Review Article

Takotsubo Cardiomyopathy: A Review

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Abstract

Takotsubo cardiomyopathy (TTC) is characterized by transient regional systolic dysfunction of the left ventricle in the absence of angiographic evidence of obstructive coronary artery disease or acute plaque rupture. In most cases of takotsubo cardiomyopathy, the regional wall motion abnormality extends beyond the area perfused by a single epicardial coronary artery. It mimics acute coronary syndrome and shows female preponderance.

Since the original description of Takotsubo cardiomyopathy showing apical ballooning due to apical akinesis or hypo kinesis with preserved or hyper contractile basal segments (the classic or apical type), three other patterns of left ventricular involvement have been described. These are the inverted (reverse) type, the mid - ventricular type and the localized type. Although the clinical presentation, outcome and management are mostly similar between the groups, patients with inverted TTC tend to be younger than those with other types of TTC. A triggering stress is usually present in patients with classic TTC, but almost always present in patients with the inverted type of TTC. Patients with the inverted TTC tend to have lower prevalence of dyspnea, pulmonary edema, cardiogenic shock, T -wave inversion and acute reversible mitral regurgitation but significantly higher levels of creatine kinase MB fraction (CK-MB) and troponins compared to classic TCC.

TTC may develop in various stressful situations. Awareness of the condition is important for its early detection and treatment and also for differentiating it from acute myocardial infarction.

ABBREVIATIONS

TTC: Takotsubo Cardiomyopathy; MR: Mitral Regurgitation; LV: Left Ventricle; ECG: Electrocardiogram

INTRODUCTION

Takotsubo cardiomyopathy (TTC) is characterized by acute, reversible left ventricular dysfunction in the absence of significant angiographic coronary stenoses, usually provoked by an episode of emotional or physical stress. The condition was first described in the Japanese population by Sato et al., [1]. It was termed the 'Tako Tsubo syndrome' as the left ventriculogram resemble an 'octopus trap' with a balloon like bottom and a narrow neck. Various other terms have been coined for the condition, such as stress - induced cardiomyopathy, apical ballooning syndrome or broken - heart syndrome.

Presentation

Takotsubo cardiomyopathy mimics acute coronary syndrome. It presents with chest pain, T - wave and ST - segment changes on ECG, elevation of cardiac biomarkers and left ventricular regional wall motion abnormalities. Heart failure or hemodynamic instability may be present. There is a marked predilection for females. It is more common in post - menopausal women, although it may occur in the younger age group. An emotional or physical stressor is often but not always present. It has been reported in stressful situations such as following anti - depressant overdose, general anaesthesia, road traffic accident, attempted suicidal hanging, anaphylactic shock and also in association with pheochromocytoma. It may also develop within the first few days after an acute cerebral event such as acute ischemic stroke, subarachnoid bleed and epileptic seizure, particularly in women with insular or posterior fossa lesions [2].

Variants

Four patterns of left ventricular involvement have been described. These are the classic type, the inverted (reverse) type, the mid - ventricular type and the localized type. In a study by Ramaraj R et al., [3], the relative frequencies of classic, inverted and mid - cavitary types of TTC were found to be 67%, 23% and 10% respectively. Although the classic pattern with apical left ventricular ballooning was originally described, from which the name Takostubo cardiomyopathy or Apical Ballooning Syndrome were derived, the inverted variant is being increasingly recognized. In comparison to the other variants, inverted TTC is

more common in younger age group and more often precipitated by physical or emotional stress.

Echocardiography

Wall motion abnormalities may occur beyond the distribution of any single coronary artery. The type of TTC depends on the location of the wall motion abnormality, as detected by ventriculography or echocardiography. In the classic variety, the apical segment (with or without the mid - ventricular segment) is akinetic or dyskinetic with hyper contractile basal segments (Figure 1). In the inverted variety, basal segments are hypokinetic with preserved contractility or hyperkinesis of the mid - ventricular and apical segment. In the mid - cavitary type, hypokinesis is restricted to the mid - ventricle with relative sparing of the apex. A rare localized (focal) variant is characterized by dysfunction of an isolated segment (most commonly the anterolateral segment) of the left ventricle.

