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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing

Takotsubo Cardiomyopathy

Authors
Sarah A. Ahmad1; Nauman Khalid2; Michael A. Ibrahim3.

Affiliations
1 Saint Francis Medical Group
2 MedStar Washington Hospital Center
3 California Northstate University College of Medicine
Last Update: May 22, 2023.

Takotsubo cardiomyopathy, also known as Gebrochenes-Herz syndrome, transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, stress cardiomyopathy, and broken-heart syndrome, is a form of non-ischemic cardiomyopathy. It is characterized by transient regional systolic dysfunction of the left ventricle mimicking acute myocardial infarction but with only minimal release of cardiac enzymes. There is a paucity of angiographic evidence of obstructive coronary artery disease or acute plaque rupture. In most cases of takotsubo cardiomyopathy, the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery. The term takotsubo means octopus trap in Japanese. It has a shape that is similar to the systolic apical ballooning appearance of the left ventricle. This activity reviews takotsubo cardiomyopathy and highlights the interprofessional team's role in the recognition and management of patients affected by it.

Objectives:
- Describe exam findings consistent with takotsubo cardiomyopathy.
- Identify the testing that should be done if takotsubo cardiomyopathy is suspected.
- Explain management considerations for takotsubo cardiomyopathy.
- Summarize a well-coordinated interprofessional team approach to provide effective care to patients affected by takotsubo cardiomyopathy.

Introduction
Takotsubo cardiomyopathy is also known as a transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, stress cardiomyopathy, and Gebrochenes-Herz syndrome, and broken-heart syndrome is a form of non-ischemic cardiomyopathy and predominantly affects post-menopausal women.[1][2][3][4][5][6][7][8] It is characterized by transient regional systolic dysfunction of the left ventricle in the absence of angiographically significant coronary artery disease or acute plaque rupture. In most takotsubo cardiomyopathy cases, the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery. The term takotsubo is a Japanese name for an octopus trap. It has a shape that is similar to the systolic apical ballooning appearance of the left ventricle.

Etiology
The exact etiology of takotsubo cardiomyopathy is not fully understood. Several mechanisms are hypothesized as possible etiologies of takotsubo cardiomyopathy, including sympathetic overdrive with increased catecholamines, coronary spasm, microvascular dysfunction, low estrogen levels, inflammation, or impaired myocardial fatty acid metabolism. Risk factors for the development of takotsubo cardiomyopathy include domestic abuse, death of relatives, natural calamities, accident or major trauma, arguments, financial or gambling loss, diagnosis of an acute medical illness, stimulant drugs such as cocaine, amphetamines, or even positive life events the so-called' happy heart syndrome.'

Epidemiology
The real incidence of takotsubo cardiomyopathy is uncertain. It makes up for 1 to 2% of patients suspected of having acute coronary syndrome.[9][10][11] One registry of 3265 patients with troponin-positive acute coronary syndrome reported a prevalence of 1.2%[9] of

takotsubo cardiomyopathy, whereas a systematic review of patients presenting with suspected acute myocardial infarction reported a prevalence of 1.7 to 2.2%.[10] There is a strong predilection of TC to afflict post-menopausal women; however, males may have a worse prognosis if affected. In the International Takotsubo Registry study (a consortium of multiple centers across Europe and America of 1750 patients), approximately 88.9% of the affected patients were females, and the mean age was 66.4 years.[12]

Pathophysiology

The precise pathophysiologic mechanism underlying takotsubo cardiomyopathy remains elusive. Various hypotheses have been postulated and include elevated levels of circulating plasma catecholamines and their circulating metabolites due to underlying stress, microvascular dysfunction or microcirculatory disorder, inflammation, estrogen deficiency, spasm of the epicardial coronary vessels, and aborted myocardial infarction.[13][14] The catecholamine hypothesis is the most widely accepted pathophysiologic mechanism of TC, and elevated levels (two to threefold elevation) of plasma catecholamines and neuropeptides (norepinephrine, epinephrine, and dopamine) have been observed in patients with TC. Catecholamines can cause microvascular spasms, dysfunction, myocardial stunning, or direct myocardial injury. Estrogen exerts protective effects on the cardiovascular system, including vasodilation, protection against atherosclerosis, and endothelial dysfunction. Therefore, post-menopausal women exhibit exaggerated vasoconstriction, altered endothelium-dependent vasodilatation, and sympathetic activation in response to psychosocial stress.[15]

