

# Emotional Stress and Tako-Tsubo Cardiomyopathy: Observations on 2 Distinct Clinical Phenotypes

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**Background:** Tako-tsubo syndrome is a transient cardiomyopathy usually precipitated by an acute emotional or physiological stress. Our study objectives were to review and analyze the impact of emotional stress on clinical variables, echocardiographic characteristics, and short-term outcomes in patients with tako-tsubo syndrome.

**Methods:** Retrospective chart review.

**Results:** Eleven patients presented with tako-tsubo syndrome (1 man and 10 women) during the 8-year period (January 2000 to January 2008). The patients were split into 2 groups, defined by presenting either after emotional stress (6/11, 54.5%) or after idiopathic/physical stress (5/11, 45.5%). The mean age was 53.8 (12.6) years. The mean peak troponin T level was 0.54 ng/mL (range, 0.03–2.06 ng/mL), and the mean left ventricular end-diastolic pressure was 15.8 (8.1) mm Hg. Emotional stress was associated with younger age ( $P = 0.024$ ), a lower left ventricular end-diastolic pressure ( $P < 0.05$ ), more ST segment changes on electrocardiogram (66.7% vs 40%), and a higher ejection fraction ( $P = 0.012$ ). The patients in the idiopathic/physical stress group required more frequent hemodynamic support.

**Conclusions:** We conclude that clinical, echocardiographic, and outcome characteristics can differentiate tako-tsubo patients presenting with emotional stress from those with idiopathic/physical stress into 2 distinct clinical phenotypes. Clinicians should monitor idiopathic/physically stressed tako-tsubo patients carefully for hemodynamic compromise.

**Key Words:** tako-tsubo, clinical phenotypes, emotional stress

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Tako-tsubo syndrome is a transient cardiomyopathy characterized by segmental wall motion abnormalities and apical ballooning.<sup>1–25</sup> This disease mimics acute coronary syndrome with reversible left ventricular dysfunction, reversible cardiac wall motion abnormalities, and dyskinesias. It is called *tako-tsubo* after a Japanese octopus fishing pot because of the appearance of the heart on end-systolic ventriculogram. This condition occurs predominantly in elderly postmenopausal women<sup>1–15</sup> with a history of recent emotional or physical stress.<sup>1,3–9,19,21,24,25</sup> Based on numerous worldwide case series and case reports, the American Heart Association and the American College of Cardiology have recognized apical ballooning or tako-tsubo syndrome as a primary acquired cardiomyopathy.<sup>2</sup>

There are several pathophysiological theories about the etiology of tako-tsubo syndrome<sup>1,3–18</sup>; the most prominent is

catecholamine-induced myocardial stunning.<sup>1,3,4,7</sup> Nuclear imaging studies with iodine 123 myocardial scintigraphy have shown that even in an apparently normally perfused myocardium, there are regional differences in myocardial wall efferent sympathetic innervation and that the anterior myocardial wall has a greater density of these nerve fibers than the apex.<sup>4</sup> These differences in sympathetic innervation of the myocardium and episodic catecholamine surges are implicated in the pathogenesis of tako-tsubo cardiomyopathy. Hormonal changes and microvascular spasm with ischemia may also contribute to this presentation.<sup>1,3,8,10,13–19,23</sup> Emotional and physical stress often precipitates the clinical presentation in these patients. Differences in clinical presentations have been observed, suggesting the possibility of more than one clinical phenotypes.<sup>6,7</sup> However, in the clinical literature, there is no comparison of groups presenting with and groups presenting without a preceding emotional stressor. Our study objective was to review and analyze the impact of emotional stress on clinical variables, echocardiographic characteristics, and short-term outcomes in tako-tsubo patients seen over an 8-year period in a university hospital.

## METHODS

### Study Design

This study was approved by the institutional review board as an exempt study, and only deidentified data from the medical records were allowed into the database. Patients were identified from billing codes for tako-tsubo cardiomyopathy/apical ballooning syndrome. The patients discharged with a primary diagnosis of tako-tsubo cardiomyopathy between January 2000 to January 2008 were included in the study. Data were collected in Microsoft Excel sheet by a physician reviewer.

