Received: 9 January 2021 | Revised: 23 January 2021 | Accepted: 27 January 2021

DOI: 10.1111/anec.12837

CASE REPORT

WILEY

Should beta-blockers be continued as a treatment for myocardial infarction in the case of Kounis syndrome?

Mari Amino MD, PhD[1,2] | Tomokazu Fukushima MD[2] | Atsushi Uehata MD[2] | Chiemi Nishikawa MD[2] | Seiji Morita MD, PhD[2] | Yoshihide Nakagawa MD, PhD[2] | Tsutomu Murakami MD, PhD[1] | Koichiro Yoshioka MD, PhD[1] | Yuji Ikari MD, PhD[1]

[1]Department of Cardiology, Tokai University, Isehara, Japan

[2]Department of Emergency Care Medicine, Tokai University, Isehara, Japan

Correspondence
Mari Amino, Department of Cardiology, Tokai University, Shimokasuya 143, Isehara, 259-1193, Japan.
Email: mariam@is.icc.u-tokai.ac.jp

Abstract

A 71-year-old male patient reported to our hospital with anaphylactic shock, and the following two issues were focused in this case. First, he was resistant to adrenaline because of taking beta-blocker, and shock was repeated until glucagon administration was initiated. Second, he developed acute coronary syndrome. Two mechanisms contributing to Kounis syndrome were differentiated: 1) adrenaline induced coronary spasm and platelet activation or 2) a mismatch between oxygen supply and demand due to an allergic reaction. Beta-blocker therapy was discontinued because his cardiac function was preserved. Secondary preventive beta-blockers in recovering myocardial infarction with severe anaphylaxis history should be carefully considered.

KEYWORDS

adrenaline, anaphylaxis, beta-blockers, glucagon, Kounis syndrome

1 | INTRODUCTION

The administration of adrenaline to resolve anaphylactic shock may be insufficient in patients taking oral beta-blockers (Lang, 1995). Additionally, adrenaline or anaphylaxis chemical mediators increase the risk of myocardial infarction (MI), referred to as Kounis syndrome (Kounis, 2016). Prior reports comprised 235,420 allergy patients have found a 1.1% prevalence and 7.0% inhospital mortality (Desai et al., 2019). Kounis classification has three variants: type 1, coronary spasm; type 2, coronary thrombus due to atherosclerotic plaque disruption and thrombus aggregation; and type 3, stent thrombosis/restenosis (Abdelghany et al., 2017).

2 | CASE REPORT

The patient was a 71-year-old male with a history of allergy to mackerel. Having worked as a landscaper for 20 years, however, he had no history of bee allergy. On a morning in August 2020, at 9:00 a.m., he began lawn mowing and was attacked by bees that stung him on the left lower eyelid, anterior forehead, left upper lip, and right dorsal hand. A colleague soon noticed his loss of consciousness and immediately called in the emergency.

Upon on-site arrival (Figure 1, left), the vital signs were as follows: Japan coma scale 1, Glasgow coma scale 4–5–6, blood pressure 60 mmHg, heart rate 99bpm (regular), respiratory rate 30/min, oxygen saturation 90%, and pupil size 3 mm/3 mm with normal light reflex. General respiratory sounds were faint, although wheezing and rale were noted. The extremities were moist, and a rash with itching was present on the abdominal skin. The emergency dispatch physician administered 0.3 mg adrenaline intramuscular injection (i.m.) twice for the prolonged shock.

The patient was transferred to the emergency department, but the hypotension returned. The third 0.3 mg adrenaline i.m. was administered, followed by intravenous administration of famotidine, dexchlorpheniramine maleate, and hydrocortisone

This is an open access article under the terms of Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2021 The Authors. *Annals of Noninvasive Electrocardiology* published by Wiley Periodicals LLC

sodium succinate. Cold sweats and nausea were detected, and the patient lost consciousness again. At this point, we discovered that he had taken oral agents, bisoprolol (2.5 mg), azilsartan (40 mg), and amlodipine (10 mg), due to previous abdominal aortic dissection and hypertension. Therefore, we immediately administered 1 mg of glucagon intravenously slow injection, after which consciousness was rapidly regained. After admission to the intensive care unit, no anaphylaxis relapses occurred, and the skin symptoms improved.

