

## Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases

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Received: April 4, 2013 Revised: May 12, 2013

Accepted: June 1, 2013

Published online: July 26, 2013

### Abstract

**AIM:** To review the initial presentation and demonstrate the importance of Takotsubo cardiomyopathy.

**METHODS:** A PubMed search using the terms "Takotsubo cardiomyopathy (TC)" and "apical ballooning syndrome" yielded 211 publications. Only those that were relevant were fully reviewed. The gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers of patients diagnosed with TC, were extracted as available. The data were organized in tables and graphics, and the incidence of the disorder was calculated and analyzed.

**RESULTS:** A total of 250 clinical cases were examined. The predominant gender that was affected was female, with a prevalence of 87.5%. The mean age of presentation was  $64 \pm 14$  years. The cases were divided by age into 10-year intervals. The age interval of 60-69 years showed the highest frequency of TC, accounting for 79 cases. The most common precipitating stressor was physical (50% of cases). Chest pain was

the primary complaint at presentation (58.8% of cases) followed by dyspnea (30% of cases). The ST segment changes category was the most common (60%), followed by T wave changes (39.6%). Of the 60% of cases with ST segment changes, 12% had concomitant T wave changes. This means that for 27.6% of the cases, the primary abnormality in the ECG was T wave changes; 87.6% of cases with TC had a change in the ST segment, in the T wave or in both. The percentage of ECGs presenting with changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion). The percentage of patients presenting with changes in the lateral segment of the heart was 46.8%, while the percentage of patients with changes in the inferior heart was 21.6% and the percentage of patients with changes in the apical region was only 16%. The prevalence of elevated creatinine kinase and/or troponin on initial presentation was 89.3%.

**CONCLUSION:** It is essential that every physician consider Takotsubo cardiomyopathy as a possible differential diagnosis when a patient is classified with acute coronary syndrome. To do so, it is necessary to know the clinical presentation of this syndrome in its early stages.

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**Key words:** Apical ballooning syndrome; Broken heart syndrome; Stress cardiomyopathy; Takotsubo cardiomyopathy; Takotsubo syndrome

**Core tip:** Takotsubo cardiomyopathy is a syndrome that, while frequently not recognized, has a significant impact and represents a significant percentage of diagnosed acute coronary syndromes. The importance of its recognition by physicians should be stressed. There are no previously published articles that analyze a sig-

nificant number of reported cases of Takotsubo cardiomyopathy, nor are prior literature reviews available that examine all the points discussed by this author relative to the initial stages of the disease.

Sanchez-Jimenez EF. Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases. *World J Cardiol* 2013; 5(7): 228-241 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/228.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.228>

## INTRODUCTION

Takotsubo cardiomyopathy (TC), apical ballooning syndrome and stress cardiomyopathy have all been used to refer to a syndrome that was described for the first time in 1991 in Japan. Five such cases were shown to have left ventriculograms with transient akinesis in the apical diaphragmatic and/or anterolateral wall but hyperkinesis in the basal wall of the heart<sup>[1]</sup>.

Many hypotheses have been proposed to explain the pathophysiology of TC, including multivessel coronary vasospasm, abnormalities of coronary microvascular function, and catecholamine-mediated cardiotoxicity<sup>[2]</sup>. Some authors consider estrogen an important factor because it changes the  $\beta_1:\beta_2$  adrenoreceptor (AR) ratio in favor of the  $\beta_2$  AR-Gi protein, which protects the myocardium from catecholamines in stressful situations<sup>[3]</sup>.

The typical initial presentation pattern as chest pain and/or dyspnea, the electrocardiographic changes and elevated serum cardiac markers observed in TC patients often result in the misdiagnosis of TC as acute coronary syndrome (ACS). For the diagnosis of TC, it is necessary to perform echocardiography to observe the wall motion abnormality and coronary angiography to confirm the absence of significant stenotic lesions<sup>[2-4]</sup>. For some authors, cardiac magnetic resonance imaging (CMRI) (Figure 1) is very important due to its unique ability to assist diagnosis with noninvasive techniques; certainly, CMRI is very helpful in the differential diagnosis of TC and myocarditis, and with patient follow-up<sup>[5]</sup>.

Many authors mention that the electrocardiographic changes that are seen in the presentation of TC are similar to those of ACS, particularly ST segment elevation myocardial infarction (STEMI); the similarities may include ST segment changes, T wave changes and QT interval changes<sup>[6]</sup>.

This article analyzes the initial clinical presentation of a large number of cases of TC that have been described in the literature and assesses various parameters with a focus on electrocardiographic changes.

## MATERIALS AND METHODS

The reviewed articles were found on PubMed using the search terms “Takotsubo cardiomyopathy” and “api-

cal ballooning syndrome”. Three filters, namely “case reports”, “free text available” and “humans”, were used. After setting those filters, 211 articles were found. Of these, only those relevant to TC, which accounted for 197 articles, were fully reviewed. Of these, eight were eliminated because they did not include electrocardiograms or because the final diagnosis was not TC. Therefore, the study was conducted using 189 articles in total.

The criteria used to define TC, were those used by each author in each clinical case. One case of right ventricular Takotsubo<sup>[7]</sup> and several cases of reverse Takotsubo, broken-heart syndrome and stress cardiomyopathy were also included.

The following data were extracted upon availability: gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers.

There was no age restriction for inclusion of cases in the study. Cases were classified by age using intervals of 10 years for better management of information. Two patients, a 16-year-old and a 90-year-old, fell outside the first interval of 20-29 years and the last interval of 80-89 years. The median and mean age of the patients and the standard deviations of these values were calculated.

