Review Article

Stress Cardiomyopathy (Takotsubo)

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Introduction

Takotsubo Cardiomyopathy (CT), also known as stress-induced cardiomyopathy, is a reversible syndrome that usually presents as an acute coronary syndrome, especially in postmenopausal women. The pathophysiology involves multiple factors, including coronary vasospasm, microcirculation dysfunction, catecholaminergic aggression, and sympathetic hyperactivity. The diagnosis of the classic presentation is the presence of a segmental alteration in the form of ballooning or dyskinesia in the antero-septo-apical region of the left ventricle, associated with hyperdynamia of the basal segments, in the absence of obstructive coronary disease that justifies this alteration in contraction. Initially, it was believed that CT was a self-limiting condition with a good prognosis; however, it is currently recognized as a pathology with a high rate of complications and high morbidity and mortality in the short and long term. Even though the first description was made more than 30 years ago, in 1990, by Sato, the etiology and pathophysiology are still not fully defined, and we still do not have an international guideline for standardizing diagnosis and treatment.

Epidemiology

CT is diagnosed in 1% to 3% of acute coronary syndromes and 0.5% to 0.9% of acute ST-segment elevation myocardial infarctions.[1] It is usually underdiagnosed because the clinical presentation resembles acute coronary syndrome. It characteristically has a higher prevalence in postmenopausal women (80-90%), although patients aged < 50 represent about 10% of cases.[2] Among younger patients, we observed a higher prevalence of males and atypical forms of CT, with a lower rate of comorbidities, a higher prevalence of psychiatric and neurological disorders, and a higher prevalence of in-hospital complications.[2] CT has also been described in neonates and children, with equal distribution between genders, and often with ventricular dysfunction and heart failure.[3]

CT shows an in-hospital mortality rate similar to acute myocardial infarction with ST-segment elevation, with an annual mortality rate of 5.6% and cerebrovascular events of 9.9%. The recurrence rate ranges from 1.5% to 22%, being more frequent in patients < 50 years old.[4]

Keywords

Takotsubo; Neuro-Adrenergic Cardiomyopathy; Takotsubo Cardiomyopathy; Stress Cardiomyopathy.

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– Pathogenesis

The main characteristic of Takotsubo is the association of hyperdynamia of the basal portions with anterior or apical akinesia or dyskinesia of the left ventricle, which results in an anatomical configuration of ventricular ballooning. Less frequently, we may have alterations in other segments, such as the mesoventricular and basal segments, and in one-third of the patients, we observed involvement of the right ventricle. These changes in contractility have no anatomical correlation with the distribution of coronary flow. Evolutionarily, changes in contractility are reversible, with full or partial resolution of ventricular dysfunction in hours or weeks.

The different types of changes in contractility, as well as their anatomical distribution, are possibly due to variations in the trunks of sympathetic cardiac activation and the distribution pattern of neuro-adrenoreceptors. These present a more prevalent pattern that makes the apical characteristic the most frequent, but we may have less prevalent variations that confer the different types of the location of the segmental alterations observed in the Takotsubo.[5-12]

Several pathophysiological mechanisms for the development of Takotsubo have been proposed, considering sympathetic stimulation as the main factor. The presence in the acute phase of Takotsubo of high levels of serum adrenaline and noradrenaline and of norepinephrine in the coronary sinus indicates hyperactivity of the adrenal medulla as well as local myocardial neuro-adrenergic activity.[13,14]

These catecholamines, through different mechanisms, induce contractile hyperstimulation and cardiomyocyte aggression, which are the substrate for the development of apical ballooning in Takotsubo.[15]

The frequent demonstration of the presence of physical or emotional stress as a trigger in most patients with Takotsubo,[16] or the association with pathologies of high adrenergic activity such as pheochromocytoma, central nervous system diseases, post-cerebrovascular accident or convulsive crisis, emphasize the central role of sympathetic activity as the main factor for the development of Takotsubo.[17-20] The development of apical ballooning after the infusion of catecholamines, or attenuated after using beta and alpha-blockers, has also been demonstrated.[21-27]

Pathophysiological mechanisms of sympathetic hyperactivity:[28,29] (Figure 1)

a) Cardiotoxicity due to hyperactivation of myocardial neuroreceptors:

In the myocardium, we have sympathetic activity mediated by beta 1 and 2 neuroreceptors and alpha receptors. These

