

Epilepsy and Takotsubo cardiomyopathy: a scope review

*Epilepsia e cardiomiopatia de Takotsubo:
uma revisão de escopo*

*Epilepsia y miocardiopatía de Takotsubo:
una revisión del alcance*

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Resumo

Introdução. A incidência de morte súbita é alta em pessoas com epilepsia crônica, principalmente na presença de comorbidades cardiovasculares, desse modo, há uma convergência entre epilepsia e doenças cardiovasculares, porém a literatura carece de revisões sistemáticas acerca da interface entre epilepsia e cardiomiopatia de Takotsubo. **Objetivo.** Verificar a associação entre cardiomiopatia de Takotsubo e distúrbios neurológicos, especialmente epilepsia. **Método.** Trata-se de uma revisão de escopo, com base na lista de verificação PRISMA. Foi realizada uma busca avançada e de alta sensibilidade utilizando os descritores "epilepsy" e "Takotsubo cardiomyopathy" combinados com o operador booleano AND, nas bases de dados PubMed, Scientific Electronic Library Online, Portal Regional Biblioteca in Health e Periódicos CAPES. **Resultados.** Foram identificados 373 artigos e após a aplicação dos critérios de elegibilidade, foram selecionados 14 trabalhos para compor a amostra bibliográfica deste estudo. Demonstra-se a relação de pessoas com epilepsia desenvolvendo cardiomiopatia de Takotsubo, principalmente mulheres com idade avançada, com comorbidades como hipertensão arterial, diabetes mellitus e hipercolesterolemia, podendo as alterações serem evidenciadas por meio de eletrocardiograma e ecocardiograma transtorácico. **Conclusão.** A depressão do segmento ST na parede anterior e a inversão da onda T no eletrocardiograma podem sugerir cardiomiopatia de Takotsubo em pessoas com epilepsia, e esse monitoramento é importante devido ao potencial de convulsões levarem a problemas cardíacos. A ecocardiografia transtorácica é útil para identificar eventos adversos em pessoas com a comorbidade. O conhecimento sobre epidemiologia e os achados complementares descritos podem facilitar o raciocínio clínico para o diagnóstico e manejo da condição.

Unitermos. Epilepsia; cardiomiopatia de Takotsubo; morte súbita

Abstract

Introduction. The incidence of sudden death is high in people with chronic epilepsy, especially in the presence of cardiovascular comorbidities, thus, there is a convergence between epilepsy and cardiovascular diseases, however the literature fails on systematic reviews analyzing the interface between epilepsy and Takotsubo cardiomyopathy. **Objective.** To verify the association between Takotsubo cardiomyopathy and neurological disorders, especially epilepsy. **Method.** This is a scope review, based on the PRISMA checklist. An advanced and high-sensitivity search was performed using the descriptors "epilepsy" and "Takotsubo cardiomyopathy" combined with the Boolean operator AND, in PubMed, Scientific Electronic Library Online, Portal Regional Biblioteca in Health, and CAPES Periodicals. **Results.** A total of 373 articles were identified and after applying the eligibility criteria, 14 papers were selected to compose the bibliographic sample of this study. It demonstrates the relationship of people with epilepsy developing Takotsubo cardiomyopathy, especially women with advanced age, with comorbidities such as arterial hypertension, diabetes mellitus and hypercholesterolemia, and changes could be evidenced through electrocardiogram and transthoracic echocardiogram. **Conclusion.** ST-segment depression in the anterior wall and T-wave inversion on the electrocardiogram may suggest Takotsubo cardiomyopathy in people with epilepsy, and this monitoring is important because of the potential for seizures to lead to cardiac conditions. Transthoracic echocardiography is useful for identifying adverse events in people with the comorbidity. Knowledge about epidemiology and the complementary findings described can facilitate clinical reasoning for the diagnosis and management of the condition. **Keywords.** Epilepsy; Takotsubo cardiomyopathy; sudden death

