Recent Progress in the Diagnosis and Management of Tako-Tsubo Syndrome

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Abstract

Tako-Tsubo Syndrome (TTS), also known as apical ballooning syndrome or “broken heart syndrome”, was discovered by Japanese investigators 27 years ago, and was initially assumed to be a rarity. However, TTS is relatively common, especially among ageing women and in the setting of severe physical/emotional stress. TTS represents an aberrant β2-adrenoceptor mediated myocardial inflammatory response to catecholamine stimulation, most commonly seen in the ageing female heart. It remains under-diagnosed in most hospitals. Initially, TTS was essentially a diagnosis of exclusion, typically made after emergency coronary angiography in patients presenting with ST segment elevation who had no relevant coronary artery disease. However, at least 50% of patients with TTS never show ST elevation. We therefore propose a diagnostic algorithm for

(a) Initial tentative diagnosis
(b) Definitive positive diagnosis (i.e. not by exclusion)
(c) Quantitation of severity of attacks of TTS,

Which should expedite the avoidance of catecholamine administration to these patients.

Key aspects to consider are:

1. Clinical presentation (including demographics and prior circumstances).
2. ECG changes.
3. Biomarkers (marked elevation of plasma NT-proBNP levels with minimal troponin elevation).
4. Catheterisation findings (especially for patients with initial ST elevation).
5. Cardiac MRI, which demonstrates oedema, as well as the absence of acute myocardial infarction.

Keywords

Tako-tsubo syndrome, Myocardial inflammation, N-terminal-pro BNP, Acute coronary syndrome

Introduction

Tako-Tsubo Syndrome (TTS), also known as stress cardiomyopathy, apical ballooning syndrome and “broken heart syndrome” is increasing recognized as a relatively common and frequently under diagnosed health problem, particularly in aging women. The name “Tako-Tsubo” reflects the original description of TTS, by Japanese investigators, on the basis of the similarities between the shape of the affected left ventricle and that...
of a Japanese octopus trap. TTS accounts for about 10% of cases initially diagnosed as ST Elevation Myocardial Infarction (STEMI) in women over 50 years of age [1]. It has been recently reported in two large cohort studies [2,3] that TTS is associated not only with substantial early in-hospital mortality rates (due to lethal arrhythmias and cardiogenic shock), but also with medium-term mortality similar to that of post myocardial infarction. There are also high levels of residual disability for at least 3 months [4], and a risk of recurrence of about 3% per annum [5,6].

Clinically, TTS is characterized by variable combinations of chest pain and dyspnoea, often associated with severe initial hypotension, and sometimes with ventricular tachyarrhythmias. Episodes are often precipitated by severe emotional or physical stress and recently an association with psychiatric disease has been noted [2]. Traditionally, TTS has been diagnosed largely via exclusion of Acute Myocardial Infarction (AMI). Indeed, the diagnosis of TTS is inherently difficult and complicated by selection bias, for example with failure to investigate this potential diagnosis in the very elderly, or in postoperative patients in whom rises in plasma troponin levels are noted. Although it was initially considered that the presence of any coronary disease precluded the diagnosis [7], it is certainly possible to diagnose TTS on the basis of characteristic Left Ventricular (LV) wall motion abnormalities [dissociated from the distribution of Coronary Artery Disease (CAD)] and associated myocardial oedema [8].

While it was initially considered that TTS was a relative rarity, at least in Caucasians, little scientific effort was devoted to either understanding its pathogenesis, developing reliable diagnostic algorithms, or establishing effective short- and long-term treatments. The generalities were that the precipitation of TTS had something to do with a “surge” of catecholamine release or exposure, for which there was ample clinical evidence [9-11]. Therefore, many patients were prescribed β-adrenoceptor antagonists, on theoretical grounds only. Nevertheless, for example by avoiding catecholine administration for severe initial hypotension, and sometimes with ventricular tachyarrhythmias. Episodes are often precipitated by severe emotional or physical stress and recently an association with psychiatric disease has been noted [2]. Traditionally, TTS has been diagnosed largely via exclusion of Acute Myocardial Infarction (AMI). Indeed, the diagnosis of TTS is inherently difficult and complicated by selection bias, for example with failure to investigate this potential diagnosis in the very elderly, or in postoperative patients in whom rises in plasma troponin levels are noted. Although it was initially considered that the presence of any coronary disease precluded the diagnosis [7], it is certainly possible to diagnose TTS on the basis of characteristic Left Ventricular (LV) wall motion abnormalities [dissociated from the distribution of Coronary Artery Disease (CAD)] and associated myocardial oedema [8].