The precipitating stressors were grouped into four categories: physical (physical effort, organic disease or medical condition); emotional (psychological, anxiety or family situation); undetermined (unclear whether the precipitating stressor was emotional, physical or both); no stressor (no identifiable stressor in the history); and not available (not available in the review article). The prevalence of each precipitating stressor was then calculated.

Due to the variable nomenclature assigned by the authors to the main complaint at presentation, it was decided that this nomenclature should be merged into single terms that described all patients who showed similar symptoms. The term “chest pain” was used to include chest discomfort, chest tightness and retrosternal discomfort. “Dyspnea” was used to include respiratory distress, shortness of breath, orthopnea and pulmonary congestion. “Hypotension” included hemodynamic instability, right heart failure and cardiogenic shock. “Loss of consciousness” included ventricular fibrillation and cardiopulmonary arrest, and “palpitations” included tachycardia. After all signs and symptoms were classified, they were listed and their prevalence was calculated based on the total number of cases.

The presence of a minimum of one ECG description was set when choosing the articles. The first ECG was extracted and was preferred for every case. If the time at which the test was taken was not specified, the test made available in the article was assumed to be the first and only test performed and was used in this study. If multiple tests were performed during the initial case presentation, the test that was performed first was extracted. All electrocardiographic descriptions of each case were obtained. The ECG data were grouped into the following categories: ST segment changes, T wave changes, Q wave changes, QT prolonged, normal category and others. If

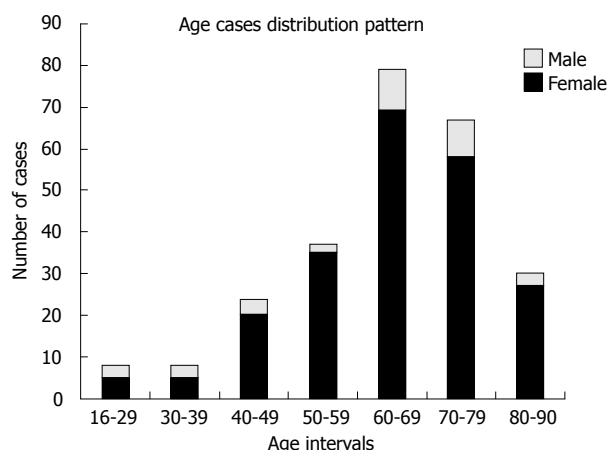


Figure 1 Graphic showing total cases grouped by age intervals.

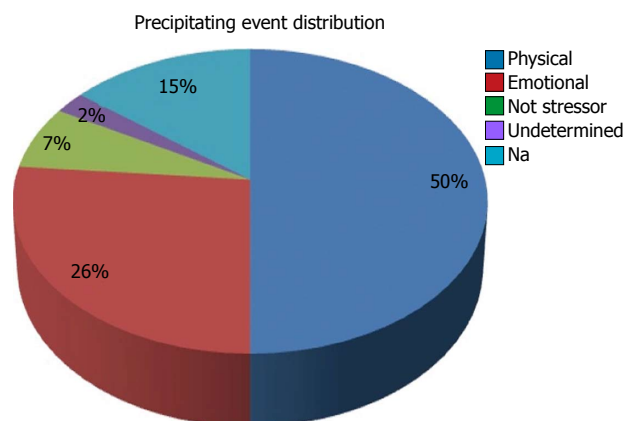


Figure 2 Graphic showing precipitating stressors grouped in categories for all cases studied.

Table 1 Electrocardiographic findings organized by frequency in presentation

Electrocardiogram description	Cases (n)	Incidence (%)
ST segment changes	150	60.00
T wave changes	99	39.60
Prolonged QT	26	10.40
Normal	16	6.40
Q wave	11	4.40
AV block	7	2.80
LBBB	6	2.40
RBBB	6	2.40
AF	5	2.00
VT	3	1.20
VF	3	1.20
Ventricular bigeminy	2	0.80
Other <sup>1</sup>	1	0.40

<sup>1</sup>Other: U wave, Osborn wave, Torsade de Pointes, ventricular atrial retrograde conduction, ventricular pace rhythm, premature ventricular contractions, ventricular ectopic beats, multifocal ventricular contractions, ventricular asystole and escape junctional rhythm. AV block: First, second and third degree atria-ventricular block; LBBB: Left bundle branch block; RBBB: Right bundle branch block; AF: Atrial fibrillation; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

the ECG showed documented long-standing changes such as LBBB (left bundle branch block) or AV block, the cases were not considered in this study. The incidence of each of these categories in the ECG data was calculated (Table 1).

The ST segment category was also divided into four groups based on the following specific changes: ST segment elevation, ST segment depression, flattened ST segment and non-specific ST segment changes (Table 2). The incidence of each based on the ST segment changes category and on the total population was calculated.

The analysis of the T wave changes was also divided into four groups: T wave inversion, hyperacute T wave, flattened T wave and non-specific T wave changes (Table 2), and the incidence of each based on both the T wave category and the total cases was calculated.

The ECG findings were classified by anatomical re-

gion of the heart into inferior, lateral, septal, anterior and non-specific, based on the altered leads<sup>[8]</sup>. The incidence of abnormalities in each region was calculated and further analyzed (Table 3).

The serum cardiac markers creatinine kinase (CK-MB) and/or troponin were classified as normal or elevated; the latter category included mild, moderate and severe elevation. The results extracted were the first test during the admission or the first test result after suspecting a case. The prevalence of each marker elevation was calculated.

## RESULTS

One hundred and eighty-nine case report articles, each of which included one or more individual clinical cases, were analyzed; in total, 250 clinical cases were examined (Table 4).

### Gender

The predominant gender was female; it accounted for 219 cases with a prevalence of 87.5%.

