

# Takotsubo cardiomyopathy: a possible metabolic disorder

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## Abstract

Takotsubo cardiomyopathy is considered a transient nonischemic cardiomyopathy of possible metabolic etiology. Based on the morphology of the left ventricle and presumed etiology, this condition has been described using several different names including transient left ventricular apical ballooning, ampulla cardiomyopathy, stress-induced cardiomyopathy, neurogenic stunned myocardium, broken heart syndrome and acute catecholamine cardiomyopathy. The term “takotsubo” means octopus trap and is derived from the Japanese to describe the characteristic appearance of the left ventricle in this condition. In the typical or classic form of takotsubo cardiomyopathy the apical and mid-segment contractile function of the left ventricle is depressed with compensatory hyperkinesis of the basal part thus acquiring an octopus trap or balloon shape during systole. However, several other forms have also been described. The left ventricular dysfunction is not confined to any single area of the coronary artery and the coronary angiogram typically shows nonobstructive coronary arteries. The exact etiology is not known; however, abnormal catecholamine metabolism and response is believed to be the most likely explanation. Preceding emotional and physical stress is recognized in at least 30% of patients. The clinical presentation is acute and mimics ST-elevation myocardial infarction due to symptoms of chest pain, electrocardiographic changes and raised troponin. The widespread availability of primary percutaneous coronary intervention and awareness of takotsubo cardiomyopathy has led to an increasing number of patients being diagnosed with this condition. The treatment is supportive, the prognosis is excellent, and the left ventricular dysfunction is transient, and most patients make a full recovery without myocardial fibrosis or any long-term sequelae. ■ Heart Metab; 2014;62:36–40

**Keywords:** Acute catecholamine cardiomyopathy; ampulla cardiomyopathy; broken heart syndrome; neurogenic stunned myocardium; stress-induced cardiomyopathy; takotsubo cardiomyopathy; transient left ventricular apical ballooning.

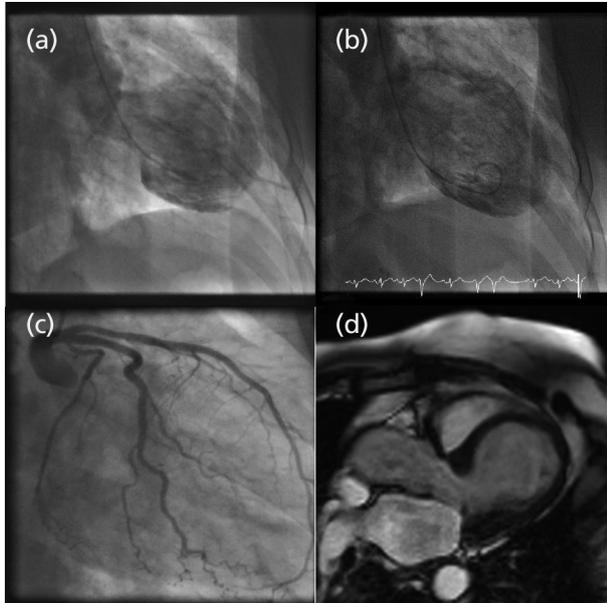
## Introduction

Takotsubo cardiomyopathy (TC) is considered a transient nonischemic cardiomyopathy of possible metabolic etiology in origin [1]. This condition was first described by a case series of five Japanese patients in 1991 [2]. Takotsubo is a Japanese term that means

octopus trap [3]. This name has been used due to the systolic appearance of the left ventricle found in the classic form of takotsubo cardiomyopathy, which is characterized by a reversible non contractile left ventricular (LV) apex with a compensatory hyperdynamic basal part in the presence of nonobstructive coronary

### Abbreviations

**ACS:** acute coronary syndrome; **LV:** left ventricular; **TC:** takotsubo cardiomyopathy



**Fig. 1** (a) Left ventriculogram in systole showing no contraction in the apical region and apical ballooning. (b) Left ventriculogram in diastole demonstrating no difference in apical shape in comparison to systole. (c) Cardiac catheterization revealing unobstructed left coronary system. (d) Cardiac magnetic resonance showing left ventricle in systole, clearly demonstrating lack of contraction at apex and ballooning of left ventricle (typical octopus pot-like appearance). Reproduced from Zeb et al. [1] with permission from BMJ Publishing Group Ltd.

arteries (Figure 1) [3]. As a result of the appearance of the left ventricle this condition is also known as transient apical ballooning syndrome, or apical cardiomyopathy [1]. Clinically, TC is indistinguishable from acute coronary syndrome (ACS) due to acute cardiac sounding chest pain, ST segment changes on a 12-lead ECG and elevated cardiac enzymes [1]. However, the main distinguishing characteristic in the acute setting is the absence of epicardial coronary occlusion and the transient nature of LV dysfunction in the long term. Therefore TC is a diagnosis of exclusion, and in most cases it is mandatory to exclude obstructive coronary artery disease [4, 5].

