

A Review of Takotsubo Cardiomyopathy

By Thomas Xiong

Author Bio

Thomas Xiong is a grade 11 student in Toronto, Canada. He wants to join the healthcare profession in the future, and he is working hard to gain experience in this field. He has completed biology summer programs and is a proud competitor of the British Biology Olympiads. In addition, he has volunteered at multiple cancer organizations, where he has led a team of students to create educational posters and presentation slides on various types of cancers and their treatment options. Outside of this aspiration, he enjoys many hobbies, including Clarinet, band, traveling, reading, and art. Through publishing this article, he hopes to gain experience in research, which includes but is not limited to developing his ideas, discussing them with colleagues, and articulating a comprehensive argument from his thoughts.

Abstract

Takotsubo cardiomyopathy, also known as apical ballooning syndrome, stress cardiomyopathy, and, more commonly, broken heart syndrome, is a temporary heart condition that occurs when an individual experiences sudden extreme emotion that rapidly weakens the left ventricle. This article aims to provide a general overview of takotsubo cardiomyopathy and discuss its history, stressors, clinical and underlying symptoms, populations at risk, clinical studies, and potential treatments. Although rare, these factors are essential to understand, as the effects of Takotsubo could devastate patients' health. By learning about the mechanisms of Takotsubo, effective treatment plans could be implemented quicker and improve prognosis. This article presents that Takotsubo contains many similar qualities to heart attacks, and some treatment options could be considered for both diseases. It is challenging to prevent Takotsubo through medication since the cases are mostly acute and unpredictable. However, treating maladies that often come with Takotsubo could lessen the effects on the patient.

Keywords: Takotsubo cardiomyopathy; apical ballooning syndrome; stress cardiomyopathy; ventricle; cardiac disease.

Introduction

First described in Japan by Hikaru Sato, MD, Ph.D., in 1990, Takotsubo cardiomyopathy derived its name from a traditional octopus trap with a narrow neck and wide base¹. The condition causes apical ballooning of the left ventricle, which gives it a shape similar to the octopus trap on a cardiac ventriculogram (Figure 1).

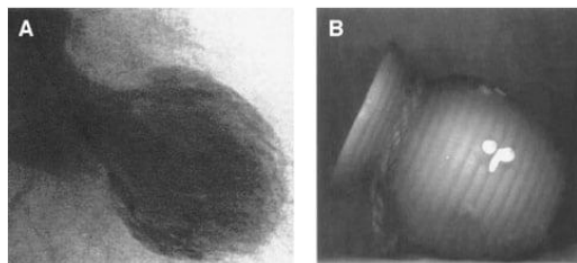


Figure 1. (A) Ventriculogram (B) Octopus pot “Takotsubo”²

Interest in Takotsubo cardiomyopathy spiked in 2004 after the Niigata Chuetsu earthquake in Japan, where cases diagnosed in the week following the quake equalled the number of patients diagnosed in the previous decade (1994-2004)¹. A rise in rates of Takotsubo also accompanied recent earthquakes in New Zealand. These statistics indicate that physical and emotional stressors may cause Takotsubo. While most people with this condition experience a stressful trigger, around 30% of patients do not have an identifiable trigger³. Emotional stressors of Takotsubo include but are not limited to^{3,4}: Grief, fear, anger, and extreme emotions. Physical stressors of Takotsubo include but are not limited to^{3,4}: High fever, stroke, seizure, difficulty breathing, significant bleeding, and low blood sugar. These stressors are prevalent conditions among populations that have recently experienced natural disasters.

Since 2006, diagnosed cases of Takotsubo have been on the rise⁵. This could be partly attributed to the increased awareness of Takotsubo, but could also reflect the rising trend of emotional stress and a lack of capacity to deal with such pressures. For example, in the United States, reports of loneliness have increased linearly since the 1970s⁶. Furthermore, Takotsubo disproportionately affects women. Its prevalence is roughly 2% in patients presenting with clinical manifestations of acute coronary syndrome,

but rises to 10% if only women are considered. However, this figure is most likely under-recognized as the condition is sometimes undiagnosed⁷, but this number is growing. As of 2012, roughly 7000 cases of Takotsubo have been reported in the United States, an increase in incidence of over 20 times⁷. Moreover, the risk of Takotsubo is often underestimated, and its pathogenesis is unclear.

