

Takotsubo (Stress-Induced) Cardiomyopathy in Two Women with Suspected Myocardial Infarction

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Takotsubo cardiomyopathy is a nonischemic cardiomyopathy characterized by reversible left ventricular dysfunction that is seen predominantly in postmenopausal women. Also known as stress-induced cardiomyopathy, broken heart syndrome, and transient left ventricular apical ballooning syndrome, it classically presents with signs and symptoms similar to those of an acute coronary syndrome (ACS), with the onset of symptoms typically provoked by an intense emotional or physical event. Coronary angiography in patients with takotsubo cardiomyopathy usually reveals normal arteries and a characteristic wall motion abnormality: the apical portion of the left ventricle is transiently hypokinetic or akinetic, and there is compensatory hyperkinesis of the basal walls, causing the apex to have a ballooned out appearance during systole. The syndrome was named “takotsubo cardiomyopathy” by clinicians in Japan because the shape of the left ventricular apical ballooning resembles a traditional Japanese octopus trap, or *tako-tsubo* (Figure 1).

Takotsubo cardiomyopathy increasingly is being recognized as a cause of reversible left ventricular dysfunction, especially in postmenopausal women. Because its initial presentation is similar to that of ACS, physicians should be aware of its distinguishing features. This article reports 2 cases of takotsubo cardiomyopathy and discusses the pathophysiology, clinical features, and management of the syndrome.

CASE PRESENTATIONS

Case 1

A 60-year-old woman presented to the emergency department (ED) with acute onset of substernal chest pain and dyspnea immediately after learning that her cousin had died. Her past medical history was significant for

hypertension, dyslipidemia, and gastroesophageal reflux disease, and she was taking trandopril/verapamil ER, atorvastatin, and lansoprazole. The patient was admitted and placed on a nitroglycerin drip, which provided relief of her symptoms. Myocardial enzyme assay showed elevated levels of troponin I (11.62 ng/mL [normal, < 1.5 ng/mL]) and creatine kinase-MB (CK-MB; 20.3 ng/mL [normal, < 15 ng/mL]), and an electrocardiogram (ECG) showed left axis deviation and nonspecific ST changes (Figure 2). The morning after presentation, she was given low-molecular-weight heparin and transferred to the coronary care unit (CCU) at our institution for evaluation of suspected ACS. Upon arrival, her troponin I and CK-MB levels were slightly elevated at 3.46 ng/mL and 15.62 ng/mL, respectively. Her ECG showed nonspecific ST abnormalities in leads V₁ through V₆ with progression to T-wave inversion during her hospital stay. Emergent cardiac catheterization showed mild nonobstructive coronary artery disease, and left ventriculogram revealed an ejection fraction of 25% with anterolateral, apical, and diaphragmatic akinesis (Figure 3). On the basis of these cardiac catheterization findings of normal coronary arteries, severely reduced ejection fraction, and apical akinesis, the patient was diagnosed with takotsubo cardiomyopathy. She was monitored in the CCU and treated with aspirin, a

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β -blocker, and an angiotensin-converting enzyme (ACE) inhibitor and continued on her statin. Three days later, she was discharged and warfarin was added to her hospital medications because of her severely depressed left ventricular function. A follow-up transthoracic echocardiogram performed 8 weeks after discharge demonstrated resolution of the wall motion abnormalities and return of normal left ventricular function with an ejection fraction of 50% to 55%.

Case 2

A 70-year-old woman presented to the ED with onset of substernal chest discomfort that began immediately before she gave a speech at a town council meeting approximately 3 hours prior to presentation. Her past medical history was significant for diet-controlled hyperlipidemia, essential tremors for which she was taking propranolol, and insomnia for which she was taking zolpidem. An ECG was reported as normal, and myocardial enzyme assays revealed elevated levels of troponin I (8.20 ng/mL) and CK-MB (22.5 ng/mL). The patient was given aspirin, a β -blocker, and enoxaparin, started on a nitroglycerin drip, and transferred to our CCU for further evaluation of suspected ACS. Upon arrival, her myocardial enzymes remained elevated (troponin I, 8.43 ng/mL; CK-MB, 23.28 ng/mL), and ECG showed QTc prolongation and flattening of T waves in the anterior leads but no significant ST-segment changes (Figure 4). Emergency cardiac catheterization with coronary angiography revealed mild nonobstructive atherosclerotic disease. Left ventriculogram demonstrated an ejection fraction of 25% with global hypokinesis, which was most pronounced in the apical and septal regions. Based on these findings, the patient was diagnosed with takotsubo cardiomyopathy. The patient was placed on a β -blocker, ACE inhibitor, aspirin, and a statin and monitored in the CCU for 3 days. She was discharged on these medications with the addition of warfarin for anticoagulation because of her severely depressed left ventricular function. A transthoracic echocardiogram obtained 4 weeks after discharge showed normal left ventricular function with an ejection fraction of 55% and resolution of wall motion abnormalities.

