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Takotsubo Syndrome: Still Graveyard of Case Reports?

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<http://dx.doi.org/10.5772/intechopen.76525>

Abstract

Takotsubo syndrome, or previously named as Takotsubo cardiomyopathy, is an increasingly recognized acute reversible form of heart failure, which is typically seen in postmenopausal women following emotional or physical stress. Although several mechanisms regarding pathophysiology had been proposed, the most common ones include catecholamine toxicity, diffuse epicardial coronary artery spasm and microvascular dysfunction. A vast majority of patients with TTS (>90%) have good prognosis as they regain normal left ventricular systolic function in 3–6 months after the acute phase. Increased awareness among physicians led to the recognition of a great number and variety of conditions associated with TTS and played a key role for the development of new diagnostic criteria. However, there are still big gaps in the management and treatment of this syndrome to be supported with further well-designed randomized controlled trials.

Keywords: Takotsubo syndrome, Takotsubo cardiomyopathy, apical ballooning syndrome, brokenheart syndrome, stress cardiomyopathy

1. Introduction

When Sato et al. [1] first described Takotsubo Cardiomyopathy (TTC) 28 years ago, they were probably unaware of carrying out a new area of debates in daily cardiology practice. The name “Takotsubo” was inspired from a Japanese octopus trap used by Japanese fisherman.

To date, more than 75 names were used for description of TTC in the literature with the most commonly used three names include *Takotsubo cardiomyopathy*, *Takotsubo syndrome* and *apical ballooning syndrome* [2]. ‘Broken heart syndrome’ definition was used in sarcasm to emphasize the close relationship between disease and stressful triggers; however, joyful incidents have also been shown to be associated with TTC thus called ‘happy heart syndrome’ [3].

Although diagnostic criteria of TTC were described long ago, recent debates focus on definition (rather than treatment) whether this form of heart failure is a cardiomyopathy or a syndrome [4]. Growing body of evidence including diseases, conditions, toxins or drugs associated with Takotsubo Syndrome (TTS) has provided a wide insight into disease pathophysiology. The authors favoring the use of TTS save the idea that patients with TTS suffer severe myocardial ischemia and show most of the indirect signs of ischemia (ECG changes, troponin rise, chest pain and wall motion abnormalities). The mechanism underlying TTS can not be solely explained with ischemia and vascular impairment via contemporary data. Nonetheless, Redfors et al. [5] demonstrated that myocardial perfusion at TTS onset is normal despite increased catecholamine levels. The definition of cardiomyopathy defined as '*myocardial disorder in which the heart muscle is structurally or functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality*' qualifies and covers TTS as a cardiomyopathy but several controversial subjects need to be addressed such as (1) transient nature of the disease, (2) lack of genetic origin, (3) presence of certain trigger factors, (4) close relationship with catecholamine excess, (5) lack of macroscopic fibrosis or significant necrosis in histopathological examination, (6) presence of intense myocardial edema in the acute phase of TTS. On the other hand, current evidence is not consistent with the authors suggesting classification of TTS in the context of acute coronary syndromes [4].

The most recent comprehensive assessment of TTS was performed in a position statement by European Society of Cardiology (ESC) which suggested the use of TTS definition instead of TTC. Therefore, it makes more sense to use TTS instead of cardiomyopathy in consistence with current data and ESC recommendations. Moreover, they subdivided TTS into primary and secondary forms [6].

The main characteristics of TTC include chest pain associated with ECG changes, which mimic ACS, transient left ventricular systolic dysfunction, modest elevated levels of cardiac troponin and the absence of obstructive coronary artery disease documented by coronary angiography [7].

It is hard to say that increased number and variety of case reports have contributed to a completely clear understanding of this disease. Just think of a disease that can be associated with coronary ischemia, heart failure, arrhythmia, sudden death and also usually transient and in benign nature. When all components of this syndrome are taken into account, a multidisciplinary approach and additional research in the context of etiology, pathophysiology, triggering factors and optimal treatment seem essential for better understanding.

