

# Sildenafil-inducing allergic angina in elderly with intertwining sinus arrhythmia, wavy triple sign, wavy double sign (Yasser's signs), and mild covid-infection; interpretation and management

## 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-Zafra (KZ) syndrome. Sinus arrhythmia is a variation of normal sinus rhythm (NSR) that is associated with an irregular rate in which the change in the R-R interval is greater than 0.12 seconds. Wavy triple and Wavy double ECG signs (Yasser's sign) are new specific diagnostic and therapeutic signs seen in the cases of hypocalcemia. Mild COVID-19 infection means you have symptoms like cough, sore throat, and fatigue, but no dyspnea.

**Patient concerns:** An elderly married male farmer patient was admitted to the intensive care unit with angina, hypotension, generalized hives, Wavy triple, and Wavy double ECG signs after ingestion of sildenafil tablet with mild COVID-19 infection in a previous chronic obstructive pulmonary disease (COPD).

**Diagnosis:** Sildenafil-inducing Kounis syndrome in the elderly with intertwining sinus arrhythmia, Wavy triple sign, Wavy double sign (Yasser's signs), and mild COVID-19 infection.

**Interventions:** Electrocardiography, oxygenation, IV fluids, and echocardiography.

**Outcomes:** A dramatic clinical and electrocardiographic improvement had happened.

**Lessons:** Sildenafil-inducing Allergic angina and anaphylaxis may be innovative cardiovascular findings. Mild COVID-19 infection, sometimes, can be insignificant. An associated sinus arrhythmia may be a good cardiovascular sign. The dramatic improvement in both clinical and electrocardiographic ST-segment depressions and elevations supports the efficacy of both anti-ischemic and anti-allergic measures.

**Keywords:** allergic coronary syndrome, phosphodiesterase-5 inhibitor, kounis-zafra syndrome, wavy triple sign, wavy double sign, Yasser's sign, hypocalcemia, coronary artery spasm, sinus arrhythmia, **anaphylaxis, ischemic heart disease.**

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**Abbreviations:** ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAS, coronary artery spasm; CBC, complete blood count; COPD, chronic obstructive pulmonary disease; ECG: electrocardiography; ED, erectile dysfunction; ICU, intensive care unit; IHD, ischemic heart disease; IV, intravenous; KZ syndrome, Kounis-Zafra syndrome; LAD, left axis deviation; NSR, normal sinus rhythm; MI, myocardial infarction; O<sub>2</sub>, oxygen; 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.<sup>1,2</sup> It is available as oral tablets of 25 mg, 50 mg, and 100 mg strength for ED.<sup>2</sup> 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.<sup>2,4</sup>

Allergic angina and allergic myocardial infarction (MI) are broad-spectrum mast cell activation disorders accompanied by acute coronary syndromes (ACS) and are known as Kounis-Zafra (KZ) syndrome.<sup>2,5</sup> Allergic angina was first described by Kounis and Zavras in 1991 as an "allergic angina syndrome", "allergic angina" or "allergic myocardial infarction".<sup>6,7</sup> 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.<sup>7</sup> The allergic angina commonly starts within one hour of exposure to the offending allergen. Longer onset KZ syndrome also has been reported.<sup>8</sup> Variant presentations of the syndrome have been reported.<sup>7</sup> 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 without 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.<sup>6,8-10</sup> Sinus arrhythmia is a variation of normal sinus rhythm (NSR) that is associated with an irregular rate in which the change in the R-R interval is greater than 0.12 seconds. The P waves are typically monoform which is consistent with atrial activation originating from the sinus atrial node (SAN). During respiration, intermittent vagus nerve activation occurs, which results in beat-to-beat variations in the resting heart rate (HR). Its presence typically indicates good cardiovascular health.<sup>11</sup> A wavy triple ECG sign (Yasser's sign) is a new specific diagnostic sign seen in 97.3% of the cases of hypocalcemia. Wavy triple ECG sign can be used as a therapeutic guide in patients with hypocalcemia.<sup>12</sup> A wavy double ECG sign (Yasser's sign) was also prescribed in hypocalcemia which is mostly seen with either tachycardia or bradycardia.<sup>12,13</sup> Mild COVID-19 infection means you have symptoms like cough, sore throat, and fatigue, but no dyspnea. Most patients who have mild COVID infections can be treated at home.<sup>14</sup>

