CLINICAL REVIEW

Takotsubo Cardiomyopathy

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BACKGROUND: Takotsubo cardiomyopathy is a novel, yet well-described, reversible cardiomyopathy triggered by profound psychological or physical stress with a female predominance.

OBJECTIVE: This review is designed to increase general clinician awareness about the diagnosis, incidence, pathogenesis, and therapies of this entity.

DATA SOURCES: A complete search of multiple electronic databases (Pubmed, EMBASE, Science Citation Index) was carried out to identify all full-text, English-language articles published from 1980 to the present date and relevant to this review.

REVIEW METHODS: The following search terms were used: takotsubo cardiomyopathy, stress-induced cardiomyopathy, and left ventricular apical ballooning syndrome. Citation lists from identified articles were subsequently reviewed and pertinent articles were further identified.

RESULTS: Takotsubo cardiomyopathy is typically characterized by the following: 1) acute onset of ischemic-like chest pain or dyspnea, 2) transient apical and mid-ventricular regional wall-motion abnormality, 3) minor elevation of cardiac biomarkers, 4) dynamic electrocardiographic changes, and 5) the absence of epicardial coronary artery disease. The pathogenesis of the syndrome is unknown but has mostly been associated with acute emotional or physiologic stressors. Dote, Sato, Tateishi, Uchida, Ishihara (*J Cardiol.* 21(2):203–214, ¹⁹⁹¹); Desmet, Adriaenssens, Dens (*Heart.* 89(9):1027–1031, Sep., ²⁰⁰³); Bybee, Kara, Prasad, et al. (*Ann Intern Med.* 141(11):858–865, Dec 7, ²⁰⁰⁴); Sharkey, Lesser, Zenovich, et al. (*Circulation.* 111(4):472–479, Feb 1, ²⁰⁰⁵) The short and long-term prognosis of these patients is overwhelmingly favorable and often only requires supportive therapy.

CONCLUSION: Whether an emotional or physical event precedes one's symptoms, it is apparent that takotsubo cardiomyopathy case presentations mimic ST-segment elevation myocardial infarction, and thus is an important entity to be recognized by the medical community.

KEY WORDS: takotsubo cardiomyopathy; stress-induced cardiomyopathy; left ventricular apical ballooning syndrome; broken heart syndrome.

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CASE PRESENTATION

M.G. is a 63-year-old female with a previous medical history significant for hypercholesterolemia and family history of premature coronary disease. On January 21, 2005, M.G. learned of the sudden unexpected death of her mother, causing tremendous emotional stress. Within the subsequent hours, she developed severe back pain, prompting her to seek emergency room care. On presentation, her heart rate was 84 beats per minute and the blood pressure was 111/53 mmHg. She was in mild discomfort due to the back pain, but no evidence of pulmonary congestion (clinically or radiographically) or elevated right-sided pressures. Her electrocardiogram was abnormal with ST segment elevations in V2–V6 consistent with an acute myocardial infarction (Fig. 1), and she was subsequently taken to the cardiac catheterization lab within three hours of symptom onset.

The catheterization revealed near normal coronary arteries with the exception of a mild 30% lesion in the mid-left anterior descending artery. The ventriculogram showed severe hypokinesis of the anterolateral, apical, and inferoposterior segments. The base of the heart contracted normally and the estimated ejection fraction was 25% (Fig. 2).

By this time, cardiac biomarkers returned positive for myocardial infarction (with peak CPK of 259 IU/L, CK-MB of 11 IU/L, and troponin of 2.8 ng/mL). After the catheterization, the patient was treated with oral beta-blockade and ACE inhibition and intravenous unfractionated heparin until cardiac markers normalized. An echocardiogram (not retrievable for review) done during the admission confirmed the findings of the ventriculogram and did not reveal any valvular disease. A follow-up ECG on day 3 revealed deep inverted T-waves in leads V2–V6, a Q wave in lead V2, and a prolongation of the corrected QT interval from 433 to 473 milliseconds. On day 4 the T wave inversions were not as dramatic and the Q wave was no longer present in lead V2. She was discharged on hospital day 5 on warfarin, ramipril, carvedilol, isosorbide mononitrate, and atorvastatin.

One month later, M.G. had a follow-up appointment with her cardiologist and a repeat electrocardiogram and echocardiogram was performed. The ECG revealed a normal sinus rhythm, normal R wave progression, and normal T waves. There was no evidence of prior myocardial infarction (Fig. 3). The echocardiogram demonstrated near normal left ventricular function with an estimated ejection fraction of 50%.

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Figure 1. ECG on initial presentation of patient M.G.

Myocardial perfusion imaging was also normal and a serologic workup was negative for a hypercoagulable state. As a result of the above, M.G. was diagnosed as having had takotsubo cardiomyopathy secondary to profound emotional stress.

