

## Short and Long-Term Outcome of Stress-Induced Cardiomyopathy: What Can We Expect?

Vânia Filipa Andrade Ribeiro<sup>1</sup>, Mariana Vasconcelos<sup>1</sup>, Filipa Melão<sup>1</sup>, Ester Ferreira<sup>1</sup>, Gracieta Malangatana<sup>2</sup>, Maria Júlia Maciel<sup>1</sup>

Centro Hospitalar São João<sup>1</sup>, Porto; Hospital Pedro Hispano<sup>2</sup>, Porto - Portugal

### Abstract

**Background:** Stress-induced/Takotsubo cardiomyopathy (TC) is an increasingly recognized diagnostic entity.

**Objective:** This study was aimed to assess the prevalence and clinical predictors of short and long-term outcome of patients (pts) diagnosed with TC.

**Methods:** We included all consecutive pts admitted in our department, from November 2006 to August 2011, who met the Mayo Clinic criteria for TC diagnosis.

**Results:** We evaluated 37 pts (35 women) with a mean age of  $63 \pm 13$  years. TC was precipitated by a stressful emotional event in the majority (57%) and chest pain was the most common symptom (89%). Twelve pts (32%) had ST-segment elevation and 15 pts (41%) had T-wave inversion on the electrocardiogram at admission. Severe left ventricular (LV) dysfunction was found in 16 pts (43%) and the mean troponin I level was  $2.6 \pm 1.8$  ng/mL. The in-hospital complication rate was 30%, with cardiogenic shock being the most common situation. Physical stress, severe LV systolic dysfunction and peak brain natriuretic peptide (BNP) were predictors of acute complications. On the other hand, we found no association between peak troponin I and electrocardiographic presentation. Thirty-five pts were followed for a mean time of  $482 \pm 512$  days, without clinic recurrence.

**Conclusion:** In our cohort of pts, TC was associated with a high in-hospital complications rate. Physical stress, LV dysfunction and peak BNP could predict acute adverse outcomes. (*Arq Bras Cardiol.* 2014; 102(1):80-85)

**Keywords:** Takotsubo cardiomyopathy; Stress, Psychological.

### Introduction

Stress-induced/Takotsubo cardiomyopathy (TC) is an increasingly reported syndrome characterized by transient systolic dysfunction in the absence of obstructive coronary disease, which mimics myocardial infarction.

The precise incidence of SC is unknown, but recent studies have shown a prevalence of approximately 2% of patients presenting with acute coronary syndrome in the United States and Europe<sup>1</sup>.

An emotional or physical stressor frequently precedes the development of symptoms, but the pathophysiology of TC is unclear. Several hypotheses have been proposed, including catecholamine-mediated cardiotoxicity, spasm of the microvascular coronary circulation and endothelial cell dysfunction<sup>2-4</sup>.

In this report we evaluate the clinical features of 37 patients with this disorder, consecutively admitted in our tertiary

hospital center, and the predictors of adverse events at short and long-term in this population.

### Methods

From November 2006 to August 2011, we retrospectively identified 37 patients with TC who had undergone left heart catheterization for acute coronary syndrome in our tertiary hospital center. All patients presented to our emergency department or were transferred from an outside hospital. The inclusion criteria for Takotsubo cardiomyopathy, according to the Mayo Clinic, were: transient LV wall motion abnormalities involving the apical/ and or midventricular myocardial segments with wall motion abnormalities extending beyond a single epicardial coronary distribution; absence of obstructive epicardial coronary artery disease or angiographic evidence of acute plaque rupture that could be responsible for the observed wall motion abnormality; new ECG abnormalities such as transient ST-segment elevation and/or diffuse T-wave inversions or troponin elevation; absence of pheochromocytoma or myocarditis.

The patients' demographics, clinical presentation, electrocardiographic findings, cardiac biomarker levels and complications were assessed during hospital stay. All patients underwent left ventriculography and echocardiographic evaluation, at admission and follow-up. Clinical follow-up was

**Mailing Address:** Vânia Filipa Andrade Ribeiro •

Alameda Prof. Hérnani Monteiro. Postal Code 4200-319, Porto - Portugal

E-mail: ribeiro\_vania@hotmail.com

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performed with outpatient visits. Cardiac magnetic resonance was performed in thirteen patients. Recurrence of symptoms, re-hospitalization, functional status and death were recorded.

Data was analyzed using SPSS version 20.0 and the association between baseline variables and acute complications was estimated through odds ratio (OR) for categorical variables and paired T test for continuous variables.

