Takotsubo Syndrome Therapy: Current Status and Future Directions

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Abstract

Tako-Tsubo Cardiomyopathy (TTC), which is now known as Tako-Tsubo Syndrome (TTS) is a transient left ventricular (LV) systolic dysfunction of uncertain pathogenesis, which occurs predominantly in ageing women. There is considerable uncertainty regarding the management of TTS-related acute and chronic issues and most of the evidence regarding therapy come from retrospective data and case studies. In this review, we have tried to concise the available information on the TTS therapeutics to help clinicians make treatment decisions for patients diagnosed with TTS. At the same time, we have highlighted some of the uncertainties regarding TTS therapy, in particular, the inability of b-blocker therapy to improve survival or prevent recurrence. We have also emphasized the issue of incomplete recovery in some cases of TTS where there is ongoing inflammation and evidence of impaired myocardial energetics despite normalization of LV ejection fraction. Although there is no scientific evidence on how to improve or fasten the recovery of TTS, we believe therapy improving energy efficiency may play some role in future. Lastly, we would like to reiterate that in the absence of randomized studies evaluating medical therapy in TTS, the treatment for this syndrome remains entirely empirical and should be individualized according to the patient characteristics at the time of presentation.

Keywords: Takotsubo Cardiomyopathy; Takotsubo Syndrome; Treatment; Therapy and Therapeutics

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Introduction

Tako-Tsubo Syndrome (TTS), also known as stress cardiomyopathy, apical ballooning syndrome or “broken heart syndrome” is a transient myocardial dysfunction with an unknown pathogenesis and variable natural history.2, 3 It predominantly effects aging women and presents as an acute coronary syndrome (ACS) in the absence of an acute plaque rupture.4 Among the whole population presenting with ACS, TTS occurs roughly in 2% of cases, while in women presenting with ST-elevation myocardial infarction (STEMI) the frequency could be as high as 10%.5, 6 Even though, emotional or physical stressor commonly precedes TTS, it can occur in the absence of any clear precipitant. Interestingly, cases of TTS have been described in literature way before the term “Takotsubo” was coined.7, 8 In one of the initial reports Cebelin et al, demonstrated the presence of typical TTS changes in the histologic sections of the myocardium of 11 victims of homicidal assaults who died without internal injuries. Interestingly, these patients did not have histological changes of ischemia or infarction in the myocardium.7

There is an ongoing debate regarding the underlying pathogenesis of TTS and at the moment, the only thing we know with some certainty is that there is a higher rise in the plasma catecholamine levels in TTS patients when compared to the patients with the acute coronary syndrome. However, it is important to emphasize that some studies published after the initial catecholaminergic hypothesis by Wittstein et al.9, have been unable to replicate the same levels of catecholamines in TTS patients.10 On the other hand, use of various catecholamines in animal models of TTS has produced ventricular changes similar to what have been found in TTS.11 Also, characteristics changes of TTS have been noted in patients with phaeochromocytoma. It would not be unreasonable to regard TTS as a type of myocarditis where inflammation is induced by a sudden rise in catecholamine levels.5, 12, 13 The evidence of inflammation of the myocardium in TTS has been confirmed by the histological heart samples and by usual biochemical markers of inflammation. Nef et. al. performed biopsies from the interventricular septum during the acute and recovery phase of TTS and found changes of inflammation14. Inflammatory changes including infiltration of the myocardium by macrophages have been shown by other authors even when the common causes of myocarditis such as infection has been ruled out.15

The need for therapy

Until 2000, there were only a few case reports about TTS, published mainly by Japanese investigators. However, the number of publications rose dramatically as the awareness about
TTS increased in Europe and North America and since 2008 there have been nearly 300 publications each year in peer-reviewed medical journals (Figure 1). With increasing numbers of TTS cases being diagnosed many registries have been developed in Japan, USA, Australia and Europe to clarify the clinical features and natural history of the disease.

The findings from the registries have clarified that TTS is neither benign nor uncommon. Kurowski et al found 30-day mortality very similar between TTS and pair matched patients with anterior STEMI. Acute episodes of TTS can be complicated by hypotension, shock, cardiac arrhythmias, thromboembolic complications and heart failure. These factors and underlying non-cardiac issues can increase morbidity and mortality in the acute phase of TTS. Hypotension and shock are the most common complication in the acute phase of the disease with high heterogeneity in its presentation.

