

## Takotsubo Cardiomyopathy: An Insight into a Rare Disease

### Introduction

Takotsubo cardiomyopathy is a well-established clinical entity that becomes an important differential diagnosis in patients who present with acute coronary syndrome, especially postmenopausal women. The clinical suspicion of this condition is extremely important for primary care physicians, particularly those practicing at centers with no cardiac catheterization facilities, as this disease can be mistaken for an acute myocardial infarction and patients may be subjected to hazards of thrombolytic therapy. This syndrome has many other synonyms such as stress or ampulla cardiomyopathy, apical ballooning syndrome (ABS) and broken heart syndrome. This syndrome is characterized by depressed wall motion of the apical segments of the left ventricle with sparing of the basal segments leading to distinguished configuration of octopus trap during systole on cardiac imaging.

### Clinical Features

#### *Signs and symptoms*

The majority of patients are postmenopausal women with a recent emotional or physical stress in their life such as loss of a relative, financial strain or diagnosis of a lethal medical illness. The symptoms of ABS are very similar to those experienced by patients with acute coronary syndrome. The most common symptom is chest pain; however, a small subset of patients can have dyspnea as their presenting complaint. Upon examination these patients are mostly hemodynamically stable but rare cases of cardiogenic shock and ventricular failure with hypotension have been reported in the literature. In a case series from Japan, 67% of the patients had chest symptoms at presentation and 15% presented with cardiogenic shock.<sup>1</sup>

### Laboratory Findings

#### *EKG findings*

The EKG findings can be varied in a patient with ABS. It can range from marked diffuse ST elevation (very similar to acute ST elevation myocardial infarction) to completely normal EKG. In those patients who have diffuse ST elevation at the time of initial presentation, the EKG shows complete resolution of ST elevation, with T wave inversion over the next 48–72 hours. Other findings seen on EKG are ST-segment depression, QT interval prolongation and pathological Q waves.

#### *Cardiac markers*

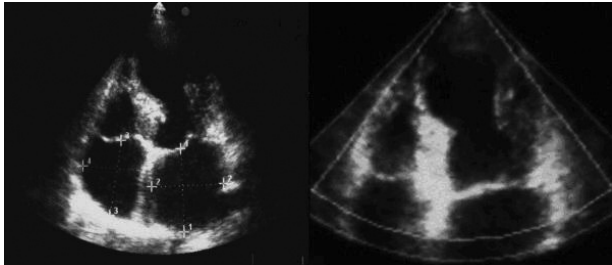
The cardiac enzymes (CPK-MB and troponins) are often elevated in patients with stress induced cardiomyopathy but the elevation is only mild to moderate. In a systematic review of 14 case studies the cardiac markers were elevated in 86.2% of the patients.<sup>2</sup>

#### *Imaging studies*

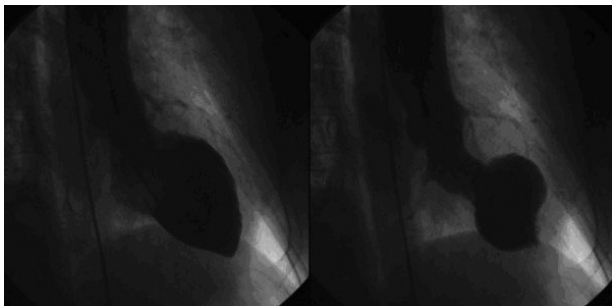
Left ventriculography and echocardiography show the typical akinesis of the apical two-third portion of the left ventricle with depressed ejection fraction and apical ballooning in systole. In a systematic review of case series the mean ejection fraction in these patients was 20–49%. The ejection fraction improved to normal in the majority of these patients. Some patients have evidence of dynamic left ventricular outflow tract (LVOT) obstruction with systolic anterior motion of the mitral valve similar to hypertrophic cardiomyopathy. Nuclear imaging of the heart shows reversible perfusion defects and the magnetic resonance imaging shows wall motion abnormalities in the left apical and mid ventricular wall not conforming to any single coronary artery. Though Takotsubo cardiomyopathy is primarily a disease of the left ventricle, right ventricular

dysfunction has also been reported in some patients. In a case series of 32 patients about 26% had evidence of right ventricular involvement on cardiac magnetic resonance imaging.<sup>2,3</sup>

**Figure 1.** Transthoracic echocardiogram on admission. Apical 4 chamber view showing apical ballooning of the left ventricle (left). Zoom detail of the same view (right).



