The Egyptian Heart Journal (2014) 66, 43–48

Egyptian Society of Cardiology

The Egyptian Heart Journal

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ORIGINAL ARTICLE

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

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Received 30 August 2013; accepted 29 November 2013
Available online 30 December 2013

KEYWORDS

Sildenafil;
Coronary artery disease;
Stable angina

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.

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, post-marketing surveillance data after approval of sildenafil by

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Peer review under responsibility of Egyptian Society of Cardiology.

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http://dx.doi.org/10.1016/j.ehj.2013.11.004

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]