Review Article

IS IT USEFUL TO REVIEW DIAGNOSIS CRITERIA IN ARRHYTHMOGENIC RIGHT VENTICULAR DYSPLASIA? UPDATE FROM LITERATURE DATA AND CASE REPORT

Carmen GINGHINĂ[1,2*)], Irina PĂTRĂNESCU[2], Ioana GHIORGHIU[2], Aura POPA[2], Ioana Smărăndița LĂCĂU[3], Radu CIUDIN[2]

1) University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania Member of Academy of Romanian Scientists.
2) "Prof. Dr. C.C. Iliescu" Emergency Cardiovascular Diseases Institute, Bucharest, Romania
3) "Elias" Emergency Universitary Hospital, Bucharest, Romania

Abstract

The purpose of this study is to determine whether it is useful to review the diagnostic criteria for arrhythmogenic right ventricular dysplasia (ARVD) and to compare the original criteria established in 1994 with the new criteria imposed by the current Task Force of European Society of Cardiology in 2010. Next, we choose a case report to highlight the diagnostic methods and means by which they are applied in current practice taking into account the guidelines indications. In the center of these complex and modern diagnostic methods, clinical judgement, remains a key element.

Keywords: *arrhythmogenic dysplasia, ventricular tachycardia, epsilon wave, syncope.*

Rezumat

Scopul acestei lucrări este de a determina dacă este utilă revizuirea criteriilor de diagnostic pentru displazia aritmogenă de ventricul drept (CAVD), precum și de a realiza o comparație între criteriile originale stabilite în 1994 și noile criterii impuse de Grupurile de Lucru ale Societății Europene de Cardiologie din 2010. În continuare am ales ca exemplu un caz clinic pentru a evidenția metodele de diagnostic precum și mijloacele prin care acestea sunt aplicate în paractica curentă, ținând cont de indicațiile ghidurilor. În centrul acestor metode complexe și moderne de diagnostic, judecata clinică rămâne în continuare un element cheie..

Cuvinte-cheie: *displazie aritmogenă, tahicardie ventriculară, unda epsilon, sincope.*

*) Corresponding author: *Carmen Ginghină, Ph.D., "Prof. Dr. C.C. Iliescu" Emergency Cardiovascular Diseases Institute,* ***e-mail:*** *carmenginghina2010@gmail.com*

"You see only what you look for; you recognize only what you know."

Merril C. Sosman, [1]

In 1977, *Fontaine* and colleagues provided an anatomical and clinical description of several cases of ARVD (Arrhythmogenic Right Ventricular Dysplasia) discovered during surgical treatment of ventricular tachycardia [2]. "*Dr. Fontaine introduced me to this condition when I visited him in Paris in 1979. At that time he had personally seen 15 cases with ARVD since 1973. Since the patients were referred from a large geographic area, I realized that this was a condition that physicians were not recognizing because it was unknown to them. I decided to spend my sabbatical year studying this entity. Together with others at the* Jean Rostand Hospital, Ivry, France*, we published a composite clinical description of ARVD in 1982 [3]. In the 15 years since the publication of this paper, there has been considerable progress in our understanding of this disease in the following areas*", writes M. Sosman.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a predominantly genetically determined and heritable form of cardiomyopathy (30-50% of cases have a familial distribution) characterized by pathologically replacement of myocytes with adipose and fibrous tissue leading to arrhythmias, right ventricular failure, and sudden cardiac death [4]. The estimated prevalence of ARVC/D in the general population ranges from 1 in 2, 000 to 1 in 5, 000, men are more frequently affected than women, with an approximate ratio of 3:1. ARVC/D can be inherited as an autosomal dominant disease with reduced penetrance and variable expression, autosomal recessive inheritance is also described. There have been 12 genes identified which are linked to ARVC/D, encoding several components of the cardiac desmosome [4].

The pathogenesis of ARVD is largely unknown. Apoptosis appears to play a large role. It is unclear why the right ventricle is mainly involved. Other authors suggested a pathogenic role for viral infection [4]. The disease process starts in the subepicardial region and works its way towards the endocardial surface, leading to transmural involvement (possibly accounting for the aneurysmal dilatation of the RV) [5]. Residual myocardium is confined to the subendocardial region and the trabeculae of the RV. These trabeculae may become hypertrophied. Aneurysmal dilatation is seen in 50% of cases at autopsy. It usually occurs in the diaphragmatic, apical, and infundibular regions (known as the *triangle of dysplasia*). The left ventricle is involved in 50-67% of individuals. If the left ventricle is involved, it is usually late in the course of disease, and confers a poor prognosis [6].