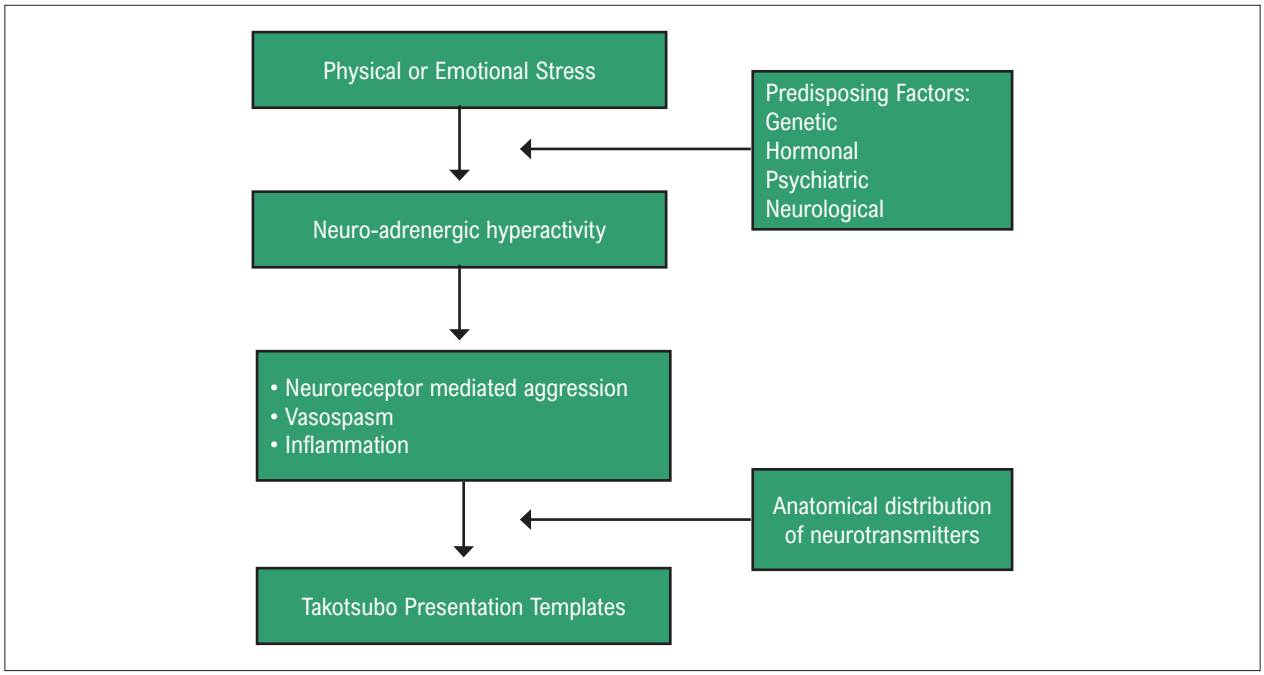

Figure 1 – *Pathophysiology of development of Takotsubo.*

neuroreceptors mediate the physiological stimuli of the sympathetic system in the myocardium in positive inotropic, lusitropic, and chronotropic modulation, and when chronically hyperactivated, it is associated with myocardial dysfunction.[16]

Sympathetic hyperactivation causes the phenomenon observed in Takotsubo of regional increase in myocardial contractility associated with depression of contractility with ballooning mediated by several pathophysiological mechanisms: hyperactivation of neuroreceptors, inflammatory activation, coronary vasoconstriction, endothelial injury, cardiomyocyte band necrosis and activation of the cellular apoptosis cascade, causing changes in the myocardium in Takotsubo.

The neuro-adrenergic stimulus mediated by norepinephrine released in the synaptic vesicle in the myocardium or by serum adrenaline released by the adrenal gland promotes the activation of myocardial beta-neuroreceptors and alpha-receptors. The stimulation of beta 1 receptors (B1-R), mediated mainly by norepinephrine, promotes the activation of stimulatory G protein (PtnGe), which activates the increase in cyclic Amp that promotes the increase in protein kinase A (PtnQA). PtnQA increases the activity of voltage-gated calcium channels by increasing the calcium levels in the cytosol, causing calcium release by the sarcoplasmic reticulum through activating the ryanodine pump, which is sensitive to calcium in the cytosol. This calcium will bind to the troponin C site, favoring ventricular contraction. In hyperactivation of B1-R, we will have a large increase in PtnQA, which causes a reduction in calcium reuptake by the sarcoplasmic reticulum mediated by Phosfolamban/SERCA2a activity, which becomes dysfunctional, causing an accumulation of calcium in the cytosol. This calcium accumulation is related to several alterations in cardiomyocyte physiology: depression of contractility, inflammatory activation, activation of the apoptosis cascade with reduction of cardiomyocyte mass, promotion of band necrosis, and increase in arrhythmogenic potential by altering phases 2 and 3 of the action potential. Therefore, B1-R hyperactivation promotes increased myocardial contractility and simultaneous myocardial aggression, both mediated by increased calcium in the cytosol.[26-29]

Hyperactivation of B2-R mediated by serum adrenaline causes a change in the stimulus pattern via PtnGe to inhibitory PtnG, which promotes the activation of Nitric Oxide Synthetase with increased nitric oxide, which causes depression of contractility and inflammatory activation. The BR have a heterogeneous distribution in the myocardium, with a higher prevalence of B2-R in the anterior and apical region and B1-R in the basal regions of the heart. This heterogeneous anatomical distribution would be the genesis of hypercontractility in the basal portions of the heart and ballooning or akinesia in the apical and anterior regions frequently observed in Takotsubo.[30]

b) Coronary Vasospasm:

Sympathetic activity causing vasospasm of epicardial coronary arteries has been proposed as a possible cause of Takotsubo, although most patients do not demonstrate coronary spasm even when provocative vasoconstrictive agents are used. The suggestion is that in Takotsubo, oxidative stress induced by sympathetic hyperactivity causes endothelial dysfunction and favors changes in coronary microcirculation.[31-35]

c) Microcirculation dysfunction:

