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# Diagnostic imaging, its role and limitations in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy

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### **Summary**

ARVD/C is a genetic disorder of cardiac muscle that leads to replacement of myocytes with fibrofatty connective tissue. The disease primarily involves the right ventricle and leads to development of ventricular arrhythmias.

The incidence of ARVD is about 0.02% in general population.

The first clinical signs of ARVD are usually clinically apparent in young adults (under the age of 50). It accounts for a large number of sudden cardiac deaths in the young.

ARVD is the most difficult type of cardiomyopathy to diagnose due to variability of symptoms and diagnostic difficulties despite use of both non-invasive and invasive methods.

A number of clinical tests are employed to state the diagnosis of ARVD, including medical history review, electrocardiogram (ECG), echocardiography, right ventricular angiography, genetic testing and histological examination. The diagnosis of ARVD is based on a combination of major and minor criteria – so called revised criteria published in Circulation in 2010.

Diagnostic imaging is a major factor in diagnosing ARVD, although each imaging method has its disadvantages.

Cardiac MRI is currently considered the gold standard in noninvasive diagnostics of ARVD.

MRI allows confirmation of global or regional RV akinesia, dyskinesia, or dyssynchrony, as determined by threshold values. On the other, hand the results of MRI alone are not sufficient to diagnose ARVD and other criteria must also be taken into account.

MeSH Keywords:

Arrhythmogenic Right Ventricular Dysplasia • Cardiomyopathies • Diagnostic Imaging

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#### **Background**

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is the disease of cardiac muscle characterized by progressive atrophy of myocytes, which are then replaced by fibrous and fatty tissue. This process involves primarily the free right ventricular wall, followed by various degrees of left ventricular involvement, contributing to development of electrical instability in the myocardium

that predisposes to occurrence of ventricular arrhythmias, usually of left bundle branch block morphology, which may evolve into ventricular fibrillation and lead to sudden cardiac death [1,2].

There are three patterns of ARVD/C expression:

 a. Alassical – limited to right ventricle or with little left ventricular involvement that appears in late stages of the disease.

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- b. Predominance of left ventricular involvement associated with early or predominating involvement of left ventricle.
- c. Concomitant involvement of both ventricles from the beginning of illness [3].

Prevalence of AVRD/C in general population is estimated at about 0.02% [4]. More frequent occurrence – up to 0.8%, was noted in some regions of Italy and Greece [1,5]. Disease usually manifests clinically in young patients, under the age of 50 [6,7], and is an important cause of sudden cardiac death among young, fit people (in this population, it constitutes the cause of 5% of sudden cardiac deaths in the USA and 25% in some regions of Italy) [8].

However, it is thought to occur much more frequently and underestimation of its prevalence may be related to a relatively common asymptomatic course of the disease and diagnostic difficulties associated with use of conventional, noninvasive methods.

Clinical symptoms usually appear between the  $2^{nd}$  and  $5^{th}$  decade of life (most often around the  $30^{th}$  year of life). Most common clinical symptoms reported by patients include: palpitations, syncope, dyspnea or atypical chest pain, and are usually provoked by stress or exertion.

Symptomatic ventricular arrhythmias or sudden cardiac death are frequent clinical manifestations, but patients may also remain asymptomatic. Ventricular arrhythmias may present as premature ventricular complexes or sustained ventricular tachycardia of LBBB morphology, or as ventricular fibrillation, which is the most common cause of sudden cardiac death in ARVD/C patients [9]. Left ventricular involvement more frequently leads to ventricular arrhythmias and heart failure.

Diagnosis of ARVD/C is based on the analysis of clinical picture and results of auxiliary examinations. In the course of the diagnostic process one should analyze such parameters as clinical condition and family history, cardiac morphology and function, changes in electrocardiogram and histopathology. The diagnostic algorithm in patients with clinical suspicion of ARVD/C typically encompasses firstly noninvasive diagnostic tests, including 12-lead ECG, signalaveraged ECG and amplified ECG, Holter ECG as well as cardiac imaging. In case of confirmation or high probability of diagnosis on the basis of the diagnostic criteria, invasive diagnostics (e.g. right ventricular angiography, endomyocardial biopsy, electrophysiological study) should be considered in order to confirm the diagnosis or to exclude other potential causes of patient symptoms, such as e.g. cardiac sarcoidosis.

