ORIGINAL ARTICLE

Acute effect of sildenafil on myocardial ischemic territories in patients with stable coronary artery disease

Mohamed Salem *, **Ahmed Bendary, Shaimaa Moustafa, Ahmed Ramzy, Osama Sanad**

Department of Cardiology, Benha Faculty of Medicine, Benha University, Benha, Egypt

Abstract *Objectives:* To test the safety of sildenafil in patients with stable coronary artery disease (CAD).

Methods: Sixty-one patients with stable CAD, documented by coronary angiography were included in this phase I study. Patients were randomized to either single dose sildenafil or matched placebo. Speckle tracking echocardiography was done at baseline and 60 min after sildenafil/placebo intake to calculate peak systolic strain (PSS) of the most severely affected myocardial segments and the global longitudinal PSS.

Results: The baseline mean segmental PSS in the sildenafil group changed by 52%, $-3 \pm 1\%$ at baseline versus $-7 \pm 2\%$ after sildenafil intake, $P = 0.01$. However, no significant changes were reported in the placebo group, $-7 \pm 3\%$ at baseline versus $-7.25 \pm 3\%$, $P = 0.1$. The baseline mean global longitudinal PSS in the sildenafil group changed by 9% ($-15 \pm 4\%$ at baseline versus $-18 \pm 3\%$ after sildenafil, $P = 0.03$). In placebo patients, the change was only 3% from baseline ($-14.8 \pm 2\%$ at baseline compared to $-15 \pm 2\%$ after placebo intake, $P = 0.1$). Sildenafil was well tolerated without clinical or hemodynamic deterioration after its intake.

Conclusion: Sildenafil intake is safe in patients with stable CAD, it induced marginal improvements in the peak systolic strain of different myocardial ischemic territories.

© 2013 Production and hosting by Elsevier B.V. on behalf of Egyptian Society of Cardiology.

1. Introduction

Sildenafil citrate is a potent orally active phosphodiesterase type 5 inhibitor that is effective in the treatment of male erectile dysfunction of organic, psychogenic or mixed etiologies and significantly improves rates of successful sexual intercourse in men with erectile dysfunction.[1] However, postmarketing surveillance data after approval of sildenafil by

* Corresponding author. Tel.: +20 133106725; mobile: +20 1092773227.

E-mail address: masalem@yahoo.com (M. Salem).

Peer review under responsibility of Egyptian Society of Cardiology.

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. Although it has been suggested that these events were not unexpected given the characteristics of the population who were prescribed sildenafil, the issue which needs explanation is that many of these events occurred only shortly after ingestion of the drug and before any attempt at the sexual activity.[2] However, it is not possible to determine whether these events were directly related to the use of sildenafil, the patient's underlying cardiovascular risk, or a combination of these and other factors such as 'coronary steal'. Since phosphodiesterase is also present in vascular smooth muscle, it is hypothesized that if sildenafil had any direct cardiovascular effect, it could be best detected by measuring the effects of this drug in those with CAD.[3] Left ventricular longitudinal mechanics at rest are attenuated in patients with CAD, this means that measuring speckle tracking-derived longitudinal strain may be an useful tool in predicting the extent of CAD.[4] In this study we tested the safety of single dose sildenafil in patients with chronic stable angina.

2. Patients and methods

2.1. Study design

This study included 61 consecutive patients with stable CAD who were randomly allocated into a randomized placebo-controlled phase-I study (2:1 randomization) to either sildenafil or a matched placebo. We aimed to study the acute effect of a single dose sildenafil on myocardial ischemic territories. The study was done at the cardiology department, Benha University Hospital, Benha, Egypt in the period from December 2011 to December 2012. All patients signed an informed consent. Key inclusion criteria were: patients with age range 40–70 years, who have chronic stable angina documented by coronary angiography with affection of at least one of the main epicardial coronary arteries (including the LAD artery). Key exclusion criteria were: previous myocardial infarction, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG) operation, left main disease or single-vessel left circumflex (LCX) or single-vessel right coronary artery (RCA) disease, contraindication to sildenafil such as stenotic valvular lesions, and patient refusal.