2. Epidemiology

Although the exact incidence of TTs is not known, increasing number of case reports and associated conditions are added into the literature. In an European cohort, TTs were reported to be responsible for 1.7% of admissions for acute coronary syndrome and to have an incidence of

0.3% for all coronary angiographies [8]. Another study investigating the prevalence of TTS in the United States examined more than 33 million hospitalizations and found an incidence of 6837 (0.02%) patients with a diagnosis of TTs [9]. The majority of the patients were aged from 65 to 79 (43.2%) and women (90.4%). Women older than 55 years of age were at nearly fivefold increased risk of developing TTS than women <55 years old [10]. The real prevalence of TTs is assumed to be underestimated owing to lack of widespread access to coronary angiography and detailed postmortem examination of patients with fatal arrhythmias and sudden cardiac death. The International Takotsubo Registry (InterTAK Registry) has been the largest study cohort of patients with TTS which included 1750 cases from 26 centers in Europe and United States [11]. Although full results have not been published yet and contemporary information about the prevalence of TTS was not available, it was interesting to find that 15.3% of patients with TTS had evidence of concomitant coronary artery disease (CAD) in contrast with the common belief that exclusion of CAD is necessary to establish TTS diagnosis.

3. Triggering factors

In contrast with the common belief of close relationship with emotional triggers (broken-heart syndrome), InterTAK registry demonstrated that physical triggers were more common than emotional triggers (36 vs. 27.7%) while the remainder had no obvious triggering factor. Furthermore, physical triggers were found to be an independent predictor for in-hospital complications [3].

The most common emotional triggers include death of a first-degree relative, severe fear or anger episodes, anxiety disorders, financial or legal matters and less frequently (less than 10%) joyful events such as birthday parties or weddings. Physical triggers are events mostly associated with catecholamine surge including cases of stroke, subarachnoid hemorrhage, surgery, malignancy, drug abuse, psychiatric illness, and so on.

History of a neurologic or psychiatric disorder was detected in more than half of the patients with TTS in the InterTAK registry [3]. The same registry also revealed age and the presence of emotional triggers as protective from in-hospital complications. One-third of patients with sub-arachnoid hemorrhage has TTS [12].

4. Pathophysiology

The relationship between triggering factors and TTS naturally caused accusation of catecholamine excess in the pathogenesis of TTS [13]. Although catecholamine excess hypothesis in TTS was supported by several times higher concentrations of plasma catecholamines including epinephrine, norepinephrine and dopamin in the acute phase of TTS when compared with levels in STEMI and also increased local myocardial release of catecholamine, benefit of b-blockers were derived from trials including patients with heart failure rather than patients with TTS [14].

Another evidence favoring the authors suggesting use of 'Takotsubo syndrome' instead of cardiomyopathy definition is the common existence of endothelial dysfunction in patients with TTS. Myocardial ischemia caused by vasospasm which is triggered by stress and increased catecholamines in coronary vasculature with endothelial dysfunction represents a reasonable cascade of pathophysiology underlying TTS. However, further studies are needed to elicit the role of endothelial dysfunction in TTS as just one of the contributing factors or an essential component. Epicardial coronary spasm was demonstrated in only 20% of patients with TTS in two different studies and confirmed by acetylcholine testing in another study [7, 15]. Spontaneous coronary artery dissection and coronary microvascular dysfunction were the other postulated mechanisms responsible for TTS. Reversible coronary microvascular dysfunction was demonstrated by transient improvement in perfusion defects after infusion of intracoronary adenosine and complete recovery 1 month later [15]. In the postmenopausal period, reduced levels of estrogen end up with increased sympathetic tonus and endothelial dysfunction. When combined with age and the common prevalence of classical risk factors for cardiovascular disease in the typical postmenopausal woman patient profile of TTS, additive effect of increased catecholamines (direct toxicity via circulation or nerve terminals), reduced estrogen levels and endothelial dysfunctions should be considered.

The pattern of LV dysfunction in TTS (apical ballooning) was subject to a great number of studies. Increased expression of β_2 -adrenoreceptors in apical segments than basal segments of left ventricle was shown in animal studies whereas norepinephrine β_1 -adrenoreceptors had reverse distribution. This finding was supported by a rat model treated with high-dose epinephrine bolus (to mimic catecholamine storm) culminating in apical myocardial depression and basal hypercontractile response. Lack of the same response with equivalent bolus of norepinephrine suggested an epinephrine-specific response [5]. Another hypothesis proposes similarities between preconditioning/ischemic stunning and TTS pathogenesis through

