REVIEW

TAKOTSUBO SYNDROME

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Abstract: *Takotsubo syndrome, also known as Takotsubo cardiomyopathy, stress-induced cardiomyopathy, transient apical ballooning and broken heart syndrome, is a disease characterized by transient regional left ventricular systolic dysfunction. It is usually determined by emotional or physical stress. Even though it was thought to be a self-limiting condition, Takotsubo syndrome is now known to be associated with important short and long-term morbidity and mortality. Takotsubo syndrome affects 2-3% of all patients and 5-6% of female patients presenting with acute coronary syndrome (frequently women in the sixth decade). The Takotsubo syndrome cases are mostly preceded by acute emotional or physical triggers such as: family death, financial loss, anxiety, excessive work, domestic abuse, anxiety, fear for medical procedures, severe pain, sepsis, post-surgeries, and cancer. Diagnosis of Takotsubo syndrome can sometimes be difficult due to clinical manifestations similar to acute myocardial infarction. Myocardial necrosis biomarkers (Troponin I, Troponin T and Creatinin kinase) are elevated, with values comparable to those in patients with acute myocardial infarction. Transthoracic echocardiography usually shows akinetic or dyskinetic apical and mid-ventricular segments of the left ventricle compared to the hyperkinetic basal segments ("apical ballooning" aspect) and left ventricle systolic dysfunction. The positive diagnosis of Takotsubo syndrome is made on coronary angiography, normal or non-obstructive coronary artery disease.*

Keywords: *emotional stress, ballooning aspect, excessive cathecolamines*

DOI https://doi.org/10.56082/annalsarscimed.2023.2.21

INTRODUCTION

Takotsubo syndrome, also known as Takotsubo cardiomyopathy, stress-induced cardiomyopathy, transient apical ballooning, and broken heart syndrome, is a disease characterized by transient regional left ventricular systolic dysfunction. Stress—either emotional or physical—usually determines it [1].

The term Takotsubo was described from a Japanese word meaning "octopus" according to the apical ballooning aspect of the left ventricle [2]. Patients present with chest pain, electrocardiographic changes, troponin elevation, anteroseptal-apical ballooning of the left ventricle with hyperkinetic basal segments and left ventricular dysfunction in the absence of obstructive coronary artery disease [1].

Even though it was thought to be a self-limiting condition, Takotsubo syndrome is now known to be associated with important short and long-term morbidity and mortality.

EPIDEMIOLOGY

Takotsubo syndrome affects 2-3% of all patients and 5-6% of female patients presenting with acute coronary syndrome (frequently women in the sixth decade) [3]. It is thought that there are more cases of Takotsubo syndrome than reported due to increasing rates of stress and anxiety. Interestingly, Takotsubo syndrome is more frequent in women from western countries compared to Japan, where Takotsubo syndrome is more common in male patients [4,5].

ETIOLOGY-RISK FACTORS

1. Emotional or physical stress

The Takotsubo syndrome cases are mostly preceded by acute emotional or physical triggers such as family death, financial loss, anxiety, excessive work, domestic abuse, anxiety, fear for medical procedures, severe pain, sepsis, post-surgeries and cancer. Patients with physical triggers have a higher prevalence of cardiovascular risk factors and other underlying comorbidities [6,7].

2. Hormonal factors-lack of estrogen

90% of patients with Takotsubo syndrome are postmenopausal women. Lack of estrogen leads to endothelial dysfunction, which is considered to be involved in the higher incidence of Takotsubo syndrome in postmenopausal women (normally, estrogen improves coronary blood flow, having a protective role against the excessive effects of catecholamines, calcium overload, and oxidative stress) [8].

3. Genetic factors

Some reports described familial cases of Takotsubo syndrome, suggesting the possibility of a genetic disorder while others described a possible polygenic basis. Patients with Takotsubo syndrome associate L41Q polymorphism with G protein-couped receptor kinase (GRK5). The L41Q polymorphism of GRK5 responds to catecholamine stimulation and improves the response of β-adrenergic receptors. Catecholamine excess determines the balloon aspect of the left ventricle by the negative inotropic effect of β-receptor decoupling or ischemia caused by an imbalance of α1-adrenergic coronary artery vasoconstriction and β-adrenergic vasodilatation [9].

