REVIEW

Takotsubo Syndrome: A Brief Review in Light of New Evidence

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Abstract

"Takotsubo *Syndrome*" (TTS) is now recognized as a distinct entity within the spectrum of stress-induced cardiomyopathies. It is believed that enhanced sympathetic stimulation induces transient myocardial stunning through a variety of mechanisms that include epicardial spasm, ischemia due to microvascular dysfunction, and direct cardiomyocyte toxicity from catecholamine-mediated calcium overload. Once associated with emotional or significant physical stress, it is now clear that even minor stressors can trigger the syndrome and that roughly 30% of patients with TTS have no identifiable trigger at all. Traditionally regarded benign, TTS is now recognized as a potentially fatal condition with serious complications and considerable short-term mortality, similar to that of acute coronary syndromes. The major features of the TTS regarding clinical characteristics, pathogenesis and treatment options are herein briefly reviewed. ***Rhythmos 2016;11(4):90-95.***

Key Words: Takotsubo syndrome; cardiomyopathy; acute coronary syndrome; catecholamines; echocardiography

Abbreviations: LV = left ventricle; TTS = Takotsubo syndrome

Introduction

Formerly referred to as "Takotsubo Cardiomyopathy", the "Takotsubo *Syndrome*" (TTS) is now recognized as a distinct entity, increasingly diagnosed in clinical practice, within the spectrum of stress-induced cardiomyopathies. Some authors prefer to distinguish between four different types of stress cardiomyopathy, namely "Transient Left Ventricular Dysfunction After Acute Emotional or Physical Stress" (Takotsubo Cardiomyopathy), "Left Ventricular (LV) Dysfunction Associated With Intracranial Hemorrhage, Ischemic Stroke and Head Trauma", "Transient LV Dysfunction in Acute Medical Illness", "LV Dysfunction in Pheochromocytoma and With Exogenous Catecholamine Administration".[1,2] However, the implication of common pathophysiological mechanisms and the similar clinical presentation could make us reckon that they represent different variants of a single clinico-pathological continuum. In this article the major characteristics of the TTS regarding clinical features, pathogenetic pathways and treatment options are briefly reviewed.

Definitions

Originally described in 1991 in Japan,[3] TTS became familiar to the western world by late 1990's. It was systematically studied by the Mayo Clinic researchers who proposed diagnostic criteria in 2004 and reviewed ones in 2008.[4,5] (Table 1). Meanwhile, other groups have committed themselves to the study of TTS and finally in 2016 the European Society of Cardiology published a position statement that incorporated recent advances in diagnosis and treatment of TTS, proposing a set of 7 diagnostic criteria (Table 2) and providing detailed algorithms to distinguish it from other acute cardiac conditions.[6] TTS is considered a type of acute and usually reversible heart failure episode, often clinically indistinguishable from acute coronary syndromes but characterized by the lack of relevant coronary artery disease that could explain the extensive wall motion abnormalities observed in most cases.

Table 1. Mayo Clinic 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

CAD = coronary artery disease

Table 2. Heart Failure Association Diagnostic Criteria for Takotsubo Syndrome

1. Transient regional wall motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible ECG abnormalities (ST-segment elevation, ST depression, LBBB, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present).
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).

Epidemiology/Clinical presentation

As the clinicians become more and more familiar with TTS, it is diagnosed increasingly and it represents 5-10% of the cases presented as probable acute coronary syndrome.[7,8] Typically, it involves postmenopausal women, it is preceded by an emotional trigger and it manifests with ST segment elevation (Fig. 1), moderate rise in cardiac enzymes and wall motion abnormalities with a pattern of apical ballooning apparent in ventriculography, cardiac ultrasound or cardiac magnetic resonance (Fig. 2a). With evolving understanding and increased clinical awareness, new atypical forms have been described and regional disturbances in wall motion can take almost every possible combination as depicted in Table 3.

