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ARRHYTHMOGENIC CARDIOMYOPATHY OF THE RIGHT VENTRICLE: CLINICAL AND PHYSIOPATHOLOGICAL ASPECTS

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Abstract: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive hereditary clinical entity, physiologically characterized by mutations encoding the heart muscle, and predominantly affects the right ventricle. The objective of the study carried out is to evaluate and consolidate the main available evidence on arrhythmogenic right ventricular cardiomyopathy and its main clinical and pathophysiological aspects, using studies and articles published in the last 5 years. Integrative, exploratory and qualitative review of research, through searches in the scientific databases PubMed, VHL and SciELO. The established inclusion criteria were: original articles available in electronic format, in full, written in Portuguese, English or Spanish, with a time limit from 2019 to 2024. The investigation was carried out in March 2024. With the research carried out, 360 articles were found, 210 of these were selected for reading and, according to the objective of this work, 10 were included in the research. In summary, despite being rare, ARVC is related to potentially fatal changes, such as malignant arrhythmias that lead to sudden death, which makes evident the importance of conservative and in-depth studies to define the incidence in the general population, which is still ill. known and its etiopathogenic mechanism, such as genetic or acquired disease, or sequelae of myocarditis.

Keywords: Arrhythmogenic dysplasia of the right ventricle, pathophysiology, clinic and diagnosis.

INTRODUCTION

Initially recognized as ventricular tachycardia due to a structural problem of the right ventricle by Fontaine and Marcus in 1982, arrhythmogenic right ventricular cardiomyopathy (ARVC) is currently understood as a hereditary pathology characterized by the replacement of right myocardial tissue with fibrous or fibro-fatty tissue (ELIAS NETO, et al. 2019).

Epidemiologically, arrhythmogenic right ventricular cardiomyopathy is considered a rare disease with low prevalence in the general population (LUNA-ALCALA, et al. 2024). Furthermore, clinically, ARVC is characterized by ventricular arrhythmias and right ventricular dysfunction. Regarding the natural history of the disease, this condition can be classified into four distinct phases: concealed, arrhythmic, right ventricular failure, and biventricular failure (CORRADO, et al. 2020).

Regarding pathophysiology, there is an impairment of the intercalated discs between cardiac cells, which promotes a decrease in the action potential velocity during muscle contraction. This results in a progressive cardiomyopathy associated with ventricular arrhythmias (SHAH, *et al.*, 2024).

For diagnosis, genetic and non-genetic causes and complementary tests such as; electrocardiogram, echocardiogram, magnetic resonance imaging. Treatment may include antiarrhythmic drugs, implantable cardioverter defibrillators, and catheter ablation (PANTERRE, *et al.*, 2021).

The aim of this study was to gather updated information on the pathophysiological and clinical aspects of arrhythmogenic right ventricular cardiomyopathy.

METHODS

The present study is an integrative review, at an exploratory level and takes the form of qualitative research, on arrhythmogenic right ventricular cardiomyopathy and its clinical and pathophysiological aspects. This was done through searches in the scientific databases PubMed, VHL (Virtual Health Library) and SciELO (Scientific Electronic Library Online). Initially, the topic was chosen (Arrhythmogenic right ventricular cardiomyopathy: clinical and pathophysiological aspects) and the question was defined: What are the clinical and pathophysiological characteristics that make arrhythmogenic right ventricular cardiomyopathy a potentially fatal condition? In this step, terms in Portuguese were chosen through the Health Sciences Descriptors (DeCs) and terms in English through Medical Subject Heading (MeSH). The locations where the search would take place were established, as well as the inclusion and exclusion criteria for studies.

The established inclusion criteria were: original articles available in electronic format, in full, written in Portuguese, English or Spanish, with a time limit of 2019 to 2024 and that were compatible with the objective of the research. The investigation was carried out in March 2024. The following Boolean operators were used to search the databases: AND and OR, to improve the search in the databases. Therefore, we will use the following descriptors in Health Science (DeCS) and Medical Subject Headings (MESH): Arrhythmogenic dysplasia of the right ventricle AND physiopathology , OR clinic AND diagnosis , which were performed in different combinations. Concomitantly, opinion articles, dissertations, letters to the editor and studies that were not compatible with the research objective were excluded.

