Takotsubo cardiomyopathy is a recently described and poorly recognized clinical entity perhaps best known for its ability to mimic both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), especially in post-menopausal women and following stressful situations. Because of this, it is an important consideration in the differential diagnosis for patients presenting with symptoms and signs consistent with acute coronary syndrome (ACS). Apical ballooning of the left ventricle seen on echocardiography or left ventriculogram with preserved motion or hyperkinesis of the basal segment is the signature appearance of this condition; however, a diagnosis cannot be made until coronary artery disease is ruled out with angiography. The pathophysiology of this condition appears to be related to transient myocardial stunning secondary to high levels of circulating catecholamines. This appears to be via a different mechanism than that seen in response to myocardial ischemia, but the exact mechanism remains unknown. Although Takotsubo cardiomyopathy is thought to comprise 2% or less of all presentations of ACS, this is thought to represent an underestimate of the true incidence. Increasing awareness of the condition as well as the trend towards urgent angiography and primary PCI as the favoured treatment of STEMI are expected to reveal previously undiagnosed or misdiagnosed cases.

Background

In 1990, Satoh and colleagues described a unique cardiomyopathy which has since become known as “Takotsubo cardiomyopathy,” “transient apical ballooning,” “stress-induced cardiomyopathy,” and “broken heart syndrome.” Classically, this condition manifests itself as acute-onset retrosternal chest pain, shortness of breath, and EKG changes consistent with transmural anterior wall infarction, most commonly ST-segment elevation in the appropriate precordial leads. It is seen most commonly, but not exclusively, in post-menopausal women who have experienced a sudden physical or emotional stress, and is accompanied by a characteristic appearance of the left ventricle on echocardiography or left ventriculography and the absence of hemodynamically significant coronary artery disease in the distribution of the left anterior descending (LAD) artery. Takotsubo cardiomyopathy, therefore, represents a diagnostic difficulty in that it must be rapidly and accurately distinguished from anterior STEMI in order to facilitate correct clinical decision-making regarding therapy for the patient with ACS. Since 1990, the clinical features of Takotsubo cardiomyopathy have been described, and diagnostic criteria established by various groups; these invariably emphasize the transient and reversible nature of Takotsubo cardiomyopathy, and the absence of significant coronary artery disease, ruling out ischemic heart disease as a cause of ventricular dysfunction.

Clinical and Investigative Features

Much of what is known about the clinical presentation and course of Takotsubo cardiomyopathy derives from published case reports. Since its initial description in the literature in 1990, Takotsubo cardiomyopathy has been reported with increasing frequency both in and outside of Japan. There is a small rise in serum troponin and creatine kinase levels with similar kinetics to that seen in ACS. High plasma catecholamines are found in a majority of patients at presentation; however, their role in the pathogenesis remains poorly understood and these are not generally measured unless there is concern about pheochromocytoma. It is not clear whether serial measurements are of value for clinical decision-making. Patients with Takotsubo cardiomyopathy, because they do not have significant coronary artery disease, are thought to have a more favorable clinical course than their peers presenting with MI.

At initial presentation, it is often difficult to differentiate Takotsubo cardiomyopathy from
STEMI via electrocardiography, as ST-segment elevations in the appropriate precordial leads are seen in electrocardiograms (EKGs) performed on both sets of patients. As the hyper-acute phase passes, the EKG will evolve, often revealing deep T wave inversions in the anterior leads and QT prolongation. Much attention, therefore, has been devoted to identifying and characterizing the sensitivity and specificity of EKG patterns which may suggest STEMI over Takotsubo cardiomyopathy, or vice versa. Ogura and colleagues suggest that a constellation of EKG findings—namely, absence of reciprocal changes, absence of abnormal Q waves and a ratio of the ST segment elevations in leads V4-6 over elevations in V1-3 > 1—may be highly specific for Takotsubo cardiomyopathy when these exist together. Inoue and colleagues confirmed that the absence of reciprocal changes and abnormal Q waves on EKG may be helpful in differentiating between patients presenting with Takotsubo cardiomyopathy and those with anterior MI secondary to occlusion of the proximal LAD. Bybee and colleagues suggest that patients with Takotsubo cardiomyopathy typically present with lower ST segment elevations than their peers who present with bona fide anterior MI secondary to occlusion of the LAD. However, as the electrocardiographic differences between Takotsubo cardiomyopathy and anterior STEMI are subtle and easily missed and the clinical features of these two conditions overlap, urgent coronary angiography to rule out significant coronary artery disease and echocardiography or left ventriculography to demonstrate the characteristic apical ballooning remain necessary for diagnosis.

