
Case report

Postoperative ST-segment elevation: was vasospasm caused by anaphylaxis or by its treatment with epinephrine?

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Background: Anaphylaxis must be recognized and treated promptly to avoid significant morbidity and mortality. In this clinical setting, electrocardiographic changes can be multifactorial.

Objective: To discuss vasospasm as a cause of myocardial ischemia and its possible triggering by anaphylaxis itself or by the administration of epinephrine.

Methods: We describe a patient with multiple previous allergies who received intravenous epinephrine to treat suspected anaphylaxis. She immediately developed crushing chest pain with ST-segment elevations in the inferior leads. Throughout the discussion, we address differential diagnoses, physiologic features, and treatment.

Results: Her symptoms and electrocardiographic changes were consistent with vasospasm, which resolved after treatment with sublingual nitroglycerin. However, the reaction was sufficient to cause an elevation in the troponin T level and, therefore, myocardial damage on the cellular level.

Conclusions: Cardiovascular complications, including electrocardiographic changes, may be induced by anaphylactic mediators or by medications used for its treatment.

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INTRODUCTION

Anaphylaxis must be recognized and treated promptly to avoid significant morbidity and mortality. Most clinicians know that the treatment of choice is epinephrine, but there is often confusion regarding specific indications for various doses and routes. Although epinephrine can be lifesaving, it is important to be cognizant of adverse effects that may follow its administration, and the subsequent need for monitoring. In this case report, we discuss vasospasm as a cause of myocardial ischemia and its possible triggering by anaphylaxis itself or by the administration of epinephrine. Throughout the discussion, we address differential diagnoses, physiologic features, and treatment.

CASE REPORT

A 55-year-old woman with breast cancer underwent a small reexcision of the right breast as an outpatient 1 month after undergoing a lumpectomy with positive margins. Her medical history included hypertension and high cholesterol, both diet controlled; a head injury 10 years earlier, from which she had recovered completely; and no chemotherapy or irradiation for breast cancer. She had never smoked. The only

medication she was taking was fexofenadine hydrochloride (Allegra; Sanofi-Aventis, Bridgewater, NJ) for seasonal allergies.

The patient had a history of multiple severe allergies that included penicillin, metronidazole, ciprofloxacin, erythromycin, latex, and intravenous contrast. The allergies produced reactions ranging from hives to anaphylaxis with throat closure. She had used an epinephrine autoinjector (EpiPen; Dey LP, Napa, CA) 3 times in the past.

She underwent an uneventful 40-minute general anesthetic with endotracheal intubation. She received propofol with lidocaine and succinylcholine for induction, nitrous oxide–sevoflurane–oxygen maintenance, and no antibiotics. During this period, she was exposed only to latex-free products.

In the recovery room, her vital signs were as follows: blood pressure, 160 to 165/80 to 85 mm Hg; heart rate, 70 to 90 bpm; respiratory rate, 16 to 18/min; and oxygen saturation, 94% to 98% on room air. She complained of pain and significant nausea. To control these symptoms she received, sequentially, intravenous fentanyl, promethazine (Phenergan; Baxter Healthcare Corp, Deerfield, IL), and ondansetron hydrochloride (Zofran; GlaxoSmithKline, Lake Forest, IL), followed by subcutaneous scopolamine (hyoscine American Pharmaceuticals Partners Inc, Schaumburg, IL). Twenty minutes after receiving scopolamine (and more than an hour after taking any other medication), she complained of dyspnea and felt her typical throat closure accompanied by chest tightness.

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On examination, she developed stridor, her voice became raspy, and breath sounds were decreased bilaterally. She complained of pruritus, although no rash or hives were observed, and her lips and tongue were noted to be swollen. Her vital signs at the time included a blood pressure of 190/77 mm Hg, a heart rate of 80 bpm, a respiratory rate of 22/min, and saturation of 98% on room air.

Because of her rapidly progressing respiratory distress, she was immediately given epinephrine, 100 μ g intravenously, along with diphenhydramine hydrochloride (Benadryl; Pfizer Consumer Healthcare, Morris Plains, NJ), 50 mg intravenously. Within 30 seconds of receiving epinephrine she was able to breathe easily, but 10 seconds later she stated, "I'm going to pass out," and approximately 20 seconds of nonsustained ventricular tachycardia (NSVT) was concurrently observed on the monitor. At this time, her blood pressure was 90/34 mm Hg. One minute later, her presyncopal symptoms had resolved and her vital signs had returned to normal (blood pressure, 136/72 mm Hg; heart rate, 62 bpm; and saturation, 100% on a 5-L nasal cannula). One minute later, 100 mg of hydrocortisone hemisuccinate was administered. However, now she complained of heavy, substernal chest pain that was different from the typical chest tightness that she usually experiences during anaphylactic episodes. An electrocardiogram was obtained immediately and showed 3-mm ST-segment elevations in leads II, III, and aVF (Fig 1). She was given 162 mg of chewable aspirin along with 3 consecutive

