BALWIERZ, Magdalena. Arrhytogenic Right Ventricular Cardiomyopathy – What Is New since 2023 European Society of Cardiology Guidelines? Current Knowledge, Literature Review. Quality in Sport. 2025;38:58173. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.38.58173
https://apcz.umk.pl/QS/article/view/58173

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.01.2025. Revised: 05.02.2025. Accepted: 07.02.2025 Published: 07.02.2025.

Arrhythmogenic right ventricular cardiomyopathy- What is new since 2023 European Society of Cardiology guidelines? Current Knowledge, Literature Review

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ABSTRACT

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically conditioned disease, characterized by gradual fibro-fatty replacement of myocardium and tendency to ventricular arrhythmias and heart failure. ARVC is included in a group of inherited similar clinical entities characterized by similar remodeling changes, named in general arrhythmogenic cardiomyopathies (ACM). The new guidelines of European Society of Cardiology (ESC) for the management of cardiomyopathies (2023) redefine arrhythmogenic left ventricular cardiomyopathy (ALVC), left dominant ARVC, or arrhythmogenic dilated cardiomyopathy (DCM) (but often without fulfilling diagnostic criteria for ARVC) as non-dilated left ventricular cardiomyopathy (NDLVC). The diagnostic process is based on Task Force criteria (2010) and Padua Criteria (2020) according to ESC guidelines and includes: right ventricle dysfunction evidence, endomyocardial biopsy results, defects of repolarization and conduction, arrhythmias and family history. However, in 2024 European Task Force consensus with modified guidelines was proposed. The treatment focuses on arrhythmias and heart failure management, prevention of sudden cardia death and family screening. Multidisciplinary approach is required to the proper management of the patients.

Aim of the study: The aim of the study is to review the current knowledge of ARVC, especially, novelties since 2023 ESC guidelines for the management of cardiomyopathies.

Material and methods: This article presents the current knowledge of the diagnosis of ARVC, especially on the basis of the guidelines of European Society of Cardiology and more recent experts' consensus. Literature analysis, which contain recent report in ARVC diagnosis were analyzed using the PubMed platform. The search included the keywords: "arrhythmogenic right ventricle cardiomyopathy", ,,arrhythmogenic cardiomyopathy", "Task Force criteria for ARVC diagnosis", "ventricular arrhythmias".

Keywords: Arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic cardiomyopathy, ventricular arrhythmias, Task Force criteria for ARVC diagnosis

Introduction

Diagnostic criteria: history and modification

The first Task Force criteria for the diagnosis of ARVC were proposed in 1994. [1] Modification was published in 2010 and clarified the details of right ventricle dysfunction and remodeling presence, highlighted the significant role of cardiac magnetic resonance (CMR) and added the details about ECG changes and family history. It was believed that fibro- fatty replacement of cardiac muscle considers only right ventricle, without or with mild left ventricle contractility impairment. However, it turned out that also only left or both ventricles can be affected. [2] Reevaluation of the diagnostic criteria and better insight into the disease caused publishing Padua Criteria in 2020, which differentiate dominant- right, dominant- left and biventricular types. [3] European Society of Cardiology (ESC) guidelines for management of cardiomyopathies regard Padua criteria as a standard in ARVC diagnosis. [4] Eventually, the most recent European Task Force consensus from 2024 includes redefinition and upgrade of the diagnosis. [5]

Etiology and epidemiology

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disorder, characterized by gradual replacement of fat and fibrous tissue and myocardial atrophy. [6] Remodeling extend from the epicardium to endocardium, primarily affecting the "triangle of dysplasia", which includes the region between the anterior section of the pulmonary infundibulum, the apex, and the infero-posterior wall. Interventricular septum is rarely involved. [7]

Initially, ARVC was described by the term “dysplasia”, although the myocardial defect is not congenital, so “cardiomyopathy” is more accurate definition. [8] Improving knowledge about the disease and its left- sided variants made the term “arrhythmogenic cardiomyopathies” (ACM) more adequate in describing the whole group of clinical entities.

The disease occur at a frequency of 1:5000 to 1:2000, with higher prevalence among men. [9] Mean age of the first symptoms oscillates around the age of 35. [10, 11] Autosomal dominant inheritance is the most common, while the penetrance depends on age, gender (higher among men) and physical activity.

