

Takotsubo cardiomyopathy: an overlooked cause of chest pain

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ABSTRACT

Takotsubo cardiomyopathy (TTC), also known as apical ballooning syndrome, broken heart syndrome, or stress-induced cardiomyopathy, is defined as a transient disturbance of the left ventricle, which is quite often associated with electrocardiographic abnormalities that may mimic acute myocardial infarction. The syndrome is also characterized by a mild alteration of cardiac biomarkers in absence of coronary blood flow obstruction on the coronariography. Clinical presentation is often manifested by angina, dyspnea, syncope, and arrhythmias. Peculiarly, the left ventricle takes the form of “tako-tsubo” (a Japanese word for “octopus trap”) on the imaging workup. The authors report the case of a post-menopausal, hypertensive, dyslipidemic and type-II diabetic woman admitted at the emergency service with acute chest pain post physical exertion. Electrocardiogram showed signs of ischemia and myocardial necrosis markers were mildly increased. Echocardiography and ventriculography showed apical and mid-ventricular akinesia, with mild atherosclerotic coronary lesions. Thus diagnostic workup and the outcome followed the diagnostic criteria for TTC. The authors called attention to the potential of overlooking this diagnosis, since this syndrome is still not widely recognized.

Keywords

Takotsubo Cardiomyopathy; Ventricular Dysfunction, Left; Heart Failure; Catecholamines.

INTRODUCTION

Takotsubo cardiomyopathy (TTC) – also called apical ballooning syndrome, broken heart syndrome, or stress induced cardiomyopathy – is defined as transient left ventricular (LV) dysfunction and is frequently associated with electrocardiographic changes mimicking an acute myocardial infarction (AMI). The syndrome is also characterized by a mild release of cardiac biomarkers in the absence of coronary obstructive disease, and the left ventricle morphology of “tako-tsubo” (a Japanese word for “octopus trap”) on the imaging examinations.^{1,2} In 2006, the American Heart Association labeled the disease as an acquired cardiomyopathy.³

Approximately 1.5-2.2% of all patients initially diagnosed with AMI actually represent cases of TTC. This rate augments 6-12% when only cases of anterior myocardial infarction are considered. Up to 90% of patients with TTC are women with a higher incidence of occurrence after menopause.⁴⁻⁶ Considering the women who are admitted with the suspicion of acute coronary syndrome (ACS), 5.9-7.5% are in fact TTC cases.⁷ However, the true estimative remains obscure due to limitations the diagnostic workup.³

The pathophysiology of the disease is still not completely understood. It has been postulated that TTC is a multifactorial disease in which a number of

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factors are involved besides the individual vulnerability. However, the most widely accepted mechanism refers to catecholamine-mediated cardiotoxicity. According to this theory, high levels of epinephrine promote the increased intracellular influx of calcium, resulting in myocardial and coronary hyperactivity, and consequently transient LV dysfunction.^{3,8} In this setting, TTC has been reported to occur during dobutamine infusion for diagnostic purposes.⁹ Also, pheochromocytoma can precipitate TTC events.¹⁰ Epicardial arteries vasospasm, functional abnormalities of the coronary microvasculature, neurogenic and psychiatric mechanisms, hormonal changes, age, female gender, and genetics are other mechanisms also associated with TTC physiopathogeny.^{2,8,10}

The clinical picture can be diverse, ranging from mild and non-specific features to a life-threatening presentation.¹⁰ However, chest pain (67.8%), dyspnea (17.8%), cardiogenic shock (4.2%), and ventricular fibrillation (1.5%) are the most typical and most frequent clinical presentations.^{2,4}

Electrocardiographic changes are characterized by ST segment elevation in more than 80% of cases, followed by diffuse T-wave inversion and QT widening. Nevertheless, non-specific electrocardiographic changes – or even a normal ECG – may be present early in the initial workup.¹⁰ Pathological Q waves are present in 6-31% of patients after 1-3 days.^{2,10} According to Kosuge et al.,¹¹ the presence of positive T waves on aVR and the lack of negative T waves on V1 exhibited 94.5% of accuracy in the diagnosis of TTC.