It is now very clear that acute TTS episodes are associated with morbidity and mortality, however, our knowledge about the long-term history of TTS was limited until 2010 when researchers reported the chronic issues related to TTS. Among many publications evaluating the natural history of TTS was that of Parodi et al., who found that the recurrences of symptoms of chest pain and dyspnea in the absence of LV abnormalities are very common and lead to frequent hospitalizations. Similarly, in a systematic review, we reported that the annual recurrence rate of TTS is about 1.5% and the cumulative incidence of recurrence increased from 1.2% at 6 months to nearly 5% at 6 years. Furthermore, in a recent publication Neil et al. demonstrated that despite normalization of the left ventricular (LV) ejection fraction there is ongoing inflammation of the myocardium, which persists, at least, up to 3 months and correlates with impairment of quality of life. These findings are in line with the findings published by Dawson et al. who demonstrated that acute episodes of TTS are associated with profound cardiac energetic impairment, which did not resolve completely by 4 months. These findings from various studies argue for the fact that the development of therapeutics should not only be directed at the acute episodes of TTS but also towards the rapid recovery of LV along with a reduction in the rate of recurrence.

With our increased knowledge, we have learned that TTS, which was thought initially to be a very benign disorder mimicking ACS, can actually lead to short-term mortality and long-term morbidity in a significant proportion of patients. Furthermore, not only our knowledge of predictors of acute and chronic debility is limited, there are no clear evidence-based strategies for management of these issues.

The critical important aspects for TTS therapeutics can be divided into 3 broad areas:

a) Prevention of TTS in critically ill patients

b) The acute phase: The main issues in the acute phase are the prevention and treatment of hemodynamic decompression or shock, management of arrhythmias and prevention of thromboembolic events.

c) The potential for recurrence: Beta-blocker therapy does not influence to prevent recurrence.

d) The “recovery” phase: Recovery myocardial inflammation in TTS is slower than initially thought and our knowledge regarding predictors of slow or delayed recovery is still limited. Therapeutics in this phase are based on initial human and animal studies.

a) Prevention of TTS in critically ill patients

An important subset of patients who are prone to develop TTS is critically ill patients in the intensive care units (ICU). It is easy to miss TTS in such patients and the incidence of TTS in intensive care is probably underestimated. Most of the patients with TTS in the intensive care unit are treated as ACS because of relative contraindication to coronary angiography. When actively observed TTS has been found to be present in nearly 20% of patients in ICU in one report. It is important to keep TTS in mind while looking after a troponin positive ICU patient. The diagnosis of TTS can be suspected from the rise in N-terminal probrain natriuretic peptide (NT-proBNP), typical electrocardiographic (ECG) features of TTS and transthoracic echocardiographic changes even in the absence of coronary angiography.

The generous use of the catecholamine based inotropic medications is probably one of the contributing factors to the high incidence of TTS in the ICU (Figure 2). The vicious cycle...
of TTS with the use of catecholamines and worsening of shock has been nicely demonstrated by Redfors at al. in an editorial.28 We recommend avoidance of catecholamine based inotropic medications and preference of non-catecholamine based vasopressors or mechanical circulatory support if there is any suspicion of TTS in a critically ill patient in the ICU.

b) The acute phase

The acute phase of TTS can be complicated by essentially 3 major complications; shock, arrhythmias, and risk of thromboembolism.

Shock is one of the major causes of early mortality in patients with TTS and it occurs in roughly 10% of patients diagnosed with TTS.20, 29 Treatment of shock is extremely challenging, because catecholamine based inotropes, which are the foundation of pharmacological management of cardiogenic shock can lead to further hemodynamic derangement by worsening TTS related cardiogenic shock.34 Hence, before the use of vasopressors or mechanical circulatory support if there is any suspicion of TTS related shock is based on personal preference or theoretical knowledge. Moreover, it is hard to evaluate the effectiveness of these therapies without a randomized trial because the improvement with a particular strategy may simply represent the natural course of the disease.

