*Original Article*

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# Possible predictive factors for recovery of left ventricular systolic function in Takotsubo cardiomyopathy

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**Summary** **Takotsubo cardiomyopathy (TTC) is a transient systolic dysfunction of the left ventricle which is usually seen in elderly women, often following a physical or emotional stressful event. Little is known about the prognostic factors affecting the recovery of systolic function. Thirty-six patients diagnosed with TTC from January 2006 to January 2017 at our hospital were included. Median time to recovery of ejection fraction (EF) was calculated to be 25 days. Early recovery of ejection fraction was defined as less than or equal to 25 days (group 1) and late recovery was defined as more than 25 days (group 2). Demographic and clinical factors were compared between the groups. Fifty percent patients had early recovery of EF with a mean time to recovery of 7.11 days and 50% had late recovery of ejection fraction with a mean time to recovery of 58.38 days. Younger age at presentation was associated with early recovery of systolic function (58.83 ± 2.7 years *vs*. 67.33 ± 2.7 years, $p = 0.032$). Presence of an identifiable triggering event was associated with early recovery (83% in group 1 *vs*. 50% in group 2, $p = 0.034$). Generalized anxiety disorder was seen more commonly in the group with early recovery (78% in group 1 *vs*. 45% in group 2, $p = 0.040$). In conclusion, younger age, generalized anxiety disorder and presence of triggering event were seen more commonly in patients with early recovery of left ventricular systolic function in Takotsubo cardiomyopathy.**

***Keywords:*** Takotsubo, cardiomyopathy, left ventricular ejection fraction, predictors, recovery

## 1. Introduction

Takotsubo cardiomyopathy (TTC) or acute stress induced cardiomyopathy initially described in Japan in 1990, is increasingly being recognized around the globe with the characteristic features of apical systolic ballooning and absence of coronary obstruction while mimicking acute coronary syndrome (ACS) (*1*). The incidence of TTC has been reported to be 1.7% to 2.2% among patients presenting as ACS (*2*). Although there is no significant racial predilection, most of these reported cases were among Asian and Caucasian women. About 89% of the patients affected were female with an average age of 67.7 years (*3*). The pathogenesis involves myocardial stunning or direct toxicity by catecholamine surge associated with an emotional or physical stress (*4*). Clinical presentation is similar to ACS with chest pain, syncope, dyspnea, or symptoms of heart failure or as arrhythmias. ST and T changes are common on EKG and cardiac biomarkers are often elevated (*5*). Cardiac catheterization shows no significant coronary occlusion, but demonstrate the characteristic left ventricular apical ballooning during systole. The most commonly used diagnostic tool is the Mayo Clinic diagnostic criteria which requires all four criteria to be satisfied for the diagnosis of TTC (*6*).

In a position statement by Lyon *et al.*, recovery of left ventricular systolic dysfunction was attained by 12 weeks (*7*). However, another study by Park *et al*., on 26 patients with TTC showed that 20 of them had normalization of left ventricular function in 7 days making it impossible to define a clear-cut recovery

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period (*8*). 21.8% of the patients with TTC developed serious in-hospital complications which was similar to the rate in acute coronary syndrome patients (*5*). Multiple studies to identify the factors associated with poor survival and increased mortality have been published (*9-11*). Some of the factors identified were low left ventricular ejection fraction (LVEF), severe mitral regurgitation, increased pulmonary artery pressure and right ventricular involvement. The factors which affect time to recovery of left ventricular systolic function, however has not been widely reported (*12*). We aimed to identify these factors affecting recovery to generate a better understanding about the pathophysiology and try to fill the gap in knowledge regarding management of TTC. Since majority of the care and follow up until full recovery of TTC are done in outpatient settings following hospital discharge and has not been studied well, we aimed to include hospitalization data as well as from the outpatient follow up visits.