Hence, further research on Takotsubo needs to be conducted. Many misconceptions about the disease have emerged, partly due to the lack of knowledge and disproven results from earlier reports. As a whole, Takotsubo is incorrectly considered to be a benign disease of “clean” coronary arteries caused by an emotional trigger that can “self-heal.” In reality, Takotsubo is not a benign disease⁷, is not always preceded by an emotional trigger⁷, and does not require “clean” arteries. Based on the current literature on Takotsubo, this study will focus on presenting a comprehensive view of the disease to reduce some pitfalls and misinterpretations during diagnosis and management.

Post-menopausal women, and women in general, are most at risk of developing Takotsubo, with the risk of development increasing five times after age 55⁷. Up to 90% of Takotsubo diagnoses are of women¹. Although the exact reason for this is unknown, it is hypothesized that the female hormone estrogen protects the heart from the harmful effects of stress. For example, estrogen clears up LDL (Low-Density Lipoprotein) and increases the presence of HDL (High-Density Lipoprotein). It also removes free radicals within the blood, which may improve takotsubo symptoms, as it might lower the local oxidative stress¹. As women age, their estrogen levels decline, and they become vulnerable to Takotsubo. Other risk factors of Takotsubo include depression, anxiety, or other mental illnesses⁷.

Despite the disease being described over 30 years ago, the cause of the disease, its exact physiological processes and courses of standard treatment are still unclear. However, with more cases being identified, a symptoms and diagnostic criteria have been established.

Symptoms and Diagnostic Criteria

Symptoms of Takotsubo closely resemble those of a heart attack, for example, sudden, severe chest pain, shortness of breath, intense sweating, and dizziness. However, Takotsubo may be felt within minutes up to hours of the trigger, whereas heart attack symptoms are felt as soon as blood and oxygen supply is cut off⁸.

The Revised Mayo Clinic Criteria are widely used for the diagnosis of Takotsubo. To be diagnosed with Takotsubo, four of the following conditions must be met⁹:

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

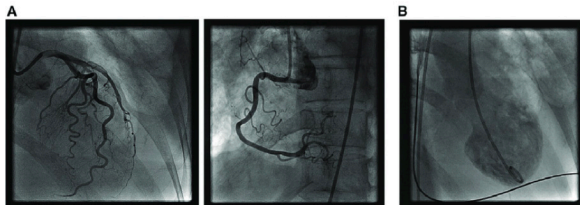


Figure 2. (A) Coronary angiogram demonstrating normal left and right systems. The heart is functioning as normal (B) Left ventriculogram demonstrating apical ballooning consistent with Takotsubo,¹⁰ with the left ventricle being enlarged

In practice, Takotsubo is most commonly diagnosed when cardiac catheterization of a patient with a suspected heart attack reveals no blockage, as shown in Figure 2.

Potential mechanisms of action (MOA)

Although Takotsubo and heart attacks share similar symptoms, their underlying causes differ. A

complete or near-complete blockage of a coronary artery generally causes heart attacks. While in Takotsubo, arteries are not blocked, arterial blood flow may be reduced due to a weakened left ventricle.

During Takotsubo, the heart muscle suddenly becomes weakened, and the left ventricle balloons at the heart's apex. The shape change affects the heart's ability to pump blood and may lead to permanent changes to the heart's pumping motion. Takotsubo may delay the twisting motion of the heart, and its squeezing movement may be reduced. Parts of heart muscle were also found to be replaced with fine scars, reducing the heart's elasticity and preventing it from contracting properly. These results may explain why Takotsubo survivors have similar long-term life expectancies to survivors of heart attacks¹¹.