Resumen

Introducción. La incidencia de muerte súbita es alta en personas con epilepsia crónica, especialmente en presencia de comorbilidades cardiovasculares, por lo que existe una convergencia entre epilepsia y enfermedades cardiovasculares, pero la literatura carece de revisiones sistemáticas sobre la interfase entre epilepsia y miocardiopatía de Takotsubo. **Objetivo.** Verificar la asociación entre la miocardiopatía de Takotsubo y los trastornos neurológicos, especialmente la epilepsia. **Método.** Esta es una revisión de alcance, basada en la lista de verificación PRISMA. Se realizó una búsqueda avanzada y de alta sensibilidad utilizando los descriptores "epilepsy" y "Takotsubo cardiomyopathy" combinados con el operador booleano AND, en las bases de datos PubMed, Scientific Electronic Library Online, Portal Regional Biblioteca in Health and Revistas CAPES. **Resultados.** Se identificaron 373 artículos y después de aplicar los criterios de elegibilidad, se seleccionaron 14 trabajos para componer la muestra bibliográfica de este estudio. Demuestra la relación de las personas con epilepsia que desarrollan miocardiopatía de Takotsubo, principalmente mujeres de edad avanzada, con comorbilidades como hipertensión arterial, diabetes mellitus e hipercolesterolemia, pudiendo evidenciarse las alteraciones mediante electrocardiograma y ecocardiograma transtorácico. **Conclusión.** La depresión del segmento ST en la pared anterior y la inversión de la onda T en el electrocardiograma pueden sugerir una miocardiopatía de Takotsubo en personas con epilepsia, y dicho control es importante debido a la posibilidad de que las convulsiones provoquen problemas cardíacos. La ecocardiografía transtorácica es útil para identificar eventos adversos en personas con la comorbilidad. El conocimiento de la epidemiología y los hallazgos complementarios descritos pueden facilitar el razonamiento clínico para el diagnóstico y manejo de la condición. **Palabras clave.** Epilepsia; miocardiopatía de Takotsubo; la muerte súbita

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INTRODUCTION

Takotsubo cardiomyopathy, known as broken heart syndrome, is a reversible left ventricular dysfunction in the

absence of coronary artery disease, which may or may not involve the apex. Its etiology is related to physical or mental stressors, subarachnoid bleeding, stroke, and convulsions and its occurrence is related to neurological diseases such as epilepsy¹. This pathology doesn't still have well-defined pathophysiology. The most accepted mechanism involves central and local sympathetic stimulation, with the presence of coronary artery vasospasm and excessive release of catecholamines².

This mechanism induces the injury of myocytes, which can be triggered by a stress situation, through the sympathetic nervous system. It contributes to transient disturbance of the left ventricle and the consequent clinical condition of Takotsubo Cardiomyopathy, with chest pain and dyspnea³.

Epilepsy is a chronic neurological disorder that causes convulsive or nonconvulsive epileptic seizures. The clinical condition includes motor, sensitive, sensory and autonomic manifestations. To diagnose epilepsy, there must be an epileptic syndrome that's an unprovoked crisis or the probability of other similar seizures after two unprovoked crisis in 10 years or two unprovoked epileptic seizures and a time greater than 24 hours⁴.

Increased intracranial pressure can occur after a seizure⁵. The pressure may be associated with an additional acute or severe edema in patients with sodium channel mutations, increasing the risk of sudden death. In addition,

edema was found in patients with epilepsy who died of sudden cardiac death^{5,6}.

Some studies that correlate Takotsubo cardiomyopathy and epilepsy have pointed out events that precede epileptic seizures: alcohol intoxication, stroke, post-aneurysm, post-trauma, post-hemorrhage, hyponatremia, posterior reversible leukoencephalopathy, post-general anesthesia, meningioma and alcohol withdrawal, which may possibly be associated as causes for the incidence of epilepsy and, consequently, of cardiac recurrences, requiring further studies to elucidate such factors⁷⁻⁹.

Sudden cardiac death has a high incidence in patients with chronic epilepsy, especially when it's associated with factors like advancing age (mainly over 40 years), the presence of cardiovascular comorbidities (coronary heart disease, angina pectoris, heart attack), hereditary or acquired channelopathies in young people and ventricular fibrillation, the leading cardiac cause⁹. In children, sudden death is associated with epileptic conditions that have genetic mutations and it presents more severely^{7,10}.

Based on the above, it's possible to see that there is a correlation between sudden death, epilepsy, and cardiovascular diseases. The objective of this study was to verify the association of Takotsubo cardiomyopathy and neurological disorders, especially epilepsy.

METHOD

This study was a scoping review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (2020)¹¹. The following research question was applied: "What is the association between Takotsubo Cardiomyopathy and patients with neurological disorders, especially epilepsy?".