## Results

Thirty-five patients (95%) were women with a mean age of  $63 \pm 13$  years (Table 1). The majority of patients had cardiovascular risk factors: twenty-seven patients (73%) had hypertension, nineteen (51%) had dyslipidemia and six (16%) had diabetes. The most common presentation was chest pain (89%), but three patients (8%) presented with dyspnea and one (3%) presented with lipothymy. A trigger was identified in twenty-nine patients (78%). The commonest trigger was emotional stress (57%). A physical trigger was present in eight patients (22%) and included an elective surgical procedure, chronic obstructive pulmonary disease exacerbation and recent hospitalization. The admission ECG revealed ST-segment elevation in twelve patients (32%) and widespread T-wave inversion in twenty-five patients (41%) (Figure 1). Other ECG findings included sinus tachycardia and new Q waves. Five patients (14%) had no ECG alterations. Troponin I was positive in all cases with a mean peak level of  $2.6 \pm 1.8$  ng/mL. Mean peak value of brain natriuretic peptide (BNP) was  $1160 \pm 1564$  pg/mL. Left ventricular assessment demonstrated the classical apical ballooning appearance in thirty-four patients (92%) and mid-wall variant was demonstrated in three patients (8%) (Figure 2). The mean ejection fraction by echocardiography was 40%.

Acute complications occurred in eleven patients (30%), with cases presenting more than one complication (Table 2). Cardiogenic shock was the most common situation, but two patients developed acute pulmonary edema. Rhythm disturbances were also observed. One patient had an episode of rapid atrial fibrillation, cardioverted with amiodarone. Third-degree AV block was documented in two patients, one of them requiring a permanent pacemaker due to the persistence of AV block after recovery of the systolic function. The echocardiographic evaluation performed in all patients identified two cases of significant LV outflow gradient and two cases of intraventricular thrombus.

There were no deaths. The mean duration of hospital stay was  $7.9 \pm 5.6$  days, with longer hospitalization in patients with complications ( $12.0 \pm 8.7$  vs.  $6.1 \pm 2.1$ ,  $p = 0.05$ ), as expected. Physical stress (odds ratio: 6.4; 95% confidence interval: 1.2 to 34.6), severe LV systolic function at admission (odds ratio: 12.2; 95% confidence interval: 2.1-71.0) and peak BNP ( $2324.7 \pm 2107.2$  vs.  $512.8 \pm 542.9$ ,  $p = 0.024$ ) were predictors of acute complications. On the other hand, we found no association between peak troponin I, electrocardiographic presentation and time of symptom evolution (Table 3).

Thirty-five patients had follow-up at mean time of  $482 \pm 512$  days. We recorded one death (hemorrhagic cerebrovascular event). No rehospitalizations or TC recurrences

**Table 1 - Baseline characteristics of the study population**

Characteristic	Total (n = 37) Value
Age (years), mean $\pm$ SD	63 $\pm$ 13
Female	35 (95%)
<b>Cardiovascular risk factors</b>	
Diabetes mellitus	6 (16%)
Hypertension	27 (73%)
Dyslipidemia	19 (51%)
Smoking (actual or previous)	2 (5%)
<b>Clinical presentation</b>	
Chest pain	33 (89%)
Dyspnea	3 (8%)
Lipothymy	1(3%)
<b>Triggering factor</b>	
Emotional stress	21 (57%)
Physical stress	8 (22%)
No trigger	8 (22%)

SD: standard deviation.

**Table 2 - In-hospital complications in the study population**

In-hospital complication	n (%)
Cardiogenic shock	4 (11%)
Intraventricular thrombus	2 (5%)
Atrial fibrillation	1 (3%)
Pulmonary edema	2 (5%)
Third degree AV-block	2 (5%)
Significant left ventricular outflow gradient	2 (5%)

AV: atrioventricular.

were identified. Only 22 patients (63%) were asymptomatic; six patients (16%) complained of atypical chest pain and twelve patients (32%) were in NYHA class 2 (premorbid class 1 functional status). All patients recovered normal left ventricular function. Cardiac magnetic resonance was performed in thirteen cases and late gadolinium enhancement was present in only one case (small intramyocardial area).

## Discussion

We report the clinical features and outcomes of all TC patients consecutively admitted in our hospital over a period of 58 months. This is the largest single-center Portuguese cohort reported to date.

