Recurrent Coronary Artery Spasm Induced by Vasopressors During Two Operations in the Same Patient Under General Anesthesia

Naotaka Kishimoto, DDS, PhD, Munenori Kato, DDS, Yasunori Nakanishi, DDS, Akari Hasegawa, DDS, and Yoshihiro Momota, DDS, PhD

Department of Anesthesiology, Osaka Dental University, Osaka, Japan

Variant angina is caused by coronary artery spasm (CAS) with ST-segment elevation. We herein report a case of recurrent CAS during 2 operations in the same patient. An 80-year-old woman was scheduled to undergo tracheostomy, submandibular dissection, left partial maxillectomy, and coronoidectomy. We administered ephedrine and phenylephrine to manage hypotension during general anesthesia. Immediately after the administration of these drugs, the ST segment elevated. We decided to cease the operation and transport the patient to the department of cardiology. Computed tomography angiography revealed pneumomediastinum. The cardiologists considered that the electrocardiography findings had changed secondary to pneumomediastinum. About 6 weeks later, a second operation was scheduled. We administered ephedrine and phenylephrine to manage hypotension during general anesthesia. Immediately after the administration of these drugs, ST-segment elevation occurred. We discontinued use of these drugs, and the ST-segment elevation did not recur. We considered that the cause of the ST-segment elevation was vasopressor-induced CAS because the vasopressors were administered immediately before the occurrence of CAS. Vasopressors such as ephedrine or phenylephrine are frequently used to manage hypotension during general anesthesia. Therefore, anesthesiologists should consider the occurrence of CAS before using vasopressors and know how to manage CAS well.

Key Words: Coronary artery spasm; ST-segment elevation; Ephedrine; Phenylephrine; General anesthesia.

In 1959, Prinzmetal et al.¹ reported an unusual syndrome of cardiac pain that occurred during rest, not exertion, and involved electrocardiographic ST-segment elevation. This syndrome is now known as Prinzmetal's angina or variant angina.² Variant angina is caused by coronary artery spasm (CAS).^{2,3} Perioperative CAS may be associated with acute myocardial infarction, severe arrhythmia, and sudden death.⁴⁻⁶ Therefore, early diagnosis and treatment are important. Several reports have described perioperative CAS.^{3,7-10} However, recurrent CAS in the same patient under general anesthesia is rare.⁴ We herein report a case of recurrent CAS caused by vasopressors during 2 operations in same patient under general anesthesia.

Received February 9, 2017; accepted for publication March 31, 2017.

Address correspondence to Naotaka Kishimoto, Department of Anesthesiology, Osaka Dental University, 1-5-17 Otemae, Chuo-ku, Osaka 540-0008, Japan; kishimoto@cc.osaka-dent.ac.jp.

Anesth Prog 65:44-49 2018 | DOI 10.2344/anpr-64-04-04
© 2018 by the American Dental Society of Anesthesiology

CASE PRESENTATION

An 80-year-old woman (height, 156 cm/61 in; weight, 52 kg) was scheduled to undergo tracheostomy, submandibular dissection, left partial maxillectomy, and coronoidectomy after being diagnosed with carcinoma of the left upper gingival and buccal mucosa. The patient had a history of hypertension and hypothyroidism and took candesartan and levothyroxine. Her preoperative blood pressure (BP) and heart rate (HR) were 122/81 mm Hg and 75 beats per minute (bpm), respectively. Her serum concentrations of free thyroxine and thyroid-stimulating hormone were 1.67 ng/dL (reference range, 0.70–1.48 ng/dL) and 0.05 μ IU/mL (reference range, 0.35–4.94 μ IU/mL), respectively. Therefore, her hypertension and hypothyroidism were relatively well controlled by these medications. Preoperative 12-lead electrocardiography (ECG) showed an incomplete right bundle branch block and sinus bradycardia (HR, 56 bpm) (Figure 1).

