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Review

Takotsubo cardiomyopathy systematic review: Pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy

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ABSTRACT

Takotsubo cardiomyopathy (TTC) is characterized by transient left ventricular apical ballooning with the absence of coronary occlusion, which typically occurs in older women after emotional or physical stress. The pathophysiology of TTC is not well established, though several possible causes such as catecholamine cardiotoxicity, metabolic disturbance, coronary microvascular impairment and multivessel epicardial coronary artery spasm have been proposed. A number of diagnostic criteria have been suggested in the world and not unified as single, but the most common accepted one is Mayo Clinic proposed criteria. Since the clinical presentation of TTC is usually similar to acute coronary syndrome, differential diagnosis is essential to exclude other diseases and also for its treatment. Imaging modality including echocardiogram, angio CT and cardiac MRI, and lab tests for catecholamine, troponin T, creatine kinase MB and B-type natriuretic peptide can be useful to differentiate TTC from other diseases. Prognosis is generally favorable and in-hospital mortality is from 0% to within 10%.

1. Definition

In 1990, takotsubo cardiomyopathy (TTC) was initially reported by Sato et al. in Japan [1,2]. "Takotsubo" is named after Japanese octopus trap, whose shape is similar to the appearance of the patient's left ventricle in systole. (Fig. 1) TTC is described as a transient reversible cardiomyopathy, which typically occurs in older women after emotional or physical stress [3–5]. The presenting features of TTC are similar to those of myocardial ischemia after acute plaque rupture, but the characteristic distinctions are regional wall motion abnormalities that extend beyond a single coronary vascular bed and the absence of epicardial coronary occlusion [6,7]. Over more than next 2 decades after the first report, this condition became widely recognized in Japan and subsequently gained international recognition [4,8]. In the process, this condition acquired multiplicity of individual descriptive names such as apical ballooning syndrome, acute stress cardiomyopathy and broken heart syndrome [9].

TTC is defined as below in Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy [10].

> "*Takotsubo (ampulla) cardiomyopathy is a disease exhibiting an acute left ventricular apical ballooning of unknown cause. In this disease, the left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap). There is nearly complete resolution of the apical akinesis in the majority of the patients within a month. The contraction abnormality occurs mainly in the left ventricle, but involvement of the right ventricle is observed in some cases. A dynamic obstruction of the left ventricular outflow tract (pressure gradient difference, acceleration of blood flow, or systolic cardiac murmurs) is also observed.Note: There are patients, such as cerebrovascular patients, who have an apical systolic ballooning similar to that in takotsubo cardiomyopathy, but with a known cause. Such patients are diagnosed as "cerebrovascular disease with takotsubo-like myocardial dysfunction" and are differentiated from idiopathic cases.*"

2. Epidemiology

One study in the United States results show there were 6837 patients diagnosed with TTC in the Nationwide Inpatient Sample database of 2008 and women were found to have higher odds of developing TTC (odd ratio 8.8). In absolute number of admissions, 6178 (90.4%) were women, and 660 (9.6%) were men. Patients aged from 18 to 34 were 127 (1.9%), patients aged from 35 to 49 were 581 (8.5%), patients aged from 50 to 64 were 1975 (28.9%), patients aged from 65 to 79 were 2952 (43.2%), and patients ≥ 80 years old were 1202 (17.6%). Women > 55 years old had 4.8 times higher odds for developing TTC when compared with women < 55 years old[11].

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Fig. 1. Takotsubo.

3. Pathophysiology

The pathophysiology of TTC is not well established, but several possible theories on mechanisms with this disorder have been proposed [5,12,13].

3.1. Catecholamine cardiotoxicity

A number of features of stress cardiomyopathy suggest that TTC may be caused by catecholamine-induced microvascular spasm or by direct catecholamine-associated myocardial toxicity. Wittstein et al. reported that plasma levels of catecholamines (i.e., epinephrine, norepinephrine, and dopamine) among patients with TTC were 2 to 3 times the values among patients with myocardial infarction [5]. Akashi et al. proposed a possible mechanism for the pathogenesis of this catecholamine levels [12]. In response to sudden, unexpected, severe emotional distress, neurons of the central autonomic network expressing estrogen receptors are activated, followed by marked increases in sympathetic neuronal and adrenomedullary hormonal outflows. Epinephrine released from the adrenal medulla and norepinephrine from cardiac and extracardiac sympathetic nerves reach adrenoceptors in the blood vessels and heart. Contraction of the resistance vessels rapidly increases systemic blood pressure and cardiac afterload. Meanwhile, within the heart, high circulating levels of norepinephrine and epinephrine, along with increased release and decreased reuptake by sympathetic nerves, induce catecholamine toxicity in the cardiomyocytes via occupation of adrenoceptors. In postmenopausal women, the loss of estrogen effects exaggerates the responses of central neurons and cardiac cells and possibly attenuates the production of cardioprotective substances.