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Extent of Problem and Clinical Categories

Concept of “Primary” vs. “Secondary” TTS

In the majority of cases, TTS has been diagnosed in ageing women presenting either with an episode of chest pain and/or dyspnoea occurring either randomly or in the setting of recent physical or emotional stress. This is now termed “primary” TTS. “Secondary” TTS has been described among individuals in whom TTS develops in the setting of another acute medical problem which has led to substantial catecholamine release, such as intracranial hemorrhage [12] or phaeochromocytoma [13]. While the distinction between primary and secondary TTS may be blurred, there is a case for regarding all cases of perioperative, or medication-induced TTS as secondary. Secondary TTS should theoretically be less subject to risk of recurrence than primary, and the reportedly greater mortality rates and higher proportion of males affected by secondary TTS [2,14,15] are not surprising.

Definite vs. Putative TTS

It is in practice impossible to be quite certain of a diagnosis of TTS without performing either a cardiac catheterisation or a Cardiac Magnetic Resonance Imaging (CMR) procedure: indeed there is a strong case for performing both of these procedures in the vast majority of patients. On the other hand there are a number of clinical features and other clinical investigations which can help to make a presumptive diagnosis of TTS prior to performing a definitive investigation. A presumptive diagnosis can assist in planning appropriate therapy early, for example by avoiding catecholine administration in hypotensive individuals. Of course, diagnosing TTS as a presumptive cause of arrhythmic death remains too hard a challenge at present, and therefore the number of such deaths remains completely uncertain.

The Diagnostic Process: Inherent Difficulties

The diagnosis of TTS is inherently difficult and complicated by selection bias. The condition has usually been recognized, particularly in early series of cases, as a result of cardiac catheterisation of patients presenting with acute chest pain in which the initial diagnosis was an acute coronary syndrome (including a substantial proportion of patients initially diagnosed as STEMI). However, a number of large studies have suggested that in at least 60% of cases of TTS, presentation tends to mimic Non-ST Elevation Myocardial Infarction (NSTEMI), with a variety of associated ECG changes [16]. A final difficulty is that very elderly, frail patients presenting with...
prolonged chest pain, especially without ST elevation, may not undergo cardiac catheterization, and therefore the diagnosis of TTS may easily be missed.

**Consideration on the basis of coronary angiography**

By definition, TTC is a disorder characterized by acute development of segmental (usually periapical) LV systolic dysfunction. A number of diagnostic criteria have been proposed by several groups [7,17-20]. The most commonly utilized definition of TTS [8], while reasonably accurate, reflects the historical practice of making the diagnosis via cardiac catheterization, and therefore largely by exclusion. The theoretical problems with this are twofold: since TTS has a different pathogenesis from that of “fixed” CAD, and since myocardial ischaemia may induce catecholamine release, there are good reasons why both TTS and CAD may co-exist [21]. In general, if fixed CAD affects the precise region of the LV as that exhibiting hypokinesis, it becomes difficult to diagnose TTS (although not impossible: see below). However, a discrepancy between the regional distribution of the hypokinesis and that of the coronary disease strongly suggest the diagnosis of TTS. There is an additional theoretical difficulty in exclusion of single or multi-vessel coronary spasm as an underlying disorder [22]: in practice total exclusion of spasm is usually impracticable. However, once again, the distribution of hypokinesis in TTS rarely accords with the course of a single coronary artery.

**Beyond coronary angiography**

As indicated above, the differential diagnosis of TTS includes both myocardial ischaemia and infarction. A number of differences between TTS and acute myocardial in-

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**Figure 1:** Twelve-lead ECG and rhythm strips for a patient with TTS presenting without initial ST segment elevation.

**Note:** 1) Widespread (anterior and inferior) symmetrical T-wave inversion, currently without marked QTc prolongation; 2) Brief episode of torsade de pointes, the predominant early arrhythmia in TTS.
Summary: Diagnostic Algorithm for TTS and for Quantitation of Severity of Episodes

The difficulties inherent in developing presumptive and/or definitive diagnostic criteria for TTS have been addressed previously by Lyon, et al. [18]. In view of recent trends towards a pivotal role for CMR, our view of the position is summarized in (Figure 2) and discussed briefly below. First, it must be remembered that in patients with ST segment elevation on the initial ECG, the diagnostic process effectively begins with emergency coronary angiography.

Presenting features and haemodynamic disturbances

The distinct epidemiological, clinical and biochemical features of TTS need to be considered. TTS is often precipitated by exposure to severe emotional and physical stress. It occurs especially but not exclusively in women aged > 50 years, and often complicate other severe illnesses. TTS is usually characterized symptomatically by chest pain and/or dyspnoea, often associated with hypotension [18]. Clinically, there is a substantial risk of early development of torsade de pointes ventricular tachycar-

![Diagram](image)

**Figure 2:** Schematic diagram of current diagnostic algorithm for rapid presumptive followed by definitive diagnosis of TTS, depending on occurrence or otherwise of initial ST segment elevation.