In 1994 a group of European Society of Cardiology experts put forward the diagnostic criteria for ARVD/C (Table 1) [10].

A number of modifications of the above criteria were developed in the following years in order to increase their sensitivity, particularly in the diagnostics of weakly symptomatic forms of the disorder and in the diagnosis of asymptomatic first-degree relatives of ARVD/C patients. Mentioned

modifications encompassed, among other things, more extensive characterization of electrocardiographic and echocardiographic findings, inclusion of genetic testing, as well as considering and describing the extent of left ventricular involvement [11,12].

Currently, the diagnosis of ARVD/C is based on the assessment of so-called revised ARVD/C criteria published in the Circulation journal in 2010 [13] encompassing six fundamental categories of diagnostic criteria (disorders of right ventricular function and size, tissue characteristics, repolarization disorders, depolarization/conduction abnormalities, arrhythmias, family history), each category containing so-called major and minor criteria (Table 2).

#### Goal

The goal of this work was to present diagnostic imaging modalities that may be utilized in the diagnosis of ARVD/C and to discuss their capabilities and limitations ensuing from both methodology and clinical interpretation of acquired images, with particular consideration paid to the role of magnetic resonance imaging in the assessment of current ARVD/C diagnostic criteria.

## Cardiac imaging modalities in the diagnostics of ARVD/C – capabilities and limitations

#### Plain chest x-ray

Shows enlargement of heart silhouette dependent on the degree of disease advancement with cardiopulmonary index increased >0.6, straightening of left heart border and signs of congestion in pulmonary circulation [14]. However, this method is characterized by low sensitivity and specificity.

#### Right ventricular angiography

This method, previously considered the "gold standard" in the diagnostics of ARVD/C due to high specificity and great positive as well as negative predictive value.

Performed in two projections, it allows for assessment of right ventricular structure and function. Coexistence of subvalvular or anterior, subinfundibular protrusion of right ventricular wall and presence of trabecular hypertrophy is characterized by 96% sensitivity and 87.5% specificity in the diagnosis of ARVD/C.

There are indisputable limitations to this method: invasiveness, frequent induction of ventricular arrhythmias related to catheter manipulations and contrast administration, as well as subjectivity of the assessment. Currently, due to greater availability of noninvasive methods, right ventricular angiography does not play a significant role in ARVD/C diagnostics.

#### Radioisotope ventriculography

Provides information, i.a. regarding ventricular size (usually enlarged), ejection fraction (usually reduced) or pattern of ventricular contraction (asynchrony is usually present).

