

Stress-Related Cardiomyopathy or Tako-Tsubo Syndrome: Current Concepts

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SUMMARY

Tako-Tsubo syndrome, also referred to as stress-related cardiomyopathy or apical ballooning syndrome is a condition that has been recently described mimicking an acute coronary syndrome in its clinical, analytical, electrocardiographic and echocardiographic characteristics. The diagnosis is made on the basis of coronary arteries with absence of significant obstruction, a typical left ventricular shape and complete recovery of ventricular function. This condition occurs mostly in post-menopausal women under some form of physical or mental stress. Treatment is empirical and similar to that of acute myocardial infarction, with special attention in the administration of beta blockers and anticoagulation therapy. Although associated complications, such as heart failure, may occur in the acute phase, its clinical course is favorable and recurrence is exceptional. These features, as well as the physiopathology of this syndrome that is becoming more frequent in our environment, are discussed in this review.

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Key words >

Myocardial Infarction – Tako-Tsubo - Heart Failure - Female -Chest Pain

DEFINITION AND CLASIFICATION

Tako-Tsubo syndrome is an acute and reversible cardiomyopathy with symptoms mimicking acute myocardial infarction, increase in biomarkers levels and ischemic electrocardiographic changes. Image tests usually show the characteristic apical ballooning with compensatory hyperkinesis of the basal segments. In some cases left ventricular function is severely depressed and patients may present with Killip class IV (cardiogenic shock). Surprisingly, left ventricular dysfunction usually resolves rapidly after initial presentation; biomarkers are mildly elevated, which is inconsistent with the extension of myocardial affection, and coronary angiography reveals no critical coronary lesions.

The disease occurs in all races and some atypical presentations have been described. Inverted Tako-Tsubo cardiomyopathy is a variant in which the compromise is localized in the inferior or basal segments (Figure 1, C-D); other atypical presentations include involvement of mid-ventricular segments (with normal apex contractility, Figure 1, F-G), of both ventricles, or exclusive involvement of the right ventricle. All forms of presentation have a similar physiopathological substrate. In this review we shall refer to the typical Tako-Tsubo cardiomyopathy. (2-7)

DIAGNOSTIC CRITERIA

Several diagnostic criteria have been described, as those proposed by Abe (8) or by the Mayo Clinic. (9) The later were slightly modified in 2008. (10) All four diagnostic criteria must be met (Table 1).

EPIDEMIOLOGY

The real incidence is uncertain. Apical ballooning is increasingly reported in the literature and recognized in clinical practice as more interventional procedures in the acute setting are performed. (11) Several studies in the United States have estimated that it may account for approximately 1-2% of suspected acute coronary syndromes. (10, 12) A German series and a French study reported an incidence of 0.1-2.3%, and 0.9%, respectively. (13) According to the American Heart Association, approximately 732.000 patients are discharged each year with a diagnosis of myocardial infarction. (14) Thus, the annual incidence in the United States would be of 14000 cases. About 90% of them occur in postmenopausal women. In our series, 85% of patients are women with a mean age of 69 years. (4, 15) Mean age ranges from 58 to 75 years in the published literature, (10, 16); yet it has also been described in very elder subjects and in children. (17)

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Fig. 1. **A.** Left ventriculography during diastole of a typical variant. **B.** Left ventriculography during systole, showing hypercontractility of the basal segments. **C y D.** Atypical variant with compromise of the inferior segments. **E y F.** Mid-ventricular involvement. **A, C, E:** Images during diastole. **B, D, F:** Images during systole.

