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A potential association between myocardial ischemia and epinephrine for anaphylaxis: A case report and literature review

Seigo Urushidani, MD^{a,b,*}, Akira Kuriyama, MD, MPH^a^a Emergency and Critical Care Center, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-8602, Japan^b Division of General Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

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ABSTRACT

A previously healthy 60-year-old man presented to our emergency department with anaphylactic shock. We initiated fluid resuscitation with Ringer's lactate solution; injected 0.3 mg epinephrine intramuscularly; and administered d-chlorpheniramine maleate 5 mg, famotidine 20 mg, and methylprednisolone 80 mg intravenously. His symptoms resolved within 10 min. Thirty minutes after the epinephrine injection, he complained of sudden chest discomfort. Physical examination provided no evidence of anaphylaxis. The 12-lead electrocardiogram (ECG) showed ST-segment depression on leads II, III, aVF, and V3-6. Transthoracic echocardiography revealed normal ventricular contraction. After administration of 0.3 mg of sublingual nitroglycerin, his chest pain resolved immediately and his ECG normalized. A coronary angiogram showed normal coronary artery perfusion. The next day, his high-sensitivity troponin I was slightly elevated. We suspected that he had myocardial ischemia caused by coronary artery spasm. The symptoms of biphasic reaction of anaphylaxis are inconsistent, and using epinephrine for myocardial ischemia following anaphylaxis may aggravate the condition. Nonetheless, epinephrine is the drug of choice for treating anaphylaxis with critical airway, respiratory, and circulatory compromise. Thus, physicians should not hesitate to use epinephrine for patients who present with life-threatening conditions due to suspected anaphylaxis. Physicians should observe patients closely following epinephrine administration, and if they develop some symptoms, should carefully examine the patients because the treatments of anaphylaxis and myocardial ischemia differs. Physicians should be alert to the risk of myocardial ischemia after treatment of anaphylaxis, especially following epinephrine administration.

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1. Case report

A 60-year-old man presented to our emergency department (ED) with a 30-min history of dyspnea and feeling faint after dinner. He was a smoker but had no history of hypertension, diabetes mellitus, dyslipidemia, or taking any illegal drugs.

On arrival, his vital signs were: respiratory rate 20 breaths/min, pulse 120 beats/min, and temperature 36.9 °C. He had a Glasgow Coma Scale score of 12 (E4, V2, M6). His radial arterial pulse was weak, and his blood pressure was not measurable. On examination, he had inspiratory stridor but no chest rales, no abdominal tenderness, and erythema on his face and trunk. A 12-lead electrocardiogram (ECG) showed a heart rate of 113 beats/min in sinus rhythm, with no ST-segment changes (Fig. 1A). He was diagnosed with anaphylactic shock. We initiated fluid resuscitation with Ringer's lactate solution; injected 0.3 mg epinephrine intramuscularly; and administered d-

chlorpheniramine maleate 5 mg, famotidine 20 mg, and methylprednisolone 80 mg intravenously. His symptoms resolved within 10 min.

Twenty minutes after his symptoms had resolved (30 min after epinephrine administration), the patient writhed with sudden chest discomfort. He had no inspiratory stridor or erythema on his face, trunk, or extremities, and his heart and lung sounds were normal. A 12-lead ECG showed ST-segment depression on leads II, III, aVF, and V3-6 (Fig. 1B). Transthoracic echocardiography revealed normal ventricular contraction. Sublingual nitroglycerin 0.3 mg was administered for suspected angina pectoris, his chest discomfort resolved immediately, and his ECG normalized. A coronary angiogram showed normal coronary arteries, so we suspected that coronary vasospasm was the cause of his myocardial ischemia. He was admitted and treated with oral diltiazem and provided with antismoking education. He was discharged after 3 days without recurrence of anaphylaxis or chest pain.

2. Discussion

Myocardial ischemia is known to occur in some people in association with anaphylaxis. Kounis and Zavras described myocardial ischemia caused by an acute allergic reaction in 1991 [1], and so the condition

* Corresponding author at: Emergency and Critical Care Center, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-8602, Japan.
E-mail address: m00009@jichi.ac.jp (S. Urushidani).