Time-course electrocardiographs (ECGs) are shown in Figure 2. A normal finding was observed on ECG-1. However, after adrenaline administration, lead III in ECG-2 revealed a q wave plus low QRS voltage and 1 mm of ST elevation, low QRS voltage in V1-V6, and a tendency toward prolonged QT intervals. Follow-up blood tests showed a significant increase in cardiac enzymes (Table 1). Since the patient had no chest symptoms and preserved ejection fraction (EF 60%), and the golden time passed for percutaneous coronary intervention (PCI), conservative treatments were selected. ECGs showed various changes afterward (Figure 2), and elevated enzymes persisted until at least day 6 (Table 1).

A coronary computed tomography scan on day 5 revealed stenosis of the left anterior descending (LAD) coronary artery (Figure 3a); therefore, PCI was enforced for segment 6 on day 13 (Figure 3b). Nitrite and antiplatelet agents were administered, and calcium antagonist was increased to the maximum dose instead of beta-blockers for control in both MI and blood pressure. An ^{123}I-metaiodobenzylguanidine nuclear medicine study (^{123}I-MIBG; Fuji Film RI Pharma, Tokyo, Japan), which evaluated sympathetic nerve denervation, revealed reduced uptake at the wall anteroinferior to the apex at day 30 (Figure 3c). Analysis of the patient's heart rate variability using high-resolution ambulatory ECG showed vagal hyperactivity while awake and relative sympathetic hyperactivity while asleep, thereby indicating autonomic circadian disorder (Figure 3d).

3 | DISCUSSION

The two main considerations in this case were as follows: 1) the impact of adrenergic sensitivity on anaphylaxis against a backdrop of oral beta-blocker therapy and 2) the necessity of beta-blockers during the chronic phase in patients with Kounis syndrome.

First, oral beta-blockers reportedly blunt the physiological responses of beta-receptors to catecholamine, and furthermore, the stimulation of alpha- and beta-adrenergic receptors by adrenaline tend toward relatively alpha-stimulation and increases the risk of both severe bradycardia and cardiac arrest (Lang, 1995). In adrenaline-refractory cases, the use of glucagon is appropriate because it increases the concentration of cyclic adenosine