## 2. Materials and Methods

We conducted a retrospective review of the medical records of patients diagnosed with TTC at Monmouth Medical Centre from January 2006 till January 2017. The study was approved by the Institutional Review Board at our hospital. We identified patients diagnosed with TTC using the ICD 9/ICD 10 diagnostic codes. Electronic medical records (including scanned documents from previous paper charts) of these patients were reviewed. We included patients who were more than 18 years old, had transient akinesia or dyskinesia of left ventricular (LV) apical and mid-ventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution and new EKG abnormalities (either ST segment elevation and/or T wave inversion) or modest elevation in cardiac troponins as per the Revised Mayo Clinic Diagnostic Criteria (*6*). The exclusion criteria were presence of obstructive coronary disease or angiographic evidence of acute plaque rupture, myocarditis or pheochromocytoma. From a total of 45 patients with diagnosis of TTC during the study period, 36 patients were included for analysis. 7 patients were excluded due to lack of follow up echocardiograms and 2 patients were excluded due to lack of coronary angiography.

The echocardiograms of patients who met the inclusion criteria at the time of diagnosis and follow up were reviewed by an independent board certified cardiologist and LVEF was determined using Modified Simpson Rule (*13*). Follow up echocardiograms were obtained for all patients at these time intervals: 1 week, 4 to 6 weeks, 12 weeks, 6 months, 9 months and 1 year after the event and the data was obtained from the outpatient cardiology records. A value of LVEF more than or equal to 50% on follow-up was defined as recovery.

Based upon one-year follow up data, we calculated 25 days to be the sample median for recovery time of LVEF. Patients were then divided into 2 groups; group 1 included patients with early recovery before or at 25 days and group 2 included patients with delayed recovery after 25 days of the event. We used median as a measure of central tendency because of the presence of an outlier, one of the patients had a recovery of left ventricular systolic function at 12 months while rest of the patients recovered in ≤ 12 weeks. Figure 1 summarizes the study in a flowchart. Demographic and clinical characteristics were compared. Presence of generalized anxiety disorder was considered positive if the patient was taking prescription anxiolytic agents with a diagnosis of anxiety disorder made by a psychiatrist as an out-patient. A triggering event was defined as a stressful incident immediately before admission that resulted in significant physiological disturbance capable of having acute cardio-vascular affect. Triggering events were further categorized as emotional or physical. Emotional triggers included those causing psychosocial stress such as grief, anger, anxiety, fear. Physical stress included exacerbation of chronic medical conditions, medical or surgical procedures or any acute illness. Cardiogenic shock, cardiac arrest, life threatening arrhythmias, congestive heart failure and death were considered as adverse cardiac events.

Categorical variables were expressed as numbers or percentages and continuous variables were expressed as mean ± standard deviation or median with first inter-quartile range. Continuous variables were compared between the two groups using Student *t* test or Mann-Whitney *U*-test. Categorical variables were compared using $\chi^2$ or Fischer exact test. Statistical significance was defined as a $p$ value < 0.05. All data were analyzed using SPSS 20.0 (SPSS Inc Chicago, Illinois)

## 3. Results

The study population included 36 patients with a mean age of 63.08 ± 12.06 years. Majority of the population (83.3%) were women. The prevalence of psychiatric disorders in the patient population was 61.11%, diabetes mellitus 13.89% and hypertension 47.22%. A triggering event preceding presentation was documented in 66.67%. Physical stressors which included surgical procedures, and acute non-cardiac illness like hypoxic respiratory failure from community acquired pneumonia, ischemic stroke, COPD exacerbation, alcohol intoxication and small bowel obstruction were more common (50%). Emotional stressors such as extreme grief, anger, anxiety and fear were documented in 16.67% of the patients. The baseline clinical and demographic characteristics of all

patients is summarized in Table 1.

