Caring for the Takotsubo Cardiomyopathy Patient
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ABSTRACT
Takotsubo cardiomyopathy is characterized by an atypical pattern of wall motion abnormalities seen during coronary angiography or echocardiogram as excessive abnormal movement of basal with midventricular and apical hypokinesis. These findings occur in the absence of obstructive coronary artery disease. The disorder was named due to its distinctive resemblance to traditional Japanese octopus fishing pots called *tako-tsubo*. The heart presents with a wide base and a long thin neck when viewed in an echocardiogram. Takotsubo cardiomyopathy was first identified in Japan in 1990 and, since then, has been gaining increased attention and being diagnosed worldwide.

Keywords: broken heart syndrome, stress cardiomyopathy, Takotsubo cardiomyopathy
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BACKGROUND
Takotsubo cardiomyopathy (TCM) was first identified in Japan in 1990 and, since then, has been gaining increased attention around the world and is diagnosed internationally. TCM is characterized by an atypical pattern of wall motion abnormalities as seen on coronary angiography or echocardiogram as excessive abnormal movement of basal with midventricular and apical hypokinesis. These findings occur in the absence of obstructive coronary artery disease. The disorder was named due to its distinctive resemblance to traditional Japanese octopus fishing pots called *tako-tsubo* (Figure 1). The heart presents with a wide base and a long thin neck when viewed on an echocardiogram. The wall motion abnormalities are reversible within a few days to weeks, and the condition has good prognosis if diagnosed early and treatment is timely. However, TCM remains a major life-threatening disorder because it can lead to serious complications. Research reports that 10% of patients with TCM develop ventricular wall rupture, cardiogenic shock, and malignant arrhythmia, with a mortality rate of about 8%. Research has shown that 1%-2% of patients who have a positive troponin or ST elevation that is suspected to be acute coronary syndrome or acute myocardial infarction (MI) have TCM. This heart condition often mimics acute MI, but, unlike MI, there is no specific biomarker for diagnosis of TCM. This may change at some time in the future. A recent study reported a subtype of circulating microRNAs (miRNAs) to be sensitive and specific in the identification of TCM in the acute phase. miRNAs are a group of endogenous and noncoding, small RNAs that regulate the function of target mRNAs. This study reported that miRNAs are associated with MI, cardiomyopathy, heart failure, and atrial fibrillation. In addition, coronary angiography is necessary to rule out MI when patients present with symptoms of acute coronary syndrome and TCM is suspected. The etiology of TCM remains unclear despite several proposed theories.

RISK FACTORS FOR TCM
There is consensus that TCM is most often triggered by a major stressful psychological or physiologic event. Catastrophic personal circumstances have been cited as triggers for TCM, such as death in the family, financial adversity, legal issues, or health deterioration. In addition, natural disasters can lead to secondary traumatic conditions, one of which is TCM.
Several reported cases have demonstrated the impact of major physical and emotional stressful events on the development of TCM. For instance, on September 4, 2010, the city of Christchurch, New Zealand was struck by 2 major earthquakes (7.1 and 6.3, respectively) within 9 hours. Research was conducted to determine whether there there was an association between the earthquakes and adverse health events. The study concluded that the earthquakes were linked to a substantial increase in ST-elevation myocardial infarction and a few stress TCM cases. Another case report described development of TCM as a sequela of elective cardioversion for atrial fibrillation. TCM can affect children and young or older adults, as well as any race and gender. In a systematic review of 104 cases of TCM (1965-2013), investigators noted that young patients with TCM were more likely to be female and have a history of physical rather than mental stress. Another review, in which race was reported, patients were typically Asian (57.2%) or Caucasian (40%), and only 2.8% were of other races. Across studies, demographics indicate that women were more likely to have TCM than men, with postmenopausal women (mean age 67 years) at greatest risk. This is congruent with another study showing that women > 55 years old had a 4.8-fold higher risk of developing TCM compared with those < 55. The study further noted that smoking, alcohol abuse, anxiety, and hyperlipidemia contributed to the development of TCM.

Similarly, among the 1,769 patients included in the International Takotsubo Registry study, patients with TCM were predominately female (89.8%). A slightly higher percentage indicated physical triggers (36%) rather than emotional triggers (27.7%), and 7.8% had both physical and emotional triggers. Of note, 28.5% of patients had no clear etiology.