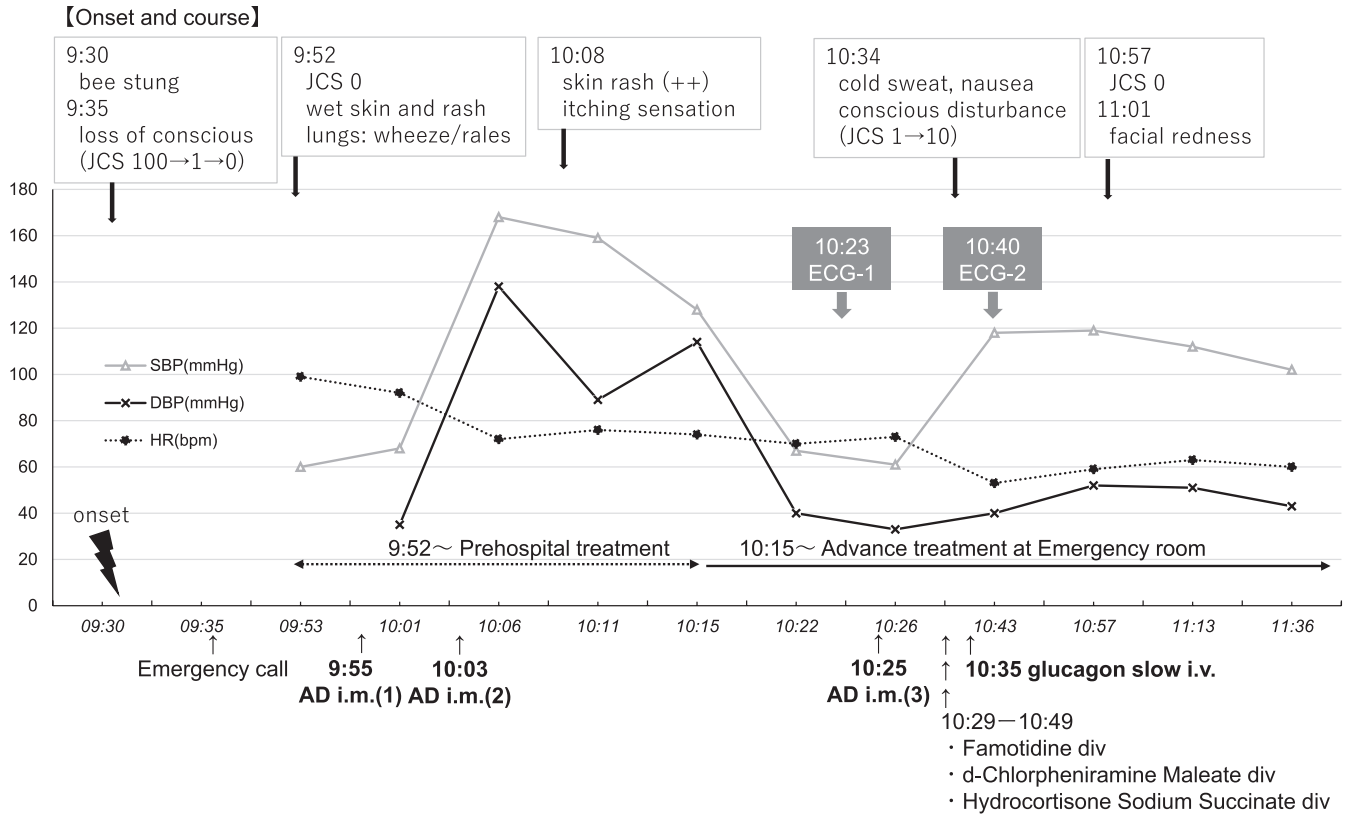
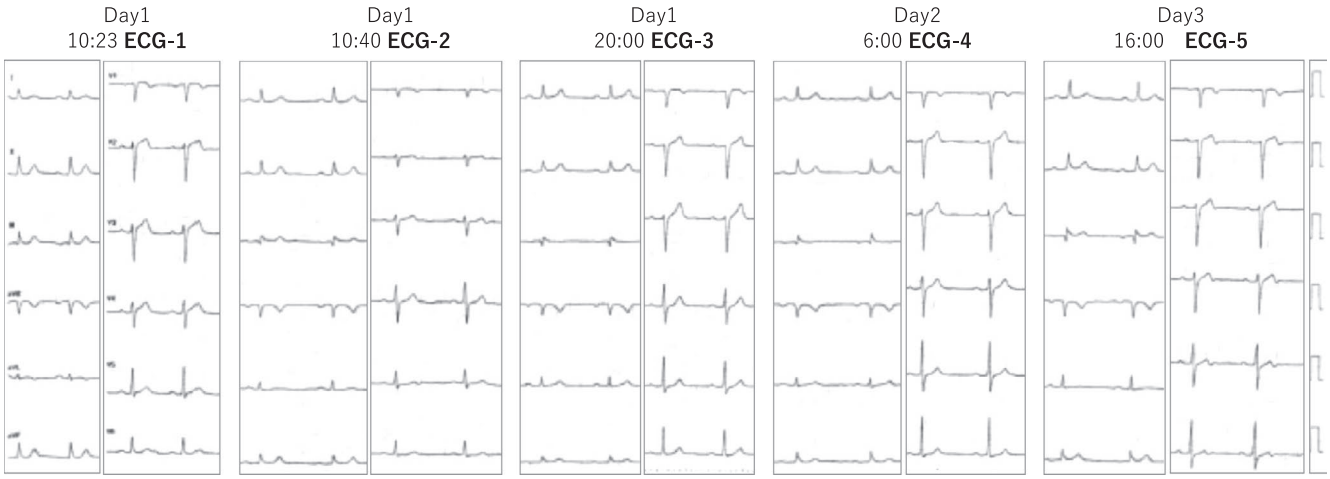