The specific mechanism of action (MOA) leading to Takotsubo is unknown. However, catecholamines, the chemicals released during the stress condition, such as epinephrine and norepinephrine, are hypothesized to contribute to apical ballooning of the heart, leading to Takotsubo. The administration of catecholamines in animal heart models has been shown to cause Takotsubo-like changes¹. There have also been reports of humans experiencing Takotsubo after being administered high doses of catecholamines¹².

However, it is unlikely that catecholamines are the sole cause of this syndrome, as most humans exposed to stressful situations, which result in the release of catecholamines, do not experience Takotsubo.

Potential treatments

Currently, the standard-of-care for Takotsubo has not been established, as its definitive MOA is unclear. However, a battery of treatments exists to manage the known pathophysiologic consequences and complications after the occurrence of the disease (Table 1)^{13,14}.

Table 1. Complications of Takotsubo and recommended therapies

Complications	Recommended Therapy
Asymptomatic/Normotensive/Normocardic	Supportive care, void anticoagulants, continuous ECG Monitoring for emergence of arrhythmias and QTc prolongation
Angina	Sublingual or intravenous nitroglycerin, organic nitrates, β -blockers
Dyspnea	Monitored closely. Diuretics, nitrates, and β -blockers, depending on the presence/absence of tachycardia, hypertension, bradycardia, hypotension, and evidence of LVOT, mechanical respiratory support
Hypertension	Short or ultrashort acting β -blockers
Hypotension	Monitored closely. Intravenous fluid intake, α_1 -agonist
Bradycardia and/or Atrioventricular Blocks	Small doses of atropine
LVEF < 30% and/or Large Apical Akinesis/Dyskinesis	Closely monitored for HF, cardiogenic shock, atrial arrhythmias and lethal MA, and thrombus formation
Thrombus and Prevention of Embolism	Unfractionated heparin, low-molecular-weight-heparin (LMWH), vitamin K antagonists, aspirin, and/or P2Y12 receptor antagonists such as clopidogrel, prasugrel, or ticagrelor, or the new oral anticoagulants
Left Ventricular Outflow Tract Obstruction	Intravenous metoprolol, esmolol, or landiolol
Heart Failure	Aspirin, avoid Positive inotropic agents and vasodilators
Mitral Regurgitation	Follow principles of therapy for LVOTO
Right Ventricular Involvement	Monitored for hypotension, RV failure, RV thrombus
Cardiogenic Shock	Estimating or measuring cardiac output, SVR, and organ perfusion
Heart Rupture	Avoided by early employment of β -blockers
Atrial Arrhythmias	β -blockers
Ventricular Arrhythmias	Short-acting β -blockers
Cardiac Arrest	Monitor thoracic ECG signals indicative of stellate ganglia nerve input to the heart
Pericarditis	Thrombolytic therapy, anti-coagulants, and glycoprotein IIb/IIIa inhibitors
Adrenergic Cardiac Innervation	α -lipoic acid therapy

Prevention

When preventing the recurrence of Takotsubo, it has been shown that β -blockers, ACEi/ARB, and aspirin have not prevented a recurrence, lowered its severity, or improved survival. There has also been no clinical data supporting the use of estrogens to prevent Takotsubo¹³. Instead, endocrinological and malignant comorbidities should be treated to reduce the impacts of Takotsubo.

Case Studies

Three case studies of Takotsubo patients will be examined. Although Takotsubo often presents with other physical stressors, such as illnesses, the disease can appear acutely without warning. The first two patients are presented alongside other stressors, while the third is presented with Takotsubo alone.

