Review

Takotsubo cardiomyopathy

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Academic Editor: Giuseppe Andò
Submitted: 19 September 2021   Revised: 9 November 2021   Accepted: 10 November 2021   Published: 20 January 2022

Abstract

Takotsubo cardiomyopathy (TTC) is a clinical condition of transient acute heart failure correlated to regional wall motion abnormalities extending beyond the distribution of a single epicardial coronary artery. It is classified into four major types: apical, basal, mid-ventricular and focal. Sympathetic nerve stimulation and catecholamine storm are the main players in the pathogenesis of TTC. The clinical course of disease is generally benign but it may end with life-threatening complications. Coronary angiography, left ventriculogram, transthoracic echocardiography and cardiac magnetic resonance imaging (CMR) are the main tools for making diagnosis. Except for critical cases with hemodynamic instability and/or complications, the overall management is limited to conventional heart failure therapy.

Keywords: Takotsubo cardiomyopathy; Heart failure; Apical ballooning syndrome; Acute coronary syndrome; Cardiac MRI

1. Introduction

Takotsubo cardiomyopathy (TTC) also known as « broken heart syndrome », « stress-induced cardiomyopathy » and « apical ballooning syndrome » is a clinical entity characterized by transient wall motion abnormalities of the left ventricle causing acute reversible heart failure that is not linked to obstructive coronary artery disease [1]. Its clinical presentation, typically precipitated by emotional or physical stressors, mimics acute coronary syndrome (ACS). It was firstly described by Hikaru Sato in 1990 [2] and the term « Takotsubo » derived from the octopus pots used by Japanese Fishermen which resemble the heart's form in the setting of apical TTC [3]. Temporary regional wall motion abnormalities exceeding a single epicardial vascular distribution, no evidence of significant coronary artery disease, new electrocardiogram (EKG) and/or cardiac biomarker modifications and absence of underlying pheochromocytoma or myocarditis are the main diagnostic criteria [4]. The observed EKG abnormalities include ST-segment elevation particularly in the anterior leads, ST-depression, T-wave inversion, prolonged QT-interval, ventricular tachychardia and fibrillation [5], thereby causing misdiagnosis of TTC as ACS especially when these changes are associated with positive cardiac troponin level. This overlap in clinical presentation emphasizes on the importance of early coronary angiography according to the clinical setting for differential diagnosis. Otherwise, TTC may mimic variant diseases like subarachnoid hemorrhage, intracerebral bleeding, pheochromocytoma and cocaine abuse which can be easily distinguished via the obvious clinical manifestation. The inter TAK Diagnostic Score is a novel clinical score developed to differentiate TTC from ACS in the acute stage with high specificity and sensitivity levels [6]. Noteworthy that relevant coronary artery disease may coexist in a high proportion of TTC patients and negatively impacts the overall prognosis [7]. Since the first reported case, the prevalence of TTC is steadily increasing and represents 1–3% of all ACS and 5–6% of ST-segment elevation myocardial infarction (STEMI) presentation in women [8–10]. TTC is markedly more common in women especially in post-menopausal period. Indeed, women with a mean age of 67–70 years account for 90% of TTC [11–13]. The risk of TTC is 10 times higher in women than men and 5 folds greater in women aged above 55 years compared to those aged below 55 years [14]. The hypothesis behind female preponderance was that men are more protected against cardiac adverse effects of catecholamines as they are more frequently exposed to physical stress [14]. The modifications in sensitivity and density of myocardial adrenergic receptors from base to apex during menopause may explain the age-sex difference in women [14]. It is worthy to mention that TTC occurs in adulthood and childhood noticing that the youngest reported case in the published literature was in a premature neonate [15]. There are several described variants of TTC with specific cardiac features but sharing in common the clinical signs, symptoms, pathophysiological mechanisms and the presence of identifiable preceding stressful trigger in two-third of cases [16]. Triggers are divided into two main categories: the emotional or psychological stressors such as grief, fear, panic, anger, anxiety, financial or emlployment problems, embarrassment, natural disasters and happy heart syndrome [17–19] which were

more common in female patients [11] and the physical stressors including physical activities, medical conditions and procedures [1,20,21] which were more frequently observed in male patients [11]. Herein, we briefly review the different types, pathophysiology and treatment of TTC.