FIGURE 1 Onset and course. AD, adrenaline; DBP, diastolic blood pressure; ECG, electrocardiography; HR, heart rate; i.m., intramuscular injection; i.v., intravenous injection; JCS, Japan coma scale; SBP, systolic blood pressure

monophosphate in the myocardium without β-receptor involvement (Figure 4a). However, it should be noted that rapid bolus injection may induce vomiting, so patients with consciousness disturbance should be airway secured in the supine position. In addition, the drug for lifesaving in anaphylaxis can by itself induce anaphylaxis. Sodium metabisulfite is commonly used as an antioxidant in the food and pharmaceutical industries, and every commercially adrenaline contains sodium metabisulfite (Kounis et al., 2020). Metabisulfite developed urticaria, angioedema, and nasal congestion through an IgE-mediated mechanism (Sokol & Hydick, 1990), increased discomfort during injection of lidocaine added with adrenaline (Campbell et al., 2001), and induced anaphylactic shock during the administration of epidural anesthesia for caesarian sections (Soulat et al., 1991).

Second, ACS in the present case probably developed within a brief time after the second administration of adrenaline. Adrenaline sometimes stimulates a potent coronary spasm (Ferry et al., 1986), and secondary promotes platelet activation via sympathetic stimulation (Table 2) (Larsson et al., 1989; Laustiola et al., 1986; Wallén et al., 1999). Adrenaline also induced autonomic imbalance in the Figure 4b. In this case, the patient's heart rate was 99 bpm before adrenaline intramuscularly administration, which reduced it to 70 bpm. Increasing cardiac rate by β1 stimulation was not observed. Therefore, adrenaline appears less likely to be the cause



	ECG-1	ECG-2	ECG-3	ECG-4	ECG-5
Findings	NSR	NSR, III q wave + QRS low voltage, ST ↑ (1mm), V1-6 QRS low voltage	NSR, IAV-block, III flat T	NSR, IAV-block, III flat T	NSR, IAV-block, III ST ↑, V2-6 terminal T inversion
Heart rate (bpm)	71	52	56	51	56
PR interval (ms)	198	208	242	238	226
QRS width (ms)	102	102	102	114	112
QT interval (ms)	374	426	402	410	396
QTc interval (ms)	397	407	393	386	386

FIGURE 2 Longitudinal electrocardiography (ECG) changes. AV block, atrial ventricle block; NSR, normal sinus rhythm. The gray area shows the highest value among the examinations

TABLE 1 Laboratory data

	Day1			Day2	Day3	Day4	Day5	Day6	Day10
	10:23	16:00	22:00	6:00	6:00	6:00	6:00	6:00	6:00
WBC (/μl)	7,900	15,900	13,900	11,400	8,100	7,000	6,800	7,400	8,000
CK (U/L)	86	447	490	406	178	105	80	65	63
CK-MB (U/L)	19	–	66	52	–	–	–	–	–
CK-MB%	22.1	–	13.6	12.9	–	–	–	–	–
GOT (U/L)	17	73	87	91	47	27	22	18	16
LDH (U/L)	237	276	264	282	263	253	283	262	189
CRP (mg/dl)	<0.09	–	–	1.09	0.77	0.38	0.19	0.12	<0.09
TropT (ng/ml)	14	1,122	1,624	1,080	635	763	598	380	10

Note: Gray area: Higher than the hospital's normal threshold.

