Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

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Disclosures

The authors have no conflicts to disclose.

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Abstract

Background—In 1994, an International Task Force proposed criteria for the clinical diagnosis of ARVC/D which facilitated recognition and interpretation of the frequently non-specific clinical features of ARVC/D. This enabled confirmatory clinical diagnosis in index cases through exclusion of phenocopies, and provided a standard upon which clinical research and genetic studies could be based. Structural, histological, electrocardiographic, arrhythmic, and familial features of the disease were incorporated into the criteria, subdivided into major and minor according to the specificity of their association with ARVC/D. At that time, clinical experience with ARVC/D was dominated by symptomatic index cases and sudden cardiac death victims: the overt and/or severe end of the disease spectrum. Consequently, the 1994 criteria were highly specific but lacked sensitivity for early and familial disease.

Methods and Results—Revision of the diagnostic criteria provides guidance on the role of emerging diagnostic modalities and advances in the genetics of ARVC/D. The criteria have been modified to incorporate new knowledge and technology to improve diagnostic sensitivity, but with the important requisite of maintaining diagnostic specificity. The approach classifying structural, histological, electrocardiographic, arrhythmic, and genetic features of the disease as major and minor criteria has been maintained. In this modification of the Task Force Criteria, quantitative criteria are proposed and abnormalities are defined based on comparison with normal subject data.

Conclusions—The diagnosis of ARVC/D based on modification of the original Task Force criteria is a working framework to improve the diagnosis and management of this condition.

Keywords

cardiomyopathy; diagnosis; echocardiography; electrocardiography; magnetic resonance imaging

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is predominantly a genetically determined heart muscle disorder that is characterized pathologically by fibrofatty replacement of the right ventricular myocardium.[1] In the early stage of the disease, structural changes may be absent or subtle and confined to a localized region of the right ventricle (RV), typically the inflow tract, outflow tract, or apex of the RV, the "triangle of dysplasia".[2] Progression to more diffuse RV disease and left ventricular (LV) involvement is common.[3] Predominant LV disease is also recognized, typically of the posterior lateral wall.[4] Post mortem diagnosis may require extensive sampling and transillumination.[5] Disease expression is variable. In the early 'concealed' phase, individuals are often asymptomatic, but may nonetheless be at risk of sudden cardiac death, notably during exertion.[6] In the overt 'electrical' phase, individuals present with symptomatic arrhythmias and RV morphological abnormalities are readily discernible by conventional imaging. Later, diffuse disease may result in biventricular heart failure while ventricular arrhythmias may or may not be present. The ultimate phenotype may resemble dilated cardiomyopathy. Clinical manifestations vary with age and stage of disease.[7]

ARVC/D is considered to be familial with autosomal dominant inheritance, although there are recessive forms (e.g. Naxos Disease, Carvajal Syndrome), which are associated with a cutaneous phenotype.[8,9] Genetic variations have been found in the desmosomes that are responsible for cell to cell binding.[10,11] (Figure 1) Seven genes have been identified that are associated with ARVC/D: plakoglobin (JUP),[12] desmoplakin (DSP),[13] plakophilin-2 (PKP2),[14] desmoglein-2 (DSG2),[15,16] desmocollin-2 (DSC2),[17,18] transforming growth factor beta-3 (TGFβ3),[19] and TMEM43[20] Mutations in RYR2 coding the ryanodine receptor have been reported as a subtype of ARVC/D with a notable paucity of structural RV disease but with fibrofatty replacement of RV myocytes on histopathological examination. At present, catecholaminergic polymorphic ventricular tachycardia is generally considered as a distinctly separate disorder from ARVC/D, although interpretation of the clinical criteria used to make this diagnosis can be ambiguous.[11] Preliminary observations suggest that the mechanical defect of the desmosomes alters function of the gap junction. ECG changes and arrhythmias may develop prior to histological evidence of myocyte loss or clinical evidence of RV dysfunction.[21,22] It has been proposed that similar clinical phenotypes occur based on disruption of a "final common pathway" by mutations in genes encoding proteins in the defined desmosomal pathway.[23] Recognition of the genetic basis of ARVC/D facilitates examination of the pathogenesis in relation to arrhythmogenesis and disease progression.[24]

It has been suggested that patients with ARVC/D may be predisposed or susceptible to viral myocarditis which could lead to a decrease in cardiac function and accelerate progression of the disease.[25–27] The link between ARVC/D and myocarditis is still undefined.