**Table 1.** European Society of Cardiology ARVD/C diagnostic criteria for 1994 [10].

I. Global and/or regional functional and structural abnormalities (diagnosed with echocardiography, angiography, MRI or radioisotope examinations)		<ul> <li>Major criteria:</li> <li>significant enlargement of right ventricle and decreased RV ejection fraction without or with little left ventricular involvement</li> <li>aneurysms of right ventricle</li> <li>significant regional right ventricular enlargement</li> <li>Minor criteria:</li> <li>mild global enlargement of right ventricle and/or reduced right ventricular ejection fraction with preserved left ventricular function</li> <li>mild regional enlargement of right ventricle</li> <li>regional right ventricular hypokinesis</li> </ul>
II. Histopathological examination of the wall of right ventricle		Major criterion: replacement of normal myocardium with fibrofatty tissue demonstrated in endomyocardial biopsy
III. Repolarization disturbances in ECG		Minor criteria: inverted T waves in right ventricular precordial leads (V2,V3) in individuals >12 years of age in the absence of RBBB
IV. Depolarization and conduction abnormalities in ECG		Major criterion: epsilon wave or so-called localized QRS prolongation in precordial leads V1—V3 (>110 ms) Minor criterion: late potentials in SAECG
V. Arrhythmias		Minor criteria:  • sustained or non-sustained ventricular tachycardia of LBBB morphology recorded in ECG, 24-hour Holter ECG or during an exercise test  • numerous ventricular extrasystolic beats (>1000/24 h in Holter ECG)
VI. Family history		<ul> <li>Major criterion: familial disease confirmed at postmortem examination or biopsy</li> <li>Minor criteria:</li> <li>premature sudden death (&lt;35 years of age), most likely due to ARVD/C, in the family</li> <li>diagnosis of ARVD/C in the family based on the present criteria</li> </ul>
Table 2. Diagnosis of ARVD/C.		<b>Table 4.</b> The main changes observed in magnetic resonance images (MRI).
Definite diagnosis	2 major or 1 major + 2 minor or 4 minor (from various categories)	Morphological
Borderline diagnosis	1 major + 1 major or 3 minor (from various categories)	
Probable diagnosis	1 major or 2 minor (from various categories)	
<b>Table 3.</b> The Mmain changes reported in computed tomography exams examinations (CT).		<ul> <li>Impairment of right ventricular wall thickening during systole</li> <li>Right ventricular dilatation</li> <li>Right atrial dilatation</li> </ul>
<ul> <li>Right ventricular enlargement</li> <li>Abundant epicardial fat</li> <li>Intramural fatty deposits</li> <li>Accordion sign and right ventricular bulging</li> <li>Presence of low-absorbance trabeculations</li> </ul>		Systolic/diastolic dysfunction of right ventricle  Echocardiography  Two-dimensional

Application of specific radionucleotides enables visualization of abnormal sympathetic myocardial innervation, while MIBG<sup>123</sup> and Tal<sup>201</sup> imaging allows for early detection of left ventricular involvement, which may significantly increase diagnostic sensitivity of this method in ARVD/C [15,16].

#### Two-dimensional

It constitutes an important tool in ARVD/C diagnostics and monitoring due to its noninvasiveness, low cost, widespread availability and easy implementation. Right ventricular outflow tract dilatation >30 mm in long axis projections is considered a parameter of greatest sensitivity and specificity in the diagnosis of ARVD/C. Assessment

of fractional area change (FAC – usually <32%) as well as the presence of regional wall motion abnormalities (usually involving the anterior wall and the apex) are also of great significance [17].

Three-dimensional, tissue Doppler and strain echo

These methods are widely used in the diagnostics of ARVD/C and measurements of right ventricular dimensions and its ejection fraction to a great extent correlate with magnetic resonance measurements (with evident advantage over 2-D echocardiography). On the other hand, tissue and strain Doppler techniques are characterized by high sensitivity in the diagnosis of mild forms of ARVD/C [18,19].

#### Contrast

It allows for more precise outlining of right ventricular margins and thus, better assessment of ventricular volume as well as segmental and global right ventricular function [20].

#### Computed tomography (CT)

Multislice CT scanners enable qualitative and quantitative assessment of the right ventricle with high temporal and spatial resolution, as well as tissue evaluation/characterization in a manner similar to magnetic resonance (i.a. through its capability to detect intramural fatty components). The possibility to assess presence of fatty components within the left ventricle even in patients without left ventricular wall motion abnormalities is also of great significance [21] (Table 3).

This method is cheaper, faster simpler to perform, less operator-dependent and, due to a shorter acquisition time, less susceptible to breathing and motion artifacts in comparison to magnetic resonance examination. It is also the method of choice in patients with claustrophobia, tachyarrhythmias and in patients with implantable stimulating devices [22].

However, limitations of tomography include: transverse acquisition plane only, ionizing radiation, application of nephrotoxic contrast medium and relatively poorer temporal resolution compared to magnetic resonance [23].

