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Takotsubo cardiomyopathy from pathogenesis to diagnosis: state-of-the-art

Cardiomiopatia de Takotsubo da patogênese ao diagnóstico: estado da arte

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ABSTRACT: Takotsubo cardiomyopathy (TCM) is a condition typically characterized by hypokinesia, dyskinesia or transient akinesia of the left ventricle apex. It lasts up to four weeks and is triggered by physical or emotional stress. With higher incidence among postmenopausal women, it consists of a clinical syndrome mistaken for acute myocardial infarction (AMI), due to the common clinical and laboratory findings. Approximately 2 of every 100 acute coronary syndrome diagnoses are in fact TCM. Although it was described in 1990 and requires different therapy, international consensus on diagnostic criteria is still lacking. This article seeks to review the publications of the last 30 years on the topic concerning epidemiology, pathogenesis, clinical manifestations, laboratory findings, diagnostic methods and criteria, in order to list measures that enable differentiating AMI from TCM in clinical practice.

Keywords: Takotsubo cardiomyopathy; Ventricular dysfunction; Ventricular dysfunction, left; Acute myocardial infarction.

RESUMO: A cardiomiopatia de Takotsubo (CMT) apresenta-se, normalmente, por hipocinesia, discinesia ou acinesia transitória do ápice do ventrículo esquerdo, com duração de até quatro semanas, desencadeada por estresse físico ou emocional. Com maior incidência entre mulheres pós-menopausa, consiste em uma síndrome clínica confundida com infarto agudo do miocárdio (IAM), devido aos achados clínicos e laboratoriais em comum. A cada 100 diagnósticos feitos de síndrome coronariana aguda, cerca de 2 tratam-se da CMT. Apesar de ter sido descrita em 1990 e exigir terapêutica distinta, ainda não há consenso internacional no que se refere aos critérios diagnósticos. Este artigo busca revisar as publicações dos últimos 30 anos sobre o tema em relação a epidemiologia, patogênese, manifestações clínicas, achados laboratoriais, critérios e métodos diagnósticos, enumerando medidas que permitam diferenciar IAM de CMT na prática clínica.

Descritores: Cardiomiopatia de Takotsubo; Disfunção ventricular; Disfunção ventricular esquerda; Infarto agudo do miocárdio.

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INTRODUCTION

Takotsubo cardiomyopathy (TCM) or Takotsubo syndrome, also known as stress-induced cardiomyopathy, apical ballooning syndrome or broken heart syndrome, is a reversible and acute form of heart failure. It is characterized by reduced fraction of ejection and associated with emotional or physical stress, that usually lasts up to four weeks[1-6]. It was initially described by Sato et al.[1] in 1990, having the anterolateral elevation of the ST segment and transient antero-apical dyskinesia with compensatory basal hyperkinesia as main characteristics.

TCM mimics chest pain and other symptoms and signs of acute coronary syndrome (ACS), especially acute myocardial infarction (AMI), as well as common electrocardiographic aspects, which is why about 1.7% to 2.2 % of the initial diagnoses of ACS are actually TCM. For this reason, it is a disease of great importance and should always be considered as a differential diagnosis of acute chest pain[4,7-9].

The nomenclature of this cardiomyopathy refers to the similarity observed by the descriptors of the disease between the Japanese trap (Tsubo) used to capture octopuses (Tako) and the aspect exhibited by the ventricle affected at the end of the systole, in the ventriculogram[4,9,10]. This article seeks to address epidemiology, pathophysiological aspects, clinical manifestations and laboratory findings on TCM from original studies, reviews and reports published in the last 30 years, gathering data that facilitate the differentiation between ACS and TCM by the clinical physician.

METHODS

Research was carried out in PubMed / Medline, Scopus, Google Scholar, SciELO, Lilacs and institutional thesis and dissertation libraries using the terms “takotsubo cardiomyopathy”, “takotsubo syndrome”, “apical ballooning”, “cardiomyopathy by stress”. Original articles, review studies and case reports, in English, Spanish and Portuguese, published from 1990 and 2020, were included, resulting in 115 articles.