No premedication was given, and the patient walked into the operating room. ECG after entering the

Figure 1. Preoperative 12-lead electrocardiography. An incomplete right bundle branch block and sinus bradycardia (heart rate, 56 bpm) were present.

operating room showed a normal sinus rhythm (HR, 69 bpm) (Figure 2A). After administration of 3 mg of midazolam, an oral surgeon commenced a surgical tracheostomy. The tracheostomy tube was inserted into the trachea 40 minutes after the administration of midazolam. Bucking occurred during insertion of the tracheostomy tube despite the fact that lidocaine had been injected into the patient's trachea before insertion. After confirmation of capnographic waveforms on the monitor, general anesthesia was induced with a bolus of propofol (50 mg), fentanyl (100 µg), and rocuronium (50 mg), and maintained with air (2.5 L/min), oxygen (0.5 L/min), and 4% desflurane. The patient's BP and HR changed from 126/60 mm Hg and 68 bpm before induction of general anesthesia to 96/48 mm Hg and 72 bpm after induction, respectively. We administered ephedrine (4 mg); the BP then increased to 201/166 mm Hg, and marked ST-segment elevation was noted on the monitor (Figure 2B). The ST-segment elevation returned to baseline about 5 minutes later. The patient's BP and HR were 90/44 mm Hg and 72 bpm, respectively, 30 minutes after induction of anesthesia. We administered phenylephrine (0.1 mg); the patient's BP then rose to 196/110 mm Hg, and the ST-segment elevation recurred. We decided to cease the operation after completion of only the tracheostomy. After finishing the tracheostomy, we discontinued the desflurane and administered sugammadex (200 mg). The

ST-segment elevation returned to baseline when the patient woke from general anesthesia. She did not complain of chest pain or discomfort. We transported the patient to the general hospital (next to our dental

Figure 2. Intraoperative electrocardiography during the first operation. (A) Before induction of general anesthesia. (B) Immediately after administration of ephedrine during general anesthesia.

Figure 3. Intraoperative electrocardiography during the second operation. (A) Before induction of general anesthesia. (B) Immediately after administration of ephedrine during general anesthesia.

hospital) by ambulance because our hospital contains no department of cardiology. The patient's consciousness was clear when she arrived at the general hospital. Twelve-lead ECG at the general hospital showed an incomplete right bundle branch block and no other abnormalities. The patient's cardiac contraction remained almost normal; her ejection fraction and fractional shortening were 70.3% and 39.6%, respectively, on ultrasonic cardiography. The concentrations of the cardiac markers creatine phosphokinase-MB and troponin I were 1.0 IU/L (reference range, 8.0–13.0 IU/L) and 3.6 pg/mL (reference range, 0.0–50,000.0 pg/mL), respectively. Coronary computed tomography (CT) angiography showed no significant coronary stenosis or obstruction; however, subcutaneous emphysema and pneumomediastinum were evident. The cardiologists suspected that the ECG changes had been caused by pneumomediastinum as a complication of the tracheostomy. He presumed that the patient's heart had been compressed by air in the mediastinum. Cefazolin was intravenously administered to prevent infection associated with the subcutaneous emphysema and pneumomediastinum in the general hospital. The subcutaneous emphysema and pneumomediastinum resolved, and the patient returned to our hospital 4 days after her transport to the general hospital. The tracheostomy tube was removed that day. During hospitalization, the oral surgeons told the patient and her family that our hospital would be unable to manage general complications of tracheostomy, such as pneu-

momediastinum, if they recurred at the time of reoperation. The surgeons also told them that the patient could undergo the operation at the general hospital as an option. However, the patient and her family strongly wished for the patient to undergo the operation in our hospital. The oral surgeons decided to conduct left partial maxillectomy and coronoidectomy without tracheostomy or submandibular dissection. Sixteen days after tracheostomy removal, the patient was discharged from our hospital.

