Takotsubo cardiomyopathy: Review of broken heart syndrome

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In fiction, Takotsubo cardiomyopathy is a genuine physiologic condition that was first described in medical literature 30 years ago. The condition also is known as broken heart syndrome, stress cardiomyopathy, and apical ballooning syndrome. These names describe a syndrome in which severe emotional or physical stress causes the left ventricle to dilate, leading to acute heart failure.

ABSTRACT
Takotsubo cardiomyopathy, also known as broken heart syndrome, apical ballooning syndrome, or stress cardiomyopathy, occurs when a stressful emotional or physical event causes the left ventricle of the heart to dilate, leading to acute heart failure. The syndrome was first described in Japan in 1990. Signs and symptoms of Takotsubo cardiomyopathy are similar to acute myocardial infarction. The syndrome presents with similar ECG and biomarker indications, so it often goes undiagnosed until coronary angiography is performed and reveals no blockage. Treatment is largely supportive. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) may reduce the likelihood of recurrent episodes. Overall, the prognosis is very good, with about 95% of patients making a full recovery.

Keywords: Takotsubo cardiomyopathy, broken heart, stress, myocardial infarction, catecholamines, chest pain

Learning objectives
- Discuss the epidemiology and clinical presentation of Takotsubo cardiomyopathy.
- Differentiate Takotsubo cardiomyopathy from acute coronary syndrome.
- Describe the prognosis of patients presenting with Takotsubo cardiomyopathy.

At the time this article was written, Brenton Boyd was a student in the PA program at Mercer University in Atlanta, Ga. Tia Solh is a clinical assistant professor in the PA program at Mercer University. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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key points
- in takotsubo cardiomyopathy, also known as broken heart syndrome, severe stress causes left ventricular dilation leading to transient heart failure.
- although most patients recover fully, mortality is higher than previously thought, rivaling that of ami.
- worldwide, 90% of patients with takotsubo cardiomyopathy are postmenopausal women.
- the exact pathophysiology of the syndrome is not known, and clinical trials to determine the best treatment have yet to begin.

Described, in retrospect, this is thought to be the first report of takotsubo cardiomyopathy outside of japan. interest in the syndrome spiked in 2004 after the niigata chuetsu earthquake in japan. the number of new takotsubo cardiomyopathy cases diagnosed in the week following the earthquake equaled the total number of cases seen over the previous decade. more recently, earthquakes in new zealand also have been associated with increased rates of takotsubo cardiomyopathy. although the syndrome was identified over 30 years ago, its exact pathophysiology remains a mystery. additionally, no randomized controlled trials have been performed to determine the best course of treatment. thus, takotsubo cardiomyopathy remains a subject of scientific inquiry and medical curiosity.

Pathophysiology
in takotsubo cardiomyopathy, severe stress produces ballooning of the left ventricle. in 75% to 80% of patients, this occurs at the apex of the left ventricle, producing the classic appearance of takotsubo cardiomyopathy reminiscent of the aforementioned japanese octopus traps. in 10% to 20% of patients, midventricular ballooning occurs. in rare cases, basal, biventricular, or focal ballooning have been observed. ventricular ballooning produces transient ST-segment elevation on ECG, increased levels of troponin and B-type natriuretic protein (BNP), and a reduced ejection fraction resulting in acute systolic heart failure.

Triggers
both physical and emotional stress can trigger takotsubo cardiomyopathy. in a retrospective study of 1,750 patients from western countries, 36% had a physical trigger, 27.7% had an emotional trigger, and 7.8% had both triggers; the remaining 28.5% had no identifiable trigger. The most commonly identified physical triggers of takotsubo cardiomyopathy include surgery and acute respiratory failure. the most common emotional triggers are death of a loved one, relationship conflicts, fear, anger, and anxiety. Practically, the distinctions between physical and emotional triggers may be murky, as triggers such as surgery and acute respiratory failure are likely to be emotionally as well as physically stressful.

Although the precise pathophysiology of takotsubo cardiomyopathy is unknown, several pathological mechanisms have been proposed. due to the correlation of stressful triggers and the onset of takotsubo cardiomyopathy, the adrenergic system is suspected to play a key role in its pathophysiology. specifically, catecholamines such as epinephrine and norepinephrine, which are released during times of stress, are thought to contribute to apical ballooning via direct myocardial toxicity and/or disruption to the cardiac microvasculature. increased serum catecholamine levels as well as local release of catecholamines in cardiac nerve endings have been observed in patients with takotsubo cardiomyopathy. this catecholamine surge is believed to promote vasospasm of both the epicardial vessels and the cardiac microvasculature. These vasospasms contribute to an increased cardiac workload, followed by a supply-demand mismatch and, ultimately, postischemic myocardial stunning. Furthermore, the administration of exogenous catecholamines has been shown to cause reversible takotsubo-like changes in the hearts of animal models. there are also reports of human patients experiencing takotsubo cardiomyopathy after the administration of high doses of catecholamines. Serum catecholamine levels of patients with takotsubo cardiomyopathy are more than double those of patients with acute myocardial infarction (AMI), demonstrating a correlative relationship between takotsubo cardiomyopathy and increased catecholamine levels.