### Age

The age of the patients ranged from 16-90 years. The mean age at presentation was  $64 \pm 14$  years, with a 95%CI of  $64 \pm 2$  years and a median of 66 years. Figure 1 shows the number of cases grouped by 10-year intervals with respect to age. The age interval with the highest number of cases is 60-69 years; it includes 79 cases.

### Precipitating stressor

Figure 2 shows the distribution of precipitating events among all cases. The 6 (2%) cases listed as “undetermined” were difficult to categorize. For example, a patient who had an operation was very stressed and anxious about the surgery results<sup>[9]</sup>. In the cases where the stressor was not available, the author did not mention whether there was a precipitating factor.

### Main complaint at presentation

Table 5 shows the frequency of presentation of all cases

**Table 2** ST segment, T wave change categories organized by incidence

	Cases (n)	Category incidence <sup>1</sup> (%)	Global incidence <sup>2</sup> (%)
ST segment changes			
ST segment elevation	135	90.00	54.00
ST segment depression	11 <sup>3</sup> (21 <sup>4</sup> )	7.30	4.40
ST segment non-specific changes	3	2.00	1.20
ST segment flattened	1	0.70	0.40
T wave changes			
T wave inversion	91	91.90	36.40
Hyperacute T wave	4	4.00	1.60
Flattened T wave	2	2.00	0.80
Non-specific T wave changes	2	2.00	0.80

<sup>1</sup>Percentage calculated based on total ST segment changes cases (150); percentage calculated based on total cases with T wave changes (99);

<sup>2</sup>Percentage calculated based on total cases in the study (250); percentage calculated based on total cases in the study (250); <sup>3</sup>Total number of cases presenting with ST segment depression alone (without concomitant ST segment elevation); <sup>4</sup>Total number of cases presenting with ST segment depression.

**Table 3** Incidence of electrocardiographic change categories shown by anatomical region

Category and Localization	Cases (n)	Category incidence <sup>1</sup> (%)	Global incidence <sup>2</sup> (%)
ST segment elevation			
Anterior	89	65.90	35.60
Lateral	66	48.90	26.40
Inferior	26	19.30	10.40
Septal (apical)	24	17.80	9.60
Not specified	22	16.30	8.80
ST segment depression <sup>3</sup>			
Anterior	4	36.40	1.60
Lateral	6	54.50	2.40
Inferior	5	45.50	2.00
Septal (apical)	0	0.00	0.00
Not specified	2	18.20	0.80
T wave changes <sup>4</sup>			
Anterior	43 (2 <sup>5</sup> )	43.40	17.20
Lateral	45 (1 <sup>5</sup> )	45.50	18.00
Inferior	23	23.20	9.20
Septal (apical)	16	16.20	6.40
Not specified	15	15.20	6.00

<sup>1</sup>Percentage calculated based on the total number of cases in each category;

<sup>2</sup>Percentage calculated based on the total number of cases in the study (250); <sup>3</sup>Only cases with ST segment depression as the main finding; <sup>4</sup>Only cases with T wave changes as the main finding, does not include T wave changes accompanying ST segment elevation or ST segment depression;

<sup>5</sup>Only 3 cases that were not T wave inversions.

grouped with respect to symptoms and signs. Chest pain and dyspnea together were encountered in only 49 (20%) cases.

### Electrocardiogram at admission

Table 1 shows the incidences of various types of electrocardiographic abnormalities in the TC cases. Of the 60% of cases with ST segment changes, 12% had concomitant

T wave changes, indicating that the main abnormality in the ECG for 27.6% of cases was T wave changes and that 87.6% of cases with TC had a change in the ST segment, in the T wave or both. Slow R progression was found in 3 cases, and tachycardia was found in 17 cases; one case of an anterior infarct of indeterminate age<sup>[10]</sup> was classified into the normal category.

Table 2 shows the incidence of specific ST segment changes. The incidence of ST segment depression in the total population (250 cases) and in the ST segment category (150 cases) was 4.4% and 7.3%, respectively. These calculations are based on 11 cases that presented with ST segment depression alone without concomitant ST segment elevation. The total number of cases regarding ST segment depression was 21; thus, 10 cases had concomitant ST segment elevation changes in the ECG. Table 2 shows the incidence of the T wave changes by group.

Table 3 shows the relative frequency at which various anatomical regions were affected in the electrocardiogram. The percentage of ECGs that showed changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion), and the percentage that showed changes in the lateral segment of the heart was 46.8%. The percentage of ECGs showing changes in the inferior heart was 21.6%, while the percentage that showed changes in the apical region was only 16%.

### Serum cardiac markers

The prevalence of elevated serum cardiac markers or normal cardiac markers was calculated from the extracted data. The “not available” data cases were not considered in the calculation. The prevalence of elevated CK-MB and/or troponin in patients initially presenting with TC was 89.3%, and the prevalence of negative or normal levels of these cardiac enzymes at presentation was 10.7%.

## DISCUSSION

After an exhaustive search of articles describing clinical cases of TC, with emphasis on those that provided the minimum electrocardiographic data, a large number of articles and cases were found. These were analyzed to obtain the data required for this research.

The data obtained in this study indicate a pyramidal trend in age of occurrence of TC. The peak of TC incidence occurs in the 60 s; from this point, there is a gradual decrease in TC incidence as age increases or decreases, with a steeper slope in the direction of the younger population. The high female prevalence of the disease and the age distribution of its occurrence provide support for at least one hypothesis of its pathophysiology, *i.e.*, that lack of estrogen is an important causal factor of this syndrome<sup>[11]</sup>.

