Stress-induced cardiomyopathy following cephalosporin-induced anaphylactic shock during general anesthesia

Cardiomyopathie provoquée par le stress à la suite d'un choc anaphylactique causé par la céphalosporine durant une anesthésie générale

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Abstract

Purpose Anaphylaxis may be caused by various agents during general anesthesia. Sympathetic discharge may occur during anaphylaxis, which can trigger transient cardiomyopathy. We describe a case of stress-induced cardiomyopathy that occurred in association with an anaphylactic reaction during general anesthesia.

Clinical features A 32-year-old female undergoing laparoscopic enucleation of an ovarian cyst developed a severe anaphylactic reaction after cephalosporin infusion during general anesthesia. Her vital signs responded favourably to immediate resuscitative maneuvers, but cardiovascular collapse reappeared with transient ventricular tachycardia shortly after her transfer to the

intensive care unit. ST-segment elevation appeared in electrocardiographic leads V₂–V₆ and echocardiography showed diffuse regional wall motion abnormalities in the midventricular level. Increased MB fractions of creatine kinase and troponin T levels indicated myocardial necrosis, but cardiac catheterization demonstrated normal coronary arteries. Management was supportive and she was discharged 2 days after the onset of anaphylactic symptoms, without sequelae. A diagnosis of stress-induced cardiomyopathy of a midventricular type following anaphylaxis was made on the basis of the clinical features and the findings of cardiac evaluations.

Conclusions Transient, reversible left-ventricular dysfunction is a recently recognized phenomenon that may occur in the setting of anaphylactic reactions during the perioperative period.

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Résumé

Objectif L'anaphylaxie peut être provoquée par différents agents pendant une anesthésie générale. Une décharge sympathique peut survenir pendant l'anaphylaxie, ce qui peut provoquer une cardiomyopathie transitoire. Nous décrivons un cas de cardiomyopathie provoquée par le stress survenue en association avec une réaction anaphylactique pendant l'anesthésie générale.

Éléments cliniques Une femme de 32 ans subissant une énucléation d'un kyste de l'ovaire par laparoscopie a manifesté une réaction anaphylactique grave après avoir reçu une perfusion de céphalosporine pendant l'anesthésie générale. Ses signes vitaux ont bien réagi aux manœuvres de réanimation immédiates, mais une défaillance cardiovasculaire est apparue, accompagnée d'une tachycardie

ventriculaire transitoire, peu après son transfert à l'unité des soins intensifs. Un sus-décalage du segment ST a été observé dans les dérivation V_2 – V_6 de l'électrocardiogramme, et l'échocardiographie a montré des anomalies régionales de contractilité de la paroi au niveau médio-ventriculaire. Des fractions MB plus élevées de créatine kinase et des niveaux de troponine T indiquaient une nécrose myocardique, mais une cathétérisation cardiaque a démontré des artères coronaires normales. Une prise en charge de soutien a été mise en place et la patiente a reçu son congé de l'hôpital sans séquelles deux jours après le début des symptômes d'anaphylaxie. Un diagnostic de cardiomyopathie de type médio-ventriculaire provoquée par le stress suite à une anaphylaxie a été posé sur la base des éléments cliniques et des résultats des évaluations cardiaques.

Conclusion La dysfonction transitoire et réversible du ventricule gauche est un phénomène reconnu récemment qui peut survenir dans un contexte de réactions anaphylactiques pendant la période périopératoire.

Recent reports and review articles have described a transient left ventricular (LV) dysfunction that resembles acute myocardial infarction, but with normal coronary arteries.^{1–6} Various definitions have been proposed to describe this syndrome, such as stress-induced cardiomyopathy, Takotsubo cardiomyopathy, broken heart syndrome, apical ballooning syndrome, and transient LV dysfunction syndrome. This cardiomyopathy is usually triggered by stressful situations and can occur during the perioperative period when emotional and physical stress is common in patients undergoing operations. Several reports describe the onset of this unusual cardiomyopathy during induction of anesthesia and the intraoperative period.^{2,3} It can also occur immediately, hours, or days after surgery.^{4–6}

Anaphylaxis occasionally develops during anesthesia, but it is unclear whether anaphylactic reactions are associated with stress-induced cardiomyopathy. To date, there has only been one published case of Takotsubo cardiomyopathy associated with anaphylaxis after food ingestion,⁷ and Han *et al.*⁸ described midventricular hypokinesis similar to this syndrome during contrast media-induced anaphylaxis. We report an unusual case of severe anaphylactic shock during general anesthesia followed by stress-induced cardiomyopathy. Consent for publication was obtained from the patient according to patient health information guidelines of the Yonsei University Health System.