A high-sensitivity search was carried out for the selection of studies in September/2022, based on the Medical Subject Headings (MeSH) and Descriptors in Health Science (DeCS): "epilepsy" and "takotsubo cardiomyopathy" combined with the boolean operator "AND" in the database Medline (PubMed). With the same descriptors, an advanced search was carried out on the databases Scientific Electronic Library Online (SciELO), Biblioteca Virtual de Saúde (BVS), and periódicos CAPES, again joined with the boolean operator "AND".

Observational studies from 2012 to 2022 were included. Duplicates, reviews, letters to the editor, abstracts, incomplete articles, published errata, and studies not related to the subject were excluded.

The articles found were exported to the Rayyan¹², web platform for initial screening, guided by the eligibility criteria. Duplicates were deleted, titles and abstracts were read, followed by complete papers when eligible. This stage was conducted by two evaluators (GGCL and YSF), independently and blindly, and the divergences were resolved by consensus.

The articles were systematized in a database using Microsoft Excel® software, considering the following variables: author and year of the published, title, study design, research site, study sample, main results/outcomes, results related to electrocardiogram (ECG), troponin I levels, transthoracic echocardiogram (TTE) and left ventricular ejection fraction (LVEF), study views.

Quantitative data were presented based on Descriptive Statistics, in absolute numbers, according to factors related to pathologies. Regarding qualitative information, a table was elaborated showing the characterization of the studies and their main results. This stage was conducted by two reviewers (AGM and DBR), independently. The information is presented in the table as described in the studies.

RESULTS

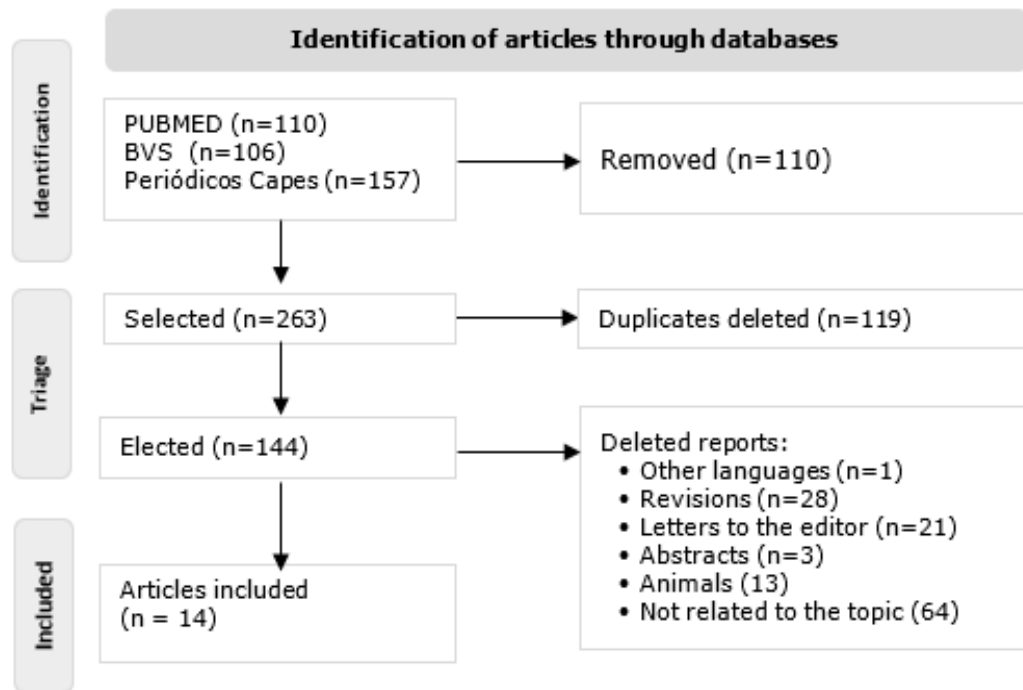
Sample parameters of the studies

The initial search identified 373 studies (PubMed=110, SciELO=0, Biblioteca Virtual de Saúde=106, Periódicos CAPES=157). After applying the eligibility criteria, to compose the bibliographic sample of this study, 14 papers were selected (Figure 1).

Aligned with the research question, studies that did not establish an association between epilepsy and Takotsubo cardiomyopathy in people were excluded, i.e., studies with animals (n=13), studies that did not address epilepsy (n=43) or Takotsubo cardiomyopathy (n=16), or in which these

variables were presented in isolation and no relationship between them could be established (n=2).

