Evolution of diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy and their application in clinical practice

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This article describes evolution of criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). The novel diagnostic criteria for ARVD/C published in 2020 are analyzed in detail, among which biventricular and left-dominant arrhythmogenic cardiomyopathy are identified for the first time. The need to develop novel criteria was fed on the accumulation of new data on ARVD/C, in particular, significant advances in magnetic resonance imaging technologies. The novel criteria retained high sensitivity and specificity in relation to traditional right ventricular disease form and became more sensitive in relation to the biventricular and left-dominant arrhythmogenic cardiomyopathy.

Nevertheless, the addition of left-dominant disease forms reduces the criteria specificity in general, since left ventricle involvement with a similar clinical performance can have different etiology that goes beyond the ARVD/C, even when mutations are detected in typical genes, which is demonstrated by case reports described in the article. Like the previous two versions, the novel criteria will be fully assessed only with a large sample of patients after their introduction into the routine cardiology clinical practice.

Keywords: diagnostic criteria, arrhythmogenic right ventricular dysplasia/cardiomyopathy, myocardial noncompaction, ventricular premature beats, ventricular tachycardia, myocarditis.

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Arrhythmogenic dysplasia/right ventricle cardiomyopathy (ARVD/C) in classical version is a hereditary myocardial disease characterized by fibroadipose myocardial replacement of the right ventricle (RV) and manifested by aggressive ventricular rhythm disorders [1]. This is how G. Fontaine described this disease in 1977 [2]. At that time, ARVD/C was considered a rare disease, but with the expansion of clinical and morphological beliefs about this nosology, the appearance of magnetic resonance imaging (MRI) of heart and the development of DNA diagnostics, information on the prevalence of this cardiomyopathy has changed: today, the frequency of ARVD/C, depending on population, varies from 1:1000 to 1:5000 [3, 4]. ARVD/C accounts for up to 20% of sudden cardiac death (SCD) cases in young individuals [5], which makes timely diagnosis and competent treatment of this disease extremely relevant.

The first criteria for diagnosis of ARVD/C were proposed by a group of experts in this field in 1994 [6]. They were successfully used for >10 years, but later it became clear that the criteria, while highly specific, lacked sufficient sensitivity and did not take into account recent advances in imaging and genetic testing. They underwent revision, and in 2010, the Modified Diagnostic Criteria for ARVD/C (TFC-2010) was published [7]. Since about 2017, the professional community began to actively discuss the refinement of these criteria taking into account the accumulation of data on biventricular and left ventricular forms of ARVD/C. As a result, in 2020, a group of leading experts developed updated (called Padua criteria) criteria for ARVD/C [8], which are analyzed in detail using clinical cases as examples in this article.

ARVD/C diagnosis is complex and requires a complex approach, because there is no diagnostic method that can unequivocally confirm or exclude this diagnosis. Even endomyocardial biopsy (EMB) and DNA diagnostics are not absolute in ARVD/C. Since myocardial fibrotic-fatty replacement is focal and localized subepicardially at early stages of the disease, EMB sensitivity in ARVD/C diagnosis does not exceed 70% [9]. As for DNA diagnostics, despite significant progress in this field, not all genes responsible for the development of this cardiomyopathy have been described, so a negative result has no excluding power.

The first criteria for diagnosing ARVD/C, proposed in 1994, included structural, histological, electrocardiographic, arrhythmic and hereditary signs of the disease [6]. There are large and small criteria in each category, depending on their specificity to ARVD/C. Based on the number of large and small criteria, the diagnosis is understood as reliable, probable or possible. These criteria had high specificity, but were not without a number of drawbacks. Firstly, they focused exclusively on the right ventricular variant of ARVD/C, which was considered to be the main one at that time. Secondly, due to insufficiently high sensitivity, the criteria often did not "work" in early forms of the disease [7]. In the TFC-2010 criteria, which we have used up to now (Table 1), several fundamental differences appeared: quantitative parameters were introduced (volume and RV systolic function, percentage of preserved cardiomyocytes at fibrous replacement), and the presence of fat in RV myocardium was no longer considered mandatory due to its insufficient specificity for ARVD/C. TFC-2010 has been shown to be more sensitive than the criteria in 1994, but not inferior in specificity [7, 10].

A paper on arrhythmogenic cardiomyopathies in a broad sense was published in 2019 [11]. It summarizes data on diagnosis, SCD risk stratification and management of patients with any cardiomyopathy for which rhythm disturbances are typical, in the absence of myocardial ischemia, significant hypertension and valve lesion. In addition to ARVD/C, this included hypertrophic and restrictive cardiomyopathies, left ventricular (LV) noncompact myocardium (NCM), storage diseases, mitochondrial diseases, including Kearns-Seir syndrome, and also canalopathies. In our opinion, combining such heterogeneous diseases under a single term "arrhythmogenic cardiomyopathies" is inappropriate, since their genetic basis, pathogenesis, clinical manifestations, treatment, and prognosis are fundamentally different. Thus, further improvement of diagnostic criteria of classical ARVD/C taking into account left ventricular and biventricular variants is still relevant.

Such criteria were proposed by a group of scientists from Padua in 2020 (Table 2) [8]. Specialists from Italy have the most experience in ARVD/C, since Veneto, where Padua is located, is the endemic region for this cardiomyopathy [12]. In addition, the expert board included other recognized experts from Great Britain, Greece, Germany, the United States, Norway, and Switzerland.

