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# Takotsubo Syndrome and Its Genetic Relationship: Case Report and Narrative Literature Review

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## ABSTRACT

***Introduction:*** **Takotsubo Syndrome (TTS) is presented as a temporary loss of systolic function, it is usually associated with emotional or physical stress. However, its pathophysiology is not well defined. Thus, this article seeks the relationship between the genetic factor and the development of Takotsubo Syndrome.**

***Methodology:*** **The study is about a narrative review and two case reports on TTS.**

***Results:*** **TTS is related to the excess of catecholamines, and its genetic linkage is strongly considered due to recent studies where occasionally it has been noticed its hereditary connections, such as: increased cardiac sensitivity to catecholamines and cardiac vulnerability to adrenergic stressors, impaired regulation of norepinephrine release, syndrome fragile X, and CD36 deficiency.**

***Discussion:*** **There is still no conclusion of the leading factors to TTS. However, being female, being in the postmenopausal period, and exposed to stressful conditions are some of the risk factors that can develop the disease, and which are better accepted by the scientific community.**

***Conclusions:*** **Although TTS is a disease of low prevalence, it is increasingly present in the routine of the cardiologist. The great difficulty lies in its diagnosis as it does not present a pathognomonic symptom and it is similar to other diseases, such as ACS. This causes it to pass absent-mindedly during the emergency primary investigation. Thus, there is a need to expand studies related to this disease and to investigate its genetic association.**

**Keywords:** Cardiology, differential diagnosis, Takotsubo cardiomyopathy.

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## I. Introduction

Takotsubo Syndrome (TTS), also called Takotsubo cardiomyopathy, stress cardiomyopathy, transient left ventricular apical ballooning syndrome (LV-ABS), transient left ventricular dysfunction syndrome or broken heart syndrome, manifests as a disorder in VE mimicking an Acute Myocardial Infarction (AMI). However, TTS is characterized by temporary loss of systolic function, usually associated with emotional or physical stress [1]. Clinically, it presents itself as typically anginal chest pain, electrocardiographic changes, and myocardial necrosis marker [2].

Among the diagnoses for coronary syndromes, TTS has a prevalence of 2%. Nevertheless, it is a problem that is gaining attention in the scientific literature because it is a topic that involves many predisposing factors such as age, sex, and quality of life [3]. Furthermore, the disease is more prevalent in postmenopausal women ages between 65 and 751. In addition, there are risk factors for the development of broken heart syndrome that are related to the quality of life of each patient, such as smoking, alcohol consumption, hyperlipidemia and anxiety [2], [4].

The pathophysiology of this involvement is not well defined, but several mechanisms for its development [5] have been described before. It is known that when the patient suffers trauma or the loss of a loved one, there is a possibility of catecholamine release, causing excessive myocardial adrenergic stimulation and a marked increase in calcium in myocytes [6]. Otherwise, the experience of trauma stimulates the subcortical brain circuit, resulting in the release of norepinephrine in the hypothalamus. This process causes stimulation of the adrenal gland function and, consequently, it causes an increase in cortisol release and an increase in the release of catecholamines [5], [6]. Thus, due to this entire

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process, the patient evolves to the expression of characteristic symptoms of acute myocardial syndrome, yet in a transitory way [5], [6].

Despite being a very similar disease to acute coronary syndrome and also sharing many symptoms, TTS has a very favorable prognosis for the patient, due to the transitory characteristic of its electrocardiographic alterations [7].

Even though this article seeks the relationship between the genetic factor and the development of Takotsubo syndrome, it also brings the report of two patients (sisters) who were diagnosed with Takotsubo syndrome within a period of two years.