#### Magnetic resonance (MR)

It currently considered the method of choice in diagnostic imaging of ARVD/C, as it provides multidimensional imaging with high temporal and spatial resolution that allows for reproducible morphological and functional assessment of the right ventricle (Table 4).

Cine MRI, characterized by high blood-tissue contrast, is used in the assessment of right ventricular function and the analysis involves manual or automatic tracing of myocardial and epicardial borders on the acquired cross-sections in all heart cycles, with ECG-gated SSFP (steady state free precession) sequences, such as e.g. FIEST or true FISP, being preferred to gradient echo imaging (e.g. FLASH, FASTCARD) due to higher temporal resolution and excellent

contrast between the myocardium and blood pool allowing for better evaluation of wall motion as well as greater precision of volume measurements.

Magnetic resonance enables detection of segmental and diastolic impairment of right ventricular function that may evolve into global and systolic dysfunction in the course of the disease, which may be visible in other imaging studies [24].

Moreover, it may be used for mapping blood flow velocities through the tricuspid valve and evaluate right ventricular strain using myocardial tagging technique.

Magnetic resonance imaging plays an important role in screening of first-degree relatives of ARVD/C patients due to the ability to detect mild impairment of cardiac contractility among subjects with normal chamber sizes and volumes.

"Black blood" technique is considered optimal for assessment of details of cardiac morphology. Due to improved blood-tissue contrasting magnetic resonance allows for, i.a. localization and quantitative evaluation of intramural fatty infiltration and thus, demonstrating pathological features of the disease [25]. In late gadolinium enhancement (LGE) sequences it also enables visualization of intramural fibrosis [26].

However, one should remember that assessment of fatty infiltration and cardiac fibrosis is not one of the MRI criteria for diagnosis of ARVD/C, but should be considered auxiliary, especially since confirmed fibrosis is an accepted prognostic factor for occurrence of ventricular arrhythmias and right ventricular dysfunction.

Assessment of the above-mentioned changes requires non fat-suppression T1-weighted sequences for evaluation of fatty infiltration and LGE sequences (10–15 minutes following contrast administration) for assessment of fibrosis. It has also some limitations related to, i.a. thin wall of the right ventricle, which may necessitate establishing different inversion time for the right ventricle in LGE sequences, and the presence of numerous artifacts associated with movement, breathing, blood flow or arrhythmias.

Demonstration of intramural fatty tissue alone is characterized by low sensitivity in the diagnosis of ARVD/C compared to other parameters, such as segmental right ventricular wall motion abnormalities. Physiological presence of epicardial fat, particularly in the area of coronary sulcus, anterolateral wall and apex of the right ventricle, makes it difficult to differentiate it from intramural fatty infiltrations, especially considering small right ventricular thickness and limited spatial and contrast resolution of the study [27].

Demonstration of fatty tissue is also considered a diagnostic parameter of low specificity and repeatability [28,29], since high-signal foci in T1-weighted sequences related to the presence of fat may be also found in patients without ARVD/C, including the elderly, obese individuals, patients on long-term steroid treatment, subjects with idiopathic

right ventricular outflow tract tachycardia, or those with congenital myopathies [30].

Breath withholding plays an important role in the study technique, as it reduces motion artifacts and improves visualization of myocardial details. Techniques, such as: HASTE, turbo FLASH, SSFSE are very rapid sequences that shorten the acquisition time and reduce motion artifacts at the expense of partial blurring of image details. Therefore, use of these techniques is limited to situations when, due to severe arrhythmia, we are unable to attain high-quality images using other black blood techniques.

The advantages of magnetic resonance lay in its noninvasiveness and the fact that it does not utilize X-rays, which makes it highly valuable in the diagnostics and follow-up of patients with clinical suspicion of ARVD/C. Moreover, it is believed to possess prognostic significance due to the ability to predict arrhythmia-free survival [31].