Background

The original 1994 International Task Force criteria for the clinical diagnosis of ARVC/D were based on structural, histological, electrocardiographic, arrhythmic, and familial features of the disease.[28] (Table 1) Abnormalities were subdivided into major and minor according to the specificity of their association with ARVC/D. Electrocardiographic abnormalities such as complete and incomplete right bundle branch block (RBBB) were excluded because of their lack of specificity. Right precordial T wave inversion, though well recognized in ARVC/D, was considered a minor criterion owing to its presence in other conditions, including anterior ischemia and right ventricular hypertrophy. Arrhythmia of right ventricular origin, another cardinal feature of ARVC/D, was designated a minor

criterion because of its occurrence in other diseases, particularly idiopathic right ventricular outflow tract tachycardia. Furthermore, the 1994 criteria focused on right ventricular disease manifestations, and stipulated the absence or only mild left ventricular involvement because of the need to exclude common disorders such as ischemic heart disease and dilated cardiomyopathy.

At the time of the publication of the original Task Force guidelines, clinical experience with ARVC/D was dominated by symptomatic index cases and sudden cardiac death victims: the overt and/or severe end of the disease spectrum. Consequently, the 1994 criteria were highly specific but they lacked sensitivity for early and familial disease.[29–31]

Over the past fifteen years additional ECG markers have been proposed.[32–34] In addition there has been recognition of the genetic basis of disease with the potential for mutation analysis, and growing experience with quantification of imaging criteria of ARVC/D as well as the introduction of newer techniques such as contrast-enhanced echocardiography, three dimensional echocardiography, cardiovascular magnetic resonance (CMR) with late enhancement, and electroanatomic voltage mapping.[35–40] Left ventricular involvement may occur early in the course of the disease with some frequency. [4,41]

Since publication of the Task Force Criteria cardiovascular evaluation of the relatives of ARVC/D index cases and, more recently, genotype-phenotype association studies have highlighted the shortcomings of the criteria in the diagnosis of familial disease.[7] Modifications of the original criteria have been proposed to facilitate clinical diagnosis in first-degree relatives who often have incomplete penetrance of the disease.[42] According to these recommendations, in the context of proven ARVC/D in a first degree relative, the diagnosis of familial ARVC/D is based on the documentation of one of the following in a family member:

1. T wave inversion in right precordial leads, V_1, V_2 and V_3 in individuals over the age of 14 years.

2. Late potentials by SAECG.

3. Ventricular tachycardia of LBBB morphology on ECG, Holter monitor, or during exercise testing or >200 PVCs in 24 hours.

4. Either mild global dilatation and/or reduction in RV ejection fraction with normal LV or mild segmental dilatation of the RV or regional RV hypokinesis.

Revision of the diagnostic criteria is important to provide guidance on the role of emerging diagnostic modalities and to recognize advances in the genetics of ARVC/D. The criteria have been modified to incorporate new knowledge and technology to improve diagnostic sensitivity, but with the important requisite of maintaining diagnostic specificity, and include quantitative parameters for Task Force Criteria particularly for the imaging studies. (Table 1) The approach of classifying structural, histological, electrocardiographic, arrhythmic, and genetic features of the disease as major and minor criteria has been maintained.

Methods

A limitation of the previous Task Force Criteria was the reliance on subjective criteria for assessing ventricular structure and function and for evaluation of myocardial histology. In this modification of the Task Force Criteria, quantitative criteria are proposed and abnormalities are defined based on comparison with normal subject data. (Table 1) The data from 108 probands with newly diagnosed ARVC/D, age 12 years or older, who were enrolled in the National Institutes of Health supported Multidisciplinary Study of Right

Ventricular Dysplasia,[43] were compared with that of normal subjects. (See appendix) The criteria were selected on the basis of analysis of sensitivity and specificity from ROC curves. For analysis of each test (i.e. echocardiogram, MRI etc.) proband data was excluded if that test was crucial for the diagnosis of the individual patient. This was done to eliminate bias in estimating the sensitivity and specificity of that particular test. In general, when determining the sensitivity and specificity of a new screening test it is recommended that none of the screening test elements are used in making the primary diagnosis; this principle also holds when establishing diagnostic criteria.

Results

There were 44 proband MRIs compared with 462 normals; 69 proband echocardiograms compared to 450 normals, 69 proband SAECGS compared with 103 normals, and 68 proband Holters compared with 398 normals The minor criteria for echocardiography were selected where specificity and sensitivity are equal (sensitivity equals specificity). (Table 2) The major criteria were selected as the value that yielded 95% specificity. Sensitivity and specificity for the MRI criteria were made independently for each sex and considering both RVEDV/BSA (size) and RVEF (function) simultaneously using the OR logistical function. If either RV size or function are positive in conjunction with RV wall motion abnormality, then the subject would be classified as having a major criteria for the MRI. The sensitivity of RV size alone or function alone ranged from 41 to 50% for major criteria and 31 to 41% for minor criteria with specificity of 96 to 100%. Using the OR logistical function improved the sensitivity of the MRI to 79 – 89% for major criteria and 68 – 78% for minor criteria.