The myocardial histological changes in TTC strikingly resemble those seen in catecholamine cardiotoxicity in both animals and humans [12,14–16]. High plasma catecholamine levels in patients with pheochromocytoma are well known to induce reversible cardiomyopathy [14]. Recent evidences suggest that the pathophysiology of TTC may lie in changes in β-adrenergic receptor (AR) signaling [17–19]. High levels of circulating epinephrine trigger a switch in intracellular signal trafficking, from G_s protein to G_i protein signaling through the β_2AR. This change in signaling is negatively inotropic, and the effect is greatest at the apical myocardium, in which the density of β-adrenoceptors is highest [17]. Biased agonism of epinephrine for β_2AR-G_s at low concentrations and for G_i at high concentrations underpins the acute apical cardiodepression observed in TTC, with an apical-basal gradient in β_2ARs explaining the differential regional responses. This epinephrine-specific β_2AR-G_i signaling may have evolved as a cardioprotective strategy to limit catecholamine-induced myocardial toxicity during acute stress [19].

Another study demonstrated elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload [5,20]. Catecholamines are also a potential source of oxygen-derived free radicals, which can interfere with sodium and calcium transporters, possibly resulting in myocyte dysfunction through increased transsarcolemmal calcium influx and cellular calcium overload [21]. The myocardial histological changes, which differ from those in ischemic cardiac necrosis, include contraction band necrosis, neutrophil infiltration, and fibrosis. These findings probably reflect consequences of high intracellular concentrations of Ca^{2+}, and it has been proposed that Ca^{2+} overload in myocardial cells produces the ventricular dysfunction in catecholamine cardiotoxicity [14]. Contraction-band necrosis has been described in clinical states of catecholamine excess such as pheochromocytoma and subarachnoid hemorrhage [22,23].

3.2. Metabolic disturbance

Metabolic changes in stunned myocardium, including alterations in glucose and fatty acid uptake, have been studied [24–29]. One theory is the possible existence of myocardial stunning secondary to a primary metabolic disturbance characterized by dysfunctional metabolism of cardiomyocytes, affecting either glucose or fatty acid metabolism, or due to mitochondrial disturbances [24–26,30]. In an experimental dog model, Di Carli et al. showed a prolonged reduction of F-18 FDG uptake in stunned myocardium subjected to multiple cycles of ischemia and reperfusion—so-called repetitive stunning [26]. Perrone-Filardi et al. first described reverse perfusion-glucose metabolism mismatch (reduced F-18 FDG uptake with relatively normal resting blood flow) in patients with repetitive stunning [27]. The precise mechanism for this reduced glucose uptake in stunned myocardium remains unknown.

One study suggested that myocardial fatty acid metabolism is more severely impaired than myocardial perfusion, in parallel with an apical akinetic region during the early phase, and that impaired multivessel coronary microcirculation is involved, at least in part, in takotsubo-like LV dysfunction [30].

3.3. Coronary microvascular impairment

Microvascular dysfunction includes an abnormality in endothelial dependent vasodilation, resulting in excessive vasoconstriction leading to coronary vasculature spasm. Martin et al. reported that patients with TTC have abnormal vasoreactivity and sympathetic responses to acute mental stress testing in the laboratory setting. This is manifested as impaired endothelial dependent dilation, excessive vasoconstriction, and catecholamine release [31].

Since abnormal left ventricular wall motion occurs in a relatively large area of the apical myocardium in patients with TTC and because the abnormalities are dynamic rather than fixed, disturbances in the coronary microcirculation might occur. In addition, by using the TIMI frame count method, Kurisu et al. demonstrated that coronary blood flow was severely impaired in all coronary arteries, in agreement with LV asynergy immediately after onset, and that coronary blood flow improved but the impairment was sustained even after resolution of takotsubo-like LV dysfunction [30]. Yoshida et al. reported impaired coronary perfusion and severe myocardial metabolic abnormalities in patients with TTC on the basis of results of thallium-201 myocardial single-photon emission computed tomography and ^{18}F-fluorodeoxyglucose myocardial positron emission tomography (PET) [12,32]. Elesber et al. demonstrated the presence of microvascular dysfunction in a significant proportion of patients with this syndrome and noted a correlation between microvascular dysfunction and the severity of myonecrosis and ECG abnormalities [12,33].

3.4. Multivessel epicardial coronary artery spasm

Reversible ventricular dysfunction might result from epicardial coronary artery spasm and consequently regionally stunned myocardium [12]. Increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease [5,34]. In an angiographic