Review Article

Arrhythmogenic Left Ventricular Cardiomyopathy – State of Art: From Genotype to Phenotype

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Abstract

Arrhythmogenic cardiomyopathy with exclusive or predominant involvement of the left ventricle has been described recently. It has a heterogeneous genetic basis with different clinical phenotypes ranging from ventricular arrhythmias and sudden death (SD), symptoms suggestive of acute myocarditis with chest pain and troponin elevation, symptoms of heart failure, to asymptomatic patients. A high level of suspicion is needed for a correct diagnosis and implementation of a genotype-based therapy, to prevent its most feared complication, SD. This review aims to describe arrhythmogenic left ventricular cardiomyopathy as a genetic heart disease, with initial and/or predominant involvement of the left ventricle and its varied phenotypic expression, providing a basis for clinical reasoning and "red-flags" for the diagnosis, as well as for SD risk stratification.

Introduction

Arrhythmogenic cardiomyopathy (ACM) is characterized by progressive replacement of myocardium by fibro-fatty tissue, presence of ventricular arrhythmias, and an increased risk of sudden death (SD). ACM may progress to heart failure (HF) or have a myocarditis-like presentation.[1-3] Although the cause of ACM has been attributed to pathogenic genetic variants, some forms possibly associated with autoimmune disease have been reported.[1,4] In 1982, ACM was described by Marcus et al.[5] as a condition that affected exclusively the right ventricle. For this reason, it was initially called right ventricular (RV) arrhythmogenic dysplasia since the histopathological changes were believed to be caused by alterations during embryogenesis of the right heart.[1]

Based on the establishment of the genetic etiology and the genotype/phenotype, the term dysplasia was replaced by the term arrhythmogenic RV cardiomyopathy (ARVCM), which was then included in the group of genetic cardiomyopathies in the 2006 American Heart Association (AHA) classification as classified as a familial/genetic cardiomyopathy by the European Society of Cardiology in 2008.[6,7]

In according to the Heart Rhythm Society (HRS),[8] in addition to specific phenotypes of genetic etiology, systemic infiltrative diseases, inflammatory diseases and infectious diseases like sarcoidosis, amyloidosis, myocarditis, and Chagas disease are included in the wide spectrum of ACMs, since all these conditions share a clinical progression to atrial fibrillation, conduction disturbances and ventricular arrythmias. However, the pathophysiological substrate is distinct, and there has been a trend to include, in the group of ACM, phenotypes resulting from specific genetic changes that leads to fat replacement of the myocardium, which in turn results in ventricular arrythmias and risk of SD.[1,9-11]

Today, three main phenotypes are described: the original ARVCM, in which only the right ventricle is affected, without involvement of the left ventricle; a phenotype with involvement of both ventricles (biventricular ACM); and a phenotypic variant called arrhythmogenic left ventricular cardiomyopathy (ALVCM), with predominant involvement of the left ventricle.[1,10,11]

This new classification was developed based on histopathological findings from different necropsy studies, genotype-phenotype correlations and cardiovascular imaging tests, which altogether allowed a detailed characterization of the myocardium and interstitial cells.[1,12,13] ACM may overlap with other phenotypes, more commonly with dilated cardiomyopathy (DCM), marked by the presence of ventricular dilation and dysfunction in addition to ventricular arrhythmias.[3,8,9,12,14] ACM is one of the main causes of SD among the young and athletes, with a prevalence estimated to range between 1:1000 and 1:5000.[13,15,16]

For more than three decades, ARVCM has been the most widely described and discussed form of ACM among cardiologists in the fields of arrhythmology, and sports medicine. However, over the last years, attention has been given to the

Keywords

Arrhythmogenic Right Ventricular Dysplasia; Death, Sudden; Arrhythmias, Cardiac; Genotype

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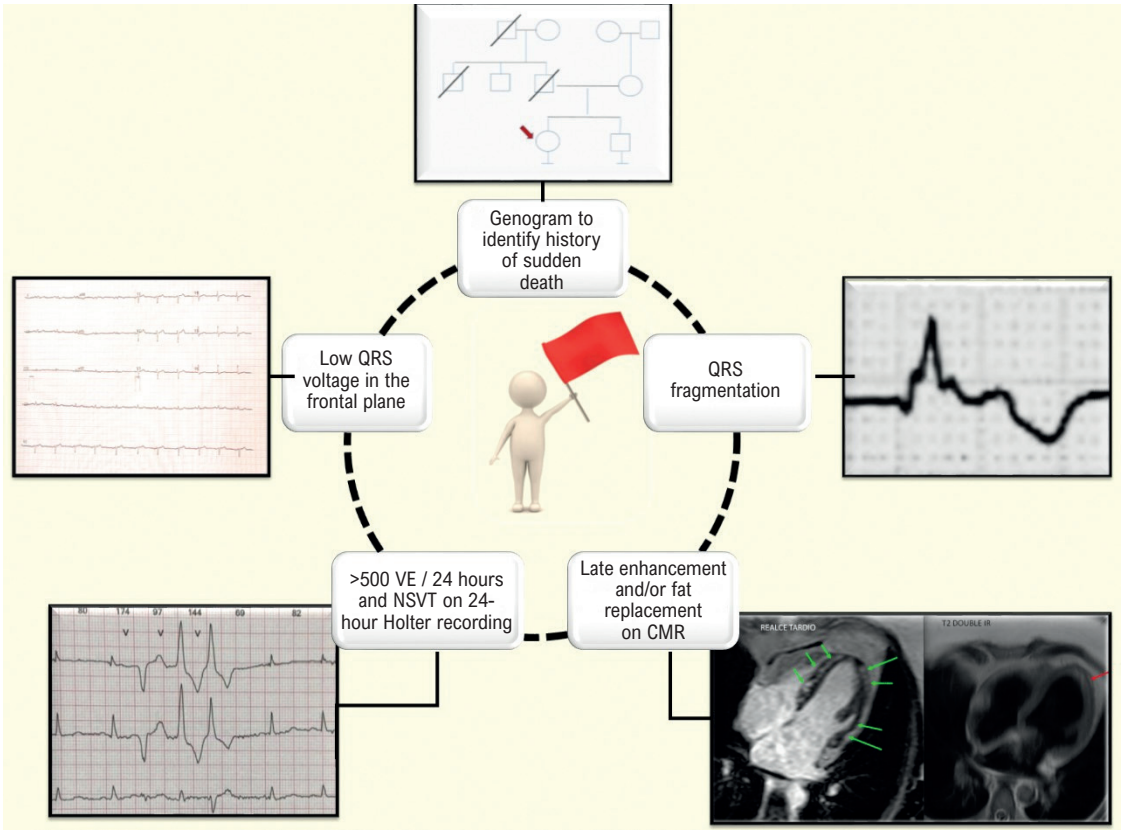
Central Illustration: Arrhythmogenic Left Ventricular Cardiomyopathy – State of Art: From Genotype to Phenotype



