

A Case Series and Review of Takotsubo Cardiomyopathy: Does Stress Really Cause the Stress Cardiomyopathy?*

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ABSTRACT

Objective: We sought to describe clinical characteristics of emergency department patients ultimately diagnosed with Takotsubo Cardiomyopathy (TCM) and to explore the causal role that stress may play in its pathogenesis. *Methods:* We performed a retrospective chart review analyzing all myocardial infarction patients with non-obstructive coronary artery disease on cardiac catheterization to assess for the presence of TCM. Various clinical data, including the presence of stressors, from emergency department records were reported. We also analyzed factors from several studies (including ours) to assess the true causality of stress in the development of TCM. *Results:* Twelve ED patients out of 2,179 charts reviewed were identified as having TCM. Most were female, post-menopausal, and had chest pain, but only half had a specific stressful event identified in the ED. One-third of patients had no stressful event identified during their hospital stay. Several other studies suggest that stressful events are associated with increased diagnoses of TCM, but we found that causality of stress cannot be substantiated. *Conclusion:* Stressful events are often not identified in emergency department patients ultimately diagnosed with TCM. The causative nature of stress in the development of TCM cannot be firmly established from any existing data.

Keywords: Takotsubo, Cardiomyopathy, Myocardial Infarction, Acute Coronary Syndrome, Stress

1. Introduction

Takotsubo Cardiomyopathy (TCM), also known as stress-induced cardiomyopathy, is a rare type of acute coronary syndrome that has recently been described in the literature [1]. TCM often resembles ST-elevation myocardial infarction in both clinical and electrocardiographic features. The pathophysiology of TCM includes transient wall motion abnormalities extending beyond the distribution of any single coronary artery, left ventricular apical ballooning seen on ventriculography, and absence of any significant atherosclerotic disease [1]. TCM was initially recognized in Japan, and is named after “tako-tsubo,” a narrow-necked octopus trap, which resembles the apical ballooning seen on ventriculography [2-4]. It is estimated that TCM represents 0.7 to 2.5% of patients presenting with a suspected acute coronary syndrome (ACS) [1].

Little is known about the etiologic mechanisms for the characteristic wall motion abnormalities. Furthermore, optimal management has not been established, as much of

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the current data on TCM are from case series and systematic reviews [1,5]. TCM appears to have a predilection for elderly women and is classically associated with a severe emotional, psychological, or physical trigger, leading to the adoption of the term, stress cardiomyopathy [1,5]. It is unclear whether the stress seen in TCM is simply an association or a definite cause of the syndrome.

The two goals of this study are: 1) describe clinical characteristics of patients presenting to the Emergency Department (ED) who were ultimately diagnosed with TCM, and 2) explore the possible relationship between a specific stressor and development of TCM.

2. Methods

Data were abstracted by one author from a retrospective chart review of patients between January 2003 to September 2008 by searching for discharge diagnosis of Takotsubo Cardiomyopathy, apical ballooning syndrome, myocardial infarction, and physician recall of past patients. Both inpatient and ED records pertaining to rele-

vant hospitalization were reviewed. Approval by local institutional review committee was obtained. All data were from a single, urban, level 1 trauma, academic, tertiary care center with an ED census of 75,000 patients per year. Subjects were included if they had coronary catheterization revealing non-obstructive (less than 50%) coronary artery disease, ventriculography study demonstrating apical ballooning, and EKG changes from baseline. Patients were excluded if they were not initially evaluated in the ED, were diagnosed with pheochromocytoma or myocarditis, or had used cocaine within one week of presentation.

Charts were reviewed and the following data were collected onto a standardized abstraction form: history of present illness including presence of chest pain, dyspnea, syncope and specific stressor; initial and peak troponin levels; final EKG interpretations; medications administered in the ED; serial ED vitals; and timing of cardiac catheterization lab activation (when necessary). Physical stressors were defined as specific somatic complaints (e.g., vomiting), and emotional stressors were defined as psychological or social (e.g., death of a family member). Medication-related hypotension was defined as systolic blood pressure (SBP) less than 90 mm Hg or a drop in 40 mm Hg from baseline SBP with symptoms occurring within 30 minutes of medication administration. Means and standard deviations were given for continuous data. Proportions and differences between groups are described with 95% confidence intervals (CI). Statistical analysis was performed using Stata (Version 10, College Station, TX).

