Estimation of Risk Factors for Cardiogenic Shock in Takotsubo Cardiomyopathy: A Retrospective Study

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Highlights

Background
Presentation of Takotsubo cardiomyopathy (TCM) widely varies amongst the patients, ranging from asymptomatic patients to cardiogenic shock or even cardiac arrest. The underlying risk factors inherent to the patient that predispose to a catastrophic presentation have not been delineated well in the past. Objective: To distinguish risk factors and presenting characteristics of patients diagnosed with cardiogenic shock from TCM.

Methods
Total 51 angiography-confirmed TCM patients admitted in Upstate Hospital from 2010 – 2014 were compared retrospectively, 13 presenting with cardiogenic shock.

Results
While TCM was predominantly common in elderly females, four of the total six male TCM patients presented with shock (Odds ratio= 8.0, p=0.027). TSH was higher in cardiogenic shock group. Patients with shock had significantly higher incidence of ST elevations on EKG and higher peak troponins. Moreover, ST elevations were predominantly in the inferior, anteroseptal and lateral leads in the shock group as compared to only the septal leads in the control group. Echocardiography revealed lower LV ejection fraction, LV outflow tract obstruction and concomitant significant mitral regurgitation in shock patients. No correlation was found with age, BMI, coronary disease risk factors (diabetes, hypertension, smoking), coincident infection, electrolyte imbalance, QTc interval length.

Conclusions
Risk factors and pathophysiology for cardiogenic shock in TCM were identified. TCM in males is rare, but male gender is a risk factor for shock.

Keywords: Takotsubo; cardiogenic shock; echocardiography

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Background/Objectives:
Takotsubo cardiomyopathy (TCM) is characterized by acute transient ischemic left ventricular dysfunction usually accompanied by electrocardiographic (EKG) changes and elevated cardiac biomarkers in the absence of significant coronary artery disease. TCM can have a fairly complex and catastrophic presentation but early diagnosis and appropriate treatment results in very low mortality. The severity of TCM presentation varies between patients and is likely related to the variable degree of myocardial ischemic damage, ventricular systolic dysfunction and circulatory failure. Prevalence of complications including cardiogenic shock is reported to be as high as 20% patients (1–4) though the pathogenesis remains elusive and under-estimation can be disastrous. Pre-existent literature has attempted to identify various risk factors that may predispose to cardiogenic shock in such patients, including the role of gender, age, BMI, coronary disease risk factors (diabetes, hypertension or smoking), electrolyte imbalance, extent of ischemic damage and pathological changes in myocardium identified on echocardiography(5–8). An understanding of the risk factors inherent to the patient as well as the disease related manifestations linked to presentation with shock can help early risk-stratification, assessment of severity, anticipation of the future course and guide appropriate therapy. The premise of the
present study was to determine the factors that were linked to presentation with shock in our hospital, further the understanding of the pathogenesis and early, accurate estimation of poor outcome. The hypothesis was to test the previously proven risk factors and define new factors. This study would be most clinically relevant in emergency department during the initial triage of TCM patients.

Methods
Study population
We did a retrospective case control study with age matched cohort selected from patients admitted in a single tertiary facility- SUNY Upstate Hospital, Syracuse, NY. Appropriate Institutional Review Board exemption was obtained (IRB exemption number 719685-1). Inclusion criteria was based on the proposed Mayo Clinic criteria (9): Adults(>18 years) with presentation mimicking myocardial infarction with ST-T wave changes in electrocardiogram(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. Patients with pre-existent heart failure with left ventricular ejection fraction(LVEF)<45% were excluded from the study. A total of 51 patients were discharged with a diagnosis of TCM between January 2010 and December 2014 meeting the above mentioned criteria.

Definitions
Cardiogenic shock(CS) was defined as systolic blood pressure<90 mm Hg requiring inotropic/vasopressor support or presentation with cardiac arrest/ventricular arrhythmia requiring resuscitation. LV outflow tract obstruction(LVOTO) was defined as outflow tract peak instantaneous pressure gradient >=30 mmHg on continuous wave Doppler and systolic anterior motion of mitral leaflet on 2D-images and confirmed via Doppler, occurring prior to the use of inotropic agents. 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. Concomitant infection was defined as patients meeting sepsis criteria at presentation with a known source of infection at discharge or death.