In recent years the role of genetic testing of probands and their families increased significantly. Event in 60% of ARVC patients are identified with pathogenic or likely- pathogenic variants. [12] In the most cases mutation of desmosomal proteins’ genes are responsible for the disease,

especially: plakophilin-2 (*PKP2*), desmoplakin (DSP), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and plakoglobin (*JUP*). Non- desmosome genes- causes include: alpha- T- catenin (*CTNNA3),* LUMA protein (*TMEM43),* N- cadherin *(CDH2),* lamin A/C *(LMNA),* desmin *(DES),* titin (*TTN),* phospholamban *(PLN),* rianodine receptor type 2 *(RYR2)*. [4, 13]

The most frequent gene identified in 36- 92% of probands is *PKP2*, mostly autosomal dominant, the most commonly leading to right- dominant phenotype. On the other hand, *DSP* mutations are associated with high risk of serious complications such as ventricular arrhythmias, sudden cardiac death (SCD) and end- stage heart failure. [14]

It was believed that ACM was caused by only desmosomal variants, but recent studies suggest that genes outside the desmosome can also contribute to the disease, leading to desmosome dysfunction and involving nearly all components of the intercalated disc. Pathological remodeling is a consequence of disruption of the intercellular discs, located at the ends of cardiac myocytes which contain three types of connections: adherens junctions, desmosomes and gap junctions. These connections provide both mechanical coupling between myocytes and rapid conduction of electrical impulses. It can lead to heart disfunction and arrhythmias. [15]

Differential diagnosis should also include non-genetic conditions (e. g. myocarditis, cardiac sarcoidosis, right ventricle infarction, congenital heart defects with volume overload), which may present with a phenotype similar to inherited ACM ("phenocopies") and meet the diagnostic criteria. [16, 17]

Symptoms and clinical presentation

The diagnosis of ARVC should be considered in adolescents or young patients with palpitations, ventricular extrasystoles and arrhythmias with left bundle branch block morphology and superior axis, syncope with probable cardiac etiology, cardiac arrest. Especially ECG changes like reversed T waves in right precordial leads (V1- V3), low QRS voltages in the peripheral leads and terminal activation delay in the right pre-cordial leads are bringing the suspicion of ARVC. Echocardiographic features like right ventricular dilatation, increased trabeculation or aneurysms should be taken into careful insight. [4, 18] Progression of the disease may be described by three phases. In the first one- “concealed phase”, patients are usually asymptomatic, but due to the start of structural changes, still at risk of arrhythmias and SCD. An “electrical phase” is characterized by symptomatic arrhythmias with palpitations and syncope. Abnormalities may be detected by imaging tools. The last phase, “end- stage”, manifests by right ventricle dilatation and dysfunction, also of the left ventricle. Biventricular

type can mimic another conditions, such as dilated cardiomyopathy. [18] The most common reason for starting the diagnostic process are arrhythmic symptoms. [19]

Diagnostic tests

The diagnostic process conducting should be carried out using varied diagnostic tools. Basic elements in ACM detecting are ECG, Holter monitoring, imaging including echocardiography, cardiac magnetic resonance (CMR) and nuclear methods, genetic testing. In particular cases endomyocardial biopsy is necessary. In further management laboratory tests, exercise testing, and cardiac catheterization should be considered.

ECG and Holter monitoring

Crucial ECG findings in ACM patients are repolarization, depolarization changes and conduction abnormalities. In Holter monitoring ventricular arrhythmias including extrasystoles may be detected. Task Force 2010 diagnostic criteria include negative T waves in the absence of complete right bundle branch block (RBBB) in V1- V3 right precordial leads and epsilon waves in patients older than 14 years of age - major criteria, and, as minor criteria, presence of inverted T waves in V4- V6 leads. Revised Padua Criteria and European Task Force 2024 deleted the last criterium and presented inverted T waves in V4- V6 left precordial leads in the absence of left bundle branch block (LBBB) for the diagnosis of left ventricular phenotype. Epsilon waves were downgraded to minor criterium. What is more, minor criteria considering negative T waves in V3 were slightly changed in 2024. [2, 3, 5] They were indicated to occur at a various frequency, dependently on the observer, which indicates that this ECG sign is being misdiagnosed. Moreover, epsilon waves were shown to be associated with advanced structural defects which meet the diagnostic criteria earlier. [20] Inverted T waves in V1-V3 right precordial leads showed a correlation to increased right ventricle volumes and contractility disfunction, while changes in V4- V6 were more linked to the left ventricle involvement. [21] Depolarization abnormalities as major criteria include also terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of RBBB. Task Force 2010 criteria provided minor criteria, which has been deleted: late potentials on signal-averaged electrocardiogram (SAECG) in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 m, filtered QRS duration ≥114 ms, duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms and root-mean-square voltage of terminal 40 ms ≤20 μV. [2] SAECG is used to enhance the ECG signal-to-noise ratio and detect features, such as late potentials, that are not visible with standard