About 3 weeks after discharge, the patient returned to our hospital for the reoperation. No premedication was given, and the patient walked into the operating room. ECG after entering the operating room showed a normal sinus rhythm (HR, 67 bpm) (Figure 3A). General anesthesia was induced with a bolus of midazolam (5 mg), fentanyl (150 µg), and rocuronium (40 mg). After performing mask ventilation for 3 minutes with oxygen at 6 L/min, nasotracheal intubation was performed. General anesthesia was maintained with air (2.5 L/min), oxygen (0.5 L/min), sevoflurane (1.5%), remifentanyl (0.1–0.2 µg/kg/min), and 3 boluses of fentanyl (up to 150 µg). Twenty minutes after starting the operation, the patient's BP and HR were 84/50 mm Hg and 65 bpm, respectively. We administered phenylephrine (0.1 mg), and her BP and HR were 160/78 mm Hg and 67 bpm, respectively. At that time, the ST segment elevated. The ST-segment elevation returned to baseline about 5 minutes later. Fifteen minutes later, the patient's BP and HR were 78/38 mm Hg and 64 bpm, respectively. We administered ephedrine (2 mg), and her BP and HR increased to 158/78 mm Hg and 73 bpm, respectively, and the ST segment elevated again (Figure 3B). The ST-segment elevation returned to baseline about 10 minutes later. We discontinued use of the vasopressors because we suspected that they had caused the ST-segment elevation. We then began administration of nicorandil, a coronary vasodilator, at 3 mg/h until the end of the operation. After administration of nicorandil, the patient's ECG showed maintenance of a normal sinus rhythm. The left partial maxillectomy and coronoidectomy were completed with no other problems. The durations of the operation and general anesthesia were 5 hours 30 minutes and 7 hours 15 minutes, respectively. The patient did not complain of chest pain or discomfort after waking from anesthesia. Fifteen days after the operation, the patient was examined at the department of cardiology at the general hospital next to our hospital to determine the cause of the CAS. However, the cardiologist decided not to conduct a further investigation, such as coronary angiography with ergonovine or acetylcholine, because the patient had no symptoms and such investigation was associated with a risk of death. The patient was

discharged from our hospital 3 weeks after the operation.

DISCUSSION

We experienced a case involving ST-segment elevation that occurred twice in the same patient under general anesthesia for 2 different operations. Several diseases are associated with ST-segment elevation, including acute myocardial infarction,¹¹ Brugada syndrome,¹² and Takotsubo cardiomyopathy.¹³ However, we considered that the cause of the ST-segment elevation in the present case was CAS for the following 2 reasons: First the, ST-segment elevation was transient. It appeared during both operations and continued for about 5 to 10 minutes. In general, ST-segment elevation secondary to CAS is transient. Several studies have reported that ST-segment elevation dramatically returned to baseline.^{3,4,8} The coronary artery is obstructed by an atherosclerotic plaque and clot in patients with myocardial infarction, but the coronary artery is not physically obstructed in those with CAS. We suppose that an ST-segment elevation will dramatically improve if CAS is relieved by appropriate treatment. We do not believe that the cause of the ST-segment elevation in the present case was myocardial infarction because the patient's creatine phosphokinase-MB and troponin I concentrations were not high, and no stenosis or obstruction was present on coronary CT angiography. Furthermore, we do not believe that the cause was Brugada syndrome. Brugada syndrome is characterized by an ECG pattern of right bundle branch block and ST-segment elevation in the right precordial leads (Brugada ECG pattern). Patients with Brugada syndrome have an increased risk of ventricular arrhythmia, syncope, and sudden death.^{12,14} The patient in this case did not show a Brugada ECG pattern on preoperative 12-lead ECG. She also had no history of ventricular arrhythmia and syncope. Finally, we also excluded Takotsubo cardiomyopathy as a cause. This syndrome is characterized by ECG changes such as ST-segment elevation, T-wave inversion, or a prolonged QT interval. Takotsubo cardiomyopathy is also known as broken heart syndrome. It is a stress-induced cardiomyopathy associated with transient and segmental left ventricular dysfunction or transient apical ballooning.^{13,15} However, the ultrasonic cardiography findings of the patient in this case were nearly normal after the first operation.

Second, the vasopressors ephedrine and phenylephrine were administered immediately before the ST-segment elevation occurred. We administered these drugs for management of hypotension during general anesthesia. Hirabayashi et al.⁸ reported a case in which