A newly diagnosed disease, an upcoming operation, the induction of anesthesia, a new medication, a stress test or a major physical effort are only some of the physical stressors that can cause TC. This research show that



Table 4 Total number of cases analyzed tables

No.	Age (yr)	Ref.	No.	Age (yr)	Ref.	No.	Age (yr)	Ref.
1	30	Muller <i>et al</i> <sup>[8]</sup>	85	69	Haghi <i>et al</i> <sup>[70]</sup>	169	68	Lisi <i>et al</i> <sup>[140]</sup>
2	67	Yaoita <i>et al</i> <sup>[9]</sup>	86	69	Haghi <i>et al</i> <sup>[70]</sup>	170	71	Rotondi <i>et al</i> <sup>[141]</sup>
3	73	Izumi <i>et al</i> <sup>[10]</sup>	87	43	Haghi <i>et al</i> <sup>[70]</sup>	171	82	Kawano <i>et al</i> <sup>[142]</sup>
4	62	Kobayashi <i>et al</i> <sup>[11]</sup>	88	69	Haghi <i>et al</i> <sup>[70]</sup>	172	79	Hutchings <i>et al</i> <sup>[143]</sup>
5	65	Ker <i>et al</i> <sup>[12]</sup>	89	52	Di Valentino <i>et al</i> <sup>[71]</sup>	173	55	Hutchings <i>et al</i> <sup>[143]</sup>
6	78	Lau <i>et al</i> <sup>[13]</sup>	90	68	Stähli <i>et al</i> <sup>[72]</sup>	174	82	Zuhdi <i>et al</i> <sup>[144]</sup>
7	62	Hayashi <i>et al</i> <sup>[14]</sup>	91	65	Vivo <i>et al</i> <sup>[73]</sup>	175	45	Stout <i>et al</i> <sup>[145]</sup>
8	65	Peraira Moral <i>et al</i> <sup>[15]</sup>	92	81	Sacha <i>et al</i> <sup>[74]</sup>	176	76	Daly <i>et al</i> <sup>[146]</sup>
9	81	Wedekind <i>et al</i> <sup>[16]</sup>	93	53	Fiol <i>et al</i> <sup>[75]</sup>	177	78	Daly <i>et al</i> <sup>[146]</sup>
10	81	Davin <i>et al</i> <sup>[17]</sup>	94	61	Oberson <i>et al</i> <sup>[76]</sup>	178	65	Saito <i>et al</i> <sup>[147]</sup>
11	79	Teo <sup>[18]</sup>	95	29	Magno <i>et al</i> <sup>[77]</sup>	179	75	Silberbauer <i>et al</i> <sup>[148]</sup>
12	51	Arroyo <i>et al</i> <sup>[19]</sup>	96	82	Kim <i>et al</i> <sup>[78]</sup>	180	47	Biteker <i>et al</i> <sup>[149]</sup>
13	79	Consales <i>et al</i> <sup>[20]</sup>	97	71	Kume <i>et al</i> <sup>[79]</sup>	181	74	Merli <i>et al</i> <sup>[150]</sup>
14	64	Maruyama <i>et al</i> <sup>[21]</sup>	98	78	Kume <i>et al</i> <sup>[79]</sup>	182	72	Merli <i>et al</i> <sup>[150]</sup>
15	80	Nguyen <i>et al</i> <sup>[22]</sup>	99	77	Kume <i>et al</i> <sup>[79]</sup>	183	71	Merli <i>et al</i> <sup>[150]</sup>
16	84	Nishikawa <i>et al</i> <sup>[23]</sup>	100	74	Kume <i>et al</i> <sup>[79]</sup>	184	75	Merli <i>et al</i> <sup>[150]</sup>
17	53	Sakihara <i>et al</i> <sup>[24]</sup>	101	78	Kume <i>et al</i> <sup>[79]</sup>	185	57	Virani <i>et al</i> <sup>[151]</sup>
18	66	Ono <i>et al</i> <sup>[25]</sup>	102	78	Ahn <i>et al</i> <sup>[80]</sup>	186	64	Virani <i>et al</i> <sup>[151]</sup>
19	48	Daly <i>et al</i> <sup>[26]</sup>	103	55	Mahida <i>et al</i> <sup>[81]</sup>	187	44	Virani <i>et al</i> <sup>[151]</sup>
20	76	Iengo <i>et al</i> <sup>[27]</sup>	104	53	Bianchi <i>et al</i> <sup>[82]</sup>	188	64	Virani <i>et al</i> <sup>[151]</sup>
21	44	Pison <i>et al</i> <sup>[28]</sup>	105	61	Hwang <i>et al</i> <sup>[83]</sup>	189	69	Chia <i>et al</i> <sup>[152]</sup>
22	52	Pison <i>et al</i> <sup>[28]</sup>	106	55	Ikeda <i>et al</i> <sup>[84]</sup>	190	57	Yazdan-Ashoori <i>et al</i> <sup>[153]</sup>
23	81	Desmet <i>et al</i> <sup>[29]</sup>	107	75	Ikeda <i>et al</i> <sup>[84]</sup>	191	78	Shah <i>et al</i> <sup>[154]</sup>
24	78	Desmet <i>et al</i> <sup>[29]</sup>	108	64	Suzuki <i>et al</i> <sup>[85]</sup>	192	24	Volman <i>et al</i> <sup>[155]</sup>
25	65	Desmet <i>et al</i> <sup>[29]</sup>	109	88	Teraoka <i>et al</i> <sup>[86]</sup>	193	68	Salemi <i>et al</i> <sup>[156]</sup>
26	71	Desmet <i>et al</i> <sup>[29]</sup>	110	60	Hara <i>et al</i> <sup>[87]</sup>	194	50	Coutance <i>et al</i> <sup>[157]</sup>
27	48	Desmet <i>et al</i> <sup>[29]</sup>	111	89	Kurisu <i>et al</i> <sup>[88]</sup>	195	66	Parker <i>et al</i> <sup>[158]</sup>
28	66	Desmet <i>et al</i> <sup>[29]</sup>	112	77	Kurisu <i>et al</i> <sup>[88]</sup>	196	81	Oe <i>et al</i> <sup>[159]</sup>
29	52	Desmet <i>et al</i> <sup>[29]</sup>	113	73	Verberne <i>et al</i> <sup>[89]</sup>	197	68	Fazal <i>et al</i> <sup>[160]</sup>
30	48	Desmet <i>et al</i> <sup>[29]</sup>	114	60	Subramanyam <i>et al</i> <sup>[90]</sup>	198	46	Afonso <i>et al</i> <sup>[161]</sup>
31	45	Desmet <i>et al</i> <sup>[29]</sup>	115	41	Sanchez-Recalde <i>et al</i> <sup>[91]</sup>	199	38	Afonso <i>et al</i> <sup>[161]</sup>
32	66	Desmet <i>et al</i> <sup>[29]</sup>	116	41	Barrales-Villa <i>et al</i> <sup>[92]</sup>	200	52	Afonso <i>et al</i> <sup>[161]</sup>
