‘GET QT’: Clinical Criteria to Differentiate Takotsubo Cardiomyopathy from STEMI

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Abstract

Background
Introduction: Presentation of Takotsubo cardiomyopathy (TCM) may closely mimic ST-elevation myocardial infarction (STEMI) and clinicians are often faced with a dilemma when cardiac catheterization is unavailable or contraindicated.

Methods
Age-matched 42 TCM and 55 STEMI patients admitted in SUNY Upstate Hospital, Syracuse, NY were retrospectively compared for characteristics at presentation.

Results
Results: 12 TCM patients (26%) had ST elevation in the initial EKG. Mean QTc interval was significantly prolonged in TCM (469ms vs 443ms, p=0.001). The peak Troponin T (TnP) level in TCM was significantly less (1.15ng/ml vs 6.04ng/ml; p=0.001) and the time to peak troponin T (Tp) was lower (3.7 hours versus 12.4 hours, p=0.001). Mean LV ejection fraction (EF) was 36% in TCM versus 47.4% in STEMI (p=0.001). Significance (p<0.05) was noted for 5 predictors on multiple regression namely: Gender, EF, TnP, QTc interval and Tp. A prediction model was then developed, giving a score of one for each positive finding: female gender, EF< 40%, TnP< 2ng/ml, QTc> 470ms in the initial EKG and Tp< 6 hours (GET QT criteria). The presence of 3 or more predictors had a sensitivity of 88.8%, specificity of 95.1% and negative predictive value of 90.9% to diagnose TCM. Though there have been recent publications proposing various criteria to distinguish the two diseases, this is the first proposing highly specific and all-inclusive combined laboratory, EKG and echocardiography criteria.

Conclusions
Females with early and low peaking troponins prolonged QTc; low EF were likely to have TCM. With the proposed prediction model—presence of 3 or more factors is highly specific to diagnose TCM.

Keywords: Myocardial infarction; Takotsubo cardiomyopathy; ST-elevation, EKG; cardiac biomarkers; echocardiography

Citation: Vaidya GN, Jaiswal A, Madhira B. ‘GET QT’: Clinical Criteria to Differentiate Takotsubo Cardiomyopathy from STEMI. International Cardiovascular Forum Journal. 2016;5:53-57. DOI: 10.17987/icfj.v5i0.324

Background/Objectives
Takotsubo cardiomyopathy (TCM) is characterized by transient ischemic left ventricular dysfunction and the presentation often mimics clinical features of an acute myocardial infarction (AMI). Indeed, ST elevation is one of the most common electrocardiogram (EKG) findings in patients with TCM. To avoid missing STEMI, and the opportunity for timely reperfusion, current guidelines advocate using diagnostic coronary angiography as the first-line diagnosis. Clinicians, however, are often faced with a dilemma when cardiac catheterization and thrombolytic therapy are relatively contraindicated, unavailable or can cause potential adverse consequences. Meanwhile, in patients presenting with hemodynamic instability, misdiagnosing TCM as STEMI will potentially lead to initiation of harmful pharmacological or device treatment leading to worsening hemodynamic compromise. Therefore, distinguishing TCM from AMI in the absence of invasive procedures remains crucial and variously attempted in recent literature. In the present study, we have retrospectively investigated TCM and STEMI patients to identify clinical and laboratory parameters with useful predictive diagnostic value to differentiate the two clinical modalities and guide appropriate therapies.

Methods
We did a retrospective case control study with an age matched cohort selected from patients admitted in a single tertiary facility- SUNY Upstate Hospital, Syracuse, NY. Appropriate Institutional Review Board approval was obtained. Inclusion criteria for TCM cases was based on the proposed Mayo Clinic criteria 1: Adults (>18 years) with presentation mimicking myocardial infarction with ST-T wave changes in the initial EKG and/or elevation of troponins, typical echocardiographic picture of acute onset regional wall motion abnormalities with or without apical ballooning and no or insignificant (<50% stenosis)
coronary artery disease (CAD) on catheterization. Only patients with complete reversal of LV ejection fraction (EF) within the next few months were included. Following patients were excluded: Pre-existent heart failure with EF<45%, chronic kidney disease stage III or more with estimated glomerular filtration rate <60ml/ min. A total of 154 patients were discharged with a diagnosis of TCM over the period from January 2012 to December 2014 but only 42 patients met the above mentioned criteria and were studied as cases. Most of the excluded patients were those with inadequate diagnostic workup, such as no cardiac catheterization. 55 age-matched STEMI patients admitted between January 2013 and November 2014 who underwent immediate PCI were used as controls. These patients were included irrespective of the culprit vessel, which would avoid a selection bias and a more practical final result. 12-lead EKG's were recorded at a speed of 25 mm/s and amplification of 10 mm/mV. ST elevation was defined as ≥2 mm in leads V2–V3 and ≥1 mm in other leads in two or more contiguous leads, significant inverted T wave as ≥0.5 mm. Since females have prolonged QTc, the QTc duration data was gender-controlled using hierarchical regression.