The role of inflammation in takotsubo cardiomyopathy is depicted by cardiac magnetic resonance imaging, which shows myocardial edema, necrosis, fibrosis, and late gadolinium enhancement.[16] Coexisting cases of myocarditis, pericarditis, or autoimmune conditions such as systemic lupus erythematosus or Sjogren syndrome have been described in the literature, suggesting that chronic inflammatory conditions with acute flares may provide a substrate for the emergence of takotsubo cardiomyopathy.[17][18][19] Microvascular dysfunction is demonstrated by abnormal coronary flow reserve, thrombolysis in myocardial infarction (TIMI) frame count, TIMI perfusion grade, and quantitative flow ratio.[20][21][22][23][24]

An impaired microvascular function has also been demonstrated by measuring the index of microvascular resistance by introducing a pressure wire in the coronary arteries.[25] There is some evidence that the prevalence of diabetes mellitus is low in takotsubo cardiomyopathy patients, suggesting that blunting of autonomic response in diabetes may have a protective effect against the development of Takotsubo cardiomyopathy, the so-called "diabetes paradox."[26][27][28]

Histopathology

Endomyocardial biopsy of patients with takotsubo cardiomyopathy demonstrates reversible focal lysis of myocytes, mononuclear infiltrates, and contraction band necrosis.

History and Physical

Takotsubo cardiomyopathy presentation is similar to acute coronary syndrome. This disorder is frequently triggered by intense emotional or physical stress, for example, the unexpected death of a family member, domestic abuse, significant confrontation, medical diagnosis, natural disaster, and/or financial loss. In the International Takotsubo Registry study, the most common symptoms are chest pain, dyspnea, and syncope. Some patients may present with symptoms and signs of heart failure, tachyarrhythmias, bradyarrhythmias, sudden cardiac arrest, or severe mitral regurgitation. There may be a late-peaking systolic murmur on auscultation due to left ventricular outflow tract obstruction. There may also be symptoms and signs of transient ischemic attack or stroke-like presentation due to apical thrombus embolization. Approximately 10% of patients with stress cardiomyopathy develop cardiogenic shock.

Evaluation

The diagnosis of stress cardiomyopathy should be suspected in adults (particularly postmenopausal women) who present with a suspected acute coronary, particularly when the clinical manifestations and electrocardiographic abnormalities are out of proportion to the degree of elevation in cardiac biomarkers. It is important to emphasize that takotsubo cardiomyopathy is a diagnosis of exclusion that can only be made after coronary angiography because of the indistinguishable features from acute coronary disease.[29][30][31] Several diagnostic criteria were

proposed for the diagnosis of takotsubo cardiomyopathy, including the Mayo Clinic criteria, the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria), and others.[32]
The most widely accepted criteria are the Mayo Clinic diagnostic criteria for the identification of stress cardiomyopathy. Outlined below are the key features; all are required to meet the diagnosis: [33][34]

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond.
2. A single epicardial vascular distribution and frequently, but not always, a stressful trigger.
3. The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
4. New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
5. The absence of pheochromocytoma and myocarditis.

Electrocardiographic findings Patients with TC often exhibit a dynamic pattern of electrocardiographic (ECG) changes akin to the ECG staging in pericarditis.[35] ST-segment elevation develops in stage 1, followed by normalization of the ST segment in stage 2. T wave inversions develop in stage 3, whereas complete normalization of T waves or very rarely persistence of T wave inversions occurs in stage 4. There may be some overlap in stages 2 and 3, and all patients may not exhibit all stages.