Usually, TTS presents with chest discomfort or dyspnea of sudden onset, accompanied by heart failure signs or arrhythmias and biochemical evidence of myocardial damage. Most commonly a trigger event physical or psychological is apparent (Table 4). [6] The patient may be hospitalized because of the TTS per se (primary TTS) or may have already been admitted for other reasons and TTS comes up as a superimposing condition (secondary TTS) probably triggered by the physical stress (medical or surgical) related to the underlying disease. In this instance, TTS may show atypical clinical features and present as acute pulmonary edema, shock or arrhythmia. [9]

ECG findings

Takotsubo syndrome is accompanied by electrocardiographic changes generally indistinguishable from those of acute myocardial infarction. In almost half the cases ST segment elevation in precordial leads prevail (Fig. 1a). [8] However T-wave inversion and Q waves occur often and LBBB is not uncommon (Fig. 1b). According to some authors there may be a predilection of changes for certain leads. In a French study, anterior leads were most frequently associated with ST-segment elevation, whereas T-wave inversion was more commonly associated with lateral leads, and Q-waves with septal leads. [10] Efforts to establish criteria for the differentiation between ACS and TTS have been made but they are not considered sufficient for routine use so far. [11-13] Normal ECG as well as ST segment depression is seldom encountered. The ECG typically evolves in the next few days with T wave inversion and QT interval prolongation (QTc often exceeding 500 ms), carrying a risk for torsades de pointes (Fig. 1b). Although not an absolute criterion, marked QT prolongation should guide diagnostic thought towards TTS since this finding is not very common in STEMI. Interestingly, ECG abnormalities may remain for several weeks after the normalization of left ventricular contractility. [8]

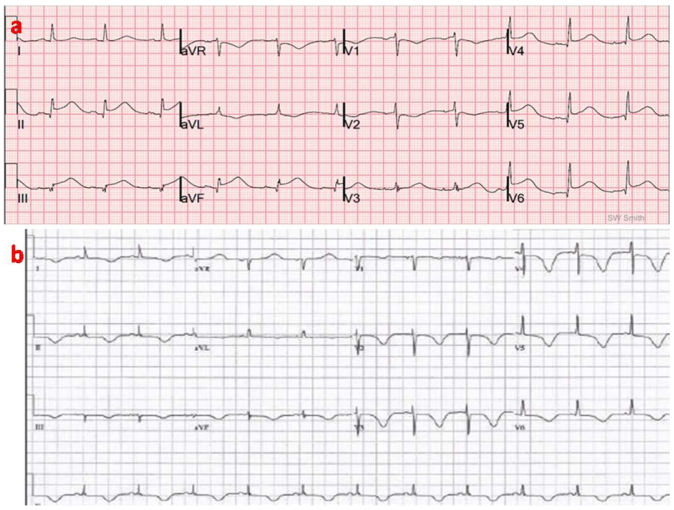

Figure 1. **a**. ST segment elevation ECG pattern in TTS. **b.** T wave inversion with QTc prolongation

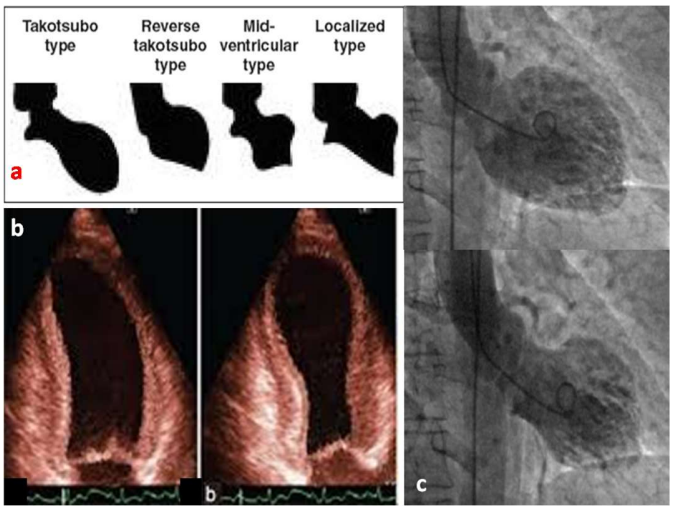

Figure 1. **a**. Wall motion abnormality patterns in TTS. **b**. characteristic apical ballooning in echocardiography. **c**. apical ballooning in left ventriculography

