

## Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

### Proposed Modification of the Task Force Criteria

Frank I. Marcus, MD, Chair; William J. McKenna, MD, DSc, Co-Chair; Duane Sherrill, PhD; Cristina Basso, MD, PhD; Barbara Bauce, MD; David A. Bluemke, MD, PhD; Hugh Calkins, MD; Domenico Corrado, MD, PhD; Moniek G.P.J. Cox, MD; James P. Daubert, MD; Guy Fontaine, MD, PhD; Kathleen Gear, RN; Richard Hauer, MD; Andrea Nava, MD; Michael H. Picard, MD; Nikos Protonotarios, MD; Jeffrey E. Saffitz, MD, PhD; Danita M. Yoerger Sanborn, MD, MMSc; Jonathan S. Steinberg, MD; Harikrishna Tandri, MD; Gaetano Thiene, MD; Jeffrey A. Towbin, MD; Adalena Tsatsopoulou, MD; Thomas Wichter, MD; Wojciech Zareba, MD, PhD

**Background**—In 1994, an International Task Force proposed criteria for the clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) that facilitated recognition and interpretation of the frequently nonspecific clinical features of ARVC/D. This enabled confirmatory clinical diagnosis in index cases through exclusion of phenocopies and provided a standard on 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 categories 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 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 of 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 on the basis of comparison with normal subject data.

**Conclusions**—The present modifications of the Task Force Criteria represent a working framework to improve the diagnosis and management of this condition.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00024505.

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**Key Words:** arrhythmias, cardiac ■ arrhythmogenic right ventricular cardiomyopathy/dysplasia ■ death, sudden, cardiac ■ diagnosis ■ echocardiography ■ electrocardiography ■ magnetic resonance imaging

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

(RV) myocardium.<sup>1</sup> In the early stage of the disease, structural changes may be absent or subtle and confined to a localized region of the RV, typically the inflow tract, outflow tract, or apex of the RV, the “triangle of dysplasia.”<sup>2</sup> Progression to more

From the University of Arizona (F.I.M., D.S., K.G.), Tucson, Ariz; The Heart Hospital, London, United Kingdom (W.J.M.); University of Padua Medical School, Padua, Italy (C.B., B.B., D.C., A.N., G.T.); National Institutes of Health, Clinical Center (D.A.B.), Bethesda, and Johns Hopkins Hospital (H.C., H.T.), Baltimore, Md; University Medical Center Utrecht, Utrecht, the Netherlands (M.G.P.J.C., R.H.); Strong Memorial Hospital (J.P.D.) and University of Rochester Medical Center (W.Z.), Rochester, NY; St. Luke’s-Roosevelt Hospital Center (J.S.S.), New York, NY; Hopital La Salpetriere (G.F.), Paris, France; Massachusetts General Hospital (M.H.P., D.M.Y.S.) and Beth Israel Deaconess Medical Center (J.E.S.), Boston, Mass; Yannis Protonotarios Medical Centre, Hora Naxos, Greece (N.P., A.T.); Cincinnati Children’s Hospital, Cincinnati, Ohio (J.A.T.); and Marienhospital Osnabrück, Osnabrück, Germany (T.W.).

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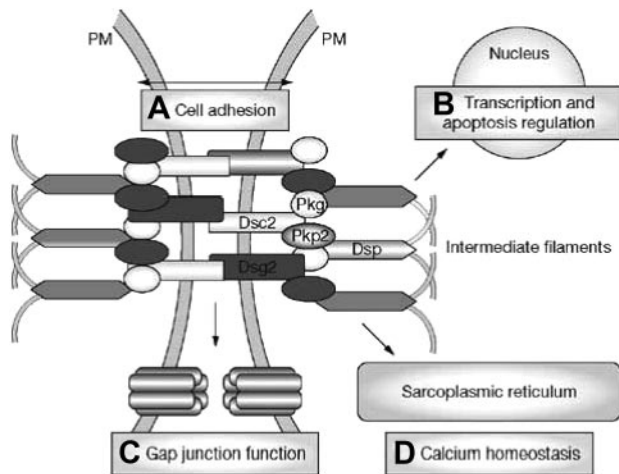
Correspondence to Dr Frank I. Marcus, Sarver Heart Center, 1501 N Campbell, Rm 5153, Box 245037, Tucson, AZ. E-mail [fm Marcus@u.arizona.edu](mailto:fm Marcus@u.arizona.edu)