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Red flags for arrhythmogenic left ventricular cardiomyopathy: positive family history, electrocardiographic changes, and fibrosis on cardiac magnetic resonance. VE: ventricular extrasystoles; NSVT: nonsustained ventricular tachycardia; CMR: cardiac magnetic resonance.

phenotypic presentation characterized by the predominant and early involvement of the left ventricle, with or without minor abnormalities of the right ventricle, the ALVCM.[3,9,12,14,15] Because of its better characterization, clinical cardiologists and HF specialists have started to recognize ALVCM as a "new" entity, whose prevalence and clinical importance have been redefined.

This review aims to describe ALVCM as a genetic heart disease, with initial and/or predominant involvement of the left ventricle and its phenotypical expression, providing the basis for clinical reasoning and red flags for the diagnosis, and for risk stratification for SD. In addition, we will address current perspectives in the treatment and prevention of arrhythmic death, to draw attention to a possible hidden, hereditary, rare disease, with a phenotype that can be confused with other diseases and, for this reason, is underdiagnosed and has a non-negligible risk of SD.

Genetic basis of AMC

The genetic etiology of AMC is heterogeneous and is usually characterized by dominant autosomal inheritance associated with genes that encode desmosomal proteins, mostly PKP2, DSP, DSG2, DSC2 and JUP. However, the penetrance is incomplete and the expressivity variable, which may make the diagnosis difficult.[16-18] The involvement of other genes not related to desmosomes may also occur.[1,13]

Desmosomes are structures that provide intercellular adhesion by junctions between cytoskeletal filaments and cytoplasmic membrane of adjacent cells, and participate in signaling, differentiation and tissue morphogenesis pathways. Desmosomes, together with adherens junctions, gap junctions and ionic channels, form the "area composita", responsible for the electromechanical coupling between cells. The loss of function of this structure leads to the rupture of cardiac syncytium, impaired electrical impulse propagation and subsequent arrhythmogenesis. Besides, cell death occurs during development of fibrosis. The elucidation of these molecular changes has led to advances in the understanding of the pathophysiology and clinical manifestations of ACM and of patient prognosis.[13,16-18]

The first genetic evidence of ACM was observed with Naxos disease and Carvajal syndrome, both with a recessive

autosomal pattern, early presentation in childhood and adolescence, and cutaneous changes characterized by palmoplantar keratosis and woolly hair. Naxos disease affects individuals with the pathogenic homozygous frameshift mutation (c.2040_2041delGT) in JUP, encoding plakoglobin (OMIM: 601214). Carvajal syndrome affects mainly the left ventricle, usually leading to a DCM phenotype with left ventricular (LV) dysfunction and need for heart transplantation; this presentation is attributed to mutations in the DSP gene. These descriptions have guided the clinical reasoning for the identification of a wider spectrum of arrhythmogenic heart diseases, including other forms of presentation in addition to RV dysfunction.[1,15,17,18]

Studies on genotype-phenotype correlations have shown a stronger correlation of specific genes, such as the DSP and the FLN, followed by the PLN, DD and LMNA with the ALVCM phenotype.[1,3,9,19] Figure 1 illustrates the main genes related to ACM and their phenotypes.

Filamin C, encoded by the FLNC gene, is an important structural component that binds to actin filaments in the sarcomeric Z-disc of cardiac and skeletal muscle. It was initially associated to myofibrillar myopathy, although the clinical presentation of cardiomyopathy alone has been associated with DCM and ALVCM phenotypes, with an increased risk for ventricular arrythmias and SD. Patients with pathogenic variants in FLNC usually present extensive subepicardial (ring pattern) late gadolinium enhancement (LGE) in the left ventricle on cardiac magnetic resonance (CMR), and typical electrocardiographic abnormalities, with T-wave changes and low QRS voltage. It is worth pointing out that truncated variants of FLNC have been rarely reported in patients with the "classical" form of ACM. Besides, the most common ACM phenotype reported has been the ALVCM, characterized by a late onset of the disease (after 40 years of age), with extensive myocardial fibrosis on CMR or in autopsies.[3,9,10,13,19]

Other phenotypes associated with FLNC are restrictive cardiomyopathy and hypertrophic cardiomyopathy, both with a high severity of ventricular arrythmias and risk of SD. The term "filaminopathies" has been used to characterize this group of cardiomyopathies that have an increased risk of arrhythmias and SD.[20-22]

Pathogenic variants in the DSP gene are associated with a clinical phenotype similar to myocarditis, with precordial pain, increase of troponin levels and absence of coronary disease. In these episodes, known as "hot phase", the patient develops RV systolic dysfunction and myocardial fibrosis. This genotype-phenotype correlation among the pathogenic variants in the DSP and the MCAVE genes has been called "DSP cardiomyopathy".[2,3,9,13,23,24]

Desmin, encoded by the DES gene, plays important structural and signaling roles in the myocytes, crucial for the cytoskeletal organization and maintenance of cardiomyocyte structure. Similar to FLNC, the DES was also originally described to be associated with a myopathy. Phenotype overlapping is also common; in a meta-analysis with 159 patients with 40 mutations in the DES, up to 50% of patients had cardiomyopathy, with phenotypes, in descending order: DCM (17%), restrictive cardiomyopathy (12%), hypertrophic cardiomyopathy (6 %) and ACM (1%).[25] Cardiac phenotypes of mutations in the DES gene include biventricular ACM with characteristics of ARVCM, associated or not with features exclusive to ALVCM, high incidence of ventricular arrhythmia and SD, electrocardiogram (ECG) with low-voltage QRS and changes in inferolateral ventricular repolarization.[3]

