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# Sildenafil-inducing Trifasicular Heart Block and Angina in the Elderly with Implicated Kounis-Zafras Syndrome and Suspected Hypertrophic Cardiomyopathy; Interpretation and Management

Yasser Mohammed Hassanain Elsayed

*Critical Care Unit, Kafr El-Bateekh Central Hospital, Damietta Health Affairs, Egyptian Ministry of Health (MOH), Damietta, Egypt*

Correspondence should be addressed to Yasser Mohammed Hassanain Elsayed, Critical Care Unit, Kafr El-Bateekh Central Hospital, Damietta Health Affairs, Egyptian Ministry of Health (MOH), Damietta, Egypt

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## ABSTRACT

### RATIONALE

Sildenafil is a phosphodiesterase-5 inhibitor (PDE5-I) drug used to treat erectile dysfunction (ED) and pulmonary arterial hypertension. Allergic angina and infarction are broad-spectrum mast cell activation disorders accompanied by acute coronary syndromes (ACS) and are known as Kounis-Zafras (KZ) syndrome. Heart block is one of the most serious arrhythmias. The higher degree of heart block such as trifasicular heart block, the more terrible factor. Hypertrophic cardiomyopathy (HCM) is an autosomal dominant considered the most common cause of sudden death in healthy younger athletes.

### PATIENT CONCERNS

An elderly married male Driver patient was admitted to the intensive care unit with angina, and trifasicular heart block after ingestion of a sildenafil tablet with implicated Kounis-Zafras syndrome in a later suspected hypertrophic cardiomyopathy.

### DIAGNOSIS

Sildenafil-inducing trifasicular heart block and angina in the elderly with implicated Kounis-Zafras syndrome and later suspected hypertrophic cardiomyopathy.

### INTERVENTIONS

Electrocardiography, oxygenation, and echocardiography.

### OUTCOMES

A dramatic clinical and electrocardiographic improvement had happened.

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**LESSONS**

Sildenafil-inducing angina with trifasicular heart block may be innovative cardiovascular findings. Later an associated hypertrophic cardiomyopathy may be an incidental. The dramatic improvement in both clinical and electrocardiographic trifasicular heart block supports the efficacy of both anti-ischemic measures. Kounis-Zafras syndrome may be implicated in sildenafil-inducing trifasicular heart block and angina in the Elderly.

## KEYWORDS

Phosphodiesterase-5 inhibitor; Left posterior fascicular block; Kounis-Zafras syndrome; Trifasicular block; Hypertrophic cardiomyopathy; Bundle branch block; Ischemic heart disease

## ABBREVIATIONS

ACS: Acute Coronary Syndrome
AMI: Acute Myocardial Infarction
CAS: Coronary Artery Spasm
CBC: Complete Blood Count
ECG: Electrocardiography
ED: Emergency Department
HB: Heart Block
HCM: Hypertrophic Cardiomyopathy
ICU: Intensive Care Unit
IHD: Ischemic Heart Disease
KZ syndrome: Kounis-Zafras Syndrome
LAD: Left Axis Deviation
LAFB: Left Anterior Fascicular Block
LPFB: Left Posterior Fascicular Block
NSR: Normal Sinus Rhythm
MI: Myocardial Infarction
O2: Oxygen
PVC: Premature Ventricular Complex
RAD: Right Axis Deviation
RBBB: Right Bundle Branch Block
SAM: Systolic Anterior Motion
VR: Ventricular Rate

## INTRODUCTION

Sildenafil was the first approved US FDA phosphodiesterase-5 inhibitor (PDE5-I) drug used to treat erectile dysfunction (ED) on March 27, 1998, and pulmonary arterial hypertension [1,2]. It is available as oral tablets of 25 mg, 50 mg, and 100 mg strength for ED [2]. Hypotension especially in patients who are on alpha-blockers, priapism, non-arteritic anterior ischemic optic neuropathy (NAION), headaches, flushing, dyspepsia, nasal congestion, back pain, myalgia, nausea, dizziness, and rash are commonly reported adverse effects [2-4]. Kounis-Zafras (KZ) syndrome are broad-spectrum mast cell activation disorders accompanied by acute coronary

