Review Article

Takotsubo cardiomyopathy or broken heart syndrome: A review article

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Abstract

Stress-induced cardiomyopathy or Takotsubo cardiomyopathy is a recently increasing diagnosed disease showed by transient apical or mid left ventricular dilation and dysfunction. This sign is similar to acute myocardial infarction but without significant coronary artery stenosis and intra coronary clots. On the other hand there are important and essential differences in their management. Consequently, our physicians should know about its pathophysiology, diagnosis and treatment.

KEYWORDS: Stress induced cardiomyopathy, Takotsubo cardiomyopathy, Broken heart syndrome, Apical ballooning syndrome, Ampulla cardiomyopathy.

Figure 1. traditional Japanese octopus trap

Transient left ventricular apical ballooning syndrome also called Takotsubo cardiomyopathy, Stress-induced cardiomyopathy (SICM), Broken heart syndrome and Ampulla cardiomyopathy. It was initially described in Japanese articles in 1990 and has since been diagnosed by transient LV apical hypokinesia without significant coronary artery stenosis in angiography or cardiomyopathy.\textsuperscript{1} The mid-ventricle and apex of the heart, when viewed by echocardiography or catheterization, has a spherical bottle with narrow neck in time of heart systole which resembles the old Japanese octopus trap called “Takotsubo” (Figure 1).\textsuperscript{2} Almost, patients are postmenopausal women with typical or atypical angina referred after an intensive emotional or surgical stressor such as serious environmental stimulations, suddenly loss of one loved him/her, complicated medical diseases, and noncardiac surgery with Electrocardiographic changes and elevation of cardiac biomarkers.\textsuperscript{3} Usually, coronary angiogram doesn’t show stenotic lesions. Transthoracic echocardiography or ventriculography manifest transient apical left ventricular dilation with compensatory increased basal wall motion.\textsuperscript{4} The etiology is unknown; however, several pathologic reasons have been detected.\textsuperscript{5} Initially, left ventricular ejection fraction is low; afterwards it recovers within one month.\textsuperscript{6} SICM is a newly emerging clinical situation that is often under-diagnosed and mimic myocardial infarction with ST elevation, however high clinical suspicion can correctly recognize this transient cardiomyopathy. In order to recognize new aspects of this syndrome in the recent years that weren’t included in previous reviews, we

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searched ISI, PubMed, Cochrane and Scopus indexed papers and we found 214 articles that were directly related to our subject. Those were the database for collection and organization of the best and newly updated information for the present review.

**Epidemiology**

SICM is diagnosed approximately in 1–2% of patients with history, signs and symptoms similar to acute myocardial infarction. Most patients with SICM are postmenopausal women. A systematic review of 14 studies by Gianni et al and Prasad et al showed 89% and 90% female predominance with age range of 58–77 and 58–75 years respectively.

**Etiology**

The etiology of the SICM has not been clearly recognized but Catecholamine induced myocardial stunning in patients face different kinds of stressors is established by serum catecholamine level elevation in more than the 70% of these patients. Strong evidences support this hypothesis. Myocardial scintillography with $^{123}$I-metaiodobenzylguanidine (MIBG) in these patients cleared a decreased uptake of radioactive tracer in several segments of left ventricle, emphasizing a severe adrenalin secretion produced by stress. The large interindividual differences in MIBG of patients with SICM may reflect variable responses to adrenergic stimulation; it may be justified by genetic inheritance at adrenalin synthesis, functions, storage, and elimination that may show an essential role in presentation of SICM in patients. Studies showed the higher density of beta-adrenergic receptors is located in apical heart, so the circulating catecholamine excessively influences this segment which results in apical negative cardiac myocyte inotropy. However, others suggest that the akinetic appearance of this region can be related to the high systolic apical circumferential wall stress.

The reason of high prevalence in postmenopausal women is unknown but a hypothesis has proposed that reduced estrogens and their implications on microvascular system after menopause might be the main cause. Animal studies have shown estrogen attenuates immobility effects of stressors on the myocardium.

Yoshida et al reported that endomyocardial biopsy shows "mixed cellular infiltrates (mononuclear lymphocytes and macrophages) with or without contraction band necrosis or interstitial fibrosis" in these patients, but did not report evidence of viral or bacterial myocarditis on biopsies or in serological studies.

Kleinfeldt et al detected a mutation in gene of FMR1 (alleles with sizes between 40–55 triplet permutations) in the patients with SICM for the first time, also Kumar et al reported a familial apical ballooning in a mother and daughter which may explain why only a minority of postmenopausal women appear to be susceptible.

