Two Cases of Takotsubo Syndrome Related to Tracheal Intubation/Extubation

Triin Jakobson¹, Nikolai Svitškar¹, Kadri Tamme¹,², Joel Starkopf¹,², Juri Karjagin¹,²
¹Anaesthesiology and Intensive Care Clinic, Tartu University Hospital,
²Anaesthesiology and Intensive Care Clinic, University of Tartu, Estonia

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Summary. Takotsubo cardiomyopathy is an acute, reversible left ventricular dysfunction with characteristic contractility disorder and is usually preceded by emotional or physical stress. Two cases of Takotsubo cardiomyopathy related to tracheal manipulation are presented. Both the patients had all the typical symptoms and signs of Takotsubo cardiomyopathy, and both of them recovered completely within weeks. Tracheal manipulation is a well-known stress factor during the perioperative period, and experience from these two cases stresses the crucial role of measures aimed to stress reduction. Proper premedication and calm environment are recommended to produce anxiolysis before intubation. The administration of α- and β-blockers is also recommended to inhibit sympathetic stress caused by tracheal manipulation.

Introduction
Takotsubo cardiomyopathy or apical ballooning syndrome or stress-induced cardiomyopathy is an uncommon syndrome first described in Japan in 1990 (1). The syndrome is provoked by sudden emotional or physical stress as described in different situations, such as an earthquake (2) or surgery (3). Clinical signs are consistent with acute coronary syndrome or myocardial infarction. Women account for more than 90% of victims of the condition (4). The induction of general anesthesia, especially intubation, is a well-known cause of stress in a perioperative setting. Two cases of Takotsubo syndrome in female patients in whom the syndrome was possibly related to tracheal manipulation are reported.

Case Reports
Case 1
A 68-year-old woman was admitted for elective laparoscopic cholecystectomy due to cholelithiasis. Her previous medical history included bilateral mastectomies due to cancer, hysterectomy due to myoma, and arterial hypertension, well controlled with lacidipine (4 mg daily). At the preoperative visit, her physical status was assessed as ASA II. She was moderately anxious about the forthcoming procedure, and 7.5 mg of oral midazolam was prescribed orally for the night before operation. She arrived at the operating room at 12:16 PM directly from the ward. Standard monitoring, including 5-lead ECG with ST segment analysis, was initiated on arrival. Her blood pressure was 135/80 mm Hg, heart rate was 75 beats per minute, and oxygen saturation was 98%. Anesthesia was induced with etomidate and fentanyl; rocuronium was given for precurarization and succinylcholine for intubation. Immediately after intubation, the patient’s blood pressure rose to 200/110 mm Hg while broad QRS complex tachycardia (110 beats per minute) appeared. Lidocaine at a dose of 50 mg was given intravenously, and the rhythm changed to bigeminus; after 1-mg metoprolol, the rhythm returned to sinus and remained between 50–60 beats per minute. Marked elevation of ST segment in leads II and V₅ was noted, while the blood pressure remained stable (160–170/85–100 mm Hg). The surgery was postponed. A standard 12-lead ECG revealed upsloping ST-segment elevations. Within the next 45 minutes, emergency angiography was performed, which revealed no stenotic lesions in coronary arteries. Echocardiography showed an ejection fraction (EF) of 39%, cardiac index (CI) of 2.53 L/(min·m²), akinetic areas in the apical segments in the lateral wall and septum, also in the middle segments of the front and lower lateral wall and hyperkinetic basal area of the lateral wall. A moderate increase in creatine kinase-MB (CK-MB; 6.79 ng/mL, reference, 3.77) and troponin T (TnT; 0.22 ng/mL, reference, 0.01) was observed 2 hours after the incident.

The patient was extubated in the evening of the same day. She did not complain of chest pain. She spent 9 more days at the Department of Emergency Cardiology in stable condition without complaints. Echocardiography 4 days after the incident demonstrated an EF of 45% and akinesis in the same areas. Her in-hospital treatment consisted of aspirin, beta-blockers, and low-molecular-weight heparin. Two
weeks after the discharge, echocardiography revealed no akinetic areas and perfectly normal left ventricular function with an EF of 59% and CI of 2.7 L/(min m²).

**Case 2**

A 49-year-old woman with Budd-Chiari syndrome and liver fibrosis was scheduled for orthotopic liver transplantation. Her preoperative Child-Pugh grade was A (score 5). She had no heart disease in her medical history, and her preoperative ECG was normal.

Course of the surgery and anesthesia was uneventful. After 10 hours in the operating theatre, she was transferred to the ICU on mechanical ventilation, slightly sedated with midazolam and fentanyl. Hemodynamic parameters were stable; CI remained between 3.8 and 4.7 L/(min m²) for the next 12 hours. No signs of myocardial ischemia or heart failure were seen, and liver function showed a normal recovery. Sixteen hours after surgery, she was extubated in fairly stable condition. Soon thereafter, a gradual decrease in CI with the excessive signs of pulmonary edema developed. Based on ST-segment elevations in the 12-lead ECG, markedly increased biomarkers (TnT, 3.15 ng/mL; and CK-MB, 24.87 ng/mL), and movement abnormalities on the apical and midventricular segments of the left ventricle, myocardial infarction was suspected. Emergency angiography revealed no stenotic lesions in any of the coronary arteries. Due to cardiogenic shock (CI, 1.8–2.1 L/[min m²]; oliguria), she needed inotropic support, mechanical ventilation, and renal replacement therapy. Echocardiography showed an extremely poor left ventricular function with an EF of 28% and a large akinetic area not matching the distribution area of any single coronary vessel. During the next 2 weeks, the heart function improved gradually; after 3 days she was extubated, the EF remained low on the fourth postoperative day and improved to 43% and 50% on the 8th and 13th postoperative days, respectively. Urine production restored after 15 days. On the 19th day, she was transferred to a surgical ward in stable condition.