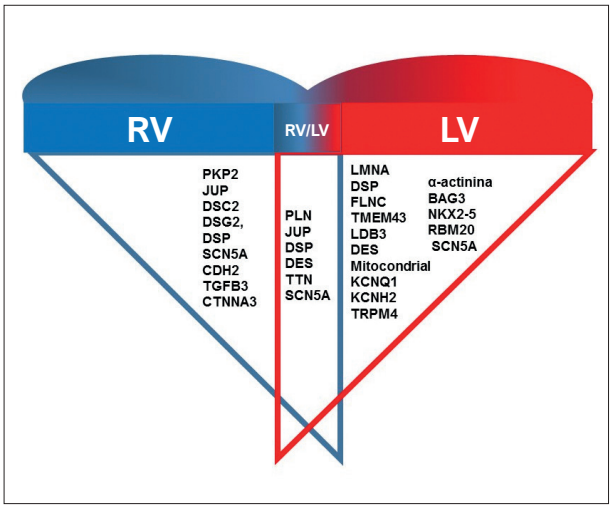

Figure 1 – *Genes associated with arrhythmogenic cardiomyopathy according to the phenotype. RV: right ventricle; LV: left ventricle.*

Progression to HF, with LV dysfunction, is more related to genes like LMNA, BAG3, TMEM43 and PLN.[12] The LMNA gene encodes lamin A/C a nucleoskeletal intermediate filament with complex cellular functions, including the maintenance of nuclear structural integrity, regulation of gene expression mechanosensitivity, and mechanical transduction by lamin-associated proteins. Pathogenic variants in LMNA are associated with a wide spectrum of diseases, including muscular dystrophy (e.g., Emery-Dreifuss muscular dystrophy), Hutchinson-Gilford progeria syndrome, and cardiac manifestations. Regarding cardiac manifestations, genetic variants in LMNA were initially reported in patients with DCM often associated with conduction disturbance and arrhythmic instability, that are not correlated with LV systolic function.[3] PLN encodes phospholamban, a protein that inhibits sarcoplasmic reticulum calcium ATPase. Variants in this gene lead to changes in calcium flow, and predisposition to arrhythmias and LV dysfunction.[12]

Therefore, the determination of a genetic etiology helps in the genotype-phenotype correlation, identifying those individuals more likely to develop adverse cardiovascular events, and consequent ventricular dysfunction and SD. The genotype identified contributes to the definite diagnosis of ALVCM, risk stratification, influencing decision-making processes as the use of implantable cardioverter defibrillators (ICDs).[8,12]

Clinical diagnostic reasoning

Patients with ACM may present four clinical phenotypes: (1) initial phase, asymptomatic, but with risk of SD; (2) symptoms caused by ventricular arrhythmias; (3) chest pain, simulating

a myocarditis; or (4) HF due to myocardial remodeling.[26] There are some red flags for the clinical suspicion of ALVCM (Central Illustration).

During clinical assessment, in addition to the investigation of cardiovascular symptoms, a detailed family history, with a genogram of at least three generations is essential, not only of arrhythmias and SD, but also of neuromuscular disorders and other organ diseases.[1,8,10] The diagnosis of ACM should be considered in families with a history of recurrent myocarditis.[27]

Subclinical presentation

The patient may be referred for a positive family history or for suspected sequelae of myocarditis due to fibrosis on magnetic resonance. Despite the absence of important clinical symptoms, electrocardiographic changes, suggestive of ACM, may be seen on ECG and on 24-hour Holter recordings. The main electrocardiographic manifestations are changes in repolarization, atrioventricular blocks, ventricular extra-systoles and, in some cases, nonsustained ventricular tachycardia (NSVT). Nearly 13% of patients are asymptomatic at diagnosis.[28]

Presentation with arrhythmias

In this classical and most common presentation of ACM, symptoms of palpitation, syncope and aborted SD, caused by ventricular arrythmias or atrioventricular blocks are observed. The earliest and most common clinical presentation is arrythmia.[8,16] In a cohort of 53 ACM patients, palpitation was the most common symptom (73.6%), and syncope was the initial symptoms in 22.6% of patients. A family history of SD is found in approximately 9.4% of patients.[28] Generally, symptoms of ALVCM are not different from those of ARVCM, and both ventricles may be affected in early stages, with a greater involvement of the side where the disease begins.[28]

Myocarditis-like presentation (hot phase)

Recently, it has been reported that ALVCM patients may present with chest pain, elevation of troponin levels, and acute electrocardiographic changes with normal coronary anatomy.[2,3,27] This has been described as a form of ALVCM and named as "hot phase". In some cases, these episodes may be the initial clinical presentation of the disease in the pediatric population, representing the occurrence of acute periods, and a differential diagnosis from acute myocarditis.[2,3,9,27,29] In the cohort in the study by He et al.[28] approximately 10% of patients had precordial pain as the first symptom of ACM.[28]

Since the first reports of the disease, inflammatory infiltrates have been described in myocardial biopsies and autopsies of patients with ACM.[2,3,27] In a study with a series of patients with ALVCM, fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) could detect the presence of myocardial inflammation.[30]

In a systematic review[3] for evaluation of clinical findings of ACM patients during the "hot phase", mean age during the presentation was 24 ± 14 years (2 – 71 years), 86% of patients showed left ventricular epicardial late gadolinium enhancement, and at the time of hot-phase episodes, 49% received a diagnosis of ACM, 19% of DCM, and 26% of acute myocarditis. Regarding the genetic study, 69% had pathogenic variants in the DSP, 9% in the PKP2, and 6% in the DSG2. In this review,[3] the "hot phase" phenomenon was likely to be induced by exercise in 50% of cases, and the pediatric population was highly represented, which makes it mandatory to carefully investigate young patients admitted with clinical features of acute myocarditis and their relatives searching for myocarditis, HF or SD. At this stage of disease, it is believed that inflammation, in the absence of a viral genome, which has been already documented in heart biopsies and autopsies of ACM patients, is a consequence of cellular lysis as the primary event, due to lack of desmosome integrity, resulting in amplification of cell death.[3,24] Tissue characterization, family history and genetic test are essential diagnostic tools for the differential diagnosis.