Figure 1. Study selection flowchart.



The sample size for this research was 4.548 participants with Takotsubo cardiomyopathy in total. Among these, 1.810 (40%) had epilepsy-associated Takotsubo cardiomyopathy, 72.38% (76) women. The age of the patients ranged from 32 to 83 years. Seven studies (50%) were conducted in countries on the European continent (Table 1).

Table 1. Authorship, sample and main findings of the selected articles.

Author/year	Type of study	Research Sample	ECG	Troponin I Levels	TTE	LVEF
Blanc 2015 ¹³	Observational study	Total research sample: 13.251 Admitted for Takotsubo cardiomyopathy: 87 patients Patients with acute neurological disorders: 6 Women: 5 Men: 1 Age: 63.7±20.1 years	The most frequent changes were ST-segment elevation and T-wave inversion	Average 1.8 ng/mL	Reduction of left ventricular ejection fraction (46 ± 12%) with apical hypokinesia in most cases	-
Belcour 2015 ¹⁴	Observational study	Total research sample: 32 Age: 50±18 years; Gender: 21 men; Analyses performed at 5 times: H0, H6, H12, H24, H48	Sinus rhythm at all times; from H0 to H48, seven patients (22%) had localized repolarization changes and three (9%) had diffuse changes.	H0=0.1 (0-0.50); H6=0.45 (0.1-0.62); H12=0.3 (0.1-0.6); H24=0.17 (0.1-0.43); H48=0.11 (0-0.19)	-	-
Cammann 2021 ¹⁵	Observational study	161 patients with neurological disorders. Seizure: 57 (8 with epileptic condition, 26 with generalized onset seizure, 07 with focal-onset seizures, 13 with seizures of unknown onset). Age 61.8±13.2 (N=57). Gender: female 52/57 (91.2) and male 5/57 (9.8)	Sinus rhythm in 40/41 (97.6); ST-segment elevation in 15/42 (35.7); ST-segment depression in 4/41 (9.8); and T-wave inversion in 15/41 (36.6)	Maximum level: 25.00 ng/L (7.42-44.04), in 45 of the 57 patients	Apical ballooning (37/57), Middle ventricle (15/57), basal (2/57); focal (3/57).	41.0±10.7 (N=53)
Tsuji 2020 ¹⁶	Case report	Woman, 40 years old	ST-segment elevation in leads II, III and aVF	Peak of 1872.1 pg/mL	Apical ballooning at initial evaluation	-
Damera 2022 ¹⁷	Case Report	Male, 56 years old.	T-wave inversion in precordial leads	Peak of 1.77 ng/mL	Hyperkinetic base and apical ballooning	15% at admission
Garcia-Malvar 2014 ¹⁸	Case report	Woman, 55 years old	ST-segment elevation and T-wave inversion in precordial leads (V2-V6)	High (peak troponin level: 0.79 ng/mL)	Anterior apical, lateral apical and apical septal akinesia	
Kyi 2017 ¹⁹	Case report	African-American woman, 61 years old.	ST-segment elevation in anterolateral leads.	Peak of 38.97 ng/mL	Apical hypokinesia.	40%

Table 1 (cont.). Authorship, sample and main findings of the selected articles.