## II. Methodology

This is a narrative bibliographic review and two case reports on Takotsubo Syndrome. The literature search was carried out in the bibliographic databases LILACS, NCBI, PUBMED and MAYO CLINIC in May 2021, using the descriptors "Takotsubo Cardiomyopathy" and "Hereditary". Furthermore, the Boolean operator "AND" was used among the descriptors. The inclusion criteria were articles published in English in the period between 2016 and 2021, due to the goalsearch for the most recent articles on the subject. In regard to the exclusion criteria, there were no articles included that did not address the topic in the title and abstract, and those that were repeated among the bibliographic databases. Thus, 17 articles were found in LILACS, 21 in PUBMED, 12 in the NCBI database and 1 in the Mayo Clinic database, with a result of 30 articles. Of this total, only 2 were selected from the NCBI database, 7 from PUBMED, 12 from LILACS and 1 from the Mayo clinic. Therefore, 14 articles resulted to compose the literature. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used as quality evaluation criteria.

Furthermore, this study was submitted to and approved by the Research Secretariat, under protocol number 5.023,305.

## III. Case Reports

### *A. Case Report 1*

The patient, a 62 years old female, arrived at the referral hospital in the city where she lives, complaining of symptoms that indicate Acute Coronary Syndrome (ACS) on April 7, 2017. She reported that her mother had died on that same day. Upon arrival at the emergency room, an ACS care protocol was performed (electrocardiogram in 10 minutes). The ECG showed an elevation of the ST segment in the precordial leads from V3 to V6, characterizing an ischemic process in the anterolateral wall of the heart.

The patient was promptly referred to cardiac catheterization, showing absence of coronary obstructions and the left ventricle had a slightly increased end-diastolic volume with an area of moderate hypokinesia in the middle-anterior and middle-inferior segments. The pressure of the aorta artery (AO) was 138 /69 mmHg and left ventricular pressure (VE-PS/PD2) = 138/10 mmHg. An echocardiogram was performed, which showed LV end systolic diameter of 20 mm (RV 25 to 40 mm), end diastolic volume of 62 ml (RV 73 to 156 ml), systolic volume of 49 ml (RV 54 to 99 ml), and end-systolic volume of 13 ml (VR 18 to 57 ml). A prolapse of the anterior mitral leaflet was presented, without regurgitation.

Given the clinical picture with signs and symptoms of acute coronary syndrome, an ECG showing anterolateral elevation and absence of coronary obstructions in cardiac catheterization, and segmental dysfunction of the left ventricle, confirmed the diagnosis of Takotsubo syndrome.

### *B. Case Report 2:*

The patient, a 59-year-old female, arrived at the referral hospital in the city where she lives, as did her sister (case 1), also with symptoms of Acute Coronary Syndrome (ACS) on June 18, 2019. She reported periods of emotional stress during anamnese, due to her aunt who was bedridden and under her care. A protocol for ACS with an electrocardiogram showing ST-segment elevation in the inferior wall was performed in the emergency department (Fig. 1 and 2).

The patient was promptly referred for cardiac catheterization, which showed dominant right coronary artery according to the pattern of coronary circulation, and coronary arteries with no significant obstructive lesions. Left ventriculography showed a left ventricle with normal end-diastolic volume and apical dyskinesia. Given the clinical picture with signs and symptoms of acute coronary syndrome, an ECG showing anterolateral elevation and absence of coronary obstructions in cardiac catheterization, and segmental dysfunction of the left ventricle, confirmed the diagnosis of Takotsubo syndrome.

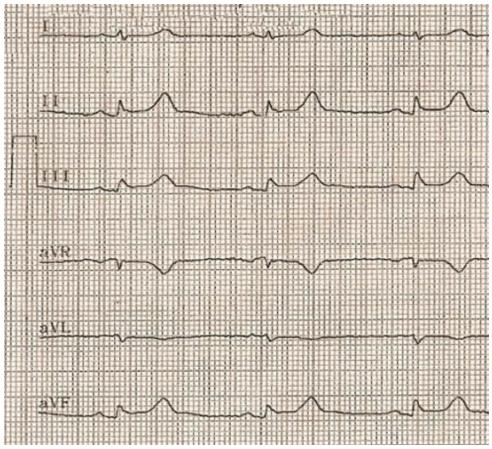


Fig. 1. Case Report 2 ECG of the DI, DII, DIII, AVR, AVL and AVF derivation.

