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# When Stress Causes a Heart to Break

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When Stress Causes a Heart to Break

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## ABSTRACT

Tako-tsubo cardiomyopathy is a rare but serious form of heart disease. It present like acute coronary syndrome but, unlike acute coronary syndrome, tako-tsubo is not caused by narrowing in the coronary arteries. This syndrome predominately affects post-menopausal females and is typically associated with a stressful event. The stressful event can be either emotional or physical. The left ventricle is left temporarily stunned from large amounts of catecholamines that are theorized to be present because of the stressful event. The Left Ventricles will typically take on the appearance of an octopus trap or the “tako-tsubo” in Japanese.

**Keywords:** Tako-Tsubo Cardiomyopathy, Apical Balloon Syndrome, Stress Induced Cardiomyopathy, Broken Heart Syndrome, Cardiomyopathy

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## Introduction

Both the medical community and the general public accept the fact that too much stress can negatively impact cardiovascular health and may lead to a Myocardial Infarction (MI).<sup>1</sup> There is, however, another heart condition that has been linked to high levels of stress. This condition has an even higher correlation with stress than does an MI. This condition goes by several different names including Tako-Tsubo Cardiomyopathy (TTC), Apical Balloon Syndrome, Stress Induced Cardiomyopathy, as well as the Broken Heart Syndrome.

The syndrome was first described over 20 years ago in Japan.<sup>2</sup> The name Tako-Tsubo is a Japanese word for a traditional octopus trap. This oftentimes transient condition presents with the patient having symptoms typical of a heart attack. However, during angiogram the absence of clinically significant coronary blockage is observed, but during ventriculography the left ventricle presents with a ballooned apex that resembles the traditional Japanese octopus trap. In nearly all cases of TTC the patients experience a precipitating stressful event, thus, the commonly referenced name of the “Broken Heart Syndrome.” The stressful event may be emotional, physical, or both. Whatever the cause of stress, studies have shown that acute stress plays a pivotal role in the development of the syndrome. The purpose of this paper is to describe the etiology, pathophysiology, symptomology, risk factors and treatment of TTC.

## Methods

Both CINAHL and MEDLINE databases were searched for full text articles using the following key words: broken heart syndrome, apical balloon syndrome, stress cardiomyopathy, and Tako-Tsubo. Date restrictions were placed from 2004 to 2014. The one exception to the date range restriction was use of the original article that first described the syndrome in 1991.

## Case Study

J.D. is a 71 year old Caucasian female. She presents to her local Emergency Department with complaints of sudden chest pain and difficulty breathing that started one hour prior to arrival. She has experienced “similar” symptoms in the past while experiencing anxiety, but states “they have never been this severe”. She was informed yesterday that her daughter, who lives with her, was diagnosed with a rare form of cancer. She has been very emotional since this discovery and is having trouble coping. Her daughter has lived in the home for the last year after a separation from her husband. J.D. lost her husband of 50 years to a heart attack 3 months ago. She woke up early this morning and could not go back to sleep. While lying in bed thinking about the recent events in her life, her symptoms began. At first she thought it was an “anxiety attack” but then realized that she could not catch her breath. She reports severe pain in the center of her chest that feels like pressure. She also reports feeling nauseous but did not “throw up”. The difficulty breathing and chest pain started to improve when she arrived at the ED. Her past medical history includes hypothyroidism, osteoporosis, anxiety, depression, panic attacks, gastro esophageal reflux disease, chronic headaches, and fibromyalgia. Her past surgical history includes a C-section, cholecystectomy, and appendectomy. She has a family history of heart disease. Her father died of a heart attack when he was seventy, and she has a brother that has had several stents placed. She takes citalopram, lansoprazole, levothyroxine, calcium, multivitamin, and vitamin-D. She states that she has an allergy to PCN, but is unaware of the reaction. An EKG was done upon arrival to the E.D. Her EKG demonstrates ST elevation in leads V3 through V4, leads 1 and 2 with no reciprocal changes. Reciprocal changes are an electrophysiological change that demonstrate inverted voltage and are typically seen in the opposite lead of the affected lead. They are almost exclusively seen with myocardial damage.

