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Lessons from the trials

Takotsubo cardiomyopathy: A potentially serious trap (Data from the International Takotsubo Cardiomyopathy Registry)

Kerolos Wagdy, Mohamed ElMaghawry*

Department of Cardiology, Aswan Heart Centre, Aswan, Egypt

*Email: Mohamed.elmaghawry@aswanheartcentre.com

ABSTRACT

Takotsubo cardiomyopathy (TTC) is an acute cardiac condition characterized by transient left ventricular dysfunction with wall motion abnormalities, most commonly in the form of apical ballooning. Despite being considered as a generally benign condition, many studies have emphasized potentially sinister outcomes associated with TTC. In this article, we review the most recent results of the International Takotsubo Registry, which investigated the clinical features, prognostic predictors, and outcomes of 1750 patients.

Keywords: takotsubo, stress induced, cardiomyopathy, epidemiology, outcomes

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Takotsubo ya
hakanaki yume o
natsu no tsuki
Mere octopus traps,
Evanescent dreams beneath
A midsummer moon
Bashō, Japanese poet (1688)

INTRODUCTION

Takotsubo cardiomyopathy (TTC) is an acute cardiac syndrome characterized by transient left ventricular dysfunction with wall motion abnormalities, most commonly in the form of apical ballooning. *Takostsubo* is a Japanese octopus fishing trap, which best describes the characterstic left ventricular apical ballooning that occurs during the acute phase of the disease (Figure 1). The clinical entity was first described in 1990, and since then many reports have further described the clinical features of the disease.[1] However, the collective data concerning the epidemiology, pathophysiology, management and clinical outcomes of takutsubo cardiomyopathy are still considered limited. Recently, the International Takotsubo Registry, a consortium of 26 centres in Europe and the United States, published the clinical features and outcomes of 1750 patients with TTC in the *New England Journal of Medicine*.[2]

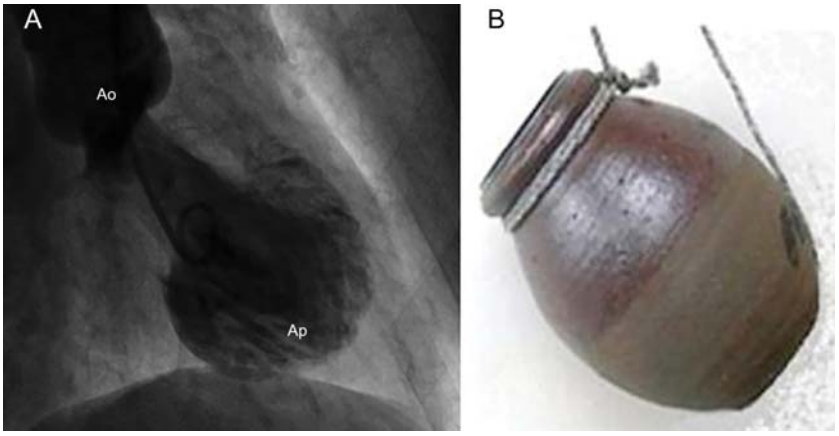

Figure 1. A: Ventriculography frame in systole, showing apical akinesia ("apical ballooning") Ap: left ventricular apex; Ao: aortic root. B: Traditional Japanese octopus fishing pot. The "takotsubo" is a jar that is lowered into the water by fishermen in the afternoon. The octopus head gets strapped inside the pot and collected the next day.

STUDY DESIGN AND RESULTS

The International Takotsubo Registry was established at University Hospital Zurich in collaboration with 25 other cardiovascular centers across nine countries (Austria, Finland, France, Germany, Italy, Poland, Switzerland, the United Kingdom, and the United States). The registry investigated the clinical features, prognostic predictors, and outcomes of 1750 patients diagnosed with TTC between 1998 and 2014. In addition, a subgroup of 455 TTC patients was compared with age- and sex-matched patients with acute coronary syndrome.