Presentation with HF

This is considered the end stage of ACM, in which cardiac remodeling with structural changes, and left and RV dilation and dysfunction occur.[22,26] Dyspnea on exertion may be the initial symptom in up to 39% of cases.[28] In a study conducted by Bariani et al.,[9] LV dilation was found in 61% of patients, while HF signs and symptoms were present in only 6% of cases.[9] Reduced ejection fraction (EF) with values lower than 45-50% may also be an indication for ICD, depending on the genetic variant involved.[8]

Prophylactic ICD may also be considered for individuals with pathogenic variants in PLN, FLNC and RBM20, ventricular dysfunction and left ventricular EF (LVEF) < 50%, in combination with two or more of these risk factors: nonspecific syncope, LGE on CMR, or sustained ventricular tachycardia (SVT) induced by electrophysiological studies. LMNA variants were initially identified in patients with DCM, usually characterized by cardiac conduction disease and a high degree of arrhythmic instability which does not correlate with LV systolic function. This evidence led to the indication for ICD implantation in patients carrying a pathogenic variant of the LMNA gene, showing a LVEF below 45% in the presence of risk factors.[2,8]

Diagnosis

Due to the absence of highly specific and sensitive findings and symptoms of ACM, a considerable number of diagnostic criteria have been proposed since 1994, with an update in 2010,[15] until the most recent international criteria published in 2020, known as the Padua criteria.[1,10,12] These try to cover all possible phenotypes of ACM, since the disease may not affect exclusively the right ventricle.

The main innovation of these diagnostic criteria consists in the use of tissue characterization by dark-blood LGE-CMR, without fat suppression, for detection of fibro-fatty myocardial replacement of one or both ventricles. Until then, tissue changes were only detected by endomyocardial biopsy.[1,10,12] CMR shows a high level of agreement with myocardial biopsy in detecting fibrosis and contributes to the identification of phenotypes based on LGE distribution in the left, right or in both ventricles.[1,10]

Table 1 – 2020 International criteria for diagnosis of arrhythmogenic cardiomyopathy (Padua criteria)

Category	Diagnostic criteria of ARVCM	Diagnostic criteria of ALVCM
I. Morpho-functional abnormalities, and global or regional dysfunction	*Major* *(By 2D TTE, CMR or angiography)* • Regional RV akinesia, dyskinesia, or bulging plus one of the following factors: • Global RV dilatation (according to age, sex and BSA) • Global RV dysfunction *Minor* *(By 2D TTE, CMR or angiography)* • Hypokynesia, dyskinesia or aneurysm of RV free wall	*Minor* • Global LV systolic dysfunction (depression of LVEF on TTE [<55%] or CMR [<58% for athletes and <57% for non-athletes] or reduction of echocardiographic global longitudinal strain with or without LV dilatation • Regional LV hypokinesia or akinesia of LV free wall, septum, or both
II. Tissue characterization	*Major* *(By CMR)* • Transmural LGE (stria pattern) of ≥1 Bull's Eye segment(s) of the RV inlet, outlet or apex *(By EMB)* • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue	*Major* • LV LGE (stria pattern) of ≥1 Bull's Eye segment(s) of LV free wall (subepicardial or midmyocardial), septum, or both (excluding septal junctional LGE)
III. Repolarization electrocardiographic abnormalities	*Major* • Inverted T waves in right precordial leads (V1-V3) or beyond V3 in individuals with complete pubertal development in the absence of complete RBBB *Minor* • Inverted T waves in leads V1 and V2 in individuals with completed pubertal development in the absence of complete RBBB • Inverted T waves in V1-V4 in individuals with completed pubertal development in the presence of complete RBBB	*Minor* • Inverted T waves in left precordial leads (V4-V6) in the absence of complete LBBB
IV. Depolarization electrocardiographicabnormalities	*Minor* • Epsilon wave (low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 in the absence of complete RBBB	*Minor* • Low QRS voltages (<0.5 mV) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
V. Ventricular arrhythmias	*Major* • Frequent ventricular extrasystoles (>500 per 24 h), NSVT or SVT of LBBB morphology (with superior or intermediate axis) *Minor* • Frequent ventricular extrasystoles (>500 per 24 h), NSVT or SVT of LBBB morphology with inferior axis ("RVOT pattern")	*Minor* • Frequent ventricular extrasystoles (>500 per 24 h), NSVT or SVT with a RBBB morphology (excluding the "fascicular pattern")
VI. Family history/ genetics	*Major* • ACM confirmed in first-degree relatives who meet diagnostic criteria • ACM confirmed at autopsy or surgery in first-degree relatives • Identification of a pathogenic or likely pathogenetic ACM mutation in the patient under evaluation *Minor* • History of ACM in first-degree relatives in whom it was not possible to confirm the diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in first-degree relatives • ACM confirmed pathologically or by diagnostic criteria in second-degree relatives	*Major* • ACM confirmed in first-degree relatives who meet diagnostic criteria • ACM confirmed at autopsy or surgery in first-degree relatives • Identification of a pathogenic or likely pathogenetic ACM mutation in the patient under evaluation *Minor* • History of ACM in first-degree relatives in whom it was not possible to confirm the diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in first-degree relatives • ACM confirmed pathologically or by diagnostic criteria in second-degree relatives

ARVCM: arrhythmogenic right ventricular cardiomyopathy; ALVCM: arrhythmogenic left ventricular cardiomyopathy; 2D TTE: two-dimensional transthoracic echocardiography; CMR: cardiac magnetic resonance; RV: right ventricular; SBA: body surface area; EMB: endomyocardial biopsy; RBBB: right bundle-branch block; LBBB: left bundle-branch block; NSVT: nonsustained ventricular tachycardia; SVT: sustained ventricular tachycardia; RVOT: right ventricular outflow tract; ACM: arrhythmogenic cardiomyopathy. Adapted from Corrado et al.[10]

The 2020 international criteria are divided into six categories that may constitute either major or minor criteria (Chart 1). While major criteria are those that are absolutely essential to the diagnosis, minor criteria contribute to the diagnosis of ALVCM.[1,10,12]

The cornerstone of the diagnosis of ALVCM are electrocardiographic abnormalities and ventricular arrhythmia of LV origin; myocardial LGE (with or without edema) in CMR imaging, and presence of pathogenic and likely pathogenic variants in ACM-associated genes. It is important to highlight that the presence of these factors alone is not sufficient to establish the diagnosis of ALCVM. To confirm the diagnosis, a major structural criterion (category II), combined with a positive genetic test (Figure 2) should be present, since other conditions that similarly affect the LV (e.g., myocarditis, DCM and sarcoidosis) can express similar phenotypes.[10,12]