The microcirculation dysfunction secondary to sympathetic hyperstimulation has been observed in all patients in the

acute phase of Takotsubo, being suggested as an important pathophysiological factor determining myocardial ischemia and ventricular contractile dysfunction based on studies that have demonstrated an altered coronary microvascular response in addition to the increased apoptotic activity of endothelial cells in the microcirculation in patients with Takotsubo. Endothelial and microcirculation dysfunction result from sympathetic alpha-receptor stimulation, promoting vascular dysfunction with reduced vasodilator reserve and favoring microcirculation spasm, with consequent ischemia and contractility depression. This dysfunction in the acute phase proved to be transitory, and its recovery is related to improving the contractile function.[36-40]

d) Destabilization or rupture of coronary atherosclerotic plaque:

We can find the presence of atherosclerotic plaques in the anterior descending coronary artery of patients with Takotsubo. In these cases, the use and investigation by intracoronary ultrasound or optical coherence tomography did not demonstrate the presence of ruptured plaques or dissection, emphasizing the need to exclude the presence of unstable coronary disease to confirm the diagnosis of Takotsubo.[41-44]

Predisposing factors and triggers for the development of Taktsubo

About 70% of patients who develop Takotsubo usually have emotional or physical stress as a triggering factor, which is common in all individuals.[45]

As only a few people develop Takotsubo, this leads us to the possibility of a genetic and clinical profile predisposing to the development of Takotsubo. By analyzing records and series of cases, we can define the most prevalent clinical profile of patients with Takotsubo by identifying the presence of predisposing factors: hormonal, genetic, psychiatric disorders, and triggers due to physical or emotional stress.

Hormonal

Takotsubo is more frequent in women than men at a 9:1 ratio, predominantly in the postmenopausal phase, indicating that a decline in estrogen levels could play a role in the pathophysiology of the development of Takotsubo. Estrogen acts in the modulation of vasomotor tonus through stimulation of endothelial nitric oxide synthetase and by modulation of neuro-adrenergic vasoconstriction and reduction of central sympathetic activation.[46-49]

However, there is a lack of studies that consistently prove the correlation of reproductive hormones with the development of Takotsubo, questioning that these would not have, in isolation, a determining role in its development or prevention.[50,51]

Genetic

The possibility of genetic predisposition to Takotsubo has been suggested by some studies that have shown a familial correlation.[52] However, most studies present conflicting or inaccurate results that demonstrate a polygenic potential or genetic heterogeneity which causes dysregulation of the neuro-adrenergic system, either in its activation or in the polymorphism of the beta and alpha neuro-receptors, which allows the identification of a predisposition line.[53-57]

Psychiatric disorders and neurological disorders

A high prevalence of neuropsychiatric conditions has been observed in patients with Takotsubo, with approximately 27% of neurological diseases and 40% with anxiety and depression, as well as in patients with panic syndrome.[58] Patients with mood disorders have an exacerbated response from the sympathetic system to emotional or physical stress due to greater release with less central and peripheral norepinephrine reuptake.[59,60] The use of antidepressants such as selective norepinephrine reuptake inhibitors increased tissue levels of catecholamines. Both factors increase the sensitivity and degree of sympathetic response to acute stress making these patients susceptible to the development of Takotsubo.[61,62]

Physical and emotional stress as triggers

Physical or emotional stress triggers are observed in approximately 70 to 80% of patients. In the International Takotsubo registry, 36% of patients had physical stress, 28% emotional stress, 8% both, and 29% no stress.

Physical stress is more common than emotional stress, affects more men and hospitalized patients, and has a worse prognosis.[63]

Physical stress is due to surgical procedures, trauma, infectious diseases, medications, and pain.[64-78]

Emotional stress is more common in women, postmenopausal women, and outpatients. Situations of emotional stress can be personal or professional, with negative stimuli that generate intense sadness, anger, feelings of dissatisfaction, rejection, fear, anxiety, panic, or confrontation ("Broken Heart Syndrome"), as well as situations of natural disasters or war.[79-81] But also situations with generally unexpected positive stimuli are also related to the triggering of Takotsubo ("Happy Heart Syndrome") Table 1.[82]

Diagnosis

Among all the criteria, the most used in clinical practice are the Mayo Clinic diagnostic criteria and INTERTAK. (Table 2)

The INTERTAK diagnostic criteria incorporate new aspects: (i) dysfunction of the right ventricle or other unusual segments; (ii) no need for the presence of a physical or emotional stress trigger prior to Takotsubo; (iii) neurological alterations and pheochromocytoma as possible triggers for Takotsubo; (iv) possibility of coexistence of significant obstructive coronary disease.

It is proposed to classify Takotsubo according to the type of trigger that precedes it as type 1, 2, 2a, 2b, and 3.[83-86] (Table 3)

Anatomical types of Takotsubo: (Figure 2)

Takotsubo is a transient acute cardiac syndrome with ventricular contractile dysfunction where we have the description of five anatomical types: (Figure 2)

Table 1 – Physical and Emotional Stress Triggers

Physical Stress	Emotional Stress
Postoperative	Death of relatives or spouse
Sepsis	Depression
Renal lithiasis	Anxiety crisis
Pneumonia	Panic
Pulmonary thromboembolism	Job loss
Electrical cardioversion	Loss of competition
Atrial fibrillation ablation	End of love relationship
Hemorrhagic stroke	Earthquakes, hurricanes, floods
Car convulsive crisis	War
Epilepsy	Car accident
Pheochromocytoma	Intense positive surprise
Severe asthma attack	Marriage
Orthopedic trauma	Prize-winning
Severe pain	Reunion with a loved one
Post-chemotherapy	
Drug or alcohol withdrawal syndrome	
Hyperthyroidism	
Post-cesarean section	
Post-infusion of catecholamines	