The main results showed that TTC was more commonly diagnosed in females than in males, with a 9:1 ratio. The mean age of patients was 66.8 years. Only 71.5% of patients had an obvious trigger for TTC: emotional (27.7%), physical (36%), or both (7.8%), while the rest of the patients had no evident trigger. Apical TTC was identified in 81.7% of patients, whereas the midventricular form was found in 14.6%, and basal and focal forms were diagnosed in 2.2% and 1.5%, respectively (Figure 2).[2]

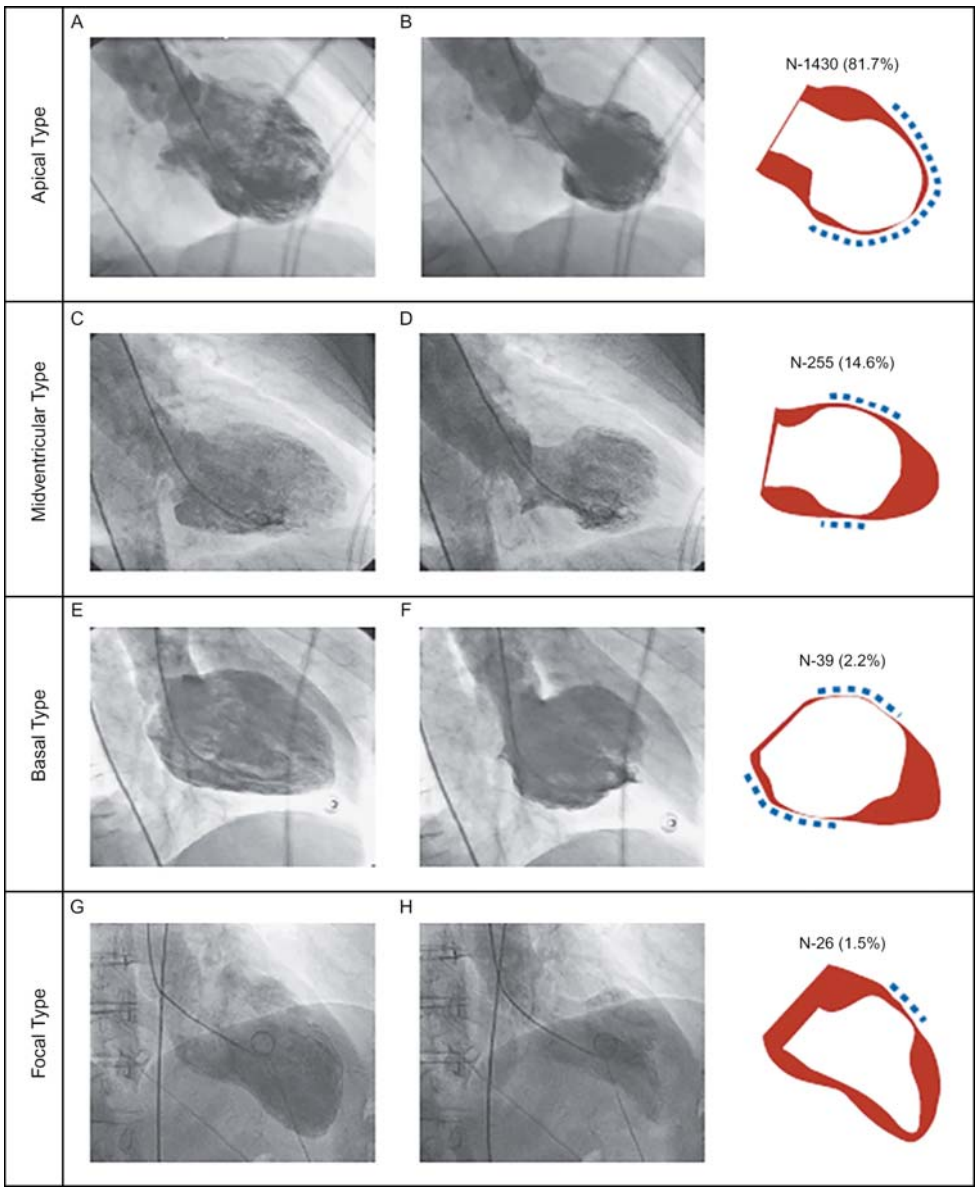

Figure 2. The four types of takotsubo cardiomyopathy. Apical type (Panels A and B), midventricular type (Panels C and D), the basal type (Panels E and F) and the focal type (Panels G and H). Source: Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med.* 2015;373 (10):929–38.