The basis of the Paduan criteria for ARVD/C is still morphofunctional and structural changes, disorders of repolarization, depolarization, ventricular arrhythmias and family history in combination with genetic data. Unlike TFC-2010, there are categories that include only large or only small criteria. The approach to varying measure of diagnosis confidence was preserved. This is of great clinical importance, because patients with a probable and possible diagnosis also require careful follow-up, and often treatment, since they are at risk of SCD

Table 1

Criteria for ARVD/C diagnostics (revision 2010) [7]

	Large criteria	Small criteria
I. Global/regional dysfunction and structural changes	**in Echo:** 1) regional akinesia, dyskinesia or RV aneurysm 2) *and* one or more signs (end of diastole): • RV (long axis) $\geqslant$32 mm (index $\geqslant$19 mm/m^2) • RV (short axis) $\geqslant$36 mm (index $\geqslant$21 mm/m^2) • *or* regional violations $\leqslant$33% **in MRI:** 1) regional akinesia or dyskinesia, or dissynchrony of RV contraction 2) *and* one or more signs: • ratio of RV EDV to the body surface area $\geqslant$110 ml/m^2 (in men) and $\geqslant$100 ml/m^2 (in women) • *or* RV EF $\leqslant$40% **in RV ventriculography:** regional akinesia, dyskinesia or RV aneurysm	**in Echo:** 1) regional akinesia or RV dyskinesia 2) *and* one or more signs (end of diastole): • RV (long axis) 29-31 mm (index 16-18 mm/m^2) • RV (short axis) 32-35 mm (index 18-20 mm/m^2) • *or* regional violations 34-40% **in MRI:** 1) regional akinesia or dyskinesia, or dissynchrony of RV contraction 2) *and* one or more signs: • ratio of RV EDV to the body surface area $\geqslant$100-109 ml/m^2 (in men) and $\geqslant$90-99 ml/m^2 (in women) • *or* RV EF 41-45%
II. Histology	preserved myocytes <60% on morphometric analysis (or <50% on accurate assessment) with fibrous myocardial replacement of the free RV wall in $\geqslant$1 area, with or without fatty tissue replacement (in EMB)	preserved myocytes 60-75% in morphometric analysis (50-65% on accurate assessment) with fibrous myocardial replacement of the free RV wall in $\geqslant$1 area, with or without fatty tissue replacement (in EMB)
III. Repolarization disorders	inversion of T deflections in the right thoracic leads (V$_1$-V$_3$) or further in persons over 14 years of age (in the absence of complete RBB block with a QRS width $\geqslant$120 ms)	• inversion of T deflections in leads V$_1$-V$_2$ in persons over 14 years of age (in the absence of complete RBB block) or in V$_4$-V$_5$ or in V$_6$ • inversion of T deflections in leads V$_1$-V$_4$ in persons over 14 years of age in the presence of complete RBB block
IV. Depolarization/conduction disorders	epsilon wave (reproducible low-amplitude signal between the end of the QRS complex and the beginning of T deflection) in the right thoracic leads (V$_1$-V$_3$)	1) late ventricular potentials (1-3 parameters) on signal-averaged Echo in absence of QRS expansion $\geqslant$110 ms on standard Echo: • filtered QRS duration $\geqslant$114 ms • duration of the final part of QRS (low-amplitude signal duration) $\geqslant$38 ms • RMS voltage of the final part of QRS $\leqslant$20 mV 2) duration of final activation of QRS $\geqslant$55 ms (from the top of S deflection to the end of QRS, including R' in leads V$_1$, V$_2$ or V$_3$ in the absence of complete RBB block)
V. Arrhythmias	unstable or sustained ventricular tachycardia with morphology of left bundle branch block and superior axis (negative or uncertain QRS complexes in leads II, III, aVF and positive in aVL lead)	• unstable or sustained ventricular tachycardia from the LV outlet tract or with morphology of left bundle branch block and inferior axis (positive QRS complexes in leads II, III, aVF and negative in aVL lead) or unknown axis • >500 VES per day (Holter monitoring)
VI. Family history	• ARVD/C in relatives of the first degree (according to diagnosis criteria) • ARVD/C, confirmed morphologically, in relatives of the first degree • identification of pathogenic mutations in the patient with a proven or probable link to ARVD/C	• ARVD/C in relatives of the first degree (when it cannot be determined whether family members meet the diagnosis criteria) • sudden cardiac death (under the age of 35) due to suspected ARVD/C in relatives of the first degree • ARVD/C, confirmed morphologically or according to diagnosis criteria in relatives of the second degree

Note: *reliable diagnosis*: 2 large criteria or 1 large + 2 small criterion (from various categories), or 4 small (from various categories); *probable diagnosis*: 1 large criteria + 1 small or 3 small criteria (from various categories); *possible diagnosis*: 1 large criterion or 2 minor criteria (from various categories).

Abbreviations: ARVD/C — arrhythmogenic dysplasia/right ventricular cardiomyopathy, VES — ventricular extrasystole, EDV — end-diastolic volume, MRI — magnetic resonance imaging, RV — right ventricle, RBB — right bundle branch, EF — ejection fraction, Echo — electrocardiography, EMB — endomyocardial biopsy of right ventricle, Echo — echocardiography.