The first case study is of a 63-year-old female presented with an 8-10 hour history of progressive dyspnea. She has completed her third cycle of Perjeta plus Herceptin and Abraxane chemotherapy for HER2-positive breast cancer. The high burden of disease in the left breast metastasized to the chest wall, lymph nodes and lungs. Her blood pressure was 142/92 mmHg, her heart rate was 110 BPM, and her oxygen saturation was 91% in room air. She had no preexisting cardiovascular disease except for “white coat” hypertension, which was well-controlled. Approximately two months ago, a baseline acquisition scan about two months ago demonstrated an ejection fraction >65% with no wall motion abnormalities. The patient showed apical ballooning consistent with Takotsubo, and a standard heart failure procedure was initiated while cancer therapy was ceased. The patient chose to pursue comfort care and died approximately one month later¹⁵. Combined with the emotional and psychological stress associated with a cancer diagnosis, combination therapy with anti-HER2 antibodies could have contributed to Takotsubos, as it possesses cardiotoxic properties¹⁵.

The second case study is of a 66-year-old female with mild coronary artery disease, emphysema, hypertension, and pancreatic cancer who presented to the hospital with worsening dyspnea, chest tightness, and diaphoresis. She recently started Capecitabine as part of her pancreatic cancer treatment and received one dose about three days before symptoms. Her heart rate was 140 BPM, but she was vitally stable otherwise. She was eventually diagnosed with Capecitabine-induced Takotsubo. Capecitabine was discontinued, while heart failure therapy was started. One week later, she recovered¹⁶.

Although Takotsubo is rare, it may be potentially devastating to the patient. Whether Capecitabine is a bystander or the offending chemical agent, it must be stopped, and heart failure therapy must be initiated. A new treatment plan must be

created for the patient to improve the prognosis.

The third case study is of a previously healthy 49-year-old female who suddenly complained of chest discomfort stretching to both arms. Her EKG showed ST segment elevation and evidence of possible inferolateral myocardial infarction. A cardiac catheter was inserted but showed no evidence of coronary artery disease that impacted circulation. Her residual ejection fraction was 30%, showing profound left ventricular dysfunction. No physical or emotional stressors were identified, and she was treated with nitrates and ACE inhibitors¹⁷.

In conclusion, Takotsubo Cardiomyopathy is a disease that could appear acutely with no previously identifiable stressors. It affects all age groups, but most significantly post-menopausal women, with annual diagnoses rising as the disease becomes more prevalent in scientific literature. Catecholamines are suspected to play a role, and medications exist that reduce complications after an episode. However, this is not enough. The specific mode of action of Takotsubo is still unknown, and an effective standard-of-care for Takotsubo has not been developed. Therefore it is essential to conduct more research into the mechanisms of action of the disease so it can be quickly identified and treated with appropriate medications and so that conditions would not go undiagnosed and potentially recur in patients.