3. Results

From the 2,179 cases reviewed of patients diagnosed with acute myocardial infarction who underwent cardiac catheterization between January 2003 and September 2008, 24 patients satisfied the criteria for the diagnosis of TCM. However, only 16 patients initially presented through the ED and 12 had available ED records. One of the 12 patients did not have complete ED records on serial vital signs or medications given, but was still included in the study.

All 12 subjects were women, with a mean age of 68 years (95% CI 59-77, See **Table 1**). Eleven (91.7%, 64.6-98.5%) patients had chest pain. Dyspnea was present in five patients (41.7%, 19.3-68.1%). From the ED medical records, two subjects had physical stressors and four subjects had emotional stressors. Upon review of inpatient medical records, additional emotional stressors were identified in four patients, for a total of 8 subjects with an identifiable stressor (66.7%, 39.1-86.2%, See **Table 2**).

The most common EKG findings were prolonged QT interval ($n = 8$) and nonspecific ST-changes ($n = 8$). ST-elevation occurred in four cases. The mean first troponin I was 1.80 ng/ml (0.1-3.5) and mean peak troponin I of 2.69 ng/ml (1.13-4.24). Eight patients had an initial troponin level that met criteria for MI at our institution (> 0.5 ng/ml). Emergent cardiac catheterization occurred in six patients. Mean time to catheterization lab activation was 104 minutes overall and 66 minutes in the 4 cases of ST-elevation identified in the ED.

To determine if there was a preload dependency among TCM patients similar to patients with inferior myocardial infarctions, blood pressures were reviewed before and after medication administration. Hypotension occurred in four of eleven (36.4%, 15.2-64.6%) patients who received nitroglycerin, morphine, and/or metoprolol. One of the five patients who received nitroglycerin developed hypotension, one of the three patients receiving morphine developed hypotension, and two of seven receiving a beta-blocker developed hypotension. All patients had IV fluids administered after their hypotensive episode was documented in the chart and all four had return of normal blood pressures prior to inpatient admissions.

4. Discussion

In our study of twelve TCM patients, all were female and most had chest pain and were post-menopausal. Despite being strongly associated with stress in prior studies, we observed that only 50% of patients in the ED had a stressor identified before the diagnosis was confirmed. Furthermore, one-third of patients had no identifiable stressor at all during their hospital stay. Even though we considered the documentation of stress in the post-catheterization inpatient notes to be reliable, which would if anything bias toward finding a relationship, there still was a surprisingly low proportion with antecedent stress. It is difficult to determine causality from retrospective studies, and our case series should be seen as pilot data contributing the emergency medicine perspective toward further understanding of this rare syndrome. The second aim of this project was to review existing literature from the perspective of causality and report what is known and unknown for TCM. There are generally five criteria examined when assessing a potential cause-effect relationship: Strength of the association, biologic credibility of the hypothesis, consistency of the findings, temporal sequence, and presence of a dose-response relationship [6].

5. Strength of Association

The greater the degree of increased risk (stress), the less likely the relationship between stress and TCM is from

Table 1. Clinical characteristics of Emergency Department patients ultimately diagnosed with Takotsubo Cardiomyopathy.