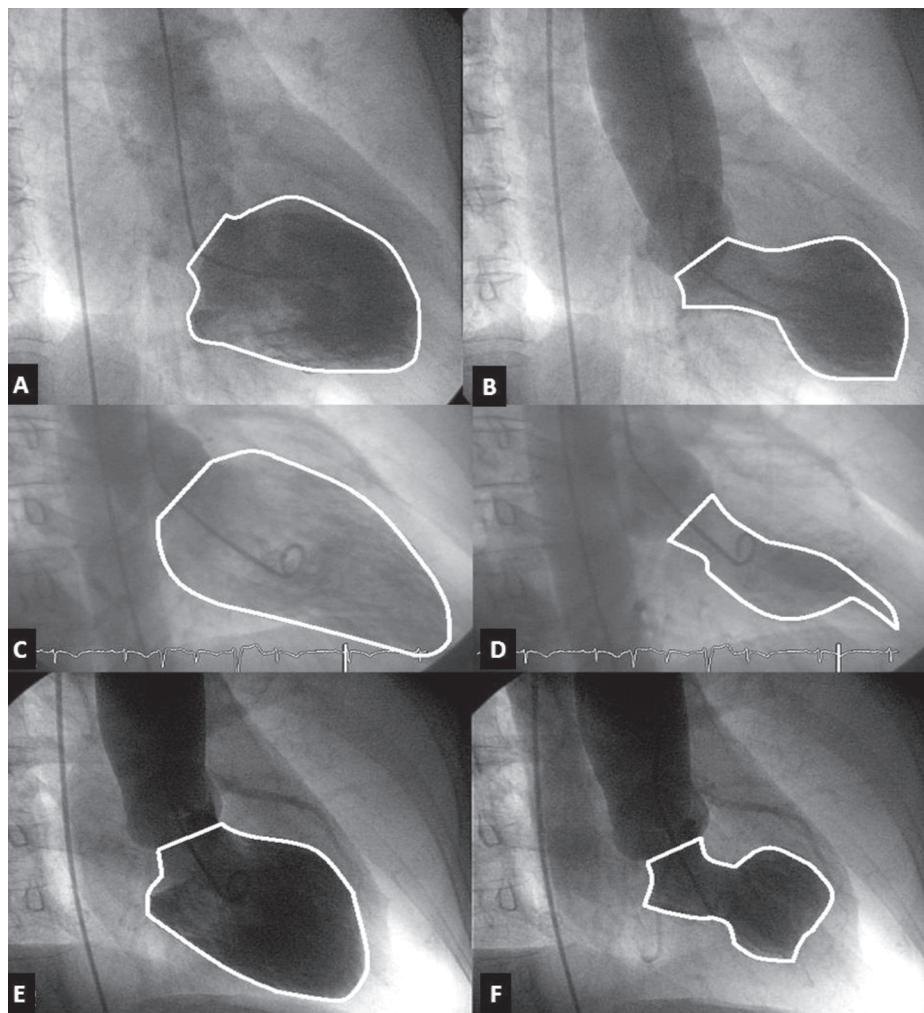


Table 1. Mayo Clinic diagnostic criteria

Mayo Clinic Criteria (2008) for diagnosis of Tako-Tsubo syndrome
1 Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
2 Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3 New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin
4 Absence of pheochromocytoma and myocarditis

Apical ballooning may be detected in patients admitted to the intensive care units with different stress levels; in these cases, the prevalence is greater in men. (18)

Some authors have reported seasonal variations in the incidence of this syndrome, with special predominance in summer (7) or in winter (19); however, we have not been able to confirm this finding in our series. The influence of family history is not clearly established. (20)

CLINICAL PRESENTATION

Chest pain is the most common presenting symptom in 50-60% of cases, characterized as rest angina. Dyspnea, syncope or cardiac arrest are less frequent.

The onset of stress-related cardiomyopathy is typically triggered by intense emotional or physical stress in 7% to 86% of cases (9, 16), and 46.2% in our patients. There was a marked increase in the incidence of Tako-Tsubo cardiomyopathy in Japan in 2004, apparently as a result of the earthquakes. (21) This association makes us believe that increased cardiovascular mortality associated with natural disasters, wars and sports events (as soccer championship) might be related with Tako-Tsubo syndrome. (10, 22) Table 2 describes the specific triggers. (10, 16, 23-25)

Table 2. Triggers associated with stress-induced cardiomyopathy

<p>Emotional stressors</p> <ul style="list-style-type: none"> – Death or disease of a relative – Bad news – Storm – Arguing with social environment – Public speaking – Legal issues – Traffic accident – Surprise party – Financial, gambling or business losses, dismissals – Change of place of residence – Accidental fall with impossibility to sit up
<p>Physical stressors</p> <ul style="list-style-type: none"> – Noncardiac surgery – Pacemaker implant – Any important disease, asthma, sepsis – Intense pain, bone fractures, renal colic, etc. – Postanesthetic recovery – Opioid discontinuation – Nortriptyline overdose – Cocaine, amphetamines or beta adrenergic agents abuse – Stress tests (exercise stress test, dobutamine) – Thyrotoxicosis – Seizures

COMPLEMENTARY TESTS

- *Cardiac biomarkers* present a mild elevation. (7, 10, 26) The prognostic importance of other markers, such as BNP, is doubtful. (27)
- *Electrocardiographic abnormalities* are the most common finding: ST-segment elevation/depression or repolarization anomalies. Two or three days after initial presentation, ST-segment abnormalities revert and T wave inversion may be seen with giant and symmetrical T waves, generally in the precordial leads. At the moment of hospitalization, T-wave inversion is more frequent among westerners while ST-segment elevation is more common among orientals. (2, 28) The electrocardiogram normalizes within a few days but always later than the normalization of left ventricular contraction. The presence of negative T waves is associated with QT interval prolongation; ventricular arrhythmias and *torsade de pointes* are infrequent. (29) Therefore, the electrocardiogram alone is not capable of ruling out myocardial infarction. (10)
- *Transthoracic echocardiography* demonstrates the initial and reversible contraction abnormalities. (30) It is also useful for the diagnosis of the me-