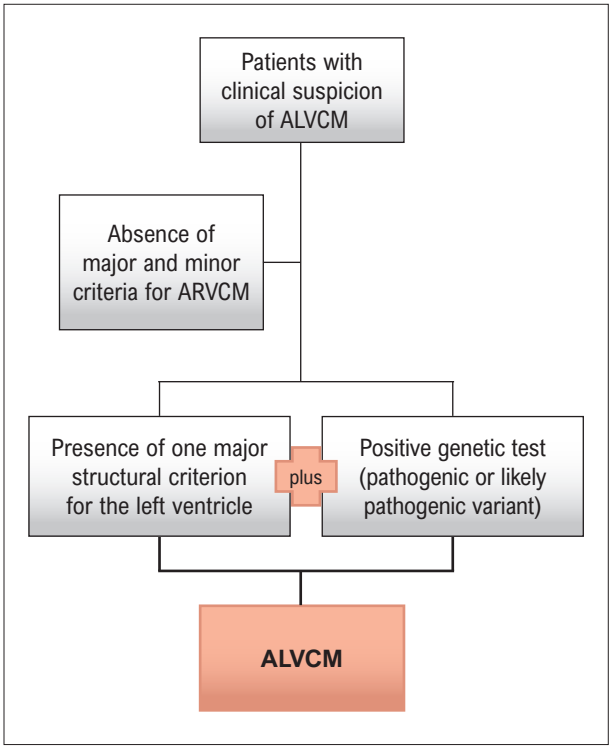

Figure 2 – *Flowchart for the diagnosis of arrhythmogenic left ventricular cardiomyopathy. ALVCM: arrhythmogenic left ventricular cardiomyopathy. ARVCM: arrhythmogenic right ventricular cardiomyopathy. Adapted from: Corrado et al.[1]*

Electrocardiographic abnormalities

The main abnormalities on the 12-lead ECG are ventricular extrasystoles and right bundle-branch block (RBBB) morphology suggesting a LV origin, low QRS voltage in limb leads, and inverted or flattened T waves in the inferior or inferolateral wall, although the ECG may be completely normal.[1,10,12] In athletes with ventricular arrhythmias, the presence of a low peak-to-peak voltage (<0.5mV) in the ECG, which is extremely rare, usually reflects the presence of a heart disease, possibly an ACM. This is caused by a reduction in the ventricular myocardial mass by fibro-fatty replacement or non-ischemic myocardial fibrosis, which makes it mandatory to continue the investigation.[1,10,31] Twenty-four-hour Holter monitoring frequently reveals episodes of NSVT, high incidence of ventricular extrasystoles (>500 in 24 hours, according to the updated diagnostic criteria), with RBBB or multifocal.[1,10,12]

Morphofunctional and tissue abnormalities

The use of different imaging techniques contributes to the diagnosis and characterization of the ACM phenotype.[8,12,32]

Echocardiography (ECO): it is the initial diagnostic test of choice for characterization of the morphofunctional phenotype. This tool can show LV dysfunction with or without dilatation, or a normal left ventricle without dysfunction or segmental changes.[2,12,13,32] The use of the global longitudinal strain can help in the early detection of myocardial dysfunction.[12,32] Echocardiographic findings are nonspecific, and hence considered as minor criteria.[1,12]

Cardiac magnetic resonance (CMR): CMR is essential to confirm ACM in all patients with involvement of the left ventricle.[32] LV fibro-fatty replacement may be regional or diffuse, and detected by CMR (stria pattern) by the presence of LGE or fat. The most common location is the basal inferolateral wall (85.9%) followed by basal anterolateral wall (83.0%), midinferoseptal wall (50.1%), midinferolateral wall (50.1%) and mid anterolateral wall (50.1%),[28] without contraction impairment, especially in less advanced stages of the disease. Although septal involvement is frequently seen in ALVCM, affecting 50% of patients, it is uncommon in ACM involving predominantly the right ventricle. The area of LGE overlaps with the areas that contain fat, and the amount of LGE is always greater than the amount of fat in the left and right ventricles. Diffuse LGE is associated with adverse events and higher risk of arrythmia and SD.[28,32] It is worth pointing out that the absence of fat does not exclude ACM, since many patients may have fibrosis as the only CMR finding.

The non-inclusion of a dark-blood sequence (without fat suppression) into standard CMR protocols for the detection of fat replacement makes the presence of LGE a non-specific finding that may be seen in other phenocopies, like myocarditis, DCM and sarcoidosis. It is important to highlight that the mere presence of findings (in the left, right of both ventricles), suggestive of AMC, does not define the diagnosis, which remains multiparametric.[3,24] The use of dark-blood sequence with fat suppression, triple inversion recovery, and T2-weighted CMR is useful to detect myocardial edema during "hot phase" episodes.[32]

FDG PET-CT has been used in the diagnostic evaluation of ALVCM. The technique allows the detection of inflammation in patients with myocarditis-like illness, associated with specific genotypes (DSP), and contributes to risk stratification for arrhythmias and atrioventricular block when the FDG uptake occurs in the anteroseptal area, which leads to the suspicion of cardiac sarcoidosis as a differential diagnosis. The use of PET-CT can also guide endocardial biopsy in patients with suspected myocarditis or sarcoidosis.[29,32]

Genetic investigation

Genotype identification is mandatory in ALVCM, especially when there are no clinical or radiological signs of RV involvement. The presence of pathogenic and likely pathogenic variants is a prerequisite for the diagnosis of ALVCM, since many other diseases, as previously mentioned, may have similar phenotypes.[1,8,10]

The identification of a pathogenic variant can contribute to risk stratification for arrhythmic death, since the genotype-phenotype relationship can predict the clinical course and the prognosis, and establish individualized interventions like ICD implantation.[1,8,10,12]

When a genetic testing is indicated, the patient must be counseled on possible results and implications for first-degree relatives, since a cascade screening should be performed. Genetic testing allows clinical surveillance of positive relatives, early detection of phenotypes and SD prevention.[10,33-36]

Differential diagnosis

Inflammatory diseases like myocarditis and sarcoidosis are phenocopies of ALVCM, which may lead to an erroneous diagnosis.[10,12,32] DCM is another differential diagnosis of ACM; similarities between these two cardiomyopathies encompass etiological, clinical and imaging aspects. Desmosomal variants have been also documented in patients with DCM, and manifestations of the disease may vary from mild forms of fibrosis in limited areas, to severe phenotypes of ventricular dilatation and dysfunction. However, the hypokinetic non-dilated cardiomyopathy, marked by an extensive scarring of the left ventricle, and little impairment of systolic function, is the typical phenotype of ALVCM, while in DCM, severe ventricular dilatation and low fibrosis. The severity of LV dysfunction in DCM is not correlated with the degree of fibrosis, which, when present (<50% of the cases), involves the septal mesocardium, while in ALVCM, fibrosis affects predominantly the subepicardium and inferolateral areas of the left ventricle. Therefore, an important warning sign is the correlation between fibrosis on CMR and the degree of LV dysfunction, and in DCM, the presence of extensive fibrosis is mandatory for LV dysfunction.[12] On the other hand, one third of DCM has an arrhythmogenic phenotype, with a high risk of SD, in analogy to ALVCM. Due to the overlapping of phenotypes, genetic testing is usually required for an accurate differential diagnosis between tese two entities.[13]