### Case presentation

A 72-year-old married male farmer Egyptian patient was admitted to the intensive care unit (ICU) with angina, dizziness, and headaches, generalized skin rash within one hour after ingestion of a single sildenafil tablet (25mg). Circumoral numbness and extremities paresthesia were associated symptoms. He gave a recent history of mild fever, generalized myalgia, dry cough, and loss of smell within one week ago and after previous contact with a patient with COVID-19 pneumonia. He gave an old history of chronic obstructive pulmonary disease (COPD). Upon general physical examination; generally, the patient appeared thin, and long, had generalized body hives, look sweaty with an irregular pulse rate (VR of 72), blood pressure (BP) of 90/70 mmHg, respiratory rate of 18 bpm, a temperature of 37°C, and pulse oximeter of oxygen (O<sub>2</sub>) saturation of 95%. There is a barrel chest on chest inspection and generalized sibilant Ronchi were noted on the chest auscultation. Tests for provocative latent tetany were positive. No more relevant clinical data were noted during the clinical examination. The patient was admitted to the ICU with oral sildenafil-inducing angina. The patient urgently was treated in the ICU with high-flow O<sub>2</sub> inhalation via O<sub>2</sub> inhalation central system (100%, by simple mask, 10L/min), IM adrenaline 0.5 mg of 1:1000 (single dose), IV hydrocortisone vial (200 mg, then 100mg BID), IV chlorpheniramine maleate ampoule (20 mg, then 10mg BID),

IV famotidine ampoule (40 mg, then 40mg BID), and IV Ringer solution (500ml, then 500ml BID). Aspirin; 4 oral tablets (75 mg, then OD), clopidogrel; 4 oral tablets (75 mg, then OD), enoxaparin SC (60 mg, BID), and atorvastatin (20 mg, OD) were added. The patient was hourly monitored for vital signs and O<sub>2</sub> saturation. The initial ECG was done on the initial ECG on presentation in the ICU showing sinus arrhythmia (of VR: 70) with ST-segment depression in inferior leads, ST-segment elevation in anterioseptal leads, and evidence of physiological left axis deviation (LAD) (Figure 1A). The second ECG tracing was taken within 20 minutes of the above ECG tracing and after ICU admission showing normal sinus rhythm (NSR) with inferiolateral ST-segment depression, anterioseptal ST-segment elevation, and Wavy triple ECG sign (Yasser's sign) (Figure 1B). The third ECG tracing was taken within a few seconds of the above ECG tracing and after ICU admission showing NSR (of VR 73) with ST-segment depression in aVF, and V4-6 leads and Wavy triple ECG sign (Yasser's sign) (Figure 1C). The fourth ECG tracing taken within 2.5 hours after the ICU treatment showed sinus arrhythmia (of VR 64) and Wavy double ECG sign (Yasser's sign; aVF and V5-6) with normalization of the above ST-segment deviations (Figure 1D). The initial complete blood count (CBC); Hb (15.3g/dl), RBCs (6.39\*10<sup>3</sup>/mm<sup>3</sup>), Hematocrit (44.3%), WBCs (9.6\*10<sup>3</sup>/mm<sup>3</sup>); (Neutrophils; 63.9 %, Lymphocytes: 29.0%, Monocytes; 4.3%, Eosinophils; 2.8% and Basophils 0%), Platelets; 159\*10<sup>3</sup>/mm<sup>3</sup>. SGPT was (39 U/L). Serum creatinine was (1.1mg/dl). RBS was (98 mg/dl). CRP was (9.6mg/dl). Ionized calcium was (3.83mg/d). The troponin test was negative. Chest x-ray was done on the day of the ICU admission showing small left hailer ground-glass opacity (Figure 2A). Later echocardiography showed a good LV systolic function of an EF of 61% and grade I diastolic dysfunction (Figure 2B). Sildenafil-inducing Kounis syndrome in the elderly with intertwining sinus arrhythmia, Wavy triple sign, Wavy double sign (Yasser's signs), and mild COVID infection was the most probable diagnosis. Nearly complete recovery was achieved within 2.5 hours. The patient was discharged within 3 days of the above management after happening of dramatic improvement in both clinical and electrocardiographic ST-segment depressions and elevations. IV Hydrocortisone (100 mg BID), oral chlorpheniramine maleate (8 mg BID) for 3 days, aspirin tablets (75 mg, OD), oral calcium, and vitamin-D preparations (BID) for 30 days were prescribed on discharge with the recommendation for future cardiac and immunological follow-up.