According to *Dalal et al*., the median age at presentation of disease is 29 years. The most common symptoms are palpitations, syncope, and sudden cardiac death in 27, 26, and 23% of patients, respectively. Cardiac arrest may also be the first manifestation of disease due to malignant arrhythmias [7].

ARVD diagnosis should be considered in young pacients with syncope effort related, ventricular tachycardia which are also found in the presented case.

Ventricular tachycardia has a typically left bundle branch block morphology due to the fact that it arrises from the right ventricle. The ventricular complexes could have multiple forms because of the multiple origins in different areas of the ventricle. Arrhythmias are induced by adrenergic stimulation and this mechanism is probably responsible for the increased prevalence of ARDV among deceased during physic exercise [5].

There are discussions about the importance of new criteria and about the sequence of investigations used to achieve a quickly diagnosis.

Next, we choose a case report to highlight the diagnostic methods and means by which they are applied in current practice.

We report the case of 21 years old boy without significant medical history, complaining of palpitations with sudden onset and irregular rhythm that occur after meals and exercise, lasting on average between 1h and 2h, which led to two syncopes. Note that the palpitations history started about three years ago, but intensified a month ago when the patient went through a time of intense mental stress accompanied by an important exercise. Mind that the young man is not a professional athlete, but during free time he plays basketball, and he does mountain climbing.

The family history was negative for cardiovascular disease. He went to see a doctor after palpitations with rapid rhythm, prolonged duration (> 2h), which occurred while he was at rest, followed by a syncope.

Clinical and biochemical examination, in ambulatory setting, were within normal limits.

ECG examination (Fig.1a and 1b) and ECG Holter monitoring (Fig.2) was performed, followed by treatment with a beta-blocker agent.

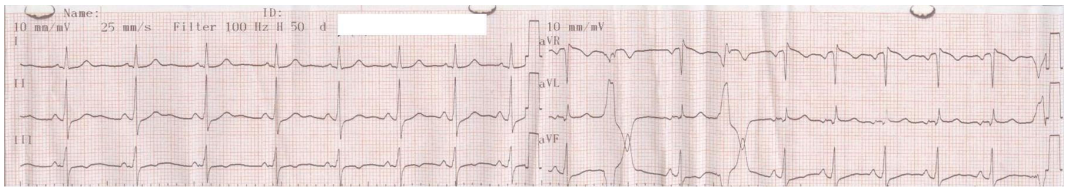

Figure 1a

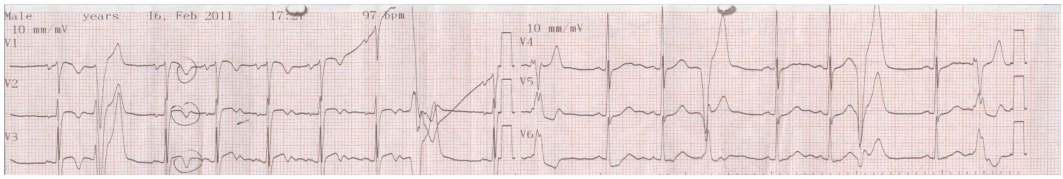

Figure 1b

Figure 1: ***Ambulatory ECG examination****: sinus rhythm, HR= 77 b / min, QRS axis at + 60 degrees, PR = 130 ms, QRS duration = 95ms, negative T waves in precordial leads V1-V3, consistent appearance of epsilon wave at the end of ORS complex, more obvious in V1 lead.*