EPIDEMIOLOGY

There is no consensus regarding the annual incidence of TCM, either due to the difficulty of carrying out surveys, or due to the lack of recognition of the syndrome by health services. The syndrome has an estimated annual incidence between 0.00006% to 0.05%. About 90% of the cases occur in postmenopausal women, aged between 62 and 76 years; incidence in whites, African-Americans and Hispanics is 67.4%, 4.4% and 4.3%, respectively[5,11-21].

In the United States, TCM incidence increased: from 2007 to 2012, the incidence increased from 52 cases / 1,000,000 to 178 cases / 1,000,000 inhabitants ($P < 0.001$), although in-hospital mortality of 1.1% remained unchanged during the period[22].

The International Takotsubo Registry (InterTAK Registry) investigated 1,750 patients and showed that 89.8% of cases were women, 66.8 ± 13.0 years-aged, of whom 79.1% were women over 50 years old[23].

In 2008, Deshmukh et al.[15] analyzed the National Inpatient Sample (NIS), the largest hospital database in the United States, and found 6,837 records of TCM patients which corresponded to an estimated prevalence 0.6 / 100,000 inhabitants for men and 5.0 / 100,000 inhabitants for women. The female gender exhibited odds ratio (OR) equals to 8.8 (95% CI: 7.3-10.5) for the disease. Women over 55 years old were 4.8 (95% CI: 4.2-5.6) times more likely to develop TCM than those under that age. Risk factors for other cardiovascular pathologies, such as dyslipidemia, stress, anxiety, smoking and alcoholism, were also significant risk factors for TCM[15].

Despite being primarily associated with emotional or physical stressors, these are not always clear to medical research. Only 44% to 75% of investigations obtain data on some stressor factor prior to dyskinesia[5,11,14].

Table 1 summarizes the physical and emotional stressors related to TCM.

Nevertheless, conventional cardiovascular risk factors should not be ruled out in the case of TCM patients. All patients included in the study performed by Cesario et al.[10] showed at least one cardiovascular risk factor. Hypertension, the most common risk factor, was present in 70% of patients. Dyslipidemia, the second most reported factor, was found in 60% of cases. There were also reports of obesity, type 2 diabetes mellitus and smoking as risk factors.

The presence of mental disorders - depression, mood and anxiety disorders -, status epilepticus, family history of cardiovascular diseases and reduction of estrogen are also considered risk factors[41,42].

Table 1 - Stress factors related to Takotsubo cardiomyopathy[6,10,11,24-43]

Physical stressor factor	Emotional stressor factor
Invasive cardiac procedure	Unexpected death of relative or close friend
Strenuous exercise	Domestic abuse
Asthmatic crisis	Confrontation
Pneumothorax	Terminal medical diagnosis
Ventricular fibrillation	Surprise party
Exacerbation of systemic disorder	Public performance
Cold exposure	Professional failure
Exacerbated Chronic Obstructive Pulmonary Disease	Car accident
Abdominal Surgery	Urban violence
Sepsis	Judgments
Digestive bleeding	Fear of procedure
Pneumonia	Unexpected meeting
Drugs (such as chemotherapy, cocaine and pseudoephedrine)	Continuous emotional stress
Chronic liver disease	Drowning
Brain stroke	Betting losses
Neoplasms	Anxiety disorder
Iatrogenic (high doses of catecholamines)	Mood disorders
Ruptured abdominal aortic aneurysm	Child custody dispute
Elective direct current cardioversion	*Status epilepticus*
Pheochromocytoma	Phobias
	Abstinence

PATHOGENESIS

Dissonant to the advancement of knowledge about several cardiovascular diseases, the exact pathogenesis of TCM remains unknown. However, the interaction of several mechanisms, such as coronary spasms, microvascular dysfunction, transient coronary occlusion, estrogen deficiency and sympathetic changes, is suggested[5,44-46].

Coronary spasms and microvascular dysfunction

Transient coronary spasms and reduced blood flow are frequent in TCM. Provided that spasms are estimated to occur in 21% to 54% of patients, it was one of the first hypotheses raised for pathophysiology[1-3,44-50].