In most patients, echocardiography usually shows the LV contractile dysfunction followed by subsequent normalization. Angiography reveals typically normal or moderate irregularities of the coronary arteries inconsistent with the observed impairment of cardiac contractility. Coronary angiography remains the gold standard for diagnosing TTC while it is permitted to rule out the diagnosis of ACS. The contrasted ventriculography reveals apical and mid-ventricular akinesia or dyskinesia with normal or increased basal region contraction, providing the characteristic hourglass shape. The ventricular contractile dysfunction reverses within a few days or weeks, without the need of invasive therapeutic measures.^{2,4,10}

The clinical presentation of TTC is generally indistinguishable from ACS, therefore it may be

classified as a type of ACS.¹⁰ However, cardiac biomarkers, such as troponin, creatine kinase, and creatine kinase muscle-brain fraction, usually show a slight elevation, reaching maximum values in the very early stage of clinical presentation.^{2,4} Brain natriuretic peptide values are often notably increased compared to patients with AMI and often reach the peak values after 24 hours,¹² and its decline to normal values may take up to 3 months.¹³

Although TTC has a good long-term prognosis, the mortality rate has been reported up to 2%.¹⁰ The most common complications are: cardiogenic shock (6.5%), ventricular thrombus (3.8%), and heart failure (3.8%);^{1,2} and less commonly, arrhythmias, mitral regurgitation, and cardiac rupture.¹⁰

CASE REPORT

A 64-year-old female patient presented at the emergency room complaining of intense acute chest pain described as a squeezing sensation at the precordial region, radiating into the jaw, accompanied by dyspnea, nausea, vertigo, and diaphoresis. Symptoms started after moderate physical exertion (stair climbing). She was previously diagnosed with type II diabetes mellitus, hypertension, and dyslipidemia, and was regularly taking metformin, telmisartan, and atenolol. At the admittance, she was alert and slightly pale. Her pulse was regular and 68 beats per minute; her blood pressure was 120/80 mm Hg and room air oximetry was 95%. Examination of her heart, lungs, and abdomen was unremarkable. Initial laboratory workup disclosed a normal peripheral blood cell count; potassium was 3.2 mEq/L (reference value [RV] 3.5-5.5 mEq/L); creatine kinase muscle-brain fraction (CK-MB)–mass was 19.7 ng/mL (RV > 5.1 ng/mL); and troponin I was 0.75 ng/mL (RV: 0.1-1.5 ng/mL = moderate risk).

On admission, the electrocardiogram revealed T wave inversion in the inferior and lateral cardiac walls (Figure 1), which became more pronounced on the subsequent day (Figure 2). Bidimensional Doppler echocardiography showed normal dimensions of the aorta and right chambers; the latter were functionally normal. The left atrium exhibited a slight enlargement. The left ventricle presented normal dimensions and the ejection fraction was 76%, although the akinesia of

the apex cordis, septum and inferior wall was evident (Figure 3). Cardiac contractility dysfunction returned to normal on the fifth day of hospitalization.

The coronary angiography disclosed coronary circulation without major obstructions. The left main coronary artery, the anterior descending artery, and the circumflex artery, as well as the right coronary artery, showed slight parietal irregularities. The first

two diagonal branches, the marginal branches, and the posterior descending and posterior ventricular arteries also exhibited slight parietal irregularities. The third diagonal branch presented a lesion of 50% at the ostium and at the medium third portion of the anterior descending artery; a myocardial bridge was present. The ventriculography showed apical and mid-ventricular akinesia (Figure 4) [video]. The ascending



Figure 1. Electrocardiogram, performed at admission, showing regular sinus rhythm, cardiac frequency of 75 beats per minute, PRi = 0.12 msec, and inversion of T wave (sign of ischemia) in the inferior and lateral cardiac walls.

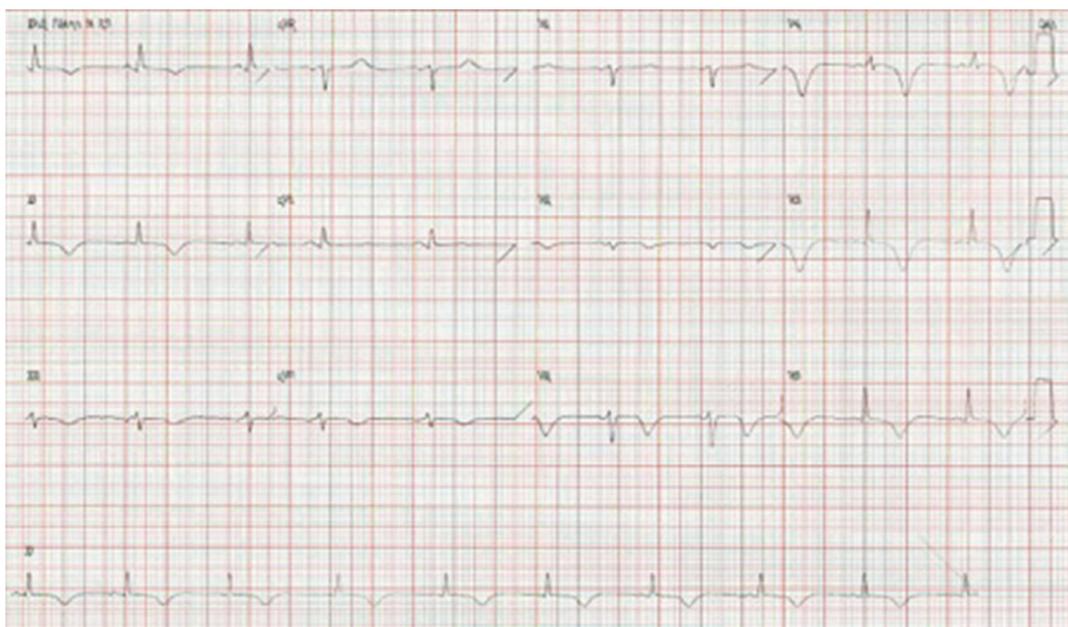


Figure 2. Electrocardiogram, performed on the second day of hospitalization, showing enhancement of the ST wave inversion, mainly in the precordial leads.

aorta was morphological, and the mitral and aortic valves were competent.