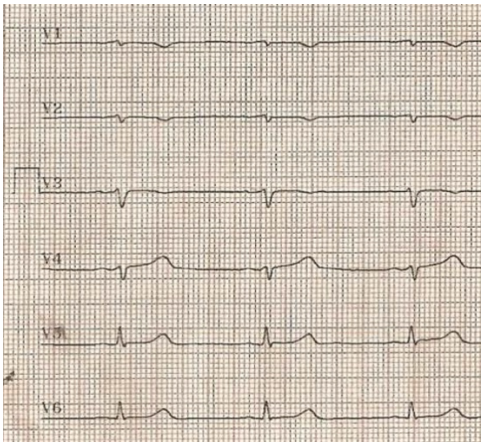


Fig. 2. Case Report 2 ECG of V1 – V6 derivation.

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## IV. Results

The articles analyzed were published in international and national journals. Thereby, 3 case reports, 3 cross-sectional studies, 1 non-randomized case-control study, 3 randomized case-control studies, 1 cohort study, 2 systematic reviews, and 1 letter to the editor were selected. The oldest study was published in the year 2016 and the most recent study in the year 2021. In addition, of the 30 studies selected for reading, 15 had greater relevance for this study and are shown in the table below. They are separated according to title of the article, authorship/year of publication, and methodology used in the study (Table I).

TABLE I: Review Results

| Article | Methodology | Authorship Year |
|---|---|---|
| Reference [16] | Cross-Sectional Study | 2020 |
| Reference [18] | Case Report | 2019 |
| Reference [12] | Case Report | 2019 |
| Reference [12] | Non-Randomized Clinical Study | 2018 |
| Reference [15] | Cross-Sectional Study | 2018 |
| Reference [22] | Randomized Case-Control Study | 2018 |
| Reference [14] | Case-Control Study | 2018 |
| Reference [11] | Case-Control Study | 2017 |
| Reference [10] | Cohort Study | 2017 |
| Reference [17] | Systematic Review | 2016 |
| Reference [21] | Letter to the Editor | 2016 |
| Reference [19] | Cross-Sectional Study | 2020 |
| Reference [8] | Systematic Review | 2021 |
| Reference [9] | Case Report | 2016 |

According to the studies found, Takotsubo Syndrome (TTS) is systemic and it is related to an excess of plasma catecholamines, just as it occurs with myocardial ischemia. There are studies that mention that there is no genetic predisposition to TTS, however, there are other studies that support the hypothesis of a genetic cause for this disease [8]-[11].

Moreover, there are factors that favor the presence of a genetic and hereditary relationship that leads to TTS, such as: being female; post-menopause; triggering stressor; sudden environmental stress; genetic mutations that are not under the sympathetic and estrogenic regulation; nucleotide polymorphisms for sympathetic regulation, as presented by [15] which show that there are regional differences in functional contractility after stress; and administration of catecholamines due to beta-2-adrenergic receptor modulation [8], [10]-[15]. Furthermore, Noah MLN et al infers that there is no evidence of genetic correlation and the development of TTS, but estrogen is an important protective factor for SCA [8].

Reference [16] found 25 genes associated with TTS, 10 of which are considered stimulators and 15 are considered inhibitors. The MGFGE gene promotes the secretion of a glycoprotein that works by relieving the post-ischemic injury [16]. The component C3 is associated with the body's response to a stressful stimulus [16]. The drastic increase of SAA1 is associated with tissue damage [16]. Alpha-2-macroglobulin, a protein of the innate immune system, is increased along with the complement and the coagulation cascade. Also, it is increased in TTS since it is considered a pathology with a pro-thrombotic state [16]. In contrast, stress can lead to TTS in the same way that it elevates the concentration of thyroid hormones and plasma albumin. Otherwise, the genetic mutation that alters lipoproteins leads to hyperlipidemia by altering the lipid metabolism, causing hyperlipidemia and possibly leading to diabetes, which is a risk factor for the development of TTS16. Likewise, [17] described modifications in genes of certain receptors that predispose to STT17 (Table II).