The original task force criteria list late potentials as a minor criteria. It has become common practice to state that the SAECG is positive if two of the three parameters, filtered QRS duration (f QRS), root-mean square voltage of the terminal 40 msecs (RMS 40) of the QRS, or duration of the terminal QRS signal less than $40\mu V$ (LAS) are abnormal, although this is not based on evidence. Analysis of each of the single parameters of the SAECG with late potentials using a 40 – 250Hz filter had a sensitivity ranging from 58 to 60% with a specificity of 94 to 96%. Two of three parameters had a sensitivity of 66% and specificity of 95% adding little advantage with regard to sensitivity and specificity. Using any one of the 3 SAECG parameters has a sensitivity of 74% and specificity of 92%.

A definitive diagnosis of ARVC/D is based on histological demonstration of transmural fibrous and/or fibrofatty replacement of RV myocardium at either biopsy, (Figure 2) necropsy or surgery.[5,44] In most patients, however, assessment of transmural myocardium is not possible. In addition, diagnosis based on right ventricular endomyocardial biopsy specimens is limited because the segmental nature of the disease causes false negatives. Use of electroanatomic voltage mapping to identify pathological areas for biopsy sampling may improve the yield.[45] RV free wall biopsy has a slight risk of perforation while the more accessible interventricular septum rarely exhibits histological changes. Nevertheless, endomyocardial biopsy may identify other conditions (e.g. myocarditis, sarcoidosis, endomyocardial fibrosis), while the recognition of myocyte loss with fibrous and/or fibrofatty replacement can be a valuable diagnostic feature.[46]

The identification of disease causing genes has led to the recognition of a broader spectrum of disease expression within families, including individuals who have predominantly LV disease, manifest clinically by inferolateral T wave changes, ventricular ectopy or VT with RBBB morphology and epicardial and/or mid-myocardial late enhancement by MRI. [4,7,38,39,41] The importance of familial disease highlights a role for mutation analysis of probands with cascade screening of relatives that offers an alternative strategy to serial non-invasive cardiovascular evaluation of families. A positive diagnosis in a family member

changes the probability of disease in an individual suspected of the disease to 1:2 from 1:1000 – 1:5000. This is reflected in the criteria for confirmed disease in a first degree relative being a major criterion for diagnosis.[42]

Discussion

The diagnosis of ARVC/D relies on the demonstration of structural, functional, and electrophysiological abnormalities that are caused by or reflect the underlying histological changes. Technical advances in MRI and 2D echo have improved the capability to image the RV with reproducible measurements of volume and systolic function which permits classification of severity and differentiation from normality.[47] (Table 2). Previous diagnostic reliance on subjective assessment of RV wall thinning and wall motion abnormalities and fatty infiltration of the myocardium by MRI has proven problematic.[48,49] Recognition of significant fatty involvement without concomitant fibrosis of the RV in normal individuals renders this unique MRI capability of limited value. Late enhancement on MRI permits myocardial tissue characterization in the left ventricle. It can be difficult to be certain of late enhancement for characterization of RV myocardium due to the thin wall of the RV and possible confusion with fat.[50]

There also have been recent developments to quantitate the extent of right ventricular wall motion abnormalities by angiography using computer based analysis as well as to determine right ventricular volumes[51,52] In addition, there is commercial software available to determine RV volumes and ejection fraction.[53] The right ventricular angiogram obtained in multiple views is considered to be a reliable imaging test to assess wall motion abnormalities but requires considerable experience. Standardized protocols for performance of these diagnostic studies (ECG, SAECG, echocardiogram, right ventricular angiogram, and MRI) are available on www.arvd.org.