Table 2

Padua criteria for ARVD/C diagnosis (revision 2020) [8]

	RV (updated TFC-2010 criteria)	LV
I. Morpho-functional changes of ventricles	*Echo, MRI or ventriculography* **Large** • local akinesis, dyskinesis or RV heave *plus one* of the following manifestations: — RV dilation (increase in EDV in accordance with nomograms for a specific imaging method) — systolic RV dysfunction (decrease in EF in accordance with nomograms for a specific imaging method) **Small** • local akinesis, dyskinesis or aneurysm of RV free wall	*Echo, MRI or ventriculography* **Small** • LV systolic dysfunction (reduction of LV EF or reduction of global longitudinal deformation in echocardiography), with or without LV dilation (increase in EDV in accordance with nomograms for a specific imaging method, taking into account age, gender and body surface area) **Small** • local akinesis or dyskinesis of the free LV wall and/or septum
II. Myocardium structural changes	*MRI* **Large** • Transmural LGE (band pattern) in ⩾1 region of RV (input, output tracts and apex in 2 orthogonal projections) *EMB (limited indications):* **Large** • fibrous myocardial replacement in ⩾1 sample, with or without adipose tissue	*MRI* **Large** • LGE in LV (band pattern) in ⩾1 segment (bovine eye in 2 orthogonal projections) of the free wall (subepicardially or intramiocardially) and/or septum (except LGE in the area of interventricular septum junction with the free wall)
III. Repolarization disorders	**Large** • inversion of T deflections in the right thoracic leads (V_1-V_3) or further in persons over 14 years of age (in the absence of complete RBB block) **Small** • inversion of T deflections in leads V_1-V_2 in persons over 14 years of age (in the absence of complete RBB block) • inversion of T deflections in leads V_1-V_4 in persons over 14 years of age in the presence of complete RBB block	**Small** • inversion of T deflections in the left thoracic leads V_4-V_6 (in the absence of complete LBB block)
IV. Depolarization disorders	**Small** • epsilon wave (reproducible low-amplitude signal between the end of the QRS complex and the beginning of T deflection) in the right thoracic leads (V_1-V_3) • duration of final activation of QRS ⩾55 ms (from the top of the S deflection to the end of the QRS, including R' in leads V_1, V_2 or V_3 in the absence of complete RBB block)	**Small** • low voltages of the QRS complex (<0,5 mV) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
V. Ventricular rhythm disorders	**Large** • frequent VES (>500/day), unstable and/or stable VT with the morphology of LBB block (except VES and VT from VT outflow tract) **Small** • frequent VES (>500/day), unstable and/or stable VT from RV outflow tract (morphology of LBB blockade, lower axis)	**Small** • frequent VES (>500/day), unstable and/or stable VT with the morphology of RBB block (with the exception of fascicular tachycardia)
VI. Family history and genetics	**Large** • ARVD/C in relatives of the first degree of kinship (according to diagnosis criteria) • ARVD/C, confirmed morphologically, in relatives of the first degree of kinship • identification of pathogenic mutations in the patient with a proven or probable link to ARVD/C **Small** • ARVD/C in relatives of the first degree of kinship (when it cannot be determined whether family members meet the diagnosis criteria) • sudden cardiac death (under the age of 35) due to suspected ARVD/C in relatives of the first degree of kinship • ARVD/C, confirmed morphologically or according to diagnosis criteria in relatives of the second degree of kinship	

Abbreviations: ARVD/C — arrhythmogenic dysplasia/right ventricular cardiomyopathy, VT — ventricular tachycardia, VES — ventricular extrasystoles, EDV — end-diastolic volume, LV — left ventricle, LBB — left bundle branch, MRI — magnetic resonance imaging, RV — right ventricle, RBB — right bundle branch, EF — ejection fraction, EMB — endomyocardial biopsy of right ventricle, Echo — echocardiography, LGE — late gadolinium enhancement.

along with patients with a reliable ARVD/C diagnosis. The fundamental difference in criteria structure is a separate part devoted to the diagnosis of left ventricular forms of ARVD/C.

Let us briefly discuss the new aspects in each of the categories.

When assessing **morphofunctional changes**, it was decided once again to abandon quantitative assessment of the degree of dilatation and systolic dysfunction of RV. This is due to the fact that in TFC-2010, the average MRI parameters of the control group (462 people) from the 2006 MESA atherosclerosis study were taken as reference values [8, 13], when the assessment of heart chambers volume was carried out using outdated techniques that are far from perfect. The updated criteria are recommended to be based on nomograms used in this population, which take into account the patient's gender, age and anthropometric indicators. In addition, RV hypo-/akinesis has been added as a separate small criterion, which makes it possible to diagnose ARVD/C at the early stages, when there has not yet been a RV dilation and a decrease in its ejection fraction (EF). A similar approach is provided for left ventricular forms of ARVD/C.

Structural changes imply the degree of myocardial fibrotic-fatty replacement. In this category, there are only large criteria based on EMB or MRI data. Due to the relatively low sensitivity of EMB [9] in the new criteria, it is recommended to perform it only in non-familial forms of ARVD/C in combination with negative results of DNA diagnostics within differential diagnosis with myocarditis, sarcoidosis. In addition, in doubtful cases, EMB will reveal a combination of ARVD/C and myocarditis, which, according to our data, occurs in more than 70% of patients with ARVD/C [14]. The histological criterion is counted in the presence of fibrous substitution in at least one sample. At the same time, the percentage of preserved cardiomyocytes that was present in TFC-2010 is not stipulated, and the presence of fat is still not considered mandatory. Fibrosis according to the LV EMB results is not considered as a criterion due to its low specificity, in addition, LV EMB is performed less frequently than RV.