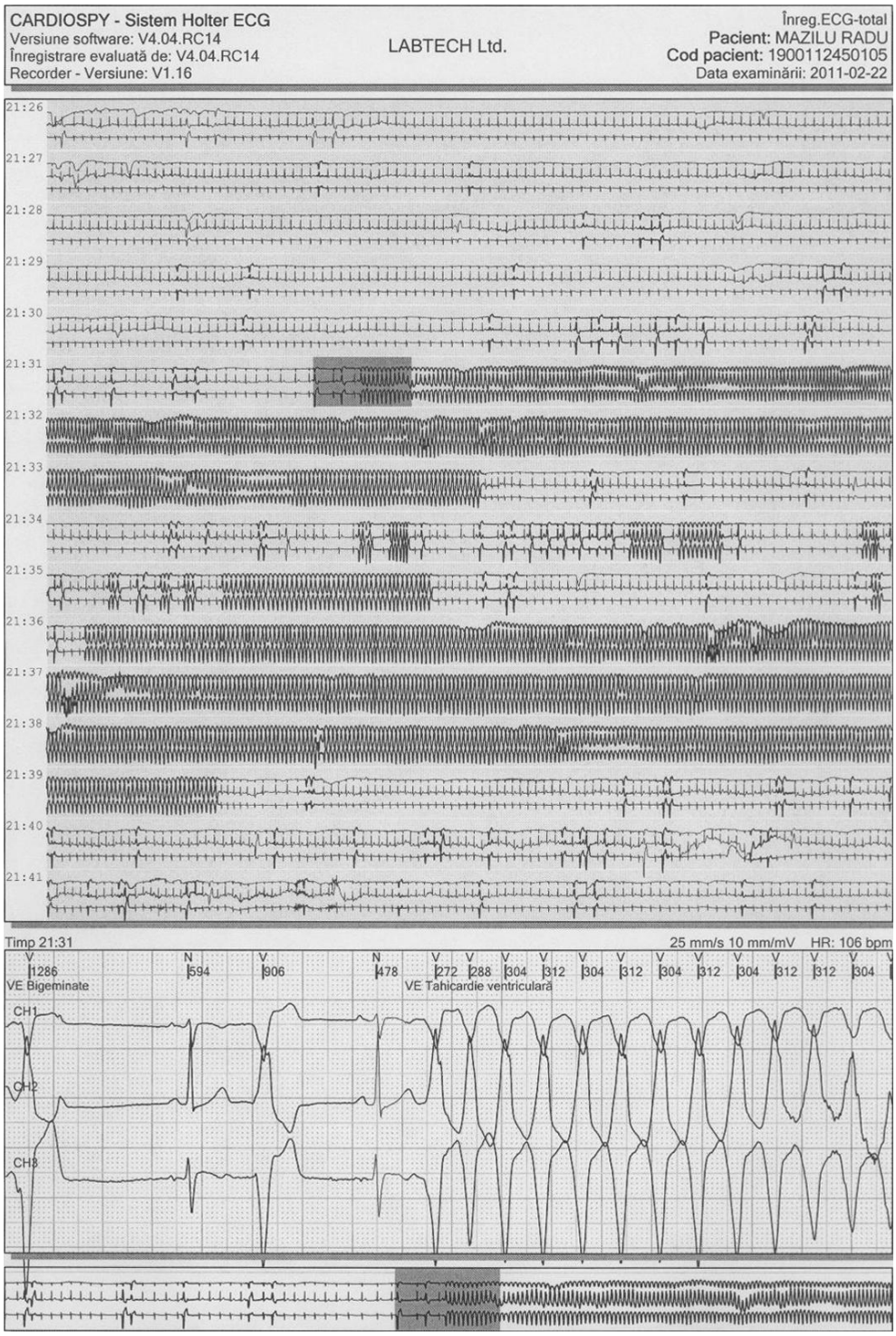

Figure 2: Holter ECG examination; shows episodes of ventricular tachycardia

Ambulatory Holter ECG examination, (done under treatment with beta-blocker agent, the recording corresponded with a symptomatic episode that the patient describes as the most intense he ever felt) indicates complex rhythm disorders: frequent supraventricular ectopic beats, premature ventricular complexes with systematisation tendency. The analysis of the entire Holter registration shows unsusteined ventricular tachycardia with two different morphologies of the QRS complex.

Given the symptoms correlated with exploration results and patient's history, ***the stage diagnosis*** was: recurrent syncope, unsustained ventricular tachycardia, premature ventricular complexes with systematic tendency (LBBB morphology), supraventricular extrasystoles.

The findings in the ECG (negative T wave in precordial leads and premature ventricular complexes with LBBB morphology), the ventricular tachycardia in Holter ECG examination the age of the patient and the temporary loss of counsciouness after palpitations occurring with exercise, all led to the suspicion of arrhythmogenic right ventricular dysplasia.