2.2. Study protocol

Oral nitrates were discontinued 24 h before the study[5]; other medications such as antiplatelets and statins were continued as clinically indicated.

According to randomization, patients were classified into 2 groups: group-I (41 patients): were given sildenafil; 50 mg orally, once, and group-II (20 patients): were given placebo (paracetamol 500 mg), once. Conventional and speckle tracking echocardiographic measurements were done at baseline, and 60 min after sildenafil or placebo intake. Patients were randomized using simple randomization (closed envelope method) and they were blinded to randomization. The study analysis was done by an independent investigator who was blinded to study randomization.

2.3. Baseline and 60 min evaluation

All patients had review of medical history, general (heart rate and systemic blood pressure) and local cardiac examination, routine laboratory work-up, twelve-lead surface ECG at baseline and after sildenafil/placebo intake, analysis of coronary angiograms to classify them as having single, double, or three-vessel disease using CASS definitions of CAD[6] and finally echocardiographic examination at baseline and after sildenafil/placebo intake in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric-Vingmed)®. Images were obtained with a simultaneous ECG signal.

2.3.1. Conventional echocardiography

Two dimensional images were acquired during breath hold and saved in cine-loop format from three consecutive beats. The biplane Simpson's technique was used to calculate LV end-systolic volume (ESV), LV end-diastolic volume (EDV), and LVEF. M-mode echo was used for the measurement of the left ventricular dimension in systole (LVIDs), and diastole (LVIDd), interventricular septum (IVSd and IVSs), posterior wall thickness (PWTd and PWTs), and LVEF. Pulmonary artery systolic pressure (PASP) was estimated by the maximum velocity over the tricuspid regurgitant jet using the modified Bernoulli equation and then adding to this value an estimated right atrial pressure.[7]

2.3.2. Speckle tracking echocardiography

Apical four- and two-chamber views as well as long-axis views were used for quantification of peak systolic strain by automated function imaging speckle-tracking analysis. This novel software analyses the motion by tracking frame-to-frame movement of natural acoustic markers on standard ultrasonic images in two dimensions. First, the LV end-systolic frame was defined by determining the closure of the aortic valve in the apical long-axis view. Then the time interval between R-wave and aortic valve closure was automatically measured and used as a reference for the four- and two-chamber views. After defining the mitral annulus and LV apex with three index points in all three apical views, the LV endocardial border was automatically traced at end-systole and the created region of interest manually adjusted to the thickness of the myocardium. Tracking quality was then validated in all segments from the three apical views. Finally, when all the 3 views have been processed i.e. apical 2-chamber, apical 4-chamber and apical long-axis views, the results were integrated and were shown as a single 'bull's eye' display with colorization according to the peak systolic strain for each segment (range from red i.e. better to blue i.e. worse) and this has been displayed as a numerical value for each segment (normal cut-level range is from −15% to −20% with positive numeric values representing dyskinetic segments), also, the global longitudinal peak systolic strain for the complete LV was provided by the software using the same 17-segment model in a 'bull's eye' plot calculated as the average of longitudinal peak systolic strain of each view.[8]

3. Statistical analysis

Data were presented as mean ± SD for continuous data and as number (%) for qualitative ones. Student's t test was used for between group analysis of continuous data, while the Chi-Square test was used for categorical data. Level of evidence < 0.05 was considered statistically significant. SPSS version 20, was used for data analysis.