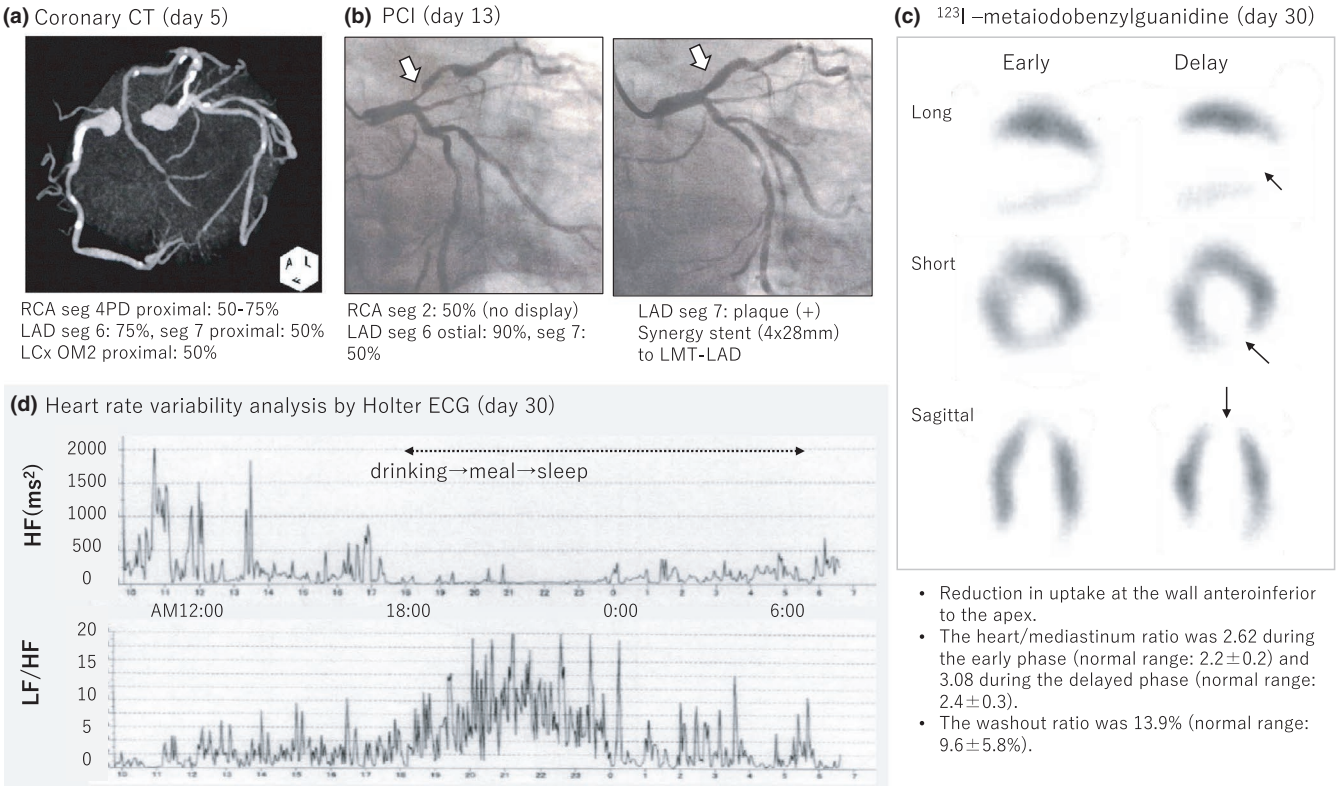


FIGURE 3 Diagnosis of cardiac disease. (a) CT, computed tomography; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; OM2, second obtuse marginal branch; PD, posterior descending; RCA, right coronary artery. (b) PCI, percutaneous coronary intervention; LMT, left main trunk. (c) ^{123}I-metaiodobenzylguanidine nuclear medicine study. (d) Heart rate variability. HF, high frequency; LF, low frequency