sublingual 0.4-mg nitroglycerin tablets (NitroQuick; Able Laboratories Inc, South Plainfield, NJ) in 15 minutes. The ST-segment elevations and the chest pain improved progressively with each dose of nitroglycerin and resolved completely after the third dose (Fig 2).

The Cardiology Service of Massachusetts General Hospital was consulted to aid with ongoing management. The differential diagnosis included vasospasm vs plaque rupture, as well as arrhythmia-induced hypotension as an unlikely cause. She was admitted to the Cardiac Care Unit for observation and subsequent cardiac catheterization. Although the patient remained free of chest pain, with no further electrocardiographic changes, myocardial cellular damage did occur, as evidenced by a peak troponin T level of 0.23 ng/mL (reference value, <0.01 ng/mL).

Given her significant anaphylactic history, including reacting to intravenous contrast, and the quick resolution of her ST-segment elevations, an allergy consult was obtained before cardiac catheterization. She was pretreated with prednisone and diphenhydramine (Benadryl). Her course in the Cardiac Care Unit, and during contrast administration, was stable. Cardiac catheterization revealed coronaries with minimal irregularities, typical for her age, a normal ejection fraction, and no regional wall motion abnormalities. The implicit diagnosis was vasospasm that caused myocardial ischemia. The patient had an uneventful recovery. She was discharged with the recommendation to have allergy testing