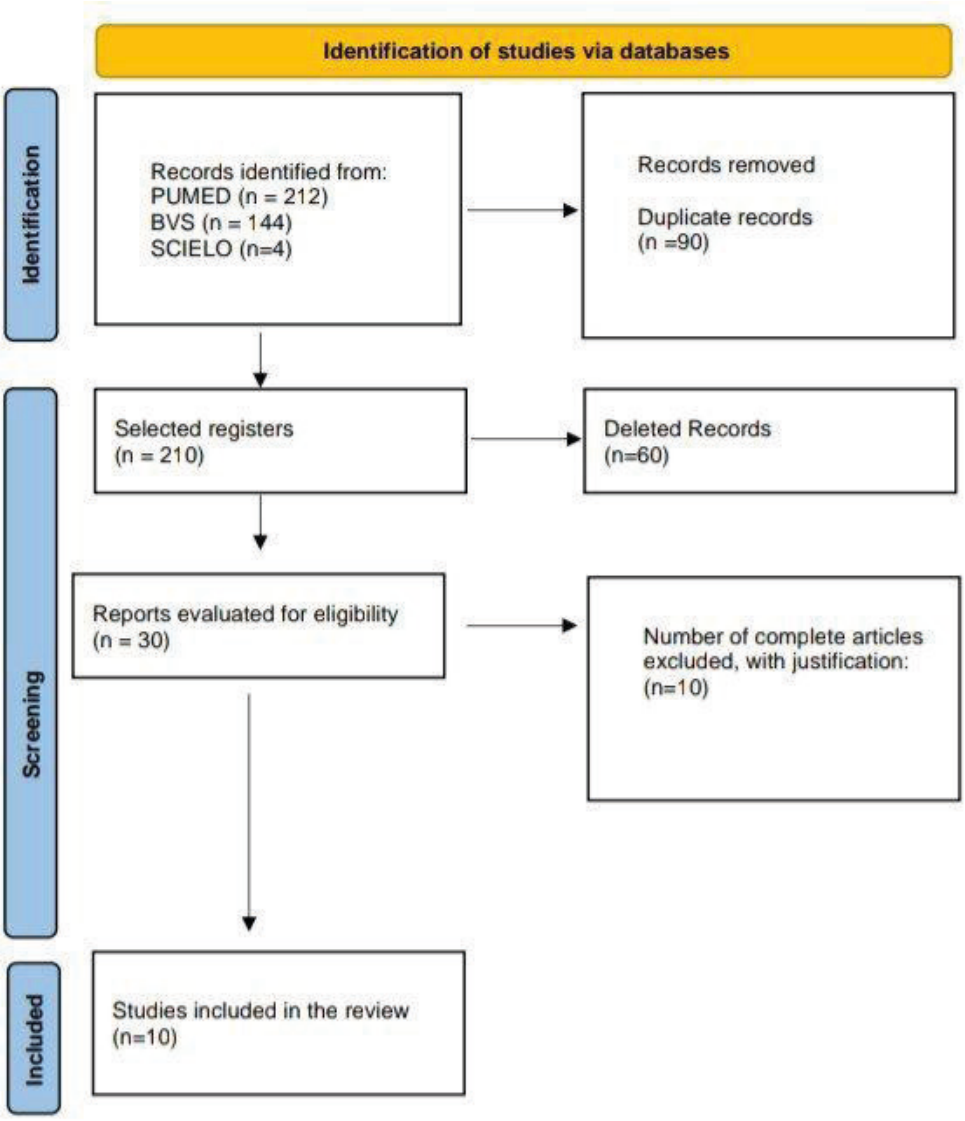

Figure 1–Schematic representation of synthesis and analysis of results.

Author/year	Objectives	Approach	Main results
CORRADO,et al.,2020	The Padua criteria are a working framework to improve the diagnosis of ACM by introducing new diagnostic criteria regarding tissue characterization findings by contrast-enhanced cardiac magnetic resonance, depolarization/repolarization ECG abnormalities and ventricular arrhythmia features for diagnosis of the left ventricular phenotype.	Research article	Over the last decade there has been an increasing awareness that the phenotypic spectrum of ACM was broader than previously expected and included biventricular and left-dominant variants. The lack of specific ITF diagnostic criteria resulted in the under-recognition of patients with the non-classic ARVC phenotype. The Padua criteria represent a working framework to improve the diagnosis of ACM with the aim to fill the gap of previous 1994 and 2010 ITF criteria, by introducing new diagnostic criteria regarding CE-CMR tissue characterization findings, depolarization/repolarization ECG abnormalities and ventricular arrhythmia features for diagnosis of the LV phenotype.

