Novel Understanding of Takotsubo Syndrome

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Summary

Takotsubo cardiomyopathy is described as a transient reversible cardiomyopathy which typically occurs in older women after emotional or physical stress. This cardiomyopathy is also recognized as a “syndrome” because it develops in conjunction with various diseases. Since the clinical presentation of takotsubo syndrome (TTS) is similar to acute coronary syndrome (ACS), TTS should be distinguished from ischemic heart disease. Although the pathophysiology of TTS has not well been established, a number of its specific features have been suggested. The predictor of mortality in TTS is still unknown. In this review article, we describe a series of treatment decisions in TTS.

Key words: Apical ballooning, Catecholamine, Acute coronary syndrome, Heart failure, Stress

Takotsubo cardiomyopathy is described as a transient reversible cardiomyopathy which typically occurs in older women after emotional or physical stress.1-4 This cardiomyopathy is also recognized as a “syndrome” because it develops in conjunction with various diseases.5 Since the clinical presentation of takotsubo syndrome (TTS) is similar to acute coronary syndrome (ACS), TTS should be distinguished from ischemic heart disease. Although the pathophysiology of TTS has not well been established, a number of its specific features have been suggested. The predictor of mortality in TTS is still unknown. In this review article, we describe a series of treatment decisions in TTS.

Epidemiology

TTS was first described in the literature in 1990 by Sato, et al. from Japan.7 Since 2000, many case reports have been published around the world. Earthquakes have been regarded as a trigger to increase the prevalence of acute myocardial infarction, and currently it is believed that TTS should also be included. In fact, approximately half of the patients with ACS in Japan were diagnosed as having TTS.8 One study from the United States showed that TTS was diagnosed in approximately 0.02% of all hospitalized patients.9 Women have higher odds of developing TTS than men (odds ratio, 8.8). Women aged 55 years and older have 4.8 times higher odds for developing TTS than women younger than 55. Smoking, alcohol abuse, anxiety states, and hyperlipidemia are commonly associated with the prevalence of TTS. The peak incidence of hospitalization for TTS is in the spring10,11 or summer.12 Japanese researchers reported that the peak of TTS onset was in the autumn and late winter in Japan.13 According to the Diagnosis Procedure Combination data presented by Isogai, et al.,14 there is no seasonal rule for the onset of TTS.

Pathophysiology

Various etiologies are presumed to cause TTS, including coronary vasospasm, plaque rupture, microcirculatory dysfunction, loss of female hormones, metabolic disturbances, and catecholamine hypothesis, although no consensus with respect to pathophysiology has yet been reached. It is reported that approximately 30% of TTS is associated with coronary vasospasm.15 Coronary vasospasm is less likely to trigger TTS because of a discrepancy between TTS and stunned myocardium in the pathological findings.

The wall motion of TTS is similar to that of myocardial ischemia after plaque rupture; however, the wall motion of TTS extends beyond a single coronary vascular bed and it has no coronary occlusion. Plaque rupture is excluded from the cause of TTS in several guidelines.

The leading hypothesis of the pathophysiology is catecholamine cardiotoxicity. One study demonstrated that the plasma levels of catecholamine among TTC patients were 2 to 3 times the values among myocardial infarction patients.16 Biased agonism of epinephrine for \( \beta_2 \) adrenoceptor (AR) Gs at low and Gi at high concentrations underpins the acute apical cardiodepression observed in TTS, with an apical-basal gradient in \( \beta_2 \)ARs explaining the differential regional responses (Figure).17 Epinephrine-specific \( \beta_2 \)AR-Gi signaling may have evolved as a cardio-protective strategy to limit catecholamine-induced myocardial toxicity during acute stress.18 A recent experimental
study suggested that β-adrenergic signaling and a high sensitivity to catecholamines could be associated with the onset of this syndrome; the enhanced reduction of integration in meta-iodobenzylguanidine myocardial scintigraphy supports this hypothesis.\textsuperscript{17,18}

Kurisu, \textit{et al.} demonstrated that coronary blood flow was severely impaired in all coronary arteries in agreement with left ventricular (LV) asynergy immediately after onset. Even though coronary blood flow was improved, the impairment remained after resolution of the takotsubo-like LV dysfunction.\textsuperscript{19} Therefore, coronary microvascular impairment has a potential to trigger TTS.\textsuperscript{20}

Since many postmenopausal women suffer from TTS, a lack of estrogen seems to affect the pathogenesis of TTS.\textsuperscript{21,22} No current or proven pathophysiological mechanism exists to explain TTS; many hypotheses are still being investigated.