Repolarization abnormalities are early and sensitive markers of disease expression in ARVC/D. T wave inversion in V_1, V_2 and V_3 and beyond in individuals over the age of 14 who are otherwise healthy is observed in only 4% of healthy women and 1% of men in this age group. Therefore it is reasonably specific in this population and considered a major diagnostic abnormality in ARVC/D.[54] Depolarization delay in right precordial leads is also common in ARVC/D.[33,34] Evaluation of the duration of terminal QRS activation (Figure 3) incorporates slurring of the S wave, as well as R prime, into a single measure of terminal activation duration (TAD).[34] Depolarization abnormalities cannot be evaluated in the presence of typical complete RBBB with terminal delay in leads I and V6. However, T wave inversion in V_1, V_2, V_3 and V_4 is uncommon in patients with RBBB who do not have ARVC/D and are frequently seen in those who do have the disease. Conventional definitions are used for ventricular arrhythmias. An abnormal signal averaged electrocardiogram is based on time domain criteria with cutoffs generated from ROC curves.[55,56] The sensitivity and specificity of any one of the time domain criteria is similar to that of any 2 or 3 of these criteria; therefore any one of the criteria are proposed as a criteria for this modality. The presence of LBBB VT with an inferior axis (R wave positive in II and III, and negative in AVL) is typical of focal RVOT tachycardia.[57] Similar features may be seen in patients with ARVC/D, but usually coexist with anterior T wave inversion and ventricular arrhythmias of varying morphologies. The presence of ventricular ectopy increases with age but >200 ventricular premature beats in 24 hours in an adult below age 50 suggests underlying myocardial disease.[58]

The revised criteria were applied post hoc to 108 newly diagnosed probands enrolled in the Multidisciplinary Study of Right Ventricular Dysplasia, a study supported by the National Institute of Health. They had been carefully evaluated including assessment of diagnostic

tests by expert core laboratories.[43] Of the 73 probands with final classification as affected, 71 remain affected and 2 were reclassified as borderline. The change from affected to borderline in the 2 was due to the echocardiogram fulfilling only minor criteria in one and only mild hypokinesis in the angiogram of the other. Of the 28 probands classified as borderline (met some but not all of the original task force criteria, i.e. one major and one minor or three minor), five remain borderline and 16 were reclassified by the new criteria as affected. Seven became unaffected (did not meet the proposed modified task force criteria).

Of seven probands previously classified as unaffected, 4 remained unaffected, 1 became affected and 2 became borderline. Therefore, the effect of the revised criteria is to increase the sensitivity of the classification, primarily in probands previously classified as borderline.

Nine of 28 probands classified as borderline by original criteria, had gene variants consistent with ARVC/D. The sensitivity of the revised criteria is not perfect as exemplified by the observation that if the genetic criteria are ignored, the proposed criteria classified 2 as unaffected and 3 remained borderline, and 4 became affected. Including the proposed genetic criteria resulted in all 9 being classified as affected.

The modified task force criteria have been applied to two different sets of phenotyped-genotyped cohorts, (Protonotarios, N et al, and Cox, MDGJ, et al, unpublished data). In both studies there was an increase in sensitivity without loss of specificity. Additionally, the ECG criteria have been applied to known ARVC/D cohorts and have shown an increase in diagnostic value.[59]

The diagnosis of ARVC/D based on modification of the original Task Force criteria is a working framework to improve the diagnosis and management of this condition. Awareness is growing that ARVC/D is the well recognized form of a broad disease spectrum that includes left dominant and biventricular subtypes. Lack of specific diagnostic guidelines contributes to under recognition of non classic disease. Future revisions of the Task Force Criteria may fill this gap by incorporating features such as ventricular tachycardia of right bundle branch morphology, subepicardial or midmyocardial late enhancement on magnetic resonance imaging, and global or regional left ventricular dysfunction in patients presenting with arrhythmia rather than heart failure. With the identification of disease causing genes, there is the potential for diagnostic mutation analysis and improved pedigree evaluation with better understanding of the natural history, pathogenesis and development of targeted therapies. Individuals who carry newly discovered disease causing genes, but who have incomplete or no disease expression will be recognized; their natural history and appropriate management remains to be determined.