ST-segment elevation occurred after the administration of ephedrine in a 69-year-old man who underwent transurethral resection of a tumor in the bladder under spinal anesthesia. The patient had no history of coronary artery disease. Postoperative coronary angiography showed no stenosis in any coronary arteries at rest. However, administration of acetylcholine into a coronary artery induced vasoconstriction accompanied by chest pain (i.e., the patient was diagnosed with CAS). From these findings, the authors presumed that the cause of the ST-segment elevation was ephedrine-induced CAS.⁸ In 2 other cases involving healthy young women, severe CAS was revealed after administration of ephedrine under combined spinal-epidural anesthesia.⁹ The possibility that ephedrine activated the α -adrenergic receptors and provoked the CAS has been pointed out.⁸ It has also been reported that phenylephrine could have induced the CAS.¹⁶ Ephedrine is an α and β -adrenergic agonist that enhances norepinephrine release from sympathetic neurons.¹⁷ Phenylephrine is an α 1-selective agonist that induces marked arterial vasoconstriction.¹⁷ Therefore, in the present case, we believe that the CAS was induced by the α -adrenergic agonist vasopressors (ephedrine and phenylephrine) and that the CAS in turn induced the ST-segment elevation. Many reports have described possible causes of CAS other than vasopressors, such as an inadequate depth of anesthesia, vagal nerve stimulation, hypotension, and allergic reaction.¹⁸ We did not use a bispectral index monitor in this case. However, considering the patient's age, we thought that the depth of anesthesia was adequate because we used 4% desflurane or 1.5% sevoflurane to maintain general anesthesia. No sudden vagus nerve stimulation occurred during general anesthesia despite the fact that the operative field was in the head and neck region. There was also no sign of an allergic reaction, such as redness or urticaria. Therefore, the possibility that CAS was induced by the above-mentioned mechanisms seems low.

This patient had a history of hypertension and hypothyroidism, but both conditions were relatively well controlled. She had no history of ischemic heart disease, and there were no findings of suspected myocardial ischemia on preoperative 12-lead ECG. Therefore, it was very difficult to predict the occurrence of CAS preoperatively. Koshihara and Hoka¹⁸ reported that 85% of patients with preoperative CAS had no findings of myocardial ischemia on preoperative ECG or postoperative coronary angiography. They also mentioned that prediction of CAS was difficult.

Prolonged CAS may result in the development of acute myocardial infarction, severe arrhythmia, and sudden death.^{4–6} Therefore, early diagnosis and treatment of CAS are important. Nitrates and calcium

channel antagonists are mainly used to treat CAS.^{3–5,8,18} These medications are effective for CAS because they dilate the coronary artery.¹⁷ In the present case, we did not treat the ST-segment elevation because it returned soon at the first operation. We administered nicorandil to prevent the recurrence of CAS during the second operation. Nicorandil is an adenosine triphosphate (ATP)-sensitive potassium channel activator. The opening of ATP-sensitive potassium channels leads to hyperpolarization of the cell membrane, which in turn reduces the probability of voltage-gated calcium channel opening. Nicorandil interferes with activation of voltage-dependent calcium channels and may also interfere with release of calcium from intracellular sequestration sites. This mechanism leads to relaxation of vascular smooth muscle. Furthermore, nicorandil increases the intracellular concentration of cyclic guanosine monophosphate through stimulation of guanylate cyclase. Nicorandil, therefore, causes coronary artery vasodilation by a nitrate-like effect, as well as ATP-sensitive potassium channel activation.^{17,19}

Subcutaneous emphysema and pneumomediastinum developed after the first operation. The attending cardiologist suspected that the cause of the ST-segment elevation was pneumomediastinum followed by cardiac tamponade. Pneumomediastinum as a complication of tracheotomy has been reported.^{20,21} The mechanism in these reports was thought to be insertion of the tracheostomy tube outside of the trachea. The tracheostomy tube was correctly placed in the trachea in the present case because we confirmed capnographic waveforms on the monitor. Therefore, the cause of the pneumomediastinum remains unknown. It may have occurred secondary to the patient's bucking during insertion of the tracheostomy tube under intravenous sedation with midazolam. Cases of pneumopericardium and cardiac tamponade induced by pneumomediastinum have been reported.^{22,23} We initially thought that pneumomediastinum followed by cardiac tamponade was the cause of the ST-segment elevation. However, no pneumomediastinum was present at the second operation. Therefore, we do not believe that this was the cause of the ST-segment elevation.

In conclusion, we experienced a case of recurrent CAS induced by vasopressors during 2 operations in same patient under general anesthesia. Prediction of CAS was very difficult because the patient had no preoperative findings of myocardial ischemia. Vasopressors such as ephedrine and phenylephrine are frequently used for management of hypotension during general anesthesia. Therefore, anesthesiologists should consider the occurrence of CAS before using vasopressors and know how to manage CAS well.

