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Recurrent Takotsubo Cardiomyopathy: The Role of Adrenergic Blockade

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Keywords: Recurrent; Takotsubo Cardiomyopathy; Beta Blockers; Alpha Blockers; Transient Left Ventricular; Apical; Ballooning; Stress Cardiomyopathy; Ampulla Cardiomyopathy

Introduction:

The Takotsubo phenomenon was first described in 1991 by Dote et al¹, who named the syndrome “Takotsubo like cardiomyopathy” because the appearance resembles a pot historically used in Japan to catch octopi. Terms used to describe this syndrome in published reports include Takotsubo Cardiomyopathy (TC), transient left ventricular (LV) apical ballooning, stress cardiomyopathy, ampulla cardiomyopathy among more than seventy names in the literature^{2, 3}. TC is much more common in women than men, particularly post-menopausal women^{4,5,6,7,8,9}. In a review of six prospective and four retrospective studies women accounted for 80 to 100 percent of cases, with a mean age of 61 to 76 years⁶.

Studies have shown a statistically significant spike in the occurrence of TC during the summer months^{10, 11}. One large case series from Europe found that TC was slightly more frequent during the winter season¹². The cardiac dysfunction seen in TC classically appears as a transient contractile dysfunction of the mid and apical segments of the left ventricle with compensatory hyperkinesis of the basal walls, producing ballooning of the apex with systole¹. TC is a diagnosis of exclusion¹³. The most recent proposed diagnostic criteria for TC is the modified Mayo Clinic includes: transient hypokinesis, dyskinesis, or akinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present; absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; New electrocardiographic abnormalities (either ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level; absence of pheochromocytoma or myocarditis³.

There are no established treatment algorithms for TC and as most patients present with an acute coronary syndrome, they are treated according to acute coronary syndrome guidelines¹⁴. TC is generally a benign condition; in-hospital mortality is 0-8%, and death is much more common in the setting of outflow obstruction and from non-cardiac causes^{15,16,17,18,19,20}.

This case series will illustrate cases of reoccurring TC and focus on pathogenesis and proposed treatments.

Cases:

Case 1:

A 52-year-old African American woman with a history of asthma, bronchiectasis, systemic lupus erythematosus, and hypertension was admitted to undergo pre-op evaluation for repair of a large thoracoabdominal aneurysm. She underwent an exercise nuclear stress test that showed moderate, reversible myocardial ischemia of the apical, inferoapical and anteroseptal walls with completely normal resting perfusion. No ejection fraction was calculated on that study. A few hours later, the patient developed chest pain and shortness of breath that lasted for several hours and spontaneously resolved. Left heart catheterization was done the following morning and revealed non-obstructive coronary artery disease with less than 50% stenosis of the left anterior descending artery along with bridging of the mid LAD. Left ventriculogram unexpectedly demonstrated akinesis of anterior, apical and inferoapical walls with an estimated ejection fraction of 40%. The patient was started on aspirin, calcium channel blocker and ACE inhibitor. She returned for surgery within one week and the admission EKG showed new T-wave inversions with QT prolongation that was not present on her prior evaluation. Transthoracic echocardiogram (TTE) performed showed completely normalized left ventricle function without wall motion abnormalities (Figure 1). Surgery was postponed for a month and when done was uneventful.

One year later the patient returned to the emergency department (ED) with chest pain and shortness of breath, which lasted for several hours. TTE done in the ED revealed moderate to severe LV dysfunction with akinesis of the distal septum, apical and inferoapical walls (Figure 2). Left heart catheterization was again performed and the LAD lesion appeared similar (<50%). However, considering the recurrent presentation with depressed LV function and wall motion abnormalities, it was felt that the LAD lesion should be stented, which was performed successfully. Repeat TTE done after four months showed complete normalization of LV function.

