

**TAKOTSUBO
SYNDROME IN
POSTMENOPAUS
WOMEN:
PATHOPHYSIOLOGICAL
PROCESSES AND
IMPORTANCE OF
DIFFERENTIAL
DIAGNOSIS**

Bianca Azevedo Berger Amaral

Universidade Vila Velha (UVV)

Vila Velha - ES

<https://orcid.org/0000-0003-3630-9635>

Laura Rafaela Marques

Universidade Estadual do Centro- Oeste
(UNICENTRO)

Guarapuava - PR

<https://orcid.org/0000-0001-6401-0054>

Ana Clara Pontes de Castro

Centro Universitário de Belo Horizonte
(UNI-BH)

Belo Horizonte - MG

<https://orcid.org/0000-0003-3985-9173>

Leticia Ramos Lopes

Universidade Vila Velha (UVV)

Vila Velha - ES

<https://orcid.org/0000-0002-7920-9397>

Anna Paula Barbarans Souza Martins

Faculdade de Ciências Médicas do Pará
(FACIMPA)

Marabá - PA

<https://orcid.org/0000-0002-3596-2475>

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Joana Bader Sadala Brandão

Universidade Nilton Lins (UNL)

Manaus - AM

<https://orcid.org/0000-0002-0868-7770>

Gleison Carlos Arantes Filho

Universidade Federal de Ouro Preto (UFOP)

Ouro Preto - MG

<https://orcid.org/0000-0003-2076-6006>

Julia Carolina Rodrigues Miranda

Universidade Anhembi Morumbi (UAM)

Piracicaba - SP

<https://orcid.org/0000-0002-4675-6773>

Rebeca de Carvalho Teixeira

Universidade Anhembi Morumbi (UAM)

Piracicaba - SP

<https://orcid.org/0000-0003-1950-8667>

Ana Carolina Lima Vieira

Faculdade Ciências Médicas de Minas Gerais

(FCMMG)

Belo Horizonte - MG

<https://orcid.org/0000-0001-9558-8254>

Marcella Marques Rodrigues de Almeida

Universidade Nove de Julho (UNINOVE)

Bauru - SP

<https://orcid.org/0000-0002-8438-4472>

Neidejany de Assunção do Sacramento

Universidad Nacional de Rosario (UNR)

Rosario - Argentina

<https://orcid.org/0000-0001-7050-6697>

Abstract: Goal: The present study consists of discussing the factors that predispose to Takotsubo Syndrome in postmenopausal women and the importance of the differential diagnosis for the application of an early management. **Methods:** Bibliographic review developed from October to November 2022, with a search in the PubMed and Scielo databases, using the descriptors “post-menopausal women”, “takotsubo cardiomyopathy”, “diagnosis” and “differential diagnosis”. 201 articles were found and selected, after the inclusion and exclusion criteria, 16 articles to compose the study. **Review:** Studies indicate that Takotsubo Syndrome (TST) has a possible neurogenic origin, triggered by stress, both emotional and physiological. This stress generates endothelial dysfunction, which causes changes in vasodilation and vasoconstriction. In post-menopause, there is a lack of sexual steroids, which have an influence on endothelial preservation in response to stress responses. Steroids such as estrogen attenuate the vasoconstriction caused by catecholamines; it is believed that the reduction of this hormone has a great influence on the pathophysiology of this disease. Acute Coronary Syndrome (ACS) is the main differential diagnosis of TTS, since they are very similar in terms of clinical picture, electrocardiographic changes and elevation of cardiac biomarkers. Through coronary angiography, it is possible to differentiate TTS from ACS, as obstruction of the coronary arteries indicates ACS. **Final Considerations:** It is necessary to expand research on the pathogenesis of TTS, in order to establish the best way to intervene in the evolution of this syndrome, since it is not a benign condition and without interventions it can result in ventricular dysfunction.

Keywords: Takotsubo syndrome; Diagnosis; Differential diagnosis; Postmenopausal Women.

INTRODUCTION

Takotsubo Syndrome (TTS), also known as Broken Heart Syndrome, is a transient cardiomyopathy manifested by the occurrence of left ventricular systolic and diastolic dysfunction, with the absence of obstructive coronary disease, often associated with acute episodes of emotional stress and physiological (ALMEIDA JUNIOR G.L.G et al., 2020). The population that most prevalently develops the syndrome are women who are in the postmenopausal period, a group whose incidence of psychiatric disorders, such as anxiety and depression, is quite high, since they are favored by the hormonal changes of this period (SY F. et al., 2013).