Levosimendan, a calcium sensitizer, is a non-catecholamine based inotrope that has been often used for the treatment of shock in TTS.22, 20, 31 Santoro et al. reported 13 cases of TTS complicated by the cardiogenic shock that were treated with levosimendan without any serious complications.32 However, one of the main side effects of Levosimendan is an arrhythmia, and since TTS patients are at risk of torsade de pointes, patients on intravenous levosimendan should be monitored closely. There have also been reports of the use of Milrinone to treat hypotension in patients with TTS.23 Mechanical circulatory support, where available, is a perfect option in severe cases of shock. However, there has been some concern about the worsening of left ventricular outflow tract obstruction with the intra-aortic balloon pump (IABP).24 Hence, before the use of IABP patient should be evaluated for left ventricular outflow tract (LVOT) obstruction. The use of left ventricular assist device (LVAD) such as; Impella and extracorporeal membrane oxygenation to manage patients with TTS related shock has been documented in the literature.25-38 Impella 2.5, which has a relatively small sheath size compared to other LVADs, can be inserted percutaneously to provide short-term hemodynamic support to patients with shock.

Arrhythmias are common in patients diagnosed with TTS and occur in nearly 20% of patients.39 Atrial fibrillation, which represents the most common form of arrhythmia in TTS,39 should be treated with short and long term anticoagulation depending upon patients’ stoke risk. Antiarrhythmic medications that prolong the QTc interval should be avoided in TTS. We would also advise against the use of electric cardioversion for rhythm control during the acute episode of TTS. DC cardioversion can stun the myocardium and could probably increase myocardial insult.40 Similarly, digoxin should be avoided as it can worsen the LVOT obstruction and instead, beta-blocker should be the first line of treatment for rate control.

Ventricular arrhythmias in patients with TTS could be secondary to the prolonged QTc interval or because of the sudden development of hypotension.41 Patients in whom QTc interval is longer than 600 ms are a high risk of torsade de pointes.42 Patients with prolonged QTc interval should be closely monitored until its normalization. Medications contributing to the QTc interval prolongation, especially anti-arrhythmic medications, and antibiotics should be stopped. Further, adequate replacement of the electrolytes should be performed. Intravenous magnesium can be used to actively treat torsade de pointes secondary to the long QTc interval.

Thrombus formation can occur in both right and left ventricular apex. The incidence of LV thrombus varies from 2 to 4%,43, 44 while that of right ventricular (RV) is unknown. From our experience isolated RV thrombus can occur in roughly 2% of patients. Usually, thrombus in the LV apex develops in the first 3 to 5 days. However, we have observed that patients who develop severe TTS (higher release of NT-BNP, RV involvement, and lower ejection fraction) can develop LV thrombus even 1 week after TTS onset (Figure 3). Patients diagnosed with TTS, in particular, patients with extensive apical dyskinesis, should be treated with unfractionated or low molecular weight heparin for the first 48 to 72 hours to reduce the risk of LV thrombus. No studies so far have assessed the duration of anticoagulation and also, if every patient diagnosed with TTS should receive anticoagulation. Given the similarity between TTS and anterior wall myocardial infarction (MI) with regards to apical LV dysfunction, our recommendations regarding anticoagulation in TTS are based on the efficacy of heparin to reduce the risk of LV thrombus in anterior MI.45 However, the apical LV dysfunction in TTS, unlike anterior wall MI, is transient and hence, longer anticoagulation with warfarin is not required unless there is definite presence of LV thrombus or there is another indication for long-term anticoagulation. Patient at the severe end of TTS spectrum should have repeat echocardiographic evaluation in the first month till wall motion abnormality has normalized. A patient who has developed LV thrombus should be treated with warfarin and a repeat echocardiogram should be performed at 3 months. We usually do not prescribe anti-platelet therapy to patients diagnosed with TTS unless there is coexistent coronary artery disease.

c) The potential for recurrence

Recurrent acute attacks of TTS are thought to occur in approximately 1 to 3% of patients per annum. However, in the absence of large prospective trials, the information on the
incidence and clinical correlates of recurrence remains unclear. Most of the data on the recurrence rate of TTS has been evaluated from observational studies, which is prone to selection bias. The results of 2 relatively large studies with nearly 4-year follow-up have shown different slightly different recurrence rate. While the Mayo Clinic data has shown the recurrence rate to be nearly 3-4% per year, the results from Tuscany registry document the rate of recurrence to be lower than 1%, 23, 46 47 We performed a large systematic review and found that cumulative incidence of recurrence was approximately 5% for 6 years and annual rate of recurrence was approximately 1.5%. 47

