Diagnosing Takotsubo Cardiomyopathy without Coronary Angiography

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ABSTRACT

Takotsubo cardiomyopathy (TC) is an acute but rapidly reversible heart failure syndrome. Coronary angiography is still the first-line diagnostic tool for distinguishing TC and acute coronary syndrome. However, in daily practice, clinicians are often faced with a dilemma especially when cardiac catheterization and thrombolytic therapy are relatively contraindicated, patient’s refusal, unavailability of diagnostic tool especially in remote area or can cause potential adverse consequences. This article aims to discuss the diagnosis of TC using clinical, laboratory and imaging parameters in the absence of coronary angiography. In electrocardiography, TC will show transient changes of ST segment elevation T wave abnormalities, pathological Q waves, new bundle-branch block and QTc interval prolongation. Other than electrocardiography, cardiac biomarkers, echocardiography, cardiac imaging can be used. There are few clinical criterias to diagnosing TC, such as Mayo Clinic criteria, GET QT criteria and interTAK diagnostic score. These multiple modalities can help distinguished TC from ACS, but further research is still needed.

Keywords: angina, takotsubo, cardiomyopathy, heart failure

INTRODUCTION

Takotsubo cardiomyopathy (TC), also referred as stress cardiomyopathy, broken heart syndrome or apical ballooning syndrome, is an acute but rapidly reversible heart failure syndrome.¹ This cardiomyopathy first described by Sato et al. in Japan in 1990.¹,² It is called “Takotsubo cardiomyopathy” because of left ventricle shape during systole, appeared to have similarities with Japanese octopus trapping pot with a round bottom and narrow neck.¹,² Gaurang et al. did retrospective case control studies with an age matched cohort and found that female constituted the majority of the TC patient,³ especially postmenopausal women.¹,² Nowadays, incidence of TC can be up to 5.9% to 7.5% in female patients.⁴

The diagnosis of TC remains very challenging due to the close similarities of symptoms to the acute coronary syndrome (ACS).¹ In order to avoid under-diagnosing ACS, over-diagnosing TC and the opportunity for timely reperfusion, coronary angiography is still the first-line diagnostic tool for distinguishing both entities.³ However, in daily practice, clinicians are often faced with a dilemma especially when cardiac catheterization and thrombolytic therapy are relatively contraindicated, patient’s refusal, unavailability of diagnostic tool especially in remote area or can cause potential adverse consequences.³ Taking all these facts into account, distinguishing TC from ACS using clinical, laboratory and imaging parameters are still needed. This article aims to discuss the diagnosis of TC using clinical, laboratory and imaging parameters in the absence of coronary angiography.
CLASSIFICATION

According to ballooning pattern, TC is classified into four groups: apical type or Takotsubo type (apical akinesia and basal hypercontraction), midventricular type (midventricular ballooning and basal/apical hypercontraction), basal type or reverse Takotsubo (basal akinesia and apical hypercontraction), and focal type (any other segmental ballooning when Takotsubo-like LV dysfunction is present) (Figure 1). In addition to apical ballooning, other types of TC can also be called atypical TC.

Figure 1. Four different type of TC during diastole (left column and red) and systole (middle column and white). The blue dashed line demonstrate region of wall motion abnormality.

ETIOLOGY AND PATHOPHYSIOLOGY

Takotsubo cardiomyopathy is usually associated with identifiable emotional or physical stress. Emotional stressors such as receiving bad news, moving to a new residence, involvement in legal proceedings or ongoing dissatisfaction with relationships at home or at work. Ghadri et al stated that not only negative stressors, TC can also be induced with positive stressors. Physical stressors typically involve major surgery, orthopedic trauma, exacerbation of obstructive airways disease. Stress will induce release of catecholamine in the body and catecholamine at high levels can result in negative inotropic effect by signaling
protein through the ventricular β-adrenergic receptors (βARs).\(^1\) This effect is greatest in apex where the density of βARs is highest.\(^1\)

Emotional or physical stressors happen to everyone, but only few people develop TC. This shows that certain individuals are more susceptible to TC. Predisposition and risk factors for TC are hormonal, genetic factors, and psychiatric and neurologic disorders. Reduced estrogen levels after menopause increases the susceptibility of TC in women as it has been associated with increased risk of LV wall motion abnormalities.\(^5\)

**CLINICAL MANIFESTATION**

Clinical manifestation in most TC patients is indistinguishable from an ACS.\(^1\) According to Gaurang et al., the most common presenting symptom in TC is chest pain (54%), followed by shortness of breath (23%), altered mental status caused by drug overdose like opioids (18%), and gastrointestinal symptoms such as nausea, abdominal pain (5%).\(^3\) Patient could also present with complications, such as heart failure, pulmonary edema, stroke, hypotension, cardiogenic shock, and even cardiac arrest.\(^1,3,5\)

**DIAGNOSIS**

If diagnostic facilities are available and patient’s consent is obtained, coronary angiography must not be replaced with other diagnostic tool, as it is the gold standard in differentiating TC and ACS.\(^7\) But in some conditions, other diagnostic tools such as electrocardiography (ECG), echocardiography, cardiac imaging combined with clinical criteria can be used to help clinician makes important decision.