Limitations

The reference values for the normals have been determined from select populations from centers with expertise in the diagnostic test (see appendix) since data on a large cohort of normals studied by all the modalities was not available from any one center. Therefore the reference values may not apply to all ethnic populations or those younger than age 12.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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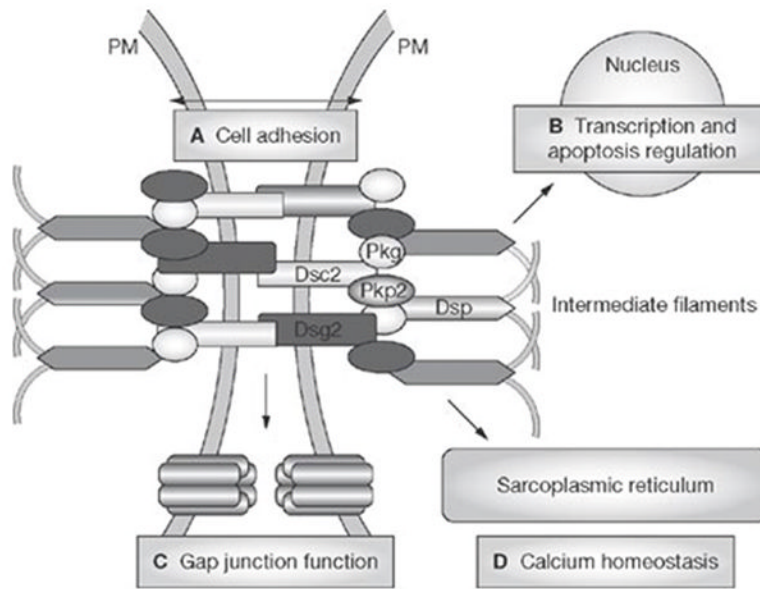
Figure 1.
The cardiac desmosome and proposed roles of the desmosome in (A) supporting structural stability through cell-cell adhesion, (B) regulating transcription of genes involved in adipogenisis and apoptosis, and maintaining proper electrical conductivity through regulation of (C) gap junctions and (D) calcium homeostasis. Abbreviations: Dsc2, desmocollin-2; Dsg2, desmoglein-2; Dsp, desmoplakin; Pkg, plakoglobin; Pkp2, plakophilin-2; PM, plasma membrane. Used with permission Awad MM, et al[11]
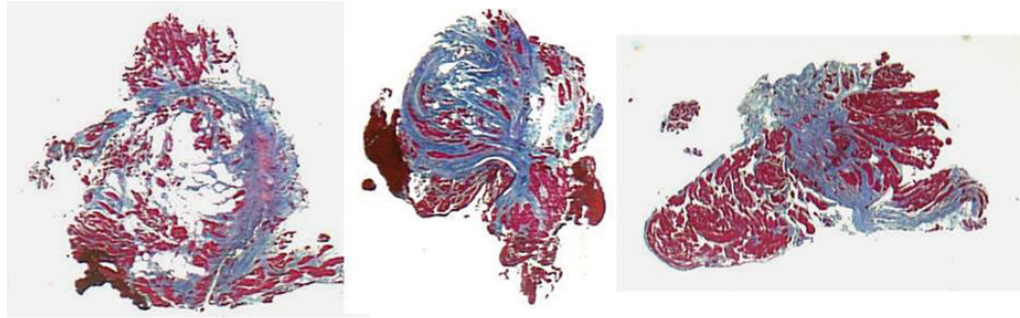
Figure 2.
Endomyocardial biopsy findings in a proband affected by a diffuse form of ARVC/D. All three biopsy samples are from different regions of the RV free wall. There is extensive fibro-fatty tissue replacement with myocardial atrophy that is a major criterion, i.e. residual myocytes <60% by morphometric analysis, or < 50% if estimated. (Contributed by C. Basso, Padua, Italy)
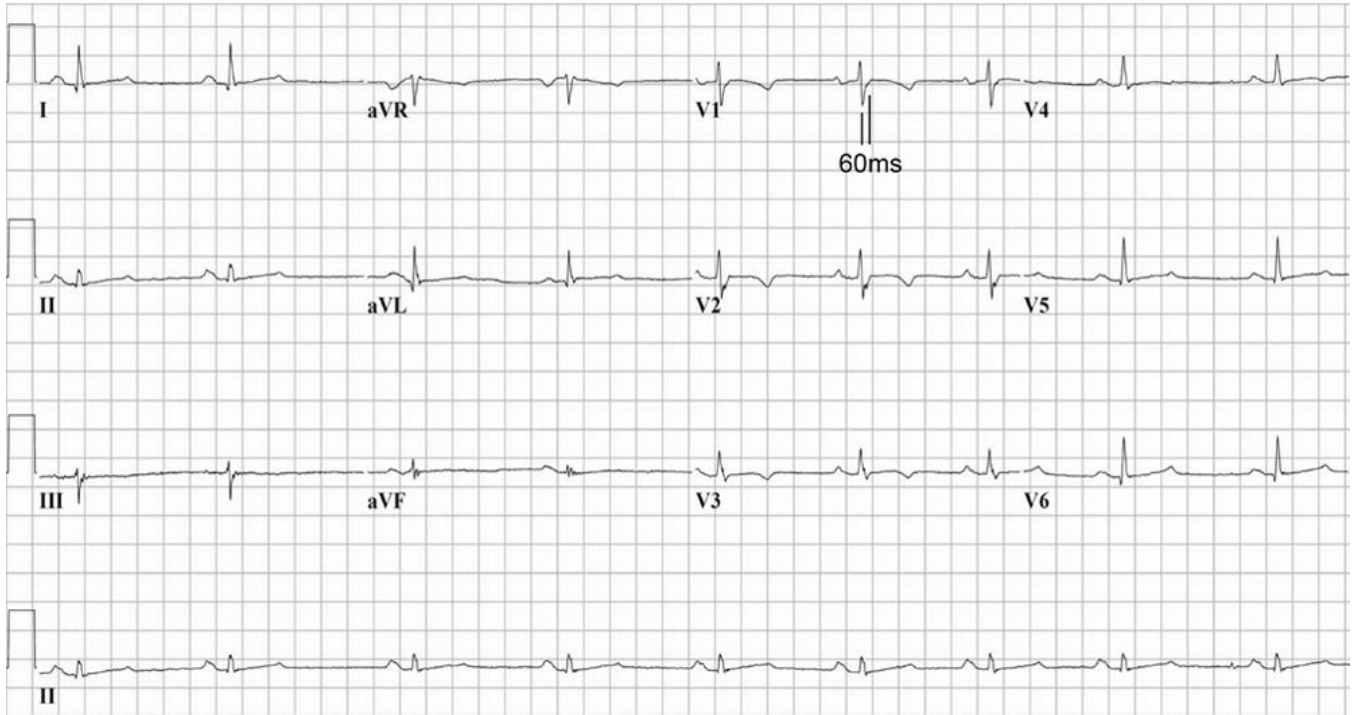
Figure 3.
ECG from proband with T wave inversion in $V_1 - V_4$ and prolongation of the terminal activation duration ≥ 55 msecs measured from the nadir of the S wave to the end of the QRS complex in V_1. (Contributed by MGPJ Cox, Utrecht, The Netherlands)