Given the clinical, laboratory, and catheterization findings the diagnosis of recurrent TC was finally recognized. Because of history of severe asthma, a beta-blocker was not started at that point and patient was maintained on Diltiazem. Two years following that admission, the patient presented to another institution with chest pain and shortness of breath. TTE again showed severely depressed LV ejection fraction of 35% with associated wall motion abnormalities. Coronary angiography demonstrated a patent LAD stent with only minor luminal irregularity. This time, a beta blocker was added to her regimen. Follow-up TTE done one year later revealed normal LV function. Since then, she has been titrated on Metoprolol succinate ER to 200 mg daily, there has been no recurrence to date of chest pain, shortness of breath or re-admission for chest pain despite multiple admissions for abdominal procedures including bowel resection.

Case 2:

An 85 year old Caucasian woman with a history of paranoid schizophrenia, hypertension, and aortic valve endocarditis status-post aortic valve replacement presented after an episode of pulmonary edema that required emergent intubation in the field. Admission EKG showed

ischemic changes and her labs were positive for elevated troponins. TTE performed in the ED showed severely reduced LV function with a large area of akinesis of the apex of the heart and moderate to severe mitral regurgitation. The patient underwent coronary angiography that showed non obstructive coronary artery disease. A diagnosis of TC was made and supportive treatment with beta-blockers and ACE inhibitors was given throughout her hospital stay. Follow-up TTE one week later showed dramatic improvement in ventricular function and the patient was discharged.

Since then, the patient had four distinct episodes of pulmonary edema in a span of six months that required readmission to the hospital. Each episode was preceded by flushing and itching and ended with a recovery of normal ventricular function documented by TTE. While she was in the hospital for her second attack, a characteristic sequence of events leading to the attack was observed. The patient was noted, in the middle of the night, to have become tachycardiac. Her blood pressure rose sharply from a baseline value of 100/60 to over 160/100 within a span of minutes, and the patient complained of shortness of breath, suffocation and orthopnea. She was aggressively treated with morphine, sublingual nitroglycerin, and then, after an IV push of metoprolol, had a significant rise in her diastolic blood pressure (170/140 mm Hg). Immediately after that, she went into hypoxic respiratory failure and required rapid intubation. The very next morning she had diuresed spontaneously, her blood pressure and heart rate returned to baseline, and the patient was extubated without any complications

The patient had undergone two complete workups during these admissions for pheochromocytoma with both plasma and urine catecholamine levels measured during as well as 24 hours following the episode. As the patient complained of itching and flushing each time, work up for elevated serotonin levels was ordered to rule out carcinoid syndrome. She had normal levels of 5-hydroxyindoleacetic acid in urine and normal serum serotonin and chromogranin A levels. The patient underwent a MIBG (iodine-131- meta-iodobenzylguanidine) scan looking for pheochromocytoma or neuroblastoma, which was negative. With the failure of selective beta blocker therapy due to diastolic hypertension, a decision was made to add a non-selective beta-blocker, with alpha and beta antagonistic properties. The patient was subsequently started on Carvedilol 6.25 mg twice daily. The patient was monitored for several days, and TTE done prior to her discharge again showed a completely normalized LV function. With no further events, the patient was discharged.

The patient returned to the ED after 3 days with another episode of flash pulmonary edema, and she was treated medically. During that admission, her Carvedilol dose was titrated up to 25 mg twice daily. At that time, an article was brought up that discussed the theory that Prazosin had been used as an antidote for a specific scorpion bite in Brazil that results in catecholamine release, pulmonary edema, and transient ventricular dysfunction. It was felt that Prazosin might benefit this patient. Prazosin was started. She had since been on Prazosin and Carvedilol and there had been no recurrence of flash pulmonary edema or cardiac events. Four years later the patient presented with fever, AV block, bacteremia complicating a minor hand burn. Transesophageal echocardiogram showed an abscess surrounding her prosthetic aortic valve and involving the interventricular septum with completely normal LV function. She was deemed inoperable by her cardiologist, cardiac surgeon and family and she expired within a few days in Hospice.

Discussion:

TC is a recently recognized syndrome. Although various authors reported a low incidence, the actual rate might be even higher because of underreporting or misdiagnosis as acute coronary syndrome. For example, many cases that are not admitted or have brief transient LV dysfunction are missed. In fact, as reported in one study, 1.7% – 2.2% of patients presenting with acute coronary syndrome had TC^{3,21,22, 23}. Park et al reported an incidence of 28% of Takotsubo-type LV dysfunction in patients admitted to the intensive care unit for non-cardiac physical illness. This syndrome can be viewed as a spectrum of disease spanning from a very mild disease at one end that doesn't require any clinical attention and hence goes unnoticed to a stage that needs hospitalization, and supportive therapy.