The diagnosis of TTS is also expedited by greater awareness of the epidemiology of the condition, the characteristic "multi-regional" ECG changes (Figure 1), as well as marked elevation of NT-pro-BNP levels and minimal myocardial necrosis [24,25]. Clinical and echocardiography factors should also be taken into account, including gender, recent illness or stress, or administration of drugs which may increase catecholamine levels [26]. Hypokinesis or dyskinesia usually predominately affects the periapical region of the Left Ventricle (LV), sometimes with sparing of contractility at the very apex, but in between 15% and 25% of cases there may be more marked mid-ventricular changes: early echocardiography (and indeed ventriculography at the time of cardiac catheterisation) therefore also assist diagnosis [27]. The routine availability of CMR imaging has revolutionized the differential diagnosis of TTS, particularly in patients in whom the diagnosis is not suspected in the first few days post onset of symptoms as described below.

S-T segment elevation (±multiregional) 
Emergency coronary angiography

- Acute coronary disease
- No acute coronary disease

Troponin, CK elevation

- BNP, NT-proBNP marked elevation
- Echocardiography: regional hypokinesis

Regional wall motion disturbance

Cardiac CMR: no infarct extensive oedema
Cardiac catheterization: No relevant coronary stenoses

No S-T elevation (±multi-regional T inversion)

Troponin, CK elevation

- BNP, NT-proBNP marked elevation
- Echocardiography: regional hypokinesis

Regional wall motion disturbance

Cardiac CMR: no infarct extensive oedema
Cardiac catheterization: No relevant coronary stenoses

Clinical presentation (chest pain etc) (associated stress, female gender)

ECG

- S-T segment elevation (±multiregional)
- No S-T elevation (±multi-regional T inversion)

Definitive diagnosis of TTS

- Cardiac CMR: no infarct extensive oedema
- Cardiac catheterization: No relevant coronary stenoses

Presumptive diagnosis of TTS

- Echocardiography: regional hypokinesis
- Cardiac CMR: no infarct extensive oedema
- Cardiac catheterization: No relevant coronary stenoses

Acute coronary disease
No acute coronary disease

BP, NT-proBNP marked elevation

Definitive diagnosis of TTS
dia, and of thrombo-embolism secondary to mural left ventricular thrombosis, although these are not usually the fundamental modes of initial presentation [28]. The most ominous clinical aspect, however, is the early development of severe hypotension, together with peripheral vasoconstriction in the majority of cases [29], and usually without substantial elevation of pulmonary capillary wedge pressure. Occasionally, paradoxical peripheral vasodilatation may occur and also severe acute mitral regurgitation may be present. Apart from avoiding further exposure to catecholamines, there is no established treatment for this shock state, and this therapeutic difficulty may also reflect the uncertain mechanism(s) for its development [18].

It is also widely recognized that TTS tends to be recurrent: a recent meta-analysis has suggested a mean annual recurrence rate of about 3% [30]. Therefore it is important to enquire whether patients have experienced similar episodes in the past. The clinical course of TTS after the first 24 hours is usually one of rapid symptomatic improvement, but without total resolution of malaise and exertional dyspnoea.

**ECG**

Most patients with TTS develop widespread T-wave inversion and QTc prolongation approximately 24 hours post presentation irrespective of the presence/absence of initial ST segment elevations. Torsade de pointes is an early complication, preceding maximal QT prolongation (Figure 1).

**Biomarkers**

It is clear that release (or administration) of catecholamines initiates many, indeed, probably most attacks [9,10]. Elevated plasma catecholamine levels have frequently been documented in TTS patients, and in our previous studies severity of attacks correlated directly with plasma normetanephrine levels [24,31]. The acute phase of TTS is associated with marked elevation of plasma BNP and NT-proBNP levels [23,24,32]. Both BNP and NT-proBNP concentrations are acutely elevated considerably beyond population norms in all cases of TTS [24]. Extent of elevation of plasma NT-proBNP concentration was directly correlated with impairment of regional LV wall motion, and inversely with LV ejection fraction, as well as with the extent of myocardial oedema on CMR [24,31]. These data therefore suggest that BNP release may result primarily from myocardial inflammation rather than purely from “heart failure” and that the extent of its release into plasma (and consequently also the rise in NT-proBNP concentrations), may be utilized not only as an aid towards diagnosis but also for quantitation of severity of TTS episode severity. Furthermore, the contrast between considerable elevation of NT-proBNP levels and relatively minor elevation of troponin (or creatine kinase) levels can potentially be utilized for provisional differentiation from acute myocardial infarction (Figure 3).