### Patient Population

We studied 11 patients who presented with tako-tsubo syndrome during an 8-year period. The diagnostic criteria<sup>1–3</sup> included the following:

- (1) Transient, reversible akinesis or dyskinesis of the left ventricular apical and midventricular segments with regional wall motion abnormalities extending beyond a single vascular territory on left ventriculogram.
- (2) Absence of obstructive coronary artery stenosis larger than 50% of the luminal diameter or angiographic evidence of acute plaque rupture.
- (3) New electrocardiographic abnormalities consisting of ST segment elevation or T wave inversion.
- (4) Absence of pheochromocytomas, myocarditis, obstructive epicardial coronary artery disease, recent head trauma, intracranial bleed, or cardiomyopathy.

Clinical variables, including demographic characteristics of patients, were obtained from a medical chart review. An emotional stressor was defined as (1) death or significant illness in a close family member within the past 30 days; (2) history

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**TABLE 1.** Clinical Variables

Patient No.	Age, yr	Sex	Presenting Complaint	Suspected Contributing Factor/Insult	Cardiogenic Shock	Comorbid Conditions
1	62	Female	Chest pain	Absent/idiopathic	No	HTN, dyslipidemia, and TIA
2	61	Female	SOB	Sepsis from pneumonia	Yes	HTN and seizure disorder
3	60	Female	Chest pain	Absent/idiopathic	Yes	HTN and dyslipidemia
4	52	Male	Chest pain	Respiratory failure from ear, nose, and throat malignancies	Yes	Squamous cell throat cancer
5	78	Female	Epigastric pain	Absent/idiopathic	No	HTN and DM 2
6	43	Female	Chest pain	Worsening depression and anxiety from family feud	No	COPD
7	52	Female	SOB/respiratory distress	Worsening depression and hypertensive urgency	No	HTN and DM 2
8	62	Female	SOB	Preoperative anxiety and stress requiring sedatives	Yes	HTN and lung cancer
9	48	Female	Chest pain	Husband killed 2 d ago	No	Seizure disorder and anemia
10	42	Female	Chest pain	Spousal feud on the same day of presentation	No	HTN and DM 2
11	32	Female	Chest pain	Postpartum depression and anxiety	No	DM 2

COPD indicates chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; SOB, shortness of breath; TIA, transient ischemic attack.

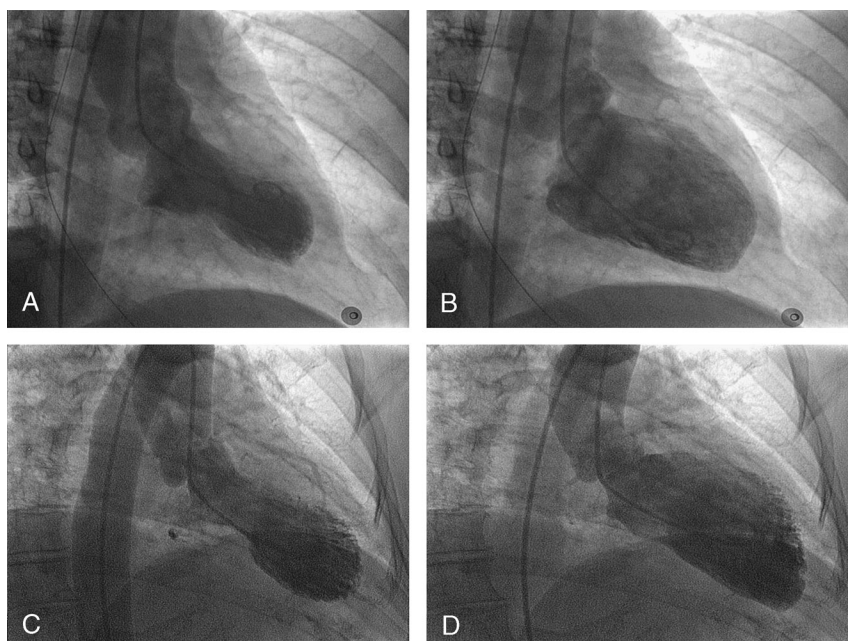
of family feud, divorce, or spousal feud within the preceding 30 days; (3) history of depression/anxiety as previous history or as new presentation in the preceding 30 days; and (4) financial or job loss or relocation of either home or job in the past 30 days. The details of these and the idiopathic/physical stressors are listed in Results. Data were collected on the presenting signs and symptoms from history and physical and routine cardiac tests, including electrocardiogram (ECG), cardiac enzymes, complete blood cell count, and comprehensive metabolic profile.