Laboratory findings Cardiac biomarkers, including troponins and CK-MB, show mild elevation. According to the International takotsubo Registry study, the median initial troponin was 7.7 times the upper limit of normal. Levels of brain natriuretic peptide (BNP) or N-terminal pro-BNP are elevated in most patients with stress cardiomyopathy and exceeded those seen in a matched cohort of patients with acute coronary syndrome (median 5.89 versus 2.91 times the upper limit of normal).[12]

Transthoracic echocardiography demonstrates the wall motion abnormalities classified as:

- Apical type (typical): there is a systolic apical ballooning of the left ventricle, with depressed mid and apical segments, and also hyperkinesis of the basal walls. This variant was found in approximately 80% of patients in the International Takotsubo Registry study. [12]
- Atypical variants: Mid-ventricular type hypokinesis (14.6%), basal type hypokinesis (2.2%), focal type hypokinesis (most commonly the anterolateral segment) (1.5%), and global hypokinesis.[12]

Most patients with stress cardiomyopathy have reduced overall left ventricular systolic function, and right ventricular dysfunction has also been reported.

Cardiovascular magnetic resonance imaging may help diagnose and evaluate stress cardiomyopathy, particularly when the echocardiogram is suboptimal, or there is coexisting coronary artery disease. Cardiovascular magnetic resonance may assist in the differential diagnosis, delineate the full extent of ventricular abnormalities, and identify associated complications. It may also demonstrate myocardial edema, necrosis, fibrosis, and occasionally late gadolinium enhancement.

Radionuclide myocardial perfusion imaging is not indicated in most patients presenting with takotsubo cardiomyopathy since most of the common presentation is acute coronary syndrome requiring cardiac catheterization. In low to intermediate-risk non-ST elevation acute coronary syndrome, radionuclide myocardial perfusion imaging may help.

Cardiac catheterization is an invasive procedure of choice when takotsubo cardiomyopathy presents as ST-elevation acute coronary syndrome or troponin-positive acute coronary syndrome. Coronary angiography will show normal coronary anatomy or mild to moderate coronary atherosclerosis.

Treatment / Management

Although takotsubo cardiomyopathy is thought to be a benign condition, the recent observation data suggest that cardiogenic shock and death rates are comparable to patients with acute coronary syndrome. Thus, initial management should focus on identifying and close monitoring patients at risk for serious complications. Predictors of adverse in-hospital outcomes include physical triggers, acute neurologic or psychiatric diseases, initial troponin greater than 10× upper reference limit, and admission left ventricular ejection fraction less than 45%.[12] Male patients have an up to a three-fold increased death rate and major adverse cardiac and cerebrovascular events primarily due to an increased burden of comorbidities.[36]

Guidelines on the management of Takotusbo cardiomyopathy are lacking as there are no prospective randomized data in this regard; thus, management is based on clinical experience and expert consensus (evidence level C). Since the initial presentation of takotsubo cardiomyopathy is similar to an acute coronary syndrome, the initial treatment involves aspirin, beta-blockers, ACE inhibitors, lipid-lowering agents, and coronary angiography to rule out obstructive coronary artery disease.[37] The therapy is guided by the patient's clinical presentation and hemodynamic status. In stable patients, treatment modalities include cardioselective beta-blockers and ACE inhibitors for a short period of around 3 to 6 months, with serial imaging studies to determine wall motion abnormalities and ventricular ejection fraction to determine progression or improvement. Anticoagulation is usually reserved for those with documented ventricular thrombus or evidence of embolic events; that occurs in 5% of patients with takotsubo cardiomyopathy. Patients with more unstable hemodynamics or those who present in cardiogenic shock in the absence of left ventricular outflow obstruction should be treated with inotropes. Alternatively, patients may derive further benefit from mechanical hemodynamic support with an intra-aortic balloon pump or, rarely, left ventricular assist devices. If left ventricular outflow obstruction is present with cardiogenic shock, inotropes should be avoided, and phenylephrine is the pressor agent of choice, often combined with beta-blocker agents.