The initial treatment following the diagnosis of TTS is essentially the same as adopted for heart failure. However, there is no clear data on the efficacy of the currently used therapy on the recurrence of TTS. Increased circulating levels of catecholamines in some of the cases of TTS have formed the basis of the use of b-blockers following the diagnosis of TTS. However, b-blocker medication has neither been found to reduce the initial nor recurrent episodes of TTS in small case reports or observational studies. 46 48 On the other hand, use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are the most commonly prescribed for TTS patients. While ACE inhibitors or ARB therapy have shown to improve survival, 16 certainly, the results from observational studies are prone to selection bias. The results of 2 relatively large studies with nearly 4-year follow-up have shown different slightly different recurrence rate. While the Mayo Clinic data has shown the recurrence rate to be nearly 3-4% per year, the results from Tuscany registry document the rate of recurrence to be lower than 1%, 23, 46 47 We performed a large systematic review and found that cumulative incidence of recurrence was approximately 5% for 6 years and annual rate of recurrence was approximately 1.5%. 47

Table 1. Management of issues related to Takotsubo cardiomyopathy during the acute and chronic phase.

<table>
<thead>
<tr>
<th>Acute Complications</th>
<th>Shock</th>
<th>Atrial fibrillation</th>
<th>Ventricular arrhythmia</th>
<th>LVOT obstruction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>b-blocker therapy for rate control</td>
<td></td>
<td>b-blocker therapy</td>
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<tr>
<td></td>
<td></td>
<td>Avoid digoxin if LVOT obstruction</td>
<td>Short and long term anticoagulation depending upon patients risk score</td>
<td>Avoid digoxin and intra-aortic balloon pump</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid rhythm control therapy in particular anti-arrhythmic medications that prolong QTc interval</td>
<td></td>
<td>Intravenous hydration if pulmonary capillary wedge pressure is normal or low</td>
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<tr>
<th>Chronic issues</th>
<th>Recurrence</th>
<th>Recovery</th>
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<tbody>
<tr>
<td></td>
<td>ACE inhibitor or ARB therapy OR b-blocker therapy along with ACE inhibitor or ARB therapy</td>
<td>ACE inhibitor or ARB therapy OR b-blocker therapy along with ACE inhibitor or ARB therapy</td>
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**Legend:** LVOT, Left Ventricular Outflow Tract, ACE, Angiotensin Converting Enzyme, ARB, angiotensin receptor

**d) The “recovery” phase**

Until now, recovery of TTS was measured by improvement in the LV ejection fraction and resolution of wall motion abnormalities. However, a large proportion of patients continue to complain of ongoing symptoms despite the normalization of LV ejection fraction, 23, 51 while it can be assumed that these symptoms reflect ongoing emotional stress in the absence of organic pathology, evidence from the recent studies has indicated towards ongoing myocardial inflammation and incomplete recovery at 3 months. The presence of myocardial oedema at 3 months, 13 elevated levels of NT-proBNP at 3 months, 12 impaired global longitudinal strain at 3 months 24 and magnetic resonance spectroscopy evidence of defective myocardial energetics at 4 months 25 all point towards an incomplete and slow recovery. These findings have also been observed in the animal models of TTS where histological abnormalities persist despite normalization of the LV ejection fraction. 52 Furthermore, there is a clear association between the ongoing symptoms in patients with TTS at 3 months and chemical and imaging myocardial abnormalities. 24

At the moment, there is no evidence-based therapy for chronic management of patients with TTS. While b-blocker therapy is regularly prescribed to patients diagnosed with TTS, the initial evidence shows a lack of efficacy of b-blocker therapy to improve survival. 16 Two probable explanations can be proposed for the lack of b-blocker therapy to reduce recurrence or survival in TTS despite a major role of catecholamines in the pathogenesis of TTS. One, the pathogenesis of TTS may involve β2- rather than β1- adrenoceptor stimulation as demonstrated by Paur et al. 53 and, therefore, β1- selective antagonists which are commonly prescribed are ineffective to improve outcomes. Secondly, it is possible that the dose of b-blocker agents prescribed in the observational studies is not high enough to block the effects of catecholamine pulse secretion. On the other hand, benefits of ACE inhibitor therapy could be either because of reduction in sympathetic activity...
Medium range dose of isoprenaline for a short duration leads to changes in the myocardium which were most pronounced at the LV apex. This study also demonstrated that isoprenaline administration leads to changes in energy metabolism in rat cardiomyocytes, a finding that has also been recently demonstrated in patients with TTS. These conclusions have been strengthened further from the findings of Willis et al., who demonstrated in an animal model the contractile dysfunction in TTS is a consequence of mitochondrial impairment, with decreased ATP synthesis capacity and increased reactive oxygen species (ROS) production. However, these metabolic derangements and energetics impairment also occur in heart failure irrespective of the disease etiology and what remains to be known how exactly the metabolic derangement in TTS is different from the conventional heart failure.