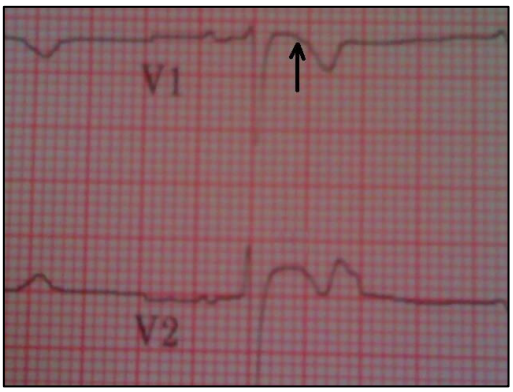

Figure 3: *Epsilon wave*-detail

The patient was hospitalized for further investigation to establish a diagnosis. On admission he performed an ECG at rest and an ECG with amplifier (+20) (Fig.3), late ventricular potentials were questioned (Fig.4), followed by investigation of cardiac morphology and function (Fig.5) and cardiac MRI examination (Fig.6).

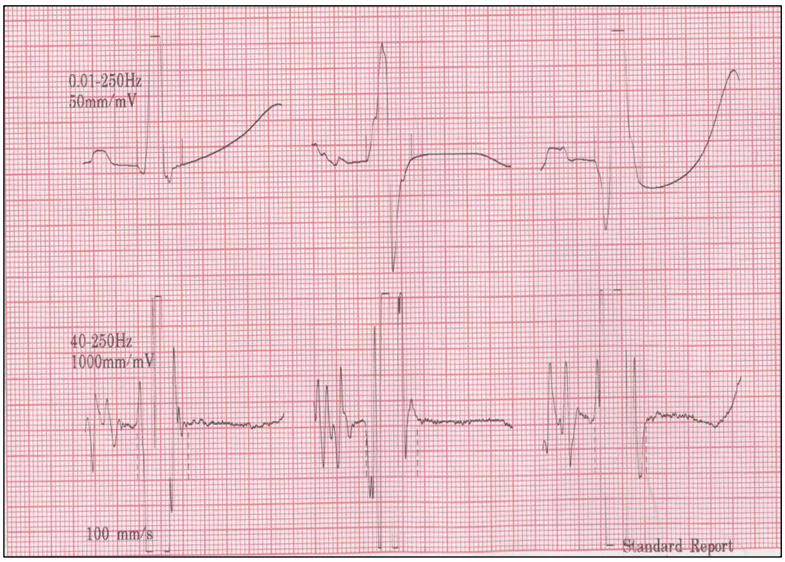

Figure 4: *Ventricular late potentials:* indicates a total duration of filtered QRS > 113 ms, a single criterion was met, the sample was negative: late ventricular potentials were absent.

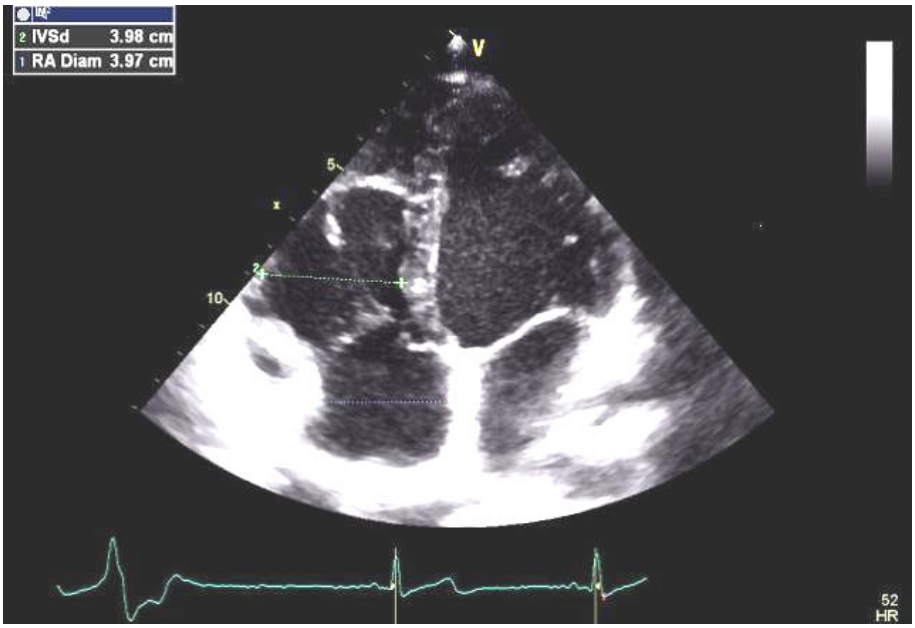

Figure 5: ***Transthoracic echocardiography:*** in apical four chambers section indicates a dilated right heart with right ventricle with a diameter of about 40 mm.