Sarcoidosis is a disease that can affect the heart. Its cardiac manifestations include potentially fatal arrhythmias due to infiltrative granulomas and fibrosis. While in the right ventricle, the free wall is involved in 40% of the cases, in the left ventricle, the septum and the free wall are the most affected areas; for this reason, sarcoidosis is usually a differential diagnosis from LV and biventricular arrhythmogenic cardiomyopathies. Some details, however, may help in differentiating between these two conditions: cardiac sarcoidosis is a multiorgan disorder, involving the lungs, skin and eyes, and the occurrence of the isolated cardiac form is rare. On CMR, myocardial granulomas may be seen in post-contrast images as LGE localized mainly in the basal lateral wall, unrelated to the coronary distribution and usually responsive to immunosuppressive therapy. A LGE in ventricular insertion points continuing to the septum and the right ventricle (the "hook sign") is also associated with a high probability of sarcoidosis. Besides, extracardiac findings may be documented, and the combination of CMR with PET-CT may finally show FDG uptake, which indicates active inflammatory lesions.[12]

Cardiomyopathies associated with neuromuscular disorders (i.e., Duchenne and Becker muscular dystrophies) may not be distinguishable from ALVCM, especially in patients who have only cardiac disease. As in ALVCM, myocardial scar evidenced by CMR is typically located at the lateral wall, with subepicardial distribution, acting as a substrate for ventricular tachyarrhythmias, and leading to a risk of SD. There is also an overlap in the genetic background, since LMNA and FLNC gene mutations may occur not only in ALVCM, but also in muscular dystrophies, and the "hypokinetic non-dilated cardiomyopathy" is the phenotype of the disease determined by these mutations.[13]

Clinical and therapeutic reasoning

The experience of our group of genetic cardiomyopathies with ALVCM has been grounded on decision-making by a multidisciplinary team (Heart Team) composed of professionals familiar with this condition, including clinical geneticists, cardiovascular imaging professionals, electrophysiologists and clinical cardiologists. The key decision-making process involves CDI implantation, interruption of high-performance exercise, and genetic counseling.

Many patients with specific genetic mutations, due to the high risk of sudden arrhythmic death syndrome, have indication of CDI implantation, even in the absence of important ventricular dysfunction. The impact of beta-blockers and other antiarrhythmic agents in suppressing symptoms is limited, and radiofrequency ablation, usually by an epicardial approach, has been successfully performed.

Although cardiac SD is the most feared outcome, there are few data in the literature regarding the contribution of SD on these variants in ACM, probably due to difficulties in the post-mortem diagnosis, leading to the underdiagnosis of SD associated with ALVCM.[8] Miles et al. recently demonstrated the involvement of the LV (87%) in the vast majority of cases of SD, through histopathological study of patients with ACM.[37]

The increasing knowledge about the arrhythmic outcome, genetic profile, and therapeutic interventions has changed the natural history of arrhythmogenic cardiomyopathy in the last decades.[8] The treatment of ALVCM involves the standard therapy of HF in patients that develop myocardial dysfunction, the identification of patients at risk of SD, their possibilities of primary and secondary prevention, and the approach for arrhythmic events that may occur over the course of the disease.

The predictive factors of sustained arrhythmias in ACM were initially obtained from retrospective analyses.[38] The risk of development of potentially fatal cardiac arrythmia is mainly associated with the following factors: history of sustained ventricular arrythmia, extension of the myocardial structural change, degree of electrical instability, including the density of ventricular extrasystoles or NSVT, cardiac syncope, age, and genetic profile.[38]

Implantable cardioverter defibrillator (ICD)

The decision for the implantation of an ICD should be made by the cardiologist in conjunction with the patient, taking into account the risks and the benefits, and life expectancy at diagnosis.

Some genetic variants, including the LMNA, PLN, RBM20 and FLNC carry a high risk of ventricular arrhythmia and SD, which are often independent of LVEF.[36] Thus, risk stratification for SD of this population, including some risk markers, is important[36] (Figure 3).

Recently, a calculator for risk prediction of SD in patients with laminopathies (https://lmna-risk-vta.fr/) was developed. An ICD should be considered for patients with a five-year estimated risk ≥ 10 % and an overt cardiac phenotype (NSVT, LVEF < 50% or atrioventricular conduction delay). In patients with the LMNA pathogenic variant and a DCM phenotype, high-intensity exercise was associated with a high risk for SD and worsening of ventricular function and then should not be recommended.[39]

ACM patients with aborted sudden cardiac death due to ventricular fibrillation (VF), pulseless ventricular tachycardia or SVT are indicated for ICD implantation as secondary prevention of SD.[8] More than 97% of ventricular arrhythmic events in ACM are caused by monomorphic SVT, with a high reversion rate with antitachycardia therapy (approximately 92% of the events), regardless of the tachycardia cycle length.[39] Therefore, the main consensuses on SD prevention in this population have recommended individualized therapeutical approaches, according to patient genetic profile.[8] Figures 4 and 5 illustrate a recommendation flowchart for ICD implantation.

A recent consensus recommends the assessment of risk factors for ventricular arrythmias in patients with ACM.[8] These factors are useful in establishing the indication for ICD implantation, particularly in patients without reduced LVEF (Figure 3). There is a class IIa recommendation for ICD implantation in patients with three major criteria, two major criteria and two minor criteria or one major and four minor criteria.

Ablation

In the last decades, much progress has been made in radiofrequency ablation techniques, including the electroanatomic mapping. Recent studies have evidenced high ventricular tachycardia-free survival rates after ablation in patients without a high risk for SD and with well-tolerated ventricular arrhythmia.[40,41]

Investigations of the effects of this therapeutic strategy on LV function are scarce, and data of the literature have pointed out the simultaneous involvement of both ventricles (Figure 6).[41,42] The epicardial approach in patients with RV involvement has already been demonstrated by several authors, and can be used in most cases, except in more severe cases in which the critical isthmus may be located in the endocardial area due to the extension of RV involvement.[43,44]

It is possible that the arrhythmogenic substrate of patients with well-tolerated monomorphic SVT is different from that of patients with malignant ventricular arrhythmias. In this sense, ALVCM may have several outcome phenotypes, directly influenced by genotype.

