

Severe myocardial ischemia after concentrated epinephrine use for the treatment of anaphylaxis: Kounis syndrome or epinephrine effect?

Cemil Izgi, MD,^a Cihan Cevik, MD,^b and Kenneth Nugent, MD^b

Epinephrine is the cornerstone of treatment for anaphylaxis, which is a life-threatening condition that requires rapid management. However, epinephrine administration can have complications. We report a patient in whom accidental concentrated epinephrine use for management of anaphylaxis caused severe myocardial ischemia.

CASE REPORT

A 37-year-old woman presented to the emergency department with generalized erythema, flushing, pruritus, abdominal pain, respiratory distress, and disturbed consciousness. Her symptoms had started acutely approximately 30 minutes after ingestion of a tablet of amoxicillin (500 mg). Within seconds of her presentation to the emergency department, her clinical status deteriorated rapidly and she collapsed. Her systolic blood pressure was 40 mm Hg and pulse rate was 82 beats/min. She was immediately placed in the Trendelenburg position, nasal oxygen was started, an intravenous (IV) line was promptly established, and rapid saline infusion was started. Two doses of .5 mg epinephrine (diluted; 1:10,000) bolus administered 5 minutes apart by the IV route failed to restore an adequate blood pressure. A third dose of 1 mg epinephrine, which was accidentally infused undiluted (1:1000), restored the blood pressure to 105/65 mm Hg. However, immediately after the last epinephrine infusion and restoration of blood pressure, the patient had chest tightness, and ST depression was observed on the monitor.

A 12-lead electrocardiogram (ECG) revealed marked ST changes, suggesting diffuse myocardial ischemia (Fig 1A). Ischemia was presumed to occur secondary to coronary artery spasm induced by epinephrine, but coronary vasodilators were not used because of concern about precipitating systemic vasodilation and hypotension. After 20 minutes of watchful waiting (a duration compatible with the half-life of IV epinephrine), her chest pain and ECG changes resolved (Fig 1B). The troponin T levels (peak .53 ng/mL; N: <.03 ng/mL) and creatine kinase-MB levels (peak 26 IU/L; N: <24 IU/L) increased during the next 24 hours. The patient later reported that she did not have any history of coronary artery disease, and her only risk factor was smoking. Transthoracic echocardiography revealed normal left ventricular systolic function and segmental wall motion. The patient did not have any dynamic ECG changes suggesting recurrent ischemia after the acute event. A 12-lead ECG was normal at discharge. Coronary angiography and cardiac stress test were deferred according to the patient's preference. The patient was discharged on the third day of hospital stay and was doing well without any medication at her 1-year follow-up.

DISCUSSION

Does this patient have Kounis syndrome?

Kounis syndrome or "allergic angina" is defined as "the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classic angina pectoris caused by inflammatory mediators released during the allergic insult."¹ This syndrome now refers to the clinical spectrum of angina pectoris to acute myocardial infarction after an allergic reaction. Beta-lactam antibiotics are one of the most common causes of Kounis syndrome, and at least 17 cases have been documented so far.² The typical patient with Kounis syndrome after beta-lactam antibiotic use is

From the ^aOzel Gaziosmanpasa Hospital, Division of Cardiology, Istanbul, Turkey; ^bTexas Tech University Health Sciences Center, Department of Internal Medicine, Lubbock, Texas.

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Reprint requests: Cihan Cevik, MD, Texas Tech University Health Sciences Center, Department of Internal Medicine, 3601 4th Street, Lubbock, TX 79430. E-mail: cihan.cevik@ttuhsc.edu