TABLE II: Genetic Mutations that Predispose to TTS [17]

| Receptor | Mutated Gene | Effect |
|---|---|---|
| Beta1-adrenergic receptor | ADRB1 | Increased cardiac sensitivity to catecholamines |
| Beta2-adrenergic receptor | ADBR2 | Increased cardiac vulnerability to adrenergic stress |
| Alpha2C-adrenergic receptor | ADRA2C | impaired regulation of norepinephrine release |
| Fragile X mental retardation | FMR1 | Fragile X Syndrome |
| CD36 | CD36 | CD36 Deficiency |

Data in the literature emphasize that for a TTS diagnosis, one should use contrast myocardial echocardiography and 3D parametric imaging contrast echocardiography [16], [18]. Another fact to be considered is the concentration of Chromogranin-A in the plasma of patients with suspicion of TTS or Acute Myocardial Infarction (AMI), however, due to the half-life of this compound and the time span for the patient to attend the hospital/medical care, there are still great difficulties in using it as a diagnostic test [19].

Stress cardiomyopathy (CM) is a systemic syndrome and a variant disorder of the copy number, in which the haploinsufficiency of overlapping genes with deletions or overexpression of duplicated genes leads to a relatively subtle modification of cardiac or adrenergic physiology, in a way that these individuals are at increased risk of suffering from CM when exposed to specific environmental triggers [20], [21].

When [22] studied the morphophysiology of Takotsubo Syndrome, they observed that innate immunity can lead to heart regeneration, leading to a full recovery of the heart to its normal physiology. These same researchers also infer that the expression of Toll-like proteins (TLR) and messenger RNA play a crucial role in the disease regeneration [22].

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Otherwise, [9] researched the genetic correlation between the development of TTS and type 1 dystrophy (MD1), therefore they reported that additional genetic alterations of CTG, a trinucleotide characteristic of MD1 disease, does not cause TTS, but patients already diagnosed with MD1 may have a higher risk of developing TTS, which is another risk related factor.

## V. Discussion

Takotsubo Syndrome was first reported in Japan in 1990 by Menezes [5]. Due to its importance and similar characteristics to the Myocardial Ischemic Syndrome, it is gaining prominence in the world's scientific literature [24]-[26]. Its name derives from a Japanese word which means octopus trap, this term was related to the pathology as a result of its morphological presentation in the Left Ventricle [27]. It was only in 2017 that this disease was first reported in Latin America [28].

There are several factors that can predispose the development of Takotsubo syndrome, including the death of a loved one or even some trauma suffered by the patient [29], [30]. In comparison with the literature, the patients presented in this study had several risk factors, among which we can mention: female gender, post-menopause period and emotional stressor [27]-[31].

Among the predisposing factors the syndrome, there is still no description of a precise genetic component [32]-[36]. There are several reports among mothers and daughters or among sisters with TTS, that suggest a genetic factor that develops the disease. Genetic predisposition is usually associated with environmental factors, recessive susceptibility and/or polygenic etiology [27], [32]-[36]. Therefore, quality of life has a great influence on triggering the pathology in question, and this may be the basis for the occurrence of TTS in two sisters who had a change of life and routines after the death of their mother and the need to take care of a bedridden aunt, respectively.

Unlike what was found in these reports, [37] infer that most of the participants in their research have a personal history of arterial hypertension, smoking, psychiatric disorders, or diabetes mellitus; and as seen in this study before, it is a disease found predominantly in women.

Otherwise, the portion of the heart affected in these patients and evidenced by the ECG has shown compliance with the literature: ST-segment superelevation with aggression to the anterolateral wall of the heart (left ventricle) [38]. And, with the clinical follow-up of the patients for a long period of time, the normalization of the ECG in the Q wave can be noticed in a way that this change results from the functional and structural recovery of the heart [38].