The concept that LV dysfunction might result from physical or emotional stress, in the absence of overt myocardial ischemia, has started to gain more widespread acceptance [5]. Following its initial description, TC was increasingly recognized and given a multitude of names that reflected both the presumed etiologies and pathological findings. These included transient

LV apical ballooning [4], neurogenic stunned myocardium [6], ampulla cardiomyopathy [7], stress-induced cardiomyopathy [8], broken heart syndrome [9] and acute catecholamine cardiomyopathy [10].

Since its first description the presentation of TC has gradually increased; MEDLINE searches for the terms apical ballooning, ampulla cardiomyopathy, takotsubo cardiomyopathy and takotsubo cardiomyopathy between 1989 and 2013 demonstrated a significantly increased frequency of publications in the past 5 to 10 years.

### Types of takotsubo cardiomyopathy

In classic TC the LV apex is non contractile, with a hyperdynamic basal part; however, several other forms have also been described including “mid ventricle takotsubo cardiomyopathy” found in 17% of cases [11, 12], in which mid ventricular contractile function is impaired, but the apex and base remain hyperdynamic. However, in the third type “basal or reverse takotsubo cardiomyopathy” the basal ventricle is non contractile with a hyperdynamic apex. In about 30% of cases both the left and right ventricle is affected, giving the appearance of dilated cardiomyopathy [12].

### Prevalence

The diagnosis of TC is made in approximately 1–2% of all cases of suspected acute myocardial infarction [13], although this estimate may be low because of under-recognition. In our experience 5.7% of patients presenting with features of ACS are diagnosed with TC [1]. Park et al demonstrated echocardiographic evidence of TC in 28% of intensive care patients, although that study was limited by the absence of coronary angiography [14].

TC has a higher prevalence among post-menopausal women and women with anorexia nervosa [15, 16]. The diagnosis of TC has become more frequent most probably due to increasing awareness and access to cardiac catheterization [1].

### Pathophysiology

The exact cause of TC is unknown. However, several hypotheses exist to explain the mechanism and pathophysiology of this disease.

### Physical or emotional stress and catecholamine excess

The onset of TC is often preceded by emotional, physical stress, or critical illness; for example, an increased

incidence of the syndrome was noticed after earthquakes in Japan [17]; a clearly recognized stressor is found in at least 30% of patients [18]. Therefore, it is speculated that abnormal catecholamine dynamics related to emotional stress may be playing a role in the pathogenesis of TC. This hypothesis has been extensively studied [1]. In a recent retrospective study, Giavarini et al reported that pheochromocytomas and paragangliomas may present as acute takotsubo-like cardiomyopathy in 11% of cases [10]. Wittstein et al demonstrated significantly elevated catecholamine levels in the plasma of patients with TC in comparison to normal individuals and patients with acute myocardial infarction with heart failure [19]. The authors also demonstrated persistently elevated level of catecholamines for more than a week while the plasma half-life is only few minutes. Kume et al demonstrated excessive catecholamine release from the hearts of patients with TC [20]. Abraham et al demonstrated the development of all variants of TC in nine patients following intravenous epinephrine and dobutamine infusion, supporting the concept that catecholamines play a role in the genesis of TC [21]. In addition, drugs with sympathetic effects have also been associated with TC [21]. Several mechanisms have been proposed to explain the catecholamine-mediated cardiotoxicity, eg, multiple coronary arteries spasm or microvascular dysfunction, direct catecholamine-mediated myocyte injury, endothelial dysfunction and intracellular calcium overload, resulting in damage to myocytes [1]. A catecholamine-induced disorder in glucose metabolism has been suggested on the basis of decreased LV apical  $^{18}\text{F}$ -fluorodeoxyglucose uptake on positron emission tomography of 15 patients with the apical variant of TC [22]. Increased LV apex endocardial surface area due to trabeculations and the presence of higher concentrations of  $\beta$ -adrenoreceptors in the apical versus basal myocardium have been proposed to be responsible for abnormal response and akinesis of the apex. However, this hypothesis fails to explain mid cavity and basal TC, unless in the future an abnormal distribution of these receptors is demonstrated in other forms of TC [1]. These observations support the hypothesis that, during times of stress when epinephrine is the main circulating catecholamine, regional differences in epinephrine-sensitive  $\beta_2$ -receptors could explain the myocardial response to the catecholamine surge seen in TC.

Lyon et al demonstrated overexpression of  $\beta_2$ -adrenergic receptors in LV myocardium of mice subjected to supraphysiological epinephrine

concentrations [23], which has been shown to have a negative inotropic effect on cardiomyocytes, possibly due to intracellular signal trafficking switch from Gs protein to Gi protein. This signal switching is also known to have a protective effect against apoptosis [24]. Ellison et al also demonstrated myocyte damage and sparing of cardiac stem cells by acute  $\beta$ -adrenergic overload, which could provide an insight into a potential mechanism for the rapid recovery of myocardial function [25].

### **Other hypotheses**

Myocarditis as a cause of TC is not well supported by the data. Viral titers do not rise after the initial event, and biopsy findings are not suggestive of myocarditis. Cardiac magnetic resonance imaging of a limited number of patients has shown no evidence of myocarditis or infarction [1].