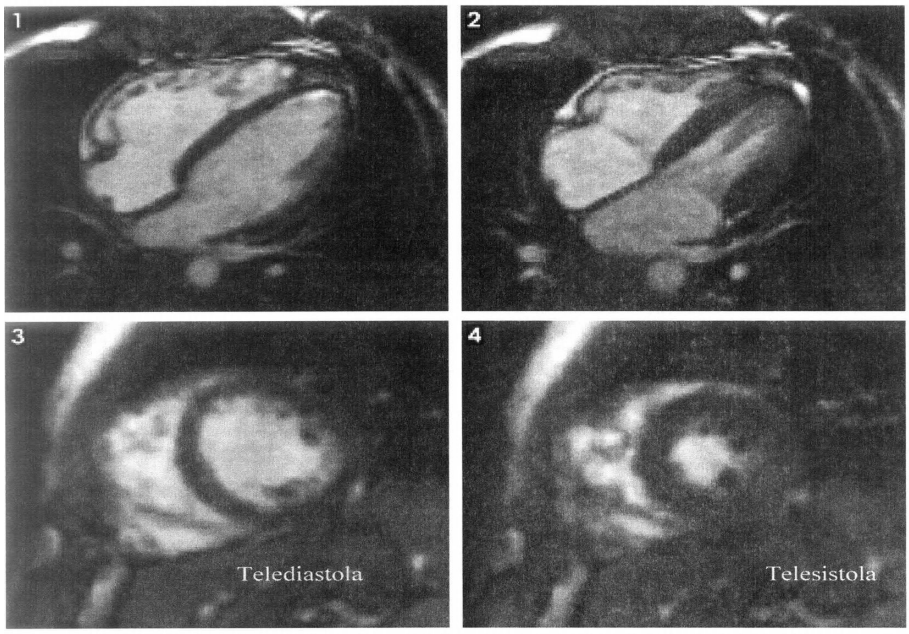

Figure 6: *Cardiac MRI examination: end-systolic images (1.2) in apical four chambers section (1.2) shows a dilated right heart with an enlarged right ventricle that is restricted by the sternum during contraction, resulting in a fold of the free wall, and end diastolic images(3.4) in parasternal short axis section, is observed the left ventricle noncompaction and the presence of trabeculae in the LV wall.*

Echocardiographic data provides us with major criteria correlated to data from ECG and Holter ECG examination have led to **final diagnosis**: ***arrhythmogenic right ventricular dysplasia***, recurrent syncope, unsustained ventricular tachycardia, premature ventricular complexes with systematic tendency (LBBB morphology), supraventricular extrasystoles.

The patient in the presented case has a class IA indication for implantable cardiodefibrillator according to the current guidelines ACC / AHA / HRS 2008 on *"Implantable Defibrillator and resynchronization therapy in patients with arrhythmias"[8]* in order to prevent sudden deaths that overlaps with class IA indication of ACC / AHA / ESC 2006 for *"Management skills of patients with ventricular arrhythmias and prevention of sudden cardiac death" [9]*.

Particularities of the presented case:

The young age at which the disease has become manifest, compared with an average age described in the literature about 29 years (Dalal et al [7]). The difference between the ECG and echocardiographic examination that was suggestive for ARVD and MRI examination that did not provide diagnostic criteria. Presence of numerous trabeculae in the LV from the middle of the cavity to the apex fulfilling the criteria for non-compaction at seven segnents only at the MRI examination, unconfirmed by echocardiographic examination (onset of dysplasia in LV)?

Disscusion

Diagnosis of ARVD can be challenging. Original diagnostic criteria were established in 1994 based on structural changes, histological, echocardiographic as well as arrhythmias and family history. When these criteria were designed experience with ARVD was dominated by studies from patients with symptomatic disease, advanced disease or who died suddenly. Consequently these criteria were highly specific but lacked sensitivity in detecting early cases of disease or familial ARVD. Also, these criteria were rather qualitative than quantitative. In addition, it is known that electrocardiographic changes and arrhythmias may occur long before histological changes or right ventricular dysfunction, which proves the importance of early detection of the disease [4].