**Electrocardiography**

The classical abnormality for TC on ECG is ST segment elevation mimicking acute STEMI (70–80%) of cases, accompanied by T wave abnormalities (64%), transient pathological Q wave (32%), reduction of the R wave amplitude or absence R wave in anterior chest leads, new bundle-branch block, and QTc interval prolongation.\(^1\) The recent studies reported ST elevation ≥1 mm in at least one of the leads V3–V5 without ST elevation in lead V1 identified TC with a sensitivity of 74.2% and a specificity of 80.6%.\(^1\)

Gopalakrishnan et al stated that there are several findings in ECG that could help differentiating TC and STEMI such as lack of reciprocal ST depression, widespread T wave inversion, low QRS voltage on presentation, attenuation of QRS voltage in serial EKGs, QTc prolongation, frontal plane ST vector, ST segment elevation in aVR without STE in V1, lower rate of Q-waves, more frequent STE in the inferior leads, higher ratio of the sums of STEs in leads V4-V6 to the sums of STEs in leads in V1-V3, lower amplitude of STE (< 1.5 mm) and a summed amplitude of the S-wave in V1 plus the R-wave in V6 < 1.5 mV.\(^8\)

Electrocardiography changes in TC is transient, such as inverted T waves that will resolve spontaneously within a few weeks to several months and abnormal Q waves in precordial leads that will resolve in few days to several weeks.\(^9\)

**Cardiac biomarkers**

Markers of myocardial damage (troponin, Creatine Kinase (CK), Creatine Kinase-Myocardial Band (CK-MB) and myoglobin) will be only slightly elevated, followed by rapid decrease.\(^9\) In TC, N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) levels rise within first 24 hour after the onset of symptoms with slow and incomplete resolution during the 3 months thereafter.\(^8\) Rhandawa et al stated that TC will have higher level of NT-proBNP than ACS.\(^11\) The mechanism of NT-proBNP release is very similar in TC and ACS, as NT-proBNP secretion is mainly provoked by myocardial stretch, caused by pump failure.\(^10\)

Frieblich et al found peak NT-proBNP / peak TnT ratio appeared most accurate to distinguish ACS from TC.\(^3,10\) They stated that ratio of peak levels of NT-proBNP/Troponin T (TnT) of 2,889,
distinguished TC from STEMI while ration of 5,000 distinguished TC from NSTEMI. Rhadawa et al further explore this cardiac biomarkers, and stated that TC can be distinguished from ACS with the use of NT-proBNP/CK-MB ratio > 29.9 (sensitivity 50% and specificity 95%). This cut off value still needs to be evaluated further.

Echocardiography

The pattern of wall motion abnormalities may suggest the diagnosis of TC. Echocardiographic findings in TC include reversible wall motion abnormalities (RWMA) extending beyond distribution of an epicardial coronary artery, basal hyperkinesis, left ventricular outflow obstruction (LVOT), reversible mitral regurgitation, and right ventricular dysfunction. It usually performed prior to coronary angiography in patients without ST-segment elevation or with ST-segment elevation but with a high risk of coronary angiography. Re-evaluation of echocardiograph is useful to demonstrate recovery of LV function is recommended. Mean of LV ejection fraction (LVEF) usually lower in TC than STEMI and ranging from 20% to 49% at the initial presentation of TC and over a period of days to weeks the dramatic improvement of the LV function (the mean LVEF 60–76%) is observed for the majority of patients. Han et al did a systematic review and stated that TC usually presents with lower LVEF than ACS with lower cardiovascular risk.

Cardiac imaging

In hemodynamically stable patients presenting > 12 hours after onset of pain, non-invasive imaging methods such as cardiac MRI might be preferred, if cardiac biomarker ratios suggest the presence of TC. Cardiac MRI allows the accurate identification of reversible myocardium damage by visualization of wall motion abnormalities in each area, quantification of ventricular function, and assessment of inflammation and fibrosis. Characteristic sign of TC in cardiac MRI is the absence of late gadolinium contrast enhancement.