2. Types of TTC

Based on the anatomical distribution of the regional wall motion abnormalities, TTC is classified into four major types. The apical type is the classical form accounting for 80% of Tako tsubo cases and characterized by basal hyperkinesis, apical ballooning and hypokinesis of the mid-ventricular and apical segments figuring out a fluoroscopic aspect of the left ventriculogram like the octopustraps in Japan [22] (Fig. 1). The basal type is the inverted variant of typical TTC and it is defined by a basal hypokinesis and apical hypercontractility [23]. Then, the mid-ventricular and focal types are the more rarer variants of TTC. The hawk's beak appearance of left ventriculogram, first reported by Roncalli *et al.* in 2007 [24], is a new angiographic sign for the mid-ventricular form of TTC, defined by hyperkinesis of the apical segment and dyskinesis of the ballooned mid-ventricular region [24,25] (Fig. 2). Patients with atypical TTC (basal, mid-ventricular and focal types) are younger, with more neurological disorders, less altered left ventricular ejection fraction, more common ST-depression on initial EKG and lower 1-year mortality than those with typical TTC [26,27]. The basal type of TTC has been recognized to be more associated with the existence of subarachnoid haemorrhage [28], pheochromocytoma [29] and epinephrine-induced TTC [30]. In addition to the four main types of TTC, further variants have been reported including the isolated right ventricular, biventricular (typical TTC with right ventricular involvement) and global forms, respectively [31–34].

3. Pathophysiology

To date, the precise pathophysiology of TTC remains uncertain and mutiple pathophysiological mechanisms including diffuse vasospasm, microcirculatory dysfunction, direct catecholamine toxicity on cardiomyocytes and activation of myocardial survival pathways have been suggested [1,35–37]. Conventionally, an enhanced sympathetic stimulation with massive catecholamine release plays the key role in the pathogenesis of TTC (Fig. 2). The correlation between the presence of precipitating stressful event and the onset of TTC supports the pivotal role of the sympathetic or adrenergic response. Increased serum and cardiac nerve endings catecholamine levels have been documented in TTC patients [38] which were two times more than that of patients with acute myocardial infarction [39, 40]. This catecholamine surge contributes to left ventricular outflow tract obstruction detected in 25% of TTC patients [41], apical ballooning [42,43] and vasospasm of the epicardial vessels and coronary microcirculation [38,44].
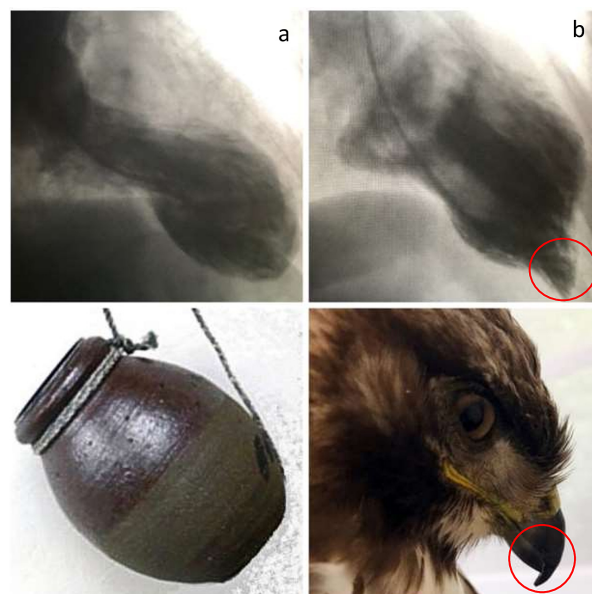

Fig. 1. Left ventriculogram showing the apical ballooning form of TTC ressembling to octopus trap (a) and the mid-ventricular type with hawk's beak appearance (b). This figure showed the case of two patients who underwent emergent coronary angiography for acute coronary syndrome, and in whom the left ventriculogram revealed the described features of apical (a) and mid-ventricular (b) Tako-tsubo respectively.