As for MRI signs of fibrous replacement, the resolution of modern tomographs and special study protocols allow to estimate even tissue characteristics of the thinned RV wall [15, 16]. In this regard, transmural late gadolinium enhancement (LGE) in RV is attributed to the large criteria of ARVD/C. For the left ventricular form, it was proposed to treat only subepicardial or intramyocardial LGE in LV as a major criterion. Nevertheless, LGE in LV should be interpreted with caution and taking into account the clinical context, since this sign is not specific

enough and often occurs not only in ARVD/C, but also in myocarditis, dilated and hypertrophic cardiomyopathies, LV NCM, sarcoidosis and amyloidosis [17-20]. The variety of causes for LGE is fully demonstrated in the work of Japanese scientists, where MRI data were compared with the results of myocardial morphological study [21].

Depolarization abnormalities in TFC-2010 included the presence of an epsilon wave as a major criterion, and the presence of late ventricular potentials on a high-resolution electrocardiogram (Echo) and increased QRS terminal activation duration $\geqslant 55$ ms as minor ones. In the updated version, there are no large criteria in this category. Epsilon wave was decided to "downgrade" to a small criterion. This sign is typical for ARVD/C, although it is not pathognomonic, but there are often difficulties with its unambiguous interpretation. In 2016, an extravagant study was conducted in which the authors of TFC-2010 were asked directly to analyze a number of cardiograms of patients with ARVD/C and to conclude whether there was an epsilon wave: the experts' opinion fully coincided only in one third of cases [22]. The increase in duration of terminal QRS activation is still considered to be a small criterion, and high-resolution Echo data were decided to be excluded altogether, because this method was rarely used in practice and, according to the authors of the Padua criteria, it is not specific enough. For diagnostics of left ventricular forms, it was suggested to consider a decrease in QRS voltages in limb leads as a small criterion. Previously, it was shown that low voltages are a predictor of heart failure development in patients with ARVD/C, including due to left-sided lesions [23]. Nevertheless, low Echo voltages are not specific for left ventricular ARVD/C. This sign can occur in widespread lesions of RV as part of ARVD/C, other cardiomyopathies (dilated, NCM), a number of accumulation diseases (especially in amyloidosis), and due to extracardiac causes.

As for **repolarization disorders**, this category underwent minimal changes: the criteria for ARVD/C with predominant involvement of RV remained the same, and for the diagnosis of left ventricular forms, a small criterion in the form of negative T waves in V_4-V_6 leads was added. Nevertheless, the negative T teeth in the left leads may also be a reflection of pronounced dilation and fibrous-fat replacement of RV [17].

The approach to assessing the main ARVD/C manifestation — **ventricular arrhythmias** — has changed slightly. If in the previous version of the criteria only ventricular tachycardia (VT) topology was important, in the Padua criteria, the source of ventricular extrasystoles (VES) is proposed to be
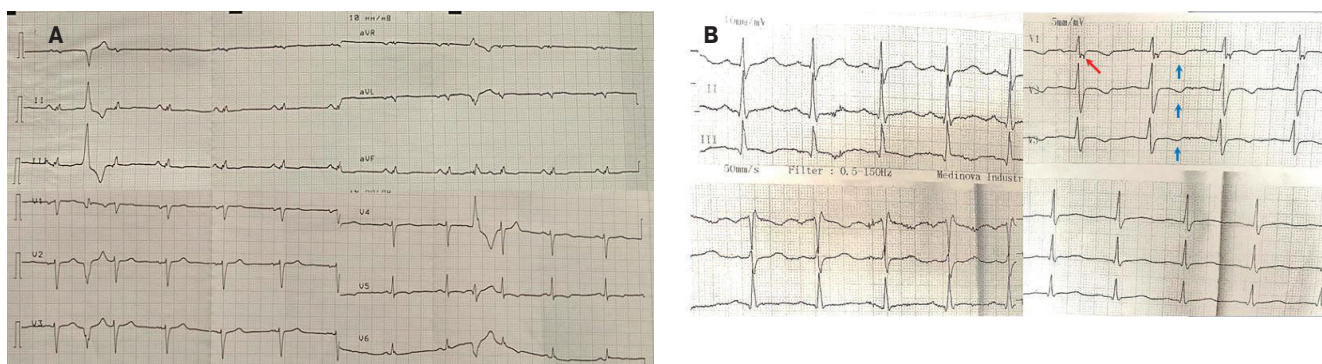
Figure 1. Cardiograms of patient E. (clinical example No. 1). **A** — Echo in 2020; **B** — Echo in 2010.
Note: red arrow shows epsilon wave, blue arrows show negative T deflections. Explanations in the text.

determined as well. The major criterion for right ventricular forms is >500 VES/day and/or VTs with morphology of left bundle branch block (LBB), and the minor criterion is >500 VES/day and/or VTs from the RV outflow tract. A small criterion for the left ventricular ARVD/C form is >500 VES/day and/or VT with the morphology of right bundle branch block (RBB).

The last category, **family history and DNA diagnostic data**, remained the same. The criteria are common for right ventricular and left ventricular forms.

