

Takotsubo Cardiomyopathy: A Clinical Review

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ABSTRACT

Takotsubo cardiomyopathy is a reversible cardiomyopathy which has increasingly been recognized in the differential diagnosis of patients presenting with acute coronary syndrome. It is characterized by transient systolic ventricular dysfunction with regional wall motion abnormalities beyond a single vascular territory and in the absence of significant epicardial coronary artery obstruction. Often, there is an acute emotional or physical stressor immediately preceding the presentation. Classical apical ballooning is seen on ventriculography or echocardiography but variants with isolated basal or mid wall akinesis have been described. Catecholamine excess and cardiotoxicity is the most compelling putative mechanism. The long-term prognosis is excellent but serious complications including cardiogenic shock and arrhythmias may occur acutely. Supportive treatment is the mainstay of therapy.

KEYWORDS: Takotsubo cardiomyopathy (TTC), Apical ballooning syndrome (ABS), Stress Cardiomyopathy

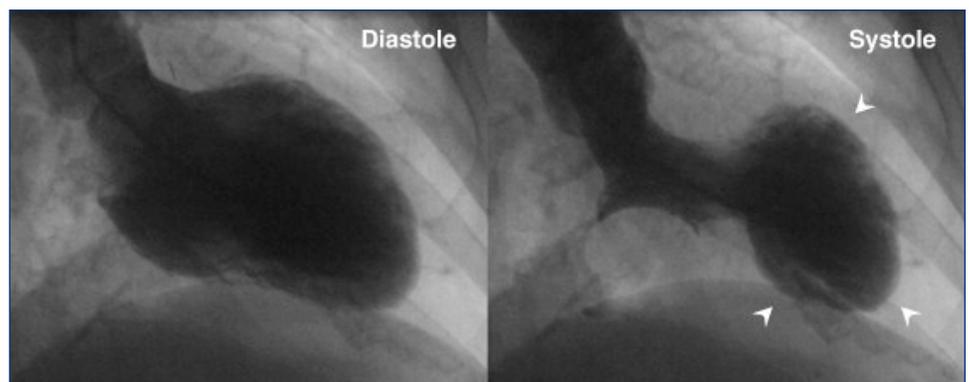
INTRODUCTION

Takotsubo cardiomyopathy (TTC) is also known as broken-heart syndrome, apical ballooning syndrome and stress-induced cardiomyopathy. It is a reversible cardiomyopathy characterized by transient systolic ventricular dysfunction with a clinical presentation indistinguishable from acute myocardial infarction but in the absence of significant coronary artery obstruction.^{1,2} It is frequently precipitated by sudden, stressful emotional events, but there are also reports of TTC following physiologic stress such as sepsis, non-cardiac surgery, and subarachnoid hemorrhage.^{2,3,4} This syndrome was reported as early as 1967 in patients under intense emotional stress such as bereavement or after homicidal assault.^{5,6} In the 1990s, Sato and colleagues coined the term

takotsubo cardiomyopathy to describe the unusual shape of the left ventricular during systole.^{7,8} Typically, the mid to apical segments of the left ventricle are akinetic and the spared, basal walls exhibit compensatory hypercontractility. Takotsubo is a pot with round base and narrow neck used in Japan for trapping octopuses and has a similar appearance to this apical ballooning. TTC occurs most commonly in post-menopausal women and has a very good prognosis. Acutely, patients are often critically ill with heart failure and secondary complications such as left ventricular outflow tract obstruction, and arrhythmias but ventricular dysfunction and symptoms resolve quickly and death is very rare. In this systemic review we will describe the clinical presentation, pathophysiology, prognosis and treatment of this syndrome.

Epidemiology and clinical presentation

Because of increasing awareness of this condition, in 2006 the American Heart Association incorporated TTC into the classification of cardiomyopathies as a primary acquired cardiomyopathy.⁹ The lack of consensus on a diagnostic criteria and the under-recognition of the disease makes it challenging to estimate the true prevalence of TTC. The best estimates come from several studies looking at consecutive patients presenting to the hospital with suspected acute coronary syndrome or myocardial infarction. Here, it has been reported to account for 1-3% of all acute coronary cases.^{10,11} Retrospective and prospective reports have noted a marked gender discrepancy in this condition.^{12,13} A recent review of published case series reveals that 90% of cases reported are in post-menopausal women



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ages 58-75 years old, with only < 3% of cases being found in those under 50 years old.^{1,14,15}

The clinical presentation of TTC is often identical to acute myocardial infarction (AMI). Most patients with takotsubo cardiomyopathy present with typical anginal chest pain, dyspnea, ischemic changes on electrocardiogram (ECG), and elevated cardiac markers, whereas syncope and out-of-hospital cardiac arrest are rare.¹⁶ Emotional stress, such as news of the death of a family member, divorce, or public speaking, is implicated as the trigger in approximately two-thirds of patients.^{3,5,6,11} However, other physical stressors such as non-cardiac surgery, sepsis, or critical illness have been reported.^{2,3,4} In one provocative prospective study, consecutive critically ill patients with no prior cardiac history who were admitted to a medical ICU underwent serial echocardiograms; 28% were noted to have transient reduced ejection fraction with imaging features consistent with takotsubo cardiomyopathy.¹⁷ Interestingly, there is a gender disparity in precipitants of TTC. In a recent TTC registry, Scheinder et al¹² observed that physical stress was a more frequent trigger in men compared to women, 57% vs 30%; these results confirm previous reports in gender difference among hospitalized patients.¹³