TAKOTSUBO CARDIOMYOPATHY

Clinical Features

We report 2 cases of takotsubo cardiomyopathy in postmenopausal women who were transferred to our institution after they initially presented with suspected non-ST elevation myocardial infarction. Patients with takotsubo cardiomyopathy typically present with symp-

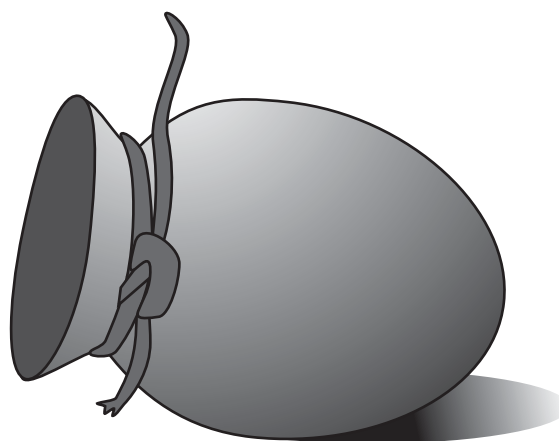


Figure 1. A traditional Japanese octopus trap, or tako-tsubo.

toms of acute myocardial infarction, such as acute chest pain and dyspnea, following exposure to a severe emotional or physical stressor. Electrocardiography generally shows ST-segment elevation and T-wave inversion; however, ECGs can be normal on initial presentation, as occurred in case 2.^{1,2} In addition, cardiac biomarker levels are slightly elevated, and coronary angiography shows normal coronaries with hyperkinetic basal walls secondary to apical dysfunction (Figure 3). In the case patients, coronary angiogram showed normal coronary arteries, but left ventriculogram showed apical ballooning with akinesis of the apex and mid ventricle and sparing of the base, which is a classic feature of takotsubo cardiomyopathy. Although we used cardiac catheterization to confirm the diagnosis in the case patients, echocardiography can be used in diagnosing takotsubo cardiomyopathy. Some groups have recommended using echocardiography in the initial evaluation of patients in whom this diagnosis is suspected.³ Echocardiography usually shows classic findings of apical ballooning of the left ventricular apex, and some patients can have additional marked right ventricular apical akinesia on their echocardiogram.

Epidemiology

Because takotsubo cardiomyopathy has been recognized fairly recently, its prevalence has been somewhat difficult to estimate. Series have estimated that this syndrome accounts for 1.7% to 2.2% of patients presenting with myocardial infarction.⁴⁻⁸ A study involving South Korean patients admitted to a medical intensive care unit for noncardiac reasons found that 28% exhibited apical ballooning on echocardiography, suggesting that the prevalence may be higher.⁹ However, echocardiography by itself is not an ideal approach to diagnosing

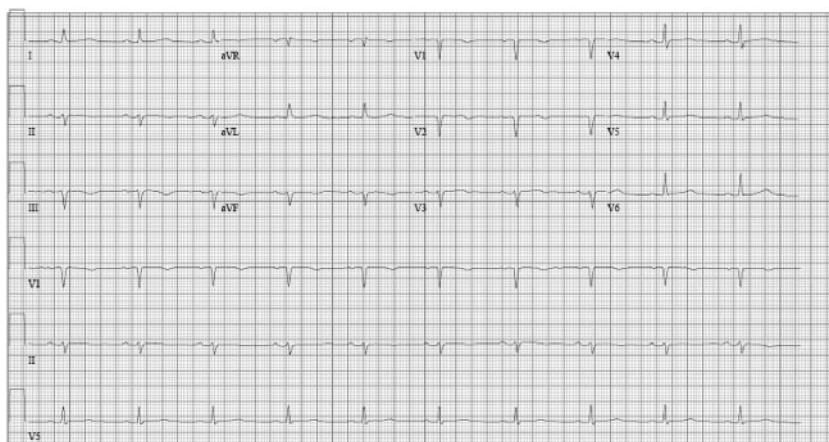
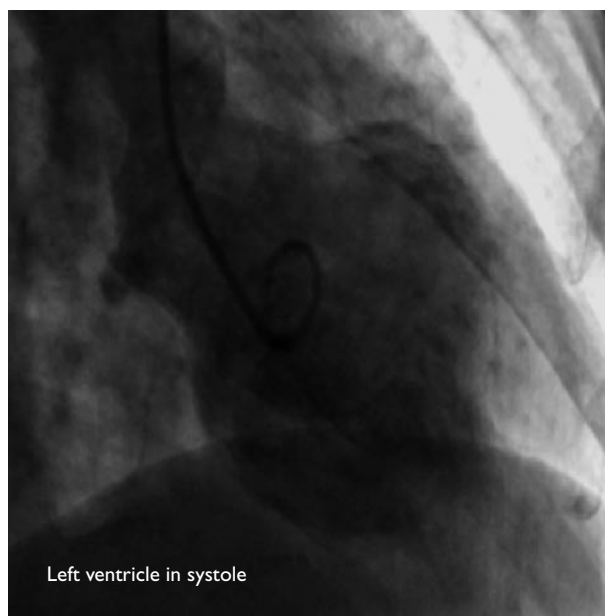