Although the evidence for the role of catecholamines in the pathogenesis of takotsubo cardiomyopathy is promis-
Vascular dysfunction

Another area of investigation is the role vascular dysfunction might play in precipitating the syndrome. Researchers have noted that migraine headache and Raynaud phenomenon, like Takotsubo cardiomyopathy, are overrepresented in women. These two conditions involve vascular dysfunction and are more common in patients with Takotsubo cardiomyopathy than in those with AMI and population controls. This hints at a possible link between vascular dysfunction and Takotsubo cardiomyopathy.

**Psychopathology**

Understanding the role of psychiatric disorders in Takotsubo cardiomyopathy may also help elucidate the disease’s pathophysiology. Panic disorder and anxiety are thought to be risk factors for Takotsubo cardiomyopathy. Because Takotsubo cardiomyopathy is triggered by stress, patients who experience higher levels of chronic stress may be at an increased risk for the syndrome. Indeed, a large multinational study found that 55.8% of patients with Takotsubo cardiomyopathy had a history of a neuro-

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**TABLE 1. Diagnostic criteria for Takotsubo cardiomyopathy**

| Revised Mayo Clinic criteria |
|-------------------------------|
| • Transient dyskinesis of the left ventricular midsegments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present. |
| • Absence of obstructive coronary disease or absence of angiographic evidence of acute plaque rupture. |
| • New ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in the cardiac troponin level. |
| • Absence of pheochromocytoma and myocarditis. |

| International Takotsubo Diagnostic Criteria |
|-------------------------------------------|
| • Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery. |
| • An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but is not obligatory. |
| • Neurologic disorders (such as subarachnoid hemorrhage, stroke/transient ischemic attack, or seizures) as well as pheochromocytoma may serve as triggers for Takotsubo syndrome. |
| • Although ECG abnormalities typically are present (ST-segment elevation or depression, T-wave inversion, and QTc prolongation), in rare cases, patients may have no ECG changes. |
| • Levels of cardiac biomarkers (troponin T or I and CK-MB) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common. |
| • Significant coronary artery disease does not exclude Takotsubo syndrome. |
| • Patients have no evidence of infectious myocarditis. |
| • Predominantly affects postmenopausal women. |
logic or psychiatric disorder, compared with 25.7% of patients with acute coronary syndrome (ACS).5

PRESENTATION
Takotsubo cardiomyopathy presents very similarly to AMI. In fact, most patients who are diagnosed with Takotsubo cardiomyopathy are originally suspected to have ACS.6 About 2% of those initially suspected of having ACS are ultimately diagnosed with Takotsubo cardiomyopathy.15

The most common symptoms include chest pain (more than 75% of patients), dyspnea (50% of patients), and dizziness (more than 25% of patients).4 Patients also may develop generalized weakness and occasionally syncope.7 Physical examination findings of patients with Takotsubo cardiomyopathy are consistent with acute systolic heart failure and commonly reveal crackles, tachycardia, hypotension, narrow pulse pressure, S3 gallop, and jugular vein distension.4 Patients also may have a systolic ejection murmur due to an obstruction of the left ventricular outflow tract and mitral regurgitation resulting from ventricular ballooning.4 Lower extremity edema is a rare finding in patients with Takotsubo cardiomyopathy.4 ECG changes, including ST-segment elevation and/or T-wave inversion, are present in most patients, as are elevations in troponin T or I, creatine kinase-MB (CK-MB), and BNP levels.4,7 In the patient history, a stressful event most often is identified 1 to 5 days before presentation.4

The overlap in the presenting signs and symptoms, ECG changes, and laboratory findings between AMI and Takotsubo cardiomyopathy make the two conditions nearly indistinguishable on initial presentation.

