Transient Left Ventricular Apical Ballooning (Takotsubo Cardiomyopathy): Mimicking Acute Coronary Syndrome

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Introduction:

Transient left ventricular apical dyskinesia accompanied by chest pain, mimicking acute coronary syndrome, dynamic reversible ST-T segment abnormalities, minimal myocardial enzymes release disproportionate to the extent of dyskinesia,in the absence of obstructive epicardial coronary artery disease is characteristic of transient left ventricular apical ballooning syndrome.[1] It was first described in the Japanese literature in 1991 by Dote and colleagues, who proposed the term *"Takotsubo cardiomyopathy"*, after a Japanese fishing pot used for trapping octopus, on the basis of the peculiar appearance of a rounded bottom and narrow neck on the end-systolic left ventriculogram (Fig.-1).[2]

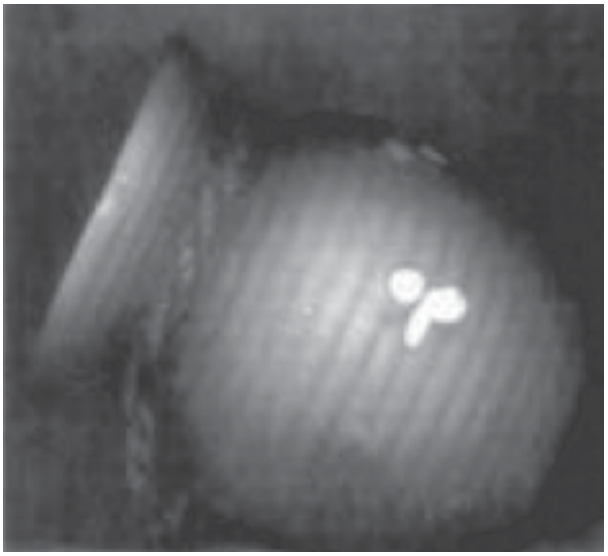

Fig.-1: *"Takotsubo", a Japanese fishing pot used for trapping octopus*

In February 2005, the clinical and neurohumoral features of myocardial stunning due to emotional stress were presented in the *New England Journal of Medicine.*[3] This study referred to the syndrome as "*stress cardiomyopathy*", but the name "*broken heart syndrome*" was also introduced, as several of the patients had presented following the death of a loved one.[4]

This article describes the condition called transient left ventricle apical ballooning syndrome, otherwise known as:

- Takotsubo cardiomyopathy
- Stress cardiomyopathy
- Ampulla cardiomyopathy
- Broken Heart syndrome or
- Transient left ventricular dysfunction

Prevalence and patient Demographics:

Although this syndrome was first recognized in Japan, is now recognized in the non-Asian populations in Europe and North America.[5] The true prevalence is unknown, with retrospective studies, approximately 2% of all patients presenting with chest pain and ST elevation have been found to have this syndrome.[6] Apical ballooning syndrome has been reported in patients with pheochromocytoma, cocaine use and other withdrawal states and has been associated with subarachnoid hemorrhage and head trauma patients.[7,8] Postmenopausal or elderly women represent more than 80% of cases, with a mean age of 62 to 75 years.[5,9]

Diagnosis and clinical features:

Clinical manifestations and morbidity are related to the degree of left ventricular dysfunction with symptom resolution paralleling the course of improvement in systolic function of the left ventricle. Treatment consists of supportive therapy while the dysfunctional LV recovers[6]. All patients experienced a particularly stressful incident, either psychological or physical, within minutes to hours of onset of symptoms.

Common physical, psychological and emotional stressors precipitating left ventricle apical ballooning syndrome are mention below -

- Extreme grief
- Unexpected death in the family
- Gambling and financial losses
- Extreme fear

• Devastating medical diagnosis
• Car accidents
• Public speaking
• Earthquakes
• Acute physical trauma
• Robbery
• Major surgical procedures

Conventional coronary risk factors such as smoking, hypertension, and hyperlipidemia did not differ from those in the general population.

Chest pain is the most common presenting symptom. Up to 90% of patients with apical ballooning syndrome report chest pain as their primary complaint following excessive stress, although some report dyspnea, palpitations, syncope or nausea.[10,11,12] As with acute myocardial infarction, features of high circulating adrenaline levels (such as diaphoresis and peripheral shutdown) are also common.

It may be complicated by:

- Left heart failure with and without pulmonary edema
- Cardiogenic shock
- Dynamic intraventricular obstruction with left ventricular intracavitary pressure gradient generation
- Left ventricular mural thrombus formation
- Left ventricular free-wall rupture
- Life threatening arrhythmia[13]
- Mitral insufficiency
- Cardiac arrest / death[5]

Investigations:

ECG changes most commonly demonstrate ST-segment elevation in the precordial leads (in 70% of cases), and there is less inferior reciprocal ST-segment depression than is typically seen with an anterior ST-segment elevation MI. There may be diffuse T-wave inversions in the anterolateral leads or serial evolution of T-wave inversions and 10% of patients develop Q-waves (most frequently in leads V2-V4). It may be associated with marked prolonged QT-interval. The QT interval prolongation usually improves within a couple of days, but the T-wave abnormalities can take days, weeks, or even months to normalize.