Figure 2. Electrocardiogram from case patient 1 showing left axis deviation and non-specific ST changes.



Left ventricle in systole

Figure 3. Left ventriculogram showing apical dysfunction with hyperkinetic basal walls.

takotsubo cardiomyopathy. Patients presenting with this syndrome are almost always women, and mean age at presentation is 58 to 77 years.^{4,10} The reason for this strong predominance in older women is unknown, but loss of estrogen may play a role. Ueyama and colleagues have shown that higher levels of serum estradiol in rats can diminish pathologic changes in heart function induced by emotional stress.¹¹

Pathophysiology

The underlying pathophysiology of takotsubo cardiomyopathy is not well understood, but the syndrome is thought to be driven by a catecholamine surge lead-

ing to myocardial stunning through an uncertain mechanism. Kurisu and colleagues demonstrated impaired regional myocardial fatty acid metabolism in 14 patients presenting with takotsubo cardiomyopathy.¹² More recently, Bybee et al described impairment of glucose uptake within apical and mid-left ventricular myocardium in takotsubo patients.¹³ These findings suggest that the takotsubo phenomenon is one of myocardial stunning. In addition, there is evidence that a surge of catecholamines in response to an emotional stressor causes this myocardial stunning. Wittstein et al,¹⁴ for example, found catecholamine levels to be 2 to 3 times higher in 13 patients with takotsubo cardiomyopathy compared with 7 patients with Killip class III myocardial infarction. It remains to be elucidated, however, exactly what role catecholamines play in the pathogenesis of the myocardial-stunning phenomenon.

Evidence to support other possible mechanisms for myocardial stunning, such as transient myocarditis, multivessel epicardial spasm, and microvascular dysfunction, is lacking or conflicting.¹⁴ Endomyocardial biopsy performed in 2 studies that evaluated the clinical features of takotsubo cardiomyopathy was uniformly negative for evidence of myocarditis.^{14,15} Studies examining coronary spasm showed that few patients experience spontaneous multivessel spasm. Moreover, attempts to induce multivessel epicardial spasm using agents such as ergonovine and acetylcholine have produced differing results.⁴ Similarly, various reports have presented conflicting evidence regarding the role of coronary microvascular dysfunction in the pathogenesis of myocardial stunning. Abe et al¹⁵ used Doppler guidewire or contrast echocardiography to evaluate coronary microcirculation in patients presenting with takotsubo cardiomyopathy and found no significant abnormality, implying that microvascular

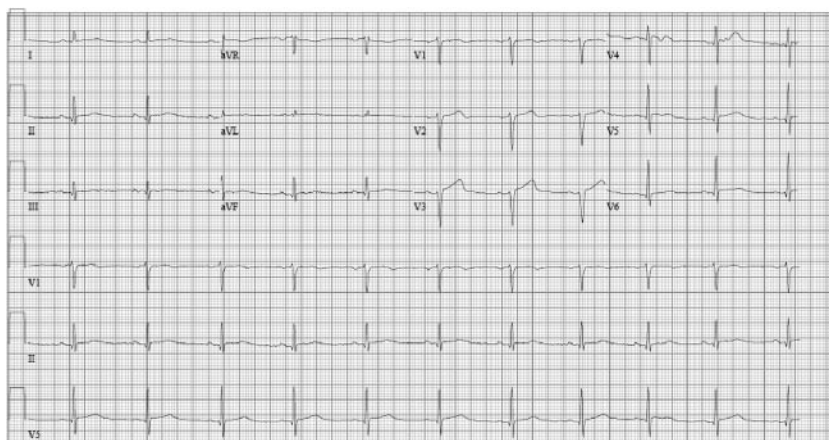


Figure 4. Electrocardiogram from case patient 2 showing nonspecific ST changes.