The mean recovery period was calculated to be 32.2 days (median; 25 days, SD 19.95). Presence of a single outlier value resulted in this difference in mean and median. 18 patients (50%) had recovery of LVEF in 25 days or less (Group 1) and 18 patients (50%) patients had recovery of function after 25 days. Mean time to recovery was 7.1 days in Group 1 and 58.4 days in Group 2. There was statistically significant difference in age at presentation between Group 1 and Group 2 (58.83 ± 2.7 *vs*. 67.33 ± 2.7 years, $p = 0.032$). Gender distribution was not statistically different in both the groups. Prevalence of generalized anxiety disorder was significantly higher in group 1 (77.78% *vs*. 44.44%, $p = 0.040$). Group 1 also had more documented preceding physical or emotional trigger (83.33% *vs*. 50%, $p = 0.034$). Prevalence of other comorbid conditions like diabetes mellitus, hypertension, autoimmune disorders, and hyperlipidemia and tobacco dependence did not differ significantly between the two groups. Cardiac enzyme levels, BNP levels and EKG changes were not significantly different between the two groups. Comparison of demographic and clinical characteristics of the two groups is shown in Table 2.

*Clinical Course and treatment* (Table 3): Left ventricular systolic dysfunction on presentation was not significantly different between the two groups (32.11 ± 8.32% *vs*. 36.34 ± 10.49%, $p = 0.188$). Majority of the population had apical form of TTC in both groups. Among patients with early recovery of systolic function, 11.11% of patients were on angiotensin converting enzyme inhibitors or angiotensin receptor blockers prior to presentation and 11.11% were using

**Table 1. Baseline Characteristics of total population**

| Variable | Incidence ($n = 36$) |
|---|---|
| Age (years, Mean ± SD) | 63.1 ± 12.1 |
| Female Sex (%) | 30 (83.3%) |
| Baseline EF (%, Mean ± SD) | 62.0 ± 5.3 |
| Mean Acute EF (%, Mean ± SD) | 34.2 ± 9.6 |
| Alcohol dependence (%) | 3 (8.3%) |
| Tobacco dependence (%) | 16 (44.4%) |
| Co-morbid medical conditions | |
| Hypertension | 17 (47.2%) |
| Diabetes Mellitus | 5 (13.9%) |
| Cancer | 8 (22.2%) |
| Psychiatric disorder | 22 (61.1%) |
| Neurological disorder | 3 (8.3%) |
| COPD | 8 (22.2%) |
| Autoimmune disorder | 4 (11.1%) |
| Triggering event | 66.7% |
| Physical trigger | 50% |
| Emotional trigger | 16.7% |