The STEMI protocol is initiated and she is taken to the cardiac catheterization lab. While waiting for her procedure she is given a bolus dose of heparin, 5000 units, ASA 324 mg and clopidogrel 300mg per the hospital policy. During her procedure she is noted to have no coronary artery disease that would explain her symptoms and ECG changes. However, at the end of the procedure during the left ventriculogram she is noted to have the characteristic ballooned apex and is diagnosed with Tako-tsubo Cardiomyopathy.

### Etiology and Pathology

As mentioned previously, one of the hallmark features of TTC is prior stress. The stress may arise from a variety of factors including death, severe illness, or injury of a family member, friend, or pet. TTC has been linked to patients who have received bad news—diagnosis of a major illness, a daughter's divorce, a spouse leaving for war, or a highly emotional argument. Other examples of emotional stressors include public speaking, legal proceedings, financial loss, a surprise party, and moving to a new residence.<sup>3</sup> Research has shown that conditions such as surgery, asthma, chronic obstructive pulmonary disease, fractures, renal colic, pneumothorax, pulmonary embolism, cocaine use, opiate withdrawal, thyrotoxicosis, or even a cardiac stress test can all lead to TTC.<sup>3</sup>

The precise etiology remains unknown, but there are two theories typically discussed in the literature. The first theory is that of a transient occlusion of more than one coronary artery. It suggests that patients with both normal and atherosclerotic coronary arteries are susceptible to vasospasm. The theory is that there is a simultaneous spasm that causes the vessels that feed the apex of the heart to temporarily close, thus creating the symptoms of a heart attack. By the time the patient is taken to the catheterization lab the spasm has stopped and the arteries are patent.

Although some mild atherosclerosis may be visible, it is considered clinically insignificant and unrelated.<sup>3</sup>

The more common and most widely accepted theory states that when the patient experiences high levels of stress, a surge of catecholamines are released into the body. The catecholamines surge throughout the body and theoretically cause a portion of the heart to become stunned or “broken”. Because there is an absence of clinically significant coronary artery disease on angiogram, there must be a sympathetic nervous system explanation for the phenomenon. This theory is supported by numerous studies that show elevated levels of catecholamines after diagnosis.<sup>4,5,6</sup> Critics of this theory argue there is no way to determine if the release of catecholamines is a result of injury, or if the release of hormones leads to the injury. One of the exclusion criteria set forth by the Mayo Clinic is the presence of a pheochromocytoma, because it would explain the high amounts of catecholamines circulating throughout the body. Whatever the cause, we do know there is an elevated level of catecholamines, with no clinically significant coronary blockage.

### Epidemiology

Although TTC was first described in Japan, it affects almost all ethnicities and not just the Asian populations as once thought. It was not until 2006 that the American Heart Association classified TTC as a primary cardiomyopathy.<sup>7</sup> When compared to coronary artery disease, TTC predominantly affects females.<sup>8</sup> This condition uniquely shows a female prevalence when compared to MI. The prevalence ranges anywhere from 63-100% of patients with TTC being female.<sup>8</sup> Most patients present in the age range of 60-80 years with a mean age of 67 years.<sup>9</sup> Because the syndrome typically manifests in post-menopausal women, there is a

plausible link between the loss of estrogen and the syndrome. TTC is estimated to occur in 1-2% of all patients presenting with possible Acute Coronary Syndrome.<sup>10</sup> This number may not be accurate, due to the number of presumed subclinical cases that do not make it to the hospital for a diagnosis or receive another primary diagnosis. Although the overall rates of TTC are low for patients presenting for ACS, when they are post-menopausal women presenting for ACS, the rate climbs from 1-2% to an estimated 6.1 %.<sup>10</sup>