IBM SPSS was used for statistical analysis. Univariate analysis was performed on all the studied variables and those having significant contributions underwent multivariate analysis. Cut-off values were derived from values giving >75% specificity individually on receiver operating curve (ROC) analysis for these variables. The non-categorical predictors were then converted to categorical variables based on values above or below the cut-off. Patients satisfying 3 or more criteria were identified through conditional analysis and the ability to identify TCM was then compared with true positive patients.

Results

Both the groups were age matched (TCM 60.5 ± 11.5, STEMI 59.1 ± 10.5; p= 0.53). Females constituted the majority of the TCM patients (n=38, 91%) while males formed majority in STEMI patients (n= 40, 73%). The mean body-mass index was 30 in TCM patients (n=38, 91%) while males formed majority in STEMI (38%, p= 0.001). Mean BMI was 29.9 ± 7 in STEMI versus 30.1 ± 10 in TCM patients (p= 0.53). The findings are summarized in Tables 1, 2.

On the initial EKG after presentation,22 (26%) TCM patients had ST-elevations. No reciprocal changes were seen in these patients, while it occurred in 83% patients with STEMI. T wave inversions (TWI) were statistically more prevalent in TCM than STEMI (67% versus 44%, p= 0.02). Characteristically, of these patients,18 (57.1%) patients had diffuse TWI beyond a single ventricular wall (figure 1), usually sparing aVR and V1. The QTc interval in TCM was significantly prolonged at 470ms as compared to 440ms in STEMI patients (p=0.001).

The initial troponin T(TnTi) was lower in TCM patients (0.59ng/ml versus 3.85ng/ml, p= 0.001) but the TnTi values in STEMI group had significant variation, with some patients having very low TnTi levels at presentation. These levels when followed in the future increased the stress response. Echocardiography showed apical involvement in 86% TCM patients as compared to 30% STEMI (p=0.001). The mean QTc interval in TCM was significantly prolonged at 470ms as compared to 440ms in STEMI patients (p=0.001).

Table 1. Characteristics of patients in both the groups; BMI: body mass index, TSH: Thyroid stimulating hormone, proBNP: pro-brain natriuretic peptide

<table>
<thead>
<tr>
<th>Findings</th>
<th>Takotsubo cardiomyopathy</th>
<th>STEMI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>61 ± 12</td>
<td>59 ± 11</td>
<td>0.537</td>
</tr>
<tr>
<td>Gender Male Female</td>
<td>4(9.5%) 38(91%)</td>
<td>40(73%) 15(27%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI(kg/m2)</td>
<td>30.1 ± 10</td>
<td>29.9 ± 7</td>
<td>0.904</td>
</tr>
<tr>
<td>Diabetes(n)</td>
<td>11(26.2%)</td>
<td>21(38.2%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Hypertension(n)</td>
<td>29(69%)</td>
<td>41(74.5%)</td>
<td>0.549</td>
</tr>
<tr>
<td>Smoking(n)</td>
<td>33(78.6%)</td>
<td>38(69.1%)</td>
<td>0.296</td>
</tr>
<tr>
<td>Concomitant infection(n)</td>
<td>13(31.7%)</td>
<td>36(57.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Potassium(mmol/L)</td>
<td>4 ± 0.58</td>
<td>4 ± 0.56</td>
<td>0.99</td>
</tr>
<tr>
<td>Magnesium(meq/L)</td>
<td>1.37 ± 0.23</td>
<td>1.62 ± 0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak troponin T(ng/ml)</td>
<td>1.15 ± 2.46</td>
<td>6.04 ± 8.94</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to peak(hours)</td>
<td>3.7 ± 5.3</td>
<td>12.4 ± 5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>3.0 ± 6.3</td>
<td>2.1 ± 1.9</td>
<td>0.490</td>
</tr>
<tr>
<td>proBNP (pg/mL)</td>
<td>7342</td>
<td>3895</td>
<td>0.131</td>
</tr>
</tbody>
</table>