A higher prevalence of acute MR is seen in classic TTC, possibly due to the altered spatial relationship between mitral leaflets and subvalvular apparatus resulting from apical ballooning [4]. Functional MR may be an important contributory factor in acute heart failure in patients with apical or mid - TTC. Systolic anterior motion (SAM) occurs in some of the patients with apical or mid - TTC and may contribute to the observed MR during acute phase of TTC [5,6]. The dynamic left ventricular outflow tract obstruction also may be partly responsible for the hemodynamic instability sometimes seen in patients with classic TTC [7,8].

Severe left ventricular dysfunction is usually present on admission but rapidly resolves in two to four weeks. Initial left ventricular ejection fraction (LVEF) may be lower in inverted TTC compared with the other types, but likely to recover earlier [3].

Electrocardiography

Prolonged QTc interval, prolonged PR interval, ST - elevation, ST depression, deep symmetric T - wave inversion and pathologic Q waves may be present (Figure 2). QTc interval may normalize within one or two days, whereas the T-wave inversion resolves
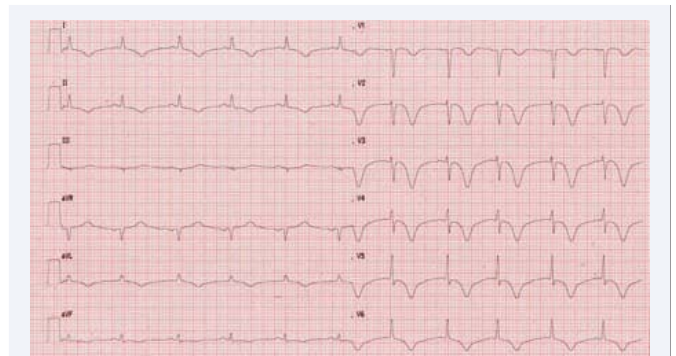

Figure 1 Takotsubo cardiomyopathy, classical type.

Figure 2 ECG in Takotsubo cardiomyopathy. Diffuse T inversion and increased QTc interval.

more slowly and often only partially. Pre cordial Q waves typically resolves before hospital discharge, with restoration of normal R-wave progression. Lower prevalence of T-wave inversion was seen in the inverted TTC group compared to the other groups [4].

Other imaging studies

Reversible myocardial ischemia is seen on myocardial perfusion imaging (SPECT). Cardiac magnetic resonance imaging confirms the pattern and degree of left ventricular dysfunction seen on echocardiography. No evidence of myocardial necrosis is usually seen on contrast - enhanced imaging. Positron emission tomography identifies a discrepancy between normal perfusion and reduced glucose utilization in the dysfunctional regions (inverse flow metabolism mismatch).

Endomyocardial biopsy

Common findings on endomyocardial biopsy are interstitial infiltrates consisting primarily of mononuclear lymphocytes and macrophages, and contraction bands without myocyte necrosis. Rarely, an extensive inflammatory lymphocytic infiltrate and multiple foci of contraction - band myocyte necrosis may be found [9].

Biochemical changes

Patients with TTC have higher plasma levels of catecholamines than that observed in patients with Killip class III myocardial infarction [9]. Plasma levels of metanephrine and normetanephrine are also proportionately increased among patients with TTC. Higher levels of cardiac troponins and cardiac enzymes are found in the inverted variant compared to the other patterns, perhaps because of the larger ventricular mass involved in inverted takotsubo compared to apical form. However, natriuretic peptides (NT-proBNP levels) are more elevated in apical and mid ventricular patterns, reflective of the more severe symptoms and the higher NYHA functional class. Increased wall stress due to dynamic outflow tract obstruction may be responsible for producing higher levels of NT-proBNP in patients with apical or mid-TTC [4,10].

