# ZEBRAS OF MEDICINE

# TAKOTSUBO CARDIOMYOPATHY: AN INTRODUCTION TO THE BROKEN HEART SYNDROME

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## Abstract

**Review**

**BACKGROUND:** Takotsubo cardiomyopathy (TTC) is an acute disorder characterised by reversible left ventricular dysfunction. It mostly affects post-menopausal women and is often seen following severe emotional or physical stress.
**OBJECTIVE:** This review aims to summarize the current knowledge on TTC, thereby informing the reader about the existence and management of the condition and how it can be distinguished from a standard acute myocardial infarction (AMI).
**RESULTS:** TTC mimics the clinical presentation of an AMI, as symptoms include sudden onset of chest pain and dyspnoea, but at coronary angiography no coronary occlusion is present. Characteristic of TTC is a balloon-like left ventricle (LV) dysfunction at LV angiography. Complications include cardiac arrest, shock, and thrombus formation. An ECG, cardiac biomarkers, echocardiography or LV angiography, and coronary angiography are needed to confirm the diagnosis. The pathophysiology is still unclear, but hypotheses focus on stress-induced catecholamine cardiotoxicity and a generalized dysfunction of the coronary microvessels. It is unclear yet why women are 9-10x more affected than men. Treatment of TTC consists of medication to restore LV function, but studies have shown that the long-term survival is comparable to that of patients who have suffered from an AMI.
**CONCLUSIONS:** TTC is a variant type of AMI that occurs more frequently in women than men and mimics the symptoms of an AMI. Its pathophysiology is still not well understood, therefore further research is necessary.

**KEYWORDS:** left ventricular dysfunction, emotional stress, infarction, cardiology

## Introduction

Takotsubo cardiomyopathy (TTC) is a disorder characterised by reversible left ventricular dysfunction [1]. They named the disorder takotsubo-like cardiomyopathy, because the shape of the left ventricle during presentation was similar to that of a Japanese octopus-trapping pot (a takotsubo). Since it was first described in 1990, it has become a widely accepted diagnosis in cardiology [2]. Other terms include *transient left ventricular apical ballooning syndrome* and *broken heart syndrome*. The last term refers to the fact that TTC is often seen following an episode of severe physical or emotional stress, which includes the metaphorical breaking of someone's heart. Its clinical presentation is strikingly similar to that of an acute myocardial infarction (AMI), but the underlying pathophysiology differs. It is estimated that 2% of all patients suspected of suffering from an AMI have TTC [3]. This review aims to inform the reader about the existence and management of TTC and how it can be distinguished from a standard AMI.

### Takotsubo cardiomyopathy

The clinical presentation of TTC is very similar to that of an AMI [4]. It is often seen following an episode of severe physical or emotional stress. The triggering event differs greatly among patients and could be anything from a sudden financial loss to having a pre-existing condition such as cancer [3]. The predominant symptoms of patients are chest pain (60-75%), similar to that of an AMI, and dyspnoea (47%). Syncope is less common. Heart failure at onset, presenting as acute pulmonary oedema, occurs in 11-28% of the patients. Other complications such as cardiac arrest, cardiogenic shock, ventricular arrhythmias, and thrombus formation are rare but do happen [1]. Sudden death occurs in 3% of the patients [5]. The total number of patients suffering from complications is estimated to be 18.9% [5]. TTC is mostly a transient condition. Once the critical phase has passed and the patient has survived, left ventricular (LV) function often normalises within weeks, although LV function does not normalise in all patients [6].

### Diagnostic tests

Because of the similarities between TTC and AMI, most of the diagnostic tools following a clinical suspicion of AMI or TTC are identical. Further investigation requires an ECG, measurement of cardiac biomarkers, echocardiography, and coronary angiography with LV angiography. We will describe the results as seen in TTC.

Firstly, ECG findings include ST-segment elevation and depression or repolarization abnormalities. Other findings include QT-interval prolongation, T-wave inversion, abnormal Q-waves, and non-specific ST-abnormalities [7]. Secondly, measurement of cardiac biomarkers of myonecrosis shows elevated levels of troponin, creatinine kinase, and brain natriuretic peptide (BNP) (including NT-Pro BNP) [8]. Thirdly, the role of echocardiography in diagnosing TTC was assessed. The study concluded that echocardiography should be the first imaging technique to be used, although in clinical practice an LV angiography is often the first confirmation of the diagnosis. Echocardiography can also be used to evaluate complications of TTC such as heart failure and is mostly used to evaluate LV function afterwards. Lastly, coronary angiography shows no signs of coronary occlusion [9].

### Diagnostic criteria

In 2004 a set of diagnostic criteria for diagnosing TTC were proposed and were re-evaluated in 2008 [4,10]. These have become known as the Mayo Clinic criteria for the diagnosing of TTC and are the most widely known. Many other criteria have been developed but there is no worldwide consensus. A recent article has proposed a new set of international

diagnostic criteria called the InterTAK diagnostic criteria [11]. These criteria are as following:

1. Patients show transient left ventricular dysfunction presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution. However, more focal wall motion abnormalities can exist.
2. An emotional, physical or combined trigger can precede the TTC event but is not obligatory.
3. Neurological disorders, as well as pheochromocytoma (a catecholamine-producing tumour), may serve as a trigger.
4. New ECG abnormalities are present. However, rare cases exist without ECG changes.
5. Levels of cardiac biomarkers are moderately elevated in most cases. Significant elevation of BNP is common.
6. Significant coronary artery disease is not a contradiction in TTC.
7. Patients have no evidence of infectious myocarditis.
8. Postmenopausal women are predominantly affected.