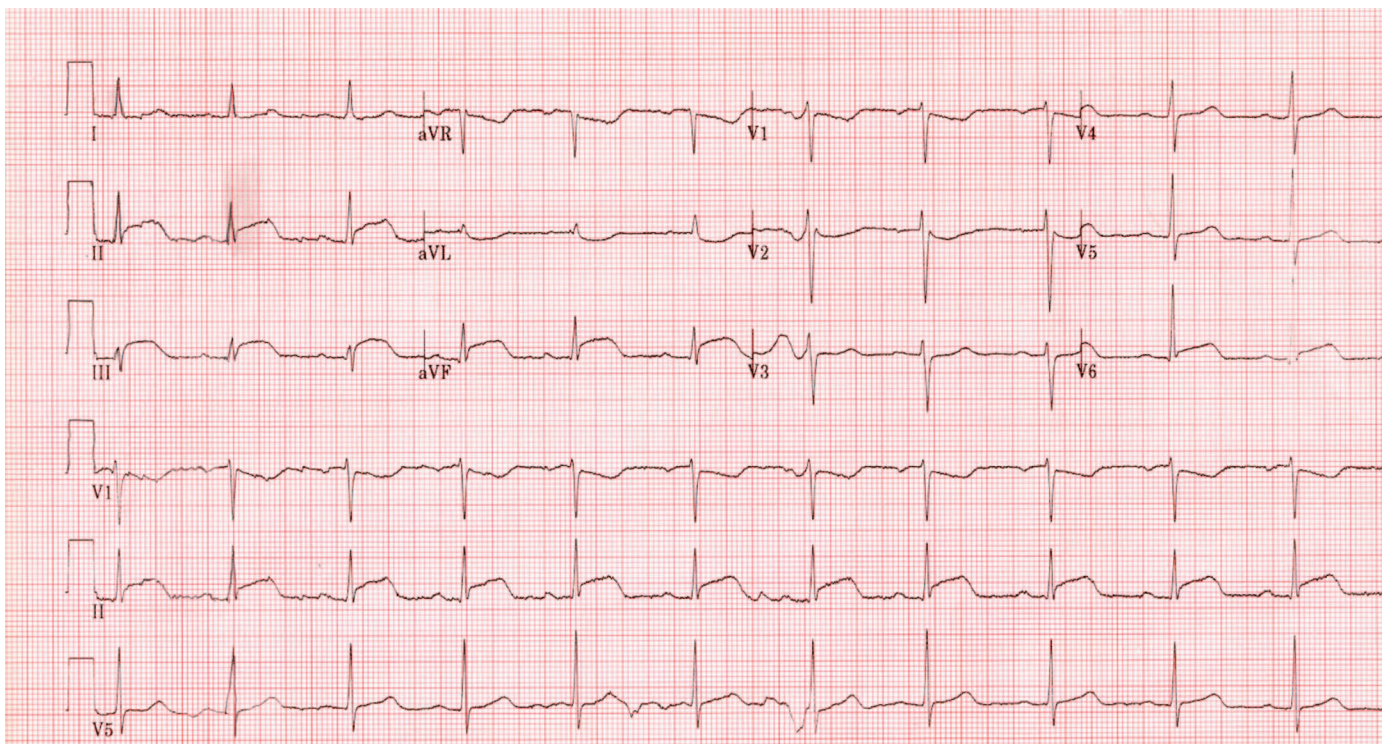


Figure 1. Electrocardiograms showing ST-segment elevations after the administration of epinephrine. Note the 3-mm ST-segment elevations in the inferior leads and the reciprocal ST-segment depressions in the anterior leads.

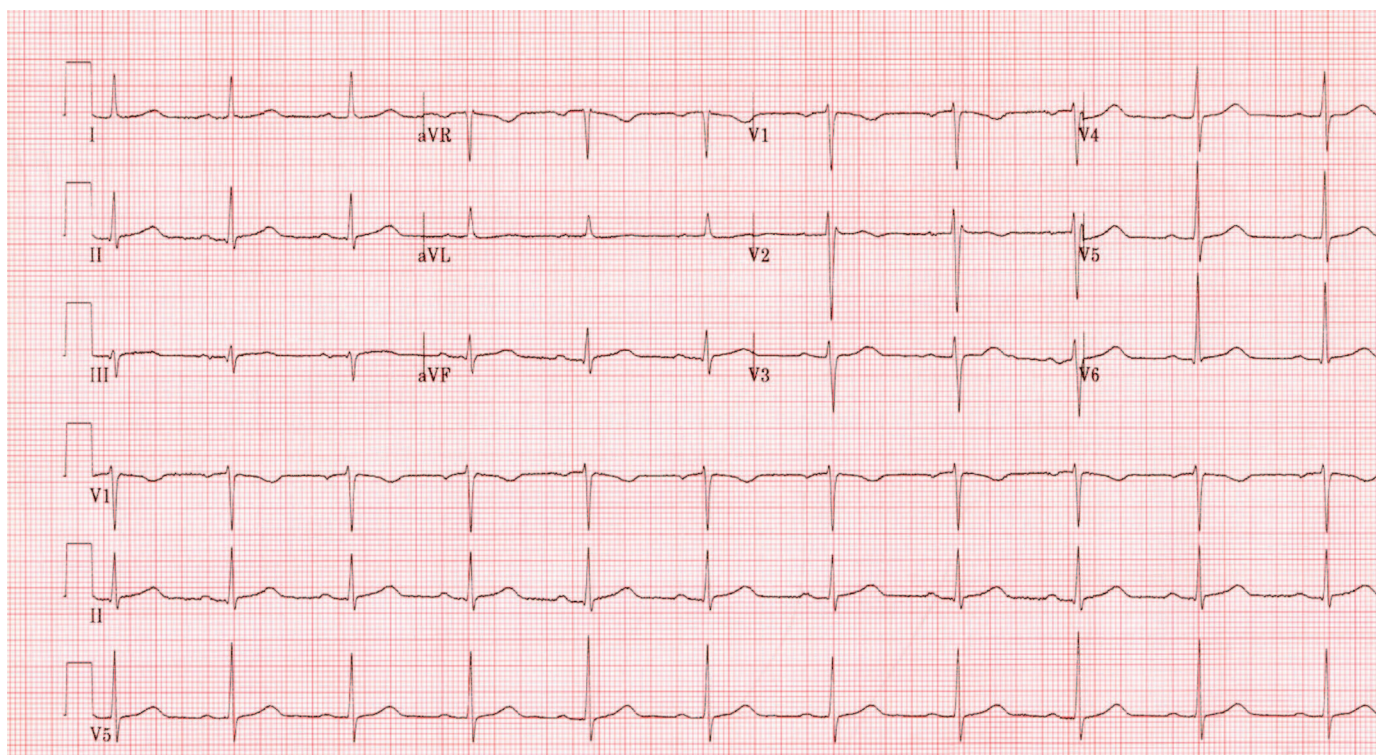


Figure 2. Electrocardiogram showing resolution of ST-segment elevations after the administration of sublingual nitroglycerin.

as an outpatient and to avoid exposure to scopolamine in the meantime.