Mechanism

Activation of sympathetic and adrenomedullary hormonal systems due to emotional or physical stress resulting in 'adrenergic storm' have been suggested as the central mechanism
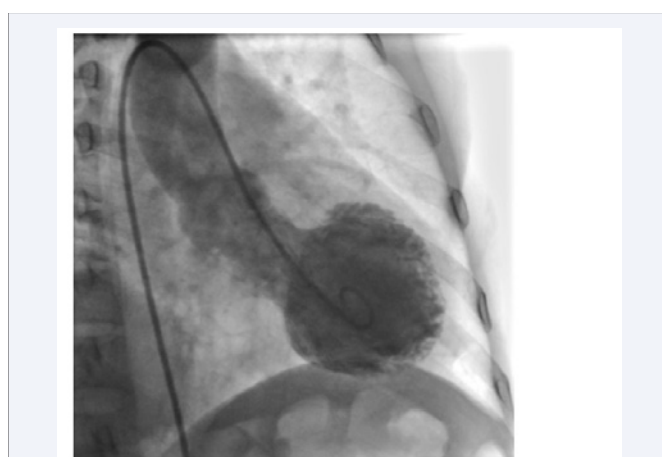
for the occurrence of TTC. The relation between the adrenergic storm and the observed myocardial stunning is however not clear. One possible mechanism is increased sympathetic tone from mental stress causing epicardial coronary artery spasm in patients without coronary artery disease [11]. In an angiographic study of patients with takotsubo cardiomyopathy, 70 percent had coronary spasm in response to provocative maneuvers, and electrocardiographic evidence of ST - segment elevation was common at presentation [12]. An alternative possibility is sympathetically mediated microcirculatory dysfunction (micro vascular spasm) causing abnormal coronary flow in the absence of obstructive disease [13] A third possible mechanism of catecholamine - mediated myocardial stunning is direct myocyte injury. Cyclic AMP mediated calcium overload, [14] interference with cellular sodium and calcium transporters by oxygen - derived free radicals [15] are some of the plausible mechanisms of myocyte injury.

The observed preponderance of women with TTC suggests a biologic susceptibility to stress - related myocardial dysfunction, although the basis of this predisposition is unknown [8]. The reason for the distribution of myocardial dysfunction in TTC is not yet well understood. Distribution, density, and sensitivity of adrenergic receptors may play an important role. Areas with a higher density of adrenergic receptors may determine the areas of hypokinesis. Adrenoreceptor density is highest in the apex compared with the base in postmenopausal women, which may explain the occurrence of the apical variant in older women [16,17]. Ramaraj et al., hypothesized that the presentation of inverted TTC at a younger age may be due to the abundance of adrenoreceptors at the base compared to the apex at a younger age [3]. Possibly, the differences in the location or amount of adrenoreceptor with ageing may affect different ballooning patterns of TTC.

Patients with takotsubo cardiomyopathy are more likely to present with psychiatric and neurologic disorders than are patients with an acute coronary syndrome. This suggests a potential link between neuropsychiatric disorders and takotsubo cardiomyopathy. The coronary microcirculation is innervated by neurons that originate in the brain stem and mediate vasoconstriction, which supports the concept that myocardial stunning due to micro vascular dysfunction in patients with takotsubo cardiomyopathy may be of neurogenic in origin [18].

Takotsubo cardiomyopathy may be can be classified as either primary or secondary Takotsubo syndrome. In primary Takotsubo syndrome, the acute cardiac symptoms are the primary reason for seeking medical care. Such patients may or may not have clearly identifiable stressful triggers. Potential co - existing medical conditions may be the predisposing risk factors but are not the primary cause of the catecholamine rise. On the other hand, a substantial proportion of cases occur in patients already hospitalized for another medical, surgical, anaesthetic, obstetric, or psychiatric condition. In these patients, sudden activation of the sympathetic nervous system precipitates an acute Takotsubo syndrome as a complication of the primary condition or its treatment. Such cases are classified as secondary Takotsubo syndrome. Their management should focus not only on the Takotsubo syndrome and its cardiac complications but also on the condition that triggered the syndrome [19].