This hypothesis has been the subject of several investigations. Patel et al.[50] reported vasoconstriction of the epicardial coronary artery in 60% of patients submitted to a vasomotricity test, as well as microvascular dysfunction – most frequently in the epicardial arteries – in 90% of them. Another study with 47 patients, 46 female and 1 male, aged 67 ± 12 years, reported abnormal coronary vasoconstriction in 85% of patients. Microvascular dysfunction was present in 83% of patients[51]. Loffi et al.[52] evaluated 27 TCM patients, 27 patients with microvascular angina and 27 patients in a control group (CG), measuring the flow of the anterior descending artery (AD), right coronary artery (RCA) and left circumflex artery (LCX) arteries using the frame count of the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC). TCM in AD showed a TFC of 22 ± 8 vs GC 15 ± 4 ($p = 0.001$). Regarding RCA, TCM group had TFC equals to 12 ± 4 vs GC 10 ± 3 ($p = 0.025$); in the case of LCX, TFC for TCM group was 14 ± 4, while it was 11 ± 3 for CG ($p = 0.006$).

Despite these studies, it is not possible to define whether the vasomotricity abnormalities occur prior to cardiomyopathy or represent results of the clinical condition, thus hindering the elucidation of TCM pathogenesis[53].

There are also studies that do not point to any microvascular dysfunction. In an analysis of 17 patients aged 54 to 91 years, Abe et al.[54] did not report significant findings on abnormalities in the coronary microcirculation or reduced flow. Another study that evaluated 59 female patients, aged 32 to 90 years, showed no significant change in the epicardial coronary arteries flow or alteration in the microcirculation[55].

In addition to coronary spasms, spontaneous coronary artery dissection is considered as the probable genesis of an ischemic process that results in cardiac stunning and TCM[6,44,56,57].

Transient coronary occlusion and atheromatous plaque

Although initially proposed as a mechanism associated with cardiac dysfunction, retrospective studies ruled out atheromatous plaque rupture as a possible contributor to TCM pathogenesis, since the changes are not limited to the specific territory of any coronary artery. Obstructions are generally lower than 50% unlike what occurs in acute myocardial infarction[48]. Plaque changes present in TCM are also found in stable angina and even in asymptomatic patients[58].

Estrogen deficiency

Several vascular effects are linked to estrogen: the ability to modulate vascular tone, supra-regulation of the endothelial enzyme nitric oxide synthase and inhibition of endothelial apoptosis[59]. Estrogen deficiency is therefore associated with a greater propensity for microvascular spasms, along with endothelial dysfunction and increased sympathetic stimuli, which explains the higher incidence of TCM in postmenopausal women[5,12,44,46]. In fact, a study showed that ovariectomized female Sprague-Dawley® rat exhibited more severe cardiac dysfunction and higher troponin concentrations[60].

The possible influence of estrogen led to the investigation of estrogen receptor polymorphism (ESR) 1 and 2. Studies involving healthy, AMI and TCM patients showed a risk relationship between allele T in the ESR1 rs2234693 locus and in the ESR2 rs1271572 locus with TCM[61,62].

Considering that estrogen supplementation as a prophylaxis for TCM is still controversial, there is no consensus on recommendations. In animal studies, association of estrogen supplementation with alpha and beta-blockers reduced sympathetic stimuli induced by stress and increased cardioprotective substances[5,12,44-46].

Sympathetic activation and increased catecholamines

Physical and psychological stress triggers a brain activating response, increasing the release of cortisol and catecholamines. Different stimuli processed by the hypothalamus, cingulate gyrus and amygdala stimulate the production and secretion of norepinephrine by the *locus coeruleus* and the production of epinephrine[40,41,56]. Elevations of 7 to 34 times of epinephrine have already been found in patients with TCM, although there is no consensus as to the mechanisms that link the elevation of epinephrine to cardiac dysfunction[40,41,48,56].

Discharge of catecholamines, released upon stress episodes, is suggested to act directly on the myocardium through sympathetic innervation. It generates calcium overload in the cardiomyocytes, thus producing the typical lesion of contraction band necrosis, characterized by hypercontrolled sarcomeres, intensely eosinophilic transversal bands, with interstitial mononuclear inflammatory response[19,40,57,63-67]. Catecholamines also stimulate the release of vascular endothelial growth factors (VEGF), epidermal growth factor (EFG) and interleukins, but the role of inflammatory reaction in the acute presentation of TCM has not yet been elucidated[66].