	Description	Chest pain	Dyspnea	Near-Syncope	Syncope	First Trop.	Peak Trop.	EKG Changes	Cath Lab Activation
1	71 yo F Vomiting; Negative stress test 1 month prior	Yes	No	No	No	1.08	1.84	Sinus tachycardia, PACs, nonspecific TW and ST abnormalities inferiorly	Yes (231 minutes)
2	73 yo F Near syncope; Son's cardiac surgery.	Yes	No	Yes	No	0.26	1.61	NSR, LAFB, Q waves inferiorly, nonspecific ST abnormalities	No
3	77 yo F Syncope after vomiting; Head injury	Yes	No	No	Yes	1.43	1.43	NSR, PACs, low voltage, TW abnormalities, poor R wave progression, prolonged QT interval	No
4	52 yo F Back pain while carrying groceries; Recent BP med non-compliance	Yes	Yes	No	No	1.07	1.83	NSR, LAFB, nonspecific TW abnormalities	Yes (130 minutes)
5	80 yo F At police station after son's arrest	Yes	No	No	No	1.49	2.13	Sinus tachycardia, LAD, nonspecific ST and TW abnormalities, prolonged QT interval	No
6	69 yo F Coffee grounds emesis	Yes	No	Yes	No	0.33	1.67	NSR, LAFB, prolonged QT interval, poor R wave progression	No
7	56 yo F Dizziness	Yes	No	Yes	No	0.59	0.59	NSR, nonspecific TW and ST abnormalities, prolonged QT interval	No
8	74 yo F On vacation	Yes	Yes	Yes	No	4.39	4.39	NSR, low voltage, nonspecific TW abnormalities.	No
9	69 yo F Argument with daughter	Yes	Yes	No	No	0.12	5.16	NSR, diffuse ST elevation and PR depression, prolonged QT interval	Yes (25 minutes)
10	36 yo F Chest pain with radiation	Yes	No	No	No	0.09	0.09	NSR, ST elevations inferolaterally, prolonged QT interval.	Yes (45 minutes)
11	75 yo F Unable to get out of bathtub	No	Yes	No	No	9.39	10.16	NSR, ST elevations anterolaterally	Yes (148 minutes)
12	84 yo F Recent pelvic fracture	Yes	Yes	No	No	1.33	1.33	Sinus tachycardia, diffuse ST elevation, prolonged QT.	Yes (47 minutes)

chance or an uncontrolled confounding factor. Therefore, we must determine if individuals who encounter a significant stressor have a higher risk of developing TCM. One study evaluated the incidence of TCM after a large natural disaster, the Mid-Niigata Prefecture Earthquake in Japan [7]. The earthquake registered 6.8 on Richter scale and had a death and injury toll of over 4,800. TCM was diagnosed in 16 patients within one month after the earthquake; all patients lived within areas registering a seismic intensity of at least 4, most (81%) of whom lived in areas greater than 6. Compared to months prior to the earthquake, there was an incidence approximately 24-fold higher in the one month after the earthquake in the three hospitals serving mid-Niigata district [7]. Large earthquakes have been associated with increased sympathetic activity in a previous study analyzing Holter monitors during an earthquake in Taiwan in 1999, meas-

uring 7.3 on Richter scale [8]. If we accept that a large earthquake is a significant stressor and that new cases of TCM were diagnosed correctly both before and after the stressor occurred, this can be seen as an example of a strong association with new cases of TCM in affected areas.

Unfortunately, there are no prospective studies evaluating incidence of TCM after large societal disasters. Most of the previous studies on emotional or stressful triggers investigated acute myocardial infarctions without specific attention to stress cardiomyopathy or to those without angiographic evidence of plaque rupture [9-12]. Since TCM is a relatively recently discovered syndrome, it is possible that patients previously diagnosed with acute myocardial infarctions based on electrocardiogram and cardiac markers actually suffered from TCM. However, it is impossible to accurately assess the strength of

Table 2. Stressors identified, sorted by location.

Case	<i>ED Medical Record</i>	<i>Inpatient Medical Record</i>
1	Vomiting	Husband with Alzheimers, sick mother and recent diagnosis of diabetes
2	Son's cardiac surgery	Son's cardiac surgery
3	None	Stress at work, syncopal episode at home
4	None	None
5	Son's police arrest	Son's police arrest
6	Dirt-like emesis	Dark brown emesis
7	None	Distressing phone noise
8	None	None
9	Arguing with daughter	Prolonged argument with daughter
10	None	None
11	Unable to get out of bathtub	None
12	None	None

association in such studies without angiographic evidence. Further limiting the ability to build a case for the strong association between stress and TCM is the notable absence of a preceding emotional or physical feature in some cases, or even the presence of other associations besides stress as possible causes of TCM—including stroke, epilepsy, asthma and other exacerbations of systemic disorders [4,13].