4. Results

4.1. Study population

The mean age was 56 ± 8 years (range from 40 to 70 years). Seventy-four percent were males, 30% were hypertensives, 23% had history of diabetes mellitus (DM), 57% were smokers, 15% were obese, and 8% had family history of CAD. Between group analysis showed a statistically significant difference between the sildenafil group and placebo group in the prevalence of hypertension (32% versus 25% in sildenafil and placebo groups respectively, $P = 0.018$), DM (27% versus 15% in sildenafil and placebo groups respectively, $P = 0.004$), smoking (66% versus 40% in sildenafil and placebo groups respectively, $P = 0.001$), obesity (17% versus 10% in sildenafil and placebo groups respectively, $P = 0.023$) and family history of CAD (10% versus 5% in sildenafil and placebo groups respectively, $P = 0.047$) Table 1. Thirty percent of study population had single vessel LAD disease, 23% had 2-vessel (LAD + LCX) disease, 25% had 2-vessel (LAD + RCA) disease and 23% had 3-vessel disease. Between group analysis showed a statistically significant difference regarding the prevalence of 2-vessel (LAD + LCX) disease (7% versus 55% in sildenafil and placebo groups respectively, $P = 0.001$) and prevalence of 3-vessel disease (32% versus 5% in sildenafil and placebo groups respectively, $P = 0.02$). There was no statistically significant difference between groups in prevalence of single vessel LAD disease (32% versus 25% in sildenafil and placebo groups respectively, $P = 0.6$) and prevalence of 2-vessel (LAD + RCA) disease (29% versus 15% in sildenafil and placebo groups respectively, $P = 0.3$).

4.2. Hemodynamic data

The mean baseline heart rate (HR) was 75 ± 11.4 bpm (76 ± 11, 72 ± 10 bpm in sildenafil and placebo groups respectively, $P = 0.04$). One hour after sildenafil/placebo intake, the mean HR was 77 ± 10 bpm (80 ± 10, 72 ± 8 bpm in sildenafil and placebo groups respectively, $P = 0.03$). Within group analysis did not show any significant change in HR in the placebo group. However, HR significantly increased in the sildenafil group from baseline to 60 min (76 ± 11 versus 80 ± 10 bpm, $P = 0.03$). The mean baseline systolic blood pressure (SBP) was 124 ± 12 mmHg (124 ± 13, 126 ± 8 mmHg in sildenafil and placebo groups respectively, $P = 0.1$). One hour after sildenafil/placebo intake, the mean SBP was 120 ± 14 mmHg (115 ± 13, 127 ± 12.5 mmHg in sildenafil and placebo groups respectively, $P = 0.02$). Within group analysis did not show any significant change in SBP in the placebo group. However, SBP showed significant reduction in the sildenafil group from baseline to 60 min (124 ± 13 versus 115 ± 13 mmHg, $P = 0.01$). The mean baseline diastolic BP (DBP) was 78 ± 9 mmHg (78 ± 10, 79 ± 6 mmHg in sildenafil and placebo groups respectively, $P = 0.09$). One hour after sildenafil/placebo intake, the mean DBP was 76 ± 10 mmHg (71 ± 11, 79 ± 7 mmHg in sildenafil and placebo groups respectively, $P = 0.03$). Within group analysis did not show any significant change in DBP in the placebo group. However, DBP showed significant reduction in the sildenafil group from baseline to 60 min (78 ± 10 versus 71 ± 11 mmHg, $P = 0.03$).

4.3. Adverse events after sildenafil intake

Twenty-six patients (64%) were symptom free after sildenafil intake. Five patients (12%) reported dizziness, while five patients (12%) reported flushing. Two patients (5%) complained of mild nonspecific chest discomfort. Three patients (7%) developed a sense of palpitation. All the above mentioned symptoms were transient and do not need any intervention.

4.4. Echocardiographic data

4.4.1. Conventional echocardiography

The mean baseline LVEF was 55 ± 10% (52 ± 10%, 60 ± 12% in sildenafil and placebo groups respectively, $P = 0.008$). The mean baseline PASP was 31 ± 11 mmHg (31 ± 13, 31 ± 10 mmHg in sildenafil and placebo groups respectively, $P = 0.2$). One hour after sildenafil/placebo intake, the mean PASP was 29 ± 10.7 mmHg (29 ± 11, 30 ± 11 mmHg in sildenafil and placebo groups respectively, $P = 0.03$). Within group analysis did not show any significant change in PASP in the placebo group. However, PASP showed significant reduction in the sildenafil group from baseline to 60 min (31 ± 13 versus 29 ± 11 mmHg, $P = 0.01$).