**The current role of cardiac catheterisation in the diagnostic process**

Immediate cardiac catheterisation remains mandatory for patients presenting with ST segment elevation, and should be considered on an urgent basis for the remainder of suspected TTS cases. Coronary arteries are typically normal but “bystander” CAD can be present. Ventriculography usually shows wall motion abnormalities including apical, mid-wall, or occasionally basal hypokinesis.

**Echocardiography/CMR**

Early echocardiography is an important priority for early investigation, especially in the absence of ST elevation, and usually demonstrates extensive wall motion impairment extending beyond the territory of a single coronary artery. Typically this is mainly apical (Figure 4) or mid-ventricular, with rapid improvement in LV regional wall motion over the next 7 days [33]. Echocardiography with concomitant echo-contrast injection and flash imaging can be utilized to establish the diagnosis of TTS in patients unsuitable for coronary angiography and/or CMR.

A number of studies utilizing CMR have demonstrated that TTS is associated with intense myocardial inflammation demonstrated by myocardial oedema, not only at the LV apex, but throughout the LV (Figure 5). This oedema resolves slowly, and remains detectable at 3 months after acute attacks [31]. Furthermore, 31P car-
ever, there is no evidence of a beneficial effect of such treatment to date [35]. On the other hand, there may well be a case for the utilization of ACE inhibitors in the long term. While no impact on rate of recovery of left ventricular function has been recorded, it appears that ACE inhibitors may reduce the risk of recurrence of TTC [15].

Given the recent demonstration of long-term mortality implications post acute episodes of TTS, the question of monitoring risk of late arrhythmic genesis arises. To date, this possibility has received little attention.

Advantages of Early Diagnosis: Therapeutic Options?

To date, no clinical trials have been undertaken in TTS. Given the association with marked elevation of plasma concentrations of catecholamines, a number of clinicians have discharged patients on β-adrenoceptor antagonists. However, there is no evidence of a beneficial effect of such treatment to date [35]. On the other hand, there may well be a case for the utilization of ACE inhibitors in the long term. While no impact on rate of recovery of left ventricular function has been recorded, it appears that ACE inhibitors may reduce the risk of recurrence of TTC [15].

While there is no consensus regarding the management of cardiogenic shock complicating TTS, catecholamine administration should be avoided, and it has been suggested on the basis of animal experiments that the calcium sensitizer levosimendan may be useful [36,37].

Diady magnetic resonance spectroscopy, currently only a research technique, demonstrates impaired myocardial energetic, persists for at least 3 months post acute episodes of TTS [34] (Figure 6). It is even possible to diagnose a recent episode of TTS in patients with previous myocardial infarction via CMR, by demonstrating a region of myocardial oedema remote from the site of the previous infarction.

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\[\text{Figure 4: Two-chamber view of LV wall motion [A) End-systolic; B) End-diastolic frames], taken at admission in a patient with typical (predominantly peri-apical) systolic dysfunction due to TTS.}\]

\[\text{Figure 5: CMR with T2-weighted imaging to quantitate oedema in a patient studied 48 hours post onset of TTS A) Transverse section of mid-left and right ventricle; B) Longitudinal section of LV. Oedema (arrows) is predominantly seen in the periapical half of the LV.}\]
Conclusions

The occurrence of TTS reflects, to a large extent, an abnormal inflammatory reaction of the aging (usually female) hearts to catecholamine exposure. Differentiation of TTS from acute myocardial infarction no longer rests purely on an angiographic exclusion process, but can be expedited by appropriate clinical awareness of the problem, utilization of careful interpretation of ECG and biomarker data, and early performance of both echocardiography and CMR. The importance of early differentiation from acute myocardial infarction currently is limited to avoidance of further catecholamine exposure and the lack of necessity to initiate anti-ischaemic therapy, but will increase as specific treatments for TTS are developed.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

References


Figure 6: Left - Exemplary T1 mapping (colour-coded) for extent of oedema, with orange/red indicating maximal levels, of a normal healthy control A) A mid-cavity Takotsubo patient; B) An apical ballooning patient; C) Right - Red dots represent the PCr/ATP ratio and blue diamond's show the mean scores for whole myocardial T1 mapping-based estimation of oedema severity in patients (acute and follow-up) versus normal healthy controls. Data are shown as mean ± SD. (from reference [33], reproduced with permission).

*p < 0.05 acute study vs. follow-up; †p < 0.05 acute study vs. healthy controls; ‡p < 0.05 follow-up study vs. healthy controls.