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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 adipogenesis and apoptosis, and maintaining proper electrical conductivity through regulation of (C) gap junctions and (D) calcium homeostasis. Dsc2 indicates desmocollin-2; Dsg2, desmoglein-2; Dsp, desmoplakin; Pkg, plakoglobin; Pkp2, plakophilin-2; and PM, plasma membrane. Reprinted by permission from Macmillan Publishers Ltd: *Nat Clin Pract Cardiovasc Med*<sup>11</sup>, © 2008.

diffuse RV disease and left ventricular (LV) involvement, typically affecting the posterior lateral wall, is common.<sup>3</sup> Predominant LV disease is also recognized.<sup>4</sup> Postmortem diagnosis may require extensive sampling and transillumination.<sup>5</sup> 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.<sup>6</sup> 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, whereas ventricular arrhythmias may or may not be present. The ultimate phenotype may resemble dilated cardiomyopathy. Clinical manifestations vary with age and stage of disease.<sup>7</sup>

ARVC/D is considered to be familial with autosomal dominant inheritance, although there are recessive forms (eg, Naxos disease, Carvajal syndrome) that are associated with a cutaneous phenotype.<sup>8,9</sup> Genetic variations have been found in the desmosomes that are responsible for cell-to-cell binding<sup>10,11</sup> (Figure 1). Seven genes have been identified that are associated with ARVC/D: plakoglobin (*JUP*),<sup>12</sup> desmoplakin (*DSP*),<sup>13</sup> plakophilin-2 (*PKP2*),<sup>14</sup> desmoglein-2 (*DSG2*),<sup>15,16</sup> desmocollin-2 (*DSC2*),<sup>17,18</sup> transforming growth factor beta-3 (*TGFβ3*),<sup>19</sup> and *TMEM43*.<sup>20</sup> Mutations in *RYR2* coding the ryanodine receptor have been reported in ARVC/D in patients with an arrhythmic presentation (stress-induced bidirectional ventricular tachycardia) in the absence of significant electrocardiographic or structural abnormalities. At present, catecholaminergic polymorphic ventricular tachycardia is considered a disorder distinct from ARVC/D.<sup>11</sup> Preliminary observations suggest that the mechanical defect of the desmosomes alters function of the gap junction. Electrocardiographic (ECG) changes and arrhythmias may develop before histological evidence of myocyte loss or clinical evidence of RV

dysfunction.<sup>21,22</sup> It has been proposed that similar clinical phenotypes occur that are based on disruption of a “final common pathway” by mutations in genes encoding proteins in the defined desmosomal pathway.<sup>23</sup> Recognition of the genetic basis of ARVC/D facilitates examination of the pathogenesis in relation to arrhythmogenesis and disease progression.<sup>24</sup>

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.<sup>25–27</sup> 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, ECG, arrhythmic, and familial features of the disease<sup>28</sup> (Table 1). Abnormalities were subdivided into major and minor categories according to the specificity of their association with ARVC/D. ECG abnormalities such as complete and incomplete right bundle-branch block were excluded because of their lack of specificity. Right precordial T-wave inversion, though well recognized in ARVC/D, was considered a minor criterion because of its presence in other conditions, including anterior ischemia and RV hypertrophy. Arrhythmias of RV origin, another cardinal feature of ARVC/D, was designated a minor criterion because of its occurrence in other diseases, particularly idiopathic RV outflow tract tachycardia. Furthermore, the 1994 criteria focused on RV disease manifestations and stipulated the absence of or only mild LV 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 or severe end of the disease spectrum. Consequently, the 1994 criteria were highly specific, but they lacked sensitivity for early and familial disease.<sup>29–31</sup>

Over the past 15 years, additional ECG markers have been proposed.<sup>32–34</sup> In addition, the genetic basis of the disease has been recognized, with the potential for mutation analysis. Experience with quantification of imaging criteria of ARVC/D has increased, and newer imaging techniques have been introduced, such as contrast-enhanced echocardiography, 3-dimensional echocardiography, cardiovascular magnetic resonance with late enhancement, and electroanatomic voltage mapping.<sup>35–40</sup>

Since publication of the 1994 Task Force guidelines, cardiovascular evaluation of the relatives of ARVC/D index cases and, more recently, genotype–phenotype association studies have also highlighted the shortcomings of the criteria. It is now recognized that LV involvement may occur early in the course of the disease with some frequency.<sup>4,41</sup> The criteria also lack sensitivity for the diagnosis of familial disease. Modifications of the original criteria have been proposed to facilitate clinical diagnosis in first-degree relatives who often have incomplete expression of the disease.<sup>42</sup>