Table 1

ORIGINAL TASK FORCE CRITERIA	REVISED TASK FORCE CRITERIA	
I. Global and/or Regional Dysfunction and Structural Alterations	**I. Global and/or Regional Dysfunction and Structural Alterations** *	
• **Major**	• **Major (by 2D echo)**	
Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) LV impairment.	Regional RV akinesia, dyskinesia or aneurysm.	
	And one of the following (end diastole):	
	Parasternal long axis view RVOT (PLAX)	≥ 32 mm
	Corrected for body size (PLAX/BSA)	≥ 19 mm/m^2
Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging).	Parasternal short axis view RVOT (PSAX)	≥ 36 mm
	Corrected for body size(PSAX/BSA)	≥ 21 mm/m^2
	or	
Severe segmental dilatation of the right ventricle.	Fractional area change (FAC)	≤ 33%
	• **Major (by MRI)**	
	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction	
	And one of the following:	
	Right ventricular end diastolic volume (RVEDV/BSA)	≥110 ml/m^2 male
		≥100 ml/m^2 female
	OR	
	Right ventricular ejection fraction (RVEF)	≤40%
	• **Major (by RV angiography)**	
	Regional RV akinesia, dyskinesia or aneurysm	
	• **Minor (by 2D echo)**	
• **Minor**	Regional RV akinesia or dyskinesia	
Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle.	**And one of the following (end diastole):**	
	Parasternal long axis view RVOT (PLAX)	≥ 29 - < 32 mm
Mild segmental dilatation of the right ventricle.	Corrected for body size (PLAX/BSA)	≥ 16 - < 19 mm/m^2[21]

ORIGINAL TASK FORCE CRITERIA | **REVISED TASK FORCE CRITERIA**

Regional right ventricular hypokinesia.

Parasternal short axis view RVOT (PSAX) ≥ 32 - < 36 mm

Corrected for body size (PSAX/BSA) ≥ 18 - < 21 mm/m²

or

Fractional area change (FAC) > 33% - ≤ 40%

- **Minor (by MRI)**

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction

And one of the following:

Right ventricular end diastolic volume/BSA ≥100 - < 110 ml/m² male

≥90 - < 100 ml/m² female

OR

Right ventricular ejection fraction (RVEF) > 40% - ≤ 45%

II. Tissue Characterization of Wall

II. Tissue Characterization of Wall

- **Major**

- **Major**

Fibrofatty replacement of myocardium on endomyocardial biopsy.