As mentioned above, the European Society of Cardiology (ESC) has developed diagnostic criteria to differentiate Takotsubo Syndrome from Acute Coronary Syndrome (ACS) that make up the InterTAK Diagnostic Score, which takes into account factors that are scaled by point counts, such as female gender, emotional or physical stress, electrocardiographic characteristics, and presence of psychiatric or neurological disease. The patient is stratified into two categories: low (< 70 points) and high probability (> 70 points) of developing TTS [39]. Thus, the patient in case 1, in her anamnesis, presented 61 points on the InterTAK Diagnostic Score and is classified as having a low probability of developing TTS. The patient in case 2 had 67 points on the InterTAK Diagnostic Score, characterizing a low probability of developing this cardiomyopathy (Table III).

TABLE III: InterTAK Diagnostic Score of Patients in Case 1 and 2 [39]

| Variables | CASE 1 Score | CASE 2 Score |
|---|---|---|
| Female gender (25 points) | P | P |
| Emotional Stress (24 points) | P | P |
| Physical Stress (13 points) | - | - |
| Absence of ST segment depression (12 points) | P | P |
| Previous psychiatric illness, acute or chronic (11 points) | - | - |
| Previous neurological disease, acute or chronic (9 points) | - | - |
| QT interval prolongation (women > 460 ms; men > 440 ms) (6 points) | - | P |

Acute Coronary Syndrome (ACS) and Takotsubo Syndrome can be otherwise confused, which is why [40] demonstrated in his article the difference between these two diseases, using several diagnostic criteria, as shown in Table IV.

TABLE IV: The Comparison of Diagnostic Criteria for ACS and STT [40]

| Diagnostic Criteria | STT | SCA |
|---|---|---|
| Transient left ventricular dysfunction | +++ | + |
| Emotional/Physical Trigger | ++ | + |
| Neurological disorders as a trigger | ++ | + |
| New ECG Abnormalities | ++ | +++ |
| Elevated cardiac biomarkers | + | +++ |
| Rule out myocarditis by infection | + | + |
| More frequent in postmenopausal women | + | - |
| Significant coronary artery disease | + | +++ |

Regarding the conduct to be adopted, patients are generally referred to imaging exams. Therefore, those with a low probability of developing TTS are directed to coronary cineangiography and those with high probability are directed to transthoracic echocardiography [39]. Although this is already a consensus among professionals, there are doubts about the most appropriate procedure to be followed due to the existence of too many diagnostic exam options, such as electrocardiogram, myocardial necrosis markers, echocardiography, coronary angiography, and magnetic resonance [40], [41], [42].

As for the pathology prognosis, TTS generally has a positive progress, but it can evolve to a worsening [43], [44] if associated with a triggering stressor. Furthermore, [44] found that chest pain is a protective factor for patients who suffered from broken heart cardiomyopathy. Therefore, a positive clinical evolution of the patients mentioned above may be present as a result of this symptom's progress.

Regarding genetic factors, there is still no consensus in the literature, as seen here, therefore, [45] infers that the genetic factor of the disease is related to recessive susceptible allele and these interact with environmental factors, however it differs from that found in this review. Reference [46] mentions that genetic susceptibility suggests a polygenic etiology, as found in this research, also mentioning that these genetic mutations are related to dysregulation of adrenergic pathways. Furthermore, despite all factors, already mentioned, that may be related to the predisposition or pathophysiology of Takotsubo's disease, this cannot be considered a genetic cardiomyopathy [47].

Likewise, factors such as cardiotoxicity by catecholamines, metabolic alterations, epicardial coronary vasospasm and microvascular dysfunction are mentioned by [48] as predisposing factors to the disease. Thee same authors also mention the role of catecholamines in decreasing the viability of myocytes and causing dysfunction of cardiac contractility [48]. On the other hand, [49] infer that stressors can acutely induce the bioavailability of cortisol and catecholamines.

## VI. Conclusion

Despite TTS being considered a low-prevalence disease, it has been shown to be more present in the daily routine of cardiologists. Furthermore, the great difficulty is in its diagnosis due to the fact that it does not present a pathognomonic symptom and it is similar to other diseases, such as Acute Coronary Syndrome. This causes it to pass absent-mindedly during the emergency primary investigation. Thus, these reports demonstrate the need to expand studies related to the referred pathology and to investigate its genetic association.