**Table 1. Comparison of Original and Revised Task Force Criteria**

Original Task Force Criteria	Revised Task Force Criteria
<b>I. Global or regional dysfunction and structural alterations*</b>	
Major	<ul style="list-style-type: none"> <li>● Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment</li> <li>● Localized RV aneurysms (akinetic or dyskinctic areas with diastolic bulging)</li> <li>● Severe segmental dilatation of the RV</li> </ul>
Minor	<p><b>By 2D echo:</b></p> <ul style="list-style-type: none"> <li>● Regional RV akinesia, dyskinesia, or aneurysm</li> <li>● <i>and</i> 1 of the following (end diastole): <ul style="list-style-type: none"> <li>— PLAX RVOT <math>\geq 32</math> mm (corrected for body size [PLAX/BSA] <math>\geq 19</math> mm/m<sup>2</sup>)</li> <li>— PSAX RVOT <math>\geq 36</math> mm (corrected for body size [PSAX/BSA] <math>\geq 21</math> mm/m<sup>2</sup>)</li> <li>— <i>or</i> fractional area change <math>\leq 33\%</math></li> </ul> </li> </ul> <p><b>By MRI:</b></p> <ul style="list-style-type: none"> <li>● Regional RV akinesia or dyskinesia or dyssynchronous RV contraction</li> <li>● <i>and</i> 1 of the following: <ul style="list-style-type: none"> <li>— Ratio of RV end-diastolic volume to BSA <math>\geq 110</math> mL/m<sup>2</sup> (male) or <math>\geq 100</math> mL/m<sup>2</sup> (female)</li> <li>— <i>or</i> RV ejection fraction <math>\leq 40\%</math></li> </ul> </li> </ul> <p><b>By RV angiography:</b></p> <ul style="list-style-type: none"> <li>● Regional RV akinesia, dyskinesia, or aneurysm</li> </ul>
Major	<ul style="list-style-type: none"> <li>● Mild global RV dilatation and/or ejection fraction reduction with normal LV</li> <li>● Mild segmental dilatation of the RV</li> <li>● Regional RV hypokinesia</li> </ul>
Minor	<p><b>By 2D echo:</b></p> <ul style="list-style-type: none"> <li>● Regional RV akinesia or dyskinesia</li> <li>● <i>and</i> 1 of the following (end diastole): <ul style="list-style-type: none"> <li>— PLAX RVOT <math>\geq 29</math> to <math>&lt; 32</math> mm (corrected for body size [PLAX/BSA] <math>\geq 16</math> to <math>&lt; 19</math> mm/m<sup>2</sup>)</li> <li>— PSAX RVOT <math>\geq 32</math> to <math>&lt; 36</math> mm (corrected for body size [PSAX/BSA] <math>\geq 18</math> to <math>&lt; 21</math> mm/m<sup>2</sup>)</li> <li>— <i>or</i> fractional area change <math>&gt; 33\%</math> to <math>\leq 40\%</math></li> </ul> </li> </ul> <p><b>By MRI:</b></p> <ul style="list-style-type: none"> <li>● Regional RV akinesia or dyskinesia or dyssynchronous RV contraction</li> <li>● <i>and</i> 1 of the following: <ul style="list-style-type: none"> <li>— Ratio of RV end-diastolic volume to BSA <math>\geq 100</math> to <math>&lt; 110</math> mL/m<sup>2</sup> (male) or <math>\geq 90</math> to <math>&lt; 100</math> mL/m<sup>2</sup> (female)</li> <li>— <i>or</i> RV ejection fraction <math>&gt; 40\%</math> to <math>\leq 45\%</math></li> </ul> </li> </ul>
<b>II. Tissue characterization of wall</b>	
Major	<ul style="list-style-type: none"> <li>● Fibrofatty replacement of myocardium on endomyocardial biopsy</li> </ul>
Minor	<ul style="list-style-type: none"> <li>● Residual myocytes <math>&lt; 60\%</math> by morphometric analysis (or <math>&lt; 50\%</math> if estimated), with fibrous replacement of the RV free wall myocardium in <math>\geq 1</math> sample, with or without fatty replacement of tissue on endomyocardial biopsy</li> </ul>
Major	<ul style="list-style-type: none"> <li>● Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in <math>\geq 1</math> sample, with or without fatty replacement of tissue on endomyocardial biopsy</li> </ul>
<b>III. Repolarization abnormalities</b>	
Major	<ul style="list-style-type: none"> <li>● Inverted T waves in right precordial leads (V<sub>1</sub>, V<sub>2</sub>, and V<sub>3</sub>) or beyond in individuals <math>&gt; 14</math> years of age (in the absence of complete right bundle-branch block QRS <math>\geq 120</math> ms)</li> </ul>
Minor	<ul style="list-style-type: none"> <li>● Inverted T waves in right precordial leads (V<sub>2</sub> and V<sub>3</sub>) (people age <math>&gt; 12</math> years, in absence of right bundle-branch block)</li> <li>● Inverted T waves in leads V<sub>1</sub> and V<sub>2</sub> in individuals <math>&gt; 14</math> years of age (in the absence of complete right bundle-branch block) or in V<sub>4</sub>, V<sub>5</sub>, or V<sub>6</sub></li> <li>● Inverted T waves in leads V<sub>1</sub>, V<sub>2</sub>, V<sub>3</sub>, and V<sub>4</sub> in individuals <math>&gt; 14</math> years of age in the presence of complete right bundle-branch block</li> </ul>