Table 2 – Takotsubo diagnostic criteria

Mayo Clinic Revised Criteria	INTERTAK criteria
• Transient dyskinesia of the LV medial segments, with or without apical involvement; the segmental alteration extends beyond the territory of an epicardial coronary artery; stress triggers often present. • Angiographic absence of obstructive coronary disease or acute plaque rupture. • Acute ECG changes, ST elevation, and/or T-wave inversion or modest troponin changes. • Absence of pheochromocytoma or myocarditis.	• Transient LV dysfunction (hypokinesia, akinesia or dyskinesia) presenting as apical or midventricular, basal, or focal segmental ballooning. May have RV involvement. We can transition between different types of segmental change. The segmental change extends beyond the territory of an epicardial coronary artery; however, we rarely have segmental changes corresponding to the territory of a coronary artery. • Physical or emotional stress, or combined, often precede a Takotsubo episode. • Neurological alteration (subarachnoid hemorrhage, stroke, seizures); pheochromocytoma can be a trigger. • Acute ECG changes, with ST elevation or ST depression, T-wave inversion and prolonged QT, and rarely normal ECG. • Moderate elevation of troponin T or I and CK-MB. Frequent elevation of BNP. • Significant coronary disease does not exclude Takotsubo. • Absence of myocarditis. • It predominantly affects postmenopausal women.

1) Classic pattern: Seen in about 70% to 80% of patients. Apical akinesia or hypokinesia with hypercontractility of the basal segments, giving the classic octopus-trap appearance that earned the name Takotsubo.

2) Mesoventricular: Seen in about 15% of patients. Hypokinesia of the middle portion of the left ventricle and hypercontractility of the apical and basal segments.

3) Inverted or Basal: Seen in about 3% to 5% of patients. Hypokinesia or akinesia of the basal and middle ventricular segments with apical hypercontractility.

4) Focal: Observed in about 5.5% of patients. Hypokinesia or akinesia of isolated segments, usually anterolaterally

5) Biventricular or isolated involvement of the right ventricle < 0.5% has an unknown prevalence, its involvement being rare.

Clinical Presentation

The clinical presentation of Takotsubo is more frequent in postmenopausal women who experience unexpected emotional or physical stress, followed by a clinical picture of precordial pain (75%), dyspnea (50%), dizziness (>25%), syncope or pre-syncope (5% to 10%), palpitations due to sinus tachycardia, or in more severe clinical forms such as acute heart failure, cardiogenic shock or sudden aborted death. The main differential diagnoses in the emergency room are acute coronary syndrome and acute myocarditis. As we usually have a clinical picture similar to an acute coronary syndrome, accompanied by electrocardiographic alterations and elevation of cardiac injury enzymes, despite the absence of obstructive coronary disease, Takotsubo was classified in the last universal definition of acute myocardial infarction as acute myocardial infarction with normal coronaries (MINOCA).[87]

Therefore, referring these patients to coronary angiography for diagnostic confirmation is necessary.[88,89]

Table 3 – Takotsubo's INTERTAK classification according to trigger type:

Class I: Takotsubo related to an emotional stress trigger
Class II: Takotsubo related to a physical stress trigger
IIa: Secondary to physical activity, medical procedures, acute illnesses.
IIb: Secondary to neurological disorders
Class III: Takotsubo with no identified trigger.

The clinical admission picture can be predominantly defined by the manifestations of the disease that caused the physical stress, such as stroke, seizures, and the manifestation of Takotsubo may be through the development of ventricular dysfunction on the echocardiogram alone or with unexpected hemodynamic disturbances, such as hypotension or shock. In patients with emotional and physical stress, we observed the clinical picture of precordial pain and palpitations, or dyspnea, more frequently.[90-92]

ECG

The ECG is abnormal in most patients with Takotsubo (>95%),[11] with changes usually suggestive of coronary