**Figure 2.** Left ventriculograms. Diastolic (left) and systolic (right) morphology of the left ventricle with the typical appearance of apical ballooning in systole.



#### Coronary angiography

The epicardial coronary arteries do not show any e/o critical obstructive lesions but there can be diffuse coronary vessel spasm due to catecholamine surge resulting from stress. Abnormalities of the coronary microcirculation are quite common in patients with stress induced cardiomyopathy and may be the cause of transient myocardial stunning seen in these patients.

#### Proposed Diagnostic Criteria for Takotsubo Cardiomyopathy

Mayo Clinic criteria (all four must be met):<sup>4</sup>

- Transient, reversible akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall motion abnormalities extending beyond a single vascular territory on left ventriculography.
- Absence of obstructive coronary artery stenosis 50% of the luminal diameter or angiographic evidence of acute plaque rupture.

- New electrocardiographic abnormalities consisting of ST segment elevation or T wave inversion.
- Absence of:
  - Recent head trauma
  - Intracranial bleeding
  - Pheochromocytoma
  - Obstructive epicardial coronary artery disease
  - Myocarditis
  - Hypertrophic cardiomyopathy

#### Pathophysiology

Despite numerous case reports of apical ballooning syndrome, the exact pathophysiological mechanism responsible for this condition has not been clearly defined in literature. Various theories have been postulated for its causation. The most convincing theory seems to be massive catecholamine surge, caused by stress precipitating this cardiomyopathy. The catecholamines further depress the myocardial function by causing myocardial stunning. Akashi et al in their scintigraphic study on eight patients of Takotsubo cardiomyopathy, demonstrated evidence of reversible cardiac adrenergic dysfunction. This hypothesis seems logical as low ejection fractions have been demonstrated in other conditions with elevated serum catecholamine levels such as patients of pheochromocytoma and subarachnoid hemorrhage. However this postulation is not flawless, and in clinical studies there has been no consistency in serum catecholamine level elevation associated with this condition.<sup>5-8</sup>

Some authors have proposed diffuse epicardial coronary artery spasm as being one of the underlying mechanisms. However, this hypothesis is questionable as different case series have shown variable results. Tsuchihashi et al reported that coronary artery vasospasm with acetylcholine could be induced in only 21% of their patients. Akashi and coworkers found that acetylcholine challenge did not induce coronary vasospasm in any of their patients.<sup>9</sup>

Another plausible mechanism seems to be dysfunction at the microvascular level. This theory seems reasonable in the presence of nonoccluded epicardial coronaries in cases of Takotsubo cardiomyopathy. Various angiographic measures of microvascular dysfunction such as myocardial blush grade and TIMI frame count have been found to be abnormal in such patients. Still, further larger studies are needed to support this hypothesis.<sup>10-12</sup>

Development of dynamic intraventricular gradient at the level of left ventricular outflow tract or mid ventricle is another way to explain the pathogenesis

of this condition. As a result of this gradient, there is increase in wall stress which causes increased oxygen demand and myocardial ischemia. This can explain the predisposition of elderly females to this condition as they have sigmoid shaped interventricular septum due to unfolding of aorta and hence are more likely to develop the intraventricular gradient. However, in clinical studies this gradient has not been as frequently reported as it should have been if this was the only mechanism for stress induced cardiomyopathy.<sup>13</sup>