The hypothesis of catecholamines involvement in the pathogenesis of TCM is in line with the regional differences observed for beta 2 adrenergic receptors, as they are present in higher intensity in the left ventricular apex region. In these patients, catecholamines response, which has ionotropic and chronotropic action, is such that it causes a switch from the stimulatory G protein (Gs) to inhibitory (Gi). This event is supposed to protect the myocardium from further damage, but in this case, it apparently generates a negative inotropic response[66].

Pelliccia et al.[40] propose a synthesis of the evidence. They suggest the possibility of a pathophysiological process characterized by a high concentration of catecholamines and coronary spasm during the acute phase of the syndrome, which increases energy expenditure as well as reduces blood supply r. In other words, an imbalance between supply and demand is stablished, generating a myocardial stun and changes in glucose and fatty acids metabolism. None of the mechanisms suggested so far, however, satisfactorily explained the pathophysiology of TCM[68].

MANIFESTATIONS

As in ACS, the most frequent manifestation of TCM is chest pain, which occurs in 75 to 80% of cases. This pain is mild to moderate at rest, which may be accompanied by dyspnea (20–46.9%), syncope (7.7%), palpitations, hypotension, nausea, vomiting, arrhythmias, febrile syndrome and important bradycardia. Unusual initial manifestations (20%) include heart failure and cardiogenic shock[11,16,22,34,66,69-73].

The initial presentation is easily confused with ACS and it is not always possible to establish the initial stressful event, making the differentiation even more complex[57]. It is worth noting, however, that AMI and TCM coexist in some patients. AMI has been suggested as a triggering factor, since the condition may cause elevation of catecholamines[74-77].

Whether TCM is a cardiomyopathy or not is still controversial. There is a suggestion that it may be an ACS. It presents myocardial ischemia, troponin elevation, ventricular abnormalities and electrocardiographic changes features of ACS. Besides, clinical presentation and possible pathophysiology differ from other cardiomyopathies[78].

ELECTROCARDIOGRAM CHANCES

The electrocardiographic findings vary depending on the time of progression of cardiomyopathy. Most commonly, there is an elevation of the ST segment (mainly in the precordial leads), negative T wave, Q waves or abnormal progression of the R waves - changes also common to AMI - as well as prolongation of the corrected QT interval (QTc)[54,55,79,80]. Initially, ST elevation is observed (lower than that observed in AMI). Subsequently, the condition progresses with inversion of the T wave, with the first peak of negativity within three days after the onset of symptoms. Between the second and the sixth day, there

is a transient resolution of the negative T wave and the ST elevation ends. Afterwards, deeper negative T waves appear, with longer QTc interval prolongation, which may persist for two to four months[5,6,11,12,81,82].

Some electrocardiographic criteria have been proposed to differentiate between AMI and TCM (Table 2). The highest sensitivity criterion is represented by the absence of reciprocal changes in lower leads, while a concomitant elevation of ST in aVR, anteroseptal and lower leads represents the highest specificity criterion.

Table 2 - Synthesis of the main electrocardiographic findings in differentiating TCM from other syndromes[83-88]

Electrocardiographic criteria	Sensitivity	Specificity
Absence of reciprocal changes in inferior leads	100%	69%
STE in aVR in the absence of STE in V1	96%	96%
Positive T wave in aVR in the absence of negative T wave in V1	95%	94%
Absence of abnormal Q	83%	69%
STE in V4–6/ STE in V1–3 ≥ 1	80%	77%
STE in V3-5 ≥ 1mm in the absence of STE in V1 ≥ 1mm	74,2%	80,6%
STE V in 3 ≥ 1mm in the absence of STE in V1 ≥ 1mm	67,7%	80,7%
STE in lead II ≥ 1mm	62,5%	92,6%
STE in aVR together with ST Supra in the lower and anteroseptal leads	12%	100%

Subtitle: STE: ST-segment elevation

TCM MARKERS

There is no consensus on the exclusive markers of TCM or their diagnostic values. There are markers common to TCM and AMI[88].