It is believed that hormonal, neuropsychiatric and genetic conditions are risk factors for the respective dysfunction, especially when associated with physical and/or psychic “tiggers”. The pathophysiological mechanism of TTS is still little known, however, several authors and research associate its cause with hyperactivity of the sympathetic nervous system in stressful situations (ALMEIDA JUNIOR G.L.G et al., 2020). The latest studies and scientific evidence confirm the association of cardiac and central inflammation with the pathophysiology of TTS, which is of great relevance for the scientific and professional community, since the presence of inflammatory processes in the disease can be used as a therapeutic focus and, thus, leverage the development of new management techniques for patients who develop the acute syndrome (SCALLY C. et al., 2019).

The main clinical characteristics of Takotsubo include angina, dyspnea, in addition to electrocardiographic changes compatible with an ischemic episode, increased levels of cardiac injury biomarkers, and segmental impairment of ventricular function (CAMPOS F.A. et al., 2020). Thus, it

is essential to analyze the factors that involve the predisposition of postmenopausal women to this disease and the differential diagnoses that surround it, given the high prevalence of this pathology in such a population and the existence of risks of complications, such as insufficiency cardiac arrest, cardiogenic shock and death resulting from this syndrome (SCALLY C. et al., 2019; ALMEIDA JUNIOR G.L.G et al., 2020).

The patient affected by TTS tends to have a good prognosis when appropriate intervention is applied early, since the reversal of ventricular dysfunction occurs within a period of weeks to three months (CAMPOS F.A. et al., 2020). In addition, premature conduct also acts to reduce the need for the use of invasive interventions (WU B.T. et al., 2013). Therefore, the objective of the present study is to discuss the factors that predispose to Takotsubo Syndrome in postmenopausal women and the importance of differential diagnosis for the application of early management.

METHODOLOGY

This is a bibliographical review developed from October to November 2022. The research was carried out according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used for the elaboration of the research through its guiding question: “What is the predisposition of Takotsubo Syndrome in postmenopausal women and its importance in the differential diagnosis for early treatment?”. In defining the strategy mentioned above, the population refers to postmenopausal women, the variables would be the predisposition to the manifestation of Takotsubo Syndrome and the possible differential diagnoses of such condition, and for the outcome importance of the differential diagnosis for early treatment

for the Syndrome. The searches were carried out through searches in the PubMed Central (PMC) and Scientific Electronic Library Online (SciELO) databases. The following descriptors were used in combination with the Boolean term “AND”: “Postmenopause”, “Post-menopausal women”, “Takotsubo Cardiomyopathy”, “Diagnosis, Differential” and “Diagnosis”, which were combined using the following strings: (Postmenopause) AND (Takotsubo Cardiomyopathy) AND (Diagnosis, Differential); (Post-menopausal women) AND (Takotsubo Cardiomyopathy); and (Postmenopause) AND (Takotsubo Cardiomyopathy) AND (Diagnosis). From this search, the articles found had their titles and abstracts read and were subsequently submitted to the selection criteria to be aligned with the objective of the study. Inclusion criteria were: articles in Spanish, French, English and Portuguese, published from 2013 to 2022 and that addressed the themes proposed for this research, studies of the systematic review type, integrative review, narrative review, case study- control, cohort study and case report; and made available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 201 articles were found. Of which, 147 articles belonged to the PMC database and 54 articles to SciELO. After reading the titles and abstracts and applying the inclusion and exclusion criteria, 14 articles in the PMC database and 2 articles in SciELO were selected for reading in full, and then a total of 16 studies were designated to compose the collection.

REVIEW

Takotsubo Cardiomyopathy or Takotsubo Syndrome (TST) is present in about 1.5 to 2.2% of postmenopausal female patients (MÖLLER C. et al., 2022). This occurrence is closely related to the deficit of sexual steroids, which have protective effects that are minimized with the climacteric. Furthermore, the risk increases with the woman's age; women aged 55 already have a higher risk compared to younger people. Currently, the pathophysiological mechanisms of Takotsubo syndrome are not fully known, but recent studies show that there is possibly a neurogenic origin, triggered by stress conditions and triggers (OLIVERI F. et al, 2020).