However, subjectivity of interpretation of changes, dependence on the quality of images and lack of standard study protocols constitute the limitations of this method. Also, magnetic resonance appears to be less efficient in the diagnostics in pediatric population compared to adults.

Therefore, it should be considered a part of multidisciplinary diagnostic algorithm and final diagnosis should be based on both clinical analysis and results of examinations in accordance with the diagnostic criteria of ARVD/C [24].

## Use of magnetic resonance in the assessment of ARVD/C diagnostic criteria

In relation to the above-mentioned revised ARVD/C diagnostic criteria magnetic resonance is applied in the assessment of the criteria from the category involving global and regional impairment of right ventricular function and size, which present as follows [13]:

#### Major criteria:

Segmental right ventricular akinesia or dyskinesia or dyssynchrony.

And one of the following:

- End-diastolic volume/BSA ≥110 ml/m² (males) or ≥100 ml/m² (females).
- Or right ventricular ejection fraction ≤40%.

#### Minor criteria:

 Segmental right ventricular akinesia or dyskinesia or dyssynchrony.

And one of the following:

- End-diastolic volume/BSA between  $100 \text{ ml/m}^2$  and  $110 \text{ ml/m}^2$  (males) or between  $90 \text{ ml/m}^2$  and  $100 \text{ ml/m}^2$  (females).
- Or right ventricular ejection fraction between 40% and 45%.

## Recommended magnetic resonance examination protocol for ARVD/C

- 1. Anatomy sequences.
- 2. Sequences for the assessment of left ventricular function.

- 3. Sequences for the assessment of right ventricular function (with evaluation of RVOT).
- 4. T1-weighted sequences (black blood).
- 5. T1-weighted (black blood), fat saturation sequences.
- 6. Late gadolinium enhancement (LGE) sequences.

#### Magnetic resonance examination report

- Sizes of heart chambers and cardiac muscle mass (per patient body surface area).
- Parameters of left and right ventricular function: enddiastolic and end-systolic volumes, stroke volume, ejection fraction, assessment of regional right ventricular wall motion impairment (inflow tract, outflow tract, apex).
- Morphological anomalies of right ventricle (e.g. aneurysms).
- 4. Foci of fat infiltration within right and left ventricle.
- 5. Presence and extent of intramural fibrosis.

Diagnostic imaging, and magnetic resonance in particular, plays an important role in excluding other potential causes of right ventricular dilatation and/or dysfunction, which may include:

- · Anomalous venous drainage.
- Dilated cardiomyopathy.
- · Cardiac sarcoidosis.
- · Myocarditis.
- · Heart steatosis.
- · Brugada syndrome.
- Uhl anomaly.

#### Concluisons

- Among all cardiomyopathies ARVD/C is most difficult to unequivocally identify due to a variety of clinical symptoms and diagnostic difficulties related to use of both invasive and noninvasive diagnostic methods.
- Diagnosis requires a multifactorial analysis taking into account through clinical examination as well as results of auxiliary examinations, such as: ECG, cardiac imaging studies (echocardiography, CT, MRI) and invasive diagnostics (e.g. endomyocardial biopsy).
- Diagnostic imaging is an important element in management of patients with suspicion of ARVD/C, wherein each
  of the available methods presents certain limitations.
- 4. MRI has a special place in the diagnostic process, as it is currently considered the method of choice for the assessment of right ventricular function and morphology.
- 5. MRI confirms or excludes fulfillment of diagnostic criteria regarding global and regional impairment of right ventricular function and size in accordance with the accepted cutoff points. However, the diagnosis of ARVD/C cannot be stated on the basis of MRI examination alone and the result of the study must be also interpreted in a particular clinical context.
- 6. Although not included in magnetic resonance criteria for the diagnosis of ARVD/C, information on the presence of intramural fatty infiltrations, fibrotic foci, abnormalities of wall morphology, increased trabeculation and RVOT dilatation may be helpful from the diagnostic point of view and should be included in the descriptions of both MRI and CT examinations.

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