DIAGNOSIS
The Revised Mayo Clinic Criteria are widely used diagnostic criteria for Takotsubo cardiomyopathy.4,7 According to the criteria, the following four conditions must be met:

• Transient dyskinesis of the left ventricular midsegments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present
• Absence of obstructive coronary disease or absence of angiographic evidence of acute plaque rupture
• New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in the cardiac troponin level
• Absence of pheochromocytoma and myocarditis.17

Additional diagnostic guidelines for Takotsubo cardiomyopathy include the Heart Failure Association-European Society of Cardiology Criteria and the International Takotsubo Diagnostic Criteria.4 Both guidelines are more extensive than the Revised Mayo Clinic Criteria and are likely more useful in research settings than in clinical practice. Table 1 shows a comparison of the Revised Mayo Clinic Criteria and the International Takotsubo Diagnostic Criteria.

In practice, the diagnosis of Takotsubo cardiomyopathy most often is made when cardiac catheterization of a patient with suspected AMI reveals no blockage, as shown in Figure 2.7 Recent research has sought less invasive methods for distinguishing Takotsubo cardiomyopathy from AMI. Several observations have been made:

• On ECG, ST-segment depression in lead aVR was shown to be 95% specific for Takotsubo cardiomyopathy versus AMI in patients with ST-segment elevation on ECG.18
• Troponin levels are similar at the onset of Takotsubo cardiomyopathy and AMI, but peak levels of troponin are higher in patients with AMI than in those with Takotsubo cardiomyopathy.5,7,8
• BNP levels are higher in patients with Takotsubo cardiomyopathy than in those with AMI.7
• N-terminal pro-BNP (NT-proBNP) levels are higher in patients with Takotsubo cardiomyopathy than in those with AMI.19

A summary of these biomarker findings is shown in Table 2. These important observations may one day lead to the ability to diagnose Takotsubo cardiomyopathy definitively outside the cardiac catheterization laboratory. Currently, however, coronary angiography remains necessary in most cases to rule out AMI and accurately diagnose Takotsubo cardiomyopathy.5

TREATMENT
To date, no clinical trials have been performed to assess treatment options or medical therapy for Takotsubo cardiomyopathy, adding another layer of mystery to the syndrome.1 Takotsubo cardiomyopathy requires inpatient care with cardiology services. Treatment is largely supportive and continues until the spontaneous return of left ventricular function, which most often occurs within 21 days of the onset of the syndrome.4 The severity of Takotsubo cardiomyopathy is wide-ranging.4 Patients with mild cases may not need any intervention. Those with severe cases, on the other hand, may require aggressive medical therapy and, if the condition is refractory, mechanical left ventricular support.4

| Biomarker     | Takotsubo cardiomyopathy | AMI |
|---------------|--------------------------|-----|
| Initial troponin level | Elevated | Elevated |
| Peak troponin level | Elevated | Markedly elevated |
| BNP level | Markedly elevated | Elevated |
| NT-proBNP level | Markedly elevated | Elevated |
Initially, the patient’s hemodynamic stability must be determined. Hemodynamically stable patients are treated for systolic heart failure. If pulmonary congestion occurs, diuretics and vasodilators (such as nitroglycerin, nitroprusside, or nesiritide) can be used.4 Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers often are used to reduce cardiac workload and control hypertension when present.4 In addition, aldosterone receptor antagonists such as spironolactone also may be beneficial.20,21 Because aldosterone may potentiate the effects of catecholamines on the cardiovascular system by further raising systemic BP, use of an aldosterone antagonist may be particularly cardioprotective in patients with Takotsubo cardiomyopathy.22 However, clinical trials of the use of these agents specifically in Takotsubo cardiomyopathy are needed to investigate this theory.22 Angiotensin receptor-neprilysin inhibitors also may be used to mitigate the effects of systolic heart failure in patients with Takotsubo cardiomyopathy.4

Patients with hypotension and low cardiac output (cardiogenic shock) can be divided into two categories: those with left ventricular outflow tract obstruction (LVOTO) and those without obstruction.4 This is assessed via echocardiography. In patients without an obstruction, inotropes such as milrinone, dobutamine, and dopamine can be used.4 Vasopressors and left ventricular assist devices may be necessary in refractory cases.4

Inotropes should not be used in patients with LVOTO, as they increase basal hypercontractility and may worsen the obstruction.4 Beta-blockers, which reduce basal contractility, and IV fluids should be initiated instead.4 Vasopressors can be used in patients with LVOTO.4 Extracorporeal membrane oxygenation (ECMO) may be necessary in severe cases of cardiogenic shock with LVOTO.4 Several studies have sought to determine if ACE inhibitors/ARBs or beta-blockers are more beneficial in patients with Takotsubo cardiomyopathy.5,23,24 The results have been inconclusive. Beta-blockers are a logical choice, given their protective effect against cardiac remodeling in post-AMI and heart failure patients. Some researchers have even proposed that beta-blockers could be used to protect against Takotsubo cardiomyopathy, considering the role of catecholamines in the syndrome.5 However, a large multinational review found that ACE inhibitors/ARBs were associated with improved survival for patients with Takotsubo cardiomyopathy but beta-blockers were not.5 The same study showed that of 57 patients who experienced recurrence, 29 were taking beta-blockers at the time of the second event.5 One systematic review and meta-analysis revealed that ACE inhibitors/ARBs reduced the rate of recurrence of Takotsubo cardiomyopathy but beta-blockers did not.23 Another meta-analysis found that neither ACE inhibitors/ARBs nor beta-blockers showed efficacy in reducing the recurrence of Takotsubo cardiomyopathy.24 All of these studies are retrospective in nature, and their mixed results highlight the need for prospective randomized studies.