Catecholamine excess (toxicity)
Epicardial coronary spasm
Myocardial ischemia
Endothelial dysfunction (\pm reduced estrogen levels)
Coronary microvascular dysfunction
Obstruction of left ventricular outflow tract
Spontaneous coronary artery dissection
Transient metabolic disorder on the cellular level
Sudden increase in ventricular afterload
Aborted myocardial infarction with spontaneous recanalization
Myocardial bridging and myocardial edema

Table 1. Mechanisms proposed for the pathophysiology of Takotsubo syndrome.

shutting down contractile apparatus in certain segments of LV and maintenance of vital functions [5]. Actually, this mechanism might be favored for mechanisms responsible for recovery process and was supported by a study demonstrating same cell survival signaling pathways of ischemic preconditioned tissue in biopsies obtained from patients with TTS [16]. The authors from the same study also suggested that transient LV outflow tract obstruction (stimulated by isoprenaline—strong adrenergic stimulus) occurs when LV contracts too forcefully and leads to a pressure gradient between the apex and the aorta thus raising wall tension in regions located more apical than the obstruction [5]. Recent studies employed with nuclear medicine techniques suggested that a transient metabolic disorder on the cellular level is responsible for apical ballooning rather than an impairment in myocardial contractile structure which may be associated with interruption of glucose metabolism via coronary microcirculation. A list of proposed mechanisms involved in the pathophysiology of TTS is shown in **Table 1**.

5. Patient evaluation

5.1. History

The most common symptom in patients presenting with TTS is chest pain (75%) as seen in acute coronary syndromes. The nature of the pain is not specific, thus not helpful in differential diagnosis. The following chief symptom is dyspnea (47%). When the high rate (87%) of patients having reduced LV ejection fraction (EF) in the setting of TTS is taken into account, less than half of the patients (47%) presenting with dyspnea may seem relatively low. Nevertheless, this discrepancy is supported by the fact that patients with TTS frequently have a benign course despite losing >50% functional left ventricular myocardium while a patient with ACS faces death in loss of a similar sized portion of LV myocardium [5, 17]. Nonetheless, it should be noted that in-hospital death rates are similar between patients with TTS and ACS. Syncope, cardiac arrest, cardiogenic shock and ventricular arrhythmias are much less common symptoms but should be kept in mind. These symptoms are more likely to occur with less common clinical subtypes other than apical ballooning. Reverse (inverted) TTS was shown to present at a younger age and with fatal ventricular arrhythmias [18].

5.2. Laboratory

Troponin levels are elevated in the vast majority of patients with TTS; however, the severity of elevation is not helpful for discriminating between acute coronary syndromes. Nonetheless, InterTAK registry significant differences in increased troponin levels between patients with TTS and ACS (1.8 vs. 6, $p < 0.001$). A first troponin measurement of more than 10 times of the upper limit of normal level was deemed as a poor prognostic factor. On the other hand, brain natriuretic levels were almost six times higher in patients with TTS than patients with ACS. When compared with ACS, troponin levels in TTS are lower. Acute ventricular insult in left ventricle triggers stretching and release of neuroendocrine peptides such as

brain-natriuretic peptide (BNP). Levels of NT-proBNP were more than twofold higher in patients with TTS than patients with STEMI (4702 vs. 2138 pg/ml, respectively) in a recent study [19].

Several reports investigating the use of other biomarkers in TTS detected elevations in serum catecholamine, neuropeptide, serotonin, carbohydrate-antigen 125 levels but none of them is preferred in daily practice. Further research is required for established utilization of those biomarkers.

5.3. Electrocardiography

TTS can present with various changes on electrocardiography. Although the most common presentation includes ST-segment elevation and/or T-wave inversion, several new electrocardiographic alterations including QT-prolongation, attenuation of QRS complexes, new bundle-branch blocks or ventricular arrhythmias have been defined [20]. It should be noted that the timing of medical contact is important for detection of ECG changes since it is a pathological process. QT prolongation is one of the distinct features from STEMI; however, differential diagnosis should not be based on ECG basis in particular ST-elevation in TTS. Typical extension of left ventricle dysfunction beyond the vascular territory of a single epicardial coronary artery is one of the key features of TTS.

5.4. Echocardiography

Transthoracic echocardiography is the primary choice of noninvasive imaging method due to its widespread and practical utility for patients with suspected TTS.