Author/year	Type of study	Research Sample	ECG	Troponin I Levels	TTE	LVEF
Koo 2015 ²⁰	Case report	Woman, 83 years old	ST-segment elevation at V2-V4	In serial measurements, 0.62µg/L and 4.87µg/L respectively	Left ventricle (LV) apical ballooning with severe systolic dysfunction (LV ejection fraction = 23%; using Simpson's methods) and focal hypokinesia of the right ventricular (RV) apex with decreased RV systolic function with decreased systolic function of the RV.	-
Rocha 2013 ²¹	Case report	Woman, 44 years old	Sinus tachycardia with T-wave inversion in V1-V3 after 12 hours	Peak of 6.48 ng/mL	Slight depression of left ventricular systolic function, hypokinesia of the apical segments with hypercontractility of the basal segments	-
Simsek 2019 ²²	Case report	Woman, 69 years old	Sinus rhythm with diffuse 1 mm ST-segment elevation.	7.13 ng/mL (normal range from 0.0-0.06 ng/mL)	Apical hypokinesia	36%
Khadka 2021 ²³	Case report	Male, 69 years old	Sinus tachycardia with ST-segment elevation at V2 and V3.	Normal range	Hypokinetic apical, lateral, anterior and inferior septal segments and anteroapical medial and apical cap segments, LV systolic dysfunction	40%
Verdoia 2021 ²⁴	Case report	Woman, 51 years old.	Focal epileptic activity located in the left fronto-parietal portion of the brain.	Discrete elevation (0.07 ng/mL)	Akinesia of the apex and periapical segments, suggestive of apical ballooning.	Around 30%
Miller 2017 ²⁵	Case report	Woman, 49 years old.	Absence of ST-segment elevation and sinus tachycardia.	Initially raised by 0.563 and after 6 hours at 0.762 (reference <0.01).	Initial: inferior and lateral wall akinesia. Post-treatment: posterior wall akinesia, septal wall dyskinesia	15-20%
Ahmed 2022 ²⁶	Observational study	1.698 patients with epileptic symptoms	-	-	-	-

ECG: Electrocardiogram; TTE: Transthoracic Echocardiogram; LVEF: Left Ventricle Ejection Fraction

Association between epilepsy and Takotsubo cardiomyopathy

Risk factors favoring the development of Takotsubo cardiomyopathy in epileptic patients such as hypertension,

diabetes mellitus, and hypercholesterolemia have been mentioned. Advanced age and female gender were prevalent features, including samples from observational studies and case reports^{13,14}.

On the other hand, one article, with 161 patients, showed that when associated with neurological disorders such as epilepsy, Takotsubo cardiomyopathy tends to be more common in young males¹⁵. Another study showed a previous convulsive history and alcoholism in most patients, and an association of convulsive epileptic status with poor medication compliance, alcohol abstinence, and stroke¹³.

In addition to status epilepticus, other clinical presentations were noted by Cammann 2021¹⁵, such as seizures of generalized onset, seizures of focal onset, and seizures of unknown onset. The same study demonstrated that neurological disorders are common triggers of Takotsubo cardiomyopathy, including epilepsy, intracranial hemorrhage, and cerebral ischemia¹⁵.

Clinical features of epileptic seizures and electrocardiographic changes

The type of seizure most often associated with Takotsubo cardiomyopathy was the generalized onset type (bilateral tonic-clonic seizures) and unknown onset, commonly followed by increased heart rate¹³.

In two articles, cardiologic changes in patients appeared within the first 48 hours after neurologic events^{13,14}. Two case reports presented the development of Takotsubo cardiomyopathy in patients undergoing heart transplantation

within approximately 1-year post-surgery^{16,17}; in one of them, the donor himself had previously manifested the cardiomyopathy¹⁶.

ECG changes were observed in most studies, with the presence in two studies of ST-segment elevation in the anterior wall^{15,18} and ST-segment elevation in seven studies: one in the anterolateral wall¹⁹, one in anterior wall²⁰, two were diffuse but one had the shark fin pattern (formed by the fusion of QRS, ST, and T waves and is associated with high mortality), one in the inferior wall, however, only in the donor with Takotsubo cardiomyopathy and without epilepsy¹⁶, one that only two patients included had¹³ and one had no wall report¹⁵.

In six articles, patients presenting with sinus rhythm were described, two of them with the presence of tachycardia^{13,15,16,21-23}. T-wave inversion in patients was present in five studies^{13,15,17,21}.

In nine articles some kind of change in transthoracic echocardiography was reported: seven of them had hypokinesia^{13,15,19,20,22}, two akinesia^{18,24}, one with posterior wall akinesia and septal wall dyskinesia²⁵ and two had hyperkinetic basis associated with hypokinesia and/or akinesia^{17,21}.

Cardiac changes in patients with Takotsubo cardiomyopathy and epilepsy

Reduced Left Ventricular Ejection Fraction (LVEF) was observed in patients in all of these studies, except in the papers of Garcia-Malvar 2014¹⁸ in which the information was

not reported, in addition Belcour 2015¹⁴ and Cammann 2021¹⁵, which ranged between preserved, intermediate, and reduced. The angiography findings were normal in all patients. Significant recovery of LVEF was reported days and/or weeks after discharge from these patients in six studies^{13,17,22-25}.