Electrocardiographic changes and cardiac biomarkers

The most common abnormality on the ECG is ST elevation and T-wave inversion in the precordial leads.¹⁸ However there is significant variability in the frequency of these abnormalities in the literature. Prasad et al¹ proposed two possible explanations for the variability. First, ST elevations are transient, thus the time from symptom onset to presentation might determine whether or not ST elevation is found. Secondly, there may be selection bias towards those patients with ST elevation, where early invasive coronary angiography and ventriculography are usually performed. Several investigators have proposed ECG criteria to differentiate TTC from acute myocardial infarction.¹⁸ The absence of q waves, reciprocal changes, ST segment elevation in V1 with sum of ST elevation in V4-6 greater than that in V1-V3 as well as ST depressions in aVR have been shown to discriminate between the two diseases with high sensitivity and specificity.^{18,19} Also, more extensive ST elevation in inferior leads were seen more frequently in TTC compared with anterior myocardial infarction.²⁰ However, these findings were described in an Asian population and in a subsequent, larger study in Caucasian population, the discriminatory ability of these findings could not be validated.²¹ Hence, there may be some population differences in presenting signs and specific ECG changes should be considered suggestive but not diagnostic of TTC.

Evolutionary changes on ECG often occur two to three days after initial symptoms and presentation, with resolution of ST elevation, followed by diffuse and deep T-wave inversion, prolongation of QT interval. Pathologic q waves

Table 1. Mayo clinical Criteria for Takotsubo Cardiomyopathy

(1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present
(2) absence of obstructive CAD or angiographic evidence of acute plaque rupture
(3) new electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin
(4) absence of pheochromocytoma and myocarditis

may be observed initially but rarely persist. T-wave inversion and QT-prolongation may persist for three to four months.²²

Modest elevation of cardiac biomarkers is often observed in TTC.^{3,23} In the systematic review of 14 studies which included 286 patients, 14% of patients had no measured troponin release.¹¹ Also, cardiac troponin levels in TTC are much less than that typically observed in acute ST elevation myocardial infarction and are out of proportions to the extensive wall motion abnormalities and hemodynamic compromise.²⁵ Troponin T levels are typically < 5ng/ml.⁴

Diagnosis

Due to the dramatic clinical presentation and high suspicion for acute myocardial infarction, most patients undergo emergent coronary angiography. Typical findings in TTC are normal epicardial coronaries, mild non-obstructive atherosclerosis, or rarely coexistent coronary artery disease.^{1,2} Therefore, TTC is a diagnosis of exclusion which can only be made after coronary angiography. It should be on the differential diagnosis in any post-menopausal women over 50 years old presenting with chest pain and ischemic ECG changes particularly in the setting of emotional stress. Furthermore it should also be considered in critically ill patients with sudden hemodynamic compromise and/or heart failure. Researchers at Mayo Clinic proposed diagnostic criteria in 2004 (modified in 2008) for TTC which includes four components. (See Table 1).¹

Cardiac imaging

Ventriculography reveals apical ballooning, with characteristic sparing of the basal segments and akinesis of the mid and apical left ventricle. However, variants of this pattern have been described including midventricular ballooning or basal and midventricular akinesis with apical sparing (inverted Takotsubo).²⁴ In patients with typical TTC, the wall motion abnormality usually extends beyond the distribution of a single coronary artery.

Other imaging modalities are complementary in diagnosis of the condition, eliciting potential complications and in directing management. Echocardiography can detect and measure the degree of left ventricular outflow (LVOT) obstruction and associated systolic motion of the anterior mitral valve

and significant mitral regurgitation. LVOT obstruction is reported to occur in 25% patients^{3,15} and can have a major impact on acute management. In patients with hemodynamic compromise and shock, inotropes would worsen this situation and betablockers and pure vasopressor pharmacologic or mechanical support may be needed. The typical findings on cardiac MRI include the absence of delayed gadolinium hyperenhancement. This is specific to TTC and can help differentiate it from myocarditis and acute myocardial infarction in which delayed hyperenhancement is present.²⁵

Pathophysiology

The pathophysiologic basis of TTC has not been conclusively determined but several mechanisms have been proposed. The underlying histopathological findings on myocardial biopsy include interstitial infiltrates of mononuclear lymphocytes and macrophages with fibrosis and contraction band necrosis; these findings are distinctly different than those of coagulation necrosis seen in typical atherosclerotic epicardial artery occlusion and myocardial infarction. Potential pathophysiologic mechanisms include: multivessel coronary artery spasm with resultant ischemia and stunning of the myocardium; aborted myocardial infarction of a long wrap around left anterior descending artery (LAD); microvascular dysfunction and myocarditis; and most prominently, catecholamine overload.