### Contractile Pattern

Stiermaier, \textit{et al.} evaluated the prognostic impact of different ballooning patterns in 285 patients with TTS.\textsuperscript{23} The patients with typical apical ballooning were significantly older and had a higher prevalence of diabetes mellitus than those with atypical ballooning. The initial LV ejection fraction was significantly lower in apical ballooning but recovered to normal values in both groups. Although 28-day mortality did not differ significantly, typical apical ballooning was associated with increased 6-month and long-term mortality rates. After complete recovery of LV function, the prognosis was similar in patients with typical and atypical ballooning patterns.\textsuperscript{23} As well as the classic apical variant of TTS, other forms have been described, including the midventricular, basal, and focal forms.\textsuperscript{24} TTS can be triggered by not only negative but also positive life events. While the patient characteristics are quite similar, the midventricular type is more prevalent among the ‘happy heart syndrome’ than among the ‘broken heart syndrome’.\textsuperscript{25} Right ventricular (RV) involvement is relatively common and reversible. RV involvement has a negative impact on hospital stay and morbidity; its identification can help predict hemodynamic instability.\textsuperscript{26,28}

### Clinical Presentation

The predominant symptom on admission is chest pain, followed by dyspnea and syncope; meanwhile, some patients have no symptoms. Less common symptoms, such as pulmonary edema, cardiogenic shock, and serious ventricular arrhythmias are quite rare. Nonspecific symptoms, including weakness, cough, and fever also have been reported.\textsuperscript{26,29} Recurrent TTS is infrequent; one study has demonstrated that the recurrence rate is highest within the first 4 years, approximately 2.9% per year, and the recurrence rate over 4 years is 11.4% after initial presentation.\textsuperscript{30} The average recurrence rate is reported to be approximately 3.8%.\textsuperscript{31}

### Diagnosis

There are several guidelines with which to diagnose TTS. The criteria proposed by the Mayo Clinic are the most commonly used around the world,\textsuperscript{32} even though TTS was first reported and named in Japan. Every criterion proposes the exclusion of significant organic stenosis or spasm of a coronary artery; however, the recent guidelines suggest that obstructive coronary artery disease is frequently observed in patients with TTS. The wall motion abnormalities usually extend to the territory of the involved coronary arteries. CT coronary angiography is employed as alternative imaging to exclude coronary stenosis when the presentation is delayed or the patient is pain free and stable on admission. The current state of knowledge on TTS according to the European Society of Cardiology Working Group is presented in Table 1.\textsuperscript{33}
Laboratory Findings

The plasma levels of both epinephrine and norepinephrine are remarkably increased in patients with TTS. Several studies have suggested that the markedly elevated catecholamine levels might be the main pathogenic factor.3,33,34 Cardiac enzymes, such as troponin T and CK-MB, are slightly increased in TTS, although the levels are lower than those in AMI.3,52 One study demonstrated an elevated troponin level in 87.0% of the patients with TTS.34 Since TTS is a disease that primarily causes dis-tention of the ventricles and is characterized by reversible myocardial dysfunction without necrosis, a greater increase in plasma BNP rather than troponin T or CK-MB has been demonstrated in TTS compared with AMI.3,34 Thus, plasma BNP levels are usually greater in TTS than in STEMI; the ratio of BNP to peak troponin levels may differentiate TTS from STEMI.3,34 In-hospital mortality is influenced by the peak concentration of troponin I and overall mortality is affected by cardiogenic shock and the elevation of BNP during admission. The assessment of troponin I and BNP will help the prognostication of TTS patients in daily clinical practice.3,34