The patients were followed up until discharge. Short-term outcomes included timing the reversibility of cardiomyopathy, total length of stay, and monitoring of ECG changes, cardiac

enzymes, and echocardiographic changes observed after the establishment of diagnosis by coronary angiography and end-systolic left ventriculography.

### Statistical Analysis

The Megastat Microsoft Excel (McGraw-Hill Higher Education, New York, NY) and SPSS software v. 11.0 (SPSS Inc., Chicago, IL) for Windows were used for statistical analysis. Descriptive statistics were used for the whole cohort and the subgroups quantitative variables. The results were expressed as mean (SD) in case of continuous variables. The Fisher exact test was used for qualitative variables, and the Student's *t* test was



**FIGURE 1.** Ventriculogram during systole (A, C) and diastole (B, D) showing apical ballooning during systole.

used in case of quantitative variables. A  $P < 0.05$  was considered significant.

## RESULTS

Eleven patients (1 man and 10 women) presented with takotsubo cardiomyopathy during the study period (Table 1). None of the patients had a prior diagnosis of coronary artery disease, including a history of myocardial infarction, acute coronary disease, coronary artery bypass surgery, or stable/unstable angina. Echocardiographic and left ventriculographic studies at the time of diagnosis showed a mean ejection fraction (EF) of 40.9% (10.4%) (range, 20%–50%). Most patients had characteristic apical ballooning on the left ventriculogram (Fig. 1). Four patients had cardiogenic shock. The length of stay for all patients was 7.9 days (range, 1–26 days). All the patients regained normal EF within 1 month with a mean EF of 65% on subsequent echocardiograms. Six patients presented after an emotionally stressful event as defined by the inclusion criteria; 5 patients had idiopathic (unknown)/physical stressors at the time of presentation (Table 1).

### Comparison of Groups With and Groups Without Emotional Stress

Emotional stressors included family feud (2/6), spousal feud (1/6), death of spouse (1/6, husband killed 2 days ago), postpartum depression/anxiety 2 weeks after delivery (1/6), and

**TABLE 2.** Clinical Comparison Between Emotional Stress and Idiopathic/Physical Stress Groups

Clinical Variable	Emotional Stress Group	Idiopathic/Physical Stress Group
Age, mean (range), yr	47 (32–62)	63 (52–78)
Sex	Female, 6/6	Female, 4/5
Length of stay, mean (range), d	5.7 (1–21)	10.6 (2–26)
ECG changes, %		
ST segment changes		
Inferior lead elevation	66.7	20
Anterolateral elevation	0	20
Heart rate, mean (range), bpm	98 (61–172)	87 (64–122)
Sinus rhythm	6/6	4/5
Cardiogenic shock	1/6	3/5
Comorbid conditions		
Coronary artery disease	0/6	0/5
Hypertension	3/6 (50%)	4/5 (80%)
Diabetes mellitus	3/6 (50%)	1/5 (20%)
Dyslipidemia	3/6 (50%)	2/5 (40%)
Smoking	2/6 (33%)	1/5 (20%)
Chest pain	4/6	3/5
WBC count at admission, mean (SD), kU/L	8.7 (2.0)	9.9 (2.0)
Troponin T, mean (range), ng/mL	0.57 (0.12–1.18)	0.51 (0.03–2.06)

bpm indicates beats per minute; WBC, white blood cell.

