

Takotsubo Cardiomyopathy, or Broken-Heart Syndrome

Diane Nykamp and John Adam Titak

Strong emotional shock, such as that resulting from a traumatizing event like the loss of a loved one, may actually cause a “broken heart.” Patients, especially women in their 60s, believed to have suffered acute coronary syndrome (ACS) may actually have experienced broken-heart syndrome, otherwise known as stress cardiomyopathy, apical ballooning syndrome, or more recently referred to as takotsubo cardiomyopathy. High levels of catecholamines can temporarily stun the heart and produce the syndrome. Takotsubo cardiomyopathy resembles ACS and can cause death, but it appears that most people recover without permanent damage.

Takotsubo cardiomyopathy is named for the distinct appearance of the left ventricle when it balloons. The syndrome was named by Sato et al. in Japan in 1990.¹ A *tako-tsubo* is a Japanese octopus fishing pot that has a narrow neck and a wide midsection that resembles a ventricle. A reversible contractility abnormality of the left ventricle causes it to take on a balloon-like appearance that can be detected with echocardiography or coronary angiography. Damage to the left ventricle causes a contractile abnormality of the apex of the heart. During contraction of the ventricle, areas around the apex show a bottom-rounded hypokinetic apex with a narrow hypercontracted base. Echocardiogram results show a left ventricle with preserved function in the base, moderate or severe dysfunction

OBJECTIVE: To report a case of takotsubo cardiomyopathy, also known as apical ballooning syndrome or stress cardiomyopathy.

CASE SUMMARY: A 68-year-old female with a history of hypertension, hyperlipidemia, and anxiety presented with symptoms that mimicked acute coronary syndrome (ACS); the chief symptom was chest tightness. An electrocardiogram showed normal sinus rhythm, with minimal ST elevation in the anterior leads. The patient was initially treated for ST-segment elevation myocardial infarction and symptoms resolved. Coronary angiography ruled out ACS and confirmed a diagnosis of takotsubo cardiomyopathy.

DISCUSSION: Takotsubo cardiomyopathy is commonly triggered by severe emotional or psychological stress and occurs primarily in postmenopausal women. A reversible contractility abnormality of the left ventricle causes the ventricle to take on a balloon-like appearance; hence the name of *tako-tsubo*, a Japanese octopus fishing pot that has a narrow neck and a wide midsection. Signs and symptoms of takotsubo cardiomyopathy mimic those of ACS. Takotsubo cardiomyopathy is best diagnosed with coronary angiography, which can rule out blockage. Treatment usually consists of carvedilol and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocking agent if left ventricular ejection fraction is less than 40%. The syndrome is usually spontaneously reversible and cardiovascular function returns to normal after a few weeks.

CONCLUSIONS: Takotsubo cardiomyopathy causes a reversible left ventricle dysfunction which occurs most commonly in postmenopausal women with or without cardiovascular disease. Recognition is detected with coronary angiography. It is thought to primarily be due to an abnormally high sympathetic stimulation after emotional or psychological stress. Treatment consists of an angiotensin-converting enzyme inhibitor and/or beta blocker if needed for left ventricular dysfunction and possibly an anxiolytic agent.

KEY WORDS: apical ballooning, broken-heart syndrome, takotsubo.

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tion in the midportion of the left ventricle, and akinesis or dyskinesis in the apex of the heart. A reduced left ventricular ejection fraction (LVEF) is common, which can be severe enough to cause heart failure, although with symptomatic support reduced LVEF and contractile abnormalities usually resolve.² The incidence of takotsubo cardiomyopathy is thought to be 1–2% overall in suspected acute myocardial infarctions.³

Author information provided at end of text.

Signs and symptoms of takotsubo cardiomyopathy mimic those of ACS, with chest pain, dyspnea, electrocardiographic changes, and increase in cardiac enzyme levels. Most patients are initially treated for myocardial infarction. Takotsubo cardiomyopathy is best diagnosed by angiography, which can rule out vessel obstruction.⁴ A reversal of the syndrome usually occurs without treatment and cardiovascular function returns to normal after a few weeks.⁴ The chance of takotsubo cardiomyopathy recurring is no more than 10%.⁵

Case Report

A 68-year-old postmenopausal white female presented to the emergency department in June 2009 with a chief complaint of chest tightness. The patient stated that the chest tightness started several days prior, brought on by stress related to her caring for her disabled husband. On the previous day, the patient was holding her dog as it was being euthanized. Upon the death of the pet, the patient experienced severe chest tightness. Chest tightness was relieved with self-administration of aspirin 325 mg. During the day prior to presentation, the patient reported worsening chest tightness after almost dropping her husband. Emergency 911 was called and she was transported to the hospital by ambulance.