On Multivariate analysis (table 3), significance (p<0.05) was noted for 5 predictors namely: Gender, EF, peak TnTp, QTc interval and time to peak Tp. A prediction model was then developed, giving a score of one for each positive finding: female gender, EF> 40%, TnTp< 2ng/ml, QTc> 470ms in the initial EKG and Tpc ≥ 6 hours

Figure 1. EKG of two TCM patients showing diffuse T-wave inversions sparing aVR & V1

| Table 1 | Original Article

DOI: 10.17987/icfj.v5i0.324
combining laboratory, EKG and echocardiographic findings for and STEMI patients in moderately larger number of patients study intended to compare the presentation findings of TCM have proposed the use of EKG criteria 8,9, cardiac biomarkers10,11 nor are they practical in critically ill patients. Previous studies distinction but these imaging studies are neither available widely in terms of outcome, 5 patients from the STEMI list expired while no deaths were noted in the TCM list.

Discussion

The presentation of TCM commonly mimics acute coronary syndrome like ST-elevation myocardial infarction (STEMI) and in the early stages may be indistinguishable. Cardiac catheterization remains the current gold standard to differentiate between the two conditions, and should remain so until a more specific criteria is developed that can definitively prove the difference. At present, advanced cardiac imaging such as cardiac CT or magnetic resonance imaging have been proposed to make the distinction but these imaging studies are neither available widely nor are they practical in critically ill patients. Previous studies have proposed the use of EKG criteria cardiac biomarkers10,11 and echocardiography1,12 to distinguish the two conditions. This study intended to compare the presentation findings of TCM and STEMI patients in moderately larger number of patients combining laboratory, EKG and echocardiographic findings for more specific prediction model.

Clinical history criteria

Our study again found higher prevalence of TCM in post-menopausal women, the cause of which may be related to higher baseline emotional burden, higher prevalence of microvascular disease than men and the loss of an estrogenic protection from catecholamine overdrives after menopause. Conditions that accelerate atherosclerosis such as diabetes and hypertension were more prevalent in STEMI group than TCM.

Chest pain was the most common presenting symptom (54%) in TCM suggesting ongoing ischemia. Interestingly, 18% patients presented with altered mental status most commonly from opioid overdose while two patients presented with Ventricular tachycardia and later found to have insignificant CAD. The cause of the inciting arrhythmia was not found and was possibly related to the ensuing ischemia from TCM.

EKG criteria

Only 12/42 (26%) TCM patients had ST elevation which is lower than in some of the previous studies. As expected, no reciprocal changes were seen in any of the TCM patients while they were seen in >80% patients with STEMI. Mean QTc was significantly prolonged in TCM (470ms versus 443ms, p=0.001). The presence of QTc prolongation in TCM has been reported in the past. The cause of this is not clearly known but has been suggested to be a result of catecholamine induced repolarization abnormality. T wave inversions were significantly more common in TCM patients and were characteristically diffuse in distribution on the EKG (figure 1). Though TCM patients had higher incidence of new bundle branch block, the difference was not found to be significant.

Laboratory criteria:

Lower TnTi, TnTp and early peaking of troponin suggest smaller ischemic burden in TCM, similar to previous publications. Some of the STEMI patients presented with low TnTi but showed an upward trend thereafter, possibly resulting in a false positive diagnosis for TCM in such patients. Nevertheless, the main distinguishing factor in favor of TCM found in our study was that the initial troponin was almost always the peak with a downtrend thereafter (Tp< 6hours).

ProBNP has been suggested as a useful marker to differentiate between TCM and AMI. Higher levels were noted in TCM in our study though the difference was not significant as proBNP was not routinely checked in all the patients.

Echocardiographic criteria

Mean LVEF was significantly lower in TCM patients (36% versus 47%) and this is despite low peaking troponin, possibly related to a diffuse but less intense myocardial injury in TCM as compared to STEMI. Apical involvement is a feature of TCM possibly from the poor reserve resulting from limited blood supply, making it vulnerable to ischemia. It is also proposed that apex is sensitive to adrenergic over-stimulation as happens with catecholamine surge.

‘GET QT’ prediction model

In current literature, there is no gold standard to confirm the diagnosis of TCM and circumvent the need for cardiac catheterization. Nevertheless, early suspicion by taking into account some of the discussed characteristics can direct physicians to appropriate management. The GET QT criteria (table 4) is a prediction model that is highly specific with a high negative predictive value but at the same time is logical, easy to understand and remember, which are the pre-requisites for an ideal prediction model. 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 TCM. To understand and remember, which are the pre-requisites for an ideal prediction model. 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 TCM. To the best of our knowledge, this is the first highly specific score combining clinical history, EKG, echocardiography and cardiac biomarkers to distinguish to two clinic entities.