The characteristic appearance upon echocardiography or left ventriculography of the heart of a patient with Takotsubo cardiomyopathy is of dilation of the apex of the left ventricle with preserved or hyper-contraction of the base of the left ventricle. The ventricle is said to resemble a Japanese octopus trap, from which the name derives. More recently, a variant form of Takotsubo cardiomyopathy has been described in which the ventricular dilation occurs not at the apex of the left ventricle, but in the mid-ventricular segment. Takotsubo cardiomyopathy involving the right ventricle has also been reported in the literature. An inverted pattern has been described in association with central nervous system injury and pheochromocytoma.

Pathophysiology
In contrast to the clinical course of anterior MI, the impairment in left ventricular function seen in Takotsubo cardiomyopathy is transient, and typically recovers within 2 months of initial presentation. Though this transient left ventricular dysfunction is thought to represent myocardial stunning of the affected portion of the left ventricle, with or without transient myocardial ischemia, much remains unknown about the pathophysiology of Takotsubo cardiomyopathy.

Recent attempts to explain the pathophysiology have settled upon high levels of circulating catecholamines as the likely pathology underlying this cardiomyopathy. One explanation is that systemic release of catecholamines following a stressful event results is sufficient to stun the myocardium. Due to the high concentration of adrenergic receptors in the apex of the left ventricle, this region is preferentially susceptible to catecholamine-induced stunning. Circulating catecholamines are hypothesized to produce left ventricular dysfunction via a mechanism different from that seen in ischemia, although Takotsubo cardiomyopathy has been seen following coronary artery vasospasm and transient catecholamine-mediated vasospasm may contribute. Interestingly, Takotsubo-like cardiomyopathy has been reported with pheochromocytoma, thereby lending credence to the suggestion of catecholamine-induced myocardial dysfunction. More recently, Ako and colleagues have noted similarity between Takotsubo-like cardiomyopathy and left ventricular dysfunction following acute brain injury, thus raising the possibility of a shared pathophysiology. Alternatively, Ibanez has proposed that the phenomenon of Takotsubo cardiomyopathy can be better explained by occlusion of the proximal or mid-segments of an exceptionally long LAD which wraps around the apex of the
left ventricle, resulting in ischemic myocardial dysfunction, followed by spontaneous reperfusion; this hypothesis is not as well-accepted, but may explain how Takotsubo cardiomyopathy may develop in patients without significantly elevated plasma catecholamines. Impaired microvascular function may also be present and explain the anatomic pattern of ventricular dysfunction extending beyond the territory of the LAD.

A genetic contribution to the etiology and/or susceptibility has been recently suggested, but has yet to be conclusively proven.

**Management**

There should be a high index of suspicion for this disorder especially in older females following a recent emotional upset or physical stress. Differentiation from ACS can be difficult. If prompt access to a cardiac catheterization laboratory is available, it is the preferred approach to accurately diagnose this disorder and rule out myocardial infarction. Understandably, if a catheterization laboratory is not readily available, some patients may be diagnosed with STEMI, and, as a result, receive thrombolytic therapy. Emergency echocardiography may have a role in imaging the anatomic dysfunction characteristic of Takotsubo cardiomyopathy. Initial therapy is usually supportive in nature, and consists of aspirin, ACE inhibitors, beta blockers, and/or calcium channel blockers, though their use is somewhat empiric. Anticoagulation with heparin (switching to Coumadin) is often used given concern about development of intramural thrombus in the ballooned apex. This can be stopped once the ventricular function normalizes in 1-2 months.

**Complications**

Pulmonary edema, mitral regurgitation, cardiac dysrhythmias and cardiogenic shock are recognized complications, especially in elderly patients, and these life-threatening complications require treatment as per usual protocol. Additional noted sequelae of Takotsubo cardiomyopathy include pericarditis, apical thrombus formation, cerebrovascular accident secondary to embolism of an existing apical thrombus and left ventricular wall rupture. The mortality attributed to Takotsubo cardiomyopathy is 1%. Although the observed rate of recurrence is low, it is important to note that long term follow-up of patients with Takotsubo cardiomyopathy is limited.

**Summary**

Takotsubo cardiomyopathy is increasingly recognized as a cause of acute chest pain and dyspnea mimicking ACS. It is distinguished from anterior MI on the basis of characteristic echocardiographic and/or ventriculographic findings, namely, left ventricle wall motion abnormalities, in the absence of critical coronary arteries stenoses. The typical wall motion abnormality seen is octopus-pot shaped dilation of the apical and midportions of the left ventricle, with normal motion or hypercontraction of the base of the left ventricle, although variant forms have been described. Although the precise pathophysiological mechanism which produces these changes in the ventricle is unknown, recent suggestions of transient myocardial stunning secondary to high levels of circulating catecholamines appear consistent with clinical observations. Overall, patients with Takotsubo cardiomyopathy have a favourable prognosis, but may experience complications related to transient left ventricular dysfunction which require supportive care.

**References**


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