The patient's past medical history included hypertension, hyperlipidemia, and anxiety. Medications upon admission included raloxifene 60 mg daily, valsartan/hydrochlorothiazide 80/12.5 mg daily, simvastatin 20 mg daily, aspirin 325 mg/day, and lorazepam 1 mg daily. Risk factors for cardiovascular disease were: age, stress, hyperlipidemia, hypertension, and family history.

Upon presentation, the patient had a blood pressure of 141/78 mm Hg, heart rate 78 beats/min, weight 88.9 kg, creatine kinase (CK) 114 U/L (reference range [female] 30–135), CK muscle and brain (MB) 3.4 U/L (0–3), and troponin 0.63 ng/mL (<0.4). Electrocardiogram results showed normal sinus rhythm, with minimal ST elevation in the anterior leads. The patient was initially treated for ST-segment elevation myocardial infarction (STEMI). Echocardiogram showed an estimated ejection fraction of 40% (55–70%). The patient was started on heparin 10 units/kg/h, carvedilol 6.25 mg by mouth twice daily, sublingual nitroglycerin 0.4 mg every 5 minutes up to 3 times if needed, simvastatin 20 mg by mouth daily, lorazepam 1 mg by mouth daily, and clopidogrel 300 mg by mouth for 1 dose, then 75 mg daily. Eptifibatide was administered at a bolus of 180 µg/kg then at a rate of 2 µg/kg/min.

Cardiac catheterization revealed 30% blockage in 3 vessels: distal left anterior descending, second diagonal, and proximal left circumflex. The left ventricular anterior and apical walls were reported as akinetic. The left ventricle inferior apical wall was also found to be hypokinetic, left

ventricular function mildly abnormal, with absence of heart failure. Diagnosis was apical ballooning syndrome and no surgical intervention was performed. An echocardiogram performed on the same day found normal left ventricular chamber size and confirmed apical hypokinesis and severe anterior hypokinesis.

The next day cardiac enzymes were again measured, with results of CK 99 U/L, CK-MB 2.4 U/L, and troponin 0.45 ng/mL. The patient was discharged after 3 days. Upon discharge, a final troponin level of 0.11 ng/mL was reported.

The patient was instructed to follow up with a cardiologist and to enroll in a cardiac rehabilitation program. Medications on discharge included: simvastatin 20 mg daily, aspirin 325 mg daily, carvedilol 6.25 mg twice daily, and valsartan/hydrochlorothiazide 80/12.5 mg daily. The final diagnosis was apical ballooning syndrome, also known as takotsubo cardiomyopathy.

Discussion

The etiology of takotsubo cardiomyopathy remains uncertain and it is likely that multiple factors are involved. One mechanism that has been reported is the result of high levels of catecholamines and stress-related neuropeptides.^{2,6} Wittstein et al. reported that plasma catecholamine levels in a group of patients were markedly elevated in the acute phase of stress cardiomyopathy when compared to acute myocardial infarction.² Abraham et al. reported stress cardiomyopathy in 9 patients after intravenous administration of epinephrine or dobutamine.⁶ The authors implicate excessive sympathetic stimulation as the key reason for the pathogenesis. Catecholamines are thought to have an effect on the coronary vascular wall, microcirculation, and myocardial cells. This effect is thought to have the pathophysiologic results of coronary artery spasm, microvascular spasm, and direct myocyte injury.⁷

Another reported theory is that catecholamines are thought to have a direct effect on the apex of the left ventricle because there is a higher concentration of receptors² or because the apical myocardium has an enhanced responsiveness to sympathetic stimulation.⁸ The apex is stimulated at a greater rate than the basal segment of the ventricle, producing a structural change, a ballooning of the ventricle.

Along with structural changes of the apex of the left ventricle, another possible mechanism in causing takotsubo cardiomyopathy focuses on microvascular dysfunction that results in vasospasm or a decrease in blood flow through the coronary arteries without evidence of stenosis or an atherosclerotic effect.^{9–11} Others believe a thrombus could temporarily occlude a coronary artery, and then dissipate before being detected during coronary angiography.^{12,13}

Postmenopausal women are more likely than men to experience takotsubo cardiomyopathy.^{2,14,15} It is estimated that 90% of patients experiencing takotsubo cardiomyopathy are females.⁷ In fact, men have higher catecholamine levels than women, but women may have a more exaggerated response to an increased level. Another mechanism thought to cause an increased incidence in women is the reduced levels of cardioprotective estrogen after menopause.⁴ Researchers have hypothesized that decreased estrogen levels in postmenopausal women may explain why the majority of patients with takotsubo cardiomyopathy are older women. In rodent models, adding estrogen to rats under stress decreased the effects of cardiac dysfunction, decreased heart rate, and decreased blood pressure. Estrogen supplementation made rats more resistant to stress and, subsequently, to takotsubo cardiomyopathy. Supplementing estrogen also increased levels of atrial natriuretic peptide and heat shock protein 70 in the heart, where they act as cardioprotectants. Estrogen also decreased induced tachycardia and ischemia/reperfusion-induced arrhythmias in rat hearts.