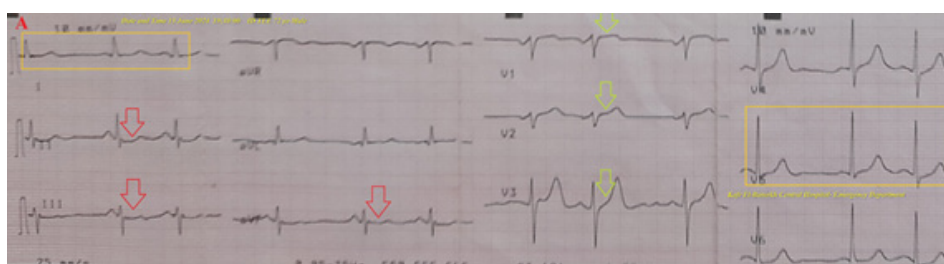


Figure 1A

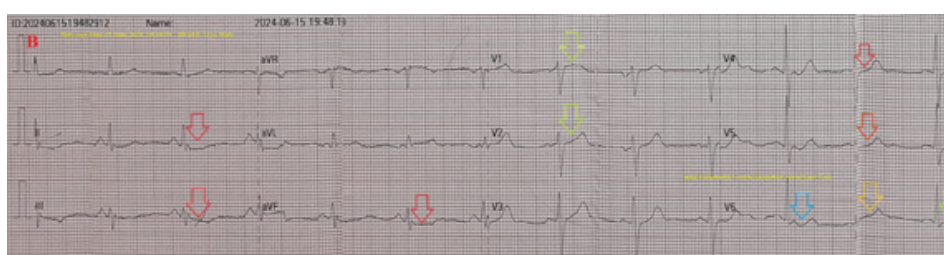


Figure 1B

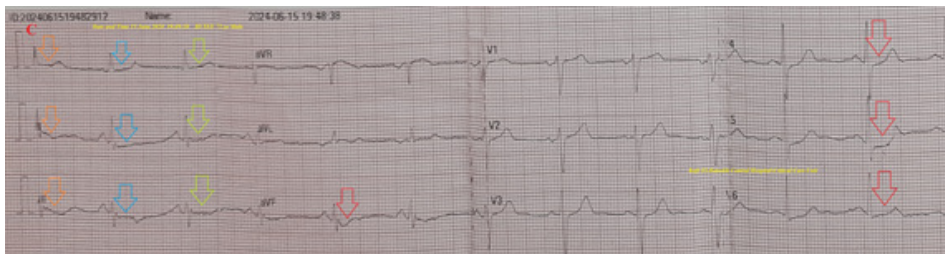


Figure 1C

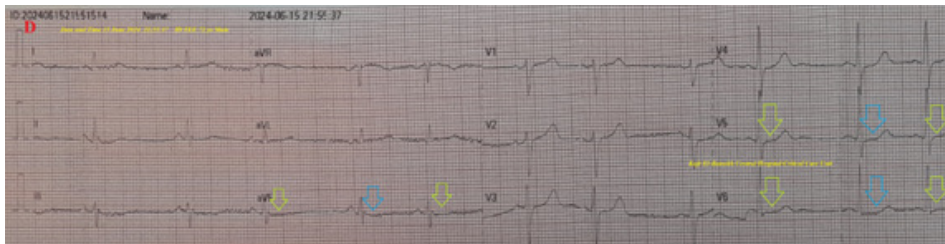


Figure 1D

Figure 1 Serial ECG tracings.

**A. tracing** was done on the initial ECG on presentation in the emergency room sinus arrhythmia (yellow rectangle of VR 70) with ST-segment depression in inferior leads (II, III, and aVF; red arrows), ST-segment elevation in anteroseptal leads (lime arrows), and evidence of physiological LAD.

**B. tracing** was taken within 20 minutes of the above ECG tracing and after ICU admission showing NSR (of VR; 74) with ST-segment depression in inferolateral leads (red arrows), ST-segment elevation in anteroseptal leads (lime arrows), and Wavy triple ECG sign (Yasser's sign; V6, light blue, orange, and lime arrows).

**C. tracing** was taken within a few seconds of the above ECG tracing and after ICU admission showing NSR (of VR 73) with ST-segment depression in aVF, and V4-6 leads, and Wavy triple ECG sign in II, III, and aVF leads (Yasser's sign; light blue, orange, and lime arrows).

**D. tracing** was taken within 2.5 hours after the ICU treatment showing sinus arrhythmia (of VR 64) and Wavy double ECG sign (Yasser's sign; aVF and V5-6, light blue and lime arrows) with normalization of the above ST-segment deviations.

