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Review Article

TAKOTSUBO SYNDROME, TAKOTSUBO CARDIOMYOPATHY: FROM VOODOO DEATH TO BROKEN HEARTS, AND ONWARDS REVIEW ARTICLE AND LITERATURE SEARCH

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A B S T R A C T

Takotsubo cardiomyopathy is rapidly reversible heart failure syndrome that usually mimics the symptoms of acute myocardial infarction with the characteristic regional wall-motion abnormalities (classically with a virtual apical ballooning caused by hypokinetic or akinetic apical or midventricular myocardium and hypercontraction of the basal segments) and absence of obstructive coronary artery disease. TC is usually associated with identifiable emotional, psychological or physical stress event and most commonly appears in postmenopausal women. The certain pathophysiological mechanism remains unknown. However, the central hypothesis is supported by the excess of catecholamines and hyperactivity of nervous system.

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INTRODUCTION

Background

Despite being a common motif in myths, religion and literature until recently the notion that one could suffer cardiac death from a broken heart was not taken very seriously by the medical establishment. Today's wide acceptance of Takotsubo syndrome as an important cardiologic diagnosis is largely the result of a series of publications in Japan in the early 90's begun by Sato *et al*[1]. Today this syndrome has many names: Takotsubo, Takotsubo Syndrome (TS), Broken heart syndrome and stress induced cardiomyopathy are all used in different contexts. The name Takotsubo comes from a pot used in Japan to trap octopus, in the typical TS the shape of the akinetic ventricular apex (Fig-1) reminded the Japanese physicians of this pot and hence the name[2].

Before these, more recent, publications the phenomenon was described many times but never reallyreceived attention from the wider medical community.

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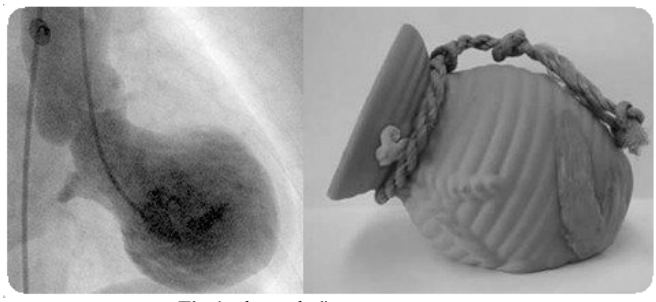


Fig 1 tako-tsubo" - an octopus trap

Among the first in the modern era to hypothesize a connection between excessive mental stress and sudden cardiac death was the Harvard anthropologist Walter B. Cannon who suggested that some deaths he observed in the Caribbean in people who had recently been cursed by witch doctors where caused simply by the stress of being aware that one had been cursed, he termed this phenomenon Voodoo death[3]. Later in the 1980's Caleb and Hirsch, two American pathologists, published a study of the histologic findings in a series of patients suffering sudden death following assault where there was no obvious physical injury to explain death[4].

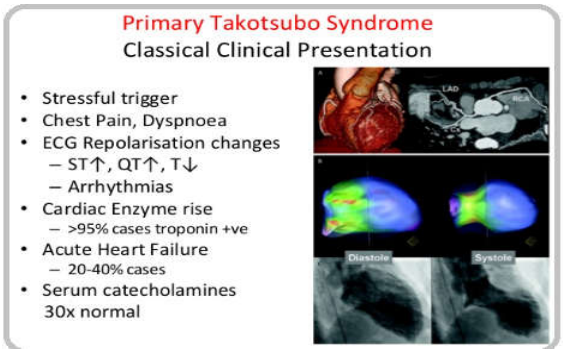
Histologically they found myocardial damage identical to the damage caused by excessive levels of circulating catecholamines.(Fig-5)

This led them to suggest that they had died of sudden cardiac stress following a surge of circulating catecholamines caused by the psychological stress of the assault, they called this phenomenon Stress induced cardiomyopathy.

This term has been revived and suggested as a more rational replacement for the term Takotsubo, with mixed success. The term Broken heart originated from the early Japanese publications where a majority of patients where recently widowed elderly women[5].

While the loss of a loved one has proven to be just one of many stressful events capable of causing TS and recent publications have shown even positive events such as receiving awards can cause TS[6], post-menopausal women have proven to be the most susceptible and account for roughly 90% of TS patients[7]. Women of child bearing age and men also develop TS but more commonly secondary to a serious medical condition such as sub-arachnoid hemorrhage.