**TABLE 3.** Echocardiographic and Angiographic Studies

	Emotional Stress Group	Idiopathic/Physical Stress Group
LV anterior wall hypokinesia	4/6 (66.7%)	4/5 (80%)
LV inferior wall hypokinesia	1/6 (16.6%)	2/5 (40%)
LV posterior wall hypokinesia	0/6	0/5
Two or more wall hypokinesia	0/6	1/5 (20%)
No wall hypokinesia	1/6 (16.6%)	0/5
EF, mean (SD) [range], %	47.5 (4.2) [40–50]	33.0 (10.4) [20–45]
LVESD, mean (SD) [range], mm Hg	131 (5.8) [125–140]	140 (46) [100–180]
LVEDP, mean (SD) [range], mm Hg	14.5 (6.4) [8–23]	17.8 (5.4) [9–33]

LV indicates left ventricular; LVESD, left ventricular end-systolic pressure.

preoperative anxiety with intraoperative/postoperative hypotension (1/6). Five patients had concurrent histories of depression, and 4 were on antidepressant medications. The mean age was 47 years (range, 32–62 years). Four patients (66.7%) had ST segment elevation in the inferior leads (Table 2). The mean EF was 47.5% (4.2%) (range, 40%–50%). Left ventricular anterior wall hypokinesia was found in 4 patients, and inferior wall hypokinesia was found in 1 patient (Table 3). One patient had cardiogenic shock. One patient had a documented gram-negative septicemia while in the medical intensive care unit after presentation.

The characteristics of the idiopathic/physical stress group were as follows. Two patients without emotional stress presented during episodes of sepsis or acute respiratory failure. Three patients had no obvious emotional stressor. The mean age was 63 years (range, 52–78 years); the only male patient was in this group. Two patients (40%) had ST segment changes: one had anterolateral ECG lead ST segment elevation, and the other had inferior lead ST changes including T wave inversion. Left ventricular anterior wall hypokinesia was found in 4 patients (80%); and inferior wall hypokinesia, in 2 patients (40%). Three patients had cardiogenic shock requiring intra-aortic balloon counterpulsation and inotropic support.

Patients in the emotional stress group were younger than those in the idiopathic/physical stress group (46.5 vs 62.6 years,  $P = 0.024$ ). The mean peak troponin T levels were similar in both groups (0.57 vs 0.51 ng/mL). The group with antecedent emotional stress had a longer length of stay ( $P = 0.4$ ), more ST segment changes on ECG (66.7% vs 40%), and a higher EF ( $P = 0.012$ ). The mean left ventricular end-diastolic pressure (LVEDP) was 14.5 mm Hg in the emotional stress group and 17.8 mm Hg in the idiopathic/physical stress group ( $P < 0.05$ ). Three patients in the latter group required hemodynamic support (vs 1 in the emotional stress group).

## DISCUSSION

The incidence of tako-tsubo syndrome is approximately 1% of patients with an acute coronary syndrome presentation. Most of these patients are postmenopausal women who present after



age 60 years.<sup>1–19</sup> The mean age in our study is 53.8 years, which was younger than the 57,<sup>11</sup> 66,<sup>12</sup> 58,<sup>14</sup> and 71 years<sup>15</sup> reported previously. Thirty-six percent of our patients were below the age of 50 years, and the youngest patient was 32 years old. Fifty-five percent of the patients presented after a recent emotional stressor as defined per inclusion criteria; this is slightly fewer than the 63% or more reported in other studies.<sup>3,7–9</sup> Forty-five percent of our patients presented during acute disease or without any obvious stressor. One presented with sepsis, and another patient presented with respiratory failure; these patients, of course, could have emotional stress associated with then acute disease state. Twenty-seven percent presented with idiopathic tako-tsubo syndrome, which is higher than the 5% to 10% incidence reported in literature.<sup>1,3,8</sup> The patients with emotional stress were younger than the other patients in our study. These differences in age and associated triggers likely have implications for the pathogenesis of this syndrome(s).