Case report

A healthy 32-year-old woman weighing 47 kg presented for laparoscopic enucleation of an ovarian cyst. The patient

had a history of allergic rhinitis and one episode of angioedema after ingesting shellfish. Her medical history was otherwise unremarkable. She was physically active and not taking any medications before surgery. There were no risk factors for coronary artery disease, and there was no family history of drug allergies.

A preoperative intradermal reaction test for antibiotics, including cefotiam, was performed as a matter of routine and produced a negative result. The results of the patient's screening laboratory tests before surgery were within normal limits, and a 12-lead ECG demonstrated normal sinus rhythm without abnormality. She was not premedicated. Upon the patient's arrival to the operating room, routine monitors, including ECG (lead II), SpO₂, and an automated non-invasive blood pressure (BP) measurement, were applied and recorded at 3-min intervals. Her initial vital signs were as follows: heart rate = 62 beats · min⁻¹, blood pressure (BP) = 109/71 mmHg, and SpO₂ = 100% while breathing room air. General anesthesia was induced with propofol 100 mg *iv*, 4% sevoflurane, and remifentanyl at 1 µg · kg⁻¹ by infusion. Tracheal intubation was facilitated with rocuronium 50 mg *iv*. Mechanical ventilation was initiated (tidal volume of 8–10 mL · kg⁻¹ with no application of positive end-expiratory pressure) to maintain normocarbica, while anesthesia was maintained with 1–2% sevoflurane in an air/oxygen mixture (FiO₂; 0.5) and continuous infusion of remifentanyl. The patient was prepared with beta-iodine and draped. Her hemodynamic values were stable for 15 min after induction until cefotiam was infused through the peripheral intravenous route. Within 5 min after administration of cefotiam 1.0 g *iv*, a marked increase in peak airway pressure (from 15 to 40 mmHg) was observed, and a near absence of breathing sounds on auscultation of both lungs suggested bronchospasm. Sudden, profound hypotension (57/32 mmHg) and sinus tachycardia (120 beats · min⁻¹) developed, followed by a downhill trend in end-tidal CO₂ (EtCO₂) and oxygen saturation. Evaluation of the patient's skin showed diffuse erythematous changes. All anesthetic agents, including the remifentanyl infusion, were discontinued and 100% oxygen was administered. Ephedrine 40 mg *iv*, along with a rapid infusion of Hartmann solution, was ineffective in restoring normotension. The patient's BP decreased further to 45/23 mmHg, and her heart rate increased to 130 beats · min⁻¹. After intravenous administration of epinephrine 1.0 mg, her BP increased to 86/41 mmHg, and it became possible to ventilate her lungs once again. However, since the patient's BP remained liable, it was stabilized with a continuous infusion of norepinephrine. Her right radial artery was catheterized for direct continuous BP measurement. Fifteen minutes into resuscitation, the patient's vital signs recovered as follows: BP = 111/70 mmHg, HR = 110 beats · min⁻¹, and EtCO₂ increased to 30 mmHg.

(Fig. 1). Hydrocortisone 200 mg *iv* and phenylamine 40 mg *iv* were administered. Arterial blood gas values were as follows: pH = 7.332, PaCO₂ = 37 mmHg, PO₂ = 266 mmHg, base excess −5.0 mEq · L^{−1}, and electrolytes values were within normal limits. Except for sinus tachycardia, there were no significant changes in the ECG (lead II). Midazolam 3 mg *iv* was administered, and hemodynamic stability was restored so that the norepinephrine

Fig. 1 Changes in hemodynamic and respiratory variables during the anaphylactic event. HR = heart rate (beats · min^{−1}); BP = mean blood pressure (mmHg); PIP = peak inspiratory airway pressure (mmHg); EtCO₂ = end tidal CO₂ (mmHg); B10, B5, and I refer to 10 min, 5 min, and just prior to cefotiam administration; T5, T10, T15, T20, and T25 refer to 5, 10, 15, 20, and 25 min after cefotiam administration

infusion was gradually reduced and discontinued. It was decided to postpone surgery, and the patient was transferred to the surgical ICU.