Interestingly, Templin et al’s research indicated a correlation between TCM and increased rates of psychiatric disorders, such as affective disorders, anxiety, and depression, when compared with those with acute coronary syndrome. The higher association became apparent because a substantial number of patients were taking 1 or more antidepressant(s) (17.1%).

PATHOPHYSIOLOGY OF TCM
The pathogenesis of TCM is not well understood, but there are 3 major hypotheses for the disorder, including coronary vasospasm, microvascular spasm, and catecholamine-induced neurogenic stunning of the myocardium neck. Other proposed mechanisms include microvascular injury secondary to reperfusion injury after myocardial infarction, microinfarction caused by myocardial microembolization, and dysregulated cardiac fatty acid metabolism. Among experts, the most commonly accepted theories are catecholamine-induced cardiotoxicity and microvasculature dysfunction.

One study of 157 cases of drug-induced TCM reported that 57 (33.6%) cases were related to exogenous catecholamine administration. There several acute medical conditions that can trigger TCM, as shown in several case studies, including postoperative surgery, cesarean surgery, post-spinal anesthesia, cardiac surgery, seizures, status epilepticus, and diabetic keto-acidosis (DKA). One case study described a 46-year-old, premenopausal, Caucasian woman who had stress urinary incontinence and TCM after the initial administration of subarachnoid anesthesia for a surgical procedure (tension-free vaginal tape) to correct the urologic defect. A 78-year-old man, who had multiple seizure episodes during his adolescent years, was treated with antiseizure medications, then developed refractory seizures and later had 2 episodes of seizure attacks, which triggered development of recurrent TCM. Patients who...
develop heart failure after DKA should be evaluated for TCM, as this is a known consequence of DKA.  

One study suggested that a natural catecholamine surge, which occurs in response to stress, is the cause of the abnormal myocardial response. This is supported by research demonstrating that, when compared with patients with MI, TCM patients had 2–3 times higher levels of serum catecholamines and neurotransmitters (epinephrine, norepinephrine, and dopamine).  

This is postulated to be due to an “excessive hypothalamic–pituitary–adrenal axis response to stress.” The association with catecholamines is supported by related research. It was reported that administration of exogenous catecholamine and pheochromocytoma (catecholamine-producing adrenal tumor) causes characteristics typical of TCM. This was congruent with another study reporting that cocaine, methamphetamine, and excessive phenylephrine use were associated with TCM development. TCM can be triggered by the injection of intravenous catecholamine, specifically epinephrine. There is a case report of a 35-year-old woman who developed stress-induced TCM after a laparoscopic myomectomy procedure for the removal of intramural fundal uterine leiomyomas, which involved injection of intramyomeral epinephrine to decrease blood loss during the procedure.

Patients with TCM present with microvascular dysfunction after an acute stressor, which impairs cardiac vascular function and leads to insufficient perfusion and resultant myocardial injury. Another theory proposes that there is an excessive response to acetylcholine, which causes vasospasm in a large coronary vessel; this ischemia may contribute to transient left ventricular (LV) dysfunction. However, this theory has been questioned because only 30% of patients were identified as having vasospasm characteristics in a challenge test. The challenge test is a “coronary spasm provocation test,” which was performed through intracoronary ergonovine or acetylcholine injection into the right coronary artery and left coronary artery and the measurement of circulating catecholamine levels. This study expanded the understanding of catecholamine’s influence, specifically noting that an increased level of norepinephrine was associated with an increased level of C-reactive protein and white blood cells. The authors reported that catecholamines were responsible for systemic inflammation by stimulation of proinflammatory cytokines or chemical mediators that resulted in myocardial dysfunction. Finally, the role of genetic transmission is unclear, but there appears to be a genetic predisposition to developing TCM; this potential association requires further research.

CLINICAL MANIFESTATIONS OF TCM
The most common symptoms of TCM are sudden chest pain and shortness of breath. Studies show that these symptoms usually begin minutes to hours after a severe and unexpected stressor. Some people may experience signs and symptoms such as fainting and arrhythmias due to severe heart muscle weakness. Studies reported that about 50% of patients with TCM experience complications in the acute phase. Occasionally, TCM results in major complications, such as cardiogenic shock, serious ventricular rhythm abnormalities, or cardiac rupture. Although rare, cardiac rupture is one of the most severe complications. Risk factors for cardiac rupture include female gender, older age, persistent ST elevation in the inferior leads, higher systolic and diastolic blood pressures, and a low ejection fraction. In addition, evidence shows that cardiac rupture occurs more often in older Asian females with higher blood pressure and higher left ventricular ejection than in those without cardiac disease. It is believed that cardiac rupture can result from hypercontractility of the LV and obstruction of the basal segment of the LV outflow, which may increase the afterload in the LV (Figure 2). Other medical complications include pulmonary edema, acute mitral valve regurgitation, right ventricular wall motion abnormalities with pleural effusion, and arterial embolism, which may result in stroke, atrial fibrillation, and ventricular dysrhythmias.