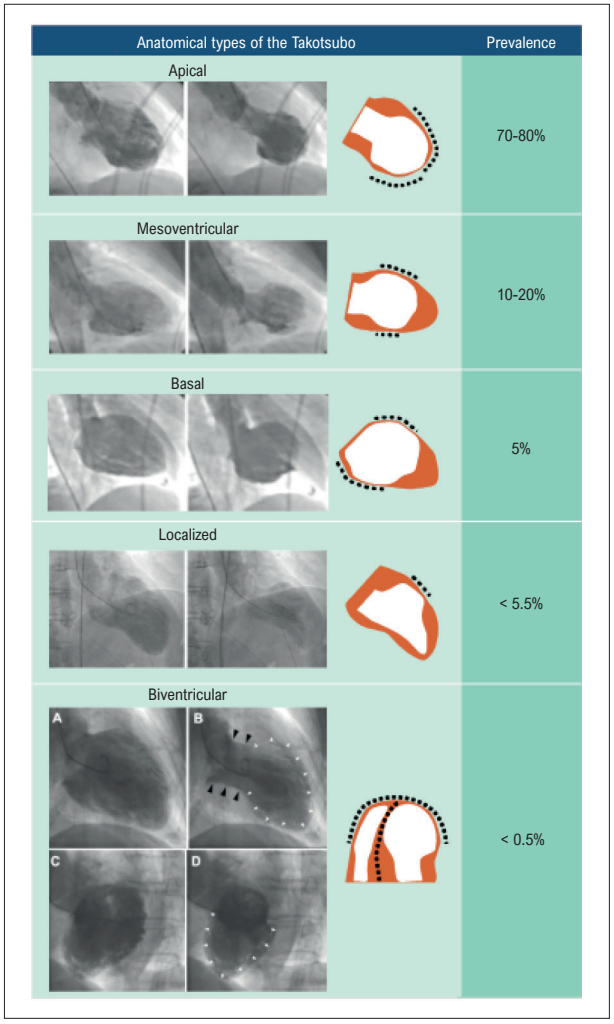

Figure 2 – *Anatomical types of the Takotsubo.*

ischemic disease in the ST segment and T wave. In the acute phase, we found ST-segment elevation in 44%, usually involving the anterior, apical, and lateral leads suggesting extensive anterior infarction, ST-segment infraction being uncommon, occurring in 8%, and T wave inversion being diffuse affecting 41%, pathological Q waves in 15%, and left bundle branch block in 5%. Twenty-four to 48 hours after the onset of symptoms, we have T wave inversion and significant prolongation of the QT interval, predisposing to polymorphic ventricular tachycardia (torsade de pointes) and ventricular fibrillation. T wave inversion and QT interval lengthening are related to the presence of myocardial edema, and subsequent gradual resolution may take days to weeks. The analysis of ECG alterations is highly accurate in differentiating acute myocardial infarction, such as the presence of ST-segment elevation in aVR and in anteroseptal leads V1 to V4, or ST-segment elevation in aVR with T-wave inversion, have high accuracy. However, due to the high prevalence of acute coronary disease with clinical and electrocardiographic characteristics similar to Takotsubo, all patients require assessment by coronary angiography with ventriculography for the differential diagnosis.[93-100]

Biomarkers

Virtually all patients with Takotsubo have an enzymatic elevation of myocardial necrosis. Troponin T, or I and CK-MB, are elevated in >90% of patients on admission. The enzymatic peak is substantially lower than that of acute myocardial infarction, demonstrating a dissociation between enzyme levels with the extent of ECG changes and ventricular dysfunction. The presence of elevated enzyme levels is correlated with a worse prognosis.

Natriuretic peptides (BNP and pro-BNP) are frequently elevated, correlating with the degree of myocardial functional changes and ventricular dysfunction. They peak within 48 hours, and it may take months to normalize. [101-103]

Echocardiogram (Table 5)

Transthoracic echocardiography (ECHO) is essential in the acute phase of CT to establish the initial diagnostic suspicion. The characteristic pattern of segmental alteration is the presence of apical and mesoventricular akinesia or dyskinesia of the anteroseptal segments with hyperdynamia of the basal segments. In addition to defining the CT pattern (apical, medial or basal), the echocardiogram will quantify the degree of dysfunction and assess the presence of complications such as intracavitary thrombus, left ventricular outflow tract obstruction (LVOT), mitral insufficiency secondary to LVOT or ventricular dilation. Although ECHO alterations may be strongly suggestive of Takotsubo, they do not allow for the differentiation or ruling out of AMI or myocarditis. ECHO is of great value in confirming the diagnosis by monitoring improvement in ventricular dysfunction or as a prognostic marker.[104-107]

Cardiac Magnetic Resonance (CMR) (Table 5)

CMR is usually after the first 24-48 hours of admission. The importance of CMR lies not only in assessing the extent of ventricular dysfunction but also in the differential diagnosis of myocarditis.

CMR findings involve ventricular functional analysis with quantification of the extent of segmental alterations, degree of ventricular dysfunction, assessment of right ventricular involvement and the presence of complications such as intracardiac thrombus and intracardiac obstruction, and morphological analysis with the investigation of myocardial edema, of inflammation and fibrosis through late gadolinium enhancement (LGE) analysis.

Myocardial edema is observed in the acute phase through the T2 technique of CMR, with the demonstration in the T2 phase of an intense increase in the signal, having a diffuse distribution, being able to be transmural, and strongly related to the regions with alteration in contractility, not having a correlation with coronary anatomy, which differentiates it from AMI and myocarditis, which presents edema without correlation with changes in contractility and is more common in the lateral and epicardial walls. LGE is usually absent, which helps differentiate myocarditis or acute myocardial infarction. However, positive LGE has been described, predominantly in the apical region, with reduced signal intensity, with reports of persistent transmural LGE. The persistence of a positive LGE is

associated with a worse evolutionary prognosis with the potential for arrhythmias.[108-114]

Nuclear medicine (Table 5)

Myocardial scintigraphy with 123I-*m*IBG has been used to assess the sympathetic system's activity in the myocardium through the activity of uptake of neuroreceptors. In the acute phase of Takotsubo, there is a reduction in myocardial uptake corresponding to regions with contractile dysfunction, consistent with dysfunction in the activity of sympathetic neuroreceptors, with a reduction in uptake in the apical and anterior regions of the myocardium being more common. These abnormalities can persist for several months, where 123I-*m*IBG has a diagnostic confirmation role in cases that remained undiagnosed or in doubt during hospitalization or patients with a previous history without confirmation. The presence of positive 123I-*m*IBG and its extension correlate with a worse prognosis in the development of heart failure and mortality.[115,116]

Coronary angiography (CAG) (Table 5)