Table 1 Baseline characteristics.

Variable	All patients $n = 61$	Sildenafil $n = 41$	Placebo $n = 20$	P value
Age (years) mean ± SD	56 ± 8	54.0 ± 6	57 ± 8	0.081
Male sex, n (%)	45 (74%)	30 (73%)	15 (75%)	0.88
Hypertension	18 (30%)	13 (32%)	5 (25%)	0.018
DM	14 (23%)	11 (27%)	3 (15%)	0.004
Smoking	35 (57%)	27 (66%)	8 (40%)	0.001
Obesity	9 (15%)	7 (17%)	2 (10%)	0.023
Family history of premature CAD	5 (8%)	4 (10%)	1 (5%)	0.047

DM = diabetes mellitus, CAD = coronary artery disease.

4.4.2. Speckle tracking echocardiography

The mean baseline segmental PSS was −5 ± 2% (−3 ± 1%, −7 ± 3% in sildenafil and placebo groups respectively, $P = 0.02$). One hour after sildenafil/placebo intake, the mean segmental PSS was −7 ± 7% (−7 ± 2%, −7 ± 3% in sildenafil and placebo groups respectively, $P = 0.1$). Within group analysis showed that mean segmental PSS changed by 52% (mean delta change) from baseline in the sildenafil group (−3 ± 1%, −7 ± 2% at baseline and one hour after sildenafil use respectively, $P = 0.01$). However, in the placebo group, mean segmental PSS changed by only 4% from baseline (−7 ± 31%, −7.25 ± 3% at baseline and one hour after placebo use respectively, $P = 0.1$), Fig. 1. The mean baseline global longitudinal PSS was −14 ± 6% (−15 ± 4%, −15 ± 2% in sildenafil and placebo groups respectively, $P = 0.1$). One hour after sildenafil/placebo intake, the mean global PSS was −16 ± 3% (−18 ± 3%, −15 ± 2% in sildenafil and placebo groups respectively, $P = 0.04$). Within group analysis showed that mean global PSS changed by 9% from baseline in the sildenafil group (−15 ± 4%, −18 ± 3% at baseline and one hour after sildenafil use respectively, $P = 0.03$). However, in the placebo group, the mean global PSS changed only by 3% from baseline (−14.8 ± 2.1%, −15.2 ± 2.2% at baseline and one hour after placebo use respectively, $P = 0.1$) (Figs. 2 and 3).

4.5. Subgroup analysis

4.5.1. Different angiographic subgroups

It was found that both mean segmental and mean global longitudinal PSS showed improvements among all angiographic subgroups with the exception of the group with 2-vessel disease (LAD + LCX) where both mean segmental and mean global PSS showed deterioration (−8 ± 3% versus −1 ± 8%, $P = 0.02$ for segmental PSS, and −18 ± 6% versus −17 ± 4%, $P = 0.03$ for global PSS).

4.5.2. Different demographic and risk factor subgroups

It was found that both mean segmental and mean global longitudinal PSS showed improvements among all subgroups, even among female patients. However, the group with DM, both mean segmental and mean global PSS showed deterioration (from −8 ± 5% to +2 ± 5%, $P = 0.001$ for segmental PSS and from −19 ± 3% to −18 ± 2%, $P = 0.2$ for global PSS).
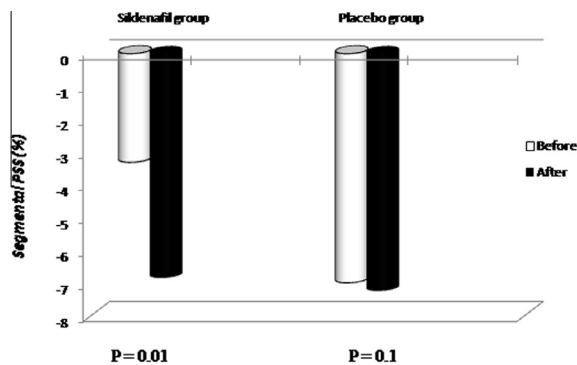