dysfunction is not the cause of myocardial stunning. Multiple reports, however, have used the Thrombolysis in Myocardial Infarction (TIMI) frame count, a validated index of coronary blood flow, to demonstrate significant abnormalities in diffuse microvascular perfusion.⁴

Management

Treatment of takotsubo cardiomyopathy is entirely empirical because of a lack of studies evaluating therapies. Due to depressed left ventricular function, most patients who are relatively stable are usually given temporary treatment for congestive heart failure, including aspirin, β -blockers, intravenous diuretics, and ACE inhibitors. Although anticoagulation is not always required, patients with an ejection fraction less than 35% require temporary anticoagulation. Some patients can be critically ill, especially in the initial period, and may require temporary intra-aortic balloon pump or even pressors. Supportive care is crucial during this initial period, after which most patients recover rapidly.^{9,16} The condition of stunned myocardium can recur even without any triggering emotional stress.⁴

The prognosis for patients with takotsubo cardiomyopathy is usually good. Patients generally regain normal left ventricular function within 2 to 6 weeks and as early as 2 days after presentation.¹⁷ A recent meta-analysis, however, showed a complication rate of 18.9% and a mortality rate of 3.9%, implying that this entity may not be entirely benign.¹⁰ The most frequent complications were cardiogenic shock, thrombus formation, and left heart failure. Other complications include dynamic intraventricular obstruction with left ventricular intracavitary pressure gradient, mitral regurgitation, ventricular arrhythmias, and left ventricular rupture.^{10,18}

CONCLUSION

Takotsubo cardiomyopathy, or stress-induced cardiomyopathy, is increasingly being reported in the literature. On initial presentation, it usually mimics ACS with increased cardiac marker concentrations with or without ST elevations on ECG. Coronary angiography shows normal coronary arteries but severe left ventricular dysfunction due to apical ballooning and basal wall hyperkinetic motion. Patients with takotsubo cardiomyopathy should be treated with ACE inhibitors and β -blockers and anticoagulation added for those with a severely decreased ejection fraction. Although the prognosis is good and left ventricular function usually returns to normal in 4 to 8 weeks, the mortality rate is 3.9%. **HP**

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REFERENCES

1. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472–9.
2. Cocco G, Chu D. Stress-induced cardiomyopathy: a review. *Eur J Intern Med* 2007;18:369–79.
3. Donohue D, Ahsan C, Sanaei-Ardekani M, Movahed MR. Early diagnosis of stress-induced apical ballooning syndrome based on classic echocardiographic findings and correlation with cardiac catheterization. *J Am Soc Echocardiogr* 2005;18:1423.
4. Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;27:1523–9.
5. Akashi YJ, Nakazawa K, Sakakibara M, et al. 123I-MIBG myocardial scintigraphy in patients with “takotsubo” cardiomyopathy. *J Nucl Med* 2004;45:1121–7.

6. Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol* 2004;94:343–6.
7. Matsuoka K, Okubo S, Fujii E, et al. Evaluation of the arrhythmogenicity of stress-induced “takotsubo cardiomyopathy” from the time course if the 12-lead surface echocardiogram. *Am J Cardiol* 2003;92:230–3.
8. Ito K, Sugihara H, Katoh S, et al. Assessment of Takotsubo (apulla) cardiomyopathy using 99mTc-tetrofosmin myocardial SPECT—comparison with acute coronary syndrome. *Ann Nucl Med* 2003;17:115–22.
9. Park JH, Kng 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.
10. Donohue D, Mohaved MR. Clinical characteristics, demographics, and prognosis of transient left ventricular apical ballooning syndrome. *Heart Fail Rev* 2005;10:311–6.
11. Ueyama T, Hano T, Kasamatsu K, et al. Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of Tako-tsubo (Ampulla) cardiomyopathy. *J Cardiovasc Pharmacol* 2003;42 Suppl 1:S117–9.
12. Kurisu S, Inoue I, Kawagoe T, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* 2003;41:743–8.
13. Bybee KA, Murphy J, Prasad A, et al. Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome. *J Nucl Cardiol* 2006;13:244–50.
14. 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.
15. Abe Y, Kondo M, Matsuoka R, et al. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol* 2003;41:737–42.
16. Villareal RP, Achari A, Wilansky S, Wilson JM. Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc* 2001;76:79–83.
17. Haghi D, Papavassiliu T, Fluchter S, et al. Variant form of the acute apical ballooning syndrome (takotsubo cardiomyopathy): observations on a novel entity [letter]. *Heart* 2006;92:392–4.
18. Ohara Y, Hiasa Y, Hosokawa S, et al. Left ventricular free wall rupture in transient left ventricular apical ballooning. *Circ J* 2005;69:621–3.

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