DISCUSSION

In this case report, we describe a patient with multiple severe allergic reactions who developed a suspected anaphylactic reaction in the postoperative period. It is possible that she reacted to the scopolamine that was administered for nausea. The timing would be appropriate, especially because it was administered subcutaneously, and her typical anaphylactic symptoms appeared 20 minutes later.

Anaphylaxis is defined clinically as a severe allergic reaction with an acute onset that meets 1 of the following 3 criteria: (1) involvement of skin (eg, hives, pruritus, and flushing), mucosal tissue (eg, swollen lips, tongue, and uvula), or both, combined with respiratory compromise or hypotension; (2) after exposure to a likely allergen, rapid development of at least 2 of the following: skin or mucosal reactions, respiratory compromise, hypotension, and persistent gastrointestinal symptoms; and (3) hypotension after exposure to a known allergen.¹ This patient meets the first 2 criteria for anaphylaxis. Some patients have abdominal symptoms of anaphylaxis, but in this patient we considered the nausea to be unrelated because it is a relatively common symptom after anesthesia and because she complained of nausea before any of the other symptoms, prompting treatment with antiemetic agents.

This patient did not have decreased blood pressure as part of her initial presentation. We speculate that her hypertension (blood pressure of 190/77 mm Hg from a recovery room baseline of 160–165/80–85 mm Hg) resulted from anxiety induced by her difficulty in breathing. Her blood pressure decreased immediately after epinephrine administration. It is possible that the hypotension was related to the normal course of anaphylaxis and would have been even worse without the epinephrine. However, the hypotension was more likely due to NSVT induced by epinephrine administration. Treatment with epinephrine was initiated quickly given the patient's sudden respiratory distress and symptoms identical to her previous anaphylactic reactions. Because the patient had established intravenous access and the immediately available epinephrine was 1:10,000 (0.1 mg/mL for intravenous administration), she was promptly treated with 100 μ g intravenously. In hindsight, intramuscular administration of concentrated epinephrine (1:1,000; 0.3 mL = 300 μ g) may have led to a better outcome.¹

Epinephrine acts to increase blood pressure by several mechanisms, including direct myocardial stimulation, increased heart rate, and peripheral vasoconstriction. The peak blood pressure is proportional to the dose, with a greater increase in systolic than diastolic pressure, and often a subsequent decline to below previous mean pressures before a return to baseline. There is less risk of arrhythmia and vasospasm with small doses and with intramuscular doses com-

pared with intravenous doses. For all these reasons, the intramuscular route is safest in cases of respiratory distress without hypotension.² Administration of epinephrine has many indications, including anaphylactic reactions, cardio-pulmonary resuscitation, and severe bronchospasm.³ Although cardiovascular adverse effects of epinephrine administration may include hypertension, arrhythmias, tachycardia, angina, increased oxygen consumption, and coronary vasospasm, its benefits outweigh its risks when administered for the proper indication.⁴ In the absence of the relatively rare circumstance of severe vasospasm, coronary blood flow is usually increased rather than decreased.²

Intubation was avoided given the quick resolution of her respiratory distress. However, the administration of epinephrine (100 µg intravenously) was followed by a short run of NSVT with accompanying symptomatic hypotension (blood pressure, 90/34 mm Hg). This resolved spontaneously but was followed by ST-segment elevation. The patient did not have any history of coronary artery disease, with only mild hypertension and high cholesterol as risk factors for the development of myocardial ischemia.

The fact that she developed chest pain could have been misleading because she had just undergone breast surgery and had been experiencing chest tightness during her anaphylactic reaction. However, the new pain was heavy and of different intensity and location than the typical chest tightness that she experienced during her anaphylactic reactions. After observing the run of NSVT and noticing the ST-segment elevation on the bedside monitor, a formal electrocardiogram was obtained immediately, allowing expedited treatment of her myocardial ischemia.

Territorial ST-segment elevations are commonly caused by plaque rupture but can also be caused by coronary vasospasm, which may have resulted from epinephrine administration or from the anaphylactic reaction itself. In addition, territorial ST-segment elevation can be caused by decreased coronary artery flow during severe hypotension, even in young patients without coronary stenoses, such as described by Monterrubio Villar et al⁵ in a patient with spontaneous right pneumothorax. Although ischemia secondary to hypotension often involves a global decrease in coronary perfusion, it can also affect 1 particular territory. This patient developed hypotension after a short run of NSVT. In this case, however, hypotension is unlikely to be the culprit given its very short duration and the lowest measured blood pressure value of 90/34 mm Hg.