In comparison with acute coronary syndrome, patients with TTC had significantly higher rates of neurological or psychiatric disorders (55.8% vs. 25.7%, $p < 0.001$) and significantly lower mean left ventricular ejection fraction (40.7 ± 11.2% vs. 51.5 ± 12.3%, $p < 0.001$).

Concerning outcomes, 21.8% of TTC patients had reached the combined end-point of serious in-hospital complications. This included death (4.1%), cardiogenic shock (9.9%), ventricular arrhythmias (3.0%), ventricular thrombus (1.3%), and ventricular rupture (0.2%). These rates of severe in-hospital complications were similar to the rates observed in the acute coronary syndrome group ($p = 0.93$). Physical triggers, acute neurological or psychiatric diseases, high troponin levels, and a low ejection fraction on admission were independent predictors for in-hospital complications. During long-term follow-up, the rate of major adverse cardiac and cerebrovascular events was 9.9% per patient-year, and the rate of death was 5.6% per patient-year. During long term follow-up, which spanned from 25 days up to 9 years, the rate of recurrence of TTC was 1.8% per patient-year (Figure 3).

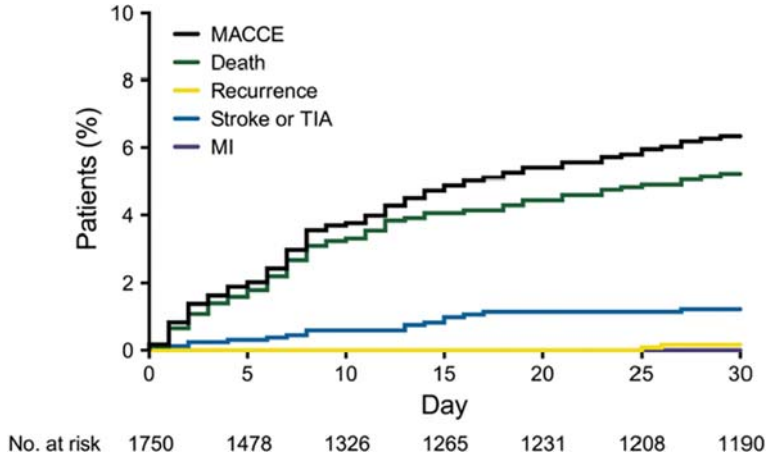

Figure 3. Kaplan – Meier Estimates of 10-Year Outcome Events of International Takotsubo Registry. MACCE: major adverse cardiac and cerebrovascular events, TIA: transient ischemic attack, MI: myocardial infarction. Source: Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373 (10):929 – 38.

DISCUSSION

Definition of takotsubo cardiomyopathy

TTC is an acute cardiac condition characterized by transient left ventricular dysfunction with wall motion abnormalities, most commonly in the form of apical ballooning.[3] It was first described in five Japanese cases by Dote et al in 1990. The authors coined the term "takotsubo" to describe the syndrome, as the left ventricular apical ballooning during the acute phase resemble a Japanese octopus fishing trap.[1] Typically, these changes occur after physical or emotional stress, therefore, the syndrome is also known as "broken heart syndrome" or stress cardiomyopathy.[4,5] In 2012, Deshmukh and colleagues analysed the data of 6,837 patients with TTC from the Nationwide Inpatient Sample database of 2008, which consisted of 33,506,406 patients. From this study, the authors estimated the prevalence rate of TTC in the population to be approximately 0.02%.[6]