Electrocardiographic Findings

ST-segment elevation is observed in almost all patients with TTS in the acute stage. Subsequently, T-wave inversion occurs; QT prolongation and transient Q waves can be seen. It is difficult to distinguish patients with TTS from those with acute anterior AMI based on ECG findings. A difference in ECG findings between TTS and AMI has been demonstrated. Patients with anterior AMI have ST-segment elevation in leads V2 - V4,3,37,38 The combination of fewer appearance of abnormal Q waves and no reciprocal changes and ST-segment elevation in leads V4 - 6 to V1 - 3 ≥1 had a greater specificity (100%) and overall accuracy (91%) than either criteria.3,9

Echocardiography

The typical findings of takotsubo-like LV ballooning consist of akinesis, hypokinesis, or dyskinesis of the apical and middle segments of the LV and preserved or hyperkinesis of the basal segments. LV myocardial dysfunction of TTS characterized by symmetric wall motion abnormalities involving the mid-ventricular segments of the anterior, inferior, and lateral walls over the apical segment should be considered peculiar to TTS and included in the differential diagnosis of TTS and ACS. These findings support the hypothesis of diffuse ventricular dysfunction secondary to myocardial stunning underlying the pathogenesis of TTS.40,41 RV apical akinesis during echocardiographic examination makes the diagnosis of this syndrome very likely.42

The median LV ejection fraction on the initial echocardiogram was 20% (interquartile range, 15 to 30%). A reduced LV ejection fraction (mean value, 40.7 ± 11.2%) was noted in 86.5% of patients with TTS on admission but in only 54.2% of patients with an ACS.3,26 The assessment of LV ejection fraction is also important in the management of TTS because LV ejection fraction and wall motion abnormalities are closely associated with major adverse events.43 In addition, the evaluation of LV outflow obstruction, valve disease, and pulmonary hypertension in TTS management is indispensable. Echocardiography simply and easily depicts the wall motion abnormalities in their acute phase. Since the diagnosis of TTS is sometimes challenging, it is favorable to perform echocardiography to identify slight clinical changes.

Nuclear Imaging

In the first nuclear study, technetium-99 m-tetrofosmin and 123I-h-methylidophenyl pentadecanoic acid (123I-BMIPP) were administered to patients without coronary disease who revealed stunned myocardium after contrast medium administration.39 The total defect score (TDS) was higher in the acute phase compared with the
Cardiac Magnetic Resonance (CMR)

CMR imaging is useful for the evaluation of wall motion abnormalities. It also detects reversible (inflammation, ischemic edema) and irreversible (necrosis/fibrosis) injuries. Eitel, et al. reported that CMR imaging showed complete normalization of LV ejection fraction and inflammatory markers in the absence of significant fibrosis in all TTS patients.46 Later gadolinium enhancement (LGE) on CMR usually represents fibrosis. In myocardial infarction, the distribution of LGE is subendocardial or transmural, indicating the extent of infarction. In nonischemic cardiomyopathy, there may be an isolated midwall or subepicardial pattern of enhancement and myocarditis produces a patchy distribution of LGE among other manifestations on CMR. However, minor LGE can be found in patients with TTS. It has been reported that minor LGE is present in approximately 9% of the patients with TTS when LGE is defined at a cutoff value of > 3 SD above the mean.47 Meanwhile, Mitchell, et al.48 reported the usefulness of CMR for assessing myocardial viability and prognosis in TTS. They demonstrated that a lack of delayed enhancement represented a lack of irreversible myocardial damage and predicted functional recovery. Although CMR can be performed noninvasively, it is not suitable for urgent examinations because a lot of time is required for scanning.49 Therefore, it illustrates the potential of multiple detector computed tomography for the noninvasive differentiation of TTS from ACS. CMR is quite useful for providing an accurate diagnosis or TTS and is also helpful to rule out ACS and myocarditis (Table II).40

Cardiac Computed Tomography (CCT)

CCT has high negative predictive values and lower risk than coronary angiography.47-49 The exclusion of coronary obstruction is necessary for diagnosing TTS; thus, CCT is a significant examination. Some studies support the role of CTT angiography in the clinical course of TTS. According to the Japanese Guidelines for TTS diagnosis, urgent coronary angiography is desirable for imaging during the acute stage. Coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion and a lesion involved in the abnormal pattern of ventricular contraction.48 In fact, CCT is used for diagnosis in the acute phase.50