DIAGNOSTIC STUDIES
There are a variety of clinical examination tools to diagnose TCM, but it is important to recognize that no single test can diagnose TCM. The diagnosis is made based on the results of standard tests to rule out MI and imaging studies that support a diagnosis of
TCM.14 These diagnostic tests include electrocardiography (ECG), cardiac biomarkers and laboratory findings, echocardiography, coronary angiography and left ventriculography, chest X-ray, and nuclear imaging.21

Cardiac biomarkers and laboratory tests are considered first in ruling out TCM because there is a very small increase in creatinine kinase and troponin compared with the extent of organ dysfunction.21 In the acute phase, levels of epinephrine, norepinephrine, and neurotransmitters, including dopamine, are increased.21 This is supported by a study in which patients who had myocardial biopsies demonstrated changes in molecular and cellular level that were associated with high exposure to catecholamine levels.21

ECG abnormalities are seen in some patients with TCM during the acute phase, but, currently, there is no one pathologic ECG rhythm used to identify TCM.21 Some of the abnormal ECG rhythm types include ST-segment elevation, ST-segment depression, pathologic Q-waves, and T-wave inversion. Also, it is important to note that some TCM patients may have a normal ECG.21

Echocardiography increases detection and reported incidence of TCM.21 Transthoracic echocardiography is used to detect large areas of dysfunctional myocardium that can extend beyond the perfusion area of a single coronary artery.21 In addition, there is abnormal LV myocardial contractility, as characterized by symmetric regional abnormalities extending equally into the anterior, inferior, and lateral walls. Structural abnormality of the myocardium is the hallmark of TCM.21

Moreover, echocardiography is useful in the early detection of severe complications such as right ventricular involvement, thrombus formation, mitral regurgitation, and ventricular rupture. Echocardiography is used to evaluate and confirm the recovery of LV function during follow-up.21

Cardiac catheterization is an important procedure that can definitively differentiate between TCM and acute coronary syndrome due to coronary artery disease. This procedure is frequently performed in patients presenting with acute chest pain and ST elevation within 48 hours from symptom onset.21

Cardiac magnetic imaging helps exclude the diagnoses of myocarditis or myocardial infarct. It can identify ventricular anomalies in patients for whom echocardiograms did not produce a definitive diagnosis.21

Figure 2. (a) Left ventricular angiogram taken in systole demonstrating apical akinesia and hyperkinesia of the basal segments. The appearance can be compared with a Japanese fishing octopus trap called a takot-subo. (b) The left ventricular angiogram taken in diastole.
TREATMENT AND MANAGEMENT OF TCM

Management of TCM involves a coordinated effort between primary care and cardiac specialty care. Nurse practitioners (NPs), whether primary or acute care, have an integral role in management of this patient population.

In the event the patient presents to primary care initially, the NP or other health care provider is tasked with obtaining a history, physical, and ordering of relevant diagnostic tests, specifically an ECG. Because TCM is difficult to differentiate from acute coronary syndromes without full diagnostics, the NP should facilitate the patient’s transport to an emergency department without delay.1,24 In the emergency care setting, laboratory and other diagnostic testing must be completed to determine etiology.