After the Japanese studies TS gradually received more attention and awareness of the diagnosis increased. Until recently TS was seen primarily as a differential diagnosis to myocardial infarction in patients presenting with sudden chest pain. (Fig-2) S Zeraatian MD[1] *et al* 2018



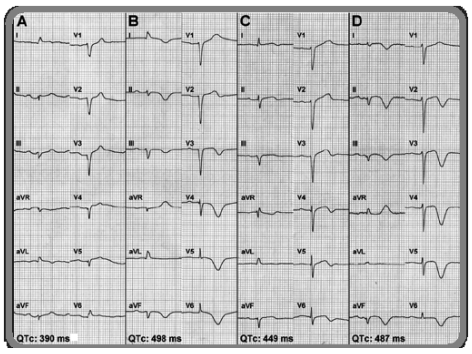


Fig 2(ECG) abnormalities in takotsubo syndrome

This was due to the similarity in presentation in some patients, TS can present with chest pain, ECG changes, elevated myocardial injury markers and akinetic parts of the ventricle on echocardiography, making it necessary to rule out myocardial infarction using coronary angiography. Patients can present with some, or even none, of the symptoms but as coronary angiography or repeated echocardiography (fig-4) is necessary for diagnosis[2] it is not unreasonable to assume that there might, at any one time, exist a significant number of TS patients that are never diagnosed properly or where the TS is simply sub-clinical and therefore never receive echocardiography or coronary angiography.

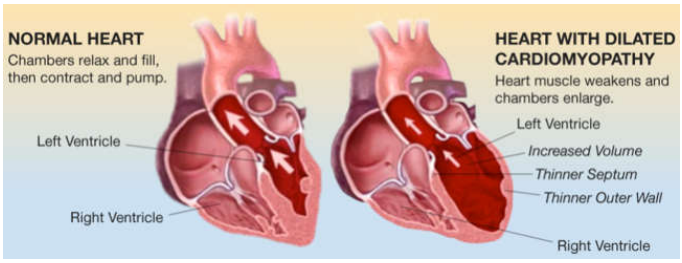


Fig 3

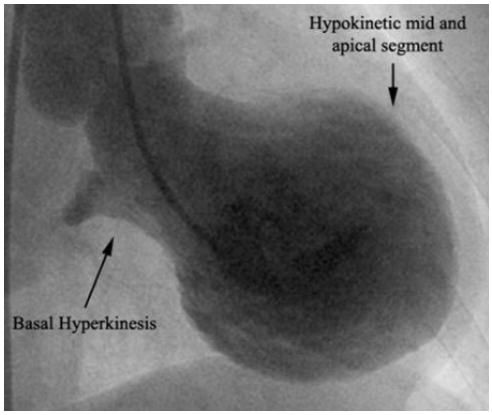


Fig 4

Although the most common TS morphology is the apical variant where the apex of the right ventricle is akinetic while the base is hyperkinetic, commonly termed typical TS, any part of either ventricle can be affected[7]. In the literature akinesia affecting the basal part of the ventricle is either termed atypical or simply basal TS and (fig-3) intermediate forms are often referred to as atypical. Initially TS was considered a benign self-limiting disease and remained so for a long time. Recent publications on American and Swedish TS patients suggest a mortality comparable to that of myocardial infarction in both short and long term[7, 8].

Pathology

As TS gained recognition in the 90's excessive amounts of circulating catecholamines was early on suggested as a possible mechanism of disease[9]. This hypothesis received further confirmation as cases where pheochromocytoma[10], over administration of catecholamines and sudden lifting of β-blockade caused TS where published. Later several publications where able to show that TS patients typically had higher levels of circulating catecholamines compared to MI patients[9], but the mechanism by which catecholamines might cause akinesia to remain elusive and today several different theories exist. (Fig-5 Pathology of takotsubo cardiomyopathy)

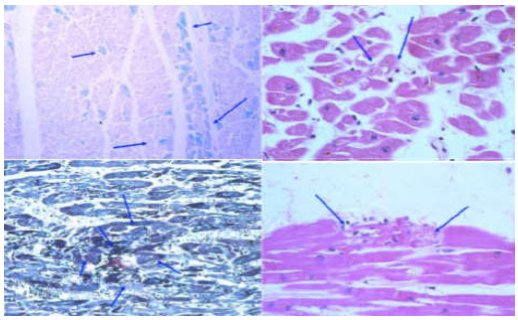


Fig 5 Pathology of takotsubo cardiomyopathy, from: Sachio Kawai, Pathology of Takotsubo (Ampulla) Cardiomyopathy Department of Cardiology, Juntendo University School of Medicine, Tokyo

Upper left: Damaged individual myocytes or a group of myocytes had increased eosinophil staining. Inner layer of the base: Luxol fast blue stain, x 200.