Throughout the research for the literature review construction, it was possible to identify that most studies did not present an objective conclusion and, therefore, they are in need of more experiments and more specific and detailed evaluations to reach a precise result.

## Conflict of Interest

Authors declare that they do not have any conflict of interest.

## References

[1] Cordeiro JVC, Lima LRS, Ferreira RRS. Síndrome de Takotsubo: um diagnóstico diferencial do infarto agudo do miocárdio. *17º Congresso de Iniciação Científica da FASB*. 2019; 17(1): 1-3. Portuguese.

[2] Campos FAD, Ritt LEF, Costa JPSl, Cruz CM, Feitosa-Filho GS, Oliveira QB, et al. Fatores associados à recorrência na síndrome de takotsubo: uma revisão sistemática. *Arq Bras Cardiol.* 2020; 114(3): 477-83. Portuguese.

[3] Parodi G, Citro R, Bellandi B, Pace S, Rigo F, Marrani M, et al. Tako-tsubo cardiomyopathy and coronary artery disease: a possible association. *Coron Artery Dis.* 2013; 24(6): 527-33.

[4] Fernandes F, Montera MW. Síndrome de Takotsubo: uma doença recorrente?. *Arq Bras Cardiol.* 2020; 114(3): 484-5. Portuguese.

[5] Casasola AB, Varela MS, Salgado OMC, Rivera PC, Salas BR, Villalobos IJT. Síndrome de Takotsubo. *Revista Medica de la Universidad de Costa Rica.* 2020; 14(2): 69-80. Portuguese.

[6] Campos MTFS, Valente FMQ, Araújo RMA, Bressan J. Mourning and Takotsubo cardiomyopathy neuroendocrine implications and nutricional management. *Rev Assoc Med Bras.* 2018; 64(10): 952-9.

[7] Cordeiro JVC, Lima LRS, Ferreira RRS. Síndrome de Takotsubo: um diagnóstico diferencial do infarto agudo do miocárdio. *17º Congresso de Iniciação Científica da FASB.* 2019; 17(1): 1-3. Portuguese.

[8] Noah MLN, Adzika GK, Mprah R, Adekunle AO, Adu-Amankwaah J, Sun H. Sex-Gender disparities in cardiovascular diseases: the effects of estrogen on eNOS, lipid profile, and NFATs during catecholamine stress. *Cardiovascular Medicine.* 2021; 8: 1-10.

[9] Bridgman PG, Finsterer J, Lacey C, Kimber B, Parkin PJ, Miller AL, Kennedy MA. CTG-repeat expansions in the DMPK gene do not cause takotsubo syndrome. *Int J Cardiol.* 2016; 203-107-8.

[10] Eitel I, Moeller C, Munz M, Stiermaier T, Meitinger T, Thiele H, et al. Genome-wide association study in takotsubo syndrome - preliminary results and future directions. *Int J Cardiol.* 2017; 236: 335-9.

[11] Pizzino G, Bitto A, Crea P, Khandheria B, Vriz O, Carerj S. Takotsubo syndrome and estrogen receptor genes partners in crime?. *J Cardiol Med.* 2017; 4-268-76.

[12] Lacey CJ, Doudney K, Bridgman PG, George PM, Mulder RT, Zarifeh JJ. Copy number variants implicate cardiac function development pathways in earthquake-induced stress cardiomyopathy. *Sci Rep.* 2018; 8(1): 7548.

[13] Ekenback C, Tornvall P, Spaak J. Takotsubo twins. *BMJ Case Rep.* 2019; 12(4): 1-4.

[14] Mattson E, Saliba-Gustafsson P, Ehrenborg E, Tornvall P. Lack of genetic susceptibility in takotsubo cardiomyopathy, a case-control study. *BMC Med Genet.* 2018; 19(1): 1-7.

[15] Wright PT, Bhogal NK, Diakonov I, Pannell LMK, Perera RK, Bork NI. Cardiomyocyte membrane struccture and cAMP compartmentation produce anatomical variation in B2AR-cAMP responsiveness in murine hearts. *Cell Rep.* 2018; 23(2): 459-69.