Upon hospital admission, most patients are evaluated by CAG to rule out the diagnosis of AMI. Takotsubo typically does not present an obstructive coronary lesion corresponding to the anatomical region with contractile alteration; therefore, it is necessary to perform CAG for diagnostic confirmation in the acute phase and differentiation of AMI or myocarditis. Because most patients with Takotsubo are elderly, we can find incipient coronary disease in about 10% of patients or other coronary arteries that do not correspond to the compromised anatomical region. In the presence of a significant coronary lesion corresponding to the anatomical region, we must use intravascular evaluation methods such as ultrasound or intracoronary optical coherence tomography to exclude plaque rupture, intracoronary thrombus, or coronary artery dissection, to confirm the diagnosis of Takotsubo. The concomitant performance of ventriculography allows for demonstrating the typical contractile dysfunctions of Takotsubo, in addition to estimating the degree of ventricular dysfunction and assessing the presence of intracardiac thrombus, mitral insufficiency and obstruction of the left ventricular outflow tract.[117-123]

Coronary angiotomography (Table 5)

Coronary CT angiography has been proposed for stable patients with low suspicion of AMI or late presentation, or as a retrospective analysis of patients with a previous unconfirmed history of Takotsubo, as a non-invasive method for ruling out obstructive coronary disease.[124]

INTERTAK scoring criteria for predicting the diagnosis of Takotsubo

The clinical presentation and alterations in the ECG and the myocardial injury enzymes of Takotsubo are very similar to AMI, and it is impossible to differentiate between both pathologies by any non-invasive method consistently. Therefore, in the acute phase, most patients need to be evaluated by coronary angiography to establish the diagnosis. The INTERTAK score criteria were developed from a diagnostic probability model involving seven clinical and electrocardiographic variables that are more prevalent in patients with Takotsubo than patients with AMI, where the greater the sum of points, the greater the probability of diagnosing Takotsubo. This model is proposed as a guide for questioning the probability of a diagnosis and not for a diagnostic statement.[125] (Table 4)

The sum of points presents a capacity to predict the diagnosis of Takotsubo in the acute phase, with a greater capacity to predict the diagnosis with a sum of values > 70 points, indicating a probability > 85%, whereas values < 35 points have a 95% possibility of diagnosis be of acute coronary disease. In elderly patients with high frailty, clinically stable, we can use the point criterion to assess the risk and benefit of performing the CAG or starting antiplatelet therapy and opting for the integrated diagnosis of multimodality imaging to define the diagnostic probability and follow-up of ventricular dysfunction.

Integrated Multimodality Diagnostics

The ability of the integrated multimodality diagnosis to confirm the diagnosis of Takotsubo and its differentiation with AMI and myocarditis, as well as the detection of cardiac complications, will be related to the clinical scenarios and evolutionary phases of Takotsubo in which they were performed. These will define differentiated actions of the different modalities in the diagnostic evaluation of Takotsubo and differential diagnoses:[126]

Classic Takotsubo: Usually caused by a triggering factor, in a female patient in the postmenopausal phase, often with precordial pain and/or dyspnea, ECG, and cardiac enzymes indicative of myocardial injury. In this scenario, the diagnosis is focused on the acute coronary syndrome, and Takotsubo is a secondary suspicion, where the appearance of apical and anterior dysfunction and basal hyperdynamia, with apical ballooning, on the echocardiogram may suggest Takotsubo. However, it does not allow for a positive diagnosis. In this scenario in the emergency room, performing CAG is necessary to rule out the diagnosis of acute myocardial infarction and define or suggest the diagnosis of Takotsubo or the case of non-significant coronary disease associated with MINOCA. Performing CMR is essential as it strengthens the

Table 4 – Clinical predictors for the diagnosis of Takotsubo

Criterion	Score	Takotsubo prediction (Or)	p
Women	25	68	p<0.001
Emotional Trigger	24	65	p<0.001
Physical Trigger	13	8.7	p<0.001
Absence of SST infrastructure	12	7.2	p<0.001
Psychiatric disorder	11	7.0	p<0.001
Neurological disorder	9	4.9	p<0.001
Prolonged QTc	6	2.8	p=0.006

diagnosis of Takotsubo or suggests myocarditis or MINOCA, in addition to assessing the extent and degree of ventricular dysfunction and the presence of cardiac complications, and has prognostic value.

Non-classical Takotsubo: is the presentation without identifying a precipitating or triggering factor, with clinical syncope, dizziness, or aborted sudden death, usually in male patients, who may or may not be elderly, without ST-segment elevation on the ECG, mild enzymatic elevation, where the echocardiogram is not strongly indicative of Takotsubo, with medial or basal segmental change. In this scenario, CMR plays a more significant role in evaluating the differential diagnosis of myocarditis, and in stable patients, we can indicate coronary angiotomography to assess the presence of CAD. In these patients, if diagnostic doubt remains, performing myocardial scintigraphy with MIBG may help establish or rule out the diagnosis of Takotsubo.

Intra-hospital Takotsubo: is usually associated with physical stress resulting from pathologies or post-procedures and may have a classic presentation of apical ballooning or atypical presentation with a segmental alteration. The echocardiogram in this scenario is important for diagnostic guidance, prognosis, and follow-up of ventricular dysfunction in terms of its response to therapy or spontaneous involution.

The differential diagnosis is related to acute myocardial infarction or metabolic cardiomyopathy in this context. In unstable patients, it is usually not feasible to perform CMR, and according to the degree of clinical suspicion, it will be necessary to perform CAG to assess the diagnosis of CAD.