Multiple epicardial coronary artery spasm as a cause of TC is not strongly supported by the literature, despite isolated reports. The presence of persistent ST segment changes in patients with TC, even when coronary angiography shows no spasm, also goes against this hypothesis.

The reason why cardiomyopathy occurs predominantly in postmenopausal women is also unexplained. However, the deficiency in estrogen activity may play a role, supported by the evidence of estrogen supplementation attenuating TC in an animal model, and the influence of sex hormones on endothelial function [26]. Interestingly, a study of 72 individuals (47% women) with subarachnoid hemorrhage reported that LV wall motion abnormality occurred only in women [27].

Cardiac syndrome X is also common in postmenopausal women, and endothelial dysfunction is thought to affect the underlying pathophysiology [28, 29]. A genetic component is suggested by the observation of the occurrence of TC in two sisters and in a mother–daughter pair [1, 30]. However, comprehensive DNA sequence analysis failed to show any association between functional variants of the genes encoding various types of adrenoreceptors and TC [30].

At present there is no evidence to suggest a difference in the pathophysiology of various morphological forms of TC; however, a common mechanism is suggested by the finding of two morphological variants in the same individual [31] and the finding of multiple morphological variants with epinephrine or dobutamine infusion [21].

### Histology

In one study the biopsy findings of myocardium consisted of mononuclear cell infiltrate and contraction band necrosis [19]. However, in another study histological analysis of myocardium of patients with TC demonstrated disorganization of contractile and cytoskeletal proteins, infiltration by mononuclear lymphocytes and macrophages in most cases, with increased extracellular matrix proteins, glycogen accumulation in the absence of apoptosis and autophagy. After functional recovery, most of these changes showed nearly complete reversibility [32]. These findings are not similar to the pathological changes observed in the stunned myocardium, which suggests that TC is a separate entity [33].

### Clinical features and diagnosis

The presentation of TC is indistinguishable from ACS, most patients present with chest pain (68%) and breathlessness (17%), but approximately 4% of patients present with cardiogenic shock and 1.5% present with ventricular fibrillation. Physical examination may be normal or show signs of heart failure [1, 18].

The classic ECG appearance consists of ST-segment elevation mimicking acute anterior ST-segment elevation myocardial infarction in about 70–80% of cases. T-wave abnormalities are present in 64%, pathological Q-waves in about 32% of cases; however, loss of R-wave amplitude has also been reported [1, 18]. To date no specific ECG markers have been identified to differentiate between TC and ACS. A small rise in troponin is present in most patients [1, 18].

Coronary angiogram is the most discriminating test showing normal or near normal coronary arteries; however, left ventriculography shows the pathognomonic appearance of LV dysfunction, which should be considered in all patients who presents with troponin-positive chest pain and unobstructed coronary arteries [1]. Echocardiogram is helpful for the visualization of acute LV dysfunction and future recovery. Cardiac magnetic resonance imaging shows the typical LV dysfunction and excludes myocarditis [34].

Recent studies have also proposed investigations to exclude pheochromocytoma and paragangliomas.

### Complications

The reported complication rate is about 19%. Cardiogenic shock is the most common severe

complication, occurring in 6.5% of patients. Other complications include LV-thrombus formation (4%), cerebrovascular accident (1.6%), ventricular tachycardia (1.6%), atrial fibrillation (1%), ventricular fibrillation (0.5%) and ventricular septal defects (0.5%). Recurrence of the syndrome is infrequent, experienced only by 3.5–10% of patients [1, 18, 35].

### Treatment

The treatment of TC is supportive. Initial treatment is based on an assumed clinical diagnosis of ACS. The combination of aspirin, cardioselective  $\beta$ -blockers and angiotensin-converting enzyme inhibitors is advocated during the period of LV dysfunction [36]. However, there are no randomized trials to guide the optimum treatment. Due to the possible abnormal response to excessive catecholamines the use of  $\beta$ -blockers is considered beneficial [34]. This is also supported by evidence from animal model studies of TC that have demonstrated resolution of ST-segment elevation by combined  $\alpha$  and  $\beta$ -adrenoceptor blockade [37]. Furthermore, Uchida et al demonstrated that  $\alpha$  and  $\beta$ -adrenoceptor blockers might play a role in the prevention of stress-induced cardiac dysfunction [38]. It has also been suggested that the use of  $\beta$ -blockers might reduce the LV outflow tract obstruction associated with hyperdynamic basal contraction [36].

### Prognosis

Although in most cases TC has a benign natural history, with an overall in-hospital mortality rate of 1.1–3.2%, individuals presenting with severe heart failure, pulmonary edema and cardiogenic shock are at high risk [35].

### Conclusion

The incidence of TC is increasing most probably due to increasing awareness and increasing access to emergency coronary angiograms designed for primary percutaneous intervention. The exact pathophysiology is less well understood; however, the available evidence suggests a cardiotoxic effect of excess catecholamines. Physical and emotional stress has been widely blamed for the excessive catecholamine surge in many cases, even though a clearly recognized stressor is found in less than 30% of patients [18]. Treatment is supportive. Fortunately, in the majority of cases, the outlook is benign and the LV dysfunction is self-limiting. ■

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