[16] Pan XY, Zhang ZW. MFGE8, ALB, APOB, APOE, SAA1, A2M, and C3 as Novel biomarkers for stress cardiomyopathy. *Cardiovascular Therapeutics.* 2020; 2020: 1-11.

[17] Limongelli G, Masarone D, Maddaloni V, Rubino M, Fratta F, Cirillo A, et al. Genetics of Takotsubo Syndrome. *Heart Fail Clin.* 2016; 12(4): 499-506.

[18] Khanra D, Shrivastava Y, Duggal B, Kapoor KK. Familial apical dilated cardiomyopathy in a young man: a novel phenotype of Takotsubo syndrome or a new entity altogheter?. *BMG Case Rep.* 2019; 12(7): e231302.

[19] Tarantino N, Santoro F, Di Biase L, Di Terlizzi V, Vitale E, Barone R, et al. Chromogranin-A serum levels in patients with takotsubo syndrome and ST elevation acute myocardial infarction. *Int J Cardiol.* 2020; 320: 12-7.

[20] Lacey CJ, Doudney K, Bridgman PG, George PM, Mulder RT, Zarifeh JJ. Copy number variants implicate cardiac function and development pathways in earthquake-induced stress cardiomyophaty. *Scientific Reports*. 2018; 8(7548): 1-12.

[21] Madias J. Recurrence, lingering recovery course, mild variants, and "chronic" forms, of takotsubo syndrome. *Int J Cardiol.* 2016; 220: 70-1.

[22] Kolodzinska A, Czarzasta K, Szczepankiewicz B, Glowczynska R, Fojt A, Ilczuk T, et al. Toll-like receptor expression and apoptosis morphological patterns in female rat hearts with takotsubo syndrome induced by isoprenaline. *Life Sci.* 2018; 199: 112-21.

[23] Bridman PG, Finsterer J, Lacey C, Kimber B, Parkin PJ, Miller AL, et al. CTG-reapeat expansions in the DMPK gene do not cause Takotsubo Syndrome. *Int J Cardiol.* 2016; 203: 107-8.

[24] Hussain I, Muthusamy P, Riaz N. Stress Cardiomiopathy: a case of apical balloning syndrome followed bt Mid-ventricular balloning syndrome as recurrence. *American Journal of Medical Case Reports.* 2016; 4(2): 38-40.

[25] Maciel BA, Cidrão AA, Sousa ÍB, Ferreira JA, Messias Neto VP. Pseudoinfarto agudo do miocárdio devido à síndrome da disfunção ventricular apical transitória (síndrome de Takotsubo). *Revista Brasileira de Terapia Intensiva*. 2013; 25: 63-7. Portuguese.

[26] Sousa JMA, Knobel M, Buchelle G, Sousa JAM, Fisher CH, Born D, et al. Transient ventricular dysfunction (Takotsubo cardiomyopathy). *Arq Bras Cardiol.* 2005; 84(4): 1-3.