Clinical picture and investigations

TTC mimics the clinical picture of acute coronary syndrome with chest pain, ST-segment elevation, cardiac markers elevation, and left ventricle wall motion abnormalities.[7,8] Several criteria have been proposed to diagnose TTC, such as the Gothenberg, Italian, Mayo Clinic, and MRI-based criteria.[9 – 12] The Mayo Clinic criteria are the most widely adopted diagnostic criteria: transient akinesis or dyskinesis of left ventricular wall motion abnormalities (ballooning) and chest pain, electrocardiographic changes (ST segment elevation or T wave inversion), no substantial obstructive epicardial coronary artery disease, and absence of pheochromocytoma or myocarditis. Yet, the clinical diagnosis of TTC remains challenging and essentially based on the exclusion of acute coronary syndrome. Investigators have been trying to establish clinical and instrumental features that are specific for TTC. ECG changes of typical TTC occur in a specific pattern. In the acute phase, prominent J waves may occur followed by mild and diffuse ST-segment elevation in precordial leads, usually in V3-6. The ST-segment elevation is later replaced by diffuse T-wave inversion and QTc interval prolongation. After 7 to 10 days the T waves normalize then they become negative again (Figure 4). The ECG completely normalizes in few weeks.[13,14] In variance to patients with anterior-apical myocardial infarction, TTC show lower maximum ST elevation $\leq$2mm, more PR depression, J wave and more ST segment elevation in lead II.[15]

Echocardiographic features of TTC include left ventricular dysfunction due to akinesia of mid-apical segments of the left ventricle (apical ballooning) (Figure 5). However, other variants have been described including mid and basal segments akinesia. In addition, some patients during the acute phase of TTC show systolic anterior motion of the anterior mitral leaflet and moderate mitral regurgitation which can also generate mid-ventricular obstruction.[16]

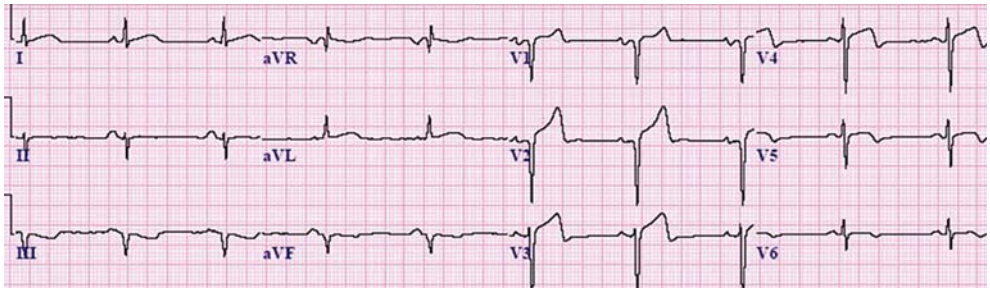

Figure 4. Typical electrogradiographic findings of the early phase of takotsubo cardiomyography showing ST-segment elevation in the anterior precordial leads (V1-V4). From internet: http://www.learntheheart.com/takotsubo-ecg/.