Left ventricular dysfunction in TTC ensues from the direct toxicity of catecholamines on cardiomyocytes. The extreme catecholamine production reduces cardiomyocytes viability by promoting intracellular calcium overload, inhibiting the expression of sarcoplasmic-Ca^{2+}-adenosine-triphosphatase (SERCA2a) gene expression and upregulating the expression of sarcolipin gene [45]. Thus, the increased phospholambam/SERCA2a ratio results in decreasing Ca^{2+} affinity and myocardial contractility [46]. The excess of catecholamines provokes multi-vessels epicardial spasm that amplifies cardiac workload resulting in a supply-demand mismatch and subsequently, a state of post-ischemic stunning myocardium [38,44]. It also activates $\alpha 1$- and type A endothelin receptors which induce vasoconstriction leading to microcirculatory dysfunction, reduction in coronary flow reserve and microvascular blood flow during the acute phase of TTC [47–49]. The participation of microcirculatory dysfunction in the pathogenesis of TTC has been supported via the improvement in myocardial perfusion, wall motion score and left ventricular ejection fraction observed after adenosine administration in the acute phase of TTC [50] and the results of endomyocardial biopsies showing apoptosis of microvascular endothelial cells [51]. The transient characteristic of TTC may be explained by the activation of two myocardial protective mechanisms. The first one is manifested by the switching of β_2-adrenoceptor from G_s to G_i coupling in response to catecholamine surge which initiates a negative inotropic
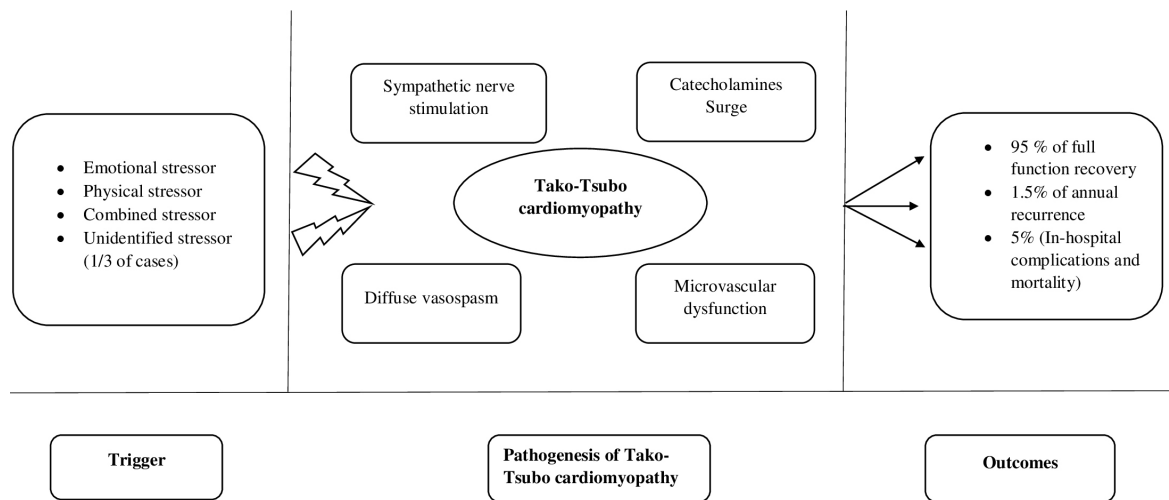
Fig. 2. Pathogenesis and outcomes of Tako-Tsubo cardiomyopathy. Physical or emotional or combined triggers were found in 2/3 of Tako-tsubo cases subsequently activating the main pathophysiological mechanisms of Tako-tsubo cardiomyopathy including the sympathetic nerve stimulation, catecholamines surge, diffuse vasospasm and microvascular dysfunction. Tako-tsubo is associated with good outcomes marked by 95% of full function recovery, 1.5% of annual recurrence and 5% of in-hospital complications and mortality.

effect restricting the degree of myocardial injury [52] and the second mechanism is represented by the activation of AKT survival pathway [53]. A role for oxidative stress in the pathophysiology of TTC has been supported by several studies which reported a correlation between the level of oxidative stress and the extension of myocardial dysfunction [54]. A recent study has reported a significant association between malignancy and TTC and showed that patients with history of malignnacy are at higher risk for TTC [55]. Despite the fact that administration of exogenous catecholamines could trigger the different ventricular ballooning forms in animal models [43,56–58], the increased level of serum catecholamines is more likely to be the consequence rather than the cause of TTC. Indeed, humans are exposed to various stressful situations and medical conditions (for example pheochromocytoma) resulting in a spike in catecholamines level without generating TTC [42,59].

4. Cardiac imaging in TTC

Transthoracic echocardiography (TTE) is the initial non-invasive test in TTC which is often performed in the emergency department. It delineates the area of dysfunctional myocardium and evaluates the left ventricular function, especially with the advanced echocardiographic techniques like tissue doppler velocities and speckle traking method that denotes transient circular impairments of radial, circumferential and longitudinal left ventricular functions on top of left ventricular twist mechanics defect [60–63]. Also, the peak systolic strain is considered more useful than speckle tracking imaging in assessing the left ventricular contractility and dynamics particularly in patients with reduced LVEF [63]. The two-dimensional speckle echocardiography may point out early systolic functional impair-