Despite its role in pathophysiology, the increase in catecholamines, unlike expectations, is not always present[87]. Mandhavan et al.[89] assessed the levels of normetanephrine and metanephrine in 10 patients with AMI and 19 with TCM and did not find significant differences (respectively, 0.64 nmol / l — 95% CI: 0.43-0.97 — vs 0.53 nmol / l — 95% CI: 0.32-0.70 —, p = 0.44, and 0.10 nmol / l — 95% CI: 0.10-0.22 — vs 0.16 — 95% CI: 0.10-0.38 —, p = 0.29) between the two groups, in addition to having found normal urinary metanephrine levels in the 24-hour urine test in TCM group. Christensen et al.[90] evaluated 32 TCM patients and found no significant differences in plasma norepinephrine.

On the other hand, Wittstein et al[91] found plasma norepinephrine levels of 2284 pg/mL (1709–2910) vs 1110 pg/mL (914–1320) (p <0.005) upon the evaluation of 19 patients, 13 with TCM and 7 with IAM Killip III. The catecholamine values were 2 to 3 times higher in TCM group compared to AMI group.

Taken together, studies suggest caution in determining catecholamines as diagnostic markers [90] and there is little practical application.

Related to stress, cortisol is also evaluated as a biomarker for TCM[87]. Mandhavan et al.[89] showed nocturnal plasma elevation in up to 50% of patients in the initial phase, whereas 23% of the control group also had elevated levels and all TCM patients had normal urinary levels.

In TCM, markers of myocardial injury, such as troponin, lactic dehydrogenase (DHL), myoglobin, creatine phosphokinase MB (CK-MB), are present, but at a lower degree of variation in comparison to AMI cases. Troponin, for example, is present at levels up to 7 times lower than those observed in AMI; its levels rise in approximately 90% of patients[87,89]. Most patients, therefore, may show a modest troponin elevation[92].

Agewall et al.[92] quantified troponin levels in patients with ACS and TCM and suggested cutoff points for both diseases. Table 3 sintetizes the findings.

In a review of 114 cases, minimum, maximum and average values of troponin I and T, CK and CK-MB (Table 3) were measured using different kits. The authors concluded that troponin T levels higher than 6 ng / mL or troponin I above 15 ng / mL are unlikely in TCM and, therefore, these can be considered cutoff points. A moderate correlation between troponin T level and initial ejection fraction ($R^2 = 0.6$) was also shown[93].

Table 3 - Expected values of biomarkers present at TCM [67]

Biomarker	Minimum value	Maximum value	Mean
Troponine I (ng/mL)	3	13	6.5
Troponine T (ng/mL)	3	7	3.6
CK (U/L)	20	3,395	556.1
CK-MB (U/L)	2	111	32.,9

Subtitle: CK: creatine phosphokinase; CK-MB creatine phosphokinase MB

Already considered as markers for AMI, the N-terminal fragment of the cerebral B natriuretic pro-peptide type (NT-proBNP) and the B-natriuretic peptide (BNP) are considered as promising markers of TCM. They are released at the time of baseline cardiac hypercontractility, with an increase proportional to sympathetic activation and level of cardiac dysfunction. The elevation occurs in the first 12 hours of symptoms, peaking in 24 hours, with mean BNP values of 617 pg / mL and NT-proBNP of 4,382 pg / mL[82,89,94].

MicroRNAs (miR) have been investigated as potential markers for cardiovascular disease, since the expression is specific for each tissue and may reflect pathological states[95]. TCM patients have significant overloading of miR-16, miR-26a, miR-1 and miR-133a compared to healthy patients who have already had AMI. When the 4 miR are sought, the resulting marker has a sensitivity of 96.77% and specificity of 70.37% regarding the differentiation between TCM and AMI[96].

Relationships for differentiation between AMI and TCM

Due to the difficulty of interpreting enzyme levels, relationships are proposed to help differentiate between TCM and AMI[97]. These relationships, together with sensitivity and specificity, are present in Table 4.