4. Psychogenic factors/ psychiatric factors

Several reports indicate a significant correlation between Takotsubo syndrome and neurologic or psychiatric disorders, when age and gender are considered. Depression, anxiety, excessive alcohol intake, suicidal behavior, and severe mental problems are among the most common psychiatric disorders [10].

5. Comorbidities

Other diseases, such as diabetes mellitus, atrial fibrillation, or underlying critical illnesses in patients with Takotsubo syndrome, are associated with a higher risk for severe evolution and an increased mortality rate.

6. Drugs as risk factors

- Antidepressants:the risk for Takotsubo syndrome is highest in serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs) and selective norepinepinephrine reuptake inhibitors (SNRIs). Tricyclic antidepressants, SSRIs and SNRIs are not recommended in patients with cardiovascular disease because of the important risk of drug-drug

interaction generating high sensitivity to catecholamines in cardiomyocytes [11].

- Chemotherapy: the mechanism of chemotherapy-induced cardiotoxicity is not completely known, but the consequences are thought to be coronary spasm, thromboxane A2 activation, and electrolyte imbalances. Examples of treatments: 5-fluorouracil, capecitabine, bevacizumab and trastuzumab [12].
- Antiarrhythmic medications, including xylocaine, flecainide, sotalol, amiodarone, and lidocaine, are risk factors for Takotsubo syndrome due to their ability to prolong the QTc interval and interfere with β-adrenergic receptors, calcium, and sodium channels [13].

CLASSIFICATION

Table 1. Classification of Takotsubo syndrome based on etiology [2].

Primary	Secondary
Idiopathic	Physical stress: severe physical trauma, surgery, asthma
Psychic stress	Drug-induced: antidepressants, catecholamine, chemotherapy

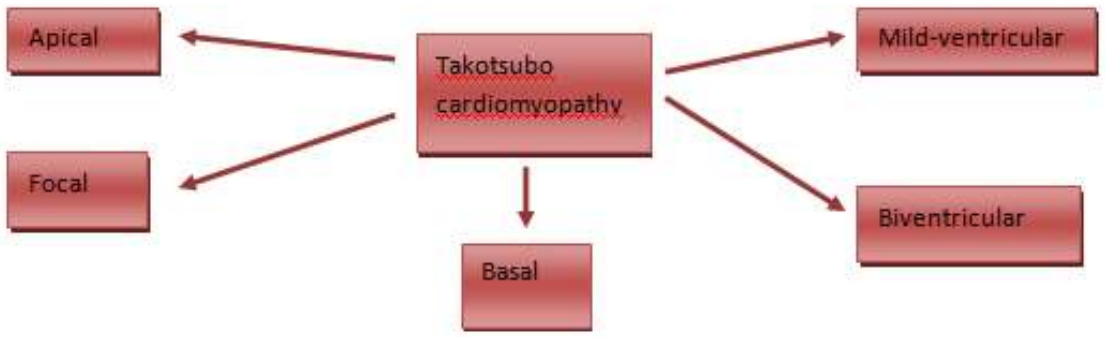

Figure 1. Classification of Takotsubo based on wall motion abnormalities [2].

CLINICAL MANIFESTATIONS

The most frequent symptom in patients with Takotsubo syndrome is chest pain similar to the one from myocardial infarction. Other symptoms are dyspnea, orthopnea and syncope. A small number of patients are asymptomatic. The physical examination is nonspecific; patients may be diaphoretic, hypotensive or show clinical signs of acute heart failure [14,15].

POSITIVE DIAGNOSIS

Takotsubo syndrome diagnosis can sometimes be difficult due to clinical manifestations similar to acute myocardial infarction. It is imperative to consider Takotsubo syndrome as a potential differential diagnosis in all patients who present with chest pain and exhibit symptoms suggestive of acute coronary syndrome in conjunction with severe physical or emotional stress.

1. Electrocardiogram

The reported changes on electrocardiogram includes ST-segment elevation (present in 80% of Takotsubo cases), transient Q waves, flattening T waves and left bundle-branch block. There were described three electrocardiographic stages of Takotsubo syndrome: stage 1- ST-segment elevation; stage 2- progressive T-wave inversion and QTc prolongation (higher risk of torsade de pointes and other ventricular tachycardias); and stage 3- gradual resolution of T-wave and QTc changes over weeks or months. The ST-segment elevation in Takotsubo syndrome is lower compared with the ST-segment elevation from acute myocardial infarction [16,17].