Within 10 min after her arrival in the ICU, her systolic BP decreased below 70 mmHg once again and ventricular tachycardia ensued. The arrhythmia resolved spontaneously within 1 min without further treatment, but the patient's hypotension continued and bradycardia (HR 45 beats · min^{−1}) followed. Atropine 0.5 mg was administered and norepinephrine was reinfused to maintain BP. Her heart rate and systolic blood pressure (SBP) increased to more than 55 beats · min^{−1} and 90 mmHg. In the ICU, the patient's trachea remained intubated while she was sedated using infusions of alfentanil and midazolam. A 12-lead ECG at this time showed ST segment elevation in leads V₂–V₆. A bedside transthoracic echocardiography performed immediately after the ventricular tachycardia showed diffuse regional wall motion abnormalities in the anterior, anterolateral, and posterolateral walls in the midventricular level of the LV (Fig. 2, Panels a, b). There was sparing of the basal and apical systolic function, and the global LV systolic function was relatively preserved (EF = 50%). The peak serum levels of creatine phosphokinase-MB fraction (CK-MB) and troponin T suggested myocardial injury and were 15.05 ng · mL^{−1} (normal range, 1–5 ng · mL^{−1}) and 0.468 ng · mL^{−1} (normal range, 0–0.1 ng · mL^{−1}), respectively. The patient made an uneventful recovery, and she was fully awake so that her trachea could be extubated 8 h after transfer to the ICU.

Fig. 2 Parasternal short axis views at the midventricular level of the left ventricle after anaphylaxis and during recovery. **a** End-diastolic view and **b** end-systolic view showing diffuse hypokinesis in the anterior, anterolateral, and posterolateral walls immediately after anaphylaxis in the intensive care unit; **c** end-diastole and **d** end-systole recovering heart on postoperative day one, showing that the hypokinesis has nearly disappeared (Arrows indicate the area of hypokinesis. Dotted lines indicate the endocardial margin of the left ventricle); AL = anterolateral papillary muscle; PM = posteromedial papillary muscle

To maintain BP, a low-dose infusion of norepinephrine infusion was maintained for >24 h.

Follow-up echocardiography the next day showed that the patient's systolic function had improved and, compared with previous echocardiograms, regional wall motion abnormalities had resolved (EF = 66%), although mild hypokinesia of the LV posterolateral wall persisted (Fig. 2, Panels c, d). The ST segment elevations resolved on the patient's ECG, and her coronary angiography revealed no evidence of obstructive coronary artery disease. She was discharged 2 days after the onset of anaphylaxis without sequelae and was able to return to normal activity, including exercise. An ECG performed before discharge showed normal sinus rhythm. On the basis of the clinical features and the echocardiographic findings, the patient was diagnosed with stress-induced cardiomyopathy of a midventricular type.

A skin prick test performed 6 weeks postoperatively was positive for cefotiam and negative for other drugs, including rocuronium, propofol, and midazolam.

Discussion

As patients receive multiple medications, anaphylaxis after general anesthetic induction may be caused by various agents. In this case, the temporal relationship between drug administration and cardiovascular collapse and positive results in the skin prick test suggest that cefotiam, a second generation of cephalosporin, was the most likely cause of the reaction. The negative results of preoperative intradermal tests can be explained by the lower sensitivity of the tests. Cephalosporin anaphylaxis is rare, with a frequency of 0.0001–0.1% of the general population.