*(Continued)*

Table 1. Continued

	Original Task Force Criteria	Revised Task Force Criteria
IV. Depolarization/conduction abnormalities		
Major	<ul style="list-style-type: none"> <li>Epsilon waves or localized prolongation (&gt;110 ms) of the QRS complex in right precordial leads (V<sub>1</sub> to V<sub>3</sub>)</li> </ul>	<ul style="list-style-type: none"> <li>Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V<sub>1</sub> to V<sub>3</sub>)</li> </ul>
Minor	<ul style="list-style-type: none"> <li>Late potentials (SAECG)</li> </ul>	<ul style="list-style-type: none"> <li>Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG</li> <li>Filtered QRS duration (fQRS) ≥114 ms</li> <li>Duration of terminal QRS &lt;40 μV (low-amplitude signal duration) ≥38 ms</li> <li>Root-mean-square voltage of terminal 40 ms ≤20 μV</li> <li>Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V<sub>1</sub>, V<sub>2</sub>, or V<sub>3</sub>, in the absence of complete right bundle-branch block</li> </ul>
V. Arrhythmias		
Major		<ul style="list-style-type: none"> <li>Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)</li> </ul>
Minor	<ul style="list-style-type: none"> <li>Left bundle-branch block–type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise)</li> <li>Frequent ventricular extrasystoles (&gt;1000 per 24 hours) (Holter)</li> </ul>	<ul style="list-style-type: none"> <li>Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis</li> <li>&gt;500 ventricular extrasystoles per 24 hours (Holter)</li> </ul>
VI. Family history		
Major	<ul style="list-style-type: none"> <li>Familial disease confirmed at necropsy or surgery</li> </ul>	<ul style="list-style-type: none"> <li>ARVC/D confirmed in a first-degree relative who meets current Task Force criteria</li> <li>ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative</li> <li>Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation</li> </ul>
Minor	<ul style="list-style-type: none"> <li>Family history of premature sudden death (&lt;35 years of age) due to suspected ARVC/D</li> <li>Familial history (clinical diagnosis based on present criteria)</li> </ul>	<ul style="list-style-type: none"> <li>History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria</li> <li>Premature sudden death (&lt;35 years of age) due to suspected ARVC/D in a first-degree relative</li> <li>ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative</li> </ul>

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 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.

\*Hypokinesia 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.

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<sub>1</sub>, V<sub>2</sub>, and V<sub>3</sub> in individuals over the age of 14 years.

- Late potentials by signal-averaged ECG (SAECG).
- Ventricular tachycardia of left bundle-branch block morphology on ECG, Holter monitor, or during exercise testing or >200 premature ventricular contractions in 24 hours.
- Either mild global dilatation or reduction in RV ejection fraction with normal LV or mild segmental dilatation of the RV or regional RV hypokinesia.

**Table 2. Sensitivity and Specificity of Proposed RV Imaging Criteria\***

	Value	Sensitivity, %	Specificity, %
<b>Echocardiogram</b>			
<b>Major</b>			
PLAX RVOT (diastole)	≥32 mm	75	95
Corrected for body size (PLAX/BSA)	≥19 mm/m <sup>2</sup>		
PSAX RVOT (diastole)	≥36 mm	62	95
Corrected for body size (PSAX/BSA)	≥21 mm/m <sup>2</sup>		
Fractional area change	≤33%	55	95
<b>Minor</b>			
PLAX RVOT (diastole)	≥29 mm	87	87
Corrected for body size (PLAX/BSA)	≥16 to ≤18 mm/m <sup>2</sup>		
PSAX RVOT (diastole)	≥32 mm	80	80
Corrected for body size (PSAX/BSA)	≥18 to ≤20 mm/m <sup>2</sup>		
Fractional area change	≤40%	76	76
<b>MRI†</b>			
<b>Major</b>			
Ratio of RV end-diastolic volume to BSA			
Males	≥110 mL/m <sup>2</sup>		
Females	≥100 mL/m <sup>2</sup>	76	90 ♂
or		68	98 ♀
RV ejection fraction	≤40%		
<b>Minor</b>			
Ratio of RV end-diastolic volume to BSA			
Males	≥100 mL/m <sup>2</sup>		
Females	≥90 mL/m <sup>2</sup>	79	85 ♂
or		89	97 ♀
RV ejection fraction	≤45%		