6. Biologic Credibility

It is known that stress can initiate a series of biological effects, including the “fight-or-flight” response. Epinephrine, norepinephrine, and dopamine all play an integral part in the sympathetic activation after a stressful trigger. However, despite significant knowledge of the biochemistry of the catecholamine system, we still do not know the specific details of its activation after stress, nor do we know exactly what stress is [14]. While there is no scientifically accepted definition of stress, several different classifications exist: physical, psychological, social, or those that challenge metabolic homeostasis [15]. Stressors can vary in duration and intensity. There are no standardized tools for assessing the scale of a stressor.

Most proposed mechanisms for the pathogenesis of TCM implicate catecholamine involvement, arguing that they serve as a trigger of diffuse epicardial vessel spasm or induce direct myocyte injury [16-18]. In one case series, a patient with left ventricular apical ballooning had

reproducible apical hypokinesis and subsequent dyskinesis with simultaneous coronary spasm and ST-T changes associated with chest pain and respiratory distress after intra-coronary infusion of acetylcholine. Immediate infusion of intra-coronary nitroglycerin quickly resolved all symptoms. The authors concluded that multi-vessel spasm leading to reversible sustained left ventricular impairment accounts for the experimental reproduction [19]. Another study found higher levels of plasma catecholamines in patients with left ventricular dysfunction after sudden emotional stress compared to those with Killip class III myocardial infarction [16]. These authors dispute epicardial arterial spasm as the mechanism responsible for myocardial stunning as none of the 19 patients in their series had angiographic evidence of spasm, there was minimal troponin elevation, and ST-segment elevation was only seen in two of the patients. They propose that elevated catecholamine levels can cause direct myocyte injury via calcium overload. Of the five patients who underwent endomyocardial biopsy, all had histological findings of elevated catecholamines. Even among the few studies that assert catecholamine responsibility for the cardiomyopathy, there is debate regarding the mechanism between sympathetic stimulation and myocardial stunning.

It has been established that cocaine's systemic effects are mediated by inhibition of catecholamine reuptake in the presynaptic neurons, leading to increased sympathetic activity. Cocaine has long been known to cause both ischemic and non-ischemic cardiomyopathy. However, the cardiomyopathy is typically global and progressive with just a rare case report of transient left ventricular apical ballooning: a postmenopausal female who smoked crack cocaine 2-3 hours before onset of symptoms [20]. If there is a catecholamine association with the transient left ventricular ballooning, why is TCM so rare among the thousands of recreational cocaine users? Case reports have also linked the elevated catecholamine state found in pheochromocytoma or catecholamine-secreting tumor with the cardiac changes identical to TCM [21,22]. Catecholamine responsibility alone does not account for the vulnerability of women, which is a very consistent finding. One study hints at genetic predisposition to physiologic response to mental stress, as homozygous status for a certain β_1 -adrenergic receptor polymorphism was associated with a three-fold higher prevalence of mental stress-induced myocardial ischemia [23]. Prasad et al. proposed a mechanism of catecholamine surge combined with individual susceptibility [24]. The susceptibility of women in particular is still puzzling.

7. Consistency of Findings

TCM was recognized as a syndrome just over two dec-

ades ago in Japan, with more recent data coming from US studies. Case series and systematic reviews in Japan, Europe and the US have identified stress as a precipitant, though in varying degrees. In the largest systematic review of TCM, which included 28 different case series reports and in aggregate 563 patients, preceding emotional stressors were identified in 195 of 443 patients (44.0%, 39.4-48.6%) and physical stressors in 146 of 403 patients (36.2%, 31.5-40.9%) [1]. Smaller systematic reviews report similar results [5,13]. In a recent study with a large registry of 70 patients not included in the above systematic reviews, 37% of patients had an identifiable emotional stressor, 30% had a physical stressor, and 33% had no identifiable stressor [25]. These data fit with our present study in which 33% (13.8-60.9%) had no identifiable stressor. Clearly, stress is common, but not ubiquitous, among patients with TCM.