There are cases of anaphylaxis as the inciting factor for coronary vasospasm causing myocardial ischemia, or even infarction, most likely due to the accompanying histamine release and cytokine milieu. Lopez-Minguez et al⁶ described a patient who developed myocardial infarction after anaphylaxis to shellfish that required rescue angioplasty despite administration of intracoronary nitroglycerin. Fox et al⁷ reported an allergy to aspirin inducing coronary vasospasm and myocardial infarction, which responded to intracoronary administration of nitroglycerin. Mast cell activation during an

allergic reaction may produce mediators that induce smooth muscle contraction, such as histamine, prostaglandins, leukotrienes, platelet aggregating factor, and a variety of cytokines. Levels of tryptase, a natural protease present in the mast cell, are elevated in patients with anaphylaxis.⁸ These mediators may induce coronary vasospasm or even atheromatous plaque rupture as long as 48 hours after an allergic reaction. Myocardial ischemia caused by anaphylaxis-induced vasospasm is known as the Kounis syndrome, which includes allergic angina and allergic myocardial infarction.⁹

Electrocardiographic changes that may occur in patients with anaphylaxis include ST-segment elevations, flattening of the T waves, nodal rhythm, and atrial fibrillation.^{10,11} Although arrhythmias are described in patients with anaphylaxis, in this particular case, we believe that the NSVT was secondary to either epinephrine administration or the anaphylaxis itself, mainly because of its limited duration of approximately 20 seconds.

Coronary vasospasm is also called variant angina or Prinzmetal angina. It is a relatively uncommon cause of unstable angina, caused by an acute constriction of the coronary arteries, which is usually induced by stimuli such as exercise, cold, hyperventilation,¹² or mental stress.¹³ On angiographic evaluation, the coronaries may be normal or may have some diffuse thickening.¹⁴ The patient described herein had only minimal irregularities and no evidence of intimal plaque rupture, both consistent with the presumptive diagnosis of vasospasm. During an episode of vasospasm, some patients experience arrhythmias, as in this case. In this patient, the presence of NSVT was self-limited but was followed by ST-segment elevation in the inferior leads. Based on the distribution, there was likely vasospasm of the right coronary artery, which is often the affected coronary artery. Acute treatment of vasospasm includes nitrates (such as sublingual nitroglycerin and, if necessary, intravenous nitroglycerin) and the avoidance of hypotension and hypoxia.¹² Aspirin is often administered concomitantly given that plaque rupture cannot be ruled out immediately.

Given the lack of any significant plaque found on coronary catheterization, it is highly probable that this patient had vasospasm, not plaque rupture, as the cause of myocardial ischemia. Furthermore, the timing of ST-segment elevations and chest pain, within minutes after the administration of epinephrine, provides at least circumstantial evidence that in her case the epinephrine was the inciting culprit. There are a few reports in the literature of coronary vasospasm induced by epinephrine when administered subcutaneously¹⁵ and intranasally¹⁶ and, in particular, when an intravenous overdose was given, eg, 2 mg mistakenly pushed instead of a different intended medication.¹⁷ Hirabayashi et al¹⁸ reported the development of coronary vasospasm induced even by ephedrine, which was given to treat hypotension from a high spinal anesthetic. The ST-segment changes ultimately responded to treatment with intravenous nitroglycerin. Cohen et al¹⁹ reported the occurrence of recurrent coronary vasospasm after coronary artery bypass grafting that responded to direct in-

tracoronary administration of nitroglycerin. Patients who experience vasospasm but have normal coronary arteries have an excellent outcome of more than 95% survival at 5 years.¹⁴ Nevertheless, long-term treatment with nitrates or calcium channel blockers is sometimes recommended to decrease the risk of significant morbidities, including disabling pain, myocardial infarction, and ventricular arrhythmias.^{12,20}

The small increase in the troponin T level seen after this event showed that vasospasm decreased coronary perfusion sufficiently to cause myocardial cell injury, whereas the rapid resolution of ST-segment elevations and the lack of any wall motion abnormalities support the absence of any lasting, clinically significant myocardial injury. This combination suggests that prompt intervention likely prevented the development of a permanent myocardial scar.

Although rare, cardiovascular complications of anaphylactic reactions and their treatment should be identified and addressed promptly. Epinephrine, administered for an indicated cause, with a proper dose and route, is often lifesaving. In general, large intravenous doses are reserved for patients with significant hypotension or cardiovascular arrest, whereas intramuscular doses of a more concentrated solution provide significant relief of respiratory distress more safely. After administering epinephrine in any form, one should monitor vital signs and be alert to the development of new symptoms.

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