The demographics of our cohort were similar to that observed in other parts of the world<sup>5-8</sup>. Most patients were female in the post menopausal age group. The majority of patients were hypertensive (73%) and diabetes mellitus was less common (16%) than typically seen in acute coronary

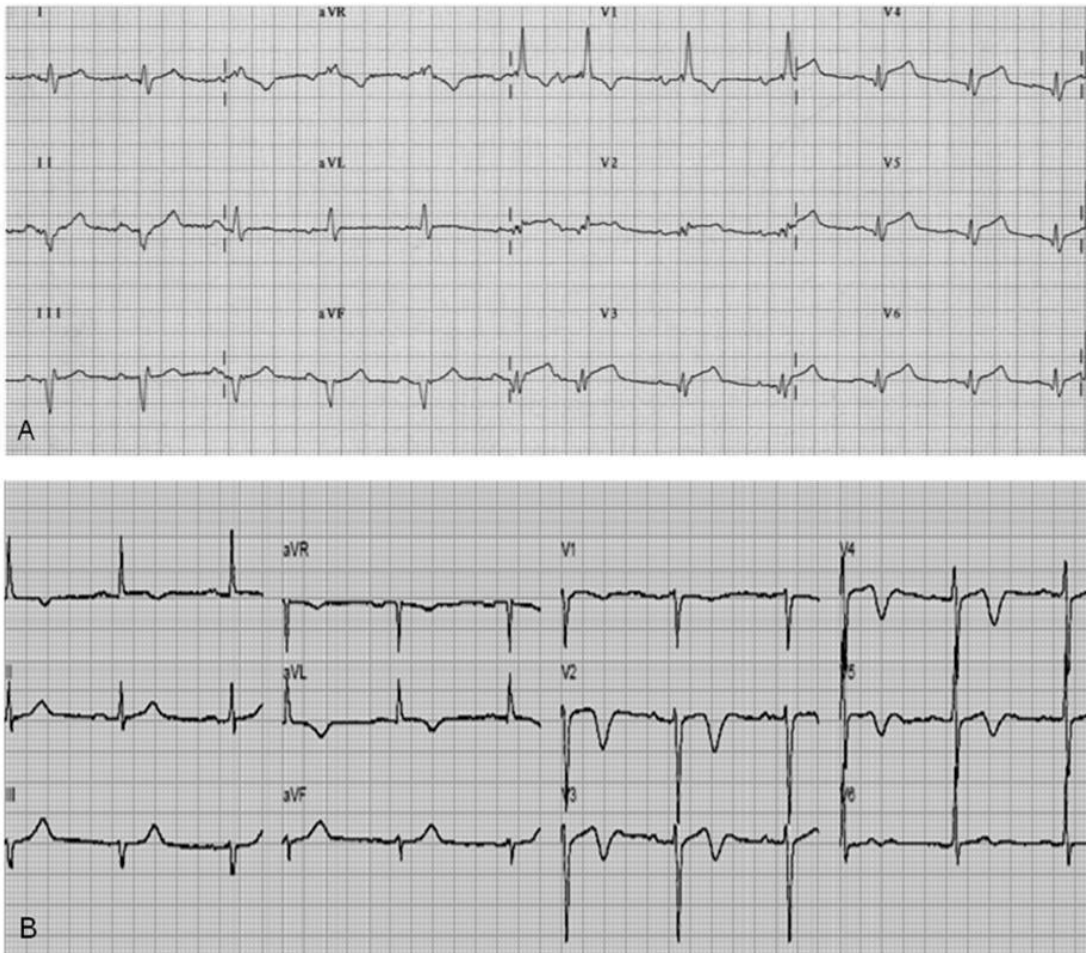


Figure 1 - Representative electrocardiographic patterns at admission with (A) ST-segment elevation in V2 to V6 and (B) T wave inversion in V2 to V5, DI and aVL.

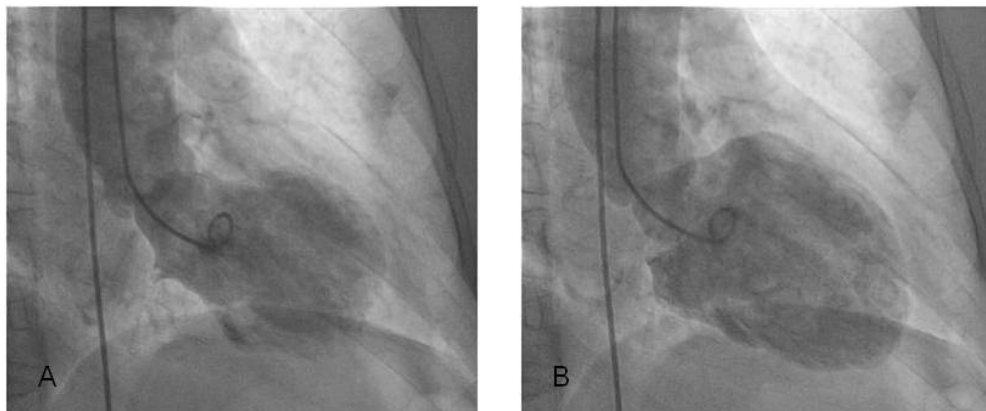


Figure 2 - Left ventriculogram at (A) end-systole and (B) end-diastole, showing a mid-wall variant with apical contraction.