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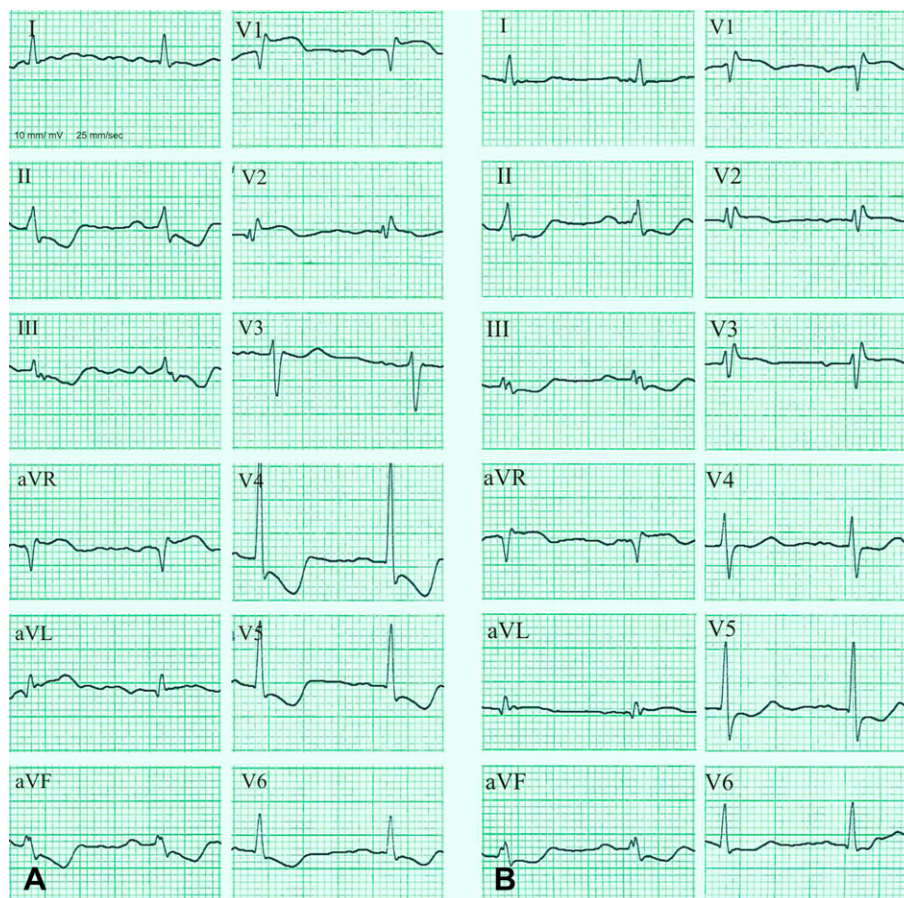


Fig 1 **A**, Within 1 minute after the infusion of the third dose of epinephrine, ST elevation in leads V1-3, I, aVL, and aVR, and ST depression in leads V4-6, II, III, and aVF were observed. **B**, Twenty minutes later, the ischemic changes markedly resolved. ECG was normal at discharge with resolution of all ischemic changes.

a middle-aged man who develops symptoms within 30 minutes of administration of the drug. Symptoms usually include rash and dyspnea associated with chest pain and hypotension. These patients usually have ST elevation in the inferior leads. Most of the patients have either normal or noncritical coronary artery disease demonstrated by coronary angiography. Therefore, coronary vasospasm produces the cardiac symptoms in these cases. Although the number of cases published is limited, this syndrome seems to have less mortality and a better short-term prognosis than the usual acute coronary syndrome.² Kounis syndrome also resembles tako-tsubo syndrome, which commonly occurs after sudden stress in patients without coronary artery disease. Chemical mediators including norepinephrine have been implicated in the pathogenesis of tako-tsubo syndrome, and this could help explain our patient's findings after the administration of high-dose epinephrine. Similarly, Abraham and coworkers³ demonstrated that IV administration of epinephrine precipitated

stress cardiomyopathy in 6 patients in their recent study. This particular report provided strong evidence that sympathetic stimulation with catecholamines or beta-receptor agonists is the central pathogenetic mechanism in this unique syndrome. However, the echocardiogram before discharge in our patient did not reveal apical ballooning, and the diagnosis of tako-tsubo cardiomyopathy was unlikely.

How should we treat patients with Kounis syndrome?

Acute coronary syndromes secondary to allergic reactions are associated with significant morbidity and mortality in hypersensitive individuals. The systemic allergic response caused by inflammatory mediators should be controlled early in the management of these patients. Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors when they develop acute coronary syndrome (especially inferior myocardial infarction) after administration of beta-lactam

antibiotics. These patients need treatment with steroids, antihistamines, fluid resuscitation, possibly epinephrine, oxygen, and antithrombotics before transfer to the cardiac catheterization laboratory. The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasodilators, including nitrates and calcium channel blockers, should be considered first-line therapy in young and previously healthy individuals because vasospasm is the primary mechanism. Corticosteroids have also been used successfully in the treatment of refractory vasospastic angina, particularly when a patient has an allergic diathesis.⁴ Acute coronary syndrome protocols should be followed in patients with a type II variant (patients with silent coronary artery disease and atheromatous vessels in whom plaque rupture precipitates an acute coronary syndrome). Opiate medications, such as morphine, codeine, and meperidine, should be used cautiously in this group of patients because they can induce mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives show only a slight activation of mast cells and should be the drugs of choice when narcotic analgesia is necessary.