The determination of the degree of diagnosis reliability by total number of large and small criteria from various categories has also not changed, but the approach to the diagnosis of various forms has changed. So, for an *isolated right ventricular form*, it is necessary to have at least one morphofunctional or structural criterion, in addition, there should be no signs of LV involvement. For the *biventricular variant*, there should be at least one morphofunctional or structural criterion of lesion of both LV and pancreas. Finally, for the form with *predominant LV damage*, the presence of structural criterion and mutations in genes typical for ACL, in the absence of changes in RV, are mandatory. The presence of mutation is particularly important because, according to the authors, it is the one that excludes other, more typical, causes of LV damages. Nevertheless, even the detection of mutations is not entirely unambiguous, because the genetics of cardiomyopathies is much more complex and numerous crossings of genotypes and phenotypes are described: mutations typical for ARVD/C can occur in NCM, in dilated, hypertrophic, and even in restrictive (for example, mutations in desmin gene) cardiomyopathies [24]. It is by adding left ventricular forms that the criteria to some extent lose their high specificity as a whole, retaining it only for the classic right ventricular form.

Clinical example 1

Patient E., 39 years old, was admitted to the Department of Cardiology of the Faculty Therapeutic Clinic n.a. V. N. Vinogradov (FTC) in January 2021 due to an episode of discomfort behind the sternum, accompanied by a feeling of compression, suffocation, presyncopal state lasting ~5 minutes, which developed at the end of November 2020. On ambulatory examination after the attack, the Echo showed changes in the form of a sharp decrease of QRS voltages in the limb leads, QS complexes in V_1-V_3 (Figure 1 A), Holter monitoring recorded 3,7 thousand VES, therefore, the patient was referred to the FTC with suggestion of myocarditis. For the first time, VES was detected 10 years ago after the first pregnancy (~1000/day), no treatment was prescribed. Already at that time the Echo showed typical changes for ARVD/C: epsilon wave and negative T waves in the leads V_1-V_3 in the absence of RBB block (Figure 1 B), but the diagnosis was not made. It is known that in February 2020, upon return from Italy, the whole family had an episode of unspecified infectious disease with fever, which does not allow to rule out a non-serious COVID-19. A new coronavirus infection (COVID-19) could be both a cause of myocarditis accession and a trigger for genetic cardiomyopathy progression.

When studying the level of anti-cardiac antibodies in the blood, an increase in the titers of antibodies to antigens of cardiomyocyte nuclei to 1:160 (normally absent), smooth muscles and the conducting system (1:160 at normal to 1:40) was obtained. On Echo at rest, the picture is similar to Echo after an attack of discomfort behind the sternum. High-resolution Echo revealed late ventricular potentials according to two out of three criteria (Std QRS 90 ms at 114 ms norm, LAS 40-60 ms at 29 ms norm), which serves as an additional confirmation of the ARVD/C diagnosis. Echocardiography (Echo)

showed a moderate decrease of LV EF (47%), other parameters were normal.

To clarify the nature of myocardial damage, cardiac MRI was performed (Figure 2): dyskinesia of RV in the area of "dysplasia triangle" was described, otherwise RV was unchanged; there were also convincing data in favor of ARVD/C with LV damage: "creeping" of fat on myocardium in the area of interventricular septum, which corresponds to the zone of disappearance of R deflections on Echo, moderate decrease of LV contractility (EF 54%) with its dilatation (ratio of end-diastolic volume/body surface area to LV 107 ml/m^2 with normal 41-81 ml/m^2), pronounced LGE subepicardial localization in LV and interventricular septum. In addition, noncompact myocardial layer in LV (ratio with compact one up to 2,1) attracted attention, which does not reach the criteria of noncompact cardiomyopathy (>2,3 according to Petersen [25]), but indicates in favor of primary cardiomyopathy. Magnetic resonance signs of LV myocardial edema were noted, which, along with a history of infection and a significant increase in the titers of anticardial antibodies, confirms the presence of concomitant myocarditis; hydroxychloroquine 400 mg/day was prescribed. Daily Echo monitoring by Holter on a "clean" background recorded 1300 VES, sotalol was administered without significant effect. Due to the small amount of VES, the latter was replaced with bisoprolol 5 mg/day. No indication for cardioverter-defibrillator implantation was found. The patient was consulted by a geneticist, and DNA diagnostics revealed a mutation and a variants of uncertain clinical significance (VUCS) in the gene *DSP*, which confirmed the diagnosis and was fully consistent with the clinical performance, since mutations in desmoplakin are characterized by left-sided involvement [8], as well as the presence of NCM [26]. The patient's diagnosis criteria are summarized in Table 3: biventricular form of ARVD/C was diagnosed, but LV damage has more complex character and seems to be caused by ARVD/C combination, myocarditis and increased LV trabecularity.