2. Laboratory tests

Myocardial necrosis biomarkers (Troponin I, Troponin T, Creatinin kinase) are elevated, with values comparable to those in patients with acute myocardial infarction but with peak values lower than those in patients with myocardial infarction. Plasma BNP and NT-proBNP concentrations are higher than in patients with ST-segment elevation myocardial infarction [18]. Furthermore, NT-proBNP levels are higher in Takotsubo syndrome apical subtype patients [19].

3. Echocardiography

Transthoracic echocardiography usually shows akinetic or dyskinetic apical and mid-ventricular segments of the left ventricle compared to the hyperkinetic basal segments ("apical ballooning" aspect) and left ventricle systolic dysfunction. The wall motion abnormality is not limited to one coronary artery territory, as in the acute myocardial infarction [19,20]. The left

ventricular dysfunction progressively improves over the course of weeks and months (on average, by day 18). However, in certain cases, persistent heart failure with preserved ejection fraction may be diagnosed. Other complications of Takotsubo syndrome observed when using transthoracic echocardiography are left ventricle thrombus, mitral regurgitation, dynamic left ventricular outflow tract obstruction and ventricular rupture [21].

4. Cardiac computed tomography angiography

Cardiac computed tomography angiography is indicated in cases of cerebral hemorrhage, terminal malignancy and septic shock when coronary angiography is contraindicated [16].

5. Coronary angiography and left ventriculography

The positive diagnosis of Takotsubo syndrome is established through coronary angiography, which reveals normal or non-obstructive coronary artery disease. Sometimes, advanced intravascular imaging techniques such as optical coherence tomography and intravascular imaging techniques can be used for better differential diagnosis [22,23]. Left ventriculography confirms the diagnosis by demonstrating apical left ventricle ballooning. The most common subtype is apical and midventricular akinesia, dyskinesia, or hipokinesia with basal hyperkinesias [24]. Sometimes the patients may present with reverse Takotsubo – basal akinesia, dyskinesia, or hipokinesia with hyperkinetic apical segments. In cases of right ventricle dysfunction, the evolution of Takotsubo syndrome is more severe and associated with complications [25].

6. Cardiac magnetic resonance imaging

Cardiac magnetic resonance has a fundamental role in the diagnosis of Takotsubo syndrome and in differential diagnosis with other causes of chest pain, elevated troponin levels and non-obstructive coronary arteries [26]. CMR characterizes myocardial edema, necrosis and fibrosis, which is important in differentiating between Takotsubo syndrome, myocardial infarction and miocarditis.

The key features of Takotsubo syndrome in its acute stage are reversible edema of the heart muscle, which may be detected using T2-weighted sequences. Myocardial edema is often present over the whole thickness of the muscle and normally resolves within about six months [27].

Fibrosis is typically undetectable during late gadolinium enhancement. Conversely, a transmural distribution of LGE was recently identified in the acute state of Takotsubo syndrome, specifically at the interfaces where the hyperkinetic and dyskinetic ballooning segments converge [28]. In myocardial infarction, the LGE distribution is focal-endocardial or transmural, while in myocarditis, the LGE distribution is mid-wall. CMR is probably the most useful tool in diagnosing Takotsubo syndrome, excluding other etiologies such as myocarditis, myocardial infarction, and myocardial infarction with nonobstructive coronary arteries (MINOCA) [16,29].

In the chronic state, CMR follow-up appreciates normal ventricular function, normal regional wall motion, no edema, no necrosis and no fibrosis [30].

Even though echocardiography is an extremely valuable tool in the diagnosis and management of Takotsubo, only CMR and endomyocardial biopsy can truly distinguish between myocarditis and Takotsubo syndrome.

CONCLUSIONS

In the last few years, many more cases of Takotsubo syndrome have been described. Clinical manifestations can mimic acute coronary syndrome, associated with electrocardiographic changes and raised cardiac necrosis biomarkers. Echocardiography is the most useful in diagnosing and monitoring the syndrome. CMR has an important role not only in positive diagnosis but also in evaluating the risk of immediate complications.

Author Contributions:

L.B.G. conceived the original draft preparation. L.B.G. and C.C.D. were responsible for conception and design of the review. L.B.G. and C.C.D. were responsible for the data acquisition. L.B.G. was responsible for the collection and assembly of the article/published data, and their inclusion and interpretation in this review. L.B.G. and C.C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article".

Acknowledgemets:

None

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