syndromes (ACS) [2]. This syndrome was first described by Kounis and Zavras in 1991 as an “allergic angina syndrome”, “allergic angina” or “allergic myocardial infarction” [5-7]. The main mechanisms include the inflammatory cytokines mediators released through mast cell activation during a hypersensitivity reaction triggered by food, insect bites, or drugs. There is a subsequent coronary artery spasm (CAS) with possible atheromatous plaque erosion or rupture [7]. The allergic angina commonly starts within one hour of exposure to the offending allergen. Longer onset KZ syndrome also has been reported [8]. Variant presentations of the syndrome have been reported [7]. Three different variants of this syndrome have been described: Type I occurs in structurally normal coronary arteries with no cardiovascular risk factors. The coronary spasm was suggested with or with no associated acute myocardial infarction (AMI). Type II occurs in patients with pre-existing ischemic heart disease (IHD), in whom the acute release of inflammatory mediators induces CAS that may lead to plaque rupture and MI. Type III occurs in patients with coronary artery stent-associated thrombosis [6,8-10]. Trifascicular heart block (HB) is the combination of bifascicular block with first-degree HB. The most important causes of trifascicular HB are ischemic artery disease (IHD), anterior myocardial infarction (MI), hypertension (HTN), CHD, primary degenerative disease of the conducting system such as Lenègre-Lev disease, aortic stenosis, digitalis toxicity, and hyperkalemia [11,12]. There are two categories of trifascicular HB: the first one is incomplete trifascicular HB; characterized by bifascicular HB with first-degree HB (MCC), bifascicular block with second-degree HB, and RBBB with alternating left anterior fascicular block/left posterior fascicular block; The second one is complete trifascicular HB; characterized by bifascicular block with third-degree HB [11-13]. Hypertrophic cardiomyopathy (HCM) is an autosomal dominant (AD) myocyte disease caused by mutations in sarcomere and sarcomere-related protein genes encoding for elements of the contractile machinery of the heart. Increased left ventricular (LV) wall thickness, dynamic LV outflow obstruction, diastolic dysfunction, IHD, arrhythmias, autonomic dysfunction, and mitral regurgitation (MR) are associated with structural changes. Previously, it is named idiopathic hypertrophic subaortic stenosis. It is considered the most common cause of sudden cardiac death (SCD) in healthy younger athletes. Fatigue, dyspnea, chest pain, palpitations, and syncope are frequent presentations. Cardiac defibrillator placement and surgery have greatly improved the survival rates of HCM [14].

## CASE PRESENTATION

A 71-year-old married male Driver Egyptian patient was admitted to the intensive care unit (ICU) with angina, palpitations, and headaches within one and half hours after ingestion of a single sildenafil tablet (25 mg). Profuse sweating was an associated symptom. He gave a recurrent history of the same attacks after ingestion of a sildenafil tablet. He gave no old history of cardiovascular diseases. Upon general physical examination, Generally, the patient appeared obese, and looked sweaty with a regular pulse rate (VR of 70), blood pressure (BP) of 130/80 mmHg, respiratory rate of 16 bpm, a temperature of 37°C, and pulse oximeter of oxygen ($O_2$) saturation of 97%. No more relevant clinical data were noted during the clinical examination. The patient was admitted to the ICU with oral sildenafil-inducing angina and trifasicular heart block. The patient urgently was treated in the ICU with high-flow $O_2$ inhalation via $O_2$ inhalation central system (100%, by simple mask, 5 L/min), Aspirin; 4 oral tablets (75 mg, then OD), clopidogrel; 4 oral tablets (75 mg, then OD), enoxaparin SC (80 mg, BID), and atorvastatin tablets (40 mg, OD) were added. The patient was hourly monitored for vital signs and O2 saturation. The initial ECG was done on the initial ECG on presentation after ICU admission showing normal sinus rhythm (NSR; of