techniques. Abnormalities in SAECG are more commonly associated with severe disease and structural changes. [22] However, due to the low specificity and sensitivity of this technique, SAECG is no longer used in ACM diagnosis.. Updated criteria propose low QRS voltages (<0.5 mV) in all limb leads with no other cause as a minor criterium for left ventricular phenotype. [3, 5]

In Holter monitoring major criteria, according to Task Force 2010, of non- sustained or sustained ventricular tachycardia of LBBB morphology with superior axis was detected. Modifications take into account also frequent ventricular extrasystoles (>500/ 24 h). These findings with inferior axis were treated as minor criterium and is known as "right ventricular outflow tract (RVOT) pattern". It's lower specificity is a consequence of frequent idiopathic RVOT origin arrhythmias. [23] Arrhythmias in ARVC is characterized by wider QRS complex (≥120 ms), more frequent notching in QRS and later QRS precordial transition in V5- V6. [24] On the other side, aforementioned features with RBBB indicate on left ventricle involvement. Additionally, minor 2024 criterium for both phenotypes is history of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology.

Imaging

Imaging plays a key role in the diagnosis and management of ARVC. The main diagnostic tools are echocardiography and CMR. [4] The most significant changes remain dilatation and dysfunction of the ventricles, contractility disorders, increased trabeculation.

Morpho- functional alterations- regional akinesia, dyskinesia or aneurysms of right ventricle constitute a minor criterium, however, completed by global dilatation or systolic dysfunction are upgraded to major criterium. [5] Lack of right ventricle enlargement or decreased systolic function may be the consequence of the segmental nature of myocardial scarring in ACM, which may not impact the overall hemodynamics of the right ventricle. [25] The left ventricle phenotype findings are not specific for the disease. Left ventricle global systolic dysfunction may be diagnosed in other conditions, e. g. ischemia, so it is considered as a minor criterium. [5] It is recommended to comply with referred values of echocardiographic parameters adapted to individual parameters, e. g. body surface area (BSA).

Echocardiography shows the greatest availability in macroscopic changes in ARVC probands detection. Parameters assessing contractility and wall motion abnormalities, ventricles' dysfunction markers and dilatation may be easily visualized in echocardiography. However, they are present commonly in more advanced stages of the disease. Another possible, but unspecific findings are increased trabeculation of right ventricle and hyperreflective moderator

band, which may be found also in athletes. More accurate and earlier diagnosis, before eye-detected changes visualization can be made on the basis of 2D echocardiographic strain, in which speckle tracking is used to measure myocardial deformation and dispersion. These abnormalities in right ventricle and increased right ventricle dispersion were associated with ventricular arrhythmias. For more adequate and precise imaging, 3D speckle tracking may be used. [26, 27]

Structural criteria may be fulfilled by CMR or endomyocardial biopsy (EMB). Previous Task Force statement considered only EMB as a reference diagnostic tool. According to imaging the diagnosis remain stating late gadolinium enhancement (LGE) in right ventricle in at least 1 region, with the exclusion of tricuspid valve area. For the left ventricle involvement LGE has to be present in at least 3 segments as a major criterium and in 1or 2 as a minor criterium. "Ring like" LGE is typically the feature of the left ventricle phenotype and is defined as involvement of adherent segments in the same part in short axis view.