Although it is consistent that an emotional or physical stressor is often but not always found, there is no consistency in defining what qualifies as a stressor. There is tremendous variability in reported precipitating factors, from the generally acceptable stressor of family illness or death listed in most studies of Takotsubo to “bad driving directions” and “unusual exercise” [4,25]. Moreover, rarely do studies report prospective acknowledgement of such stressor. Given the discrepancy between the ED records and inpatient records on identification of a stressor in our case series, there may be a consistent recall bias to “find” a stressor once cardiac studies are consistent with TCM.

8. Temporal Sequence

It is expected that the stressor precedes the onset of TCM, but the time frame is unknown. In one study investigating EKGs stored in implantable cardioverter-defibrillators of patients in New York and northern New Jersey both before and after the World Trade Center attacks found that the first arrhythmic event occurred three days following 9/11; in the first month post-9/11 there was a 2.3-fold increase in risk of tachyarrhythmias and subsequently the event rate returned to normal [26]. This study was not specifically investigating TCM, but tachyarrhythmias may be a reasonable surrogate for a similar pathophysiologic abnormality incited by acute mental stress. In the aftermath of the Mid-Niigata Earthquake, the mean interval between earthquake and onset of TCM symptoms was 2.5 days, though 11 of 16 patients developed symptoms the same day as the earthquake [7]. There is very little data present regarding the timing of stressor and onset of symptoms. The recent published registry of Takotsubo patients limited stressors to one week preceding the index event [25]. More data is clearly needed to determine if there is an appropriate temporal

pattern to the inciting stressor and onset of symptoms.

9. Presence of Dose-Response Relationship

Evidence that there is a gradient of risk (stress) associated with the degree of exposure (TCM) could also support the proposed argument of causality. However, with the data available, it is not possible to determine if “more stressful” events have more serious courses or higher rates of developing TCM. Only the previously discussed study of Mid-Niigata Earthquake hints at such an association: 13 of the 16 patients diagnosed with TCM lived in areas with a seismic intensity scale of 6 or more. Perhaps living in an area that felt more of the earthquake’s impact is more stressful. There is no available scale for judging the severity of a stressor or a patient’s ability to cope with the stressor, though varying levels of severe complications (*i.e.*, fatal arrhythmias, hypotension requiring intra-aortic balloon pump, and death) have been identified [1,25,27].

10. Conclusion on Causality of Stressor

The biologic credibility seems intriguing, but the large variety of stressors, the ill-described temporal association, and limited data supporting strength of association or dose-response relationship should raise suspicion about stress causing TCM. Future studies should prospectively identify patients with clearly defined questions regarding type and timing of stressor. Since the ED is the initial site of diagnosis of these patients in the acute phase, further collaborative research with cardiology should focus on identifying an etiology and distinguishing characteristics from other acute coronary syndromes.

11. Limitations

Our study was a retrospective chart review investigation, which contains limitations inherent to its design, including incomplete documentation of data and variance in symptomatology recorded. In addition, TCM remains an uncommon syndrome, limiting the number of cases attainable at a single institution and the ability to generalize results. Our study of twelve total cases may not be generalizable to the population at large.

12. Conclusion

Takotsubo Cardiomyopathy is an important syndrome for emergency physicians to recognize, as it is often indistinguishable from standard acute coronary syndromes. The most consistently reported findings in patients with TCM include postmenopausal age, female gender, and anginal equivalent. Our data reveals that only half of the patients had an identifiable stressor from the emergency department, when hindsight bias is at a minimum. We do not feel that stress can definitively cause TCM because

of the inconsistent presence of a stressor in multiple studies, including ours. Further research, ideally using multi-institutional databases of TCM patients, will need to be performed to determine causative factors, need for emergent cardiac catheterization, and optimal medical management.

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