Table 4 - Relationships of proposed biomarkers for differentiation between AMI and TCM[97-100]

Relationship	Sensitivity	Specificity
BNP/TnT ≥ 1,272	52%	95%
BNP/CKMB ≥ 29.9	50%	95%
NTproBNP /TnT ≥ 2,889	91%	95%
NTproBNP /TnT≥ 5,000	83%	95%
High sensitivity TnT /CKMB ≥ 0.015	85.7%	67.6%
High sensitivity TnT /CKMB ≥ 0.017	83.3%	78.1%

Units: BNP (pg/l); NTproBNP (ng/l); TnT (µg/l); myoglobin (µg/l). **Acronyms:** cerebral natriuretic peptide (BNT), creatine phosphokinase MB (CK-MB), N-terminal fragment of the pro-brain natriuretic peptide type B (NT-proBNP), Troponin T (TnT).

RADIOLOGICAL EXAMS

The essential and most frequently used test for the diagnosis of TCM is the echocardiogram. With the evolution of medical technologies, however, ventriculography and magnetic resonance have gained an essential role in TCM diagnosis[87].

The echocardiogram is a practical, non-invasive technique, easy to use in the emergency care. It reveals, in the acute phase, apical ballooning caused by akinesia, dyskinesia or ventricular hyperkinesia. Typically, abnormalities are observed to extend beyond the distribution limits of a single artery. The classic and most frequent pattern consists of compensatory baseline hyperkinesia and apical dyskinesia, and is therefore called the **apical type**. Some variants, however, are described: **mid-ventricular type**, which is characterized by hypokinesia in the middle region of the ventricle, with preservation of the apex; **basal type**, also called inverted TCM, which consists of basic hypokinesia with apex and middle region preservation (related to pheochromocytoma and subarachnoid hemorrhage); **isolated focal type**, characterized by dysfunction of cardiac segments; **global type** (or biventricular TCM), composed of hypokinesia in all cardiac segments, besides being associated with a higher risk of complications and hemodynamic instability; and **reverse mid-ventricular type**, described as hyperkinesis of the mid-ventricular region with akinesia or apex and base hypokinesia, isolated right ventricular involvement and ventricular apical dysfunction[9,11,56,87,100-106].

The typical presentation usually corresponds to 70-85% of the cases, while the ventricular apex is spared in 15% of the cases[66]. Regarding presentation morphologies, Kato et al.[107] reported 144 cases, 59% of which were basal type, 49% mid-ventricular type and 6.9% focal type, all having basal-septal segment abnormality, whereas Templin et al.[108] reported the following frequencies: 81.7% for the apical pattern, 14.6% for the mid-ventricular pattern, 2.2% for the basal pattern and 1.5% for the focal pattern.

The echocardiogram may also contribute to the detection of left ventricular outflow obstruction, which is found in 10% to 25% of TCM patients. Conventional and contrast 2D have, respectively, 56% to 72% and 88% to 96% sensitivity and thus are used for diagnosis[108-111].

Coronary angiography and ventriculography are invasive methods capable of detecting, respectively, coronary lesions, when they are present, and ventricular hypokinesia, dyskinesia and akinesia, allowing the

identification of ballooning and the same similar image patterns described for cardiac echocardiography[100]. In coronary angiography, patent arteries without obstruction and injuries are usually found[98,101]. In some patients, rupture of atheromatous plaque and transient thrombotic occlusion may be observed[95]. In 86.5% of the patients, left ventricular ejection fraction is reduced, verifiable by ventriculography, while the left ventricular end diastolic pressure is increased in 93% of patients[105]. Figure 1 depicts the findings during diastole and systole in ventriculography.