Despite the great utility of CMR in ACM diagnosis, some precautious should be taken while using this diagnostic tool. CMR gives the lowest variability in right ventricle volume measurement from other imaging techniques, but it still fluctuates around 10- 20% and is proportional to the experience of the center. [28] Secondly, in the case of myocardium thinning the sensitivity of LGE is low, but after excluding other causes of the ventricles' scarring. [25, 29] LGE is shown by 61% of patients showed in the right ventricle wall, which is a well-established indicator of dense fibrofatty replacement on contrast-enhanced CMR. [30] The 2010 Task Force Criteria were designed with an emphasis on specificity rather than sensitivity, leading to a bias that favors the detection of more advanced stages of the disease. As a result, the true value of CMR in identifying early-stage disease and providing additional insights for risk stratification may be overlooked. Global longitudinal and circumferential right ventricle strain, measured using feature-tracking CMR, were significantly lower in ARVC probands compared to both healthy volunteers and family members, even with preserved right ventricle ejection fraction. More detailed and accurate assessment of early disease involvement is being made relying on regional analysis using feature-tracking strain rather than on global parameters. [30] Despite the fact that T1 spin echo images is not adequate enough to detect fat tissue and new methods, (ECG-gated Dixon techniques) are not available commonly, 3D LGE, due to its high spatial resolution gives reliable results for detecting left ventricle scarring. [32, 33] Although isolated fat tissue is not sufficient finding, its coexistence with LGE increases the diagnostic specificity. [29]

Endomyocardial biopsy

EMB is used nowadays in particular situations, whether the diagnosis is uncertain on the basis of non- invasive diagnostic methods and to exclude conditions like inflammatory process and sarcoidosis. [23, 34] In 2010 Task Force criteria EMB was the only diagnostic test for structural criteria confirmation. Residual cardiomyocytes <60% was considered as major criterium (or <50% if estimated), while 60- 75% leftover (or 50% to 65% if estimated) was required for minor criterium. Fibrous lesions should have been present in at least 1 sample of right ventricle free wall. Fibrofatty replacement was not obliged. [2] Typical localization for taking biopsy samples was interventricular septum due to smaller probability of periprocedural complications. Ventricles' myocardium may be thinner, what brings risk of perforation, although it is more likely for this area to be involved. [35] Negative biopsy do not exclude the diagnosis. Other histological findings include inflammatory infiltration and necrosis foci. [36]

Genetic testing and family history

Genetic testing is used to identification of a pathogenic gene variant in the patient under evaluation, which is mentioned as major criterium in Padua Criteria, as well as confirmation of ACM in a first-degree relative who meets diagnostic criteria or ACM confirmed at autopsy or surgery in a first-degree relatives in histopathological examination. Minor criteria include: identification of a likely-pathogenic gene variant in the patient under evaluation, history of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria, premature sudden death (<35 years) due to suspected ACM in a first-degree relative, ACM confirmed pathologically or by diagnostic criteria in second-degree relative. [3, 5] Similar consensus was mas made in 2010. [2] However, it is important to highlight some limitations and caution needed to be exercised while genetic assessment making. Genetic testing are recommended to be performed in patients fulfilling diagnostic criteria for cardiomyopathy for better evaluation, prognostication, therapeutic stratification, or reproductive management or for cascade genetic tests in relatives. [4] The risk of misdiagnosis may be a result of disease-associated genetic variants present also in general population. [37]

Diagnosis

The diagnosis has being made on the basis of Task Force 2010 criteria for 10 years. Modifications were introduced in 2020 in Padua Criteria and in 2024 in European Task Force consensus. These two last need to be validated yet, however, they seem to be the gold standard

in next years. [2, 3, 5] The most recent 2024 diagnostic criteria are presented in Table 1. ACM classification is based on the number of criteria being satisfied. The definite diagnosis for ARVC and biventricular phenotype is stated when: 2 major or 1 major and 2 minor or 4 minor criteria are fulfilled, for borderline diagnosis: 1 major and 2 minor or 3 minor criteria and for possible diagnosis: 2 minor criteria. These statements are validated for ARVC if at least one morpho-functional or structural criteria for right ventricle diagnosis are proper and for biventricular phenotype if, additionally, at least one morpho-functional or structural criteria for the left ventricle phenotype are fulfilled. Only left ventricular phenotype is diagnosed if at least 1 major structural criterium for left ventricle involvement is stated and pathogenic or likely pathogenic for ACM- causing gene mutation.

