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Khalid N, Sareen P, Ahmad SA, Chhabra L

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Takotsubo syndrome: The past, the present and the future

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Abstract

Takotsubo syndrome is a wide spectrum disease with a dramatic clinical presentation mimicking acute coronary syndrome albeit without obstructive coronary disease and typically manifests in the backdrop of intense emotional or physical trigger. Pathophysiology is incompletely understood with multifactorial mechanistic pathways circling around a heart-brain-endocrine axis. Several anatomic and phenotypic variants exist with varied clinical manifestations. The aftermath of Takotsubo syndrome is not always benign and both short- and long-term complications can occur which may impact its prognosis. Several gaps in knowledge exist providing an impetus for tremendous future research opportunities.

Key words: Takotsubo syndrome; Triggers; Pathophysiology; Anatomic variants; Prognosis

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Core tip: Further research is necessary in order to better understand the underlying triggers and pathophysiologic principles of Takotsubo syndrome which will help optimize both in-hospital acute and long-term management pathways.

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INTRODUCTION

Chest pain and dyspnea are ubiquitous and common clinical symptoms for patients presenting to the Emergency Department and majority of these patients are initially labelled with the diagnosis of coronary artery disease, heart failure or pulmonary disease. Hitherto less well known clinical entity - Takotsubo syndrome (TTS), first described in Japan, is becoming increasingly recognized in the Western world and shares many clinical features indistinguishable from acute coronary syndrome (ACS) or acute heart failure. TTS is a heterogenous entity characterized by transient wall motion abnormalities (WMA) of the left ventricle typically without angiographically significant epicardial coronary artery disease or acute plaque rupture, manifesting with chest pain, dynamic reversible ST segment and T wave abnormalities, and modest elevation of cardiac biomarkers disproportionate to the extent of WMA^[1-4] - thus mimicking ACS in many ways (Figure 1). It has also been described as an acute heart failure syndrome characterized by left ventricular systolic and diastolic function, myocardial strain abnormalities, and significant elevation of beta natriuretic peptide. Over the past three decades, our understanding of the pathophysiologic mechanisms of this disease has improved; thanks to the widespread availability of urgent coronary angiography and technological advances in the imaging arena such as modern echocardiography, speckle strain imaging, cardiac magnetic resonance imaging, single-photon emission computed tomography and positron emission tomography, however, several knowledge gaps still remain. What has become clear now is that TTS is much more common than previously anticipated. It predominantly affects postmenopausal women^[5] and portends significant morbidity and mortality approaching that of ACS, although still underappreciated. A hallmark feature of TTS is its association with a preceding negative stressful trigger (emotional or physical) - the so-called "broken heart syndrome" or "stress-induced cardiomyopathy". However, in some cases no stressors may be identified and in few the trigger could even be a positive emotion - the soi-disant "happy heart syndrome".

Electrocardiographic manifestations of TC patients progress through similar evolutionary pattern as the ECG staging in pericarditis^[6]. Stage 1 demonstrates ST segment elevation, followed by normalization of ST segment in stage 2. T-wave inversions develop in stage 3, with subsequent normalization of T waves or rarely persistence of T-wave inversions noted in stage 4^[6]. Certainly, an overlap between these changes may exist, whereas some patients may not demonstrate all evolutionary stage changes. Several anatomic and phenotypic variants of TTS have been described with varied clinical manifestations. The most common form is the typical apical ballooning which occurs in 75%-80% of patients; it's easily recognized and is associated with typical complications including thrombus formation due to apical akinesis and left ventricular outflow tract obstruction due to basal hyperkinesis^[7]. Other less common types include midventricular, basal or inverted, biventricular, right ventricular, or focal dysfunction^[7]. Numerous putative mechanisms have been proposed for development of TTS - these include coronary vasospasm, microvascular spasm or dysfunction [as demonstrated by abnormal Thrombolysis in Myocardial Infarction (TIMI) Frame Count or TIMI perfusion grade], neurogenic stunned myocardium with underlying enhanced sympathetic activity, elevated levels of circulating plasma catecholamines and its metabolites, inflammation, estrogen deficiency, and spontaneously aborted myocardial infarction^[8-12]. A possible autoimmune and/or autoinflammatory component has also been hypothesized for TTS, akin to myocardial infarction, thereby providing an impetus to explore long-term immunological effects of TTS^[13]. Associated comorbidities and risk factor profile is similar to coronary artery disease although some reports suggest that diabetes mellitus is noted less frequently in patients with TTS suggesting a possible protective mechanism^[14,15].