ELLIOTT, et al.,2019	In this paper, we present the conclusions of an expert round table that aimed to summarize the current state of the art in arrhythmogenic cardiomyopathies and to define future research priorities.	Newspaper article	Since the first detailed clinical description of ARVC, dramatic advances have been made regarding its pathogenesis, diagnosis and management. This progress was made possible by the development of single center registries working alone or in partnership and also by the efforts of dedicated basic research laboratories. With the recognition of AC as a broad spectrum of disease, the need for national and international collaborative efforts is even greater. We hope this document will contribute to this endeavor.
KUBALA, et al., 2020	Many questions remain regarding prevention and management of coexisting tricuspid valve regurgitation, atrial arrhythmias, and intracardiac thrombosis. Although data on genotype-phenotype correlations is growing, long-term follow-up studies of families with ARVC are still lacking. Ongoing research will contribute to better understanding of this pathological condition.	Systematic review study	ARVC diagnostic and therapeutic challenges have been overcome particularly as it relates to the management of VAs. Rapid RV scar progression is uncommon. Combined and detailed endo- and epicardial catheter mapping and ablation produces good long-term outcomes and reduces the need for drug therapy. Despite the progress, many questions remain regarding ARVC. What triggers the initial scar formation and uncommon progression? How to prevent and manage adverse RV remodeling? How to better predict and treat atrial arrhythmias and best prevent intracardiac and device lead thrombosis related to low flow states? How to manage progressive RV and LV dysfunction and delay or prevent the need for transplant?
LUNA-ALCALA,et al.,2024	We present a challenging case report of a 68-year-old man who presented to the emergency department with chest discomfort, palpitations, and dizziness prior to an episode of syncope with urinary incontinence. During monitoring, ventricular tachycardia was detected and treated with cardioversion.	Case report	Diagnosis of biventricular arrhythmogenic cardiomyopathy was established based on the 2020 Padua Criteria. Although there is no recognized classification within these criteria to establish its subtype, in our case there was left ventricular predominance due to the presence of additional left ventricular categories.
MALIK, et al., 2020	The purpose of the study was to determine whether measures of right ventricular (RV) dysfunction on echocardiogram including RV strain were predictive of structural disease progression in ARVC.	Research article	RV free wall deformation is associated with the rate of structural progression in patients with ARVC. It can be a useful marker for determining which patients require closer monitoring and treatment.
MARCHETTI, et al., 2022	Arrhythmogenic right ventricular cardiomyopathy is a disease that is most often hereditary and affects the right ventricle, but also the left ventricle in a more or less obvious way. Predisposes to ventricular arrhythmias, heart failure and sudden death. Diagnosis remains a challenge and is mainly based on reference diagnostic criteria.	Update article	Once the diagnosis is established, it is essential to offer individualized care. On the one hand, the indication for installing an implanted cardiac defibrillator will be maintained in case of a history of sudden death, sustained ventricular tachycardia or advanced left or right ventricular dysfunction. It should also be considered in the presence of other risk factors. On the other hand, it will be advisable to avoid high-intensity physical activities. Finally, drug and/or ablative treatment will need to be individualized, while beta-blockers are recommended in all patients with clinically manifest arrhythmogenic right ventricular cardiomyopathy.