Several studies analyzing the role of genetic polymorphisms potentially involved in the pathogenesis of TTC have been published, the most important of which concern those affecting adrenergic receptors located on cell membranes. These reports suggest the interesting possibility that the susceptibility to TCM in individuals may be partially related to genetic factors [20,21].

Diagnosis

In the absence of critical coronary arterial disease, the diagnosis of TTC should be suspected when the history taking reveals that cardiac symptoms were precipitated by intense emotional stress and when the left ventricular dysfunction is not limited to any single coronary artery territory, with minimal elevation of cardiac enzymes despite the presence of large regions of focal akinesis in the myocardium. Development of a markedly prolonged QT interval with deep T-wave inversion on electrocardiography and rapidly improving cardiac contractility on serial echocardiography strengthen the clinical suspicion. The Mayo Clinic criteria [22] are widely used for the diagnosis of Takotsubo cardiomyopathy. These are a) transient left ventricular systolic dysfunction (hypokinesia, akinesia, or dyskinesia) extending beyond a single epicardial coronary distribution; rare exceptions are the focal (within one coronary distribution) type; b) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. If coronary stenosis is present, the wall motion abnormalities should not be limited to the distribution of the diseased coronary artery; c) new electrocardiographic abnormalities or elevation in cardiac troponin; d) absence of pheochromocytoma or myocarditis. All the four criteria are required for confirmation of the diagnosis.

Clinical outcome and prognosis

TTC accounts for about 1.2% of patients with troponin - positive acute coronary syndrome [23]. Despite subtle differences in presentation among the groups, the outcome and management are mostly similar. Most cases recover spontaneously; although in - hospital mortality risk of 0 - 8% has been reported [22]. Ventricular arrhythmia may occur, particularly torsades de pointes associated with takotsubo related QT prolongation. Rare complications are irreversible cardiogenic shock, LV rupture, embolisation of LV thrombi and complete heart block. Long - term prognosis is good. Recurrence is uncommon (2% to 5%) and may occur in a LV segment different from the one exhibiting the initial manifestation [24]. Patients with severe TTC at index admission were noted to have more recurrences [25].

Treatment

The treatment of TTC, beyond standard supportive care for congestive heart failure with diuretics and vasodilators, remains largely empirical. As catecholamine release is implicated in stress - induced myocardial stunning, beta-agonists should be avoided. In patients with hypotension, vasopressors should be used with caution to avoid exacerbation of LV outflow obstruction. Mechanical circulatory support may be used in patients with severe hemodynamic compromise. Beta blockers may be used in the presence of LV outflow gradient. A reduction in the gradient between the apex of the left ventricle and outflow has been observed with intravenous propranolol [26]. QT-prolonging medications should be avoided. TTC is a self - limited disorder

with rapid resolution of symptoms and LV dysfunction. Dyskinetic segments recover in days; therefore oral anticoagulation is not necessary. Although there may be a place for beta - blockers or angiotensin - converting enzyme inhibitors in prevention of TTC, it is seldom used as recurrences are rare.

CONCLUSION

The diagnosis of TTC should be suspected when the history taking reveals that cardiac symptoms are precipitated by intense emotional or physical stress and no critical coronary disease is present. The observed left ventricular dysfunction is not limited to any single coronary artery territory and improves rapidly on serial echocardiography.

Takotsubo Cardiomyopathy has been reported in many stressful situations. It is important for the clinician to be aware of the presence of TTC in a clinically diverse scenario so that it could be detected and treated early. It is also important to differentiate TTC from acute myocardial infarction, which has worse short and long - term prognosis than TTC. Misdiagnosing TTC for myocardial infarction could have adverse consequences for the young patient, affecting his lifestyle and livelihood.

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