Differential Diagnosis

The main differentials to consider include:

- Acute coronary syndrome
- Cocaine-related coronary syndrome
- Coronary artery spasm
- Esophageal spasm
- Myocarditis
- Pericarditis
- Pheochromocytoma

Prognosis

Although most patients with takotsubo cardiomyopathy recover, the risk of complications among hospitalized patients is similar to that of acute myocardial infarction. The reported mortality among patients with takotsubo cardiomyopathy ranges from 0 to 8%, with a mortality of 4.1% in the International Takotsubo Registry study.[34][38][39][40][12] Takotsubo cardiomyopathy prognosis depends upon its underlying trigger, and TC should be subclassified into primary and secondary forms. Primary TC occurs due to emotional/psychological stimuli, and secondary forms occur due to physical factors in a hospital setting, such as sepsis, trauma, surgery, or other critical illnesses. Secondary TC is associated with worse in-hospital and long-term outcomes.[41][42][43]

Despite the low prevalence of takotsubo cardiomyopathy in males, they often have a worse prognosis. This can be explained by the fact that males possess a higher prevalence of acute critical illnesses with elevated circulating catecholamines, potentially resulting in higher in-hospital mortality.[8]

Complications

The main complications include left ventricular outflow tract obstruction, life-threatening ventricular arrhythmias, paroxysmal or persistent atrial fibrillation, hypotension, low output syndrome, cardiogenic shock, heart failure, and thromboembolism. The incidence of the second event in patients who survive the initial event is about 5% and mostly occurs 3weeks to 3.8years after the first event.[44]

Deterrence and Patient Education

Most patients recover well from a takotsubo event, recovery time varies among patients, and clinicians are still researching the long-term effects of the condition. Some patients experience a full recovery in a matter of weeks or over a few months. However, more recent research suggests there may be ongoing effects. Each patient needs to adopt a recovery pace suitable for their particular situation.

There are also takotsubo support groups, and the cardiac nurse can direct the patient to a cardiac rehabilitation class to assist in recovery.

Enhancing Healthcare Team Outcomes

The diagnosis and management of anginal pain are with an interprofessional healthcare team that consists of the primary care provider, nurse practitioner, cardiologist, radiologist, cardiac specialty nurses, and pharmacist. When patients with chest pain are encountered, healthcare workers should consider takotsubo cardiomyopathy in the differential diagnosis. Since the initial presentation of takotsubo cardiomyopathy mimics acute coronary syndrome, initial treatment involves aspirin, beta-blockers, ACE inhibitors, lipid-lowering agents, and coronary angiography to rule out obstructive coronary artery disease. The interprofessional approach will result in improved outcomes. [Level 5]

Takotsubo cardiomyopathy is a temporary condition; hence, the treatment goals are usually conservative and supportive care. The therapy is guided by the patient's clinical presentation and hemodynamic status. In stable patients, treatment modalities include cardioselective beta-blockers and ACE inhibitors for a short period of around 3 to 6 months, with serial imaging studies to determine wall motion abnormalities and ventricular ejection fraction to determine progression or improvement. Anticoagulation is usually reserved for those with documented ventricular thrombus or evidence of embolic events; that occurs in 5% of patients with takotsubo cardiomyopathy. The outlook in most patients with treatment is good, especially with a coordinated interprofessional team managing the case, as outlined above, with the chest pain resolving in a matter of weeks.

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Disclosure: Sarah Ahmad declares no relevant financial relationships with ineligible companies.

Disclosure: Nauman Khalid declares no relevant financial relationships with ineligible companies.

Disclosure: Michael Ibrahim declares no relevant financial relationships with ineligible companies.

Bookshelf ID: NBK430798PMID: 28613549