Stress-induced cardiomyopathy is characterized by acute onset of transient LV dysfunction in the absence of atherosclerotic coronary artery disease. Since the original description of this cardiomyopathy, several variants of this entity have been reported involving different segments of the LV wall. In the present case, there was preserved function of the apex of the LV with motion abnormalities in the midventricular segments. This type of cardiomyopathy was described as a variant observed in 40% of patients with this syndrome.⁹ In our patient, the constellation of findings of transient LV regional wall motion abnormality is consistent with stress-induced cardiomyopathy in that it extends beyond: (1) the vascular distribution of any single coronary artery in echocardiography;¹⁰ (2) the ECG changes mimicking myocardial infarction; (3) the moderate elevation of cardiac enzymes; and (4) the rapid resolution of LV dysfunction and normal coronary arteries. It predominantly affects elderly women, although, as in our case, younger patients are occasionally affected. There was no

clinical evidence of concurrent conditions, such as pheochromocytoma and myocarditis, which must be ruled out in the differential diagnosis of this cardiomyopathy.¹

The pathophysiological mechanism of stress-induced cardiomyopathy remains unclear, and it has not yet been determined whether anaphylaxis is associated with stress-induced cardiomyopathy. However, cardiovascular involvement is an important feature of anaphylaxis, and acute coronary syndromes have been sporadically reported during anaphylactic reactions in individuals with normal coronary arteries.^{11–13}

Coronary arterial spasm was proposed as the main mechanism of anaphylaxis-induced coronary syndromes. It also was thought to be one of the triggering mechanisms of stress-induced cardiomyopathy. Kurisu *et al.*¹⁴ suggested that simultaneous multi-vessel coronary spasm at the epicardial artery or microvascular levels may contribute to onset of this type of cardiomyopathy. Therefore, coronary artery spasm by anaphylactic mediators may initiate stress-induced cardiomyopathy during anaphylactic reactions. Since the coronary angiography was not performed in our patient until the following day, we do not know whether coronary artery spasm existed in the acute state.

It has been suggested that the systemic catecholamine increase, with excessive activation of cardiac catecholamine receptors in the LV, plays a major role in the pathophysiology of stress-induced cardiomyopathy.^{15,16} In anaphylaxis, compensatory catecholamine is released by the renin-angiotensin-aldosterone system, and histamine stimulates the release of catecholamine by direct action on the adrenal medullary cells.^{17,18} In addition to this phenomenon, administration of catecholamines, such as epinephrine and norepinephrine, for hemodynamic support in anaphylactic shock would also increase the plasma catecholamine level. It is possible that the increased catecholamine levels during anaphylaxis may provoke stress-induced cardiomyopathy.

Accordingly, stress-induced cardiomyopathy may be precipitated by anaphylactic reactions through the two different mechanisms as described above. It is possible that some of the acute coronary symptoms, which have been reported during anaphylaxis in the presence of normal coronary arteries, might be related to this transient ventricular dysfunction.^{12,19,20}

Stress-induced cardiomyopathy has only very recently become recognized as a cause of cardiac dysfunction during the perioperative period. The prevalence of stress-induced cardiomyopathy in the perioperative setting awaits large scale prospective cohort studies. A recent study of patients admitted to the medical ICU found that LV apical ballooning occurred in 28% of cases using echocardiography.²¹ Although it was not confirmed by coronary angiography, this report suggests that cardiomyopathy may

develop in a number of patients. Considering that these perioperative events can induce severe physical and emotional stress and that the initial presentation of stress-induced cardiomyopathy is indistinguishable from acute myocardial ischemia, it is likely to be either unfamiliar or misinterpreted.

In this case, the patient recovered spontaneously with supportive therapy. Treatment of stress-induced cardiomyopathy relies on standard supportive measures. The prognosis is generally favourable, providing the patient survives the initial, severe state, since serious complications can occur during the initial phase of this cardiomyopathy. Cardiogenic shock, congestive heart failure, and death occur in 6.5%, 3.8%, and 3.2% of patients, respectively.²² Other rare complications have been reported, such as arrhythmia, pneumothorax, stroke, dynamic intraventricular obstruction, LV thrombosis, and free wall rupture.¹ It is possible that cardiovascular collapse may become exacerbated if such complications develop during the acute anaphylactic state. Intraoperative transesophageal echocardiography during anesthesia may be very useful in the detection and management of this unusual form of LV dysfunction and its complications.