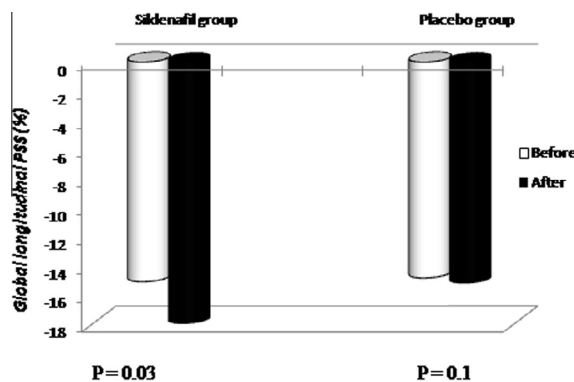**Figure 1** Segmental PSS before and after sildenafil/placebo.

Figure 2 Global longitudinal PSS before and after sildenafil/ placebo.

4.6. Predictors for changes in PSS

Logistic regression analysis has been done using changes in PSS (segmental and global) from baseline as a dependant factor, while sildenafil intake, demographic data, risk factors, number of diseased coronaries and left ventricular ejection fraction (LVEF) were used as independent factors. It was found that significant independent predictors for changes in PSS are: sildenafil intake (for segmental PSS only), DM (for segmental PSS only), presence of 2-vessel (LAD + LCX) disease (for both segmental and global PSS) and LVEF less than 50% (for both segmental and global PSS) Table 2.

5. Discussion

With the development of phosphodiesterase-5 inhibitors, the first of which was sildenafil, the question of safety of these drugs, especially in patients with latent or overt CAD, became a concern. The most recent AHA guidelines state that PDE-5 inhibitors are useful for the treatment of erectile dysfunction in patients with stable cardiovascular disease (class-I, level of evidence A).[9] In the present study, sildenafil did not cause hemodynamic deterioration, and induced improvements in PSS of ischemic segments among all study subgroups with the exception of diabetics and patients with 2-vessel disease (LAD + LCX).

To our knowledge, this is the first study to be done using such a protocol and the previous clinical experience in this situation is very limited. However, few studies had examined the effect of sildenafil (especially the acute effect) in patients with CAD using different non-invasive and invasive assessment methods (other than speckle tracking echocardiography).

The earliest other clinical experiences in the domain of sildenafil effect on coronaries were started by Herrmann et al.[5] who assessed the systemic, pulmonary, and coronary hemodynamic effects (using Doppler wire) of oral sildenafil (100 mg) in 14 men with severe stenosis of at least one coronary artery. They found that there were no significant changes in average peak coronary flow velocity, coronary–artery diameter, or coronary vascular resistance in response to sildenafil. Adelaide et al.[10] conducted a randomized, double-blind, placebo-controlled cross over trial among 105 men with CAD. All subjects underwent 2 symptom-limited supine bicycle echocardiograms
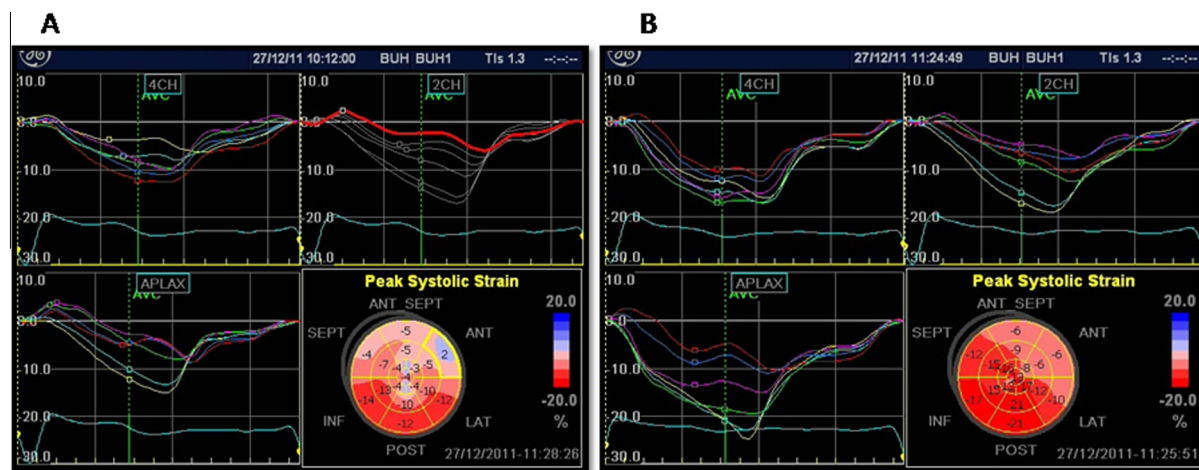
Figure 3 Echocardiographic illustration showing changes in PSS from baseline (A) to 1 h after sildenafil intake (B).