Study protocol
Commonly ordered, relevant and widely available laboratory studies were included in the study- Serum potassium, magnesium, cardiac enzymes, thyroid stimulating hormone (TSH) and pro-brain natriuretic peptide (pro-BNP). Cardiac enzymes [creatinine kinase (CK), creatine kinase MB fraction (CK-MB) and troponin T] were followed until normalization or death. Only the levels checked at the time of presentation were used in the study. Unfortunately, free T4 was not available for most patients so it was excluded from the study.

Modified Simpson’s biplane method was used for calculation of LVEF. Echocardiographic color Doppler was used for quantification of mitral regurgitation. QTc length was calculated using the Bazett’s formula and QTc prolongation was defined as QTc> 450ms for males and >460ms for females. Only patients who underwent cardiac catheterization to confirm the diagnosis of TCM were included.

Statistical analysis
IBM SPSS (version 19.0, SPSS Corp, Chicago, IL, USA) was used for statistical analysis. Qualitative data is presented as frequencies and quantitative data as mean ± standard deviation. Categorical variables were compared by using Chi-square test, and continuous variables were compared using Student’s t-test. The statistical analysis was performed individually on all the studied variables using the above mentioned tests as appropriate and they were categorized as below:

1. Clinical characteristics at presentation: age, gender, body mass index (BMI), presence of hypertension (HTN), diabetes (DM), smoking history, β-blocker use, TSH, electrolyte levels, proBNP (Table 1)
2. Clinical indicators of TCM on laboratory, EKG and echocardiography: Peak troponin value, QTc interval length, LVEF, left ventricular end-diastolic pressure (LVEDP), presence of tachycardia, new bundle branch block, ST elevation, new significant (moderate or severe) mitral regurgitation and LVOTO. (Table 2)

The factors with significant association then underwent multivariate logistic analysis in their groups. P value < 0.05 was considered significant.

Outcome/Follow-up
Echocardiography was obtained at the time of presentation and only patients with documented significant resolution of wall motion abnormality in follow up imaging within 6 months were included. Outcome data was obtained up to 6 months from discharge, including- follow up imaging, recurrence of TCM or death.

Results
A total of 45 patients (88.2%) were females while 6 patients (11.8%) were males. Thirteen patients(25.5%) presented with cardiogenic shock as defined above. The rest of the patients with normal hemodynamic status or those that did not fit the definition of cardiogenic shock were added as controls. The mean age between the groups was not significantly different (65.9 vs 61.2 years, p=0.226). The most common presenting symptom in TCM was chest pain (43%) followed by shortness of breath (20%), altered mental status most commonly from drug overdose (16%) and gastrointestinal symptoms like nausea, abdominal pain (6%). Previous psychiatric illness history such as depression or anxiety disorder was present in 49% patients and a preceding stress was identified in 47% patients. Among the other characteristics, 55% had history of alcohol use, 73% had smoking history and 39% had chronic pain issue with prescription opioid use, 29% were diabetic and 71% were hypertensive.

Comparison of clinical characteristics at presentation:
Of the clinical characteristics named in the ‘Statistical analysis’ section, only gender and TSH exhibited statistical significance (table 1). On multivariate logistic regression analysis of gender and TSH, only gender had a significant value (p= 0.027) with males having an odds ratio of 8 to present with cardiogenic shock as compared to females (95% confidence interval: 1.26 to 50.7, p= 0.027).
EKG comparison revealed diffuse T wave inversion and absence of reciprocal changes uniformly in both groups. ST elevation was present in 17 patients (33.3%), and was statistically more common in the shock group (p = 0.012). No significant difference was found in terms of incidence of tachycardia, new bundle branch block or QTc interval length (Table 2). ST elevations were predominantly in the inferior, anteroseptal and lateral leads in the shock group as compared to only septal leads in the control group, while leads V1 and aVR remained the least involved in both the groups (Figure 1). Inferior lead ST elevation was significantly more common in cardiogenic shock group (75% vs 13% patients, p = 0.001). Significant laboratory finding was a good correlation between the leads with ST elevation and other died from a non-cardiac condition more than 30 days after the presentation.