After a diagnosis of TCM, the mainstay of treatment is drug therapy to reduce cardiovascular workload. The most commonly prescribed drugs are beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and diuretics. These medications are used until LV function is restored. Beta-blockers are also indicated, initially because of their action in inhibiting the biologic effects of catecholamines; in the longer term, beta-blockers reduce the workload of the dysfunctional myocardium during the recovery process.9,22 Diuretics are prescribed to help reduce pulmonary and peripheral fluid overload. Antianxiety medicines are often added to the treatment to manage the effects of stress hormones.26 Surgical repairs are relatively rare because they are relegated to cases of cardiac rupture when there is time to move the patient into the operative arena.27

In the posthospitalization period, the role of the NP is focused on long-term medication management and ordering of diagnostic tests to determine progress to resolution of TCM. In consultation with the patient’s cardiologist, the NP can titrate and wean medications as the patient’s condition improves. With time, the NP should expect normalization of the echocardiogram.25 Literature supports normalization of echocardiograms in as little as 24 hours, but, more frequently, echocardiography will demonstrate significant improvement by 4-8 weeks.9,28 A recent study of 21 TCM patients, predominately elderly, showed there was some improvement in wall motion and ejection fraction in 49% of the patients by week 4; all patients demonstrated a return to normal cardiovascular function by 6 months.28

Equally as important is psychological care. NPs should assess TCM patients to determine the need for counseling to manage stress and reduce disease severity.26 Consultation with social workers and case managers may be necessary to address patient-specific stressors. Some patients may need referral to support groups to assist with grieving or other life changes. An ongoing, trusting relationship with an NP facilitates discussions about these sensitive topics.29

PROGNOSIS AND HEALTH OUTCOME OF TCM

A recent study showed that TCM patients usually have good prognosis, with approximately 95% of patients returning to their predisease state within 4-8 weeks.9 This is less characteristic among the elderly, where the rate of adverse events is high and complications continue after discharge.1 It was also reported that, in the International Takotsubo registry study, the rate of major adverse cerebrovascular events (including death, stroke, or transient ischemic attack) during first 30 days after admission was 7.1%.1 There are discrepant reports about mortality rates. Death rates from any cause during acute hospitalization have ranged from 1% to 2%. Long-term mortality has varied significantly between studies, ranging from a low 0% to a high 11.4%.1,21 Another study, which examined a total of 24,701 TCM patients in a national patient sample in 2008-2009, reported an in-hospital mortality rate of 4.2%, with males having higher mortality than women (8.4% vs 3.6%, P < .0001).13 Another study also showed that mortality rate was closely associated with comorbidities because most patients had underlying critical illnesses.30

The recommendation is that a follow-up clinical assessment, ECG and/or repeat cardiac imaging (transthoracic echocardiography and/or cardiac magnetic resonance) should be done before discharge, and should be considered based on test availability and clinical status at 3 and/or 6 months.24
CASE STUDY

E.A. is a 48-year-old woman without a history of heart disease who presented to the emergency department with complaints of sudden, sharp chest pain and shortness of breath for 3 hours. She was given aspirin and nitroglycerin, but the pain continued. ECG demonstrated sinus rhythm of 64 beats/min and ST-segment elevation restricted to precordial leads V2 and V3. Laboratory results showed an increased troponin level of 2.241 ng/mL. She was hemodynamically stable and was taken to the catheterization laboratory for percutaneous coronary intervention. Coronary angiography did not reveal any stenosis or coronary plaque, but LV angiography showed normal volume with contractility disturbances at the apex and hyperkinesia of the basal segment, with an ejection fraction (EF) of 58%. The patient did not require any intervention. After percutaneous coronary intervention she was treated with a beta-blocker ACE inhibitor.

Psychosocial assessment revealed that E.A. lost her 20-year-old son in a motor vehicle accident 2 weeks before hospital admission for chest pain. She reported that the sudden death of her son caused her great pain and sadness; she admitted to thoughts of suicide. During hospitalization, a psychiatrist was consulted for further evaluation and counseling. Treatment focused on supportive care and the management of the emotional stress. Upon discharge, in addition to ongoing psychiatric care, E.A. was also treated by a cardiologist as an outpatient for 1 year. At 1 year, ECG demonstrated a return of normal left ventricular function and contractility (EF 70%).

Studies have suggested that emotional and physical stress trigger TCM. One would assume that adequate proper reduction of stress level and adequate coping skills can prevent TCM. However, research has also shown that TCM can occur because of sudden good news, like a surprise party. On this note, it may be difficult to prevent TCM; instead, adequate stress level reduction and coping skills can reduce the risk of developing TCM, but without complete prevention.

CONCLUSION

TCM presents similarly to acute coronary syndrome and thus the diagnosis is often missed or delayed, and considered only when there is no evidence of obstructive coronary artery disease. It is imperative to diagnose TCM as soon as possible to begin definitive treatment because it has been shown that the condition is reversible and has a good prognosis if diagnosed and treated early.

References

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