TTS with apical involvement is the most common type (82%) followed with mid-ventricular, basal and focal type in decreasing frequency. Typical findings suggesting TTS include regional wall motion abnormality (mostly apical akinesia and basal hyperkinesia) extending beyond the territory of a certain epicardial coronary artery. End-diastolic diameter measured from the mid-ventricular plane is increased and measurement of EF is usually under 45%. Sudden insult in LV systolic function often leads to mitral regurgitation. Imbalance of wall pressure between akinetic and hyperkinetic segments within the cavity might develop left ventricle outflow tract obstruction (pressure gradient, acceleration of blood flow) in some patients.

Follow-up of patients with TTC by serial echocardiographic examinations demonstrated noticeable recovery in systolic left ventricular function. Naturally, a LVEF <45% is a predictor of a worse prognosis [6, 20].

5.5. Cardiac magnetic resonance imaging

When the clinical presentation of TTS in the acute phase is considered, cardiac magnetic resonance imaging (cMRI) is not suitable for initial evaluation. After documentation of normal or near-normal coronary arteries with coronary angiography, cMRI is the preferred imaging method for its complementary data about three-dimensional LV and RV

anatomy, documentation of regional wall motion abnormality thus TTS subtypes (apical, mid-ventricular, inverted or focal). Diffuse myocardial edema is typically present in both myocarditis and TTS; however, lack of late gadolinium enhancement in TTS is helpful for differential diagnosis from both acute coronary syndrome and acute myocarditis. Though not standard, common practice for timing of cMRI is within 7 days after the index event and 2–6 months later for assessment of improvement in systolic functions [19].

5.6. Coronary angiography

Presentation of patients with chest pain and frequently ST-elevation leads the patients undergo coronary angiography even though TTS is not the diagnosis in the first place. Detection of normal or near-normal coronary arteries should suggest TTS and the operator should perform left ventriculography for the typical appearance of left ventricular apical ballooning.

Similarly, a great portion of patients with TTS (93%) had increased LV end-diastolic pressure (>11 mm) on angiography in the InterTAK registry.

Mayo Clinical criteria included normal or near-normal coronary angiography for establishment of TTS diagnosis; however, InterTAK registry documented by coronary angiography that coronary artery disease was present in 15% of patients with TTS. Coronary angiography remains to be the major method for distinguishing TTS from ACS in spite of increasing non-invasive modalities.

5.7. Diagnosis

Although a definition accepted worldwide does not exist, the most common one used for a long time in daily practice and research area included The Mayo Clinic diagnostic criteria which were modified in 2008; (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) the absence of obstructive coronary disease 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 troponins; (4) the absence of pheochromocytoma or myocarditis. In 2016, a position statement on TTS published by European Heart Failure Association (EHFA) taskforce updated diagnostic criteria as shown in **Table 2** [6].

Addition of 'reversible' expression for ECG abnormalities and QTc prolongation, replacement of mild with significant for elevation of serum natriuretic peptides, removal of exclusion of pheochromocytoma and addition of recovery of ventricular function in 3–6 months are the first noticeable changes in the EHFA criteria.

Unlike the post-menopausal women profile of classical type, reverse type was shown to be significantly associated with younger age and mental or physical stress rather than catecholamine excess [11, 18]. Of note, death was more common in men than women with TTS [11].

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- (1) Transient regional wall motion abnormalities of LV (or RV) myocardium which are frequently but not always preceded by stressful trigger (emotional or physical)
 - (2) The regional wall motion abnormality usually (exceptions reported) extends beyond a single epicardial vascular distribution and often results in circumferential dysfunction of the ventricular segment involved
 - (3) New and reversible ECG abnormalities (ST segment elevation, ST depression, LBBB, T wave inversion and/or QTc prolongation in acute phase)
 - (4) Significant elevation of serum natriuretic peptide (BNP or NT-proBNP) during acute phase.
 - (5) Positive but relatively small elevation of cardiac troponin measured with a conventional assay (troponin-negative cases have been reported)
 - (6) Absence of culprit atherosclerotic disease including plaque rupture, thrombus formation and coronary dissection or other pathological conditions to explain the pattern of temporary LV Dysfunction, for example, hypertrophic cardiomyopathy, viral myocarditis, and so on
 - (7) Recovery of ventricular function on cardiac imaging on follow-up (3–6 months).
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Table 2. European heart failure association (EHFA) taskforce updated diagnostic criteria.