The patient was prescribed angiotensin converting enzyme, β -blocker, acetylsalicylic acid, a statin and a

nitrate. The outcome was uneventful and the patient was discharged on the seventh day of hospitalization.

DISCUSSION

Chest pain is one of the commonest complaints in every medical facility's emergency rooms and in the current units of chest pain. An estimated five to eight million patients with chest pain or other symptoms suggestive of acute myocardial ischemia are seen annually in emergency rooms in the USA.¹⁴ This number represents 5-10% of all emergency care in that country. About 1.2 million patients are diagnosed with AMI besides others that are diagnosed with unstable angina. However, about half to two-thirds of patients hospitalized with chest pain do not end up confirming a cardiac cause for their symptoms, which results in unnecessary spending of \$5-8 billion per year in the USA.¹⁴

Since the Japanese presented the very first description of TTC in 1990,¹⁵ the number of reports increased, and were consequently accompanied by a better knowledge of the clinical features, which include: the transient LV apical ballooning; ventricular wall dyskinesia/akinesia comprising the apical and mid-ventricle walls; the absence of obstructive coronary disease; and ECG changes, such as ST segment elevation or inversion of the T wave¹⁶ similar to the AMI. Therefore, AMI is the main differential diagnosis,



Figure 3. Bidimensional echocardiography, apical 4-chambers focus. Note the systolic shape of the left ventricle with the apical and mid-ventricle akinesia.

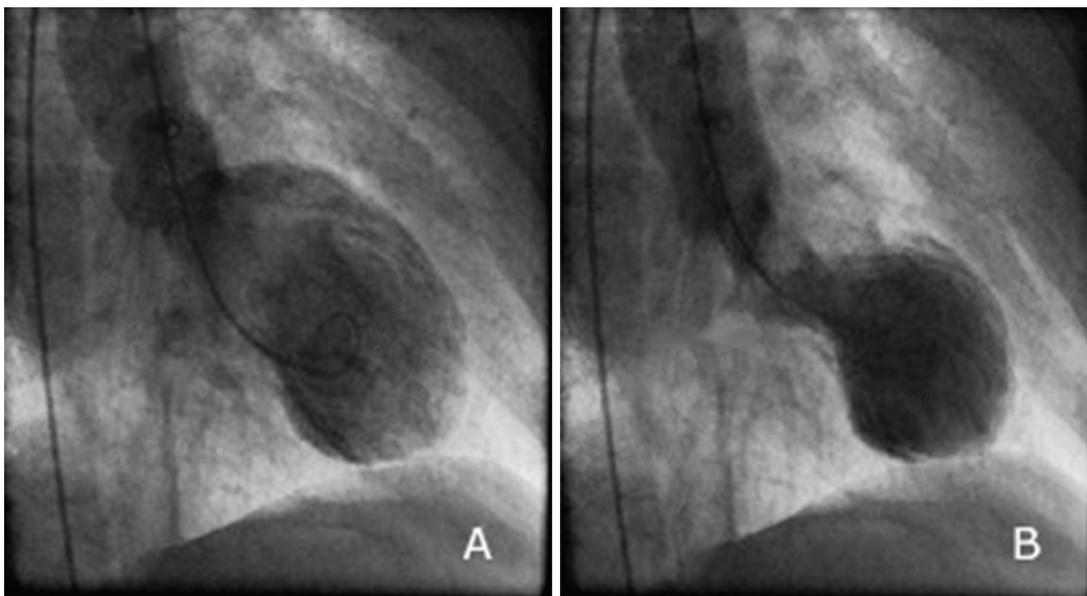


Figure 4. Ventricular angiogram. **A** - Diastole; **B** - Systole; showing the apical and mid-ventricular akinesia. Note the octopus trap vase shape in B.

and the precise diagnosis becomes challenging if echocardiography and coronary angiography are unavailable.