ACKNOWLEDGMENTS

We thank Dr Hiroaki Yoshida (First Department of Oral and Maxillofacial Surgery, Osaka Dental University) for his advice regarding the writing of this manuscript.

REFERENCES

1. Prinzmetal M, Kenamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med.* 1959;27:375–388.
2. Gersh BJ, Braunwald E, Rutherford JD. Chronic coronary artery disease. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: W. B. Saunders Company; 1997:1289–1365.
3. Ornek E, Ornek D, Murat SN, Turfan M. Angiographic documentation of coronary artery spasm induced by anesthesia. *J Anesth.* 2010;24:452–455.
4. Truong AT, Truong DT, Brown DL. Recurrent intraoperative coronary artery spasm in a patient with coronary artery aneurysm. *J Clin Anesth.* 2006;18:530–533.
5. Lee KH, Kim SH, Lim HE, et al. Effectiveness of intravenous administration of nicorandil in a patient with variant angina refractory to continuous intravenous nitroglycerin. *Int J Cardiology.* 2007;120:e9–e12.
6. Kusama Y, Kodani E, Nakagomi A, et al. Variant angina and coronary artery spasm: the clinical spectrum, pathophysiology, and management. *J Nippon Med Sch.* 2011;78:4–12.
7. Lustik SJ, Chhibber AK, van Vliet M, Pomerantz RM. Ephedrine-induced coronary artery vasospasm in a patient with prior cocaine use. *Anesth Analg.* 1997;84:931–933.
8. Hirabayashi Y, Saitoh K, Fukuda H, Mitsuhashi H, Shimizu R. Coronary artery spasm after ephedrine in a patient with high spinal anesthesia. *Anesthesiology.* 1996;84:221–224.
9. Wahl A, Eberli FR, Thomson DA, Luginbühl M. Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia. *Br J Anaesth.* 2002;89:519–523.
10. Miyoshi H, Saeki N, Nakamura R, Kurita S, Kawamoto M. A case of coronary artery spasm caused by manipulation of the neck: heart rate variability analysis. *J Anesth.* 2012;26:905–909.
11. Goldschlager N, Goldman MJ. *Principles of Clinical Electrocardiography*. 13th ed. Norwalk, CT: Appleton & Lange; 1989.
12. Tsutsumi YM, Tomiyama Y, Horikawa YT, et al. General anesthesia for electroconvulsive therapy with Brugada electrocardiograph pattern. *J Med Invest.* 2011;58:273–276.
13. Rodrigues LB, Batista A, Monteiro F, Duarte JS. ST-segment elevation during general anesthesia for non-cardiac surgery: a case of takotsubo. *Rev Bras Anesthesiol.* 2015;65:403–406.
14. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a

distinct clinical and electrocardiographic syndrome. A multi-center report. *J Am Coll Cardiol*. 1992;20:1391–1396.

15. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases [in Japanese]. *J Cardiol*. 1991;21:203–214.

16. Hayashi Y, Oda T, Saitoh T, Takei J. A case of coronary artery spasm induced by ephedrine [in Japanese]. *JJSCA*. 2004;24:612–616.

17. Hardman JG, Limbird LE, Gilman AG. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001.

18. Koshiha K, Hoka S. Clinical characteristics of perioperative coronary spasm: reviews of 115 case reports in Japan. *J Anesth*. 2001;15:93–99.

19. Kaski JC. Management of vasospastic angina—role of nicorandil. *Cardiovasc Drugs Ther*. 1995;9:221–227.

20. Fikkers BG, van Veen JA, Kooloos JG, et al. Emphysema and pneumothorax after percutaneous tracheostomy: case reports and an anatomic study. *Chest*. 2004;125:1805–1814.

21. Lin JC, Maley RH Jr, Landreneau RJ. Extensive posterior-lateral tracheal laceration complicating percutaneous dilational tracheostomy. *Ann Thorac Surg*. 2000;70:1194–1196.

22. Kyle A, Veldtman G, Stanton M, Weeden D, Baral V. Barotrauma-associated posterior tension pneumomediastinum, a rare cause of cardiac tamponade in a ventilated neonate: a case report and review of the literature. *Acta Paediatrica*. 2012;101:e142–e144.

23. Tan S, Nikolarakos D. Subcutaneous emphysema secondary to dental extraction: a case report. *Aust Dent J*. 2016;62:95–97.