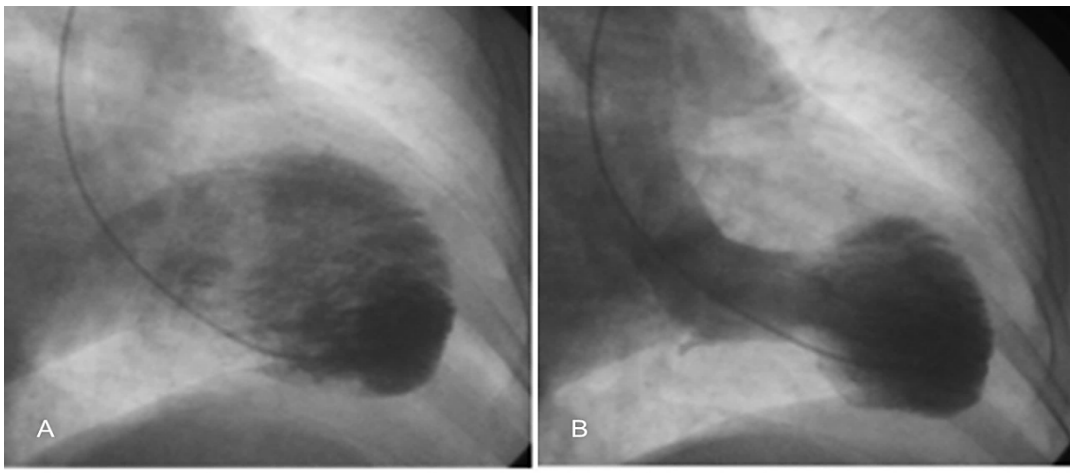

Figure 1 – Ventriculography of Takotsubo cardiomyopathy in diastole (A) and systole (B), showing apical ballooning. Adapted from Góes et al.[101]

Angiotomography can also be useful in the investigation of TCM, as well as in case of suspected TCM in order to exclude coronary obstruction[112].

Magnetic resonance imaging allows the assessment of anatomical patterns, movement variability of the ventricular wall and quantification of function and extracellular volume, in addition to providing information on pericardial and pleural effusions and on the presence of thrombi. This enables the differentiation of a reversible dysfunction, TCM, which is characterized by edema and inflammation, from an irreversible condition, such as AMI, characterized by necrosis and fibrosis[87,95].

The scintigraphy imaging can also be employed using ^{123}IMIBG, a radioactive marker analogous to norepinephrine. The exam assesses the uptake, storage and release of the marker, providing information on sympathetic nerve activity[95,100]. In a patient with TCM, there is sympathetic hyperactivity, but with reduced marker uptake in regions of akinesia. Nevertheless, scintigraphy imaging has limited practical application[96].

DIAGNOSTIC CRITERIA

Various diagnostic criteria have been proposed for assessment of TCM, given the difficulty in recognizing the pathology and differentiating it from an ACS. The first criteria were suggested in 2003 by Japanese researchers. Since then, several European, American, and Japanese organizations, as well as individual authors have proposed new observations on the diagnosis, but there is still no consensus on it[112,113].

Although little appreciated, the criteria of the Mayo Clinic, initially proposed in 2004 and revised in 2008, are widely disseminated[112-113]. The criteria presuppose the mandatory presence of four conditions to establish the diagnosis of TCM: a) hypokinesia, akinesia or transient dyskinesia of the middle segment, including the apical segment or not, exceeding the epicardial vascular distribution; b) absence of obstructive coronary disease or evidence of acute plaque rupture at angiography; c) recent abnormality on the electrocardiogram (ST-segment elevation and / or T-wave inversion) or modest elevation of cardiac troponin; d) absence of pheochromocytoma and myocarditis[114].

Given that the Mayo Clinic criteria have clinical limitations, a new form of diagnosis has been proposed: the InterTAK diagnostic score[112,113]. The InterTAK score has seven variables, each one representing a score value: female (score = 25); emotional trigger (score = 24); physical trigger (score = 13); absence of ST segment depression (score = 12), except in aVR; psychiatric disorders (score = 11); neurological disorders (score = 9); prolongation of the QTC (score = 6), totaling 100 points. A score ≥ 50 represents a sensitivity of 94.7% for the diagnosis of TCM. The cutoff value of 40 points has a sensitivity of 89% and specificity of 91%[115]. This score takes into account the focal TCM and does not rule out the possibility of pheochromocytoma or AMI in the patient's history, unlike the Mayo Clinic criteria[112].

CONCLUSION

Although reported 30 years ago, there is still no exact description of the pathophysiology of Takotsubo cardiomyopathy, even though the different findings suggest the interaction of the various mechanisms already proposed. Besides that, a universally accepted diagnostic criterion has not been established yet, which leads to several misdiagnoses. Further research using animal models is necessary to understand the pathogenesis complexity and thus clarify it. It is also necessary to disseminate knowledge about the diagnosis and the very existence of the disease, in order to avoid underdiagnosis and facilitate the recognition of pathology in emergency care.

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