Most patients with apical ballooning syndrome have mildly elevated cardiac enzymes (including creatine phosphokinase, Troponin I, and T levels) at the time of presentation. These enzyme elevations, however, are much lower than those typically observed with acute myocardial infarction.[3,14]

Echocardiography typically shows a contractile pattern of apical ballooning with a reduced left ventricular ejection fraction.

The diagnosis of apical ballooning syndrome depends on coronary angiography. As well as absence of a culprit lesion, the left ventriculogram frequently shows the characteristic akinesis or dense hypokinesis of the apical and mid-ventricular segments (the distal half of the anterior and inferior walls) with sparing of the basal segments, which cannot be explained by the occlusion of a single vascular territory (ie, the left anterior descending artery does not extend beyond the apex to supply the distal half of the inferior wall). The vast majority of patients have either normal coronary arteries or mild luminal irregularities, and significant luminal stenoses have been rarely reported.[3,10,11]

Cardiac MRI identified abnormal regional wall motion beyond any single vascular territory in 95% of patients. Gadolinium contrast enhancement failed to show evidence for increased myocardial edema; furthermore, delayed hyperenhancement indicative of myocardial necrosis was absent.[3]

Endomyocardial biopsy, performed in a limited number of cases, has uniformly failed to demonstrate histopathological evidence for myocarditis.[15,16]

According to Mayo clinic, all of the following *four* criteria must be met[5]:

1. Transient akinesis or dyskinesis of the left ventricular apical and mid ventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities (ST segment elevation or T wave inversion).
4. Absence of:
   - Recent significant head trauma
   - Intracranial bleeding
   - Pheochromacytoma
   - Obstructive epicardial coronary artery disease
   - Myocarditis
   - Hypertrophic cardiomyopathy

Mechanism of injury:

The underlying mechanism of transient left ventricular apical ballooning or Takotsubo cardiomyopathy remains

unknown. The dramatic improvement of systolic left ventricular function over a few days or weeks argues for a "functional" cause rather than necrosis caused by a "classic" acute myocardial infarction.

The characteristic ballooning of the LV apex is felt to be caused by transient myocardial injury or stunning of the distal apical myocardium, with compensatory hyperkinetic contraction in the mid and basal LV regions.[4,5,7] However, the nature and extent of the ballooning of the LV apical segments has been difficult to explain solely on involvement of the LAD coronary artery.[4,6,7,17] Multiple vessel epicardial coronary spasm or diffuse microvascular spasm, calcium overload with direct myocyte damage and abnormal fatty acid metabolism with prolonged myocardial stunning have all been proposed as possible mechanisms.[6,17]

The most popular hypothesis in the development of apical ballooning syndrome is myocardial stunning due to an epicardial coronary artery spasm. One of the important findings in apical ballooning syndrome is that most of patients have increased catecholamine levels after a stressful event. A possible mechanism underlying the association between mental stress, sympathetic stimulation, and myocardial stunning is ischemia resulting from epicardial coronary arterial spasm.[3] Angiographic study has revealed that 70% of affected patients have coronary spasm.[15] Wittstein et al. have demonstrated supraphysiologic catecholamine levels in patients with transient left ventricular dysfunction after emotional stress.

Patients with stress induced cardiomyopathy have markedly elevated levels of plasma catecholamines and stress neuropeptides at the time of admission. Clark and his colleagues have shown that in humans, intracoronary injection of neuropeptide Y causes profound distal-vessel constriction, manifested as extremely slow flow, and massive ischemia.[18]

Catecholamine-mediated myocardial stunning may be a direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic adenosine monophosphate (AMP) mediated calcium overload and are also a potential source of oxygen-derived free radicals that may cause myocyte injury.[19]

It is unclear why the apex of the heart is affected and the basal segments are spared. However, this may be partly explained by increased adrenergic receptor density in cardiac apical segments or increased apical myocardial responsiveness to adrenergic stimulation[20].In addition, patients with the syndrome exhibit a pronounced abnormality in apical myocardial fatty acid metabolism that is out of proportion to apical perfusion abnormalities[21]. This impairment of regional myocardial fatty acid metabolism demonstrates that myocardial "stunning" appears to be present in the distribution of the wall-motion abnormalities seen in this syndrome. The left ventricular apex does not have the usual 3-layered myocardial structure that is present in other regions of the ventricle; the apex behaves as a border zone when myocardial blood flow is impaired, and the apical region appears to more easily lose its elasticity after excessive expansion.[20]