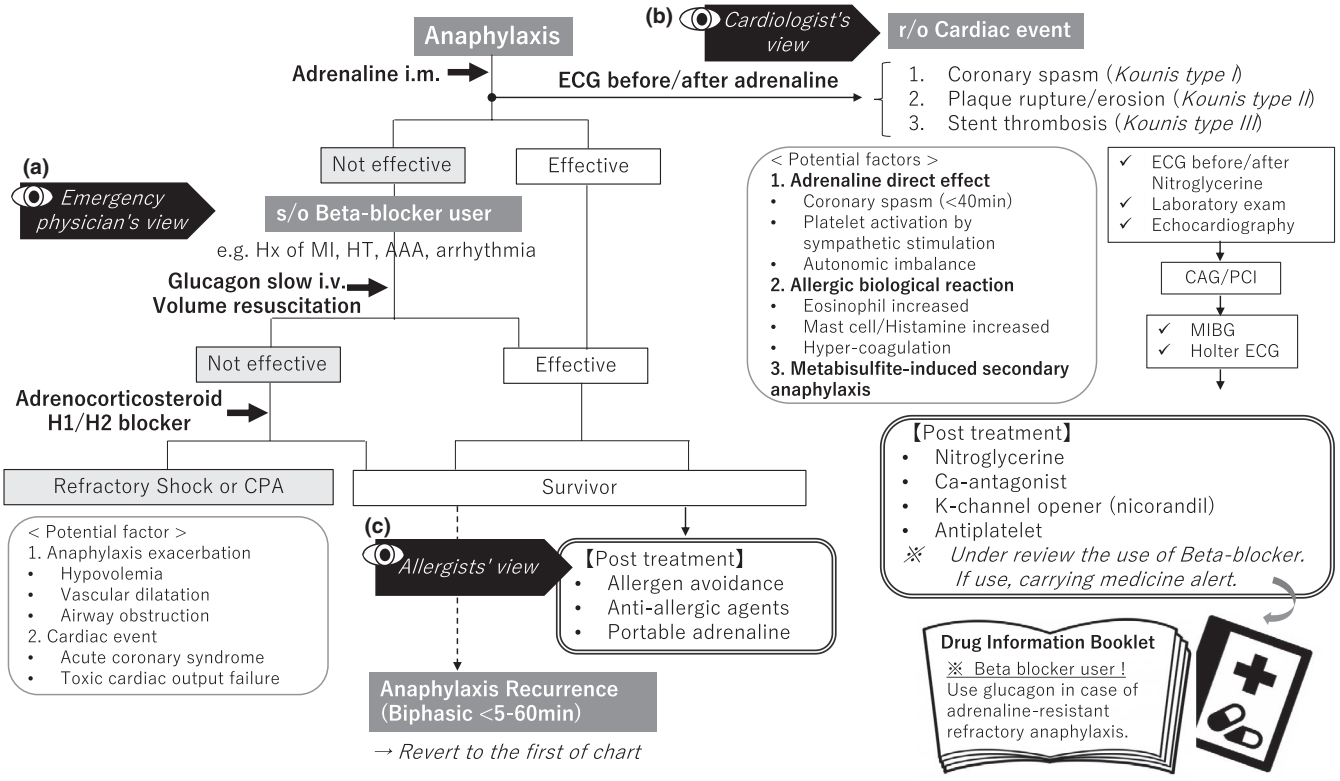


FIGURE 4 Flowchart for anaphylaxis treatment (Author's original). (a) Emergency physician's view. (b) Cardiologist's view. (c) Allergists' view. AAA, abdominal aortic aneurysm; CAG, coronary angiography; for example, H1/H2 blocker, histamine 1/histamine 2 blocker; HT, hypertension; Hx, history; i.m., intramuscular injection; i.v., intravenous injection; MIBG, ^{123}I-metaiodobenzylguanidine nuclear medicine study; MI, myocardial infarction; PCI, percutaneous coronary intervention

TABLE 2 Adrenaline effects

Receptor	Subtype	Physiological action	Cardiac effect	Extracardiac effect
β	β1	• Increasing cardiac rate • Increasing cardiac contraction • Enhanced renin secretion • Enhanced lipolysis	Heart rate↑ Cardiac output↑ Blood pressure↑	Peripheral vascular resistance↓
	β2	• Relaxation of smooth muscle (bronchi/vessel/ureter/uterus/gastrointestinal) • Reducing the release of inflammatory mediators • Degradation of glycogen • Increasing of insulin and glucagon release		Blood glucose↑ Release asthma
		• Potentiate platelet reactivity by increasing platelet production of thromboxane B2, heightening the sensitivity of platelets to adenosine diphosphate (Larsson et al., 1989; Laustiola et al., 1986)	⇒ *Risk of myocardial infarction*	
	β3	• Enhanced lipolysis • Increasing heat production		Hypermetabolism
α1		• Contraction of smooth muscle(vessel/gastrointestinal/ureter/uterus/bronchi) • Degradation of glycogen		Blood pressure↑ Hemostatic action
α2		• Suppression of insulin and noradrenaline release • Enhanced lipolysis • Contraction of smooth muscle (vessel/gastrointestinal)		
		• Potentiate platelet reactivity by increasing induced binding of platelets to fibrinogen (Larsson et al., 1989; Wallén et al., 1999)	⇒ *Risk of myocardial infarction*	

of the coronary spasm. However, at the recognition of the second shock, the possibility of Kounis type I should have been considered, and the third adrenaline administration should have been avoided.