Deshmuk, MD et al, 2012, searched the 2008 US census for admission to hospitals for patients with TTC. This study found over 6,000 patients who were discharged from the hospital with a primary diagnosis of TTC. 90.4% of the patients were women while only 9.6% were men.<sup>7</sup> The majority of the patients were between the ages of 66 and 80. Deshmuk demonstrated that women older than 55 years were 4.8 times (95% CI 4.2-5.6) more likely to develop the syndrome when compared to women younger than 55.<sup>7</sup> When women older than 55 years were compared to men of the same age, those odds went up to 10.7 times (95% CI 8.5-13.4).<sup>7</sup> Given this information, the author writing this article wonders if a conclusion may be drawn that the withdrawal from estrogen, and not just the absence of estrogen, may play a role in development of TTC. A select few cardiologists have observed that they are seeing an increasing number of patients presenting with TTC. However, this claim is not currently supported within the literature. Perhaps additional studies and queries will support this claim. One possible cause for this increase could be the recent push to stop Estrogen Replacement Therapy due to associated cardiovascular risks of MI and stroke. One researcher has shown that rats receiving estradiol supplementation had a lower rate of stress induced left ventricular dysfunction.<sup>6</sup> This gives rise to theories on the protective mechanism that estrogen may provide

to the female heart. It is important to note that there are no studies that measure the protective effect of estrogen replacement in preventing TTC in humans.

With this unique disease comes the question of whether or not patients that are in a chronic state of stress are at greater risk for developing the syndrome. Several studies questioned patients regarding their stress levels following their diagnosis of TTC.<sup>11,4</sup> Although there have been conflicting results, the majority of studies show a correlation between chronic stress and TTC, particularly when compared to patients who suffer from acute coronary syndrome (ACS).<sup>4</sup> An additional retrospective case controlled study demonstrates that when compared to ACS, TTC patients have a higher rate of anxiety, depression, physical abuse, emotional abuse, substance abuse and smoking.<sup>11</sup> This information adds to the complexity behind the theorized interplay between estrogen or lack thereof, stress, mental illness, and having a “broken heart”.

### Symptomology

TTC does not have a unique symptomology, but rather mimics that of ACS. The patient generally presents acutely. Of the possible presenting symptoms chest pain and dyspnea are the most common.<sup>6</sup> Patients may also present with nausea, shortness of breath, diaphoresis, syncope, palpitations, hypotension, shock, and rarely cardiac arrhythmias. Although it is very rare they may even present with cardiac arrest.<sup>6</sup>

### Diagnosis

TTC can only be diagnosed by assessing the ventricle either through an echocardiogram or ventriculography. It is therefore impossible to differentiate from ACS and should be treated as such because it only makes up a small percentage of patients presenting with chest pain.<sup>6</sup>

ECG may or may not demonstrate ischemic changes. If the ECG does show these changes, then they will often demonstrate ST elevation affecting the precordial leads.<sup>6</sup> An elevated troponin I level indicating myocardial damage may be present. A B-type natriuretic peptide level may be elevated indicating a high left ventricular end-diastolic pressure. The patient fitting this profile will likely be taken to the cardiac catheterization laboratory because of the fear of coronary occlusion. The angiogram for a patient with TTC reveals coronary arteries that are without clinically significant narrowing. During the left ventriculogram portion of the study, when a bolus injection of contrast is pushed into the left ventricle under fluoroscopy; the apex is noted to be hypokinetic. The apex is ballooned, giving it the appearance of an octopus trap.

There are several variants of TTC where non-apical portions of the heart are hypokinetic, but this is not nearly as common as the more traditional apical appearance. These non-apical variants are thought to make up a small percentage of TTC cases, but one study has shown that as many as 24% of presentations contained a non-apical variant.<sup>5</sup> The variants typically fall into one of two groups, a mid-variant, where the base and apex of the heart squeeze but a circumferential portion in between those two areas does not squeeze. The second variant is known as the “reverse TTC” which is where the base is seen as hypokinetic and the apex is still able to squeeze. These different manifestations are still both contained within the diagnosis of TTC and are only referred to as variants. When apical and non-apical variants are compared with one another, the apical group may represent a more severe subset as far as symptomology and complications are concerned.<sup>5</sup>

Although there is no official diagnostic criterion, the Mayo clinic proposed the following criteria for diagnosing TTC.<sup>6</sup> All four of the criteria must be present in order to diagnose the syndrome.

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement. The regional wall motion abnormalities typically extend beyond a single epicardial coronary distribution. A stressful trigger is often, but not always, present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma or myocarditis.