33	57	Desmet <i>et al</i> <sup>[29]</sup>	117	60	Fuse <i>et al</i> <sup>[93]</sup>	201	54	Sacco <i>et al</i> <sup>[162]</sup>
34	60	Desmet <i>et al</i> <sup>[29]</sup>	118	80	Kawano <i>et al</i> <sup>[94]</sup>	202	73	Daly <i>et al</i> <sup>[163]</sup>
35	69	Desmet <i>et al</i> <sup>[29]</sup>	119	63	Wong <i>et al</i> <sup>[95]</sup>	203	55	Jabiri <i>et al</i> <sup>[164]</sup>
36	41	Manivannan <i>et al</i> <sup>[30]</sup>	120	54	Kimura <i>et al</i> <sup>[96]</sup>	204	58	Madaria Marijuan <i>et al</i> <sup>[165]</sup>
37	60	Prasad <i>et al</i> <sup>[31]</sup>	121	77	Varela <i>et al</i> <sup>[97]</sup>	205	50	Traullé <i>et al</i> <sup>[166]</sup>
38	65	Chandrasegaram <i>et al</i> <sup>[32]</sup>	122	55	Elkhateeb <i>et al</i> <sup>[98]</sup>	206	32	D'Amato <i>et al</i> <sup>[167]</sup>
39	84	Wang <i>et al</i> <sup>[33]</sup>	123	59	Kaushik <i>et al</i> <sup>[99]</sup>	207	44	Artukoglu <i>et al</i> <sup>[168]</sup>
40	73	Wani <i>et al</i> <sup>[34]</sup>	124	53	Uechi <i>et al</i> <sup>[100]</sup>	208	85	Shah <i>et al</i> <sup>[169]</sup>
41	54	Wani <i>et al</i> <sup>[34]</sup>	125	67	To <i>et al</i> <sup>[101]</sup>	209	61	Crivinel <i>et al</i> <sup>[170]</sup>
42	63	Wani <i>et al</i> <sup>[34]</sup>	126	72	To <i>et al</i> <sup>[101]</sup>	210	55	Lateef <sup>[171]</sup>
43	70	Schmidt <i>et al</i> <sup>[35]</sup>	127	46	Mehta <i>et al</i> <sup>[102]</sup>	211	70	Potter <i>et al</i> <sup>[172]</sup>
44	46	Zaman <i>et al</i> <sup>[36]</sup>	128	63	Oomura <i>et al</i> <sup>[103]</sup>	212	73	Agarwal <i>et al</i> <sup>[173]</sup>
45	73	Meimoun <i>et al</i> <sup>[37]</sup>	129	27	Volz <i>et al</i> <sup>[104]</sup>	213	72	Opolski <i>et al</i> <sup>[174]</sup>
46	22	Sasaki <i>et al</i> <sup>[38]</sup>	130	79	Miyazaki <i>et al</i> <sup>[105]</sup>	214	67	Y-Hassan <i>et al</i> <sup>[175]</sup>
47	86	Surapaneni <i>et al</i> <sup>[39]</sup>	131	83	Akashi <i>et al</i> <sup>[106]</sup>	215	87	Kurisu <i>et al</i> <sup>[176]</sup>
48	24	Park <i>et al</i> <sup>[40]</sup>	132	81	Wissner <i>et al</i> <sup>[107]</sup>	216	78	Kurisu <i>et al</i> <sup>[176]</sup>
49	85	Cherian <i>et al</i> <sup>[41]</sup>	133	47	Papanikolaou <i>et al</i> <sup>[108]</sup>	217	70	Gotyo <i>et al</i> <sup>[177]</sup>
50	41	Lee <i>et al</i> <sup>[42]</sup>	134	62	Bonnemeier <i>et al</i> <sup>[109]</sup>	218	79	Singh <i>et al</i> <sup>[178]</sup>
51	30	Lee <i>et al</i> <sup>[42]</sup>	135	60	Haghi <i>et al</i> <sup>[110]</sup>	219	44	Núñez <i>et al</i> <sup>[179]</sup>
52	89	Korlakunta <i>et al</i> <sup>[43]</sup>	136	78	Rau <i>et al</i> <sup>[111]</sup>	220	62	Núñez <i>et al</i> <sup>[179]</sup>
53	69	Magri <i>et al</i> <sup>[44]</sup>	137	53	Dahdouh <i>et al</i> <sup>[112]</sup>	221	52	Núñez <i>et al</i> <sup>[179]</sup>
54	65	Rahman <i>et al</i> <sup>[45]</sup>	138	69	Moriya <i>et al</i> <sup>[113]</sup>	222	69	Núñez <i>et al</i> <sup>[179]</sup>
55	63	Khallafi <i>et al</i> <sup>[46]</sup>	139	44	Hasdemir <i>et al</i> <sup>[114]</sup>	223	69	Núñez <i>et al</i> <sup>[179]</sup>
56	75	Demirelli <i>et al</i> <sup>[47]</sup>	140	53	Mariano <i>et al</i> <sup>[115]</sup>	224	29	Jayaraman <i>et al</i> <sup>[180]</sup>
57	75	Latib <i>et al</i> <sup>[48]</sup>	141	36	Sun <i>et al</i> <sup>[116]</sup>	225	71	Carvalho <i>et al</i> <sup>[181]</sup>
58	58	Altman <i>et al</i> <sup>[49]</sup>	142	75	Dandel <i>et al</i> <sup>[117]</sup>	226	78	Guttormsen <i>et al</i> <sup>[182]</sup>
59	65	Bagga <i>et al</i> <sup>[50]</sup>	143	65	Ionescu <i>et al</i> <sup>[118]</sup>	227	53	Mrdovic <i>et al</i> <sup>[183]</sup>
60	61	Buchholz <i>et al</i> <sup>[51]</sup>	144	16	Maruyama <i>et al</i> <sup>[119]</sup>	228	84	Auer <i>et al</i> <sup>[184]</sup>
61	61	Zhou <i>et al</i> <sup>[52]</sup>	145	70	Sato <i>et al</i> <sup>[120]</sup>	229	64	Auer <i>et al</i> <sup>[184]</sup>
62	74	Mittal <i>et al</i> <sup>[53]</sup>	146	63	Shah <i>et al</i> <sup>[121]</sup>	230	64	Auer <i>et al</i> <sup>[184]</sup>
63	47	Kim <i>et al</i> <sup>[54]</sup>	147	62	Lee <i>et al</i> <sup>[122]</sup>	231	82	Auer <i>et al</i> <sup>[184]</sup>
64	60	Doesch <i>et al</i> <sup>[55]</sup>	148	67	Merchant <i>et al</i> <sup>[123]</sup>	232	63	Arslan <i>et al</i> <sup>[185]</sup>
65	66	Lopes <i>et al</i> <sup>[56]</sup>	149	86	Merchant <i>et al</i> <sup>[123]</sup>	233	66	Arslan <i>et al</i> <sup>[185]</sup>
66	64	Lopes <i>et al</i> <sup>[56]</sup>	150	76	Merchant <i>et al</i> <sup>[123]</sup>	234	70	Arslan <i>et al</i> <sup>[185]</sup>
67	76	Lopes <i>et al</i> <sup>[56]</sup>	151	42	Merchant <i>et al</i> <sup>[123]</sup>	235	71	Arslan <i>et al</i> <sup>[185]</sup>