Another possible mechanism is microvascular spasm or microcirculatory dysfunction; abnormal coronary flow is possible in the absence of obstructive disease in patients with stress-related myocardial dysfunction.[22] Using a Doppler flow wire at the time of coronary angiography, Kume et al. demonstrated a significant reduction in coronary flow reserve and flow velocity in patients with apical ballooning syndrome.[23]

The explanation for the strong female predominance with the syndrome is also unclear. However, the explanation may be related to postmenopausal alterations of endothelial function in response to reduced estrogen levels[24] and microcirculatory vasomotor reactivity in response to catecholamine-mediated stimuli.[25] Merli et al. have clarified these questions. Elderly women usually develop abnormal basal/mid-septal thickening known as sigmoid septum, which can produce high intraventricular gradients. In the presence of raised catecholamine levels due to a stressful event, severe transient mid ventricular obstruction, which divides the left ventricle into functionally different two cavities, apical chamber with high pressure and the proximal chamber with normal pressure, occurs in these patients. The combination of increased wall stress in the apical region and supraphysiologic catecholamine levels in plasma leads to subendocardial ischemia in the apex and myocardial stunning not related to a single coronary artery territory. When level of catecholamines decrease, reversal of these events occurs and myocardial stunning due to ischemia resolves.[26]

Pison L et al. reported two sisters were admitted to hospital with apical ballooning of the left ventricle. The occurrence of this syndrome in two sisters may point to a genetic aetiology.[27]

Lastly, there is some evidence that apical ballooning syndrome may be neurally mediated. Similar transient wall motion abnormalities are seen frequently in patients with subarachnoid haemorrhage, in whom the wall motion abnormality is thought to be due to neurally mediated

localised microvascular ischaemia. Histopathological features of the myocardium are very similar, with contraction band necrosis,[28] and can be prevented by cardiac sympathectomy.[29]

Recovery of LV systolic function:

Rapid and complete recovery of LV systolic function is one of the hallmarks of this syndrome. Despite the presence of extensive wall motion abnormalities at the time of admission, complete recovery of systolic function has been reported in all series to date[6]. Significant improvement in systolic function frequently occurs during the first week following the initial presentation. Patients should be hospitalized for several days and have a repeat echocardiogram prior to discharge. The anterior wall frequently takes the longest to fully recover, but the majority of patients have completely normal LV systolic function by the end of the third week. If systolic function has not normalized after 4 to 6 weeks in a patient suspected of having the left ventricle apical ballooning syndrome, the diagnosis should be reconsidered.

Treatment:

For hemodynamically stable patients, diuretics are used to treat congestion, and angiotensin-converting enzyme (ACE) inhibitors, CCB (Diltiazem, Verapamil) and beta-blockers are frequently used until recovery of LV function. Beta adrenergic blockers are also useful in suppressing ventricular arrhythmia. There are simply no data at this time to support that chronic use of ACE inhibitors and beta-blockers in these patients improves survival or helps to prevent recurrence. Unless there is a contraindication, anticoagulation should also be considered during the first few days until apical contractility begins to improve.[4]

Treatment generally is supportive when hemodynamically unstable. In a small proportion (1%–5%) there is significant haemodynamic compromise requiring inotropic therapy, vasopressor support, intra-aortic balloon counter pulsation and mechanical ventilation.

Prognosis and recurrence:

In general, the prognosis of patients with this condition is quite favorable. The in-hospital mortality rate of cases reported in the literature is only 1.1%.[6] Interestingly, physical stress has higher mortality rates when compared to patients presenting with emotional stress.[17] 3.5% patients experience a second recurrence of the disorder.[4]

Summary of Apical Ballooning Syndrome:

1. It is an important differential diagnosis of acute coronary syndrome
2. Postmenopausal females are more affected
3. Associated with acute significant stressor (physical or emotional stress)
4. Positive troponin with elevated CK, with or without typical ECG features of acute MI
5. Absence of significant coronary artery disease on angiography
6. Develops early characteristic LV apical ballooning with compensatory hyperkinetic basal and mid LV motion giving rise to appearance resembling a takotsubo.
7. Patient may be significantly haemodynamically compromised,
8. LV dysfunction reversible with good long term prognosis
9. Currently, no specific preventive therapy has been proven to be effective.

Conclusion:

Although rarely occurs, the apical ballooning syndrome must be considered by cardiologists and emergency department physicians in their differential diagnosis of the patient who presents with a suspected acute coronary syndrome. It should be considered especially when the extent of ischemic ECG abnormalities do not correlate with the enzymatic evidence for myocardial necrosis and coronary angiography confirms noncritical atherosclerotic disease. Early recognition and aggressive treatment with pharmacological agents and/or mechanical supports are indicated, because complete recovery of normal systolic function can be expected for these patients by the time of hospital discharge. The actual pathphysiology and effective long-term management of this syndrome remains to be defined.

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