Marcus et al. modified the International Task Force Criteria for the clinical diagnosis of ARVD to incorporate new knowledge and improve diagnostic sensitivity. Latest studies comparing old and new criteria showed the superiority of the new criteria because of information from advances in genetic and electrophysiological studies plus they were compared with a significantly control group. New diagnostic criteria will assist clinicians, particularly in borderline cases and 1 degree relatives of patients with ARVD who often have an incomplete expression of the disease [10].

The ECG reveals changes in more than 90% cases. The most frequent findings are: T-wave inversions in V1–V3 in the absence of right bundle branch block (minor criteria for diagnosis). Right bundle branch block, prolongation of QRS complex, epsilon wave are considered distinct markers and major criterias for the diagnosis of ARVD [4]. The

epsilon wave is caused by late potentials of low amplitude between the end of QRS complex to onset of the ST segment originating in the viable miocardum surroundead by fibro-faty tissue. From an electricaly point of view the wave reflects areas of delay and can trigger re-entry ventricular tahichycardia [5].

Fontaine named the epsilon waves. His personal account of his discovery was described in his March 5, 1997, letter to me [1], says Sosman. "... after discovering the first cases of late (or delayed) potentials recorded at the time of surgery on the epicardium of patients with resistant ventricular tachycardia. It was quite exciting to demonstrate that these late potentials located on the free wall of the right ventricle of patients with arrhythmogenic right ventricular dysplasia could be recorded on the surface by signal averaging and in some circumstances by increasing the magnification of ECG recording.

As late potentials were supposed to be the result of late activation of a limited group of fibers, the term "post-excitation" looked logical, since it was observed after the main excitation of the ventricle, leading to the QRS complex. The term "epsilon" was nice, because it occurs in the Greek alphabet after delta; thus, delta represents the preexcitation and epsilon the post-excitation phenomenon. In addition, epsilon is also used in mathematics to express a very small phenomenon..." [3]

Specific ECG markers show delay of the electric impulse in ARVD and Brugada Syndrome (BS) also. Althought BS is caracterised as an electrical disease recent data from MRI studies reveals an unexpectedly high rate of mild structural abnormalities. These findings suggest that BS may not be considered solely as a primary electrical disease. It is possible that initial electrical changes occurring in RV may play a fundamental role leading to structural changes [11]. Considering the symptoms and the ECG changes, the presented case is a tipicaly case of ARVD.

The echocardiography provides major criteria for diagnosis, the most suggestive aspect is dilatation of RV associated with local aneurysm. The investigators found that dilation of the RV outflow tract (>30 mm) using the parasternal view was an excellent parameter for diagnosing ARVD in the appropriate setting. They found, for example, that diastolic dilation of the RV outflow tract in the parasternal long axis view (>30 mm) was the most common abnormality occurring in 100% of the probands. Second, they clarified the strength of abnormal RV morphology in establishing the diagnosis. For example, anterior RV wall-motion abnormalities were common (70%), abnormally prominent trabeculations were seen in the majority (54%), and sacculations were seen in 17% [12]. In the case presented the echocardiographic examination showed enlarged right cavities (RA and RV≈ 40 mm), hypokinetic RV with heterogeneous structure of RV lateral wall and dilatation of the outflow tract providing major criteria.

MRI allows precise characterization of the function and anatomic structure of RV, highlighting the areas with akinesia, hypokinesia and regional dissincrone contraction of the RV [4]. The MRI examination of the case presented did not provide a diagnostic criterion for ARVD. Instead MRI confirmed RV dilation with increased volumes and indexed volumes and showed low RV ejection fraction = 41%, without regional or global wall motion changes or aneurysm lesions. It is also remarkable that the right ventricular free wall is compressed and in contact with the sternum. Arguments for which echocardiography was conclusive but magnetic resonance imaging did not provided

criteria for ARVD can be explained by the fact that in MRI is difficult to estimate precisely the RV free wall thickness (which is thin and has a poor spectral resolution) and presence of large quantities of fat, compared with epicardial and pericardial fat normally present [5].