PANTERE, et al.,2021	Patient, 32-year-old woman, housewife and mother of 3 children, who, in apparent health, was found dead by her husband at noon in her bed, after a night's rest. The family denies any cardiological history of the patient and her direct relatives, as well as any sudden death. At necropsy, serial cross sections showed right ventricle with adipose replacement in more than 50-80% of the mural thickness.	Case report	Of the prespecified clinical predictors, only 4 (younger age, male sex, number of ventricular premature beats, and number of leads with T-wave inversion) were associated with subsequent life-threatening ventricular arrhythmias, but not prior sustained ventricular arrhythmia and extension of functional heart disease.
PEREZ, et al., 2020	A 12-year-old male patient with cardiomyopathy manifested by ventricular arrhythmia at seven years of age (extrasystoles and non-sustained ventricular tachycardia). The paraclinical examination performed was compatible with ARVC, so it was decided to perform an electrophysiological study with ablation. The procedure achieved a slight temporary improvement. However, the arrhythmia could not be eliminated, so an automatic defibrillator was implanted. This has not presented downloads in two years of evolution.	Case report	Although ARVC is rare in pediatrics, the importance of knowing this pathology lies in the possibility of improving the prognosis in those patients who benefit from an implantable defibrillator. The pediatrician must have a high index of suspicion, and in those patients who are necessary, carry out a joint approach with the cardiologist with a view to effective treatment and follow-up.
SHAH,et al.,2024	Apply the most current knowledge to understand the complex pathophysiology of arrhythmogenic right ventricular cardiomyopathy.	Free books and documents	Providing patient-centered care for individuals with ARVC requires a collaborative effort among healthcare professionals, including physicians, nurses, pharmacists, radiology, and ECG technicians. First, healthcare providers must possess the clinical skills and knowledge necessary to diagnose, evaluate, and treat this condition – including proficiency in interpreting ECG and cardiac MRI results, recognizing potential complications, and understanding the nuances of differentiating the condition.
TADROS, et al., 2023	In this review, we aim to detail the epidemiology, etiologies, presentations, assessment and management of AC across the age range.	Systematic review study	Knowledge of arrhythmogenic cardiomyopathy is growing rapidly. It has progressed from the initial consensus that it is a RV dominant disease to more recent data showing that it can affect both ventricles or the LV in isolation. It can also occasionally be complicated with association with left ventricular noncompaction and/or congenital heart disease.

Table 1 – Characteristics of the selected studies, regarding authors, year of publication, objectives, approach and main results.

SOURCE: SOUZA LMO et al., 2024.

RESULTS

With the search in the databases, 359 articles were found, of these 210 articles were selected for reading and, according to the objective of the present work, 10 articles were included in the research: 3 from the Virtual Health Library, 5 articles from PubMed, 2 articles from SciELO as represented in figure 1.

DISCUSSIONS

Heart diseases are a group of diseases caused by changes in the ventricular heart muscle that cannot be ruled out by abnormal overload or natural deformities. Such variants may be associated with adversities in coronary circulation, chronic tachyarrhythmias, exposure to toxins, contamination or latent disorders. The traditional phenotypic split encompasses hypertrophic, dilated, restrictive and non-compacted forms (PEREZ, et al., 2020).

Arrhythmogenic Cardiomyopathy is a genetic pathology of the heart muscle that can affect the right ventricle, the left ventricle or both, whose phenotypic characteristic is the fibrofatty replacement of myocytes involving the epicardium and extending to the endocardium, resulting in ventricular arrhythmias and ventricular dysfunction (KUBALA, et al., 2020).

> Predisposes to ventricular arrhythmias, heart failure and sudden death. Diagnosis remains a challenge and is mainly based on reference diagnostic criteria. The latter, divided into major and minor criteria, consist of the following elements: structural changes demonstrated on cardiac imaging (echocardiography or magnetic resonance imaging), electrocardiographic changes, documentation of ventricular arrhythmia, histological evidence of fibroadipose infiltration of the myocardium and family medical history. Once the diagnosis is established, it is essential to offer individualized care. (Marchetti, et al.,2022)

According to Luna-Alcala (2024), arrhythmogenic cardiomyopathy is considered a rare disease, due to its low prevalence within the general population, where it varies from 1:2,000 to 1:5,000. Where clinical manifestations commonly appear during the second and fourth decade of life, however, they can rarely present before puberty or earlier as it is a hereditary pathology. (LUNA-ALCALA,et al.,2024)

> The original designation "arrhythmogenic right ventricular cardiomyopathy (dysplasia/) (ARVC)" was used by the scientists who discovered the disease, in the pre-genetic and pre-cardiac magnetic resonance (CMR) era, to describe a new heart muscle. A disease that predominantly affects the right ventricle (RV), whose cardinal clinical manifestation was the occurrence of malignant ventricular arrhythmias. Subsequently, autopsy investigations, studies of genotype-phenotype correlations, and the increasing use of contrast-enhanced MRI (CE-MRI) have shown that fibrofatty replacement of the myocardium represents the distinguishing phenotypic feature of the disease and affects not only the RV but also the ventricle. left. Over the past decade, there have been several pathological and clinical studies that have characterized the structural and electrical findings of the LV disease phenotype and provided significant information regarding the diagnosis of left-sided disease. This led to the new designation of "Arrhythmogenic Cardiomyopathy," which represents the evolution of the original term ARVC and reflects the modern concept of a biventricular muscle disease with LV involvement that may parallel or exceed the severity of RV involvement (Corrado, et al.,2020)