Another question that remains unanswered about this entity is why only the cardiac apex is selectively affected. Lack of three layered myocardial structure, low elasticity reserve, limited coronary blood supply to the cardiac apex and delayed functional recovery from global dysfunction, are the possible mechanisms.<sup>1</sup>

### Complications

Several complications can arise during the clinical course of Takotsubo cardiomyopathy. While most patients can be managed conservatively others, for example those with cardiac rupture, may require surgical intervention. Patients can experience any of the complications observed in the condition of acute myocardial infarction, such as ventricular arrhythmias, congestive heart failure, cardiogenic shock, mitral regurgitation or left ventricular free wall rupture. However, even despite the development of serious complications most patients have excellent recovery.<sup>4,14,15</sup>

### Treatment

As the presentation of this condition is very similar to acute coronary syndromes, the initial management should include standard therapy for ACS patients such as aspirin, beta blockers and heparin. Treatment can be changed once the diagnosis of Takotsubo cardiomyopathy has been confirmed following appropriate tests such as echocardiography and coronary angiography.

Although there have been no randomized studies, chronic beta blocker therapy in these patients seems appropriate as this would prevent recurrences due to catecholamine surges in future. The role of angiotensin converting enzyme inhibitors or angiotensin receptor blockers is controversial. Some authors have advocated their use in these patients until there is complete recovery of myocardial function.

Left ventricular outflow tract obstruction should be carefully looked for in these patients. In the presence of significant dynamic left ventricular outflow obstruction without e/o heart failure, gentle IV fluids with beta blocker therapy would be useful. However the presence of pump failure would mandate the use of inotropes and intra-aortic balloon pump.<sup>16,17</sup>

There have been no studies on the role of combined alpha and beta blockers in patients of stress induced cardiomyopathy.

### Prognosis

Most of the patients show complete recovery. The average recovery time is four to eight weeks and the recurrence rate is low. In a reported case series the recurrence rate for Takotsubo cardiomyopathy was 5–10%. The mortality rate is also very low and is estimated around 1–2%.

### Conclusion

Takotsubo cardiomyopathy is a disease of unknown etiology although most cases are precipitated by severe emotional stress. The symptoms present very similar to ACS so diagnosis of this condition can be challenging. Chronic beta blocker therapy has been found to be useful. Most patients recover from this condition with complete normalization of cardiac function.

Further prospective studies are needed to find the exact mechanism underlying this condition and to help define the guidelines for its management.

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### CME Questions 1a-c

Please select the best answer for the following:

A 66-year-old woman presented to emergency with left-sided chest pain. The pain started when she was at the funeral ceremony of her mother. The initial EKG showed upsloping ST-T wave in V2-V4. Her initial troponin I was elevated with normal CK and CK-MB. Her vitals were stable and cardio-respiratory examination was WNL. She was started on aspirin, heparin, beta blockers and eptifibatide. Transthoracic echo was done which revealed EF of 35% with regional wall motion abnormalities in apical and anteroapical region. Subsequently coronary angiography was done which revealed normal coronaries. Left ventriculogram showed calculated EF of 30% with apical hypokinesis and hyperkinesis of basal walls. She was discharged after 48 hrs on aspirin and metoprolol with improvement in her symptoms.

- 1a. The discharge diagnosis of this patient would be:
  - a. NSTEMI
  - b. Transient LV apical ballooning (Takotsubo cardiomyopathy)
  - c. LV aneurysm
  - d. Transmural MI
  - e. None of the above
- 1b. Possible etiologies for the discharge diagnosis include:
  - a. Transmural ischemia due to coronary artery embolization
  - b. MI
  - c. Catecholamine excess
  - d. Chest trauma
- 1c. Follow up echocardiogram in four weeks would most likely demonstrate the following:
  - a. Persistent ballooning of the LV apex
  - b. Anterior wall motion abnormality
  - c. Severe mitral regurgitation
  - d. Normal LV function without wall motion abnormalities