[27] Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi, TJ et al. International expert consensus document on Takotsubo Syndrome (part I): clinical characteristicas, diagnostic criteria, and pathophysiology. *European Heart Journal.* 2018; 39: 2032-46.
[28] Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the task force on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2016; 18 (1): 8-27.
[29] Campos MTFS, Valente FMQ, Araújo RMA, Bressan J. Mourning and Takotsubo cardiomyopathy neuroendocrine implications and nutricional management. *Rev Assoc Med Bras*. 2018; 64(10): 952-9.
[30] Prizanteli CC. Coração partido: o luto pela perda do cônjuge. M. S. Thesis, Pontifícia Universidade Católica de São Paulo, 2008. Portuguese.
[31] Fernandes F, Montera MW. Síndrome de Takotsubo: uma doença recorrente?. *Arq Bras Cardiol.* 2020; 114(3): 484-5. Portuguese.
[32] Cherian J, Angelis D, Filiberti A, Saperia G. Can takotsubo cardiomyopathy be familial?. *Int J Cardiol.* 2007; 121: 74–5.
[33] Kumar G, Holmes Júnior DR, Prasad A. "Familial" apical ballooning syndrome (Takotsubo cardiomyopathy). *Int J Cardiol.* 2010; 144: 444–5.
[34] Ikutomi M, Yamasaki M, Matsusita M, Watari Y, Arashi H, Endo G, et al. Takotsubo cardiomyopathy in siblings. *Heart Vessels.* 2014; 29: 119–22.
[35] Pison L, Vusser P, Mullens W. Apical ballooning in relatives. *Heart Vessels.* 2004; 90: 67.
[36] Caretta G, Robba D, Vizzardi E, Bonadei I, Raddino R, Metra M. Takotsubo cardiomyopathy in two sisters: a chance finding or familial predisposition?. *Clin Res Cardiol.* 2015; 104: 614–6.
[37] Naranjo-Restrepo S, Múnera-Echeverri AG, Gaviria-Aguilar MC, Gutiérrez-Prieto D, Vásquez-Trespalacios EM, Duque-Ramírez M. Características clínicas, demográficas y epidemiológicas de una cohorte de pacientes con síndrome de Takotsubo entre 2011 y 2016 en Medellín, Colombia. 2021; 34(1): 27-33.
[38] Namgung J. Electrocardiographic findings in takotsubo cardiomyopathy: ECG evolution and its difference from the ECG of acute coronary syndrome. *Clinical Medicine Insughts: Cardiology*. 2014; 8: 29-34.
[39] Oliveira AMP, Nascimento LS, Nunes PBM, Feil AC, Brum JC, Peixoto SL, et al. Síndrome de takotsubo e o uso do interTAK diagnostic score no diagnóstico diferencial com a síndrome coronariana aguda: relato de caso. *Clinical & Biomedical Research.* 2018; 38(4): 409-13. Portuguese.
[40] Caramelli B. A síndrome de Takotsubo existe como uma doença específica?. *Arq Bras Cardiol.* 2020; 115(2): 217-8. Portuguese.
[41] Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. *Arq Bras Cardiol.* 2018; 111(3): 436-539. Portuguese.
[42] Casasola AB, Varela MS, Salgado OMC, Rivera PC, Salas BR, Villalobos IJT. Síndrome de Takotsubo. *Revista Medica de la Universidad de Costa Rica*. 2020; 14(2): 69-80. Portuguese.
[43] Cordeiro JVC, Lima LRS, Ferreira RRS. Síndrome de Takotsubo: um diagnóstico diferencial do infarto agudo do miocárdio. *17º Congresso de Iniciação Científica da FASB.* 2019; 17(1): 1-3. Portuguese.
[44] Almeida Junior GLG, Mansur Filho J, Albuquerque DC, Xavier SS, Pontes A, Gouvêa EP. Registro multicêntrico de takotsubo (REMUTA) - aspectos clínicos, desfechos intra-hospitalares e mortalidade a longo prazo. *Arq Bras Cardiol.* 2020; 115(2): 207-16. Portuguese.
[45] Quesada MC, Castaño DM, Guerrero AN. Actualización de cardiomiopatia de Takotsubo. *Revista Médica Sinergia.* 2020; 5(4): e441. Portuguese.
[46] Tenuta Júnior M, Depieri JHF, Ventura MT. Cardiomiopatia de Takotsubo no pós-operatório de cirurgia abdominal: revisão de literatura e relato de caso. *COORTE*. 2020; 10: 41-50. Portuguese.
[47] Bagnasco MS, Núñes-Gil IJ. Psychological disorders in adults with inherited cardiomyopathies and Takotsubo syndrome. *Medwave.* 2016; 16(5): e6460.
[48] Casasola AB, Varela MS, Salgado OMC, Riveira PC, Salas BR, Villalobos IJT. Takotsubo syndrome. *Revista Médica de la Universidad de Costa Rica.* 2020; 14(2): 69-80.
[49] Carrasco SCY, Solís ERA, Fernandez JPS, Salguero PEE. Síndrome de Takotsubo: fisiopatologia, manifestaciones clínicas y diagnóstico. *Journal of American Health*. 2021; 4(1): 1-10. Portuguese.