Pathophysiologically, the disease mainly affects the intercalated disc, a structure crucial to cardiac function that facilitates cell-to-cell interaction between adjacent cardiomyocytes. The intercalated disc connects to intracellular actin through the transmembrane glycoprotein N-cadherin. When damage to the intercalated disc occurs, there is a loss of structural integrity of the cardiomyocytes, which worsens during mechanical stress. Other structural proteins, such as plakoglobin and desmoplakin, connect the desmosome to the myocyte cytoskeleton, providing additional support to the desmosome during mechanical stress. In addition to its structural role, the intercalated disc is also fundamental for electrical coupling between cells, mediated by sodium and potassium ion channels. A deficit in sodium current can decrease the speed of phase 0 of the action potential, resulting in a combination of progressive cardiomyopathy and ventricular arrhythmias (SHAH, et al., 2024).

Taking into account that a precise definition for ARVC has not yet been agreed, its diagnosis must follow a systematic approach that is based on the analysis of several parameters. Elliot et al. (2019) states that the fundamental aspects

to ensure a good diagnostic statement must include: arrhythmia, frequent ventricular ectopic with sustained or non-sustained ventricular tachycardia, or unexplained cardiac arrest are essential manifestations, in addition electrocardiographic, structural abnormalities, myocardial dysfunction evidenced by specific exams of images such as cardiac magnetic resonance and heredity as a central component in research.

Structural markers are essential for diagnosis and assessment of the structural progression of the pathology. According to the clinical study by Malik, et al. (2020) patients who have right ventricular tension rates at relatively normal baseline values progressed more slowly, while those with abnormal values progressed faster. Taking structural changes into account is extremely important for the patient's clinical development, as these changes are associated with arrhythmic events and the development of heart failure.

> For diagnosis, genetic and non-genetic causes must be considered. Myocardial tissue is a complex system in which structural and functional factors occur; The identification of significant changes in these factors allows the diagnosis of ARVC to be defined, through appropriate electrophysiological and morphological analysis. Likewise, genetic evaluation should be used through family screening of cases of premature cardiac events (sudden death, heart failure) with cardiac conditions (arrhythmias, conduction system anomalies) and associated non-cardiac conditions (musculoskeletal anomalies, renal failure). , visual and auditory anomalies). Abnormalities in this final common pathway can determine the development of a complex phenotype, such as dilated cardiomyopathy with significant arrhythmic potential (Panterre, et al., 2021)

Once the diagnosis is made, treatment is multifaceted, that is, it aims to prevent and treat fatal ventricular arrhythmias, heart failure and several other cardiac sequelae. This may include, according to Tadros et al. (2023): antithrombotic therapy in the case of ventricular aneurysms or depressed ventricular function or anticoagulation in the case of atrial fibrillation or known thrombosis or thromboembolism, antiarrhythmic therapies that may include beta-blockers, electrical cardioversion, in some cases endo- and epicardial catheter ablation of the focus of arrhythmia may be considered, although the risk of recurrence of arrhythmias is relatively high given ongoing myocardial pathology.

CONCLUSION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) poses a significant challenge in both diagnosis and treatment due to its complex and progressive nature. Recently, there have been significant advances in understanding ARVC, a condition typically inherited and rare with low prevalence in the general population, characterized by the replacement of right ventricular myocardial tissue with fibrous or fibroadipose tissue. It is a dominant disease in the RV that can affect either or both ventricles or the LV in isolation, clinically associated with ventricular arrhythmias, heart failure, and sudden death. Recognition of its genetic and non-genetic causes, along with clinical and imaging assessment, is crucial for accurate diagnosis and effective management.

Advances in diagnostic criteria, such as the 2020 Padua criteria, are crucial for improving identification and early treatment of ARVC patients. Following diagnosis, therapeutic interventions should be multidisciplinary, aiming to prevent fatal ventricular arrhythmias and manage heart failure, considering the impact of factors such as fibrolipid replacement and structural abnormalities on the disease course. Additionally, it is essential to provide individualized treatment, including consideration of implanted cardioverter-

defibrillator and restriction of intense physical activity, as well as personalized medical and/or ablative therapy, with beta-blockers recommended for clinically manifest patients. Therefore, early diagnosis and treatment are necessary to reduce the risk of sudden death and improve the quality of life of those affected by this pathology.

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