Clinical example 2

Patient I., 35 years old, was first admitted to the FTC department in September 2018 due to ventricular rhythm disorders persisting on amiodarone and bisoprolol therapy, moderate heart failure. Rhythm disorders were recorded for >10 years, at the age of 29 for frequent ventricular ectopy (6 thousand extrasystoles and 153 runs of unstable VT), an attempt of radiofrequency ablation of arrhythmogenic focus in LV was performed in the center n.a. V.A. Almazov without significant effect, EMB showed a picture of active lymphocytic
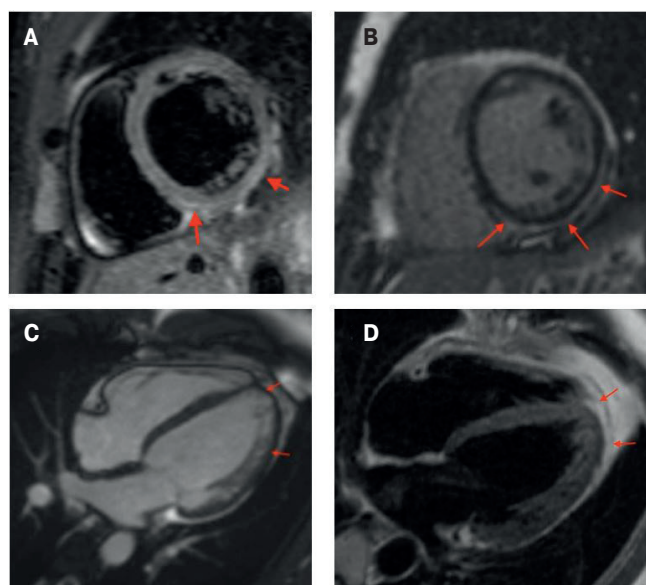
Figure 2. Cardiac MRI of patient E. (clinical example No. 1). **A** — TIRM sequence (T2 FS), short axis at the basal level, increased intensity of magnetic resonance signal from the posterior septal and posterolateral segments is visualized; **B** — PSIR sequence, short axis at the basal level, areas of delayed contrast agent accumulation (LGE) are visualized along the posterolateral segment with spreading to the posterior segment and along the posterior septal segment; **C** — cinema sequence (SSFP), 4-chamber plane, diastole, trabecular enhancement is visualized; **D** — T2-weighted sequence, 4-chamber plane, epicardial fat thickening with signs of spreading to LV myocardium and cardiac apex is visualized.

myocarditis, which was not treated. There was a history of syphilis treated in 2008, which stopped doctors from prescribing immunosuppressive therapy (its etiological role in the development and maintenance of myocarditis was not excluded). The arrhythmia was only partially suppressed with amiodarone, but the presence of untreated myocarditis made it difficult to determine the indication for implantation of a cardioverter-defibrillator. He was sent to the FTC to decide on the baseline therapy of myocarditis and the advisability of interventional treatment.

The association of subsequent exacerbations of the disease (increase in dyspnea with a fall in EF up to 33%, appearance of persistent paroxysms of VT) with infections (chickenpox, whooping cough, acute respiratory viral infection) was evidence in favor of preserving myocarditis activity. Nevertheless, as a result of complex examination of the patient and analysis of medical records, ARVD/C appears to be the main cause of ventricular arrhythmias. As early as the Echo taken at the age of 21 during the preventive medical examination, there were negative T deflections in all thoracic leads, which

Table 3

Diagnosis criteria of patient E. in the clinical example 1

Padua Criteria 2020	RV	LV	Could it be for myocarditis?
I. Morpho-functional changes of ventricles (MRI)	• RV dyskinesis	• LV EF (MRI) 54% • EDV/body surface area to LV 107 ml/m² at N 41-81 ml/m²	yes
II. Myocardium structural changes	no	• **subepicardial LGE**	yes
III. Repolarization disorders	• **inversion of T deflections in the right thoracic leads (V₁-V₃)**	no	yes
IV. Depolarization disorders	• epsilon wave	• low voltage of the QRS complex in leads from limbs	not typical
V. Ventricular rhythm disorders	• frequent VES (>500/day)	• frequent VES (>500/day)	yes
VI. Family history and genetics	**mutation and VUCS in the gene *DSP***		may be the background for the attachment of myocarditis