Category	Criteria for RV Involvement	Criteria for LV Involvement
I. Morpho-functional ventricular abnormalities	**Major** • Regional RV akinesia, dyskinesia, or aneurysm plus one of the following: - Global RV dilatation (increase of RV EDV according to the imaging test specific nomograms for age, sex, and BSA) or - Global RV systolic dysfunction (reduction of RV EF according to imaging test specific nomograms for age and sex) **Minor** • Regional RV akinesia, dyskinesia or aneurysm of RV free wall	**Minor** • Global LV systolic dysfunction (depression of LV EF or reduction of echocardiographic global longitudinal strain), with or without LV dilatation (increase of LV EDV according to nomograms for age, sex, and BSA)
II. Structural alterations	**Major** • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue, at histology **Minor** • Unequivocal RV LGE (confirmed in 2 orthogonal views) in ≥1 RV region(s) (excluding tricuspid valve)	**Major** • "Ring-like" LV LGE (subepicardial or midmyocardial stria pattern) of ≥3 segments (confirmed in 2 orthogonal views), **Minor** • LV LGE (subepicardial or midmyocardial stria pattern) of 1 or 2 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall, septum, or both (excluding patchy, focal or septal junctional LGE)
III. Repolarization abnormalities	**Major** • Negative T waves in right precordial leads (V1, V2, and V3) or beyond in individuals ≥14 years old (in the absence of complete RBBB and not preceded by J-point/ST-segment elevation)	**Minor** • Negative T waves in left precordial leads (V4-V6) (in the absence of complete LBBB)

	Minor • Negative T waves in leads V1 and V2 in males ≥14 years old (in the absence of RBBB and not preceded by J-point/ST-segment elevation) • Negative T waves beyond V3 in the presence of complete RBBB • Negative T waves beyond V3 in individuals <14 years old	
IV. Depolarization and conduction abnormalities	**Minor** • Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in 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 peak to peak) in all limb leads in the absence of other causes (e.g., cardiac amyloidosis, obesity, emphysema, or pericardial effusion)
V. Arrhythmias	**Major** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with non-inferior axis **Minor** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern") • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology	**Minor** • Frequent (>500 per 24 h) or exercise-induced ventricular extrasystoles with a RBBB morphology or multiple RBBB morphologies (excluding the "fascicular pattern) • Non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular pattern) • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology
VI. Family history/genetics	**Major** • Identification of a pathogenic ACM-gene variant in the patient under evaluation • ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first-degree relative **Minor** • Identification of a likely-pathogenic ACM-gene variant in the patient under evaluation • History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature sudden death (<35 years) due to suspected ACM in a first-degree relative • ACM confirmed pathologically or by diagnostic criteria in second-degree relative	

Table 1. European Task Force criteria for the diagnosis of arrhythmogenic cardiomyopathies.

Modifications and additions since Padua Criteria 2020 are underlined.

ACM- arrhythmogenic cardiomyopathy , BSA- body surface area , CMR- cardiac magnetic resonance, EDV- end diastolic volume, EMB- endomyocardial biopsy, LBBB- left bundle branch block, LGE- late gadolinium enhancement, LV- left ventricle, RBBB- right bundle branch block, RV- right ventricle.

Summary

Knowledge about arrhythmogenic cardiomyopathy (ACM) has quickly evolved in recent years. This fact provided the diagnostic criteria update. The most significant changes include enhancing the role of CMR in detecting characteristic lesions using LGE, which helps in identifying particular phenotypes of ACM and differentiating ACM from other cardiomyopathies. What is more, left ventricle phenotype diagnosis was supplemented with ECG criteria, which include repolarization and depolarization changes and left ventricle-background ventricular arrhythmias. ACM diagnosis should be also extended with phenocopies analysis. These non-genetic diseases, which resemble ACM phenotypes, are associated to different prognosis as well as clinical consequence and need different management. Essential diagnostic tools are imaging techniques and genetic testing.

Disclosure:

Authors' contribution:

Conceptualization: Magdalena Balwierz

Methodology: Magdalena Balwierz

Software: Magdalena Balwierz

Check: Magdalena Balwierz

Formal Analysis: Magdalena Balwierz

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Writing-Review and Editing: Magdalena Balwierz

Visualization: Magdalena Balwierz

Supervision: Magdalena Balwierz

Project Administration: Magdalena Balwierz

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict Of Interest: The author declare no conflict of interest.

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