The patient reported herein was admitted at the medical facility where she had presented with chest pain preceded by physical and emotional stress, as well as dyspnea, nausea, diaphoresis, and dizziness. It is known that physical stress (hypertensive crisis, surgery, respiratory distress, neurologic disease, or exacerbations of asthma) or severe emotional stress (e.g. anger, sadness), may precipitate TTC in approximately two-thirds of cases. While some reports note a predominance of emotional trigger factors, others show a predominance of physical stress as precipitant factor.⁵ However, in the remainder of patients, a triggering event cannot be identified. The age of our patient (64 years old) is in accordance with the data of literature, where 85-100% of cases of TTC include patients aged between 62 and 75 years.^{2,4}

Taking into account the prevalence and presence of risk factors for coronary artery disease, our patient's diagnosis was initially considered as ACS. However, after the diagnostic workup, TTC could better elucidate the condition. The electrocardiogram on the first day of admission showed T wave inversion in the inferior and lateral cardiac walls. However, such changes (besides the presented cardiac biomarker alterations) are, unfortunately, nonspecific for this specific diagnosis. Electrocardiographic alterations show poor accuracy in differentiating SCA and TTC, when analyzed separately.¹⁷

Meanwhile, a creatine kinase-mass of 19.7 ng/mL (RV: positive > 5.1ng/mL) and troponin I of 0.75 ng/mL (RV: 0.1-1.5 ng /mL, indicating moderate risk for heart damage) corroborate to a probable acute myocardial insult. Most patients with TTC exhibit a mild elevation of troponin I, differently to the kinetics of this biomarker in the typical transmural AMI. Troponin I levels above 15 ng/mL are unlikely to be associated with the diagnosis of TTC.^{17,18} In addition, the mild elevation of the cardiac biomarkers is disproportionately small for the extent of cardiac involvement seen on imaging studies.

The echocardiogram, in our case, revealed normal LV dimensions, preserved systolic function, the presence of apical and mid-ventricular akinesia, and diastolic dysfunction. In most cases of TTC,

echocardiography is performed during the acute phase (within the first 72 hours) showing findings consistent with apical dyskinesia or akinesia, and abnormalities of mid-ventricular portion contraction.¹⁷

On the fifth day of evolution, our patient was submitted to another echocardiogram, which showed normalization of the contractility alterations observed in the first examination, corroborating TTC diagnosis. In most cases, full normalization of LV function and wall motion abnormalities take from 4 to 8 weeks while a few of them can take longer.⁵

The coronariography of TTC is often normal or shows only mild irregularities, and typically, obstructive coronary lesions are infrequently found.^{1,4} Moreover, the left ventriculography showed the presence of apical and mid-ventricular akinesia, which is inconsistent with any coronary artery obstruction. However, the finding of concomitant coronary artery disease does not exclude the diagnosis of TTC.

In our case, a myocardial bridge was found at the left anterior descending artery, and we could not disregard such a finding, since currently it has been suggested that this anatomic variation is implicated in the pathophysiological mechanisms of TTC.¹⁹⁻²¹

The outcome was characterized by clinical improvement and early normalization of myocardial injury biomarkers.

The treatment of choice for TTC is based on clinical judgment and hemodynamic support measures, including the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, aspirin, statins, and diuretics, since ACS remains an important differential diagnosis in the emergency room.¹⁰ The use of thrombolytic agents is systematically avoided, since TTC etiopathogenesis is other than thrombosis.²² Anticoagulation can be indicated in case of the presence of ventricular thrombus and/or systemic embolism.^{23,24} In case of cardiogenic shock, catecholamine as inotropic agents should be considered. An alternative in these cases may be the calcium channel sensitizer, levosimendan, although it is not yet universally approved. Currently, there are no randomized controlled trials on the treatment of TTC.¹⁰

In 2007, the Mayo Clinic proposed TTC diagnostic criteria, which included electrocardiographic abnormalities (ST segment elevation with T wave

inversion); transient abnormalities of the apical and mid-ventricular wall (akinesia or dyskinesia); absence of coronary obstruction or acute rupture of atherosclerotic plaque; and the absence of recent and significant head trauma, intracranial bleeding, pheochromocytoma, myocarditis, and evidence of hypertrophic cardiomyopathy.²⁵ In our case, these criteria were fully met and the suspicion of TTC could be finally confirmed. However, only the Japanese criteria were based on a nationwide consensus.¹

The difficulties for the diagnosis of TTC are centered on the availability of the laboratory and imaging examinations, on the close similarity with the diagnosis of ACS, and the lack of suspicion. In the case report herein, Doppler echocardiography was the cornerstone in raising the suspicion of this diagnosis, which was later confirmed by the coronary angiography, the favorable clinical outcome, and the normalization of ventricular contractility disturbances.

We emphasize to health professionals, especially those working in emergency units, that they consider TTC in the differential diagnosis of chest pain. Unfortunately, this diagnosis will remain challenging and will be eventually overlooked where echocardiogram and angiography are not available. In many cases, the patients will naturally present a favorable recovery because the syndrome is transient and benign in the majority of cases.

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