A major goal of inpatient clinicians treating Takotsubo cardiomyopathy is mitigating the patient’s risk for major cerebrovascular events, such as stroke and AMI, which occur in 7.1% of patients during the first 30 days of hospital admission.7 Anticoagulation should be initiated in patients with large areas of cardiac hypokinesis.4

In the early weeks following the onset of Takotsubo cardiomyopathy, patients need to be seen frequently by a cardiologist using serial echocardiography to assess recovery. As the long-term outcomes for Takotsubo cardiomyopathy are not easily predictable, these patients require long-term cardiac care.5

PROGNOSIS AND RISKS

Overall, the prognosis of Takotsubo cardiomyopathy is good. About 95% of patients recover full cardiac function within several weeks.27 Current studies estimate the in-hospital mortality at about 5%, which is higher than previously thought.43 Most deaths occur in patients who present with hemodynamic instability.4 According to a systematic review and meta-analysis that drew data from more than 1,600 patients with Takotsubo cardiomyopathy, recurrence happened at an annual rate of about 1.5%, and the cumulative incidence of recurrence at 6 years was about 5%.23 Although men are less likely than women to experience Takotsubo cardiomyopathy, men are more likely to die from the condition than women.9 Interestingly, patients with Takotsubo cardiomyopathy triggered by physical stressors have higher mortality than those whose Takotsubo syndrome is triggered by emotional stressors, and research indicates that men are more likely to be triggered by physical stressors.1 In fact, physically triggered Takotsubo cardiomyopathy and male sex are independent risk factors for mortality in Takotsubo cardiomyopathy.6

Atrial fibrillation (AF) also has been identified as an independent risk factor for mortality in patients with Takotsubo cardiomyopathy.23 An international, multicenter study of 387 consecutively enrolled patients found that long-term mortality of patients with Takotsubo cardiomyopathy and AF was significantly higher than for those without AF.23 At 19%, in-hospital mortality also was increased in patients with Takotsubo cardiomyopathy and AF, compared with 10% for patients with Takotsubo cardiomyopathy but without AF.26 Several explanations are possible for the increased risk of mortality in patients with Takotsubo cardiomyopathy and AF. Although stroke is a well-established risk of AF, thromboembolic events only represent about 1% of the deaths observed in patients with Takotsubo cardiomyopathy and AF.25 AF likely worsens the heart failure often seen in Takotsubo cardiomyopathy via processes such as loss of atrial contraction, rapid ventricular rate, and atrioventricular desynchronization, all of which can contribute to reduced ejection frac-
tions. Of course, comorbid clinical conditions that predispose patients to AF (such as hypertension, diabetes, heart failure, or advanced age) should not be ignored as potential causes for increased mortality in patients with Takotsubo cardiomyopathy and AF. Regardless of the mechanism, clinicians should be aware of the increased risk of mortality in patients with concomitant Takotsubo cardiomyopathy and AF. Closer monitoring and more frequent follow-ups are recommended for patients with AF in the months and years following an episode of Takotsubo cardiomyopathy.

Clinicians should be aware of independent risk factors for mortality in patients with Takotsubo cardiomyopathy, such as male sex, physical triggers, and AF. Further research is needed to develop a robust system of risk stratification for Takotsubo cardiomyopathy in order to more accurately identify those most at risk for death.

CONCLUSION

Given that about 2% of patients with suspected ACS are ultimately diagnosed with Takotsubo cardiomyopathy, and the in-hospital mortality of TC is nearly 5%, clinicians should keep Takotsubo cardiomyopathy on their differential diagnosis list when a patient presents with chest pain and difficulty breathing following a physically or emotionally stressful event—particularly if that patient is a post-menopausal woman.

Although Takotsubo cardiomyopathy has an interesting history in folklore and medical literature, much remains to investigate. Elucidating the exact pathophysiology and researching further treatment targets for Takotsubo cardiomyopathy hold the promise of expanding our current understanding of the condition and improving patient care.

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