Studies addressing specific arrhythmic outcomes like tachycardia cycle length, well-tolerated monomorphic ventricular tachycardias may bring important information about these phenotypes. Consequently, patients who would benefit from an ablation procedure could be selected.

Antiarrhythmic treatment

The implementation of antiarrhythmic treatment in ALVCM aims to reduce the incidence of exercise-related, "adrenergic" arrhythmias, and to reduce treatment of patients with an ICD and high arrhythmic burden.

Beta-blockers were not effective in the treatment of patients with arrhythmogenic dysplasia of the right ventricle. Their main indication is for patients with supraventricular arrhythmias without ICD or for those with ICD but inappropriate shock delivery.

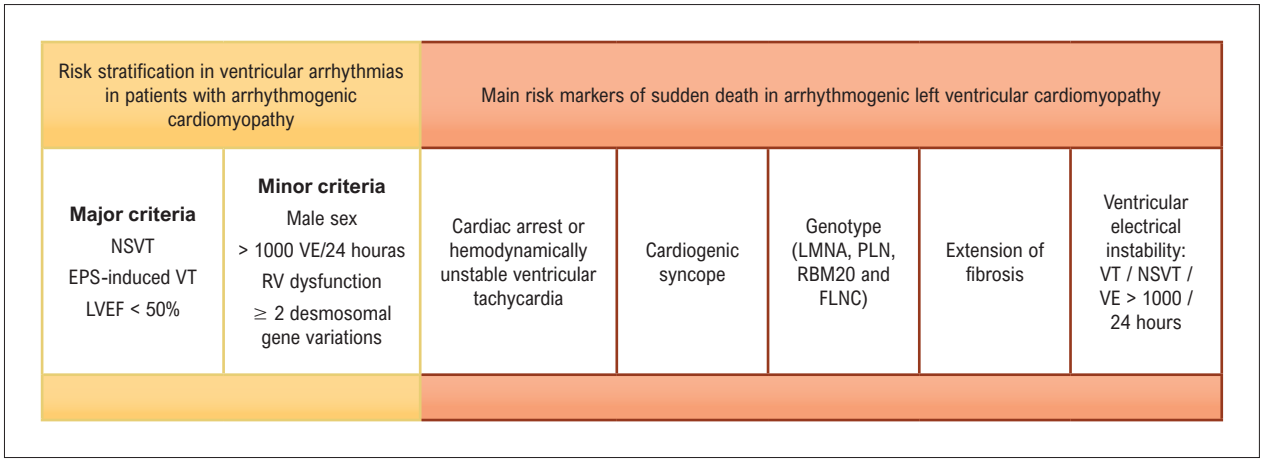

Figure 3 – *Stratification of risk criteria for ventricular arrhythmias and main risk markers of sudden death in arrhythmogenic left ventricular cardiomyopathy. NSVT: nonsustained ventricular tachycardia; EPS: electrophysiological studies; VT: ventricular tachycardia; LVEF: left ventricular ejection fraction; VE: ventricular extrasystoles; RV: right ventricular.*

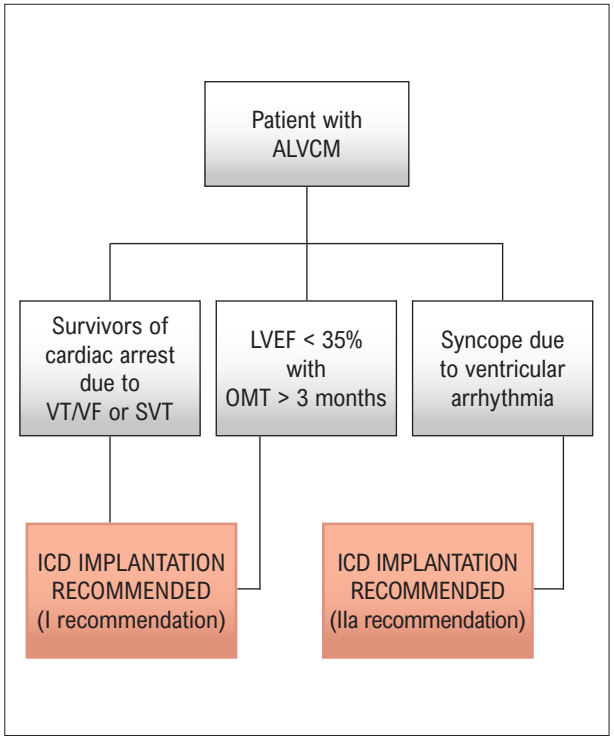

Figure 4 – *Recommendation flowchart for implantable cardioverter defibrillator implantation. ALVCM: arrhythmogenic left ventricular cardiomyopath; VT: ventricular tachycardia; LVEF: left ventricular ejection fraction; VF: ventricular fibrillation; OMT: optimized medical therapy; ICD: implantable cardioverter defibrillator. Adapted from Towbin et al.[8]*

Amiodarone and sotalol can be used for patients with ICD and adequate therapies (ventricular tachycardia or VF) and patients with symptomatic ventricular arrhythmias.

Physical exercise and arrythmogenic cardiomyopathy

Data on exercise in ALVCM are scarce. Previous studies have shown that vigorous or competitive exercises increase the risk of developing ventricular dysfunction and arrhythmias, as well as of poor survival for sustained ventricular arrhythmias.[45,48]

The four main dimensions of physical activity are: mode or type of activity, frequency, duration and intensity. It should be categorized as recreational or competitive, and resistance exercises are defined as those of moderated to high demand.[49] In addition, physical activity should be classified according to the metabolic equivalent (MET); in this context, a previous study[50] established an association between MET and several physical activities, and hence, exercise should be assessed for its intensity before being recommended (https://sites.google.com/site/compendiumofphysicalactivities/).[50]

High-intensity (>10 METs) exercises like competitive soccer, canoeing and bicycling should be discouraged. On the other hand, low-intensity (< 5METs) activities, such as walking, golf and yoga should be regularly practiced.