In both the cases, the diagnosis of Takotsubo syndrome was made based on the clinical criteria published by Bybee and Prasad: 1) transient left ventricular wall motion abnormalities involving the apical and/or midventricular myocardial segments with wall motion abnormalities extending beyond a single epicardial coronary distribution; 2) absence of obstructive epicardial coronary artery disease or angiographic evidence of acute plaque rupture that could be responsible for the observed wall motion abnormality; and 3) new ECG abnormalities, such as transient ST-segment elevation and/or diffuse T-inversion or troponin elevation (5).

**Discussion**

Takotsubo cardiomyopathy has been a poorly recognized cause of stress-related acute reversible left ventricular dysfunction, the diagnostic criteria of which have been set only recently (5). The studies suggest that the incidence of Takotsubo cardiomyopathy may be up to 2% among all the patients presenting with acute coronary syndrome and about 6% among women. More than 90% of case reports have reported women being affected (4). Thus, both of our patients present a typical risk profile of being a female of middle or older age.

No particular intervention can specifically be connected to the syndrome. It occurs in association with various medical emergencies (6) as well as different types of surgery (7). Five earlier reports have described the syndrome in patients undergoing orthotopic liver transplantation (8).

The cardiac problems were unexpected and sudden in both our patients. Cardiac deterioration after tracheal intubation in the first patient was particularly alarming. Tracheal manipulation causes a reflex increase in sympathetic activity possibly resulting in hypertension, tachycardia, and arrhythmia. A change in plasma catecholamine concentrations has also been demonstrated in response to tracheal intubation. The cardiovascular response to tracheal manipulation, although transient, may be harmful to some patients, mainly those with myocardial or cerebrovascular disease (9). Sympathetic stress related to tracheal extubation was most likely the causative factor of the syndrome in the second patient. Altogether, experience from these two cases stresses the crucial role of measures aimed to stress reduction at tracheal intubation/extubation. It is important to note that anesthetists should be aware that excessive stress at tracheal manipulation might have serious consequences not only in high-risk cardiac, but also in other patients. There is no evidence to support any specific management strategy or drug therapy for the prevention; however, providing a deeper level of anxiolysis before entering the operating room might be beneficial. Some have recommended achieving deep levels of anesthesia before intense stimulation, such as laryngoscopy, although there is not enough information to suggest that this strategy is useful. Studies on an animal model suggest that α- and β-blockade could normalize stress-induced ECG changes, so it might be rational to consider these drugs for prophylaxis (10).

Further course in both the patients followed the typical pattern of Takotsubo syndrome: the symptoms characteristic of acute coronary syndrome, but no signs of coronary artery disease on immediate angiography. The transient nature of the symptoms further supported the diagnosis.

The syndrome can be diagnosed only after the exclusion of other reasons; therefore, angiography.
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is probably the best choice in the management of a woman presenting with the acute coronary syndrome after some stressful situation (11). A typical echocardiographic finding is left ventricular wall motion abnormalities extending beyond a single epicardial coronary distribution.

The pathophysiological mechanisms of Takotsubo cardiomyopathy are reviewed elsewhere (4, 12). Different mechanisms proposed include, but are not limited to coronary artery spasm, catecholamine-induced damage, and impaired microcirculation (13). The most discussed mechanism is related to catecholamines. The vegetative innervation pattern as the reason of cardiomyopathy is inconsistent, as the base of the heart has more receptors than the apex (11). It has been shown that the over-stimulation of β₂-adrenoreceptors (AR) could lead to a negative inotropic effect mediated by protein G-coupled mechanisms. Subsequent intracellular signaling includes p38 mitogen-activated protein kinase pathway, upregulation of sodium-calcium ion exchanger, and inhibition I-type calcium channels (4). The amount of β₂-AR is higher in the apex of the heart. The ratio of β₁ to β₂ AR is smaller in the apex than in the base, and therefore, circulating epinephrine has a more pronounced effect on the apical segments than the basal ones, leading to metabolically induced stunning of the former (4, 11).

The gender difference in the prevalence of Takotsubo syndrome is poorly understood. It is not clear whether the higher occurrence in women results from better or worse protection of the myocardium compared with men. It is hypothesized that the cardioprotective effects of estrogens allow women to better survive the episodes of severe cardiac stress, which in men would potentially lead to sudden cardiac death. Contrary, it can also be speculated that men are evolutionally better protected against stress-induced cardiotoxicity of catecholamines compared with women. Neither experimental nor clinical studies directly support these hypotheses (14).

Conclusions

The cases reported show that Takotsubo cardiomyopathy is a possible reason for acute ST-segment elevation, release of cardiac markers, and broad QRS complex tachycardia in the suspected cases of periprocedural myocardial infarction. The diagnosis itself is possible only after exclusion of other, more common, reasons for acute coronary syndrome. Stress caused by tracheal manipulation may induce serious cardiac complications.

Statement of Conflict of Interest

The authors state no conflict of interest.