## Differential diagnosis

There are few diseases that need to be distinguished from TTC. As the InterTAK criteria indicate, infectious myocarditis needs to be excluded, but this will not be discussed here. In this section, the differences between TTC and a standard AMI will be briefly discussed. As said, the presentation of TTC mimics that of an AMI. Thus a physician must rely on the results of his/her diagnostic tests. A severe emotional or physical event prior to the onset of the symptoms is suggestive for TTC. However, a 2016 study retrospectively looked at the ECG of 200 TTC patients and 200 AMI patients. They found that an AMI often has a broader QRS width and more prevalent ST-depressions. TTC more often showed ST elevation without concomitant ST depression or T inversion. Isolated T-inversion was more common in TTC as well. Important to note is that an ECG in TTC often shows signs of multi-vessel pathology, whereas an AMI often shows signs of occlusion of more localized vessels (only the LAD for example). They concluded that ECG on admission proves to be helpful in differentiating between TTC and AMI with high specificity [12]. A study from 2015 also looked at ECG differences and concluded that the consequences of missing the diagnosis of an AMI were too severe. The diagnostic accuracy of the ECG criteria investigated in this retrospective study was insufficient to reliably distinguish patients with TTC from patients with an AMI [13]. Laboratory results show elevated troponin T levels, but peak levels are lower than those seen in an AMI. On the other hand, BNP levels are usually higher in TTC than in ACI [8,9]. The golden standard for differentiating between TTC and a standard AMI remains coronary angiography with LV angiography. A standard (type 1) AMI will show signs of coronary occlusion, whereas TTC will not [13]. A type 2 acute coronary syndrome is due to ischemia resulting from conditions such as anaemia, hypotension or coronary artery spasm. These will not show signs of coronary occlusion, but are beyond the scope of this review.

## Pathophysiology

The underlying pathophysiology of TTC is not well understood. The most plausible hypotheses focus on sudden catecholamine cardiotoxicity and a generalized dysfunction of the coronary microvessels. Sex and gender also seem to play an important role.

**Catecholamine cardiotoxicity**

This hypothesis for the pathophysiology of TTC involves acute catecholamine cardiotoxicity provoked by stress. A study from 2005 showed that catecholamine levels were 2 to 3 times as high in patients suffering from TTC compared to AMI [14]. It is thought that in response to stress, cardiac and extra-cardiac sympathetic nerves release high levels of epinephrine. These reach adrenoreceptors in the heart and in its blood vessels, leading to catecholamine cardiotoxicity and the resulting changes typical in TTC [15]. The fact that similar reversible cardiomyopathy is seen in patients suffering from a pheochromocytoma further supports this hypothesis [16].

**Generalized dysfunction of the coronary microvessels**

Catecholamines have a strong vasoconstricting effect on the coronary microvasculature. It is hypothesised that high levels of catecholamines, as seen in TTC, lead to a shift in the balance between vasoconstricting and vasodilating factors in the microvasculature. The result is a reduced microvascular blood flow and a reduced coronary flow reserve [11].

**Sex- and gender differences**

The prevalence of TTC differs importantly between men and women [17]. Up to 90% of all patients affected are postmenopausal women with a mean age of 62 to 76 years. The triggering event differs between men and women as well. Physical stress is more likely to induce TTC in men, whereas the triggering event in women is more likely to be emotional. The clinical presentation, in contrast to AMI, is very similar between the sexes, but men are more likely to suffer from cardiogenic shock and cardiac arrest, resulting in a higher mortality rate in men. Despite these striking differences, the exact nature of the female predominance is not well understood. It is hypothesised that it is related to the lack of oestrogen in post-menopausal women, but there is no clear evidence to support this claim [18].

## Treatment

Because of the similarities between TTC and AMI, diagnosis of TTC is often delayed and patients usually receive treatment for ischemic heart disease (AMI). This includes an anti-coagulant, a statin, a betablocker, and an ACE-inhibitor. The standard treatment for an AMI does not seem to improve the outcome of TTC however [5]. Once the diagnosis has been made patients should be treated with an ACE-inhibitor or an angiotensin receptor blocker. Betablockers are widely administered, although there is no clear evidence of a beneficial effect [19]. To reduce the risk of a thromboembolic event, patients could temporarily be treated with an anticoagulant [6]. Further treatment is determined by the complications that may arise during the acute phase. Heart failure, for instance, is treated with ACE-inhibitors, betablocker, diuretics, and nitroglycerine. Inotropes such as adrenaline must be avoided [19].

There is currently no standardized long-term treatment, but ACE-inhibitors or angiotensin receptor blockers are reported to decrease the recurrence rate of TTC. Betablockers do not seem effective. Aspirin and statins are appropriate in patients with coronary atherosclerosis [19].

## Prognosis

TTC has a recurrence rate of 10-15% with disease-free intervals ranging from three months to 14 years [6,20]. The second trigger is usually a different physical or emotional one than the first. At first, the survival of TTC was thought to be favourable compared to the survival of an AMI; even being similar to that of the general population [7]. However, recent studies show different results. They concluded that the in-hospital mortality rate of TTC was similar to that of patients who had suffered an AMI (3.7% vs. 5.3%, not statistically significant) [21,22]. Long-term follow-up of patients that survived the acute phase of TTC showed a rate of death per patient-year of 5.6%, which is higher than in the general population.

## Conclusion

TTC is a specific type of AMI that mimics a traditional AMI in its clinical presentation. Short-term complications can be severe, even including death. Long-term survival has long been thought to be similar to that of the general population, but recent studies showed it is comparable to the survival of patient that suffered from an AMI. The pathophysiology of TTC and the reason for its predominance among women are still poorly understood. However, emotional and physical stress is strongly related to the onset of TTC. More research is needed to fully understand the pathophysiology.

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