The PLN-R14del variant is responsible for arrhythmias during physical exercise, in a disproportionate manner, and should be considered in genotype-specific approaches.[51]

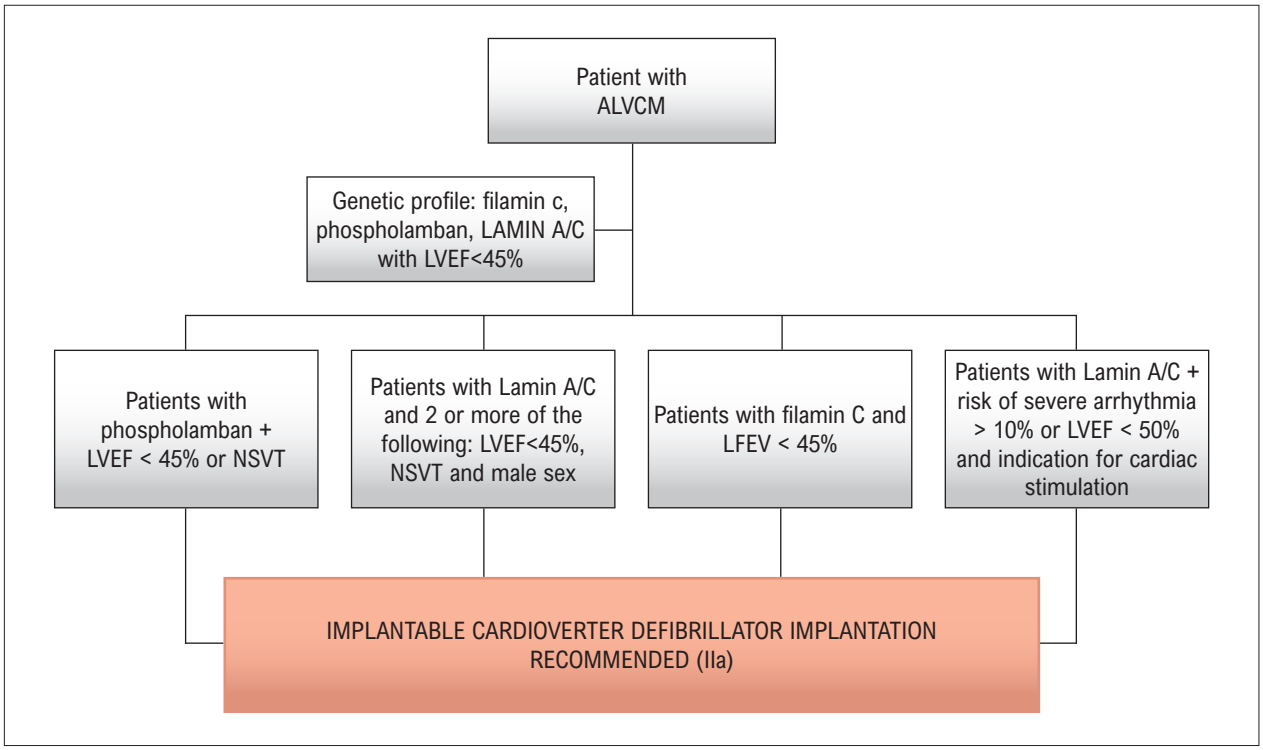

Figure 5 – *Flowchart of implantable cardioverter defibrillator implantation according to the genetic profile; ALVCM: arrhythmogenic left ventricular cardiomyopathy; LVEF: left ventricular ejection fraction; NSVT: nonsustained ventricular tachycardia. Adapted from Towbin et al.[5]*

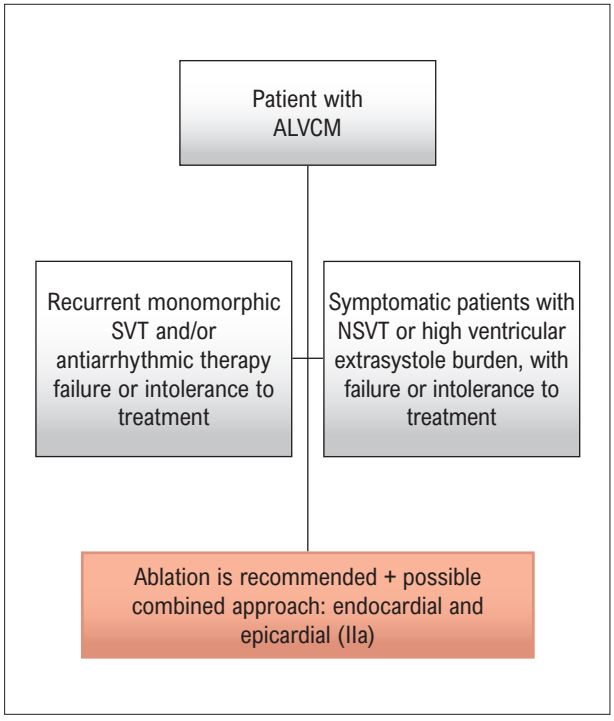

Figure 6 – *Flowchart of ablation recommendations. ALVCM: arrhythmogenic left ventricular cardiomyopath; NSVT: nonsustained ventricular tachycardia. Adapted from Towbin et al.*[8]

In contrast with limited data available for exercise recommendations for patients with an ACM positive genotype but negative phenotype, numerous studies have consistently shown that vigorous exercise is associated with increased risk for ventricular arrhythmias, independently of the genotype.[46,48,52,53]

Final considerations

The exclusive involvement of the left ventricle in ACM has been observed, and its diagnosis recently established, by means of the 2020 International Criteria. Its genetic etiology is heterogeneous, and the genotype should be determined, to establish not only the diagnosis, but also the prognosis and therapy.

In addition, there should be a high clinical suspicion in the setting of various phenotypes, mainly for the identification of asymptomatic patients and those with myocarditis-like presentation. In this regard, the red flags, including a suggestive family history, typical electrocardiographic changes, and fibrosis on LGE-CMR should be used.

The correct identification and diagnosis of ALVCM allows an individualized approach, based on the genotype-phenotype relationship, thereby preventing unfavorable outcomes and SD, the most feared complication.

Author Contributions

Conception and design of the research and Writing of the manuscript: Torbey AFM, Nascimento EA, Carvalho AB, Mesquita ET; Critical revision of the manuscript for important intellectual content: Torbey AFM, Nascimento EA, Carvalho AB, Neves DG, Couto RGT, Pimentel SVT, Maia EC, Mesquita ET.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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