As another mechanism of ACS, allergic biological reactions cause increased eosinophils and mast cells in cardiac tissue (Kounis, 2016), which leads to hypercoagulation (Figure 4b). Large amounts of released cytokines, histamine, and platelet-activating factor by degranulation from mast cells directly damage the vascular endothelium and increase vascular permeability through dynamic migration, which results in an imbalance between intercellular and intravascular plasma volume (Varricchi et al., 2019). These mechanisms differ from those of plaque destruction observed in common MI (Thygesen et al., 2018). In this patient, significant stenosis in the proximal LAD region and persistent severe hypotension might have induced a mismatch between coronary oxygen supply and demand; diagnosis of Kounis type II may be appropriate (Figure 4b).

The Japanese Circulation Society Guidelines 2018 recommend that long-term oral beta-blocker therapy is needed for MI patients with heart failure or reduced EF (Kimura et al., 2019). In contrast, it is not mandatory in our country for preserved EF patients because of the high rate of PCI. Randomized clinical trials comparing beta-blockers and Ca antagonists (JBCMI) (JBCMI Investigators, 2004) or comparing carvedilol-treated and non-treated patients (CAPITAL-RCT) (Watanabe et al., 2018) showed no significant difference in the incidence of cardiovascular death and reinfarction between groups. Contraindications to beta-blockers were present; Ca antagonist or no medication may be a substitute option.

4 | CONCLUSION

In this patient with preserved EF, Ca antagonists were the best agents instead of beta-blockers as second prevention plus nitrite and antiplatelet agents. The patient carries a portable adrenaline injection and takes oral antiallergic agents because he intended to resume his landscaping business, whereas patients in whom beta-blockers need to be continued due to low EF should be instructed to carry a drug information booklet to inform the appropriate initial treatment for anaphylaxis (Figure 4b). Insurance reimbursement is currently available for only portable epinephrine injections; however, nasal glucagon will also be hoped to covering by insurance in the future. The most crucial factor that affects the prognosis is close cooperation for the treatments among emergency physicians' management for anaphylactic shock (Figure 4a), cardiologists' assessment of beta-blocker administrations (Figure 4b), and allergists' preventive care for allergies (Figure 4c).

ACKNOWLEDGMENT

We would like to thank Editage (www.editage.com) for English language editing.

CONFLICT OF INTEREST

All authors have reported that they have no relationships relevant to the contents of this article to disclose.

AUTHOR CONTRIBUTIONS

Contributed to the conception and design of this case report, involved in drafting the manuscript and revising it critically, and agreed to be accountable for all aspects of the work: all authors.

ETHICS

Additionally, the authors have obtained the patient's free informed consent for the publication of this case report per the journal's ethical guidelines.

ORCID

Mari Amino https://orcid.org/0000-0003-4562-7141
Yuji Ikari https://orcid.org/0000-0001-5686-4324

REFERENCES

Abdelghany, M., Subedi, R., Shah, S., & Kozman, H. (2017). Kounis syndrome: A review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *International Journal of Cardiology*, *232*, 1–4. https://doi.org/10.1016/j.ijcard.2017.01.124

Campbell, J. R., Maestrello, C. L., & Campbell, R. L. (2001). Allergic response to metabisulfite in lidocaine anesthetic solution. *Anesthesia Progress*, *48*, 21–26.

Desai, R., Parekh, T., Patel, U., Fong, H. K., Samani, S., Patel, C., Savani, S., Doshi, R., Kumar, G., & Sachdeva, R. (2019). Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: A nationwide inpatient analysis. *International Journal of Cardiology*, *292*, 35–38. https://doi.org/10.1016/j.ijcard.2019.06.002

Ferry, D. R., Henry, R. L., & Kern, M. J. (1986). Epinephrine-induced myocardial infarction in a patient with angiographically normal coronary arteries. *American Heart Journal*, *111*, 1193–1195. https://doi.org/10.1016/0002-8703(86)90023-2

Japanese beta-Blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Investigators (2004). Comparison of the effects of beta blockers and calcium antagonists on cardiovascular events after acute myocardial infarction in Japanese subjects. *American Journal of Cardiology*, *93*, 969–973.