**Table 3 - Clinical predictors of in-hospital complications in the study population**

	Acute complications (n = 11)	No acute complications (n = 26)	p value	OR 95% CI
Age (years)	63.2 ± 20.3	63.0 ± 8.9	0.98	
Triggering factor			0.03	
Emotional stress	3 (27.3%)	18 (69.2%)		
Physical stress	5 (45.5%)	3 (11.5%)		6.4 (1.2-34.6)
No trigger	3 (27.3%)	5 (19.2%)		
Time from symptoms onset (hours)	16.6 ± 18.5	9.83 ± 16.2	0.28	
ECG presentation			0.49	
Normal ECG	3 (27.3%)	2 (7.7%)		
ST-segment elevation	3 (27.3%)	9 (34.6%)		
Negative T waves	3 (27.3%)	12 (46.2%)		
Troponin I peak (ng/mL)	2.5 ± .8	2.6 ± 1.8	0.98	
BNP peak (pg/mL)	2324.7 ± 2107.2	512.8 ± 542.9	0.02	
Ejection fraction			0.02	
≥ 45%-55%	1 (9.1%)	2 (7.7%)		
≥ 35%-45%	1 (9.1%)	16 (61.5%)		
< 35%	9 (81.2%)	7 (26.9%)		12.2 (2.1-71.0)
Days in hospital	12.0 ± 8.7	6.1 ± 2.1	0.05	

ECG: electrocardiogram; BMP: Brain natriuretic peptide.

syndromes. At presentation, chest pain and dyspnea were the prevalent symptoms. An emotional trigger could be identified in most cases, as seen in other studies<sup>5-11</sup>.

Our population had a high complication rate, reaching 30%, but there were no deaths. The reported complication rate in meta-analyses<sup>3,7,12</sup> of TC is about 19%, with an overall in-hospital mortality rate of 0-3.2%<sup>4,6,7,13</sup>. Cardiogenic shock is the most common severe complication, occurring in 6-10% of patients<sup>3,4,6,7</sup>. Congestive heart failure has been reported in 3-46% of patients<sup>2</sup>, with pulmonary edema in 16%<sup>7</sup>. Life-threatening arrhythmias such as third degree AV-block, ventricular tachycardia, ventricular fibrillation and cardiac arrest are described in 15% of patients<sup>7</sup>. Cases of intramural thrombus formation, significant LV outflow gradient and left ventricular free-wall rupture have also been observed<sup>2, 5,13-15</sup>.

Data related to predictors of complications are scarce. Madhavan et al<sup>16</sup> concluded in their retrospective analysis that age, physical stress, lower ejection fraction and admission troponin T level were independent predictors of acute heart failure. Recently, Takashio et al<sup>17</sup> identified the sum of ST-segment elevation in 12 leads as a significant and independent predictor of outcome in TC. However the ECG pattern on admission did not confer any prognostic significance in terms of adverse events or mortality, in other studies<sup>1,15,18</sup>.

Acute complications in our series were associated with physical stress, severe LV dysfunction at admission and higher BNP level. We found no association with peak troponin I, electrocardiographic presentation and time of symptom evolution.

Although recurrences have been reported in about 3.5-10% of cases<sup>3,6,19</sup>, none of our patients had TC recurrence. It remains unclear why TC does not reoccur in similar stressful circumstances after the initial episode.

Our study highlights some important observations. Although medium- to long-term prognosis remains favorable in TC populations, life-threatening events occur in a high percentage of cases. Patients submitted to physical stress, with severe LV dysfunction at admission and elevated BNP deserved particular concern and surveillance.

## Conclusion

TC has been regarded as a benign form of acute heart failure associated with transitory systolic dysfunction. However, in our population, a high percentage of patients experienced cardiac complications justifying the importance of prompt recognition and tight surveillance. Physical stress, ejection fraction at admission and BNP levels are valuable tools in risk stratification.

## Author contributions

Conception and design of the research: Ribeiro V, Vasconcelos M, Ferreira E, Malangatana G. Acquisition of data: Ribeiro V, Vasconcelos M, Ferreira E, Malangatana G. Analysis and interpretation of the data: Ribeiro V, Vasconcelos M. Statistical analysis: Melão F. Writing of the manuscript: Ribeiro V, Vasconcelos M. Critical revision of the manuscript for intellectual content: Vasconcelos M, Melão F, Maciel MJ.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any post-graduation program.

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