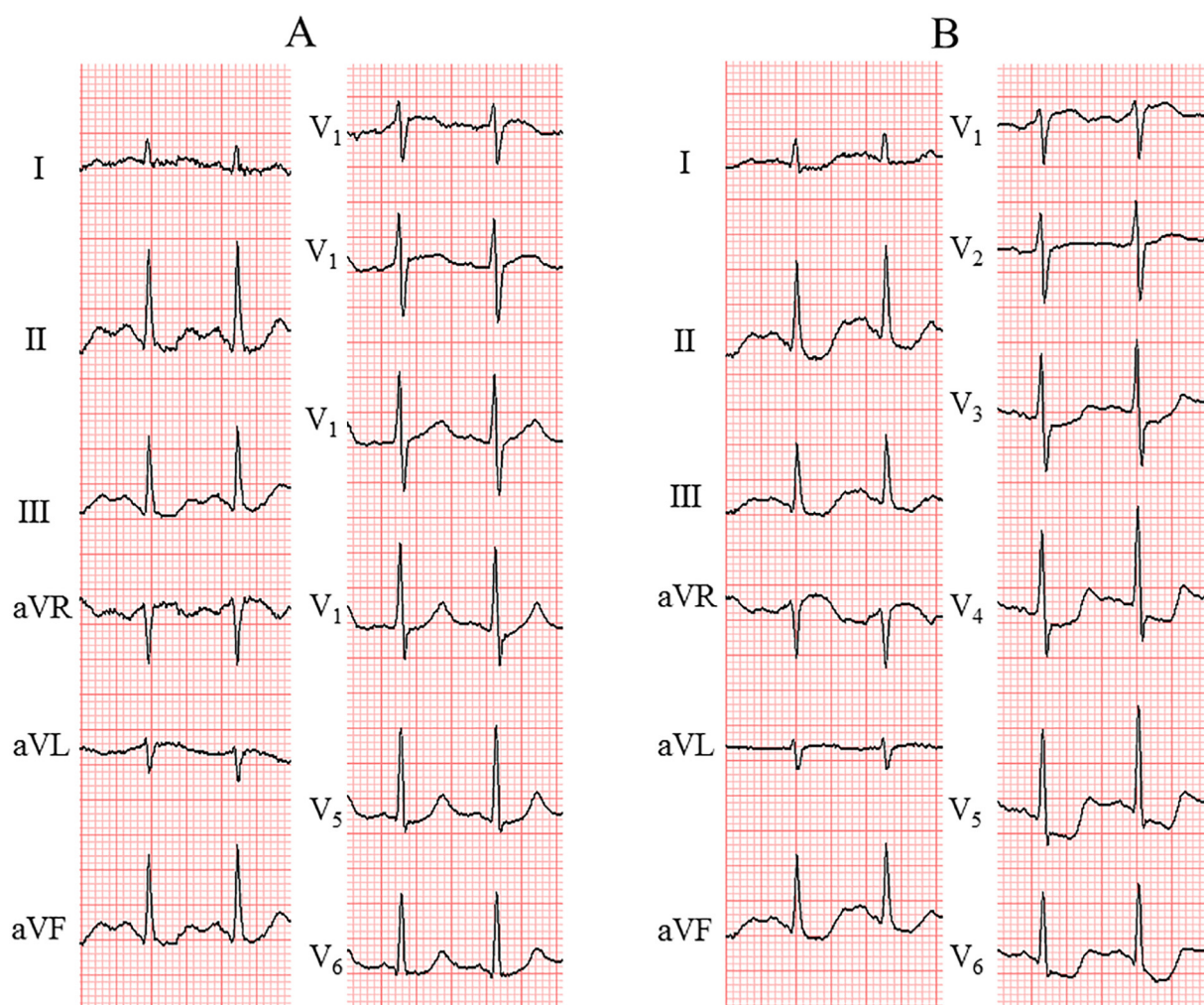


Fig. 1. (A) The 12-lead electrocardiogram (ECG) on arrival showed a sinus tachycardia with no ST-segment changes; and (B) the 12-lead ECG on 30 min after epinephrine administration showed ST-segment depression on leads II, III, aVF and V3-6.

has come to be known as Kounis syndrome. The prevalence of Kounis syndrome is estimated at about 19.4/100,000 of all admissions, and 3.4% of ED admissions due to allergy [2]. Kounis syndrome has 3 variants: Type I is coronary artery spasm caused by the acute release of inflammatory mediators in a normal or nearly-normal coronary artery; Type II is coronary artery spasm or plaque erosion in an artery with pre-existing atheromatous disease, and is caused by acute inflammatory mediators; and Type III is coronary artery stent thrombosis, in which eosinophils and/or mast cells are detected in the aspirated thrombus [3]. Our patient was a smoker, but did not have any other cardiovascular risk factors. His biphasic anaphylactic reaction raises the possibility that he had Kounis syndrome type I.