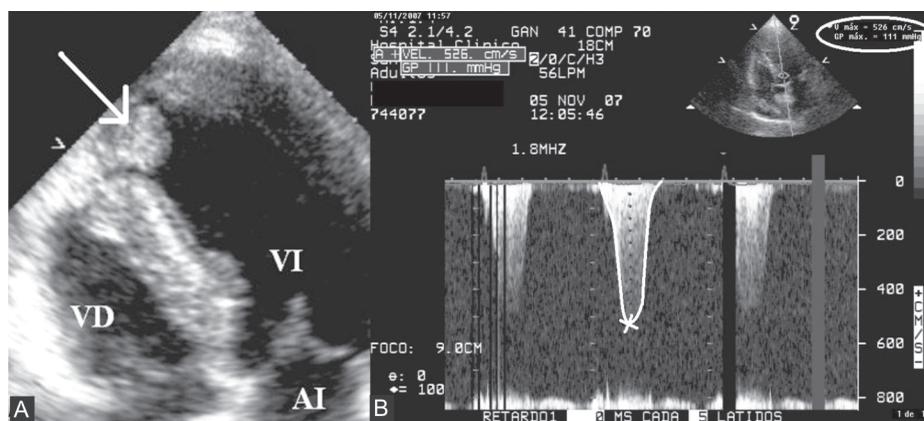
chanical complications (31), which are infrequent, or to quantify the presence of left ventricular outflow tract obstruction (which may be present in 1 out of 5 cases) (32), or mitral regurgitation (10, 33). Echocardiography may also visualize apical thrombus (Figure 2 A), which may develop due to akinesis of the left ventricular apex. Under this circumstance, anticoagulant therapy should be prescribed and maintained until complete clot resolution (generally during the first 3 months).

- *Coronary arteriography and left ventriculography* are needed to confirm the diagnosis. The absence of coronary obstructions > 50% in all major coronary arteries, ulcerated plaques or coronary thrombus corroborate Tako-Tsubo syndrome. (10) Left ventriculography usually shows the characteristic apical ballooning, and recovery of ventricular function is seen if studies are repeated during follow-up. A few studies performed using intravascular ultrasound (IVUS) have not solved the mystery regarding the physiopathology of this syndrome. (34) Despite most series exclude patients with a history of coronary artery disease (CAD), the presence of patients with CAD and one episode of Tako-Tsubo syndrome has been described in the last years, showing that both disease entities are not mutually exclusive. (35) The relation between both diseases is still unclear. (36)
- *Cardiac magnetic resonance imaging* provides precise morphologic and functional information with the added value of the evaluation of the RV. The study does not reveal focal perfusion defects and is an excellent tool for differential diagnosis; the absence of delayed hyperenhancement of the involved regions rules out myocarditis (exclusion criterion). (37, 38) Some authors recommend performing cardiac magnetic resonance imaging in all patients in whom the disease is suspected. (39)
- *SPECT-PET images* evaluate transient ventricular dysfunction and the metabolic activity within the heart. The use of ²⁰¹Tl SPECT images has detected acute perfusion defects that recover completely. In addition, ¹²³I MIBG is also useful to evaluate the uptake of the tracer in the region affected. Positron emission tomography scan has also detected perfusion defects. (44) Other authors have found impaired fatty acid metabolism rather than a disturbed myocardial perfusion. (13)
- *Endomyocardial biopsy* may reveal unspecific and reversible lesions with histological findings similar to those observed in catecholamine excess (subarachnoid hemorrhage, pheochromocytoma). (41)

PHYSIOPATHOLOGY

The hypothesis of multivessel coronary spasm was believed to be responsible of this syndrome; (42) however, using provocative tests, less than 30% of patients experienced multivessel spasm. (16) Several mecha-

Fig. 2. A. Image of an apical thrombus. The image disappeared after normalization of apical dyskinesia and three months of anticoagulant therapy. LV: Left ventricle. RV: Right ventricle. LA: left atrium. **B.** Image of continuous Doppler echocardiography with left ventricular outflow tract obstruction and a gradient of 111 mmHg (cross).