68	58	Lopes <i>et al</i> <sup>[56]</sup>	152	76	Nault <i>et al</i> <sup>[124]</sup>	236	76	Barriaes Vila <i>et al</i> <sup>[186]</sup>
69	51	Lopes <i>et al</i> <sup>[56]</sup>	153	62	Nault <i>et al</i> <sup>[124]</sup>	237	78	Barriaes <i>et al</i> <sup>[186]</sup>
70	63	Sealove <i>et al</i> <sup>[57]</sup>	154	71	Novo <i>et al</i> <sup>[125]</sup>	238	70	Barriaes <i>et al</i> <sup>[186]</sup>
71	82	Inoue <i>et al</i> <sup>[58]</sup>	155	68	Blázquez <i>et al</i> <sup>[126]</sup>	239	74	Guardado <i>et al</i> <sup>[187]</sup>
72	25	Maréchaux <i>et al</i> <sup>[59]</sup>	156	74	Ramanath <i>et al</i> <sup>[127]</sup>	240	45	Cho <i>et al</i> <sup>[188]</sup>
73	77	Arias <i>et al</i> <sup>[60]</sup>	157	70	Biswas <i>et al</i> <sup>[128]</sup>	241	68	Gallego Page <i>et al</i> <sup>[189]</sup>
74	76	Vasconcelos Filho <i>et al</i> <sup>[61]</sup>	158	61	Preti <i>et al</i> <sup>[129]</sup>	242	64	Sousa <i>et al</i> <sup>[190]</sup>
75	61	Margey <i>et al</i> <sup>[62]</sup>	159	59	Selke <i>et al</i> <sup>[130]</sup>	243	68	Jakobson <i>et al</i> <sup>[191]</sup>
76	67	Purvis <i>et al</i> <sup>[63]</sup>	160	74	Alves <i>et al</i> <sup>[131]</sup>	244	49	Jakobson <i>et al</i> <sup>[191]</sup>
77	59	Bilan <i>et al</i> <sup>[64]</sup>	161	83	Yeh <i>et al</i> <sup>[132]</sup>	245	74	Otomo <i>et al</i> <sup>[192]</sup>
78	53	Lentschener <i>et al</i> <sup>[65]</sup>	162	68	Kurisu <i>et al</i> <sup>[133]</sup>	246	75	Otomo <i>et al</i> <sup>[192]</sup>
79	61	Kyuma <i>et al</i> <sup>[66]</sup>	163	57	Rotondi <i>et al</i> <sup>[134]</sup>	247	55	Gomes <i>et al</i> <sup>[193]</sup>
80	76	Kyuma <i>et al</i> <sup>[66]</sup>	164	84	Guevara <i>et al</i> <sup>[135]</sup>	248	61	Furushima <i>et al</i> <sup>[194]</sup>
81	76	Kyuma <i>et al</i> <sup>[66]</sup>	165	69	Ukita <i>et al</i> <sup>[136]</sup>	249	84	Sakai <i>et al</i> <sup>[195]</sup>
82	81	Figueredo <i>et al</i> <sup>[67]</sup>	166	73	van de Donk <i>et al</i> <sup>[137]</sup>	250	64	Hakeem <i>et al</i> <sup>[196]</sup>
83	60	Naganuma <i>et al</i> <sup>[68]</sup>	167	66	Mawad <i>et al</i> <sup>[138]</sup>			
84	61	Láinez <i>et al</i> <sup>[69]</sup>	168	90	Xu <i>et al</i> <sup>[139]</sup>			