Under normal circumstances, free fatty acids (FFA) are the main source of myocardial energy. However, therapeutic agents shifting the source of energy from FFA to efficient glucose during the acute stage of TTS may improve energetics and lead to quicker and more complete recovery. Glucose, insulin, and potassium (GIK) regimen, which has shown mixed results in the ischemia trials, could be a possible therapeutic in patients with TTS. Similarly, medications like trimetazidine and ranolazine that partially inhibit fatty acid oxidation and augments glucose utilization could be promising in the initial and recovery phase of TTS. Perhexiline is another agent that has been used in the past as an anti-anginal could be of use. However, the potential for side effects, close monitoring of drug concentration and restricted availability of perhexiline may limit its use. The recent findings of increased generation of peroxynitrite (ONOO−) and down stream activation of poly (ADP-ribose) polymerase 1 (PARP-1) in the human myocardium of patients dying of TTS may hint towards another possible therapeutic target to improve energetic impairment.

In conclusion, we have now realized that TTS is a rather complicated disorder and not as simple as once thought. Evidence regarding treatment of TTS and its related complications comes from registry data and observational studies. In the absence of randomized control trial evaluating specific type or duration of medical therapy in TTS, the treatment for this syndrome remains

Future directions – possible targets for intervention

It is clear that our knowledge regarding TTS therapeutics comes from small retrospective studies and is indeed very superficial. To understand the underlying pathogenesis of the disease, many researchers including us have developed animal models of TTS. Isoprenaline has been widely used to induce TTS like changes in the animal heart. It is important to recognize that isoprenaline has been used for a very long time in the animal models to induce myocardial fibrosis, myocardial hypertrophy, infarction and heart failure. From the available literature, we now know that the effect on myocardium depends upon the dose and duration of isoprenaline administration. Medium range dose of isoprenaline for a short duration can produce typical changes of TTS in rat myocardium.

In 1997, way before clinicians were interested in TTS, Chagoya de Sanchez et al. demonstrated that medium dose of isoprenaline through interaction with the renin–angiotensin system or because of the anti-inflammatory effects of ACE inhibitors on the myocardium. From the current evidence, we recommend that patients diagnosed with TTS should be on ACE inhibitor therapy for a long-term and use of b-blockers along with ACE inhibitor therapy could be limited to control heart failure symptoms and to improve LV ejection fraction.

Firstly, it should also be comprehended that there is marked heterogeneity in the acute and chronic phase of TTS. Not all the patients with TTS develop hemodynamic derangement in the acute phase and, similarly, not all the patients have a slow recovery. Recognition of variables associated with slow recovery will help to select patients who should be treated differently. Secondly, it is now clear that TTS is associated with myocardial inflammation and impaired energetics. Hence, therapies that reduce inflammation and improve energetics could be utilized. ACE inhibitors have well known anti-inflammatory effects, and their use in TTS can be beneficial to fasten the recovery and limit myocardial damage. A randomized study evaluating the use of ACE inhibitors in TTS, in order to preserve myocardial energetics and thus minimize the myocardial damage and accelerate recovery is an increasingly attractive strategy.

**Figure 3.** (3a) Echocardiography at the time of admission of a patient diagnosed with Takotsubo Syndrome demonstrating involvement of both right and left ventricular apex. There is no thrombus in either of the ventricles at that time. (3b). Echocardiography on day 10 post diagnoses demonstrated a large thrombus in the right ventricle. We treated this patient with warfarin and echocardiography at 3 months showed normal right ventricle and left ventricly motion without a thrombus.
entirely empirical and should be individualized according to the patient characteristics at the time of presentation. ACE inhibitor use has been noted to be beneficial following TTS diagnosis. b-Blocker therapy can be used to treat heart failure, arrhythmias and LVOT obstruction, however, use of b-blocker therapy has not been found to reduce recurrence or improve survival in observational studies. Lastly, our review highlights the need for a large multicenter randomized study to further clarify the management of TTS.

Declarations of interest

The authors declare no conflicts of interest.

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The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”.58

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