One of the most appreciated methods for diagnosis of ARVD is right ventricular angiography, but this exploration is an invasive maneuver, not without risks. In the presented case our echocardiography and MRI have provided sufficient data for diagnosis.

Endomyocardial biopsy can document the typical histological changes ARVD but has important limitations: false negative results due to the mosaic appearance with viable miocardium surrounded by fibro-adipose tissue [13].

Original International Task Force Criteria of ARVC/D were published in 1994, are based on structural, histological, electrocardiography (ECG), arrhythmic, and familial features of the disease (Tabel 1), and were modified by Marcus et al. in 2010 [14] so it can be adjusted to recent discoveries and in order to increase diagnostic sensitivity. In case of family members modification of diagnosis criteria was proposed by Hamid et al. [12] to account for the broader spectrum of disease that is observed in family members. In first-degree relatives of a patient, confirmed to be affected by ARVC/D, the presence of right precordial T-wave inversion, or late potentials on signal-averaged ECG, or ventricular tachycardia with left bundle branch block morphology, or mild functional or morphological changes of the right ventricle on imaging, should be considered diagnostic for familial ARVC/D, as well the threshold of premature ventricular beats of 200 over 24h in Holter monitoring [4].

Positive diagnosis is based on two major criteria, two major and one minor criteria or four minor criteria (Table No. 1.).

Table no 1: ***Diagnostic criteria for arrhythmogenic right ventricular dysplasia [5].***

Comparison between classic criteria with the recently proposed criteria [5].	
Original criteria in 1994	***Revised criteria recently proposed***
Major: ***Global or regional dysfunction and structural alteration*** **Major**: Severe dilatation and reduction of RV ejection fraction, with no (or only mild) LV impairment. Localized RV aneurysms (diskinetic or akinetic areas with diastolic bulging). Severe segmental dilatation of the RV	**Major:** ***2D Echocardiography:*** Regional RV akinesia, dyskinesia or aneurysm and one of the following (measured end diastole): - PLAX ROVT ≥ 32 mm (corrected for body size ≥ 19 mm/m2) - PSAX RVOT ≥ 36 mm (corrected for body size ≥ 21mm/m2) or fractional area change ≤ 33%. ***MRI:*** Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following: - Ratio of RV end-diastolic volume to BSA≥110 ml/m2 for men and ≥100 ml/m2 in women or RV ejection fraction ≤40% ***RV angiography:***

Minor: Mild RV global dilatation and / or ejection fraction reduction with normal LV. Mild segmental dilatation of RV. Regional RV hypokinesia. ***Tissue characterization of walls.*** **Major:** Fibrofatty replacement of myocardium on endomyocardial biopsy.	Regional RV akinesia, dyskinesia or aneurysm. **Minor:** **2D Echocardiography:** - Regional RV akinesia or dyskinesia and one of the following (end diastolic) - PLAX RVOT ≥ 29 to <32mm (corrected for body size ≥ 16 and <19 mm/m2) - PSAX RVOT ≥ 32 and <36 mm (corrected for body size ≥ 18 and <21mm/m2) or fractional area change > 33% and ≤ 40%. ***MRI:*** Regional akinesia or dyskinesia or dyssinchronous RV contraction and one of the following: - Ratio of RV end diastolic volume to BSA ≥ 100 and <110 ml/m2 men and ≥90 and <100 ml/m2 in women or RV ejection fraction> 40% and ≤ 45%. **Major:** Residual myocytes <60% by morphometric analysis (or <50% if estimated), free wall with fibrous replacement of RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy. **Minor:** Residual myocytes 60-75% by morphometric analysis (or 50-65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.
Repolarization abnormalities **Minor:** Inverted T waves in right leads precordial (V2 and V3) (people aged> 12 years, in the absence of RBBB).	**Major:** Inverted T waves in right precordial leads (V1, V2 and V3) or beyons in individuals > 14 years of age (in the absence of complete RBBB QRS ≥ 120ms). **Minor:** - Inverted T waves in leads V1 and V2 in individuals > 14 years of age (in the absence of complete RBBB) or V4, V5, V6. - Inverted T waves in leads V1, V2, V3 and V4 in individuals> 14 years in the presence of complete RBBB).
Depolarization/conduction abnormalities. **Major:** Epsilon waves or localised prolongation ([110 ms) of the QRS complex in rightprecordial leads (V1–V3). **Minor**:	**Major:** Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the and T wave) in the right precordial leads (V1-V3). **Minor:** - Late potentials by SAECG ≥ 1 of 3 parameters in the absence of a QRS duration ≥ 110 msec on the standard ECG. - Filtered QRS duration ≥ 114 ms