Lower left: Middle layer of the apex: Phosphoptungstic acid hematoxylin stain, x 200.

Upper right: Injured cardiac myocytes are removed by infiltrated macrophages. Apical anterior, middle layer. Hematoxylin and eosin (H&E) stain, x 400.

Lower right: Myocardial damage was observed even in the epicardial aspect which was difficult to explain by disorder of coronary circulation. Apical posterior, external layer. H&E stain, x 400.

The similarity to myocardial stunning and hibernation where parts of the ventricle also become temporarily akinetic but in the presence of an observable ischemia suggests some form of supply/demand mismatch might be part of TS pathology but how the catecholamine surge gives rise to the akinesia remains unknown. The numerous published theories can roughly be categorized as vascular, myocardial or cardio-vascular. The vascular theories suggest that a coronary artery is occluded through spasm, an embolus dissolved before angiography or some malformation in the coronary arteries causing ventricular akinesia is secondary to local temporary ischemia.

Others have suggested that the acute increase in afterload caused by a catecholamine surge and the subsequent increase in myocardial strain causes the akinesia. There are two main 'myocardial' theories, that the akinesia is the result of the direct stimulation by circulating catecholamines of adrenergic β_2-receptors on the cardiomyocytes or that the catecholamines create conditions resulting in repeated outflow obstructions the cumulative stress of this in the myocardium giving rise to the akinesia[2]. It is also possible that some combination of these various mechanisms causes the akinesia. It's important to note that many of the proposed theories do not take the mid-ventricular and atypical Takotsubo akinesias into account focusing instead solely on the apical variant.

Clinically some patients develop TS repeatedly whereas certain patients with severe diseases suffering significant physical stress never develop TS or any wall motion abnormality at all. This suggests that there are unknown predisposing and protective factors that play an important role in the development of TS.

Symptoms and findings

As previously noted symptoms, ECG morphology, troponin and NT-proBNP levels may all closely mimic a myocardial infarction.

TS can give rise to all manner of ECG changes and there is no way to reliably differentiate between myocardial ischemia and TS based on findings[2]. Troponin and NT-proBNP levels tend to be elevated although generally less elevated than one would expect from an akinesia of the same size caused by ischemia. Thus, while echocardiography in combination with myocardial injury markers might suggest TS it still is necessary to perform coronary angiography to rule out ischemia and prevent permanent damage to the myocardium.

While the symptoms mimicking a coronary event might be the most spectacular TS presents with a variety of symptoms[7] and therefore we suggest physicians should, especially in post-menopausal women, use echocardiography liberally to rule out TS.

Treatment

At present there exist no randomized trials of any kind and therefore the scientific basis for any one course of treatment is lacking [2].

We therefore suggest treatment should follow the principle of premium nil nocere. In the acute phase we suggest inotropes be avoided if possible and although some use beta-blockers and ACE-inhibitors here there is no evidence to suggest any benefit although some benefit.

Beta-blockers, ACE-inhibitors and statins are commonly prescribed to prevent recurret TS episodes and although the current theories suggest a central role for catecholamines in the pathogenesis the clinical evidence is limited, and the treating physician will have to weigh the pros and cons of any prophylactic medication he prescribes.

A good resource for the treating physician put in this position is the European Society of Cardiologists position paper on TS[2].

CONCLUSIONS

Despite almost thirty years having passed since TS began receiving wider attention from the medical community there is much we do not know about TS. Recent studies suggesting a higher mortality than previously thought highlight the necessity of studying this syndrome further.

Disclosure: The authors declare no conflicts of interest.

Dedication

This article is dedicated to Professor Mostafa Hosseini, the clinic director, Compassionate and kindteacher in surgery Department of Hazrat Rasoul akram University Hospital, Iran Medical University, Iran-Tehran

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