Takotsubo cardiomyopathy related to neurological disorders such as epilepsy was associated with higher rates of adverse events. Examples include ventricular fibrillation, cardiac arrest, cardiogenic shock, septic shock^{15,17,26}, increased ICU admissions^{13,14,24,25}, higher in-hospital mortality^{15,26} and increased all-cause readmissions²⁶.

Outcomes

After treatment, recovery of cardiac function was reported in most studies^{13,17,18,22-25}. In 9 case reports, patients showed a satisfactory clinical response, with hemodynamic stabilization at discharge, followed only by gradually discontinued symptomatic treatment¹⁶⁻²⁵. Only one study reported death as a result of acute heart failure¹³.

DISCUSSION

Regarding the relationship between epilepsy and Takotsubo Cardiomyopathy, other authors corroborate that convulsion is associated with the development of Takotsubo Syndrome^{3,27,28}.

In addition to the authors of the articles presented in this study, several authors have described that people with

epilepsy have a higher prevalence of heart disease compared to people without epilepsy²⁹⁻³¹. Moreover, epilepsy is evaluated at a three-fold higher risk of causing sudden cardiac death compared to the general population, since up to four out of five people with epilepsy may have cardiovascular comorbidities²⁴.

The relationship between Takotsubo Syndrome and the female gender has been reported by other authors. Postmenopausal women are predominant, especially exposed to emotional or physical stress^{3,32}. Other researchers corroborate the findings that there is a relationship between risk factors such as hypertension and hypercholesterolemia with Takotsubo Syndrome^{30,33,34}.

Changes in the electrocardiogram, mainly ST-segment depression in the anterior wall^{15,18} and T wave inversion^{13,15,17,21} were described by International Expert Consensus Document on Takotsubo Syndrome³⁵ and several other researchers^{3,36,37}. Therefore, comorbidity between diseases cannot be correlated.

The following stand out in the transthoracic echocardiogram, according to the studies: hypokinesia^{13,15,19,20,22,23}, akinesia^{18,24}, and reduction of the Left Ventricle Ejection Fraction (LVEF)¹⁹⁻²⁵. Other studies have shown the same finding about hypokinesia and reduction of LVEF in both clinical conditions³.

Knowledge of the characteristics described is significant for the medical diagnosis of this pathology and the correlation between epilepsy and Takotsubo

Cardiomyopathy. Recognizing the changes of the electrocardiogram combined with clinical manifestations can facilitate the diagnosis and allow better management of patients in moments of sharpness^{24,27}.

This review presents information about the relationship between epilepsy and Takotsubo Cardiomyopathy. It also deals with other events associated with these pathologies, such as ventricular fibrillation, cardiorespiratory arrest, cardiogenic shock, septic shock, and intensive care unit admission^{13,14,24,25}.

It is important to emphasize that medications for controlling epileptic seizures, such as anticonvulsants, may have side effects that affect the cardiovascular system. However, it is necessary to point out that the relationship between the use of these medications and the development of Takotsubo syndrome is not yet fully clear, and more research is needed to better understand this possible association.

Takotsubo Cardiomyopathy is heterogeneous and triggered by several factors²⁴. One hospitalization out of a thousand patients with epilepsy also corresponds to the occurrence of Takotsubo cardiomyopathy, and these patients have a poor prognosis³⁸. Moreover, the literature consulted still presents few observative studies on the relationship between epilepsy and Takotsubo Cardiomyopathy, mainly case reports, which have repercussions on the limited number of studies included in this review.

CONCLUSION

The present review highlights the correlation between epilepsy and Takotsubo cardiomyopathy; however, it is worth noting that Takotsubo syndrome is heterogeneous and triggered by several factors, which requires an accurate diagnosis in patients with neurological disorders, especially epilepsy.

Evidence of ECG changes, especially ST-segment depression in the anterior wall and T wave inversion, may suggest a diagnosis of Takotsubo cardiomyopathy in people with epilepsy.

Clinical monitoring is necessary due to the harmful potential of seizures leading to the characteristic cardiological picture.

In the transthoracic echocardiogram of patients with the described comorbidity, it is possible to evidence hypokinesia, akinesia, reduction in LVEF, in addition to serious adverse events such as ventricular fibrillation, cardiac arrest, cardiogenic shock and septic shock. It is necessary to carry out future primary research covering more cases involving these pathologies.

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