VR 66) with RBBB, prolonged PR interval, right axis deviation (RAD), evidence of left posterior fascicular block (LPFB), and U waves in V4-6 leads (Figure 1A). The second ECG tracing was taken within 30 minutes of the above ECG tracing and after ICU treatment showing NSR (of VR; 80) with right bundle branch block (RBBB), normal PR interval, still RAD, evidence of LPFB, and U waves in 4-6 leads (Figure 1B). The third ECG tracing was taken within one minute of the above ECG tracing showing NSR (of VR 84) with RBBB, normal PR interval, still RAD, evidence of LPFB, and sporadic monomorphic premature ventricular complexes (PVCs) (Figure 1C). The fourth ECG tracing was taken within 3 hours after the ICU treatment showing NSR (of VR 72) with RBBB, normal PR interval, still RAD, and evidence of LPFB (Figure 1D). The fifth ECG tracing was taken on presentation in the emergency department (ED) for follow-up and within 3 days after the ICU discharge showing NSR (of VR 69) with still RBBB and LPFB (Figure 1E). The initial complete blood count (CBC); Hb (13.4g/dl), RBCs (5.42 × $10^3$/$mm^3$), Hematocrit (49.2%), WBCs (8.2 × $10^3$/$mm^3$); (Neutrophils; 62.0%, Lymphocytes: 29.0%, Monocytes: 8.0%, Eosinophils: 1.0% and Basophils 0%), Platelets; 214 × $10^3$/$mm^3$. SGPT was (14 U/L) and SGPT was (2 U/L). Serum creatinine was (1.1 mg/dl). RBS was (88 mg/dl). D-dimer was (0.32 mg/dl). Troponin I was less than 0.5 U/L. CRP was (12 mg/dl). The current echocardiography shows a good LV systolic function of an EF of 65%, diastolic and systolic septal hypertrophy, and systolic anterior motion (SAM) of the mitral valve leaflet (Figure 2). Sildenafil-inducing trifasicular heart block and angina in the elderly with implicated Kounis-Zafras syndrome and later suspected hypertrophic cardiomyopathy was the most probable diagnosis. Nearly complete recovery was achieved within 3 hours. The patient was discharged within 3 days of the above management after happening of dramatic clinical and electrocardiographic improvement. Aspirin tablets (75 mg, OD), clopidogrel tablets (75 mg, OD), and atorvastatin tablets (40 mg, OD) for 30 days were prescribed on discharge with the recommendation for future cardiac and immunological follow-up.

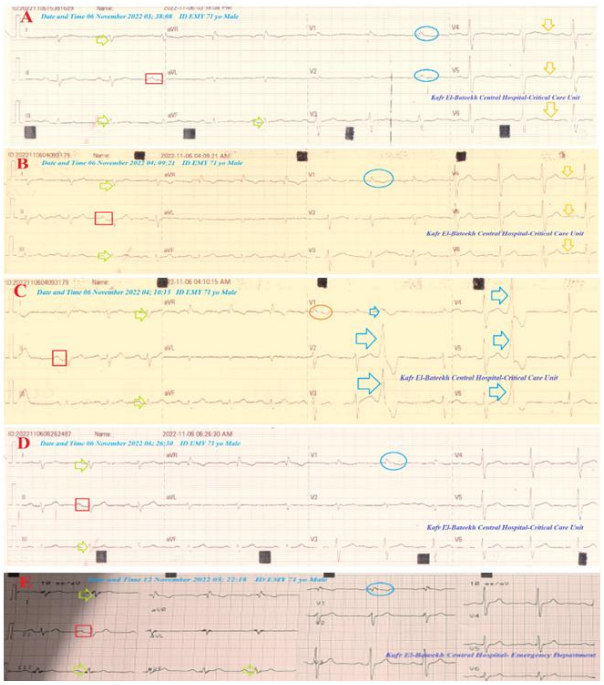


**Figure 1: Serial ECG tracings; A) Tracing** was done on the initial ECG on presentation after ICU admission showing NSR (of VR 66) with RBBB (light blue circle), prolonged PR interval (red rectangle), RAD, evidence of LPFB (lime arrows), and U waves in 4-6 leads (orange arrows). **B) Tracing** was taken within 30 minutes of

the above ECG tracing and after ICU treatment showing NSR (of VR; 80) with RBBB (light blue circle), normal PR interval (red rectangle), still RAD, evidence of LPFB (lime arrows), and U waves in 4-6 leads (orange arrows). **C) Tracing** was taken within a one minute of the above ECG tracing showing NSR (of VR 84) with RBBB (light blue circle), normal PR interval (red rectangle), still RAD, evidence of LPFB (lime arrows), and sporadic monomorphic PVCs (light blue arrows). **D) Tracing** was taken within 3 hours after the ICU treatment and showed NSR (of VR 72) with RBBB (light blue circle), normal PR interval (red rectangle), still RAD, and evidence of LPFB (lime arrows). **E) Tracing** was taken within three days after the ICU discharge and on presentation in the emergency room for follow-up showed NSR (of VR 69) with still RBBB and LPFB.