References

1. Boyd, Brenton MMSc, PA-C; Solh, Tia MSPAS, PA-C Takotsubo cardiomyopathy, JAAPA: March 2020 - Volume 33 - Issue 3 - p 24-29 doi: 10.1097/01.JAA.0000654368.35241.fc
2. Buttner, R., & Burns, E. (2021, April 29). Takotsubo cardiomyopathy. *Life in the Fast Lane • LITFL*. Retrieved June 12, 2022, from <https://litfl.com/takotsubo-cardiomyopathy-ecg-library/>
3. Shor Wittstein, I. (2021, October 16). Broken heart syndrome. Johns Hopkins Medicine. Retrieved June 12, 2022, from <https://www.hopkinsmedicine.org/health/conditions-and-diseases/broken-heart-syndrome>
4. Heart, H. (2022, May 19). Takotsubo cardiomyopathy (broken-heart syndrome). Harvard Health. Retrieved June 12, 2022, from <https://www.health.harvard.edu/heart-health/takotsubo-cardiomyopathy-broken-heart-syndrome>
5. Lee, B. Y. (2022, April 21). Broken heart syndrome has risen since 2006, especially among women. *Forbes*. Retrieved June 12, 2022, from <https://www.forbes.com/sites/brucelee/2021/11/13/broken-heart-syndrome-has-risen-since-2006-especially-among-women/?sh=69cd0f41a8ff>
6. Buecker, S., Mund, M., Chwastek, S., Sostmann, M., & Luhmann, M. (2021). Is loneliness in emerging adults increasing over time? A preregistered cross-temporal meta-analysis and systematic review. *Psychological Bulletin*, 147(8), 787–805. <https://doi.org/10.1037/bul0000332>
7. Cleveland, C. (2021, February 10). Broken heart syndrome (takotsubo cardiomyopathy): Symptoms & treatments. Cleveland Clinic. Retrieved June 12, 2022, from <https://my.clevelandclinic.org/health/diseases/17857-broken-heart-syndrome>
8. Hopkins, J. (2014, June 11). Heart attack. Johns Hopkins Medicine. Retrieved June 12, 2022, from <https://www.hopkinsmedicine.org/health/conditions-and-diseases/heart-attack>
9. Komamura, K., Fukui, M., Iwasaku, T., Hirotsu, S., & Masuyama, T. (2014). Takotsubo cardiomyopathy: Pathophysiology, diagnosis and treatment. *World journal of cardiology*, 6(7), 602–609. <https://doi.org/10.4330/wjc.v6.i7.602>
10. Jerzak, Katarzyna & Lees, Caitlin. (2018). Takotsubo Cardiomyopathy During Anti-HER2 Therapy for Metastatic Breast Cancer. *The Oncologist*. 10.1634/theoncologist.2018-0285
11. British Heart Foundation, O. (2017, June 16). Research shows broken heart syndrome causes long lasting heart damage. Welcome to the British Heart Foundation. Retrieved June 12, 2022, from <https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2017/june/research-shows-broken-heart-syndrome-causes-long-lasting-heart-damage>

12. Jacob Abraham, James O. Mudd, Navin Kapur, Kelly Klein, Hunter C. Champion, Ilan S. Wittstein, Stress Cardiomyopathy After Intravenous Administration of Catecholamines and Beta-Receptor Agonists, *Journal of the American College of Cardiology*, Volume 53, Issue 15, 2009, Pages 1320-1325, ISSN 0735-1097, <https://doi.org/10.1016/j.jacc.2009.02.020>.
13. Madias J. E. (2021). Takotsubo Cardiomyopathy: Current Treatment. *Journal of clinical medicine*, 10(15), 3440. <https://doi.org/10.3390/jcm10153440>
14. Marfella, R., Barbieri, M., Sardu, C., Rizzo, M. R., Siniscalchi, M., Paolisso, P., Ambrosino, M., Fava, I., Materazzi, C., Cinquegrana, G., Gottilla, R., Elia, L. R., D'andrea, D., Coppola, A., Rambaldi, P. F., Mauro, C., Mansi, L., & Paolisso, G. (2016). Effects of α -lipoic acid therapy on sympathetic heart innervation in patients with previous experience of transient takotsubo cardiomyopathy. *Journal of cardiology*, 67(2), 153–161. <https://doi.org/10.1016/j.jjcc.2015.07.012>
15. Lees, C., Yazdan-Ashoori, P., Jerzak, K. J., & Gandhi, S. (2019). Takotsubo Cardiomyopathy During Anti-HER2 Therapy for Metastatic Breast Cancer. *The oncologist*, 24(2), e80–e82. <https://doi.org/10.1634/theoncologist.2018-0285>
16. Ramy Abdelmaseih, Anamaris Blanco, Randa Abdelmasih, Krutika Desai, Joshua Pothan, Jay Patel, Rama Balaraman, Cardio-oncology: Capecitabine Can Sometimes be Heatbreaking Capecitabine-Induced Takotsubo Cardiomyopathy Case Report and Literature Review, *Current Problems in Cardiology*, Volume 46, Issue 8, 2021, 100854, ISSN 0146-2806, <https://doi.org/10.1016/j.cpcardiol.2021.100854>.
17. Chlus, N., Cavayero, C., Kar, P., & Kar, S. (2016). Takotsubo Cardiomyopathy: Case Series and Literature Review. *Cureus*, 8(6), e649. <https://doi.org/10.7759/cureus.649>