What are the pros and cons of epinephrine?

Whether or not to use epinephrine is a challenging decision in acute coronary syndromes secondary to an allergic reaction. Epinephrine is a life-saving medication in anaphylaxis; however, it has a narrow therapeutic window. In cases of allergic reaction and acute coronary syndrome, its risks may outweigh the benefits. First, most epinephrine preparations contain sulfite as a preservative and antioxidant, which itself may trigger anaphylaxis in sensitive individuals.

Second, epinephrine can aggravate the ischemia, prolong QTc interval, and induce coronary vasospasm and arrhythmias. Elderly patients, especially with a history of hypertension and coronary artery disease, are prone to these side effects. Therefore, epinephrine should be used even more cautiously in this group. Third, the use of IV epinephrine is still controversial in severe allergic reactions. It should be considered in patients with severe hypotension or cardiac arrest who do not respond to aggressive fluid resuscitation. The IV route of epinephrine administration can cause uncontrolled elevation in blood pressure and precipitate intracranial bleeding. Intramuscular use of epinephrine is the safer and preferred route of administration unless the patient has severe anaphylaxis. Finally, some patients may have received beta-blockers in the initial manage-

ment of the acute coronary syndrome, and the usual dose of epinephrine may be ineffective. It may also promote more vasospasm secondary to unopposed alpha adrenergic effect in patients who have received beta-blocking agents. Glucagon may be considered for patients who are already receiving beta-blockers or received them during the management of the acute coronary syndrome.

The consensus opinion on epinephrine use during anaphylaxis favors epinephrine administration as soon as anaphylactic symptoms occur.^{5,6} According to the current guidelines, there is no absolute contraindication to epinephrine use in anaphylaxis. The recommended dose and route is .2 to .5 mg of aqueous epinephrine (1:1000) administered intramuscularly in the thigh every 5 to 15 minutes. In patients with cardiac arrest, IV epinephrine (1:10,000 to 1:100,000) can be considered. Obviously, these recommendations stem from all types of anaphylaxis cases in which most of the patients did not have a concurrent acute coronary syndrome. More case studies are needed to establish the use of epinephrine in patients with Kounis syndrome.

Our patient was diagnosed with anaphylactic shock approximately 30 minutes after the ingestion of amoxicillin. She did not report any chest pain, and an ECG was not done before the third dose of epinephrine. She started to have chest tightness and accompanying ECG changes immediately after the accidental infusion of concentrated epinephrine. Her symptoms resolved without using steroids, antihistamines, or vasodilators. Although the diagnosis of Kounis syndrome cannot be ruled out, this case most likely represents an acute coronary syndrome secondary to epinephrine overdose. The Naranjo adverse drug reaction score was 9, suggesting epinephrine was the definite culprit for this insult.⁷

CONCLUSIONS

Although anaphylaxis is not uncommon, most physicians rarely see cases. This may lead to diagnostic and treatment errors. Anaphylactic mediators and, more important, epinephrine used for the treatment of anaphylaxis can induce serious cardiac ischemia. This side effect, however, should not preclude the use of epinephrine for the treatment anaphylaxis when needed. Proper administration of epinephrine will minimize the risk of its potential cardiovascular side effects, which are myocardial ischemia, life-threatening ventricular arrhythmia, and uncontrolled increase in blood pressure with the risk of intracerebral hemorrhage. The dose, concentration (dilution), and route of administration of epinephrine should be

decided according to the severity of anaphylactic reaction. The intramuscular route seems safer and appropriate for milder anaphylactic reactions. However, anaphylactic shock necessitates IV epinephrine administration with aggressive fluid resuscitation. IV preparations of epinephrine should be diluted to at least 1:10,000 and better to 1:100,000 (ie, 10 and 100 times diluted, respectively), and should never be given undiluted (1:1000). Even after the appropriate dilution, IV administration should be given as slowly as possible and with close cardiac and blood pressure monitoring.

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