**Comparison of clinical indicators of TCM:**

Echocardiography revealed low left ventricular ejection fraction (LVEF) in the shock group (26.9% vs 33.0%, p = 0.035) and higher left ventricular end-diastolic pressure (LVEDP) (35.0 vs 26.3 mmHg, p = 0.049). Apical involvement was uniform among both the groups. Among the cardiogenic shock group, 7 patients (54%) had 2 or more walls involved apart from the apex while the incidence was 10 patients (28%) in the other group. There was a good correlation between the leads with ST elevation and the regional wall motion abnormalities. LVEF was lower among males (27.5% vs 32.0%) but this was not a significant finding (p = 0.258). LVOTO was found in 14 patients (27.4%) prior to the use of inotropic agents, significantly more common in shock group (69% vs 13% patients, p = 0.001). Significant laboratory finding included a higher peak troponin in the shock group (2.32 ± 0.74 ng/ml, p = 0.035) (Table 2).

Multivariate logistic regression analysis was performed on statistically significant clinical indicators of TCM mentioned above (ST elevation, inferior lead ST elevation, LVEF, significant mitral regurgitation, LVOTO, peak troponin and LVEDP); statistical significance was found with LVOTO with an odds ratio of 7.86 (95% confidence interval: 1.11 to 55.43, P = 0.038) and ST elevation with odds ratio of 7.24 (95% confidence interval: 1.10 to 47.54, P = 0.039) (Table 3).

Three patients had recurrence within 6 months of the initial presentation, all of them survived. Total of 8 patients (15.7%) were previously on β-blocker prior to presentation and 31 patients (60.8%) were discharged on a β-blocker at home. Two of the three patients with recurrence were started on β-blocker prior to the initial discharge.

Two patients from shock group expired, one died from progressive cardiac failure resistant to treatment within 5 days and other died from a non-cardiac condition more than 30 days after the presentation.

**Discussion**

The presentation of TCM may closely mimic myocardial infarction and the severity of ventricular dysfunction may be variable resulting in a spectrum of symptoms and signs. The pathogenesis of Takotsubo cardiomyopathy remains elusive but the suggested mechanisms include widespread coronary vasospasms, catecholamine or neurogenic stunning of myocardium as a result of sympathetic overstimulation from intense and sudden stress, impairment of microvascular perfusion or less likely transient myocarditis (10,11). In the present study an attempt was made to improve our understanding about TCM through identification of factors that may precede or coincide with cardiogenic shock presentation, allowing us to use the information in clinical practice for risk stratification and anticipation of possible catastrophic change in patient’s clinical course.
It has been reported that TCM patients are more likely to develop cardiogenic shock as compared to their ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) counterparts (12). The prevalence of cardiogenic shock in TCM varies from 4 to 20% (2,3). In-hospital cardiac mortality from TCM ranges from 0 to 2% (3,13) while all-cause mortality ranges from 0 to 9% (2,6,13,14). A diagnosis of TCM as a cause of cardiac arrest and shock can only be made if the patient survives the initial insult (15). Such patients may get misdiagnosed as myocardial infarction in the absence of catheterization, thus possibly underestimating the prevalence and mortality associated with TCM.

In the present study, males were seen to have eight times the risk to have cardiogenic shock but the number of males in our study was small. A similar higher risk, however, was also found in a National Inpatient Sample (NIS) database study of 24,701 TCM patients (6). Murakami et al (16) documented an odds ratio of 4.32 amongst males to have in-hospital composite cardiac events as compared to females as well as a higher incidence of Killip Class 3-3 ventricular failure and ventricular arrhythmia. In a follow-up study of 286 TCM patients (17), male sex was found to be an independent predictor of mortality. Similarly, in a study on Medicare beneficiaries, males were seen to have worst outcomes (18) amongst TCM patients. The cause of this gender disparity is difficult to ascertain but the hypotheses could include: higher overall coronary disease burden in males, higher rate of coincident precipitating illness such as sepsis (6) and a greater influence of physical rather than emotional stress amongst males (16,19).

Anatomically, TCM is characterized by wall motion abnormalities that span beyond the territory of a single coronary artery (9). Apical involvement is a feature of TCM possibly from the limited blood supply to the apex making it vulnerable to ischemia and hypofunction. It is also proposed that apex is sensitive to adrenergic overstimulation (10). Higher Troponin T levels in cardiogenic shock group found in our study could mean a bigger ischemic burden in males, higher rate of coincident precipitating illness such as sepsis (6) and a greater influence of physical rather than emotional stress amongst males (16,19).