Residual myocytes <60% by morphometric analysis, (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in at least 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

- **Minor**

Residual myocytes 60 – 75% by morphometric analysis, (or 50 to 65% if estimated), with fibrous replacement of the RV free wall myocardium in at least 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

III. Repolarization Abnormalities

III. Repolarization Abnormalities

- **Minor**

- **Major**

Inverted T waves in right precordial leads (V₂ and V₃) (people aged >12 years, in absence of right bundle branch block).

Inverted T waves in right precordial leads (V₁, V₂ and V₃) or beyond in individuals > 14 years of age (in the absence of complete right bundle branch block QRS ≥ 120 msecs).

- **Minor**

Inverted T waves in leads V₁ and V₂ in individuals > 14 years of age (in the absence of complete right bundle branch block), or in V₄, V₅, or V₆.

Inverted T waves in leads V₁, V₂, V₃ and V₄ in individuals > 14 years of age in the presence of complete right bundle branch block.

IV. Depolarization/Conduction Abnormalities

IV. Depolarization/Conduction Abnormalities

- **Major**

- **Major**

ORIGINAL TASK FORCE CRITERIA	REVISED TASK FORCE CRITERIA
Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads ($V_1 – V_3$). • **Minor**	Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3) • **Minor**
Late potentials (signal-averaged ECG).	Late potentials by signal averaged ECG in at least one of three parameters in the absence of a QRS duration of ≥110 msecs on the standard ECG. Filtered QRS duration (fQRS) — ≥114 msecs Duration of terminal QRS < 40 μV (LAS) — ≥38 msecs RMS voltage of terminal 40 msecs — ≥20 μV Terminal activation duration of QRS ≥ 55ms 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 complete right bundle branch block.
V. Arrhythmias • **Minor**	**V. Arrhythmias** • **Major**
Left bundle branch block type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise testing).	Non-sustained or sustained VT of left bundle branch morphology with superior axis (negative or indeterminate QRS in II, III, AVF and positive in AVL) • **Minor**
	Non sustained or sustained VT of right ventricular outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III, AVF and negative in AVL) or of unknown axis.
Frequent ventricular extrasystoles (>1000/24 hours) (Holter).	Greater than 500 ventricular extrasystoles/24 hours by Holter
VI. Family History • **Major**	**VI. Family History** • **Major**
Familial disease confirmed at necropsy or surgery.	ARVC/D 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 with ARVC/D in the patient under evaluation.
• **Minor**	• **Minor**
Family history of premature sudden death (<35 years) due to suspected right ventricular dysplasia.	History of ARVC/D in a first degree relative in whom it is not possible or practical to determine if the family member meets current task force criteria.
Familial history (clinical diagnosis based on present criteria).	Premature sudden death (<35 years) due to suspected ARVC/D in a first degree relative.
	ARVC/D confirmed pathologically or by current Task Force Criteria in second degree relative.

*
Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non ARVC/D control population and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