**Table 2. Demographic and clinical characteristics of the two groups**

| Variable | Early recovery of EF (≤ 25 days), $n = 18$ | Late recovery of EF (> 25 days), $n = 18$ | $p$-value |
|---|---|---|---|
| Age – years (Mean ± SD) | 58.8 ± 2.7 | 67.3 ± 2.7 | 0.032 |
| Female Sex | 14 (77.8%) | 16 (88.9%) | 0.371 |
| Triggering event | 15 (83.3%) | 9 (50%) | 0.034 |
| Co-morbid medical condition | | | |
| Cancer | 4 (22.2%) | 4 (22.2%) | 1.000 |
| Hypertension | 6 (33.3%) | 11 (61.1%) | 0.096 |
| Diabetes | 2 (11%) | 3 (16.7%) | 0.232 |
| Generalized anxiety | 14 (77.8%) | 8 (44.4%) | 0.040 |
| Neurological disorder | 2 (11.1%) | 1 (5.6%) | 0.363 |
| COPD | 6 (33.3%) | 2 (11.1%) | 0.108 |
| Autoimmune disorder | 0 | 4 (22.2%) | 0.104 |
| HIV | 1 (5.6%) | 0 | 1.000 |
| Alcohol dependence | 2 (11%) | 1 (5.6%) | 0.288 |
| Tobacco dependence | 10 (55.6%) | 6 (33.3%) | 0.179 |
| Medications prior to admission | | | |
| ACE inhibitor | 2 (11.1%) | 3 (16.7%) | 0.630 |
| Beta blocker (non-selective, selective) | 2 (11.1%) | 6 (33.3%) | 0.109 |
| Dihydropyridine calcium channel blocker | 2 (11.1%) | 1 (5.6%) | 0.547 |
| Diuretic (Loop & Thiazide) | 2 (11.1%) | 2 (11.1%) | 0.699 |
| Anti-platelets | 5 (27.8%) | 6 (33.3%) | 0.840 |
| Statins | 3 (16.7%) | 2 (11.1%) | 0.630 |
| Presenting EF (Mean ± SD) | 32.1 ± 8.3 | 36.3 ± 10.5 | 0.188 |
| EKG changes (%) | | | |
| ST segment elevation | 8 (44.4%) | 4 (22.2%) | 0.158 |
| T wave inversion | 7 (38.9%) | 8 (44.4%) | 0.729 |
| Peak Troponins (ng/L) (Mean ± SD) | 3.3 ± 3.7 | 3.3 ± 5.3 | 0.435 |
| BNP level (pg/mL) (Mean ± SD) | 655.14 ± 769.0 | 584.98 ± 501.97 | 0.826 |
| Lipid profile (Mean ± SD) | | | |
| Total Cholesterol (mg/dL) | 168.8 ± 46.9 | 165.1 ± 32.7 | 0.817 |
| HDL (mg/dL) | 55.3 ± 23.5 | 51.8 ± 10.9 | 0.627 |
| LDL (mg/dL) | 96.7 ± 42.1 | 92.4 ± 30.8 | 0.761 |
| Triglycerides (mg/dL) | 99.4 ± 41.5 | 116 ± 73.1 | 0.458 |

**Table 3. Features on presentation and medication initiated**

| Variable | Early recovery of EF (≤ 25 days), *n* = 18 | Late recovery of EF (> 25 days), *n* = 18 | *p*-value |
|---|---|---|---|
| Echocardiographic morphology | | | |
| Apical | 17 (94.4%) | 16 (88.9%) | 1.000 |
| Mid-ventricular | 0 | 1 (5.6%) | 1.000 |
| LVOT[†] | 1 (5.6%) | 1 (5.6%) | 1.000 |
| RV[‡] apical akinesia | 0 | 1 (5.6%) | 1.000 |
| Inverted | 1 (5.6%) | 0 | 1.000 |
| Recurrence of TTC | 1 (5.6%) | 0 | 1.000 |
| > 50% Coronary artery occlusion | 2 (11.1%) | 1 (5.6%) | 0.546 |
| Medications initiated | | | |
| Beta blocker | 13 (72.2%) | 13 (72.2%) | 1.000 |
| Anti-platelets | 9 (50%) | 4 (22.2%) | 0.083 |
| ACE inhibitor | 12 (66.7%) | 11 (61.1%) | 0.786 |
| Diuretics | 2 (11.1%) | 3 (16.7%) | 0.630 |
| Statins | 4 (22.2%) | 2 (11.1%) | 0.371 |
| Digoxin | 1 (5.6%) | 2 (11.1%) | 0.546 |
| EF on recovery | 60.1 ± 5.2 | 57.2 ± 7.3 | 0.180 |
| Change in EF | 28.1 ± 10.7 | 20.1 ± 13.1 | 0.054 |

[†] Left ventricular outflow tract obstruction. [‡] Right ventricle.

beta blockers; the utilization increased to 66.67% and 72.22% respectively on discharge. Similarly, in group 2, 16.67% were using angiotensin converting enzyme inhibitors or angiotensin receptor blockers and 33.33% were using beta blockers, the utilization increased to 61.11% and 72.22% respectively at discharge. There was no statistically significant difference identified regarding medication usage between the two groups. The recovery EF was similar in both groups, 60.13 ± 5.23% in group 1 and 57.23 ± 7.31% in group 2 ($p$ = 0.180). The early recovery group had an average EF improvement of 28.1% while late recovery group had only 20.1% on up to one year follow up.