Table II. Differences in CMR Features of Takotsubo Syndrome, Acute Myocardial Infarction and Acute Myocarditis

<table>
<thead>
<tr>
<th>Site of wall motion abnormality</th>
<th>Takotsubo syndrome</th>
<th>Myocardial infarction</th>
<th>Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentric mid- and apical LV wall</td>
<td>Typically transmural in a concentric mid and apical LV wall distribution</td>
<td>Follows expected epicardial coronary artery distribution</td>
<td>Usually global unless regional edema/LGE is severe</td>
</tr>
<tr>
<td>Left ventricular impairment</td>
<td>Yes: typically impaired ejection fraction with elevated indexed end systolic volume</td>
<td>Yes: typically impaired ejection fraction with elevated indexed end systolic volume</td>
<td>Yes, but may show only mild/ borderline low normal ejection fraction</td>
</tr>
<tr>
<td>Right ventricular impairment</td>
<td>&gt; 33% of patients</td>
<td>May be seen, particularly if right coronary artery territory involved</td>
<td>Rarely impacts on right ventricular function</td>
</tr>
<tr>
<td>LGE</td>
<td>Maybe (10±40%)</td>
<td>Yes</td>
<td>Often</td>
</tr>
<tr>
<td>Site of LGE</td>
<td>Concentric transmural mid and apical LV wall</td>
<td>Typically subendocardial or transmural in recognized epicardial coronary artery distribution</td>
<td>Mid-myocardial or subepicardial in a focal non-coronary artery distribution</td>
</tr>
<tr>
<td>Type of LGE</td>
<td>Low-intensity LGE</td>
<td>Bright LGE</td>
<td>Low-intensity or Bright LGE</td>
</tr>
<tr>
<td>Microvascular obstruction</td>
<td>No</td>
<td>May be</td>
<td>No</td>
</tr>
<tr>
<td>Resolution at 3 months</td>
<td>Yes</td>
<td>Potentially but may show residual myocardial fibrosis and impairment</td>
<td></td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; LV, left ventricular; LGE, late gadolinium enhancement. Quoted from Abbas A, et al. with permission.46
Treatment

There are no specific options for the LV failure characterizing TTS because cardiac function is normalized within a few weeks. A position statement indicated a suggestive stratification for TTS patients in 2016. A risk stratification in patients with TTS is also proposed in the statement. High risk patients should be treated in an intensive care unit. Treatment is determined by the complications during the acute phase. When shock occurs, intravenous fluids, isotropic agents, or intra-aortic balloon pumping (IABP) have been established as additional support for the circulation. However, IABP is not suitable for patients with LV outflow obstruction because of a worsening pressure gradient.

The administration of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is reported to decrease the recurrence rate of TTS.47) Although the use of β-adrenocepto blockers in the acute phase of TTS is still a matter of debate, the combination of both angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-adrenoceptor blockers was an effective regimen with which to prevent the recurrence of TTS.48)

Prognosis

One study reported that patients with TTS had a poor prognosis relative to survival prediction.30 Thirty-day mortality in TTS was 4.1%, which was similar to that in ACS.31 The long-term mortality in TTS was poor compared with that in ACS; the representative predictors were men, diabetes, and Killip > 3.32 The presence of physical triggers is closely associated with higher troponin levels on admission and low EF.33 The recurrence rate of TTS is reported to be 5-11% and the duration ranges from 3 months to 14 years.34,35 The main cause of TTS is physical and psychological stress; thus, avoiding stress is vital to prevent recurrence. In addition, successful treatment of primary illness has a good prognosis because most deaths with TTS in hospital are derived from non-cardiac disease.

Conclusion

Not only cardiologists but also non-cardiologists need to fully understand TTS because this syndrome occurs in various situations. TTS is a reversible disease; when the treatment of acute complication is successful, it will lead to a good prognosis. Hence, we should fully understand the mechanism of TTS and provide appropriate treatment. The exact pathophysiology of the cause of recurrence has not been fully clarified; however, physical and psychological stress influence TTS. Clinicians should treat the primary disease appropriately to prevent the occurrence of TTS.

Disclosures

Conflicts of interest: None.

References

21. Mendelsohn ME, Karas RH. The protective effects of estrogen...