Table 3. Anatomical variants of Takotsubo syndrome

Variant	Prevalence
Apical with or without MLV variant (typical)	75–80%
MLV	10–15%
Inverted or basal	5%
Biventricular	Clinical <0.5% CMR 33%
Right ventricular	Insufficient data
Apical tip sparing	Insufficient data
Possible atypical variants (global or focal)	Insufficient data

CMR = cardiac magnetic resonance imaging; MLV = mid left ventricular

Table 4. Triggers for TTS

Endocrine disease (Pheochromocytoma, thyrotoxicosis, Addisonian crisis)
Neurological and neurosurgical conditions (subarachnoid hemorrhage, acute head injury, acute spinal injury, acute neuromuscular crises, epileptic seizures, ischemic stroke, posterior reversible encephalopathy syndrome)
Respiratory (Acute exacerbation of asthma or COPD, acute pulmonary embolism)
Obstetric (miscarriage, labour, emergency Caesarean section)
Psychiatric (Acute anxiety attack/panic disorder, Drug-withdrawal syndromes)
Gastrointestinal (acute cholecystitis, acute pancreatitis, pseudomembranous colitis)
Severe sepsis
Cardiological (Dobutamine stress echocardiography, Radiofrequency arrhythmia ablation, Electrical DC cardio-version for atrial fibrillation, Post-cardiac arrest including VF
Haematological (Blood transfusions, Thrombotic thrombocytopenic purpura)
Surgical or interventional procedures
Medication (Epinephrine injection, Nortriptyline overdose, venlafaxine overdose, albuterol, flecainide, metoprolol withdrawal, 5-fluorouracil, duloxetine, Cocaine abuse)

Cardiac biomarkers

Over 90% of TTS cases present with elevated troponin and creatine kinase (CK) levels, though disproportionately low with regard to the extensive wall motion disturbances. This figure often serves as a differentiating characteristic between TTS and coronary syndromes. Troponin and CPK do not usually exceed 1000 pg/ml and 500 U/l respectively, but these values evolve through time following a typical rise-and-fall curve.[14] Natriuretic peptides are significantly elevated, with peak levels occurring at 48 hours and normalization delayed for up to 3 months or more. [15] Serum catecholamine levels are markedly elevated in most TTS patients, an observation consistent with the current pathophysiological approach.[16] No specific biomarker exists that can reliably establish the diagnosis of TTS. However, a combination of 4 circulating microRNAs has been proposed as having a sensitivity of 96.77% and a specificity of 70.37% for TTC vs STEMI patients. [17]

Pathophysiology

Despite research on TTS for more than two decades, the exact pathophysiological procedures of this syndrome remain elusive. Only hypotheses have been presented based on certain epidemiological or clinic-laboratory features (Table 5). The hypothalamic-pituitary-adrenal axis hypothesis was derived from the observation that patients with TTS tended to have a blunted cortisol stress response.[18] Glucocorticoids suppress catecholamine turnover; thus, hypocortisolemia could accentuate cate-cholamine release and contribute to TTS development.