Ventricular late potentials	- Duration of terminal QRS <40μV (low amplitude signal duration) ≥ 38ms. - RMS voltage of terminal 40 ms ≤ 20μV - Terminal activation duration of QRS ≥ 55ms measured from the nadir of the S wave to the end of QRS, including R 'in V1, V2 or V3 in the absence of complete RBBB).
Arrhythmias **Major** **Minor:** Non sustaind or sustained ventricular tachycardia with LBBB morphology (ECG, Holter, exercise). Frequent PVC (> 1000 per 24 hours) (Holter)	**Major:** Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads D II, III, and aVF and positive in lead aVL) **Minor:** Non-sustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads D II, III, and aVF and negative in lead aVL) >500 VES per 24 h (Holter)
Family history **Major:** Family history of ARVC/D confirmed at autopsy or surgery. **Minor:** Family history of premature sudden death (<35 years) because of suspected ARVD. Family history (clinical diagnosis based on present criteria).	**Major:** ARVD confirmed in a first-degree relative who meets current Task Force criteria. ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutation categorized as associated or probably associated ARVD in the patient under evaluation. **Minor:** History of ARVD in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria. Premature sudden death (<35 years) due to a suspected ARVD in a first-degree relative. ARVD confirmed histopathologically or by current Task Force Criteria in a secound- degree relative.

In the case discussed four major criteria were met (presence of epsilon wave, ventricular tachycardia of RV outflow with configuration of LBBB morphology, negative T waves in right precordial leads, right ventricular outflow tract measured in parasternal long axis section ≥ 32 mm) and one minor criteria (the presence of frequent PVC in ECG Holter monitoring).

Pharmacological treatment uses antiarrhythmic agents. Currently there are insufficient data on their effectiveness in controlling malignant arrhythmias. A study of Hiroi et al. [16] suggests that carvedilol is not only useful for controlling arrhythmia but also for improving left ventricular function in some patients with ARVC/D. If this is inadequate to control symptoms or to prevent recurrent VT, membrane active antiarrhythmic agents, such as sotalol and, if necessary, amiodarone should be

considered. According to data of Wichter et al. [17] sotalol proved to be highly effective in patients with ARVC/D and inducible as well as non-inducible ventricular tachycardia with an efficacy of 68.4% and respectively 82.8%; In this study amiodarone did not prove to be more effective than sotalol and may not be an alternative because of frequent side effects during longterm therapy, especially in young patients. Verapamil and b-blockers were effective in a considerable number of patients with non-inducible ventricular tachycardia and may be a therapeutic alternative in this subgroup [4].

Indications for catheter ablation in subjects with ARVC/D include monomorphic and well-tolerated VT with localized forms of the disease and drug-refractory or incessant VT or frequent ICD discharges. The current mapping and ablation techniques include activation and entrainment mapping during tolerated VT and substrate ablation using threedimensional electroanatomic mapping systems [18]. In our case Holter monitoring showed episodes of ventricular tachycardia with different morphologies, which implies the existence of several arrhythmogenic areas in the right ventricle. Another aspect worthy of consideration is the fact that while benefiting from a primary successful intervention in 60-90% of cases, due to the progressive nature of the disease, recurrences are common (60%) [6].

The most important decision regarding ARVD management is to choose if implantable defibrillator (ICD) is needed. According to *Wichter et al* [19], an ICD is imperative if an aborted sudden death had occurred. In case of sustained VT and/or syncope, ICD is also indicated in the presence of risk factors (extensive RV dysfunction, LV involvement, polymorphic VT, late potentials and epsilon wave, family history).

The patient received indication according to current guidelines for implantable defibrillator with favorable results and the recommendation to continue the beta-blocker medication.

The treatment for severe right or biventricular dysfunction is in fact the
classic treatment for heart failure. Heart transplantation represents an alternative in patients with refractory heart failure [5].

The new criteria increased the importance of early diagnosis of arrhythmogenic dysplasia, thus contributing to the prevention of ventricular tachycardia and sudden death in these patients.

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