**Table 5** Frequency of the main complaints reported in the cases studie

Main complaint	Presentation frequency (%)
Chest pain	58.80
Dyspnea	30.00
Hypotension	8.40
Nausea and/or vomiting	8.00
Syncope	6.40
Palpitations	5.20
Asymptomatic	4.80
Loss consciousness	5.20
Headache	3.60
Epigastric pain	2.00
Dizziness	2.00
Weakness	2.00
Cough	1.60
Back pain	1.60
Pedal edema	1.20
Seizure	0.80
Othersa	0.40

a physical stressor is by far the most common stressor reported in TC patients. Emotional stressors are reported in a quarter of all cases and can be as serious as the death of a relative<sup>[12]</sup>; they may also be less serious, such as watching a soccer team losing<sup>[13]</sup>. The asymptomatic presentations include patients undergoing anesthesia<sup>[14]</sup> and/or medical procedures, for example, tracheal intubations<sup>[15]</sup>. In these cases, the lack of symptoms can occur due to the sedation.

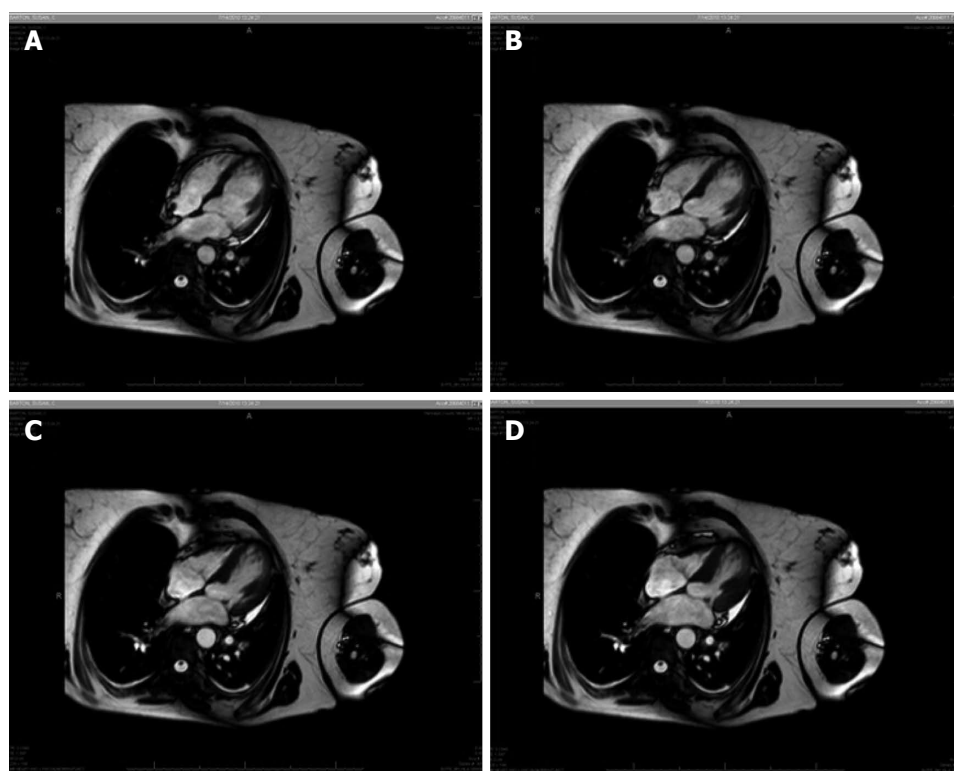
The chief complaint of the TC patients varied, depending on the causative factor, the trigger stressor and the presentation of each case. TC presents as an ACS; in the latter, the most common clinical presentation is chest pain and the second is dyspnea; this suggests that chest pain and dyspnea will be the most common presentation of stress cardiomyopathy<sup>[16]</sup>. In this study, chest pain was the most common initial symptom of the cases presented, and dyspnea was the second most common symptom. Hypotension and cardiopulmonary arrest were relatively common findings, most likely because of the severity of presentation in those patients. Furthermore, the initial

symptoms of TC are often related to the factors causing stress cardiomyopathy. For example, a patient with a seizure<sup>[17,18]</sup> or a stroke<sup>[19]</sup> can only present neurological signs and symptoms.

A very important tool used by physicians in emergency departments and hospital settings to evaluate chest pain, ACS and preoperative patients is the electrocardiogram, which is very easy to perform and is associated with very low cost. Although percutaneous coronary intervention and CMRI are also sometimes useful tools, and the initial suspicion of the TC is usually confirm by echocardiography; it is very important for physicians to know how the TC present in terms of electrocardiography because these findings, together with the patient's clinical characteristics, should orient the physician to consider this syndrome as a differential diagnosis.