Note: large criteria are highlighted in bold.
Abbreviations: VES — ventricular extrasystole, EDV — end-diastolic volume, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, LGE — late gadolinium enhancement, VUCS — variants of uncertain clinical significance.
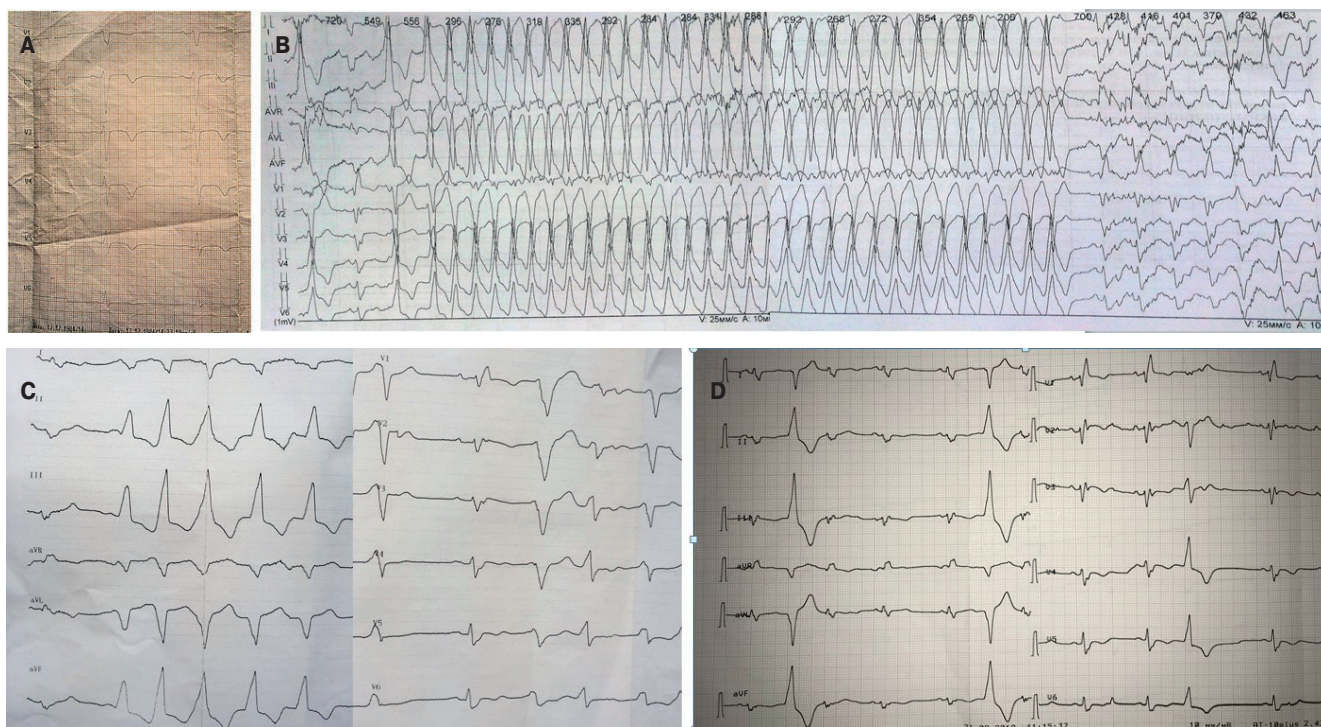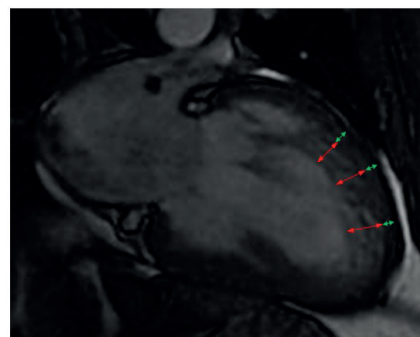

Figure 3. Cardiograms of patient I. (clinical example No. 2). **A** — Echo for medical examination at the age of 21; **B**, **C** — VT paroxysms; **D** — Echo upon admission to the clinic.

were regarded as nonspecific changes (Figure 3 A), later there was VT with the morphology of LBB block with a lower axis (Figure 3 B, C). On the Echo recorded at admission to the FTC, attention was drawn to a pronounced decrease in the voltage of QRS complexes in standard leads (Figure 3 D). It was not possible to assess the presence of an epsilon wave due to the development of complete RBB block. In Holter Echo monitoring performed during amiodarone therapy, >25 thousand Echos were recorded. VES per day, frequent episodes of unstable VT persisted. Myocardial biopsy data were requested — lipomatosis sites were mentioned in the received conclusion (attempts to obtain initial morphological material were unsuccessful).

With Echo, moderate LV dilation up to 6,2 cm was noted, with a decrease in its LV to 52%, RV — 3,4 cm. According to the MRI data, the indexed volume of

RV was >110 ml back in 2012 at 29 years old, LV EF 40% was registered in 2012 and with repeated MRI in the FTC, there were RV dyskinesis, LV EF was reduced to 40%. In addition, the last MRI revealed reliable signs of NCM (Figure 4). The addition of myocarditis is typical for both ARVD/C [14] and non-compact myocardium [27]. Blood antibody titers to endothelial, smooth muscle, and conduction system antigens increased to 1:160 (normal to 1:40), for which reason methylprednisolone 16 mg (with subsequent dose reduction to 4 mg) in combination with azathioprine 150 mg/day was added to the treatment (with subsequent replacement with hydroxychloroquine 200 mg/day). After 6 months, a positive dynamics in the titers of anticardial anti-

Figure 4. Cardiac MRI of patient I. (clinical example No. 2).
Note: cinema sequence (SSFP), 4-chamber plane, diastole, signs of non-compact LV myocardium are visualized (green arrows show compact layer, red arrows — non-compact layer).
Abbreviation: LV — left ventricle.
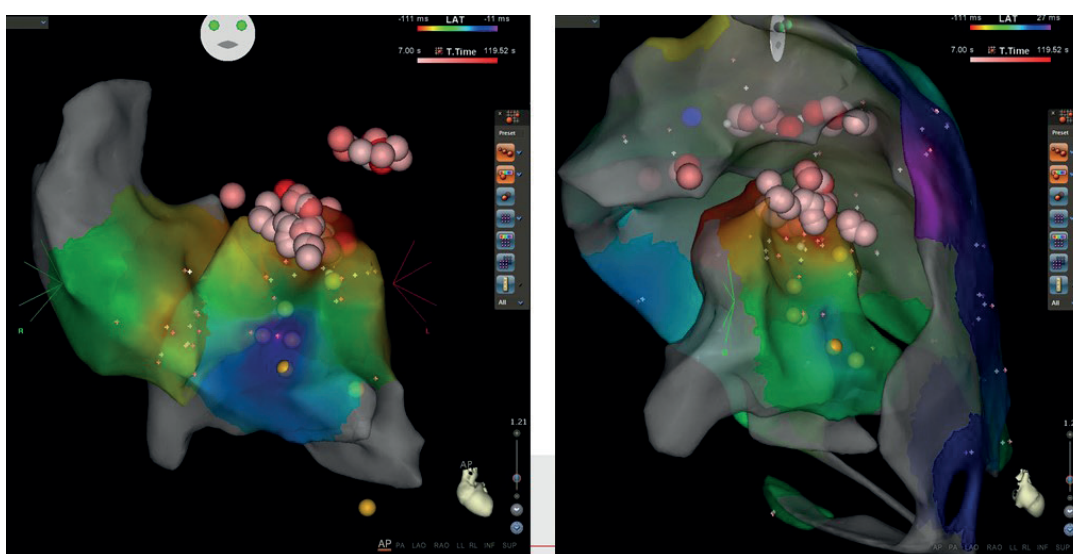
Figure 5. Mapping scheme for radiofrequency ablation in patient I. (clinical example No. 2).