In the early Japanese literature, Dote et al,⁸ in the review of their 5 cases, suggested that multivessel coronary spasm was the cause of the reversible cardiomyopathy. However, the inability of intracoronary ergometrine or acetylcholine to induce vasospasm in a majority of patients with TTC (28% of patients),¹¹ and the lack of coronary spasm during cardiac catheterization in the majority of patients presenting with TTC, makes multivessel coronary spasm unlikely. A possibility of a spontaneously aborted myocardial infarction has been put forth in patients with a long wrap around left anterior descending²¹; however, later studies using intravascular ultrasound have failed to show typical plaque rupture of a culprit lesion.²⁶ Studies showing absence of delayed hyperenhancement on cardiac MRI make myocarditis extremely unlikely.²⁵ Diminished coronary flow reserve and increased TIMI frame counts, which are markers of microvascular dysfunction, have been found in some patients with TTC.^{23,27} However, in many cases of TTC, angiography failed to show slow flow.²⁸ Though impaired microcirculation may occur in the acute phase, it is not direct evidence of causation; microcirculatory impairment can be the result of primary myocardial injury and increased wall stress.²⁸

Enhanced sympathetic activity appears to play a central role in the pathophysiology of takotsubo cardiomyopathy. The last and most plausible mechanism is a catecholamine-induced stunning of the myocardium and local cardiac sympathetic disruption. Similarly, increased sympathetic activity is also observed during acute cerebrovascular accidents and during the catecholamine-induced cardiomyopathy in

patients with pheochromocytoma.²⁹ Excessive levels of catecholamines have been observed in patients with takotsubo cardiomyopathy.³⁰ Catecholamines have been shown to induce myocardial damage,³¹ and excessive stimulation of cardiac adrenergic receptors has led to transient LV dysfunction in animal models.³² Furthermore, a recent hypothesis favors local cardiac sympathetic disruption. Y-Hassan²⁸ argues that the emerging evidence in animal models, showing local cardiac sympathetic nerve endings with local norepinephrine (NE) release and spill over to the myocardium; as well as the circular ventricular wall motion abnormality that follows the nerve end distribution rather than vascular distribution support the hypothesis of local sympathetic disruption as the pathologic mechanism underlying TTC.

Prognosis and Treatment

Takotsubo cardiomyopathy has an excellent prognosis, with full and early recovery in virtually all patients. The majority of patients have normalization of LVEF within a week and all patients by 4-8 weeks. The reported in-hospital mortality is low (0-8%) with the largest case series reporting 3% mortality; it may be increased in those with underlying conditions.¹⁴⁻¹⁶ Long-term survival is similar to the general population.¹²⁻¹⁴ In published data, the reported 4-year recurrence rate is approximately 4-10%.^{13,14,33} The mechanisms underlying recurrence or risk factors predisposing an individual patient to recurrence are not understood.

Although TTC has a favorable prognosis, several acute complications have been reported and should be anticipated. Congestive heart failure is documented in 3-46% of published cases, but hypotension and shock are rare in 4%.¹⁴ Systemic thromboembolism is reported in 5%.³⁴ LVOT obstruction has been seen in 20-25% of patients³ but symptomatic obstruction is uncommon.¹ Recent data suggest the arrhythmias, including atrial fibrillation, are present in 10-26% of cases, but fatal arrhythmias such as ventricular fibrillation are rare.³⁵

Takotsubo cardiomyopathy is a temporary condition and hence the goals of treatment are usually conservative, supportive care. The therapy is guided by the patient's clinical presentation and hemodynamic status. Despite the putative causal role of catecholamines in the disorder, patients who present in cardiogenic shock, and in the absence of LVOT obstruction, may be treated with inotropes. Alternatively patients may derive further benefit from mechanical hemodynamic support with intra-aortic balloon pump or rarely, left ventricular assist devices. If LVOT obstruction is present with cardiogenic shock, inotropes should be avoided and phenylephrine is the pressor agent of choice often combined with betablockade. Most experts advocate guideline-directed medical therapy for patients with left ventricular dysfunction. This includes cardioselective beta-blockers and ACE inhibitor for a short period of time (3-6 months).¹⁰ Full anticoagulation is usually reserved for those with documented ventricular thrombus or evidence of embolic events.

CONCLUSION

Takotsubo cardiomyopathy is an acquired, transient cardiomyopathy with an excellent prognosis. Patients present after an acute emotional or physical stressor with signs and symptoms similar to acute coronary syndrome but on coronary angiography do not have obstructive coronary artery disease. Catecholamine cardiotoxicity is the most likely causative mechanism. Typically, TTC has acute left ventricular systolic dysfunction sparing only the base of the heart and may be complicated by heart failure. Supportive treatment is the mainstay of therapy.

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