REVIEW

Introduction

Takotsubo cardiomyopathy (also known as the transient left ventricular apical ballooning syndrome, stress-induced cardiomyopathy, "broken heart syndrome," or ampulla-shaped cardiomyopathy) is a novel, yet well-described, reversible cardiomyopathy triggered by profound psychological or physical stress. Despite over 300 articles published on the subject

over the last decade, much remains unknown about this condition. Because it shares many of the clinical features of myocardial infarction due to atherosclerotic plaque rupture, despite having a different mechanism and natural history, it is important to gain a more robust understanding of this entity and improve its recognition within the medical community.

Incidence and Demographics

To date, the incidence of takotsubo in those diagnosed with acute myocardial infarction has been estimated between 1.5% and 2.2% with reports as high as 6%–12% among female patients presenting with suspected anterior wall myocardial infarction.^{3,5,6} However, due to its similarity to atherothrombosis-mediated acute coronary syndromes and its unfamiliar diagnosis, it is likely under-reported.

Figure 2. Left ventricular angiogram in diastole and systole. The findings illustrate normal basal function with severe hypokinesis of the anterolateral, apical, and inferoposterior segments (apical ballooning).

Figure 3. Follow up ECG one month later.

The mean age of patients presenting with this syndrome is approximately 62–75 years of age. In case series, approximately 85–100% of patients diagnosed with takotsubo are women. Despite this difference, there appear to be no differences in the symptoms, precipitating cause, or prognosis between men and women who present with this syndrome.⁷

Clinical Characteristics

In the early 1990s, Japanese physicians first recognized a syndrome characterized by chest pain, electrocardiographic changes, transient left ventricular apical aneurysm, and normal coronary arteries. Patients were usually women over the age of 50 after experiencing an inciting stressful event.¹ Several case reports surfaced thereafter, followed by multicenter retrospective analyses and systemic reviews of the literature of patients with similar clinical and left ventricular wall motion abnormalities.^{3,4,7,8}

Patients with takotsubo cardiomyopathy often (>90%) present with chest pain, and/or dyspnea, after an acute emotional or physical stress. On evaluation, patients' symptoms vary and may range from mildly symptomatic to critically ill, and as many as 20% require intra-aortic balloon pump or inotropic support.⁹ Despite the variation in clinical presentation, most patients have characteristic objective features. Although no validated criteria have been established, Bybee et al. have proposed criteria for the diagnosis of this syndrome (Table 1).³

The majority of patients have an abnormal, dynamic electrocardiogram beginning with precordial ST-segment elevation in greater than 80% of patients followed by typically diffuse deep T-wave inversions with QT prolongation occurs

(ranging from 450–500 milliseconds) within 48 hours³. Pathologic Q-waves are present in 6–31% of patients. Emergent angiography typically reveals normal coronary arteries or occasional mild irregularities inconsistent with the observed wall motion abnormality. Contrast enhanced left ventriculography reveals apical and mid-ventricular akinesis or dyskinesis with a normal or hypercontractile base which, at end-systole, appears like the Japanese fisherman's octopus pot called the tako-tsubo. Mild to moderate left ventricular dysfunction is present and is rapidly reversible (within days to weeks) without revascularization.¹⁰ Echocardiography often confirms the dysfunctional contractile pattern, with an initial ejection fraction ranging from 20–40% and follow up normalization to 60–75% in most

Table 1. Proposed Mayo Criteria for the Diagnosis of Takotsubo Cardiomyopathy* (Adopted from Bybee et al.)³

Proposed Mayo criteria
1. Electrocardiographic abnormalities (ST-segment elevation followed by T-wave inversion)
2. Transient apical and mid-ventricular wall motion abnormalities (akinesis or dyskinesis)
3. Absence of obstructive coronary artery disease or evidence of acute plaque rupture
4. Absence of the following:
a. Recent significant head trauma
b. Intracranial hemorrhage
c. Pheochromocytoma
d. Another etiology of myocardial dysfunction (myocarditis or hypertrophic cardiomyopathy)

*Patients must fulfill all four characteristics

patients. Cardiac biomarkers are often only mildly elevated, are maximal at the time of presentation, and generally do not follow the slow rise and fall kinetics as observed with conventional myocardial infarction.³

The short-term and long-term prognosis of these patients is overwhelmingly favorable. With medical and supportive therapy targeted against the known complications (left and/or right heart failure, transient intraventricular outflow obstruction, and cardiogenic shock), the in-hospital mortality rates range from 0–8%. Of note, the largest patient series of 88 patients had an overall in-hospital mortality rate of 1%.³ Despite this relatively benign prognosis, more serious complications (cardiogenic shock and ventricular fibrillation) have been reported with in as many as 4.2% and 1.5%, respectively.⁸ Accurate recurrence rates are difficult to assess as series follow-up dramatically varies (from 8 days to four years). Despite this shortcoming, recurrence rates appear to be rare, ranging from 0–8% in reported case series.³ There has been no randomized control trial evaluating specific type or duration of medical therapy in these patients. However, supportive medical care with angiotensin and beta-blockade (with or without anticoagulation) is often continued until left ventricular function has returned to normal.