Multivariate analysis of clinical indicators with 95% confidence intervals of odds ratio of significant variables. STE- ST elevation

<table>
<thead>
<tr>
<th>Findings</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Troponin T</td>
<td>0.78</td>
<td>0.536</td>
<td></td>
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<tr>
<td>ST elevation</td>
<td>7.24</td>
<td>1.105 to 47.54</td>
<td>0.039</td>
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<tr>
<td>Inferior lead STE</td>
<td>48.0</td>
<td>0.549</td>
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<tr>
<td>Mitral regurgitation</td>
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<td>0.221</td>
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<tr>
<td>LVOTO</td>
<td>7.86</td>
<td>1.11 to 55.43</td>
<td>0.038</td>
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<tr>
<td>LVEF</td>
<td>1.086</td>
<td>0.208</td>
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<tr>
<td>LVEDP</td>
<td>0.86</td>
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Table 3.

The role of early β-blocker in TCM has been controversial. Their use in cardiogenic shock associated with LVOTO has been suggested to allow better diastolic relaxation, better forward flow and improvement in systolic pressure (2,27,28), conversely, their role in improving short term mortality has been questioned recently (29). Similarly, the use of β-blockers to prevent recurrence has not been proven beyond doubt (2,25,30,31). Of the three patients with recurrence of TCM in our study, two had been started on β-blockers as outpatient prior to the recurrence. On the other hand, the prescription of β-blockers as outpatient jumped from 16% to 61% patients after the diagnosis of TCM and only 5% of the patients experienced recurrence. The recurrence rate of TCM is estimated to be up to 11.4% in previous studies (32,33), thus the recurrence rate was much lower in this study. Other medications like aspirin, angiotensin-converting enzyme inhibitors, statins have not been shown to prevent recurrence (31).

Another highlight of the study was the presence of significantly higher TSH in cardiogenic shock patients. This phenomenon can
be difficult to explain based on the currently available literature with reports incriminating hyperthyroidism (8,34) as well as hyperthyroidism (35-37) as the cause of TCM. The proposed mechanisms in hypothyroid patients include higher level of circulating catecholamine (38), coronary artery vasospasms (34,39), increased sympathetic reactivity(8) or pre-existent dilated cardiomyopathy(40), while similar number of hypotheses exist for hyperthyroidism. Nevertheless, hyperthyroidism was not a significant clinical risk predictor in our multivariate regression analysis. This underlines the fact that very little is known of the pathogenesis of TCM.

Published literature has attempted to identify various risk factors that may pre-dispose to cardiogenic shock in TCM patients and an understanding of these factors can help early estimation of worse outcome and initiation of aggressive approach to treatment. This study aimed to further substantiate the understanding of potential comorbidities that are associated and can be hypothesized to influence the outcome in TCM patients. Future research should be directed towards understanding the role of the identified comorbidities which may result in determination of potentially modifiable factors through prevention or early intervention in the course of the disease. Research on takotsubo cardiomyopathy is always faced with the hurdle of low power, as is the case with this study, but this should not deter future researchers as such manuscripts help in understanding the disease one step at a time.

Conclusion

In conclusion, this study highlights gender bias in prevalence of TCM among females but also identifies the possibility of males at a higher risk for cardiogenic shock, confirmation would be needed through a larger study. Left ventricular tract obstruction and diffuse ST elevations were proven to be relatively strong predictors of underlying cardiogenic shock and a suggestion was made for possible role in pathogenesis. The controversy surrounding the role of β-blocker and thyroid hormonal imbalance in pathogenesis and/or prevention of TCM was discussed. The role of some of the previously suggested risk modifying factors such as age, diabetes, coincident infection, QTc length were not substantiated.

Study limitations

The limitations of the study included the retrospective design and single facility patient selection. TCM is a rare disease and the sample size was small to moderate as compared to previous studies. Very small number of male patients in the study limited the possibility of making any conclusive statements about gender bias in the severity of presentations. In order to reduce any false positive results, we employed a strict inclusion and exclusion criteria and this resulted in inability to extrapolate the results to patients with kidney disease and heart failure. Cardiogenic shock is a relatively rare manifestation in TCM which further reduced the power of some of the tests. Power of certain lab values including proBNP were low to achieve statistical significance.

Declarations of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”[41]

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