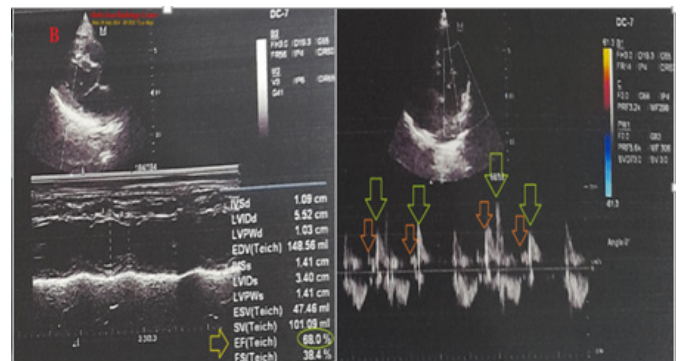


Figure 2B Later echocardiography.

Figure 2

**A. CXR film-PA view** was done on the day of the ICU admission showing small left hailer ground-glass opacity (lime arrow).

**B. Later Echocardiography** was done showing a good LV systolic function of an EF of 68% (lime arrow and circle) and grade I diastolic dysfunction (light blue and orange arrows).



Figure 2A CXR film-PA.

## Discussion

### Overview

An elderly married male farmer patient was admitted to the intensive care unit with angina, hypotension, generalized hives, sinus arrhythmia, Wavy triple, and Wavy double ECG signs within one hour after ingestion of sildenafil tablet with mild COVID-19 infection in a previous COPD.

**The primary objective** for my case study was the presence of an elderly married male farmer patient with angina, anaphylactic shock, sinus arrhythmia, Wavy triple, and Wavy double ECG signs after ingestion of sildenafil tablet with mild COVID-19 infection in a previous COPD in the ICU.

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

The presence of angina with hypotension, and generalized hives after oral ingestion of sildenafil tablet will strengthen the diagnosis of anaphylactic shock.

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

The normalization of the ECG ST-segment depression and ST-segment elevation may be directed to the CAS suggestion.

Clinically, tachypnea, numbness, and paresthesia of extremities with positive tests for latent tetany, laboratory lower ionized calcium, Wavy double ECG sign, and Wavy triple ECG sign (Yasser's signs) are more parallel to hypocalcemia (Figure 1B, 1C, and 1D).

The changeable of affected leads from ECG tracing to another tracing in the Wavy double ECG sign will be a signal to the diagnosis of Movable phenomenon or Yasser's phenomenon of hypocalcemia (Figure 1B, 1C, and 3D).

Movable phenomenon or Yasser's phenomenon of hypocalcemia is a signal for associated tachypnea in the current case.

The presence of a changeable Wavy triple sign in ECG is a hallmark of the Movable phenomenon (Yasser's phenomenon) of hypocalcemia.<sup>13</sup> The Wavy triple ECG sign (Yasser's sign) is a recently innovated diagnostic sign in hypocalcemia.<sup>12</sup> The author's interpretations are based on the following:

1. Different successive three beats in the same lead are affected.
2. All ECG leads can be implicated.
3. An associated elevated beat is seen with the first of the successive three beats, a depressing beat with the second beat, and an isoelectric ST-segment in the third one.
4. The elevated beat is either accompanied by ST-segment elevation or just an elevated beat above the isoelectric line.
5. Also, the depressed beat is either associated with ST-segment depression or just a depressing beat below the isoelectric line.
6. The configuration for depressions, elevations, and isoelectricities of the ST segment for the subsequent three beats are variable from case to case. So, this arrangement is non-conditional.
7. Mostly, there is no participation among the involved leads. The author intended that is not conditionally included in a special coronary artery for the affected leads.<sup>12,13</sup>

Tachypnea was a possible cause of hypocalcemia and subsequent Wavy triple ECG sign, Wavy double ECG sign, and Movable-weaning phenomenon of hypocalcemia.<sup>12,13</sup> Atrial fibrillation is the most implicated differential diagnosis. The ECG criteria are against it.

I can't compare the current case with similar conditions. There are no similar or known cases with the same management for near comparison. The only limitation of the current study was the unavailability of a new coronary angiography.

## Conclusion and recommendations

Sildenafil-inducing Allergic angina and anaphylaxis may be innovative cardiovascular findings. An associated sinus arrhythmia may be a good cardiovascular sign. Mild COVID-19 infection, sometimes, can be insignificant. The dramatic improvement in both clinical and electrocardiographic ST-segment depressions and elevations supports the efficacy of both anti-ischemic and anti-allergic measures.

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## Conflicts of interest

The author declares that there are no conflicts of interest.

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