Clinical Criteria

Mayo Clinic Criteria

Various attempts has been done to make clinical criteria for TC, including Mayo Clinic criteria. Mayo clinic criteria for the clinical diagnosis of takotsubo cardiomyopathy:

1. Typical left ventricle (LV) contraction pattern: transient hypokinesia, akinesis or dyskinesia in the LV mid segments with or without apical involvement accompanied with hypercontraction in the basal segments; Reversible wall motion abnormality that extend beyond a single coronary artery vascular distribution; stressful trigger is usually but not always present;

2. Absence of obstructive coronary artery disease (CAD) or angiographic evidence of acute plaque rupture;

3. Newly developed ECG abnormalities (ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin;

4. Absence of recent head trauma, intracranial hemorrhage, pheochromocytoma, myocarditis or hypertrophic cardiomyopathy.

GET QT Criteria

Vaidya et al did prospective case-control study of 42 TC and 55 STEMI patients to identify clinical and laboratory parameters with useful predictive diagnostic value to differentiate TC and STEMI, resulting GET QT criteria (table 1). The presence of 3 or more predictors in a patient had a sensitivity of 88.8%, specificity of 95.1% and negative predictive value of 90.9% to diagnose TC.

<table>
<thead>
<tr>
<th>Table 1. GET QT Criteria in Predicting Takotsubo Cardiomyopathy</th>
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<tbody>
<tr>
<td>Predictors of Takotsubo cardiomyopathy</td>
</tr>
<tr>
<td>Gender: Female</td>
</tr>
<tr>
<td>EF &lt; 40%</td>
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<tr>
<td>Troponin peak &lt; 2ng/mL</td>
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<td>Qtc &gt; 470 ms in the initial ECG</td>
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<td>Time to peak &lt; 6 hours</td>
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**InterTAK Diagnostic Score**

InterTAK diagnostic score consist of seven variables, such as female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, an QTc prolongation 6 points. Cut-off value of 40 points has sensitivity of 89% and specificity of 91%.

Differential diagnosis for TC are esophageal spasm, gastroesophageal reflux disease, myocardial infarction, myocardial ischemia, unstable angina, acute coronary syndrome, angina, aortic dissection, myocarditis, acute pericarditis, pneumothorax, cardiogenic pulmonary edema, pulmonary embolism, Boerhaave syndrome (spontaneous esophageal rupture), cardiac tamponade, cardiogenic shock, cocaine-induced cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, and coronary artery spasm.

**MANAGEMENT**

Takotsubo cardiomyopathy is managed conservatively and focused on emotional or physical stress relief, except in a situation where complications occur. Management of TC with complication is similar to that in general guideline. There are no guidelines for management of TC, but some studies stated that beta-blockers, angiotensin converting enzyme (ACE)/angiotensin receptor blockers (ARB), psychological stress relief management helped lower inpatient mortality and recurrence of TC.

Magnesium can be used in TC patient due to its mechanism to inhibit the secretion of catecholamines from the adrenal medulla. Anxiolytics might be useful in TC especially when emotional stress is the trigger for TC. Management of TC is based on the sign and symptoms appeared, as guidelines for managing this disease is still not established.

Dual antiplatelet therapy including aspirin and clopidogrel, along with anticoagulant are usually administered after diagnosis of ACS is considered. There are still contradicting opinions about antiplatelet, whereas some studies advised to stop antiplatelet after diagnosis of TC is established, other studies found that antiplatelet is beneficial in lowering morbidity and mortality of TC. Ventricular thrombus found in 1.3% patient with TC, especially in patient with severe LV dysfunction. Some studies stated that anticoagulant can prevent LV thrombus in TC patient with severe LV dysfunction.

**PROGNOSIS**

For patients who survived the acute stage of this disease, will show improvement in LV function in the first few days and complete recovery in a few months. Although complications of TC should be diagnosed and treated quickly. Compared to ACS, TC patient with physical stress trigger showed higher mortality rates than ACS whereas patients with emotional stress trigger has better outcomes. Similarly compared to ACS, male patients have poorer prognosis than female patient.

**CONCLUSION**

Takotsubo cardiomyopathy can be diagnosed using multiple modalities, such as electrocardiography, echocardiography, cardiac biomarkers, and multiple clinical criteria. Multiple modalities can help distinguished TC from ACS, but further research is still needed.

**Conflict Of Interest**
Authors confirm no conflict of interest in this paper.

**REFERENCES**


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