Many theories have been presented for the possible pathophysiology of TC. Studies have proposed the mechanism as an association with excessive sympathetic stimulation, microvascular dysfunction, and metabolic abnormalities^{24,25,26,27,28,29}. Studies have found that patients with TC have statistically significant higher levels of serum catecholamines (norepinephrine, epinephrine, and dopamine) than patients with myocardial infarctions³⁰. The apical portions of the left ventricle have the highest concentration of sympathetic innervation found in the heart and may explain why excess catecholamines seem to selectively affect its function³¹. Support for a possible pathogenic role for catecholamines comes from studies in which plasma catecholamines were measured at onset of symptoms²³. Combining the results from multiple studies plasma norepinephrine levels were elevated in 26 of 35 patients (74%)³². It has also been shown that elevated catecholamine levels and TC have been observed in a rat model of immobilization-induced stress³³.

Supraphysiologic levels of plasma catecholamine have several deleterious effects on myocytes. The pathogenesis of TC may be multifactorial, similar to catecholamine induced cardiomyopathy³⁴, pheochromocytoma³⁵ and subarachnoid hemorrhage³⁶. The catecholamine hypothesis as a cause for reoccurring TC, as in our cases, can be further supported by observation of a similar reversible cardiomyopathy with global or focal dysfunction in patients with pheochromocytoma³⁷, in the setting of acute brain injury and Guillian Barré autonomic neuropathy, which have also been postulated to be related to catecholamine excess².

Catecholamine excess has reversible toxic effects on myocardium that have been documented in cases of pheochromocytoma³⁸. Limited available endomyocardial biopsy data of pheochromocytoma patients^{22,39,40} are consistent with histologic signs of catecholamine toxicity.⁴¹ Histological examination of biopsy samples from the affected left ventricle of patients with TC has shown contraction band necrosis, which is associated with clinical states of catecholamine excess⁴². Biopsy findings ranged from no evidence of myocarditis⁴³ to interstitial fibrosis with or without slight cellular infiltration³⁶ to mononuclear infiltrates with contraction band necrosis²². In a series of 8 patients, biopsies obtained during the period of LV dysfunction revealed intracellular accumulation of glycogen, many vacuoles, disorganized cytoskeletal and contractile structure, contraction bands and increased extracellular matrix proteins⁴⁴. In another study, three of nine patients had mononuclear inflammatory infiltrates and four patients had contraction-band necrosis⁴⁵. These alterations resolved nearly completely after functional recovery.

The fact that TC is associated with minor release of cardiac enzymes suggests some microscopic damage to the myocytes. The absence of causative coronary artery disease on angiography and the diffuse rather than localized wall motion abnormalities point to an insult that is global but microscopic in nature. However, the coexistence with obstructive coronary artery disease that may not explain the wall motion abnormalities and the enzyme pattern was seen repeatedly in our experience.

As presented in the second case described above, a specific scorpion sting in Brazil, parts of the Arabian Peninsula and India results in catecholamine release, pulmonary edema, and transient ventricular dysfunction. Such scorpion stings can present with non-specific electrocardiographic changes which are characteristic of scorpion myocardiopathy^{46,47,48,49,50,51,52}. After the scorpion sting, myocardial damage was indicated by elevated enzymatic levels of succinate dehydrogenase, serum glutamic oxalacetic transaminase, creatine phosphokinase, MB isoenzyme (CK-MB) creatine phosphokinase (CPK) and CK-MB/CPK ratio⁵³, lactic dehydrogenases (LDH), LDH1 specific for heart disease, and the ratio of LDH1 to LDH⁵⁴, EKG, echocardiographic, radionuclide, and ventriculography studies^{55,56,57,58,59,60,61,62}.