Kimura, K., Kimura, T., Ishihara, M., Nakagawa, Y., Nakao, K., Miyauchi, K., Sakamoto, T., Tsujita, K., Hagiwara, N., Miyazaki, S., Ako, J., Arai, H., Ishii, H., Origuchi, H., Shimizu, W., Takemura, H., Tahara, Y., Morino, Y., Iino, K., … Yamazaki, T. (2019). JCS 2018 guideline on diagnosis and treatment of acute coronary syndrome. *Circulation Journal*, *83*, 1085–1196. https://doi.org/10.1253/circj.CJ-19-0133

Kounis, N. G. (2016). Kounis syndrome: An update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clinical Chemistry and Laboratory Medicine*, *54*, 1545–1559. https://doi.org/10.1515/cclm-2016-0010

Kounis, N. G., Koniari, I., Tsigkas, G., Soufras, G., Plotas, P., Davlouros, P., & Hahalis, G. (2020). Angina following anaphylaxis: Kounis syndrome or adrenaline effect? *Malays Fam Physician*, *15*, 97–98.

Lang, D. M. (1995). Anaphylactoid and anaphylactic reactions: Hazards of beta-blockers. *Drug Safety*, *12*, 299–304.

Larsson, P. T., Hjemdahl, P., Olsson, G., Egberg, N., & Hornstra, G. (1989). Altered platelet function during mental stress and adrenaline infusion in humans: Evidence for an increased aggregability in vivo as measured by filtragometry. *Clinical Science (Lond)*, *76*, 369–376. https://doi.org/10.1042/cs0760369

Laustiola, K., Kaukinen, S., Seppälä, E., Jokela, T., & Vapaatalo, H. (1986). Adrenaline infusion evokes increased thromboxane B2 production by platelets in healthy men: The effect of beta-adrenoceptor blockade. *European Journal of Clinical Investigation*, *16*, 473–479.

Sokol, W. N., & Hydick, I. B. (1990). Nasal congestion, urticaria, and angioedema caused by an IgE-mediated reaction to sodium metabisulfite. *Ann Allergy*, *65*, 233–238.

Soulat, J. M., Bouju, P., Oxeda, C., & Amiot, J. F. (1991). Choc anaphylactoïde aux métabisulfites au cours d'une césarienne sous anesthésie péridurale [Anaphylactoid shock due to metabisulfites during cesarean section under peridural anesthesia]. *Cahiers D'anesthesiologie*, *39*, 257–259.

Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., & White, H. D. (2018). Fourth universal definition of myocardial infarction. *Journal of the American College of Cardiology*, *72*, 2231–2264.

Varricchi, G., de Paulis, A., Marone, G., & Galli, S. J. (2019). Future needs in mast cell biology. *International Journal of Molecular Sciences*, *20*, 4397.

Wallén, N. H., Goodall, A. H., Li, N., & Hjemdahl, P. (1999). Activation of haemostasis by exercise, mental stress and adrenaline: Effects on platelet sensitivity to thrombin and thrombin generation. *Clinical Science (Lond)*, *97*, 27–35. https://doi.org/10.1042/cs0970027

Watanabe, H., Ozasa, N., Morimoto, T., Shiomi, H., Bingyuan, B., Suwa, S., Nakagawa, Y., Izumi, C., Kadota, K., Ikeguchi, S., Hibi, K., Furukawa, Y., Kaji, S., Suzuki, T., Akao, M., Inada, T., Hayashi, Y., Nanasato, M., Okutsu, M., … Kimura, T. (2018). Long-term use of carvedilol in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *PLoS One*, *13*, e0199347. https://doi.org/10.1371/journal.pone.0199347

How to cite this article: Amino M, Fukushima T, Uehata A, et al. Should beta-blockers be continued as a treatment for myocardial infarction in the case of Kounis syndrome? *Ann Noninvasive Electrocardiol*. 2021;26:e12837. https://doi.org/10.1111/anec.12837