6. Natural history

Although TTC is assumed to have a benign course in general, InterTAK registry reported the rate of death as 5.6% per patient-year. Patients with TTC may develop recurrence even after years [11]. Furthermore, the rate of serious in-hospital complications (21%) similar to that in ACS should make us question the commonly recognized benign course of the study. The rate of major adverse cardiac and cerebrovascular events including death, stroke/TIA in the first month of admission was 7.1%. Major complications include acute heart failure and cardiogenic shock, LV outflow tract obstruction, severe mitral regurgitation, fatal ventricular arrhythmias, thrombus in the akinetic segments of the ventricle. Predictors of poor prognosis include LV EF < 35%, RV involvement, QTc > 500 ms, BNP > 600 pg/ml, age < 75 years, cardiogenic shock and ventricular arrhythmias. Nevertheless, the prognosis is good for more than 90% of the patients as they regain normal systolic function in 3–6 months after the acute episode [19, 21].

6.1. Treatment

There are no randomized controlled trials to evaluate the efficacy of a certain treatment but retrospective analysis of outcomes reveals improved survival at 1 year with the use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers. Current approach includes a combination of evidence-based acute coronary syndrome and heart failure treatments [6]. Interestingly, in spite of either the ascribed role of catecholamine excess in the pathophysiology of TTC and the left ventricular systolic dysfunction, beta-blocker use was not associated with improved mortality at 1 year. However, retrospective and observational nature of the analysis should always be kept in mind, and further studies with prospective design are needed to obtain more accurate and reliable results. Symptoms of heart failure

must be closely monitored and treated and also the physician should be alert for ventricular arrhythmias during the acute phase. The risk tends to incline in time but is always present until complete recovery of LV systolic function [6].

Treatment of the patients should be categorized in two titles under acute phase and follow-up period. The risk is the highest in the acute phase so the patients should be monitored in coronary care unit with the capabilities of urgent coronary angiography, temporary and permanent pacemaker implantation, ventricular arrhythmia management and advanced heart failure therapy including LV assist devices and extra-corporeal membrane oxygenation (ECMO). In patients with cardiogenic shock, sympathomimetic agents should be avoided. Levosimendan might be a useful option in cardiogenic shock despite limited evidence [22]. Standard heart failure therapy should be implemented in patients with signs of congestion. In a series of 93 patients with TTS, incidence of ventricular fibrillation or Torsades de Pointes (TdP) was 8.6% [23]. Prolongation of QTc > 500 ms is commonly seen in patients with low heart rates, so temporary pacemaker may be life-saving for TdP episodes. Hypomagnesemia and hypokalemia should be checked and corrected as well [19]. ICD therapy should be reserved for patients without recovery of LV systolic function or recurrent ventricular arrhythmias. Notably, wearable defibrillators might be a good option during the acute phase.

During the follow-up period, more than 90% of the patients regain normal LV systolic function in 4–8 weeks. InterTAK registry found recurrence rate as 1.8% per year [3]. In order to prevent recurrences, beta-blockers were the most studied group with ACE inhibitors. In a recent meta-analysis by Brunetti et al. none of the therapies including beta-blockers, ACE inhibitors, angiotensin-receptor blockers, aspirin and statins were found effective in the prevention of recurrence of TTS [24]. Another recent regression meta-analysis found ACEI useful for prevention of recurrence [25]. Randomized controlled trials are awaited for more accurate and definitive results.

7. Future directions

Associated conditions helped better understanding of the mechanisms underlying TTS; however, mechanisms playing role in the recovery process remain largely elusive. It is obvious that randomized-controlled studies are needed to have a more clear aspect for standard therapy. The role of estrogen and progesterone in the pathophysiology of TTS should be addressed by basic scientists and clinicians. Optimal timing and treatment of patients suffering ventricular arrhythmias with ICD (subcutaneous/wearable defibrillator) is not clear and well-studied. The pathogenesis and treatment of TTS are still speculative and the risks of complications in the acute phase are underestimated. Given the variety of associated conditions and increased number of case reports, international data collection by registries like InterTAK registry should be employed and shared for a better understanding and optimal treatment.

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