The mechanism of damage caused by the scorpion venom is thought to be autonomic storm resulting in a massive release of catecholamines^{63,64}. Charybdotoxin, a blocker of calcium-activated potassium channels, is found in the venom of the Israeli scorpion *Leiurus quinquestrius* and iberiotoxin from *tamulus*⁶⁵. It is thought to lead to a catecholamine surge that causes EKG changes, cardiac arrhythmias, conduction defects, ischemia, and infarction-like patterns. All these abnormalities, including pathological Q waves disappeared after administration of species-specific scorpion anti-venom. The paper went on to describe the clinical course and outcome in 46 victims of severe scorpion envenoming treated with Prazosin, and compared them with earlier patients treated with conventional therapy (n = 45) and Nifedipine (n = 28). The incidence of complicating LV failure, acute pulmonary edema and death were 29%, 46% and 25% for conventional therapy group, 35%, 14% and 3.5% for Nifedipine treated group and 6.5%, 0% and 0% for Prazosin treated group; Although this is a historical control study, prazosin appears to significantly reduce morbidity and mortality and shorten recovery time.

There is no controlled data to define the optimal medical regimen to treat TC, but it has been theorized that it is reasonable to treat these patients with standard medications for LV systolic dysfunction. These include ACE inhibitors, beta-blockers, and diuretics, which may be necessary for volume overload states⁶⁶. Aspirin and statin therapy are reasonable in the presence of coexisting coronary atherosclerosis^{46,67}. In cases where there is a large apical aneurysm; it can even be theorized that heparin and then bridging to anticoagulation should be used. Treatment with anticoagulation has been abstracted from acute myocardial infarction data regarding acute anterior left ventricular dysfunction and the risk of stroke. In one study, patients with TC developed LV thrombus in 5% of patients⁶⁸. Of the all five patients with LV thrombus, all were started on anticoagulation and one patient developed stroke. This must be weighed against the hypothesized increased risk of cardiac rupture with apical ballooning and aspirin or heparin therapy⁸.

Consequently, the role of anti-coagulation is largely regarded on a case by case basis⁶⁹. It is reasonable to continue anti-coagulation until the left ventricular function returns⁷⁰. In our cases of recurrent TC, high dose selective beta-blockers or non-selective beta-blockers were continued long-term to protect against catecholamine sensitivity, which may predispose to this syndrome. There was a study^{71,72,73} looking at Metoprolol that was shown to diminish epinephrine-induced cardiomyocytolysis that is seen in TC. Patients who present in cardiogenic shock with TC may require the additional support of an intra-aortic balloon pump (IABP)⁷⁴. In those with evidence of respiratory compromise who do not respond to intravenous fluids and inotropic support, placement of an IABP can provide afterload reduction and enable successful recovery of myocardial function⁷⁵. The placement of an IABP has proven useful in patients who present with TC from various triggers including after mitral valve surgery, cerebral hemorrhage, 5-fluorouracil, self-administered adrenaline injection, status asthmaticus and paragangliomas^{68, 69, 76, 77, 78}. Since most patients recover normal left ventricular function IABP support is usually temporary in the intensive care unit setting.

Conclusion:

The present case series describes two cases of recurrent TC and the use of non selective beta blockers contributing to a lack of recurrence. Reoccurrence of TC has been reported in an estimated 3 to 10% of cases^{20,79}. Gianni et al identified 4 studies documenting a mean recurrence rate of 3.5%.⁸⁰ Chronic management of TC is primarily empirical, but there is emerging data supporting the role for alpha and beta blockade^{71,72,73}. In patients who are hemodynamically stable, it appears advantageous to prevent excessive sympathetic activation by combining alpha and beta blockade⁸¹.

Chronic beta-blocker therapy may reduce the likelihood of recurrent episodes of TC⁴⁷. There may be a role for continuation of adrenergic blockade with either beta blockers or combined alpha and beta-blockers indefinitely in the absence of contraindications or intolerance. Further research into the pathogenesis and treatment is needed to elucidate this relatively newly described syndrome. We hope our cases contribute to the understanding of this interesting condition and will further help in the management of patients with reoccurring TC.

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(This article may be cited as Brodsky Jordan, Katz Jonathan , James David , Samuel Ossama. Recurrent Takotsubo Cardiomyopathy: The Role of Adrenergic Blockade E-Journal of cardiology 2011;1(1):29-39.)