Finally, subarachnoid hemorrhage, thyrotoxicosis, hypoglycemia, stroke, general anesthesia, dobutamine stress echocardiography, pheochromocytoma, Addison disease, after coronary intervention in a patient with anxiety, radiotherapy, and autoimmune polyendocrine syndrome type II may resemble the pattern of reversible left ventricular dysfunction of Takotsubo syndrome.

Recently, Mansencal et al has described the new form of takotsubo (apical-sparing variant) that is not rare and differs from the typical pattern of takotsubo in mean age (range: 30–32 year), so cardiologists should be aware and recognize this partial pattern.

**Precipitating events**

The provocative events are typically severe emotional or physiological stressors. Emotional stressors were important precipitating events for stress-induced cardiomyopathy in case series report. For this reason, the name "Broken heart syndrome" was coined. Alternatively, physiological stressors can trigger an episode of apical ballooning syndrome, such as a severe medical illness, worsening of a chronic disease (e.g. heart failure), noncardiac surgical procedure, transplantation, brain death and seizure.
Presentation
The most common symptoms are chest pain (two thirds of the patients) and dyspnea similar to those with acute myocardial infarction. Cardiogenic shock may present in patients with severe reduced left ventricular ejection fraction. In ECG, ST-segment elevation is absent in two thirds of patients with SICM. The ECG changes at presentation time do not correlate with the severity of ventricular dysfunction or prognosis. Bybee et al published that the most common ECG finding is QT prolongation and Torsades de pointes was reported in patients with SCIM and QT prolongation. Cardiac troponin are typically moderately elevated in SICM, also brain natriuretic peptide levels has elevated.

Diagnosis
The principal criteria of SICM are: (1) acute emotional/physical stress before presentation with angina pectoris; (2) ischemic abnormalities on the ECG; (3) no significant epicardial coronary arteries stenosis or intracoronary thrombus on angiography (Figure 2A & 2B); (4) apical to mid ventricular ballooning with compensatory basal hyperkinesis on the left ventriculogram or echocardiogram (Figure 3); (5) disproportionately low up to moderate plasma levels of cardiac biomarkers with respect to intensity of ventricular dysfunction and (6) rapid improvement in left ventricular dysfunction and syndrome. Currently, Leurent et al suggest that cardiac Magnetic Resonance Imaging is a very useful tool in the diagnosis and management of SICM.

Treatment
Management of patients with SICM is overall supportive and conservative. We should avoid the administration of thrombolytic agents. Left ventricular depression is treated with diuretics, beta blockers and angiotensin converting enzyme inhibitors. Additionally, beta blockers may block catecholamine excess which is the potential mechanism of SICM. Moreover, beta blockers have an essential role
in reducing left ventricular outflow tract (LVOT) obstruction by decrease basal segment hypercontractility. Tamura et al believe that physicians should avoid administration of catecholamines for patients with SICM, LVOT obstruction and cardiogenic shock. Treatment with β-blockers, with careful observation for hemodynamic status, may be rationale in these patients. In 14 studies, totally 15 (2.5%) patients with left ventricular clot formation was reported over the last decade, therefore treatment with warfarin is recommended to prevent cardioembolic events.

**Prognosis**
The prognosis for SICM is good without management and cardiac function recovers during less than 1 month but, mortality rates are different from 0% to 8%. The left-sided heart failure is most common complication with or without pulmonary edema. Other complications are left ventricular mural clot, systemic or pulmonic embolic events, mitral valve regurgitation, ventricular arrhythmias, cardiogenic shock and maybe left ventricular wall rupture.

**Conclusion**
SICM is an entity of acute heart failure that can mimic acute coronary syndrome and should be considered especially in patients with normal heart. We suggest that special emphasis be placed on awareness and diagnosis of the classical clinical features of SICM, such as old woman presenting with acute chest pain after stressful emotional or physical event. Furthermore, coronary angiography and ventriculography are needed to support SICM diagnosis. Short-term management is needed, however, early intensive care is necessary for patients with left-sided heart failure. Physicians should follow patients by echocardiography for assessment of left ventricular ejection fraction during outpatient periods and emphasize on possible complications of this disease and explain the possible causes lead to SICM for patients and their families.

**Conflict of Interests**
Authors have no conflict of interests.

**Authors’ Contributions**
AG analyzed the findings and wrote the article draft. NS helped in writing the article draft, edited the article and finalized it.

**References**
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