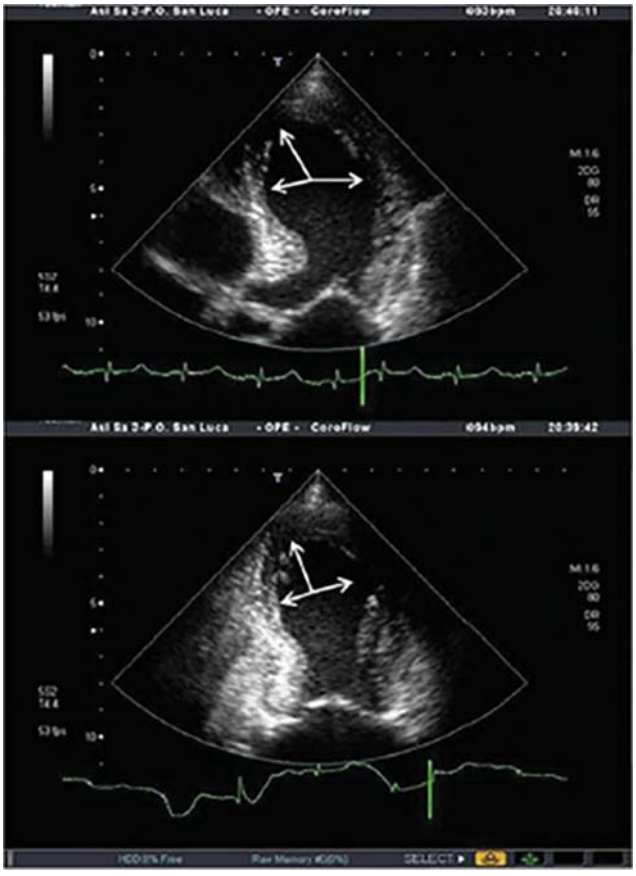

Figure 5. Transthoracic echocardiography of takotsubo cardiomyopathy; apical views showing apical ballooning. Source: Citro R, Piscione F, Parodi G, Salerno-Uriarte J, Bossone E. Role of echocardiography in Takotsubo cardiomyopathy. *Heart Fail Clin*. 2013;9(2):157–66.

Cardiac magnetic resonance rules out an acute myocardial infarction by showing the absence of gadolinium late-enhancement. Myocardial edema in the affected left ventricular segments is demonstrated by T2 sequence. Specific to TTC, the edema resolves at follow-up with the normalization of the left ventricle systolic function and ECG changes (Figure 6).[12,17,18]

Currently there are no established biomarkers for the diagnosis of TTC. MicroRNAs emerge as promising sensitive and specific biomarkers for cardiovascular disease.[19,20] A recent study proved certain circulating miRNAs can distinguish TTC from STEMI patients.[21] In addition, the significant up-regulation of the stress- and depression-related miRNAs suggests a close connection of TTC with neuropsychiatric disorders.[21]

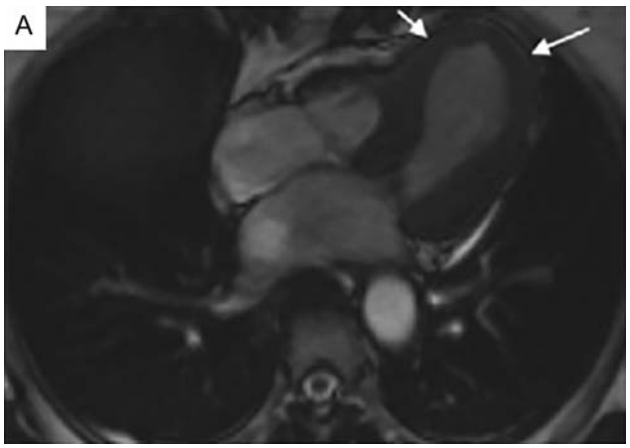

Figure 6. Cardiac magnetic resonance imaging showing typical findings of takotsubo cardiomyopathy. Cine sequence shows apical ballooning during systole (arrow). Source: Kohan AA, Levy Yeyati E, De Stefano L, Dragonetti L, Pietrani M, Perez de Arenaza D, et al. Usefulness of MRI in takotsubo cardiomyopathy: A review of the literature. *Cardiovasc Diagn Ther*. 2014;4(2):138–46.

Pathophysiology

The main hypothesis for the pathophysiology of TTC is that an increase in the level of serum catecholamines causes direct myocardial toxicity, leading to reversible myocardial inflammation, and dysfunction.[22–24] In addition, catecholaminergic surges cause acute multivessel microvascular coronary spasm, myocardial stunning, and excessive transient ventricular afterload. The sympathetic overstimulation can be caused by emotional or physical stresses (such as anger, loss of a partner, financial loss, natural disasters, severe illnesses, and severe pain), exogenous sympathomimetics (such as cocaine), or withdrawal of sympathetic antagonists, such as opioids.[25,26] Interestingly, a recent clinically-based study showed that myocardial bridging of the LAD artery was detected in 76% of TTC patients, either by angiography or MSCT. This observation proposes that TTC results from a complex physiological interplay between surging circulating catecholamines and transient coronary flow insufficiency.[27] However, further experimental and clinical studies are needed to prove this hypothesis.