Do routine cardiac studies help distinguish between patients with emotional stress and patients without emotional stress? In the published literature, significant ST-T wave changes occur in 46% to 100% of the patients.<sup>1,3,6–8,12,14,22</sup> In our patients, ST segment changes were found in 66.7% of the emotional stress group and in 40% of the idiopathic/physical stress group. Consequently, ECG changes will not separate these 2 groups. However, our patients with ST segment changes had a lower LVEDP than patients without these changes ( $P = 0.0001$ ), suggesting that the presence of electrical injury patterns did not correlate well with changes in cardiac function.<sup>25</sup> The reported incidences of left ventricular inferior and anterior wall hypokinesias in tako-tsubo syndrome are 7.1% and 34%, respectively.<sup>11</sup> More cardiac wall hypokinesia occurred in our patients, including left ventricular inferior wall hypokinesia in 27% of the patients (3/11; 1/6 in the emotional stress group and 2/5 in the idiopathic/physical stress group) and left ventricular anterior wall hypokinesia in 72% of the patients (8/11 total; 4/6 and 4/5). The mean EF in our patients was 40.9% (10.4%), which is higher than previous reports of 29% (9%),<sup>12</sup> 36% (8%),<sup>13</sup> and 37% (12%).<sup>15</sup> The mean EF was higher in the emotional stress group (47.5% [4.2%]) than in the idiopathic/physical stress group (33% [10.4%],  $P = 0.012$ ). This could partly be explained by relatively young age and fewer comorbid conditions in the emotional stress group, whereas previous literature focused on these groups as a whole.<sup>1,3,8,9</sup> Our study differs from these studies, showing higher mean EF especially in the emotionally stressed cohort. These studies reported mean EFs and did not always discuss the heterogeneity in the EF measurements found in their cohorts. The LVEDP is elevated (26 [7]) in the tako-tsubo patients.<sup>15</sup> The mean LVEDP in our cohort was 15.8 (8.1) mm Hg (range, 8–33 mm Hg). Higher LVEDPs correlated with presence of anterior wall hypokinesia ( $P < 0.001$ ) but did not correlate with inferior wall hypokinesia ( $P = 0.72$ ). In addition, LVEDP was lower in our emotional stress group ( $P = 0.012$ ), but there was significant overlap between groups.

These clinical, echocardiographic, and cardiac catheterization findings show that our patients with tako-tsubo syndrome who present after emotional stress are younger and had a higher mean EF. Sixty percent of the patients in the non-emotional stress group needed hemodynamic support with inotropes and/or intra-aortic balloon counterpulsation. Other studies have reported the requirement of hemodynamic support in 20% of tako-tsubo patients.<sup>16–18</sup> These observations suggest that patients with idiopathic/physical stressors have more cardiovascular impairment and that perhaps other factors contribute to myocardial stunning. Possible explanations include a more complex pathogenesis with catecholamine-induced myocardial stunning, inflammation, and microvascular

spasm in these patients.<sup>3–5,10,13</sup> On the other hand, our patients with emotional stress had relatively preserved myocardial function with higher EFs and lower LVEDP pressures. This suggests a transient catecholamine-induced myocardial stunning in this group.<sup>1,3,4,7</sup>

## CONCLUSIONS AND LIMITATIONS

To the best of our knowledge, this is the first study designed to compare the clinical, echocardiographic, and outcome differences in tako-tsubo patients presenting with an emotional stress and with idiopathic/physical stressors. Although emotional stress has a major role in the tako-tsubo etiology, we did identify patients without definite emotional stress at presentation (45%). The patients with emotional stress were younger, had higher EFs, and had lower LVEDPs than the other patients, showing 2 distinct tako-tsubo clinical phenotypes. The patients without emotional stress were more likely to require hemodynamic support. This may reflect less preserved cardiovascular reserve and clinicians should monitor this group carefully for hemodynamic compromise. Because our sample size is small, we cannot definitely conclude that these patients have different clinical phenotypes that depend on the presence or absence of an emotional stressor. However, because tako-tsubo syndrome is a rare condition, studies like this are needed to identify patient subsets if they exist. We think that this study could serve as a stimulus for a multicenter trial to prospectively investigate clinical phenotypes, disease pathogenesis, and outcomes in these patients.

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