Epinephrine may cause spasm of the large coronary arteries with its alpha adrenergic effect [4]. Although rare, myocardial ischemia after administration of epinephrine for anaphylaxis can occur. Campbell et al. [5] reported that myocardial ischemia occurred in one of 316 patients (0.6%) to whom epinephrine had been administered intramuscularly. There have been 8 case reports of myocardial ischemia occurring as a result of administration of a therapeutic dose of epinephrine for anaphylaxis (Table 1) [6-13]. In these previous case reports, the patients' ages ranged from 21 to 55 years; 5 patients were men [6-8,11,13] and 3 were women [9,10,12]. Epinephrine was administered intramuscularly in 4 cases [7,11-13], subcutaneously in 3 [6,8,10], and intravenously in 1 [9]. In all cases except for one reported by Brener et al. [10], myocardial ischemia occurred within 15 min following epinephrine injection [6-9,11-13]. In the case of Brener et al. [10], the patient had received 3

doses of intramuscular epinephrine before arrival at the ED, and ST-segment elevation on ECG occurred 20 min after arrival. ECG was performed in all 8 cases. Seven of the patients had ST-segment elevation [6-12] and 1 had ST-segment depression [13]. Six cases were diagnosed as myocardial infarction [6,7,9,11-13] and 2 as angina pectoris [8,10]. Sublingual nitroglycerine was effective in 4 cases [8,9,11,13]. Coronary angiography was performed in all 8 cases and showed normal coronary arteries. In all 8 cases, the suspected cause of the myocardial ischemia was vasospasm [6-13]. Our patient experienced chest discomfort 30 min after epinephrine administration. The time from epinephrine administration to the onset of his chest discomfort was longer than that in the previous cases. However, Gu et al. [14] reported that after intramuscular epinephrine administration, the time of maximum plasma epinephrine concentration is about 40 min. Thus, epinephrine-induced myocardial ischemia is the most likely explanation for our patient's condition. Previous case reports suggest that sublingual nitroglycerine might be effective in patients who develop myocardial ischemia following epinephrine administration.

We administer nitroglycerine for suspected myocardial ischemia to our patient because he had no signs of airway obstruction, respiratory failure, or shock, and his presentation did not meet the criteria for anaphylaxis. The criteria for diagnosing anaphylaxis include life-threatening airway and/or breathing and/or circulation and/or gastroenterological problems, and some patients present with symptoms such as chest discomfort [15]. Moreover, the symptoms of biphasic reaction of anaphylaxis are inconsistent [16]. Thus, there is a risk of

Table 1

Summary of the demographic and clinical characteristics of 8 cases of epinephrine-induced myocardial ischemia and our patient.

Author year	Age/Sex	Dose and the way of administration of epinephrine	The time from Epinephrine injection to onset	ST-segment on ECG	Sublingual nitroglycerine	Diagnostic modality	Diagnosis
Ferry 1986 [6]	43 M	0.3 mg s.c.	15 min	Elevation	Unknown	CK-MB	Myocardial infarction
Saff 1993 [7]	30 M	0.3 mg s.c. 0.3 mg i.m.	5 min	Elevation	Unknown	CAG	Myocardial infarction
Rubio 1999 [8]	41 M	0.5 mg s.c.	Several minutes	Elevation	Effective	CAG	Angina pectoris
Shaver 2006 [9]	29 F	0.1 mg i.v.	Immediately	Elevation	Effective	Troponin US	Myocardial infarction
Brener 2007 [10]	55 F	0.2 mg s.c. 0.2 mg s.c. 0.3 mg s.c.	About 1 h	Elevation	Unknown	CAG	Angina pectoris
Kroll 2012 [11]	38 M	0.3 mg i.m.	Immediately	Elevation	Effective	Troponin CAG	Myocardial infarction
Cunnington 2013 [12]	43 F	0.5 mg i.m.	5 min	Elevation	Not administered	Troponin CAG	Myocardial infarction
Jayamali 2017 [13]	21 M	0.5 mg i.m.	10 min	Depression	Effective	Troponin US	Myocardial infarction
Our case	60 M	0.3 mg i.m.	30 min	Depression	Effective	CTA	Angina pectoris
						Troponin US	
						CAG	

Abbreviations: M; male, F; female, s.c.; subcutaneous injection, i.m.; intramuscular injection, i.v. intravenous injection, CK-MB; creatine kinase-MB, US; ultrasound, CAG; coronary angiography, CTA; coronary CT angiography.

physicians missing myocardial ischemia in patients who experience some symptoms, including chest discomfort, after treatment of anaphylaxis. If cases of acute myocardial ischemia after anaphylaxis, such as that experienced by our patient, are considered to be a biphasic reaction of anaphylaxis, clinicians may use epinephrine and this may aggravate the patient's myocardial ischemia. Nonetheless, epinephrine is the drug of choice for treating anaphylaxis with critical airway, respiratory, and circulatory compromise. Thus, physicians should not hesitate to use epinephrine for patients with life-threatening conditions due to suspected anaphylaxis [15]. Physicians should observe patients closely following epinephrine administration, and should carefully examine patients who develop chest discomfort because the treatment of anaphylaxis and myocardial ischemia differs.

Myocardial ischemia, including Kounis syndrome, can occur after treatment of anaphylaxis. Physicians should be alert to the risk of myocardial ischemia after treatment of anaphylaxis, especially after epinephrine administration.

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Declaration of competing interest

Both authors declare that they have no conflicts of interest.

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