After clinical and hemodynamic stabilization, CMR can be performed to assess the extent of the degree of ventricular dysfunction. In this scenario, the echocardiogram plays an important role in following the evolution of ventricular dysfunction and the development of cardiac complications.

Takotsubo of late confirmation: is when patients have a previous history of suggestive diagnosis without confirmation. CMR and coronary angiotomography can help clarify the diagnosis in patients with persistent dysfunction. In patients without ventricular dysfunction, performing MIBG, which can demonstrate alterations in the uptake of neuroreceptors within 12 months after the event, may suggest the diagnosis in case it is positive but does not exclude it in case it is negative.

Treatment

Although CT was initially described as benign, approximately 52% of patients have some complications, and 11% have more than two complications contributing to a higher mortality rate.[127] The in-hospital mortality rate varies from 2.4 to 4.1%, while pulmonary edema and cardiogenic shock rates range from 6 to 9% and 9 to 11.4%, respectively.[8] In-hospital mortality from CT is higher than from uncomplicated acute myocardial infarction. Therefore CT cannot be handled as a low-risk pathology.[128]

The therapeutic approach to patients with CT is based on the pathophysiological rationale, case series publications, retrospective analyzes or expert opinion, and the use of recommendations from other guidelines regarding the treatment of complications with acute heart failure since we do not have a specific guideline for the therapeutic handling of the CT. The therapeutic approach can be divided according to the clinical presentation and in-hospital evolution into uncomplicated CT and complicated CT.[129] In uncomplicated CT, patients may be asymptomatic or present with a clinical picture of precordial pain, with changes in the ECG, enzymes, and dysfunction on the echocardiogram, without clinical signs of heart failure, hemodynamic instability, or significant arrhythmias. They usually present a benign in-hospital evolution, with normalization of ventricular function mostly until hospital discharge. Patients with complicated CT present on admission or during in-hospital evolution, acute heart failure, cardiogenic shock, thromboembolic events, or frequent ventricular arrhythmias. These patients have a worse in-hospital prognosis with higher mortality and length of stay.[129]

Uncomplicated Takotsubo therapeutic approach

Patients with uncomplicated CT usually evolve with spontaneous regression of the segmental change in ventricular contractility, so the therapeutic approach focuses on maintaining clinical support and controlling comorbidities, with prophylactic heparin and the use of antiplatelet agents and statins in the presence of coronary disease. The use of converting enzyme inhibitors has shown benefit in improving survival at the end of 1 year and reducing the risk of recurrence; however, the use of beta-blockers has not shown any clinical benefit in improving survival or recurrence at 30 days and 1-year post-discharge.[130] Despite the absence of

Table 5 – Imaging methods in evaluating the Takotsubo and its characteristics

Methods	Characteristics
Echocardiogram	• Acute phase method • Method most used in practice for early identification of segmental alteration and raising the suspicion of Takotsubo: • Segmental alteration and ventricular function • Complications: mitral regurgitation, cardiac thrombus, LVOT, pericardial effusion • Recovery follow-up
CMR	• Subacute or late phase method • Extension of segmental change, function • RV involvement • Complications: Mitral regurgitation, cardiac thrombus, LVOT, pericardial effusion • Differential diagnosis: myocarditis, CAD.
CAG	• Acute phase method • CAD and MINOCA evaluation • Segmental alteration and ventricular function • Complications: mitral insufficiency, cardiac thrombus, LVOT.
Angio CT-Coronary	• Subacute phase method • CAD and MINOCA evaluation
Nuclear medicine	• Subacute or late phase method • Late diagnostic confirmation • Late differential diagnosis of MINOCA or myocarditis

LVOT: left ventricular outflow tract obstruction; RV: right ventricle; CAD: coronary artery disease; CMR: cardiac magnetic resonance; CAG: coronary angiography.

evidence to support the use of beta-blockers, their use in clinical practice has been usual due to the pathophysiological rationale of hyperadrenergy.

In the presence of long QT, patients should be maintained on continuous electrocardiographic monitoring during hospitalization, even after ventricular function normalization, due to the high risk of malignant ventricular arrhythmias.[131]

Therapeutic approach to complicated Takotsubo

In complicated CT, complications have a variable prevalence, and we can classify them as follows:

1) Frequent: Heart Failure (3-46%), LVOT (12-25%), Cardiogenic Shock (6-20%), Mitral Insufficiency (14-25%);

2) Occasional: Atrial fibrillation (4.5%-25%), left ventricular intracavitary thrombus (2-9.2%), cardiac arrest (4-6%);

3) Rare: Tachyarrhythmias (2-5%), bradycardias (2-5%), death (1-5%).

Acute heart failure

The management of acute heart failure in patients with CT should follow the treatment recommended by the guidelines, with ventilatory support, diuretics, converting enzyme inhibitors, angiotensin receptor blockers, sacubitril-valsartan, beta-blockers and mineralocorticoid receptor antagonists and inhibitors of receptors SGLT2.[132,133] In patients with LVOT, the use of drugs that reduce pre- and afterload, such as venous or arterial vasodilators and diuretics, should be avoided, as they can aggravate the degree of obstruction.