The most commonly applied diagnostic criteria include the Revised Mayo Clinic Criteria^[16], International Takotsubo Diagnostic Criteria (InterTAK)^[17], and the Heart Failure Association-European Society of Cardiology Criteria^[18]. Transthoracic echocardiography with color and tissue Doppler is the preferred noninvasive imaging modality for patients suspected of TTS but most of these patients undergo emergent coronary angiography to rule out ACS. Correct diagnosis is critical since TTS is not a benign condition and is associated with potentially serious short- and long-term

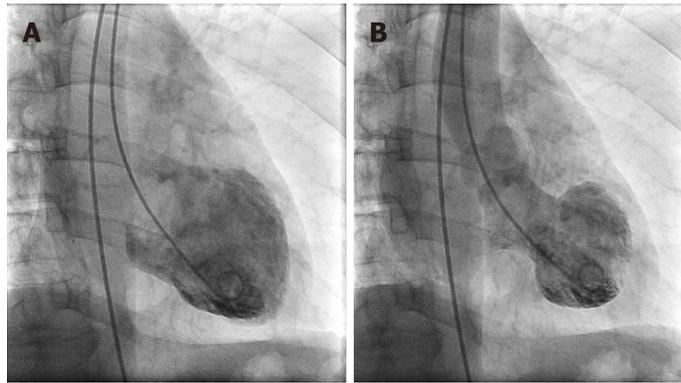


Figure 1 Ventriculogram of the left ventricle in diastole (A) and systole (B) demonstrating typical apical ballooning with apical akinesis and basal hyperkinesis.

complications such as ventricular arrhythmias, dynamic left ventricular outflow tract obstruction, pump failure with cardiogenic shock, thromboembolic sequelae, intramyocardial hemorrhage and rupture, pulmonary edema and others^[7]. In-hospital mortality remains high (about 5%) and acute management focuses on the specific complications^[7]. Physical triggers, acute neurologic or psychiatric illnesses, elevated cardiac biomarkers (troponin), and a low left ventricular ejection fraction on admission were independent predictors for in-hospital complications^[19]. Currently no evidence exists for long-term management of TTS. Nonetheless, beta-blockers are advocated especially in patients with increased sympathetic tone^[7]. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers have demonstrated a marginal benefit at 1-year^[19]. Recurrence rate is reported at 1.8% where the trigger is typically different, and the recurrence can occur at any time^[19].

CONCLUSION

TTS presents with symptoms similar to ACS characterized by transient left ventricular dysfunction typically manifesting in the setting of stressful triggers. Dynamic reversible ST segment and T wave abnormalities, modest elevation of troponin, significant elevation of beta natriuretic peptide, several anatomic variants, potentially serious short- and long-term complications, prognosis similar to ACS are some important features of this entity. Our current understanding of the pathophysiologic underpinnings has improved compared to its first description in 1990 yet there are several knowledge gaps that need to be addressed. Future potential research opportunities include exploring reasons for gender predilection, triggering factors and their role in the development and prognosis of TTS, different phenotypes of TTS, intracellular and intercellular mechanisms involved, genetic predisposition, exact pathophysiologic mechanism, specific acute- and long-term management and the role of animal models. Future larger randomized controlled studies will help resolve these queries.

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