Table 2 Predictors of changes in PSS.

		Odds ratio, 95% CI	*P* value
Sildenafil intake	Segmental PSS	3.23 (1.064–9.807)	0.03
	Global PSS	0.9 (0.1–4.2)	0.2
Male gender	Segmental PSS	1.33 (0.3–5.7)	0.1
	Global PSS	1.2 (0.3–5.1)	0.2
Diabetes	Segmental PSS	15 (3.9–57.3)	0.001
	Global PSS	0.94 (0.3–3.8)	0.2
Hypertension	Segmental PSS	1.07 (0.26–4.4)	0.2
	Global PSS	1.2 (0.3–4.6)	0.1
Smoking	Segmental PSS	0.8 (0.2–3.3)	0.2
	Global PSS	1.09 (0.2–4.1)	0.1
Obesity	Segmental PSS	1.2 (0.2–7.1)	0.1
	Global PSS	0.93 (0.18–4.3)	0.2
Single vessel LAD disease	Segmental PSS	0.93 (0.22–3.8)	0.1
	Global PSS	1.3 (0.35–5.1)	0.08
Two vessel (LAD + LCX) disease	Segmental PSS	4.9 (0.9–59.8)	0.02
	Global PSS	3.1 (0.25–36)	0.03
Two vessel (LAD + RCA) disease	Segmental PSS	0.88 (0.13–2.8)	0.2
	Global PSS	0.81 (0.15–2.6)	0.3
Three vessel disease	Segmental PSS	0.83 (0.24–4.1)	0.1
	Global PSS	0.93 (0.21–3.1)	0.08
LVEF < 50%	Segmental PSS	1.6 (0.4–6.8)	0.04
	Global PSS	2.03 (0.5–7.5)	0.03

separated by an interval of 1–3 days after receiving a single dose of sildenafil (50 or 100 mg) or placebo 1 h before each exercise test. Exercise capacity was similar with sildenafil use and placebo use. Exercise heart rate and blood pressure increments were similar in both groups. Dyspnea or angina developed in 69 patients who took sildenafil and 70 patients who took placebo. Halcox et al.[11] carried out a trial to study the effect of sildenafil on coronary and peripheral vascular function, platelet activation, and myocardial ischemia. The effect of oral sildenafil on resting coronary vascular tone (measured by acetylcholine and cold-pressor testing), endothelium-dependent and independent function and platelet activation (measured by platelet flow cytometry) was measured in 24 patients. They concluded that sildenafil dilates epicardial coronary arteries,

improves endothelial dysfunction and inhibits platelet activation in patients with CAD.

The present study has not used any method to induce myocardial ischemia; all parameters were measured at rest. This is in contrast to Herrmann et al.[5] (who used intracoronary adenosine for induction of hyperemia) and Adelaide et al.[10] (who used exercise to induce myocardial ischemia). The present study enrolled 16 female patients among the tested population, this is in contrast to others[5,10] who enrolled only male patients. The present study interestingly showed the fact that the worse is the PSS in female subjects at baseline, the greater is the improvement in its value after sildenafil use. This may open the way to further investigate such a result, and also asks a new question beyond the safety profile of the drug in

men with CAD; could sildenafil, one day, be prescribed as a therapeutic modality for those patients?