#### Treatment

Because the typical patient with TTC mimics that of ACS, the patient should initially be treated as such. This starts in the pre-hospital phase with EMS. The patient should be transported quickly to a center that has a cardiac catheterization lab, and the STEMI protocol should be initiated quickly. The center should continue to follow the STEMI protocol which may include an ECG, chest x-ray, labs, establishing IV access, supplemental oxygen, monitoring of vital signs, and involving of cardiology services. Because the patient is usually thought to have ACS they should receive the appropriate medications which are also part of most STEMI protocols. These may include aspirin, beta blockers, nitrates, heparin, lovenox, GP2b/3a inhibitors, morphine, and clopidogrel. They should be taken emergently to the catheterization lab.

Once the diagnosis of TTC is made, they can be treated appropriately. Treatment includes supportive measures until the patient recovers. TTC is a transient condition that will typically improve with time. The author is not aware of any randomized controlled studies to evaluate the optimal medications for this syndrome. During recovery the patient may need treatments for the left ventricular dysfunction. Medications that can be used are ACE inhibitors, diuretics, and beta blocking agents. It has been recommended that patients who are hypotensive and in shock should have an urgent echocardiogram to evaluate for the presence of a left ventricular outflow tract obstruction.<sup>12</sup> If an obstruction is present the use of inotropes should be avoided as this can exacerbate the obstruction. A beta blocker can be used to help resolve the obstruction and if necessary an alpha agonist can be added. In the absence of an obstruction, inotropes are generally considered safe. Fluid resuscitation should be based on the presence or absence of pulmonary edema.<sup>12</sup>

Patients may require short term anticoagulation to prevent or treat left ventricular thrombus formation.<sup>6</sup> One author recommends anticoagulation for three months following the presentation. The time can be altered if the patient did not have a clot on presentation and the apex recovers faster than 3 months.<sup>12</sup> The recovery is evidenced by a repeat echocardiogram to establish the function of the left ventricle. Some observational data suggest that most ventricles recover within one month of presentation.<sup>12</sup>

#### Case Study continued

Shortly after the catheterization procedure is completed, J. D. is noted to be hypotensive with a blood pressure of 82/45 mmHg. She states that her symptoms have returned and she is feeling both short of breath and pressure in the center of her chest. An urgent Echocardiogram is

done while still in the catheterization lab to look for the presence of left ventricular outlet obstruction or thrombus in the left ventricle. There is no evidence of obstruction or thrombus on the echo, but the results are consistent with the left ventriculogram which again demonstrate the ballooned apex. A dopamine drip is started in an attempt to treat her hypotension. Her blood pressure returns to normal and she is weaned off of the drip 2 days following admission to the hospital. She is started on an ACE inhibitor, and kept on clopidogrel upon discharge. She returns for a two week appointment and is found to be asymptomatic. A repeat Echo is done one month later that no longer demonstrates a ballooned apex. Her left ventricle has made a full recovery and her ejection fraction (EF) is now 65%. The clopidogrel is stopped at this time.

### Prognosis

The long term prognosis for patients with TTC is usually very good. During the acute phase, when the patient presents to the hospital, is generally considered the time when they are at the greatest risk for complications. Stable patients that are discharged from the hospital rarely have long term sequela from this syndrome.<sup>13</sup> If the patient does not have other significant comorbidities then generally almost all patients make a full recovery.<sup>13,14</sup> Reoccurrence rates are low, but there have been case reports that have demonstrated that TTC can reoccur.<sup>5,13</sup> There is no theory stating why the reoccurrence was suspected.

### Conclusion

TTC is a rare but serious problem for patients presenting with chest pain and ACS. The incidence is much higher with post-menopausal women and should be considered as a differential for post-menopausal women that have experienced a recent stressful event and who

are presenting with ACS symptoms. Because the incidence of TTC is higher in women who have coexisting anxiety and depression, it should be considered even more of a differential when patients fitting this profile are presenting with ACS symptoms. Patients presenting with ACS like symptoms should be treated as such until TTC can be diagnosed with LV imaging such as an Echocardiogram or a LV gram. TTC patients generally will make a full recovery and the chance of reoccurrence is low.

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