Table 4

Diagnosis criteria of patient I. in the clinical example 2

Padua Criteria 2020	RV	LV	Could it be for myocarditis?
I. Morpho-functional changes of ventricles (MRI)	· **RV EF 33%** · **EDV**/body surface area **97 ml/m²**	· LV EF (MRI) 40% · LV EDD 6,4 cm	yes
II. Myocardium structural changes	no	no	yes
III. Repolarization disorders	· **inversion of T deflections in the right thoracic leads (V$_1$-V$_3$)**	· inversion of T deflections in the left thoracic leads (V$_4$-V$_6$)	yes
IV. Depolarization disorders	no	· low voltage of the QRS complex in leads from limbs	not typical
V. Ventricular rhythm disorders	· frequent VES (>500/day), unstable and stable VT (?) with a lower axis	no	aggressive and therapy-resistant ventricular rhythm disorders are not so characteristic
VI. Family history and genetics	VUCS in the genes *DSP* and *TMEM43*		may be the background for the attachment of myocarditis

Note: large criteria are highlighted in bold.

Abbreviations: VT — ventricular tachycardia, VES — ventricular extrasystoles, EDV — end-diastolic volume, EDV — end-diastolic volume, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, LGE — late gadolinium enhancement, VUCS — variants of uncertain clinical significance.

bodies was noted, EF was steadily maintained at 55%, dyspnea was almost completely eliminated, the number of VES decreased to 510. Gradually (by the end of 2020) immunosuppressive therapy was completely abolished.

However, frequent ventricular ectopy persisted: >18 thousand were recorded during amiodarone withdrawal VES, 33 episodes of unstable VT with a heart rate of up to 130/min. Repeated radiofrequency ablation of the arrhythmogenic focus in the upper third of the anterior interventricular sulcus was performed by combined endo- and epicardial access (Figure 5), however, the procedure was ineffective: frequent (up to 15 thousand) VES, episodes of unstable VT persisted, and therefore amiodarone therapy was resumed.

DNA diagnostics was performed: VUCS were detected in the *DSP* gene, which is typical for a combination of ARVD/C and NCM [26, 28], as well as in the gene *TMEM43*, mutations in which are associated with a high risk of SCD [29, 30]. The clinical significance of VUCS needs further clarification, but bioinformatic analysis of the PolyPhen-2 variants detected considered both variants as pathogenic with a high probability. Taking into account the phenotype of two genetically determined cardiomyopathies, resistant to interventional treatment of aggressive ventricular rhythm disturbances, additional risk factors of SCD (VUCS in *DSP* and *TMEM43*, myocarditis accession, low voltages of QRS complexes), as a primary prevention of SCD, at the Transplant Center n.a. V. I. Shumakov, CRT-D was implanted (without connection of ventricular electrode). At the moment the patient is stable, receives sotalol 240 mg/day, eplerenone 50 mg/day, perindopril 2,5 mg/day. No defibrillator triggers have been recorded yet. In December 2020, had a mild form of COVID-19, no increase in shortness of breath or rhythm disturbances was noted.

As we can see from the above clinical case, despite the presence of obvious criteria of ARVD/C (Echo changes, decreased RV EF in combination with dyskinesia according to MRI back in 2012, ventricular rhythm disorders), the diagnosis was not made in time. Myocardial biopsy revealed lymphocytic myocarditis (the etiological role of syphilis was assumed), immunosuppressive therapy was not administered. Only as a result of combination of baseline therapy for myocarditis and antiarrhythmic drugs, state stabilization was achieved. According to the updated 2020 criteria, the patient has a reliable diagnosis of biventricular ARVD/C (Table 4). Nevertheless, as in the previous case, LV changes cannot be unambiguously assessed, because in addition to undoubted ARVD/C, NCM and myocarditis are present.

Conclusion

The Paduan criteria include clinical manifestations of ARVD/C, the sensitivity and specificity of which have been verified by long-term practice. At the same time, the criteria are modified to take into account new diagnostic possibilities and data obtained in the study of this cardiomyopathy during the last decade, which makes them more sensitive for biventricular and left ventricular forms of ARVD/C. Nevertheless, the addition of left ventricular forms reduces the criteria specificity as a whole, since LV lesions with a similar clinical picture can have a variety of etiologies beyond ARVD/C, even when mutations in typical genes are found. Like the previous two versions, the new criteria will be fully evaluated only prospectively on a large sample of patients, i.e. as a result of their introduction into the daily clinical practice of cardiologists.

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