There are limited data on the histopathological features of TTC in humans. However, histiological findings during the acute phase of TTC show characteristic morphologic changes similar to the cardiotoxic effects induced by catecholamines. These findings include damage of contractile proteins, enlarged diameter of myocytes, clusters of abnormal mitochondria, and abnormal nuclei.[24,28] On the other hand, in TTC, there are no signs of necrosis or oncotic cell death that are usually associated with ischemia. During the recovery phase, there is rearrangement of cytoskeletal and contractile proteins with a characteristic rapid regression of fibrosis.[29]

Rat models showed that the administration of high dose epinephrine, but not norepinephrine, caused a reversible left ventricular apical hypo-contractility associated with basal hyper-contractility, mimicking typical TTC.[30] The epinephrine-induced effect can be explained by the agonist effect of epinephrine on β2AR-Gs at low doses and for β2AR-Gi at high doses, with a differential apico-basal gradient in β2ARs distribution. The β2AR-Gi dependent epinephrine effect was further reproduced *in vitro*. This suggests that epinephrine β2AR-Gi signaling may have evolved as a cardioprotective strategy to limit catecholamine-induced myocardial toxicity during acute stress.[30]

Critique of the current study

The current results of the International Takotsubo Registry have many intriguing points. First, the registry reviewed a large number of patients based on the Mayo Clinic criteria. However, the investigators made few significant exceptions to these criteria that included coexisiting coronary artery disease and the presence of wall motion abnormality that was specific to a single artery territory. These exceptions to the Mayo Clinic criteria have led to the inclusion of larger number of patients. More importantly, they will prompt cardiologists to consider the possible diagnosis of TTC in the presence of concomitant coronary artery disease (15.3% of patients), and the presence of non-apical TTC variants

such as mid and basal types. Second, unlike the common belief, the in-hospital results of the current study emphasize the potentially sinister course of TTC. In fact, in-hospital serious complication rates were similar in patients with ACS and TTC. Third, the extended follow up period of the registry (up to 9 years) has allowed to better study the "natural history" of the disease. Even after the acute phase, TTC is not completely benign, with a rate of death per patient-year of 5.6% and a rate of stroke or transient ischemic attack of 1.7% per patient-year. Finally, and most interestingly, the study showed that the use of beta-blockers did not prevent the occurrence of TTC, as 32.5% of the patients were using beta-blockers at time of presentations. Furthermore, beta-blockers did not prevent TTC recurrence as 29 out of 57 patients with recurrent TTC were on beta-blockers. These findings question of the fundamental notion of the role of catcholamingeric surge in the pathophysiology of TTC.

On the other hand, the current study was a retrospective observational analysis that carries the inherent limitations of similar observational studies; for example, there were no direct comparisons between any diagnostic or therapeutic strategies. In addition, a large number of patients (468) had their data missing at 30-day follow up. Furthermore, the study lacked information on the cardiac magnetic resonance imaging and histopathology features of TTC.

WHAT HAVE WE LEARNT?

The clinical features and outcomes of the International Takostubo Cardiomyopathy provide key concepts for better understanding TTC. TTC does not necessarily occur after obvious physical or emotional stress. TTC is not a benign condition and it carries significant early and late serious complication risks. It can occur concomitantly in the presence of coronary artery disease and can present with non-typical forms such as mid and basal variants. More research is needed to further characterize the histopathological, electrocardiographic, imaging and clinical features of the disease. In addition, future studies ought to focus on the potential role of microRNAs as sensitive and specific biomarkers of TTC. Finally, more global cardiology awareness should be directed towards this particular cardiomyopathy that represents a potentially serious trap.

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