nisms were later proposed, such as myocarditis, non-obstructive plaques disruption with spontaneous thrombolysis, microvascular disturbances, (12) anatomical variations (long course of the left anterior descending coronary artery) (43) left ventricular outflow tract obstruction, (32) sepsis (18, 23) and catecholamine and neuropeptide cardiotoxicity. The latter is the most widely proposed hypothesis that relates to the role of stress in patients with Tako-Tsubo cardiomyopathy and was evaluated in a study that demonstrated that plasma catecholamine levels were markedly higher in patients with stress-related myocardial dysfunction compared with those of patients with Killip class III myocardial infarction. (44) This theory is based on the clinical and pathological relation with emotional (death of relatives, arguing with neighbors), physical (asthma, surgery), or neuromediated stresses (stroke, subarachnoid hemorrhage, brain trauma and pheochromocytoma). (44) The main mechanisms underlying its pathogenesis await further elucidation: coronary spasm of the major epicardial coronary arteries, microvascular spasm with reduction of the coronary flow reserve, endothelial dysfunction or direct myocardial injury (cyclic AMP mediated-calcium overload, free radicals). Lyon et al. have proposed that myocardial affection produced by catecholamines is greatest at the apical myocardium, in which the density of adrenergic receptors is highest, as it has been demonstrated in canine models. (45) For this reason, stress cardiomyopathy is a form of neuromediated myocardial stunning, but with cellular mechanisms different to those caused by transient episodes of ischemia secondary to coronary stenosis. (46) This theory requires further investigation and has been criticized. (47)

The great susceptibility of women has been explained by sex hormones differences between both genders, and also to postmenopausal changes. (10) In fact, in animal models, ovariectomized rats subjected to immobilization stress that received estrogen supplementation were more resistant to the stressor. (48)

Nevertheless, stress-related transient systolic dysfunction is not exclusive of Tako-Tsubo syndrome, as

it may also be seen in other conditions known as stress-induced cardiomyopathies. Briefly, these diseases include intracranial conditions (bleeding, stroke, trauma), pheochromocytoma, neuroblastoma, exogenous intake of catecholamines, beta-adrenergic agonists, cocaine or amphetamines, sepsis, surgery, etc. (23)

TREATMENT

There is no established treatment for patients with Tako-Tsubo cardiomyopathy. However, these patients should be evaluated and treated initially in a manner similar to patients with coronary syndromes. Complications should be treated according to the usual management strategies. Beta blockers should be initiated to antagonize the theoretical deleterious effect of catecholamines. (10) Treatment with carvedilol (a non-cardioselective alpha and beta adrenergic blocker) has not been studied in randomized trials; however, this might be a valid therapeutic option considering the similarity between this syndrome and pheochromocytoma. In patients hemodynamically unstable, intravenous fluid administration, vasoactive drugs and inotropic agents (phenylephrine, levosimendan), (49) might be necessary. In cases of severe circulatory dysfunction, orotracheal intubation, intra-aortic balloon counterpulsation or a ventricular assist device should be considered. (10, 50) Patients who are in shock should undergo urgent echocardiography to determine if left ventricular outflow tract obstruction is present (gradient, Figure 2 B). (10) Anticoagulant agents should be initiated in uncomplicated patients in whom a thrombus is demonstrated, or with severe left ventricular dysfunction (EF \leq 35%) to prevent thromboembolic events. (51)

Therapy with beta blockers can be continued. Some authors recommend annual visits until the natural history of the disease is better known. (10)

PROGNOSIS

Stress-related cardiomyopathy has a favorable prognosis compared to ST-segment elevation or non-ST-

segment elevation myocardial infarction. (12, 16, 37) However, severe complications, such as heart failure (13-23%) or death may occur (Desmet reported one death in a series of 13 patients, 7.7%). (26) In our experience with 39 typical cases, from 2003 to 2007 most patients presented Killip class I (71.8%), while class II, III and IV were less frequent (15.4%, 2.6 and 10.3%, respectively). (4, 15) None of our patients died during hospitalization, and during follow-up (mean 596 months) 2 patients were readmitted due to cardiovascular disorders and 2 other patients died (1 presented dyspnea and sudden death and the other with sepsis). (4, 15) Recurrences are infrequent (3%). (6)

BACKGROUND

Cardiopatía de estrés o síndrome de Tako-Tsubo: conceptos actuales

The popular phrase “to die of sorrow” refers to the death of person who had been very upset or as the consequence of experiencing the death of a relative. In the last years this expression has proved not be figurative. In the early nineties, Sato and Dote described a clinical entity mimicking an acute coronary infarction in its clinical, analytical, electrocardiographic and echocardiographic characteristics. (1) Surprisingly, coronary angiography shows absence of obstructions, and wall motion abnormalities recover completely within a few weeks. This dysfunction is known as Tako-Tsubo syndrome due to the shape on left ventriculography that resembles a tako-tsubo, the Japanese name for octopus traps that fishermen still use to catch octopus (Figure 1, A-B). It is also known as transient apical dyskinesia, broken-heart syndrome or stress-related cardiomyopathy.

Palabras clave > Infarto del miocardio - Tako-Tsubo - Insuficiencia cardíaca - Mujeres - Dolor de pecho

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