Table 5. Proposed pathophysiological mechanisms

Direct myocardial effect	Catecholamine hypothesis Hypothalamic-pituitary-adrenal axis hypothesis Estrogen hypothesis Cell signaling Genetic factors
Vascular	Coronary microvascular mysfunction Multivessel coronary spasm Spontaneously aborted myocardial infarction Left Ventricular outflow tract obstruction

The predilection of TTS for postmenopausal women has guided researchers towards an implication of sex hormones in the pathogenesis of TTS. Lack of estrogen causes coronary microvascular dysfunction and increased sympathetic tone. [19] Moreover, in animal models, estrogen pretreatment has been shown to protect from myocardial dysfunction induced by emotional stress. [20]

Cell signaling derangement affecting several components of the intracellular signaling pathways (switch from b2-adrenoceptor Gs to Gi protein, sarcoplasmic/ endoplasmic reticulum calcium ATPase (SERCA2) inhibition via b1-adrenoceptor) may also play a critical role in TTS development. [21,22] Obviously, a genetic predisposition cannot be ruled out, since familial cases have been reported, though rarely. Besides, adrenergic receptor polymorphisms have been described in association with cardiomyopathy in the setting of subarachnoid hemorrhage. [23,24]

Vascular etiology has been suggested as well. Microvascular dysfunction has been described in TTS in coronary angiography and by invasive and non-invasive coronary flow reserve measurement. [25-27] Diffuse coronary spasm gained popularity in the early years but it is no longer considered important in the pathophysiology of TTS. [28] The hypothesis of acute myocardial infarction undergoing spontaneous thrombolysis has been similarly downgraded, mostly due to the extensive dyskinetic regions not corresponding to a vascular territory.

Nearly one fourth of Takotsubo patients show LVOT obstruction, and some authors assumed it is the causative condition, especially in the setting of a catecholamine surge. Transient hypertension followed by hypotension combined with increased wall stress, could produce the apical ballooning by redistributing wall stress towards the apical segments. [29]

The development of numerous theories to explain a clinical phenomenon, a functional or an imaging abnormality, usually reflects uncertainty. Indeed, the pathogenesis of TTS is complicated and remains relatively

unclear. However, the most popular proposed pathogenetic mechanism is the catecholamine hypothesis. The common denominator of most of the other presumptions now emerges as the key pathophysiological feature. The trigger event is thought to cause a massive catecholamine release which exerts deleterious events on the myocardium. [28] A TTS-like cardiomyopathy has been described secondary to norepinephrine-, dopamine-, and epinephrine-secreting pheochromocytomas. [30] Furthermore, administration of high doses of catecholamines produce TTS. [31] Unluckily, increased levels of catecholamines or their metabolites in blood or urine, is not a consistent finding. [32,33] Myocardial scintigraphy with ^{123}I-metaiodobenzyl-guanidine (MIBG) and PET imaging using ^{11}C hydroxyephedrine (HED), advocate for increased catecholamine release from presynaptic neurons and impaired neuronal reuptake.[34-36]

The topography of the wall motion abnormalities is another issue that has not been convincingly explained. The current hypothesis states that adrenergic receptor as well as sympathetic nerve density may be unevenly distributed within the left ventricle, leading to regional differences in catecholamine sensitivity. [37] The density of sympathetic nerves is greater at the base of the heart but adrenergic receptors are probably more sensitive in the apex and thus apical regions are more prone to catecholamine-mediated damage. [38,39] However, no explanation is provided for the non-apical forms of the syndrome, and to make things more complex, Bonnemeier and colleagues have demonstrated that the apical ballooning and midventricular variants correlate with activation of the left and right stellate ganglion respectively. [40,41]