In summary, we describe a case of atypical stress-induced cardiomyopathy associated with cephalosporin-induced anaphylaxis during anesthesia. Possible mechanisms are discussed. There is a potential for occurrence of this cardiomyopathy during the course of an anaphylactic reaction, particularly in the perioperative period. Anaphylaxis and stress-induced cardiomyopathy are both life-threatening events in the acute phase; therefore, anesthesiologists should be aware of this recently recognized form of transient LV dysfunction and its serious complications. We suggest that echocardiography is an effective tool for both early diagnosis of cardiomyopathy in patients with anaphylaxis, and for therapy guidance during the perioperative period.

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References

1. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008; 155: 408–17.
2. Jabaudon M, Bonnin M, Bolandard F, Chanseaux S, Dauphin C. Takotsubo syndrome during induction of general anaesthesia. *Anaesthesia* 2007; 62: 519–23.
3. Takigawa N, Tokioka H, Chikai T, et al. A case of undiagnosed “takotsubo” cardiomyopathy during anesthesia. *Masui* 2003; 52: 1104–6.
4. Ramakrishna G, Ravi BS, Chandrasekaran K. Apical ballooning syndrome in a postoperative patient with normal microvascular perfusion by myocardial contrast echocardiography. *Echocardiography* 2005; 22: 606–10.
5. Jensen JB, Malouf JF. Takotsubo cardiomyopathy following cholecystectomy: a poorly recognized cause of acute reversible left ventricular dysfunction. *Int J Cardiol* 2006; 106: 390–1.
6. Lentschener C, Vignaux O, Spaulding C, Bonnichon P, Legmann P, Ozier Y. Early postoperative tako-tsubo-like left ventricular dysfunction: transient left ventricular apical ballooning syndrome. *Anesth Analg* 2006; 103: 580–2.
7. Vultaggio A, Matucci A, Del Pace S, et al. Tako-Tsubo-like syndrome during anaphylactic reaction. *Eur J Heart Fail* 2007; 9: 209–11.
8. Han Y, Yeon S. Midventricular hypokinesis as a cardiac manifestation of anaphylaxis: a case report. *J Am Soc Echocardiogr* 2006; 19: 1529.e9–11.
9. Kurowski V, Kaiser A, von Hof K, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* 2007; 132: 809–16.
10. Patrignani A, Di Cesare E, Cicogna S. Echocardiography and cardiovascular magnetic resonance diagnostic role in Takotsubo cardiomyopathy. *Int J Cardiovasc Imaging* 2009; 25: 109–12.
11. Brener ZZ, Zhuravenko I, Bergman M. Acute myocardial injury following penicillin-associated anaphylactic reaction in a patient with normal coronary arteries. *Am J Med Sci* 2007; 334: 305–7.
12. Gikas A, Lazaros G, Kontou-Fili K. Acute ST-segment elevation myocardial infarction after amoxicillin-induced anaphylactic shock in a young adult with normal coronary arteries: a case report. *BMC Cardiovasc Disord* 2005; 5: 6.
13. Austin SM, Barooah B, Kim CS. Reversible acute cardiac injury during cefoxitin-induced anaphylaxis in a patient with normal coronary arteries. *Am J Med* 1984; 77: 729–32.
14. Kurisu S, Sato H, Kawagoe T, et al. Tako-Tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002; 143: 448–55.
15. Mori H, Ishikawa S, Kojima S, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovasc Res* 1993; 27: 192–8.
16. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; 352: 539–48.
17. Hermann K, Ring J. The renin angiotensin system and hymenoptera venom anaphylaxis. *Clin Exp Allergy* 1993; 23: 762–9.
18. Marley PD. Mechanisms in histamine-mediated secretion from adrenal chromaffin cells. *Pharmacol Ther* 2003; 98: 1–34.
19. Engrav MB, Zimmerman M. Electrocardiographic changes associated with anaphylaxis in a patient with normal coronary arteries. *West J Med* 1994; 161: 602–4.
20. Fujita Y, Chikamitsu M, Kimura M, Toriumi T, Endo S, Sari A. An anaphylactic reaction possibly associated with an intraoperative coronary artery spasm during general anesthesia. *J Clin Anesth* 2001; 13: 221–6.
21. Park JH, Kang SJ, Song JK, et al. Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. *Chest* 2005; 128: 296–302.
22. Donohue D, Movahed MR. Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome. *Heart Fail Rev* 2005; 10: 311–6.