Diagnostic terminology for original criteria

This diagnosis is fulfilled by the presence of two major, or one major plus two minor criteria or four minor criteria from different groups
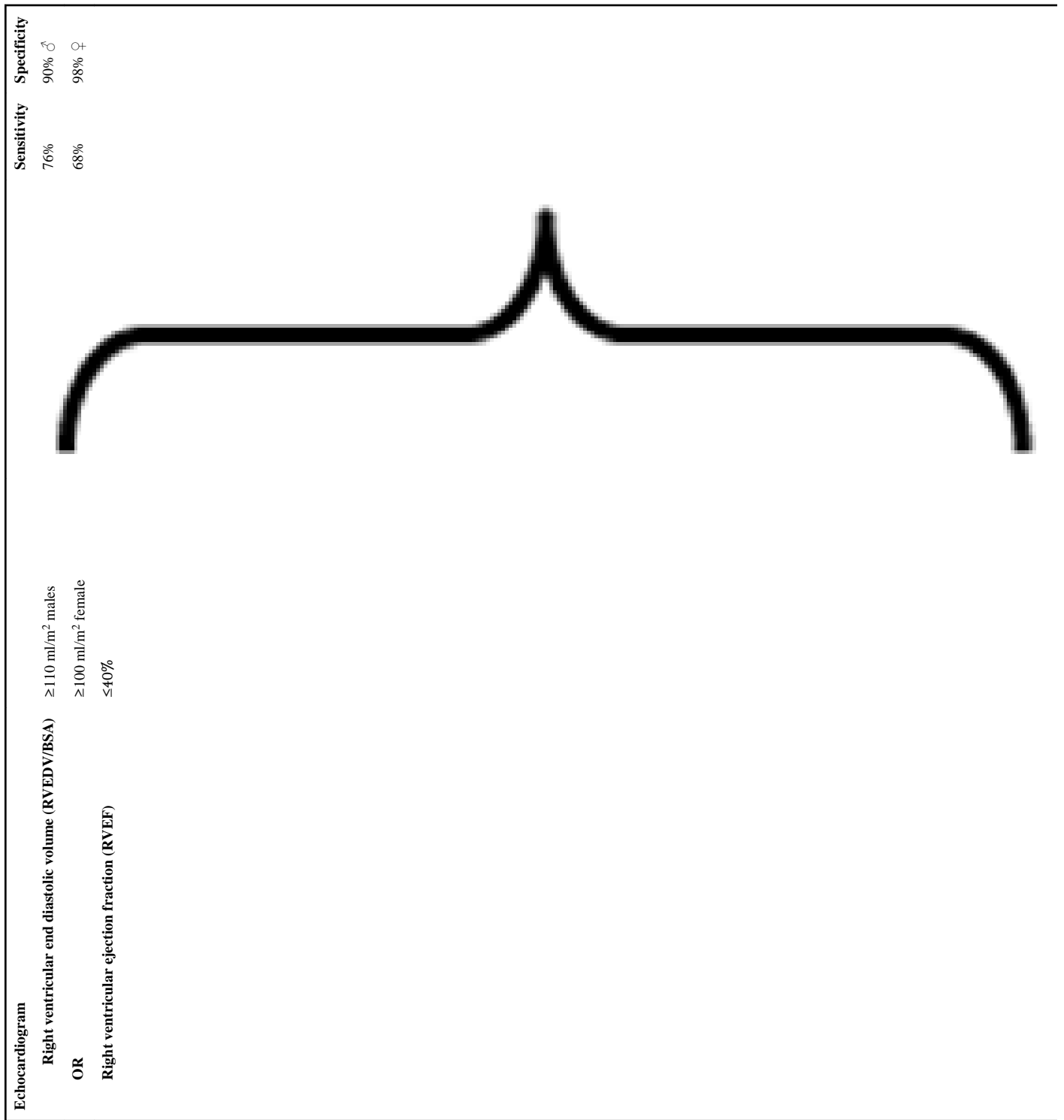
Diagnostic terminology for revised criteria

- Definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories

- Borderline: 1 major and 1 minor or 3 minor criteria from different categories

- Possible: 1 major or 2 minor criteria from different categories

Table 2

Sensitivity and specificity of proposed right ventricular imaging criteria[*]

Echocardiogram		Sensitivity	Specificity
MAJOR			
Parasternal long axis view RVOT (Diastole) (**PLAX**)	≥ 32 mm	75%	95%
Corrected for body size (PLAX/BSA)	≥ 19 mm/m^2		
Parasternal short axis view RVOT (Diastole) ((**PSAX**)	≥ 36 mm	62%	95%
Corrected for body size (PSAX/BSA)	≥ 21 mm/m^2		
Fractional area change (FAC)	≤ 33%	55%	95%
MINOR			
Parasternal long axis view RVOT (Diastole) (**PLAX**)	≥ 29 mm	87%	87%
Corrected for body size (PLAX/BSA)	≥ 16 – ≤ 18 mm/m^{2i}		
Parasternal short axis view RVOT (Diastole) ((**PSAX**)	≥ 32 mm	80%	80%
Corrected for body size (PSAX/BSA)	≥ 18 – ≤ 20 mm/m^2		
Fractional area change (FAC)	≤40%	76%	76%
Magnetic resonance imaging	**Either size or function or both** [**]		
MAJOR			

Echocardiogram		Sensitivity	Specificity
Right ventricular end diastolic volume (RVEDV/BSA)	≥ 110 ml/m^2 males	76%	90% ♂
OR	≥ 100 ml/m^2 female	68%	98% ♀
Right ventricular ejection fraction (RVEF)	$\leq 40\%$		

Echocardiogram		Sensitivity	Specificity
MINOR			
Right ventricular end diastolic volume (RVEDV/BSA)	≥ 100 ml/m^2 males	79%	85% ♂
OR	≥ 90 ml/m^2 female	89%	97% ♀
Right ventricular ejection fraction (RVEF)	$\leq 45\%$		

*
All the major and minor criteria listed in this table are in addition to the requirement that regional wall motion abnormalities must also be present

**
The sensitivity and specificity for males and females are the same as listed if, in addition to the stated wall motion criteria, there is either abnormal RV size or function or both.

PLAX Parasternal long axis view, PSAX Parasternal short axis view, BSA Body surface area, FAC Fractional area change, RVEF Right ventricular ejection fraction, RVEDV Right ventricular end diastolic volume