Management

Since in most cases TTS is a self-healing condition, supportive and preventive measures are the cornerstone of therapy. Severe cases presenting wit cardiogenic shock may need mechanical circulatory support as a bridge to recovery. Once considered benign, TTS is associated with a mortality risk similar to that of acute coronary syndromes. However, often patients tolerate well the acute functional loss of substantial myocardial mass, exceeding 60%, which would result in sudden death in case of a myocardial infarction of such extent. It is hence believed that several protective mechanisms have been activated to preserve cardiac output and tissue perfusion. Indeed, peripheral resistance decreases, in contrast to the conventional cardiogenic shock where peripheral resistance increases, probably due to counteracting circulatory protective mechanisms. [42,43] Therefore, initially the patient is treated as suffering from acute coronary syndrome. ECG monitoring is essential because of the risk of arrhythmias, especially when QT prolongation coexists. Coronary angiography and left ventriculography should be performed early, in order to differentiate between TTS and myocardial infarction. Pharmacotherapy recommendations are extrapolated from heart failure studies, since randomized trials in TTS are lacking. Diuretics, ACE inhibitors and b-blockers are usually used in mild cases, although caution is warranted because of the altered peripheral sympathetic nerve activation and the decreased peripheral resistance. [6,43] In more severe clinical presentation, the patient is admitted in the coronary care unit at least for 72 h during which the risk of complications is greatest (Table 6). In cardiogenic shock, temporary use of LV assist devices (LVADs) or extracorporeal membrane oxygenation (ECMO) is indicated. If those options are not available, low-dose levosimendan infusion can be applied as it is considered preferable compared to conventional inotropes. Intra-aortic balloon pump (IABP) use has been reported; however the low performance of IABP in randomized trials and the risk of worsening LV outflow obstruction has led the experts to counsel against its use in Takotsubo cases. [6]

Table 6. TTS complications

Complication	Rate
Acute heart failure	12-45%
LVOTO	10-25%
Mitral regurgitation	14-25%
Shock	4-20%
Arrhythmias	AF 5-15%, VT 4%, arrest 4-6%
Thromboembolism	2-8%
Wall rupture	<1%
RV involvement	18-34% (echo/MRI)
In-hospital mortality	2-5%
%-year recurrence	5-22%

AF = atrial fibrillation; LVOTO = left ventricular outflow tract obstruction; VT = ventricular tachycardia

The prognosis regarding cardiac recovery is favorable. However, although ejection fraction may normalize, detailed evaluation with novel sophisticated echocardiographic and magnetic resonance techniques have disclosed persistent abnormal features in cardiac function, such as impaired global longitudinal strain and diastolic dysfunction for several months after the acute episode. [44] Some patients report residual symptoms (fatigue, chest pain, palpitations, dyspnea) and natriuretic peptide elevation has been considered as evidence of ongoing myocardial dysfunction. [45] Moreover, recurrences do occur within the first 5-10 years and no specific preventive measure can be recommended. Beta blockade could be beneficial in terms of recurrence prevention, but the data are inconsistent. [46] Patients with a second episode of Takotsubo should have long-term follow up in order to

timely detect any deterioration and identify measures to avoid further recurrences.

Conclusion

Takotsubo syndrome is increasingly diagnosed since its first description, as a consequence of more thorough knowledge and higher suspicion index of the physicians. It is believed that enhanced sympathetic stimulation induces transient myocardial stunning through a variety of mechanisms that include epicardial spasm, ischemia due to microvascular dysfunction, and direct cardiomyocyte toxicity from catecholamine-mediated calcium overload. Once associated with emotional or significant physical stress, it is now clear, that even minor stressors can trigger the syndrome and that roughly 30% of patients with TS have no identifiable trigger at all.[47,48] The absence of an identifiable dramatic stressor, however, does not exclude a sympathetically mediated pathogenesis, since even a mild stressor may be sufficient to precipitate TS in vulnerable individuals who may have either increased sympathetic tone at baseline or enhanced myocyte or microvascular catecholamine sensitivity, due to hormonal factors, anxiety or psychological disorders, medication use, endothelial dysfunction or genetic susceptibility. Traditionally regarded benign, TTS is now recognized as a potentially fatal condition with serious complications and considerable short term mortality, similar to that of acute coronary syndromes. Unfortunately, the data on treatment options and preventive measures are scarce and management remains largely empiric. Therefore, more randomized trials are needed in order to provide robust evidence which will lead to a deeper understanding of the pathophysiology and allow for specific, targeted therapeutic maneuvers.

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