No significant difference was found in the incidence of cardiogenic shock (1 patient in Group 2), arrhythmias (2 patients in Group 2), cardiac arrest (1 in group 1 *vs*. 2 in Group 2) and chronic congestive heart failure (1 patient in Group 1 *vs*. 3 in Group 2) between the two groups. One patient in the late recovery group died of cardiac arrest within a year. The overall number of patients with adverse outcomes were significantly higher in the late recovery group (50% *vs*. 11.11%, $p$ = 0.011).

## 4. Discussion

We found that the group with early recovery was almost a decade younger than the group with delayed recovery. In a study by Citro *et al*. on TTC in older adults it was found that in-hospital complication rate for adults aged 75 or older was higher than those younger than 75 (*14*). This study shed light on the impact of age on TTC. A senescent heart has reduced capacity to recover from stress as fibroblasts have a diminished response to stimulatory signals, which may explain why it would take older adults longer to recover the left ventricular systolic function in TTC (*15,16*).

Presence of a triggering event preceding the onset of TTC was also associated with early recovery. Physical stressors seen in our patient population included hypoxic respiratory failure requiring intubation due to sepsis from community acquired pneumonia, small bowel obstruction managed medically, ischemic stroke with resolution of symptoms with tissue plasminogen activator, COPD exacerbation, alcohol intoxication and post endoscopic sinus surgery. Many of these physical stressful events were managed successfully with resolution of symptoms. Emotional triggers included anticipation of major surgery, loss of parent and argument with neighbor. We hypothesize that the presence of a stressful event, physical or emotional, once identified, if managed appropriately can lead to early recovery of TTC. In the absence of a known triggering event we are left with empirical management of TTC, while the cause may persist. It has been studied previously that in-hospital death is lower in patients where TTC was triggered by emotional stress or those not associated with a stressful trigger (*17*). In another study, being male and having a physical trigger were independent risk factors for in-hospital mortality (*18*). However no study has been done to investigate the effect of triggering event on the recovery of left ventricular systolic function. One must be aware that severity of the triggering event can have an impact on recovery, majority of the patient population in our study had triggering events that could be managed successfully with complete resolution.

Prevalence of generalized anxiety disorder was significantly higher in the group with early recovery. Anxiety has been seen more frequently in patients with TTC (*19*). If a patient has a known history of anxiety it is more likely to be noticed and managed appropriately while it may be overlooked in a patient with no known history. There may be a component of anxiety in many

cases of TTC which if addressed adequately with medications or psychiatric intervention may aid in early recovery. Detailed chart analysis of our cohort showed that patients with history of anxiety disorder were also treated more often with benzodiazepines such as lorazepam and alprazolam as compared to those with no known history of anxiety disorder; 86.4% of those with known history of anxiety disorder *vs*. 28.6% with no known history of anxiety disorder. Further studies are needed to look into the application of benzodiazepines as anxiolytics in the management of acute phase of TTC.

We acknowledge the limitations of our study. It must be noted that the sample size of our study was small and it was a single center study, hence one must be careful before extrapolating the data to a larger population. Secondly, ours was a retrospective study thus subject to missing or inaccurate reporting of events. One cannot rule out previous subclinical episodes of TTC in these patients especially the cohort with delayed recovery of ejection fraction. The clinical implications of our study should be considered as a hypothesis for prospective investigation in a larger cohort.

Nonetheless, we recommend a thorough search for a triggering event in patients with TTC, as managing the cause may lead to early recovery. We suggest that interventions to alleviate anxiety levels in patients with known history of anxiety should be undertaken, while keeping a low threshold for treating anxiety in patients with no known history.

## 5. Conclusion

According to our study, younger age, presence of a clear triggering event and generalized anxiety may be associated with early recovery of left ventricular systolic function in TTC. Delayed recovery is associated with a clinical course complicated with cardiac arrest, arrhythmias, cardiogenic shock and congestive heart failure. Further large-scale studies need to be done to identify factors predicting early recovery which will help in formulating management guidelines that are essentially absent at present.

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