The use of beta-blockers in this group of patients demonstrated clinical benefit with a higher 2-year survival rate, particularly in patients with arterial hypertension or who developed cardiogenic shock in the acute phase.[134]

Cardiogenic shock

Cardiogenic shock can occur 6% to 20% within the first 72 hours of admission. The first point to be observed in the treatment is whether the hypotension is due to LVOT or diffuse left ventricular contractile failure since 20 to 25% of patients have LVOT.[135]

Patients with LVOT can present anterior systolic movement of the mitral valve with consequent mitral regurgitation. Using vasoactive amines, inodilators, vasodilators, diuretics, and intra-aortic balloon pumps should be avoided as they worsen the LVOT obstruction. Treatment is volume expansion and a short-acting intravenous selective beta-blocker such as Esmolol.[136] In patients with cardiogenic shock refractory to pharmacological intervention, mechanical circulatory support with ECMO would be indicated, and implantation should be performed as early as possible.[137]

In patients where cardiogenic shock results from pump failure, using vasoactive amines such as noradrenaline is frequent in clinical practice. However, the European Society of Cardiology recommends that they be avoided or used in low doses due to the potential of aggravating myocardial aggression and ventricular dysfunction and prolonging the shock condition.[138] Ansari et al. demonstrated in patients that used vasoactive amines when compared to those who did not, higher in-hospital mortality (3.2% vs. 28.5%, $p < 0.01$), 30-day mortality (17.2% vs. 51.4%, $p < 0.01$) and long-term mortality (38.7% vs. 80.9%, $p < 0.01$), with logistic regression analysis was a determining factor of worse prognosis. (HR 2.2, 95% CI 1.0–4.8; $p= 0.04$).[139]

In patients with arterial hypotension or cardiogenic shock, levosimendan, and milrinone, in the absence of LVOT, are alternatives to vasoactive amines because they do not activate neuro-adrenergic receptors. Using Levosimendan in several cases demonstrated clinical and ventricular function improvement without developing adverse events or LVOT. Levosimendan should be given at a dose of 0.1 mg/kg/min without bolus for 24 hours.[140,141]

Patients with cardiogenic shock, who do not show an initial response to pharmacological support, should be evaluated as soon as possible by the shock team for the implantation of mechanical circulatory support. The intra-aortic balloon alone did not demonstrate benefits in improving survival, and the use of ECMO associated with Impella or IAB should be evaluated.[142-144]

Arrhythmias

Patients with CT may have supraventricular or ventricular arrhythmias, with the potential for thromboembolic complications and increased mortality. Acute atrial fibrillation should be initially managed with anticoagulation and heart rate control with short-acting intravenous beta-blockers; electrical cardioversion may be indicated in hemodynamically unstable patients. Malignant arrhythmias can occur in 8% of patients, 75% with ventricular tachycardia and ventricular fibrillation.[145,146] Treatment in the acute phase may involve magnesium sulfate, short-acting intravenous beta-blockers, and electrical cardioversion. Amiodarone effectively controls ventricular arrhythmias, but we must observe whether there is a long QT, which can be aggravated by amiodarone. In frequent VT unresponsive to pharmacological treatment associated with long QT, we can use a pacemaker to increase the heart rate, and in patients with hemodynamic instability or cardiogenic shock, the implant of mechanical circulatory support with ECMO.[147,148]

Intracardiac thrombus

Intracardiac thrombus (ICT) formation in the left ventricle on CT can occur in up to 2.5% of patients, and the development of cardioembolic events in 0.8% of this population. Thrombus formation can occur in the in-hospital phase or within 2 weeks after discharge. In the presence of ICT, we risk systemic embolization events of 1% to 2%. The presence of apical ballooning, LVEF < 35%, and high levels of Troponin I are predictors of the development of ICT, and prophylactic anticoagulation with DOACs is indicated. Apical ballooning without associated troponin elevation does not require prophylactic anticoagulation. In the presence of ICT detected by echocardiogram or cardiac magnetic resonance, anticoagulation with DOACs is indicated and should be maintained for at least 3 months.[149-151]

Follow-up of patients after hospital discharge [152-155]

In the post-hospital discharge follow-up, we have several objectives to be evaluated, such as 1) involution of the segmental alteration and improvement of the ventricular function; 2) involution of intracavitary thrombus; 3) involution of myocardial edema; 4) CT follow-up; 5) evaluation of ventricular arrhythmias.

An echocardiogram and magnetic CMR are performed for anatomical and functional assessments 30 days and 3 months after discharge. Along with this assessment, the risk of developing arrhythmias should also be assessed, especially in patients with persistent long QT or with ventricular arrhythmias observed on the 24-hour electrocardiogram. Patients with intracavitary thrombus must remain anticoagulated with DOACs for at least three months, with follow-up by echocardiogram or CMR. The maintenance of ACE inhibitors/ARBs in patients with ventricular dysfunction improves survival at the end of 1 year, and no benefit was observed with the use of beta-blockers.[152]

The long-term prognosis of CT is benign, with over 90% of patients completely recovering within 2 months. The long-term recurrence rate varies between 1.8% and 10%. For women over 50, persistent ventricular dysfunction, emotional lability, psychiatric disorders, and vasovagal reflex alteration present a greater risk for recurrence. Male patients, who had advanced heart failure at admission, and people with diabetes had lower long-term survival.[153,154] The use of ACEI/ARBs or beta-blockers was not effective in reducing the recurrence rate.[130] This was also observed in the treatment or correction of factors or triggers, such as anxiety, depression, bronchial asthma, or the fact of avoiding invasive procedures.

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