Table 2.

<table>
<thead>
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<th>STEMI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc(milliseconds)</td>
<td>469.88 ± 44.6</td>
<td>443.24 ± 26.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Tachycardia(n)</td>
<td>16(38.1%)</td>
<td>11(20%)</td>
<td>0.049</td>
</tr>
<tr>
<td>New bundle branch block(n)</td>
<td>8(19%)</td>
<td>4(7.3%)</td>
<td>0.081</td>
</tr>
<tr>
<td>T wave inversion(n)</td>
<td>28(66.7%)</td>
<td>24(43.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF(%)</td>
<td>36.07 ± 8.7</td>
<td>47.45 ± 10.26</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2. Comparison of EKG and echocardiography findings, QTc: corrected QT interval, LVEF: left ventricular ejection fraction

Figure 2. Presence of 3 or more predictors in a patient yielded a ROC area under the curve of 0.931(p= 0.000)
Various criteria have been suggested in the recent literature. Nascimento et al.16 made an interesting proposition of using the product of peak troponin and LVEF (troponin-ejection fraction product) as a specific distinguishing criteria, with a value of ≥250 having a specificity of 87%. As in our study, this study also carried the same inherent problem of using TnTp instead of the TnTi.17,18 On the other hand, Randhawa et al.19 proposed the ratios of simultaneously ordered initial BNP/troponin T and BNP/CKMB as specific markers for the distinction. Using the TnTi has the inherent risk of giving a false positive result for TCM as most of the AMI patients present with a low troponin but usually show an up trend depending on the stage of the presentation, so its utility is low. A similar result was found in our study and a conscious decision was made to use the TnTp instead.

This study does not intend to circumvent the need for a cardiac catheterization (PCI) in critically ill patients. In patients presenting with acute chest pain, ST-elevation, troponin elevation, hemodynamic instability; PCI should be pursued without any delay. On the other hand, in patients presenting in a sub-acute setting and in whom PCI or thrombolysis will pose a risk-benefit dilemma, the proposed prediction model can help guide therapy. Strong clinical suspicion combined with ‘GET QT’ can direct physicians to appropriate management. As you may recall from the “Methods” section, we found 154 patients discharged with diagnosis of TCM but only 42 were included in the study, many excluded due to lack of angiography during the admission. In case of most of these excluded patients, the cardiologist made an active clinical diagnosis of TCM based on their clinical suspicion in the absence of angiography. Such patients were young, presenting after a clear stressor such as drug overdose and in absence of coronary artery disease risk factors. This would be the ideal scenario for applying the criteria to support such a clinical suspicion. This study aims to encourage future researchers to undertake larger prospective studies to define dependable criteria to distinguish the two diseases with significantly different treatments and outcomes.

**Study limitations**

The limitations of the study included the retrospective design and single facility patient selection. Due to the female preponderance of TCM, some gender bias was expected. TCM is a rare disease and the sample size was moderate as compared to previous studies. In order to reduce any false positive results, we employed strict inclusion and exclusion criteria and this resulted in inability to extrapolate the results to patients with kidney disease and heart failure. Not all laboratory tests were performed at admission thus limiting the effective power for those tests (BNP, TSH). BNP is not a test included in the cardiac enzyme panel ordered for most such patients at admission and it is often not ordered, possibly even making this proposed criteria more clinically relevant.

**Conclusion**

Takotsubo cardiomyopathy patient is a likely diagnosis in female patients presenting with early peaking, low Troponin T levels; EKG showing prolonged QTc and echocardiography showing low EF. With the GET QT prediction model, presence of 3 or more factors was highly specific for the diagnosis of TCM. These criteria are most useful for patients with subacute presentations or in patients with relative/absolute contraindications to thrombolytic therapy or PCI.

**Abbreviations**

Takotsubo cardiomyopathy (TCM), left ventricle (LV), acute coronary syndromes (ACS), ST-elevation myocardial infarction (STEMI), electrocardiogram (EKG), T wave inversions (TWI), ST-elevation (STE), LV ejection fraction (EF), initial troponin (TnTi), peak troponin T (TnTp), time to peak (Tp), acute myocardial infarction (AMI), coronary artery disease (CAD), receiver operating characteristic (ROC)

**Declarations of Interest**

The authors declare no conflicts of interest.

**Acknowledgements**

Mr Mark Chilton, B.S, M.S., CCRP for research coordination. The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals.” 19

**References**