ment by assessing the global and longitudinal strain. It has a prognostic value by predicting the in-hospital adverse clinical outcomes in the acute setting of TTC [64]. Furthermore, acute impairment of diastolic function parameters (E/A ratio, mean, e' and A wave duration) has been observed in the context of TTC which improves in parallel with systolic function recovery [65]. After echocardiography, CMR becomes a valuable non invasive imaging test used to assess TTC in some complicated cases. In general, physicians complete a normal or near normal coronary angiography in ACS patients with left ventriculography searching for TTC especially when precipitating trigger is present. Then, performing CMR in complicated cases provides useful data to confirm diagnosis, make differential diagnosis, detect complications, stratify risk, follow-up and assess left ventricular function, wall motion abnormalities and biventricular involvement [66,67]. Myocardial oedema, a constant CMR feature, reflects the extension of myocardial inflammation in acute TTC [67–69]. Positive late gadolinium enhancement (LGE) may appear for three reasons: increased cardiomyocytes interstitial water content [70], collagen-1 fiber density [71] and the presence of contraction band necrosis [72,73]. There is evidence that microvascular dysfunction plays an important role in the pathogenesis of TTC, therefore the usefulness of quantitative perfusion CMR which is not practically used in TTC patients, for the evaluation of microvascular ischaemia has been reported [74]. Noteworhty that microvascular dysfunction was significantly more associated to apical TTC than the other types [75]. The apex is the most distal part irrigated in a watershed area of blood supply between the epicardial coronary arteries and subsequenlty, it is more susceptible to blood interruption. Moreover, CMR detects the

potential complications of TTC such as systolic heart failure, intra-cavitary thrombus, acute pericarditis and left ventricular outflow tract obstruction [76]. TTC patients with positive LGE were at higher risk for cardiogenic shock and prolonged recovery interval [77] without difference in long-term adverse outcomes compared to those with intact myocardium [78]. The prognostic value of LGE in TTC is not well-settled and remains under investigation.

5. Laboratory findings in TTC

A markedly elevated level of brain natriuretic peptides (BNP) is usually observed in most TTC patients. The rational for this finding extends from the knowledge of the pathophysiology of this cardiomyopathy characterized by regional wall motion abnormalities. The excessive production of BNP is linked to the left ventricular pressure overload ensued from regional hypercontractility (basal in the classic type and apical in the basal form) acting in a manner similar to left ventricular hypertrophy and aortic stenosis [79]. BNP level peaks in a week, then normalized within the following months [79]. Furthermore, cardiac enzymes namely troponin, CK and CK-MB were released in TTC making difficult to distinguish TTC from myocardial infarction based on cardiac biomarkers alone. However, the diagnosis of TTC seems to be unlikely in patients with troponin T level greater than 6 ng/mL and troponin I level greater than 15 ng/mL [80].