Treatment of takotsubo cardiomyopathy usually requires only supportive care in the acute stage because a reversal of the syndrome occurs without treatment. Arrhythmias associated with takotsubo cardiomyopathy commonly occur in the acute phase but are not treated prophylactically.⁴ The use of inotropic agents is contraindicated during the acute phase because they are by nature proarrhythmic as well, the risk of which increases in a setting that already involves increased circulating catecholamines.

In animal models, treatment with estrogen has been shown to be beneficial in the prevention of takotsubo cardiomyopathy. Estrogen plays a major role in the delayed occurrence of coronary heart disease in women. Alpha and beta receptors are found in the central nervous system as well as in cardiac tissue. Our patient was on raloxifene, a selective estrogen receptor modulator, which is indicated in postmenopausal women to prevent osteoporosis. Results from the RUTH trial¹⁶ showed that raloxifene has no protective effect on cardiac tissue in postmenopausal women.

Researchers are investigating agents that prevent cardiac changes in the event of unusually high levels of catecholamines. In rat models, high concentrations of catecholamines, which stimulate adrenoceptors, produced ST segment changes and left ventricular dysfunction. The use of a combined α - and β -blocker, calcium-channel blockers, and nitroglycerin has prevented the occurrence of ST-segment elevation.¹⁷ Ueyama has also reported that the use of a combined α - and β -blocker has prevented left ventricular dysfunction.¹⁷

Our patient was initially treated for STEMI before the diagnosis of takotsubo cardiomyopathy was made with coronary angiography. When she was discharged, medications included: simvastatin, valsartan/hydrochlorothiazide,

carvedilol, and aspirin. Simvastatin and valsartan/hydrochlorothiazide were continued for coexisting hypertension and hyperlipidemia. The patient had a prescription from her primary care physician for lorazepam 1 mg for anxiety given to her at an office visit after discharge.

Carvedilol is a mixed vasodilating α_1 - $\beta_{1,2}$ blocker. This agent, with β -blocking properties, is used to protect against catecholamine sensitivity that may trigger another event. Because epinephrine promotes platelet activation by stimulating platelet α_2 adrenoceptors, a combination α_1 - and β -blocker can effectively prevent this from occurring.⁴ Carvedilol has also shown a greater increase in mean LVEF in trials comparing it to metoprolol after myocardial infarction.¹⁸⁻²⁰ Because takotsubo cardiomyopathy causes left ventricular hypertrophy, an agent that increases LVEF is advantageous.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blocking agents may also be prescribed for patients with takotsubo cardiomyopathy to protect left ventricular function and to control hypertension. ACE inhibitors are indicated for all patients with LVEF <40%.²¹

When our patient entered the cardiac rehabilitation and wellness program she had a prescription for lorazepam 1 mg for anxiety. Lorazepam may aid in controlling the stress that led to takotsubo cardiomyopathy, although it did not prevent the initial event. Currently, the patient is enrolled in a cardiac rehabilitation and wellness program for exercise and education to reduce stress. Table 1 lists medications that are used in the management of takotsubo cardiomyopathy.²²

Takotsubo cardiomyopathy causes a reversible left ventricle dysfunction that occurs mostly in postmenopausal women with or without cardiovascular disease. It is thought to primarily be due to an abnormally high sympathetic stimulation after emotional or psychological stress. Medications used in its management in our patient include carvedilol to protect against catecholamine sensitivity, aspirin for secondary prevention coronary disease, simvastatin for hyperlipidemia, valsartan/hydrochlorothiazide for hypertension, and lorazepam for anxiety.

Table 1. Medications Used in the Management of Takotsubo Cardiomyopathy^a

Agent	Indication
ACE inhibitors	Left ventricular dysfunction (if needed)
Anxiolytic	Anxiety (if needed)
Aspirin	Antiplatelet agent/anticoagulant
β -blocker	Left ventricular dysfunction (if needed)

ACE = angiotensin-converting enzyme.

^aInitial treatment is for acute coronary syndrome, specifically ST-elevated myocardial infarction.

Diane Nykamp PharmD, Professor, Pharmacy Practice, College of Pharmacy and Health Sciences, Mercer University; Clinical Pharmacist, St. Joseph's Hospital, Atlanta, GA

John Adam Titak, PharmD Student, College of Pharmacy and Health Sciences, Mercer University

Reprints: Dr. Nykamp, College of Pharmacy and Health Sciences, Mercer University, 3001 Mercer University Dr., Atlanta, GA 30341, fax 678/547-6683, Nykamp_D@Mercer.edu

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