Regarding the non-invasive assessment of acute hemodynamic responses (i.e. heart rate, systolic and diastolic blood pressures) to sildenafil at rest, the results of the current study were concordant with Adelaide et al.[10] in the fact that no major hemodynamic deterioration occurred at rest in response to sildenafil. Taking into consideration that sildenafil did not significantly change the average peak coronary flow velocity (measured by means of Doppler wire) in Herrmann et al.[5] one could expect that PSS of the corresponding ischemic myocardial segments (measured by speckle tracking) would not deteriorate after sildenafil intake. This was actually the case in all subgroups in the current study that showed marginal changes in PSS after sildenafil use. However, the fact that patients with DM were the only demographic group that showed marked and statistically significant deterioration in segmental PSS after sildenafil use is worth mentioning. No studies, to our knowledge, have investigated this issue but it could be explained presumptively on the basis of 'coronary steal phenomenon' secondary to affection of the development of coronary collateral vessels by the diabetic syndrome.[12]

6. Conclusion

Our data suggest that sildenafil could be considered safe for treatment of erectile dysfunction in men with stable CAD; it induced improvements in the peak systolic strain of different myocardial ischemic territories in patients with angiographically documented disease who have chronic stable angina. The drug is well tolerated acutely with minimal side effects.

7. Study limitation

(1) Small sample size.
(2) All parameters were measured at rest.
(3) Radial and circumferential strains were not measured.
(4) Regional wall motion abnormalities before and after sildenafil were not measured.
(5) The predictive value of the lesion severity on strain was not measured.

Conflict of interest

We confirm that authors have no conflict of interest.

References

1. Rosenberg K. Sildenafil citrate for SSRI-induced sexual side effects. *Am J Psychiatry* 1999;**27**:156–7.
2. Wysowski D, Farinas E, Swartz L. Comparison of reported and expected deaths in sildenafil (Viagra) users. *Am J Cardiol* 2002;**89**(11):1331–4.
3. Kekilli M, Beyazit Y, Purnak T, Dogan S, Atalar E. Acute myocardial infarction after sildenafil citrate ingestion. *Ann Pharmacother* 2005;**39**:1362–4.
4. Liang H, Cauduro S, Pellikka P, Wang J, Urheim S, Yang E, et al. Usefulness of two-dimensional speckle strain for evaluation of left ventricular diastolic deformation in patients with coronary artery disease. *Am J Cardiol* 2006;**98**:1581–6.
5. Herrmann H, Chang G, Bruce D, Mahoney P. Hemodynamic effect of sildenafil in men with severe coronary artery disease. *NEJM* 2000;**342**:1622–32.
6. Bernard R, Lioyd D, Martial G, Davis K, Rogers W, Maynard C, et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease: report of the collaborative study in coronary artery surgery (CASS). *Am J Cardiol* 1981;**48**:765–77.
7. Topol E, Brian P, Deepu N, Califf R, Prystowisky E, Kellan A, et al. Chronic stable coronary disease. In: Topol J, editor. *Textbook of cardiovascular medicine, 3rd ed.*, 17. Cleveland: Lippincott Williams & Wilkins; 2007. p. 228–49.
8. Geyer H, Caracciolo G, Abe H, Welansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010;**23**:351–69.
9. Levine G, Steinke E, Bakaeen F, Elaine E, Bozkurt B, Conti B, et al. Sexual activity and cardiovascular disease: a scientific statement from the American heart association. *Circulation* 2012;**125**:1058–72.
10. Adelaide M, Douglas W, Ajay N, Leckel M, Pellikka P. Cardiovascular effects of sildenafil during exercise in men with known or probable CAD. *JAMA* 2002;**287**:719–25.
11. Halcox J, Nour K, Zalos G, Mincemoyer R, Waclawiwi M, Rivera C, et al. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. *J Am Coll Cardiol* 2002;**40**:1232–40.
12. Kontaras K, Varnavas V, Kyriakides Z. Does sildenafil cause myocardial infarction or sudden cardiac death? *Am J Cardiovasc Drugs* 2008;**8**:1–7.