilton LV, Shakir SAW. Evaluation of the safety of sildenafil for male erectile dysfunction: experience gained in general practice use in England in 1999. *BJU Int* 2004; 93: 796–801.
31 Hatzichristou DG. Sildenafil citrate. Lessons learned from 3 years of clinical experience. *Int. J Impot Res* 2001; 13: 261–267.
32 Famularo G, Polchi S, Di Bona G, *et al*. Acute aortic dissection after cocaine and sildenafil abuse. *J Emerg Med* 2001; 21: 78–79.
33 Tiryakioglu SK, Tiryakioglu O, Turan T, *et al*. Aortic dissection due to sildenafil abuse. *Interact Cardiovasc Thorac Surg* 2009; 9: 141–143.
34 Lamejer CM, Tielliu IFJ, van Driel MF, *et al*. Type B aortic dissection after the use of Tadalafil. *Ann Thorac Surg* 2012; 93: 651–653.
35 Nachtnebel A, Stollberger C, Ehrlich M, *et al*. *Aortic dissection and related syndromes*; Baliga R, Nienaber C, Isselbacher EM, Eagle KA, Eds; Springer: Germany, 2007; 260:17–43.
36 Sharabi FM, Daabees TT, El-Metwally MA, *et al*. Effect of sildenafil on the isolated rat aortic rings. *Fund Clin Pharmacol* 2005; 19: 449–456.
37 Tantini B, Manes A, Fiumana E, *et al*. Antiproliferative effect of sildenafil on human pulmonary artery smooth muscle cells. *Basic Res Cardiol* 2005; 100: 131–138.
38 Huber BC, von Xiegler F, Bamberg F, *et al*. Cardiac arrest associated with sildenafil ingestion in a patient with an abnormal origin of the left coronary artery: a casa report. *BMC Cardiovasc Dis* 2011; 11: 49–51.
39 Brindis RG, Kloner RA. Sildenafil in patients with cardiovascular disease. *Am J Cardiol* 2003; 92: 26M–36M.
40 Edwin F, Tettey MM, Frimpong-Boateng K. Ecomment: acute aortic dissection in children and young adults—the role of sildenafil. *Interact Cardiovasc Thorac Surg* 2009; 9: 143.