There would be an activation of the sympathetic nervous system caused by adrenergic discharges and, consequently, the release of catecholamines mediated mainly by the limbic system and hypothalamus. It is estimated that such catecholamines are directly involved in the pathogenesis of the Syndrome, since evidence reports an increase due to muscle spasm that occurs in the acute phase of the disease (ANGELINI P. et al., 2021). In addition, stress induces an important endothelial dysfunction, characterized by disharmony between vasodilator and vasoconstrictor factors. Such a dysfunction would explain the fact that patients with TTS present lower flow vasodilation years after the episode occurred. From the perspective of Ghadri J. R. et al. (2018), genetic factors can also be interconnected with its manifestation, and the sum of environmental motivations, polygenic inheritance and recessive alleles, could amplify the symptomatology of the syndrome. In addition, the syndrome is also accompanied by some neurological events such as stroke, subarachnoid hemorrhage and seizure (GHADRI J.R. et al., 2018).

Estrogen positively influences endothelial preservation in the face of stress responses, by attenuating vasoconstriction caused by catecholamines and decreasing the physiological response to it and, therefore, reducing the sympathetic response (AMADIO P. et al., 2021). Due to such potential, it is believed that this female sex hormone plays an expressive clinical importance in prevention and also directly influences the pathophysiological mechanisms of the syndrome (WAQAR A. et al., 2022).

The differential diagnosis of Takotsubo Syndrome is still considered a challenge, due to its atypical and varied clinical presentation. Symptoms such as chest pain, dyspnea, palpitations, syncope and fatigue make the syndrome differentiation a difficult task, especially in the emergency setting (SCHLOSSBAUER S.A. et al., 2017). According to Sy F. et al. (2013), due to the many similarities between their clinical and laboratory presentations, Takotsubo Syndrome has Acute Coronary Syndrome (ACS) as the primary differential diagnosis. Electrocardiographic changes, elevated cardiac biomarkers and chest discomfort in the syndrome can easily mimic the ACS picture (SY F. et al., 2013). Despite the absence of significant coronary stenosis, according to Almeida Junior G.L.G. et al. (2020), Wu B.T. et al. (2013) and Zorzi A. et al. (2016), acute myocardial infarction (AMI) is the main syndrome of interest for diagnosing TTS. Likewise, other pathologies can also be considered as differentials, such as myocarditis, excess of endogenous and exogenous catecholamines, aortic dissection and pulmonary embolism. Consequently, its diagnosis is often considered challenging, which makes it essential to collect a detailed clinical history and consider the patient's psychosocial factors, such as conditions of great physical or emotional stress

(GOPALAKRISHNAN P. et al., 2017; ZORZI A. et al., 2016).

According to Han P. et al (2020) patients with TTS may have less chest pain and more dyspnea in the acute phase when compared to patients with ACS. Studies have also shown that the fundamental criterion for differentiating the diagnosis of TTS and ACS involves the absence of significant occlusion in the coronary arteries causing contraction dysfunction. Furthermore, the severity of coronary artery atherosclerosis is lower in patients with TTS when compared to patients with ACS, and patients with TTS have fewer cardiovascular risk factors compared to ACS individuals, raising the hypothesis of a different pathophysiology between the two diseases (HAN P. et al., 2020). Such differences are due to the fact that ACS alterations involve cardiomyocyte necrosis or myocardial ischemia caused by coronary occlusion, in comparison with the pathophysiology of Takotsubo Syndrome, which would involve other mechanisms related not only to a myocardial inflammatory state but also acute coronary microvascular dysfunction and possible autonomic disorders (HAN P. et al., 2020).

Due to the syndrome's characteristic of having a sudden and unexpected onset, it is necessary, in addition to anamnesis, to perform complementary tests to clarify the diagnosis, mainly in order to rule out other possible conditions such as those already mentioned in the present study and which present similar symptoms. Thus, the first test for patients complaining of chest pain is the electrocardiogram (ECG). In TTS, the ECG shows a characteristic elevation in the ST segment and also ST depression, and T wave inversion. In addition, molecular biomarkers can necessarily be measured, including troponin I and T, which in cases of manifestation of the syndrome are slightly

increased. Brain natriuretic peptides (BNP) and the N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) also show a greater elevation than in cases of acute myocardial infarction (WU B.T. et al., 2013).