6. Treatment

To date, the management of TTC is mainly supportive and based on the conventional medical therapy for heart failure view the lack of clinical trials. Treatment may be continued at least till the normalisation of left ventricular function, usually occuring 3–4 weeks after the onset of TTC syndrome. It also varies in parallel with the severity of the clinical presentation from single symptomatic treatment in mild cases to agressive mechanical cardiac support in severe refractory cases [42]. Heart failure medications like β-blockers, angiotensin-converting enzymes inhibitors (ACEi), angiotensin II receptor blockers (ARB) and angiotensin receptor-neprilysin inhibitors are indicated in hemodynamic stable patients [42,81,82]. Diuretics and vasodilators could be used to treat pulmonary congestion [42]. Aldosterone antagonists may have additional benefits with cardioprotective impact in TTC patients view the synergistic effect of aldosterone and catecholamines on the cardiovascular system [83–85]. Early hospital discharge within 48–72 hours is possible for those with LVEF ≥45% and not facing any complications [86]. Compared to β-blockers, a systematic review and a meta-analysis study have reported that ACEi/ARB were associated to an improvement in survival and reduction in the rate of recurrence [87,88] while another study revealed the lack of efficacy of ACEi/ARB and β-blockers on preventing TTC recurrence [89]. In opposition, the use of β-blockers especially esmolol, propranolol and metoprolol decreases the incidence of left ventricular out flow obstruction in the setting of TTC [90–93] and overall 1-year mortality in the context of cardiogenic shock [94,95]. Inotropes (milrinone, dobutamine and dopamine), vasopressors and mechanical left ventricular assist devices may be mandatory in TTC patients and cardiogenic shock [42]. Data from case series have also reported the safety and feasibility of levosimendan, a calcium sensitizer, in TTC patients [96]. However, inotropes should be avoided in the context of left ventricular out flow tract obstruction as that may aggravate the obstruction while extra-corporeal membrane oxygenation and impella may be helpful in the advanced severe cases [42]. TTC patients are at risk for cerebrovascular events which occur in 7.1% of cases throughout the first 30 days of hospitalisation [97], thereby initiating prophylactic anticoagulation therapy is preferred in high risk patients, like the presence of large area of myocardial hypokinesis [42] or apical variant with high initial troponin level [98]. Otherwise, the use of antiplatelet therapy is still debatable in TTC [99,100]. No reduction in major cardiovascular events at 30 days and 5 years follow-up was observed after aspirin intake in TTC [101]. Lastly, it is important to assess and manage the emotional and/or physical trigger on top of the coexisting comorbidities because most of the long-term mortality in TTC seems linked to non-cardiac conditions [102].
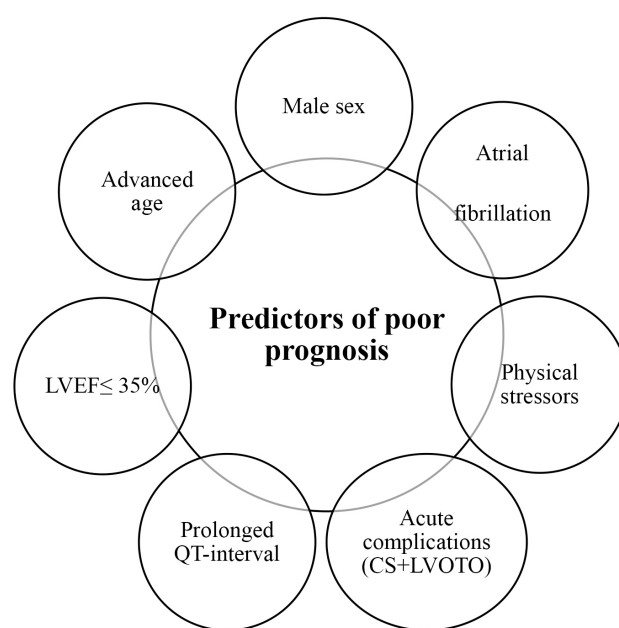

Fig. 3. Independent predictors of poor prognosis in Tako-Tsubo cardiomyopathy. Advanced age, male sex, reduced left ventricular ejection fraction below 35%, prolonged Qt-interval, presence of physical stressors, atrial fibrillation and acute complications like cardiogenic shock or left ventricular outflow tract obstruction represent the independent predictors of poor prognosis in Tako-tsubo cardiomyopathy.

7. Prognosis

Since a long time ago, the overall prognosis of TTC has been considered acceptable with a complete recovery rate of 95% [37,93,99]. The reported incidence of in-hospital mortality and annual recurrence were 5% [40,41] and 1.5% [85], respectively. Recent data suggest that outcomes in TTC is comparable to ACS and InterTAK Prognostic score was developed to stratify the patient's risk [103]. A score level above 22 define high risk patients [103]. The mortality is significantly higher in men [91], and in patients with old age [102,104], atrial firbrillation (two times more) [105,106] and physical stressor [84,100]. Deaths mainly occur in patients with hemodynamic instability on initial presentation [40]. Although, prolonged QT interval on electrocardiogram [107,108], reduced left ventricular ejection fraction below 35% [109,110] and the presence of acute complications (left ventricular out flow tract obstruction, free wall or septal rupture and cardiogenic shock) are independent predictors of poor outcomes (Fig. 3).

8. Conclusions

TTC is usually a benign disease course enrolling several variants in accordance to the anatomic distribution of regional wall motion abnormalities that share in common the clinical symptoms, EKG changes, increased cardiac biomarkers, pathophysiology and therapeutic strategies. To date, it seems that diffuse vasospasm and microvascular dysfunction ensuing from adrenergic storm play a crucial role in the pathogenesis of TTC. Searching for potential complications such as left ventricular outflow tract obstruction is essential before starting treatment, especially in patients with hemodynamic instability. Future prospective trials for risk stratification and target medical therapy standardization are required.

Author contributions

AM—contributed to conception, design and writing of the article; CD, FCP, VN, TL, FB, ME, SB and JR—contributed to conception and design; DC—contributed to design and writing of the article and provided important intellectual contribution to the manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of the manuscript and thanks to all the peer reviewers for their opinions and suggestions.

Funding

Conflict of interest

The authors declare no conflict of interest.

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