Notably, the definitive diagnosis of TC is confirmed by echocardiographic follow-up performed days or weeks after the initial presentation and showing normalization of the wall motion and left ventricular abnormalities. The CMRI has demonstrated value in the evaluation and follow-up of patients with TC; however, the test of choice is the echocardiography due to its low cost and accessibility<sup>[20,21]</sup> (Figure 3).

Changes in the ST segment of the ECG were the most common finding in all cases; these changes are typical of the presentation of ACS and are most likely the reason for the initial management of most TC cases as ACS<sup>[22,23]</sup>. Changes in the T wave are the second most common finding in the study population. Again, changes in the T wave are very common in acute myocardial ischemia and infarction<sup>[23]</sup>, explaining the frequent initial diagnosis of ACS in patients with TC. Notably, for some authors, T wave changes are the most common findings among TC patients<sup>[24]</sup>. The QT interval is prolonged in approximately 10% of patients, a substantially high incidence. There is perhaps a relationship between the QT interval measurement and TC; there is a need for more research into this possibility. The ischemic heart can present with increased QT dispersion, but this observation has not yet been proven to have any practical useful-



**Figure 3** Cardiac magnetic resonance imaging for Takotsubo cardiomyopathy. A: Diastole: both ventricles are distended and full of blood; B and C: Systole: both ventricles contracting; D: End of systole: the right ventricle shows a normal pattern, while the left ventricle has a ballooning shape.

ness<sup>[25]</sup>. For the physician, it is important to know that a small percentage (approximately 6%) of TC cases present with a normal ECG during admission. There were also a few cases of multiple presentations in the study; ventricular tachycardia or ventricular fibrillation, for example, can hide the expected electrocardiographic changes.

Among the ST segment changes, ST segment elevation was the most common finding, accounting for 90% of the ST changes. It is the most common presentation of a STEMI, and in this study it occurred in more than half of all cases. Although it was present in almost 10% of incidences, ST depression was not very prominent finding; in half of the cases in which it occurred, it was accompanied by other major findings such as ST segment elevation. Other ST segment presentations, such as flattened ST segments, were not commonly found in the initial ECG at admission.

T wave changes showed a distribution similar to that of ST segment changes. The incidence of the T wave inversion was very high, approximately 92% of all T wave changes. This pattern is very common in the ischemic heart. In fact, in this study, overall T wave presentation occurred in almost one third of the patients, a very significant number. When this type of electrocardiographic change is present, TC should be considered a probable diagnosis. Other T wave presentations, such as hyperacute T wave, flattened T wave and nonspecific changes, very uncommonly presented as the only finding in the ECG.

The anatomical site most commonly affected by stress cardiomyopathy is the left ventricle, but there have been cases with right ventricular akinesis<sup>[7]</sup> and even cases in

which both ventricles are affected<sup>[10]</sup>. Electrocardiographic presentations of this syndrome are highly variable. In this study, it was documented that in TC the ECG changes in frequency starting from the anterior region as the most commonly affected, followed by the lateral, the inferior and finally the septal region. The clinician must remember these patterns when making a differential diagnosis and never rule out the possibility of a TC based on the ECG.

During the initial presentation of TC patients, there is a very high prevalence of serum cardiac marker elevation, making this diagnosis consistent with ACS (specifically STEMI and NSTEMI). Some authors have indicated that the distinction between TC and ACS is reflected in the level of cardiac enzyme elevation<sup>[26,27]</sup>. These findings contain important information that should raise the physician's clinical suspicions regarding this syndrome.

## COMMENTS

### Background

Takotsubo syndrome has the same presentation as acute coronary syndrome (ACS) but is usually associated with history of a trigger stressor, which can be emotional or physical. Although a number of ideas have been proposed to explain its pathophysiology, there is evidence that catecholamines and estrogen play an important role. Many physicians do not readily think of Takotsubo cardiomyopathy (TC) when presented with a patient with cardiac chest pain or even with a ST segment elevation myocardial infarction (STEMI), and other physicians are not even aware of the existence of the syndrome. For this reason, it is likely that many patients are misdiagnosed. The presentation similarities of TC with ACS include symptoms, electrocardiogram (ECG) changes and serum cardiac marker levels.

### Research frontiers

In some health facilities, the initial management of a STEMI is based on intra-

venous fibrinolysis, which is performed without confirmation of coronary artery obstruction using percutaneous coronary intervention (PCI). Takotsubo patients can have the same presentation as STEMI patients but normal or clean coronary arteries. This and other evidence makes the PCI management of choice in STEMI patients.

### Innovations and breakthroughs

Although this article does not focus on patient prognosis, it is important that future research addresses the relationship between initial presentation/initial electrocardiographic changes and prognosis. Cardiac magnetic resonance imaging is a new tool that may prove useful in both initial diagnosis and noninvasive follow-up of this syndrome.

### Applications

The results of the study are important in clinical practice. They can help inform physicians to include TC in the differential diagnosis of patients who present to the emergency department with cardiac chest pain.

### Terminology

TC is a condition that has acquired many names over time; these include Takotsubo syndrome, stress cardiomyopathy, apical ballooning syndrome and TC. ACS is a term applied to situations in which the blood supplied to the heart muscle is suddenly blocked; it includes unstable angina, STEMI and non-ST segment elevation myocardial infarction. Troponin and creatinine kinase (CK-MB) are cardiac markers used to classify and assist with the diagnosis of myocardial infarction. CK-MB is an isoenzyme composed of a muscle portion and a brain portion; it is very specific for myocardial muscle.

### Peer review

It is necessary for every physician to know the clinical presentation of TC in its early stages. As mentioned above, this entity should be included in the differential diagnosis of "ACS" patients. The present work represents an interesting examination of value for clinical practice and stresses an important issue in the field of cardiology.

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