Acute emotional stressors (i.e., accidents, deaths, quarrels, life-changing events) have been implicated in 14–38% of reported cases of this syndrome, whereas physiologic triggers (such as acute medical conditions or surgery) were reported in 17–70% of patients.³ However, some reports have had up to 20% of patients experience no triggering event.⁷ Many authors have recognized that approximately 70% of patients' stressors represent a lifetime crisis that often precedes the onset of symptoms by hours. There are reports of even natural disasters impacting on the disease process. Watanabe et al. reported on acute cardiac events, including takotsubo cardiomyopathy, after the earthquake in Niigata, Japan on October 23, 2004. They found an increase in takotsubo cardiomyopathy which was postulated to be a result of the emotional stress provoked by such a natural disaster.¹¹ Given the variability in the presentation of this syndrome, it is likely, although not proven, that patients presenting with takotsubo cardiomyopathy may represent a late manifestation within a spectrum of a disease. As such, subclinical and misdiagnosed cases of milder degrees of myopathy likely exist.

Pathophysiology

Since the early reports of takotsubo cardiomyopathy, many theories regarding the cause for this syndrome have been proposed. One early theory suggested that multiple epicardial coronary artery vasospasm and subsequent ischemia results in stunned myocardium. Additionally, microvascular vasospasm and/or dysfunction have also been implicated and shown to be abnormal in a subset of women with takotsubo cardiomyopathy.¹² However, studies on both the macrovasculature and microvasculature have yielded conflicting results.^{3,9,13,14}

Although the mechanism of takotsubo is unknown, the temporal relationship between the stressful event and the onset of symptoms argues in favor of a causal link. Emotional stress and the corresponding increase in catecholamines have been reported in many patients following takotsubo cardiomyopathy. Elevated catecholamine levels have been shown to cause direct myocyte injury via an increase in intracellular calcium and oxygen-free radicals. This pathologic process is

seen in catecholamine-induced cardiomyopathy (i.e., secondary to a pheochromocytoma) which histologically and morphologically results in abnormalities similar to takotsubo cardiomyopathy.^{15,16} Although measurement of catecholamine levels in patients presenting with takotsubo cardiomyopathy have been conflicting, this may be in part due to the extremely short half-life of epinephrine (3 minutes) and given the fact that most patients arrive to the emergency room at least 30 minutes (>10 half lives) after the inciting event.¹⁷

Researchers have implicated gender-related differences in response to sudden bursts of sympathetic stimulation as a potential cause of the gender bias seen in this syndrome. Some have inferred that women may have more potential epinephrine stores available for sudden release, which may explain the gender-related disparity in this syndrome.¹⁷ Although the explanation for such a predilection still remains unknown, reduced estrogen levels seen in post-menopausal women may alter endothelial function, making them more vulnerable to sympathetic-mediated myocardial stunning and perhaps stress-related myocardial dysfunction.^{10,18}

Sympathetic hyperactivity and subsequent myocardial insult are also associated with other medical conditions (status asthmaticus, subarachnoid or intracerebral hemorrhage, and stroke). The mechanism of this neurogenic myocardial stunning is believed to relate to an excess of catecholamines, as seen in takotsubo cardiomyopathy.⁴ However unlike the segmental involvement in takotsubo cardiomyopathy, these processes tend to spare the apex and involve the basal segments. The explanation for apical involvement and basal sparing in takotsubo cardiomyopathy is unknown yet may be related to an increase in apical myocardial sensitivity to sympathetic stimulation or to an increased density of catecholamine-sensitive receptors seen in this region.^{17,19} Further, myocarditis may present with similar findings as seen takotsubo cardiomyopathy. However, investigators have not demonstrated biopsy-proven evidence of myocarditis in cases of takotsubo and thus are not thought to be an important causative factor.

Ibanez et al. suggested that ruptured atherosclerotic plaque, resulting in temporary left anterior descending (LAD) occlusion, was the cause of the unique cardiomyopathy seen in patients presenting with takotsubo cardiomyopathy. In their small subset of patients, it was hypothesized that a variant LAD, extending apically and diaphragmatically, underwent transient plaque rupture followed by early reperfusion, giving rise to the unique clinical characteristics of this syndrome.²⁰ Although this coronary anatomy is not observed in all patients, it has been suggested as an alternative explanation in some cases. Despite a lack of significant coronary artery disease and the distribution of myocardial wall motion abnormalities in all three coronary artery territories, myocardial perfusion imaging defects have been reported in a subset of takotsubo patients.²¹ Although these findings are not completely understood, some investigators believe they lend credence to impaired coronary microcirculation as a causative mechanism.

CONCLUSION

The case of M.G. shows that in vulnerable individuals, psychological stress can cause a takotsubo cardiomyopathy. Whether an emotional or physical event precedes one's

symptoms, it is apparent that takotsubo case presentations mimic ST-segment elevation myocardial infarction and thus is an important entity to be cognizant of and understand. As more becomes known about this syndrome and more physicians are aware of the diagnosis, the incidence, pathogenesis, and specific preventative therapies will be ascertained. For now, it is clear that further investigative work is needed on this most unique cardiovascular disease.

Conflict of Interest: None disclosed.

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