The dosage of catecholamines is not a reliable diagnostic criterion, since the direct correlation of the intense increase of catecholamines with the onset of the Syndrome cannot be proved, therefore, they are not measured to establish the diagnosis. The elevation of Acetylcholine, on the other hand, allows its dosage to be reliable for an accurate diagnosis within a week of the onset of the Syndrome, and is therefore shown to be effective in predicting the path of treatment to be instituted and to prevent recurrence, in order to improve the prognosis of the disease (ANGELINI P. et al., 2021).

Regarding imaging exams, coronary angiography is extremely important for the diagnosis, since muscle spasm can generate alterations in the left ventricle, such as immobility of the middle and apical segments of the left ventricle and excessive activity in the basal segments. It is also important to emphasize that the differentiation between TTS and ACS presents coronary angiography (coronary angiography) as the gold standard diagnostic test (SCHLOSSBAUER S.A. et al., 2017). It is possible to exclude the possibility of ACS by the absence of obstruction of the coronary arteries. Transthoracic echocardiography (TTE) is necessarily performed in the acute phase of the Syndrome, as it demonstrates discordant ventricular movement alterations between the middle and apical segments in relation to the basal one. In addition, the presence of abnormalities on imaging tests with hypokinesia, akinesia or dyskinesia in the left ventricular wall, with rare but possible involvement of the right ventricle, making it plausible, finally, to make an

accurate diagnosis of Takotsubo Syndrome (ASSAD J. et al., 2022).

As knowledge about TTS has evolved, the criteria for its diagnosis have been renewed. The most commonly used diagnostic criterion today is that of the Mayo Clinic, which consists of four components: 1) transient hypokinesia, dyskinesia, or akinesia in left ventricular (LV) segments, with or without apical involvement; abnormalities in regional wall motion beyond a single epicardial vascular distribution; a stressful trigger is often but not always present; 2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3) recently detected ECG changes (ST-segment elevation and/or T-wave inversion) or significantly elevated serum cardiac troponins; and 4) absence of pheochromocytoma or myocarditis (GOPALAKRISHNAN P. et al., 2017).

Also in 2018, a guideline was published by the European Society of Cardiology (ESC), presenting a new international score of diagnostic criteria, the InterTAK diagnostic score, with the aim of estimating the chance of a patient presenting TTS and helping in the differential diagnosis with SCA with high sensitivity and specificity. Through it, points are assigned to seven parameters, including clinical and electrocardiographic variables (female gender [25 points], emotional stress [24 points], physical stress [13 points], absence of ST-segment depression [12 points], disease previous psychiatric illness, acute or chronic [11 points], previous neurological disease, acute or chronic [9 points] and QT interval prolongation (women > 460ms; men > 440ms) [6 points] The score ranges from 0 to 100 points. A score above 70 points stratifies the patient as having high probability for Takotsubo Syndrome (GHADRI J.R. et al., 2018). Thus, it becomes evident that the combination of clinical characteristics

associated with the use of diagnostic forms, such as Electrocardiogram (ECG), echocardiography, coronary angiography, CMR and biomarkers may provide a more accurate diagnosis of TTS.

FINAL CONSIDERATIONS

The present study demonstrated that postmenopausal female patients are the most affected by TTS, especially older women, since there is a deficit of sex steroids, increasing their risk for cardiovascular manifestations. Individuals with this syndrome have diverse clinical profiles that are easily related to ACS and AMI, but when compared in a reliable and thorough manner through an efficient clinical examination and imaging studies, it is possible to differentiate them, even if there is still no clear diagnostic criterion for TTS. Although the pathogenesis is not completely understood, the mechanisms of action appear to correlate with excess catecholamines in stressful settings. TTS is not a benign condition and if left untreated it can lead to severe ventricular dysfunction. It is evident that, due to its diverse symptomatology, there are still several challenges in what would be the accurate diagnosis of such a condition, requiring the development of research that seeks specific diagnostic criteria that effectively allow an agile diagnosis of TTS, thus allowing the indication of treatments and improvements in the prognosis of patients.

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