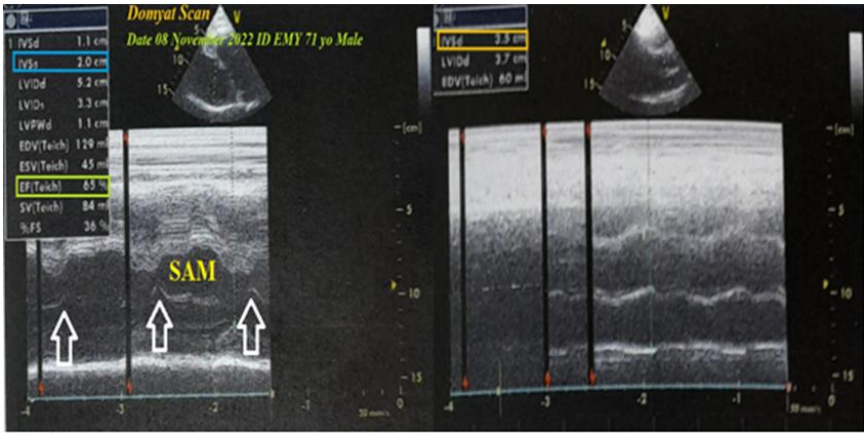


**Figure 2: Echocardiography** showing a good LV systolic function of an EF of 65% (lime rectangle), diastolic and systolic septal hypertrophy (light blue and orange rectangle), and SAM of anterior mitral valve leaflet (white arrows).

## DISCUSSION

***Overview***

An elderly married male driver patient was presented to the intensive care unit with angina and trifasicular heart block after ingestion of a sildenafil tablet with implicated Kounis-Zafras syndrome in a later suspected hypertrophic cardiomyopathy.

The primary objective for my case study was the presence of an elderly married male Driver patient with angina and trifasicular heart block after ingestion of a sildenafil tablet with implicated Kounis-Zafras syndrome in the ICU.

The secondary objective for my case study was the question of how would you manage the case?

The presence of a combination of RBBB with left posterior fascicular block suggests a bifascicular block. With added prolonged PR interval or first-degree HB, the diagnosis of trifasicular heart block is strengthened (Figure 1A).

The current angina after oral ingestion of sildenafil with no previous history of IHD indicates the presence of type I K-S syndrome. The coronary artery spasm was the suggested interpretation [6,8-10].

The normalization of prolonged PR interval or first-degree HB in the ECG may be directed to the efficacy of anti-ischemic measures (Figure 1B- Figure 1E).

Occurrence of angina after ingestion of sildenafil tablet indicates its possible causation. Naranjo's probability scale in the current case study was +10. This means that there was a definite relationship between these adverse drug effects and sildenafil ingestion (Table 1). Kounis-Zafras syndrome probably will be implicated in pathogenesis.

| Question | Yes | No | Do Not Know | Score |
|---|---|---|---|---|
| 1. Are there previous conclusive reports on this reaction? | 1 | 0 | 0 | 1 |
| 2. Did the adverse event appear after the suspected drug was administered? | 2 | -1 | 0 | 2 |
| 3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | 1 | 0 | 0 | 1 |
| 4. Did the adverse event reappear when the drug was readministered? | 2 | -1 | 0 | 2 |
| 5. Are there alternative causes that could on their own have caused the reaction? | -1 | 2 | 0 | 2 |
| 6. Did the reaction reappear when a placebo was given? | -1 | 1 | 0 | 0 |
| 7. Was the drug detected in blood or other fluids in concentrations known to be toxic? | 1 | 0 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | 1 | 0 | 0 | 1 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | 1 | 0 | 0 | 0 |
| 10. Was the adverse event confirmed by any objective evidence? | 1 | 0 | 0 | 1 |
| | Total Score: +10 | | | |

**Table 1:** Naranjo algorithm-adverse drug reaction (ADR) probability scale in the case report.

Later echocardiographic incidental evidence for systolic septal hypertrophy and systolic anterior motion (SAM) of mitral valve leaflet (Figure 2) may suggest a diagnosis of hypertrophic cardiomyopathy.

Acute pulmonary embolism is the most implicated in ECG differential diagnosis. The history is against it.

I can’t compare the current case with similar conditions. There are no identical or known cases with the same management for near comparison.

The only limitation of the current study was the unavailability of more investigation for hypertrophic cardiomyopathy.

## CONCLUSION AND RECOMMENDATIONS

Sildenafil-inducing angina with trifasicular heart block may be innovative cardiovascular findings.

Later an associated hypertrophic cardiomyopathy may be an incidental.

The dramatic improvement in both clinical and electrocardiographic trifasicular heart block supports the efficacy of both anti-ischemic measures.

Kounis-Zafras syndrome may be implicated in sildenafil-inducing trifasicular heart block and angina in the Elderly.

## CONFLICTS OF INTEREST

There are no conflicts of interest.

## ACKNOWLEDGMENT

I wish to thank my wife for saving time and improving the conditions to help me.

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