Abbreviations as in Table 1.

\*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.

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 they include quantitative parameters for Task Force criteria, particularly for the imaging studies (Table 1). The approach of classifying structural, histological, ECG, arrhythmic, and genetic features of the disease as major and minor criteria has been maintained.

**Methods**

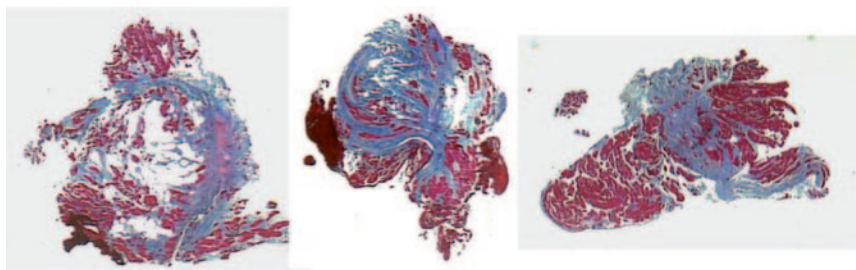
A limitation of the previous Task Force criteria was the reliance on subjective criteria for assessing ventricular structure and function and for evaluation of myocardial histology. In this modification of the Task Force criteria, quantitative criteria are proposed and abnormalities are defined on the basis of comparison with normal subject data (Table 1). The data from 108 probands with newly diagnosed ARVC/D, age ≥12 years, who were enrolled in the National Institutes of Health–supported Multidisciplinary Study of Right Ventricular Dysplasia,<sup>43</sup> were compared with those of normal subjects (online-only Data Supplement). The criteria were selected

on the basis of analysis of sensitivity and specificity from receiver operating characteristic curves. For analysis of each test (eg, echocardiogram, magnetic resonance imaging [MRI]), proband data were 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 be used in making the primary diagnosis; this principle also holds when establishing diagnostic criteria.

**Results**

There were 44 proband MRIs compared with 462 MRIs of normal subjects, 69 proband echocardiograms compared with 450 echocardiograms of normal subjects, 69 proband SAECGs compared with 103 SAECGs of normal subjects, and 68 proband Holters compared with 398 Holters of normal subjects. 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 with consideration of both the RV end-diastolic





**Figure 2.** Endomyocardial biopsy findings in a proband affected by a diffuse form of ARVC/D. All 3 biopsy samples are from different regions of the RV free wall. There is extensive fibrofatty tissue replacement with myocardial atrophy, which is a major criterion (ie, residual myocytes <60% by morphometric analysis or <50% if estimated). Contributed by C. Basso, Padua, Italy.

volume indexed to body surface area (size) and RV ejection fraction (function) simultaneously by using the *OR* logistical function. If either RV size or function was positive in conjunction with RV wall motion abnormality, then the subject would be classified as having a major criterion 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% to 89% for major criteria and 68% to 78% for minor criteria.

The original Task Force criteria list late potentials as a minor criterion. It has become common practice, though not based on evidence, to state that the SAECG is positive if 2 of the following 3 parameters are abnormal: filtered QRS duration (fQRS), root-mean square voltage of the terminal 40 ms of the QRS, or duration of the terminal QRS signal <40  $\mu$ V. Analysis of each of the single parameters of the SAECG with late potentials by using a 40- to 250-Hz 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 had a sensitivity of 74% and specificity of 92%.

A definitive diagnosis of ARVC/D is based on histological demonstration of transmural fibrofatty replacement of RV myocardium at biopsy (Figure 2), necropsy, or surgery.<sup>5,44</sup> In most patients, however, assessment of transmural myocardium is not possible. In addition, diagnosis based on RV 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.<sup>45</sup> RV free wall biopsy has a slight risk of perforation, but the more accessible interventricular septum rarely exhibits histological changes. Nevertheless, endomyocardial biopsy may identify other conditions (eg, myocarditis, sarcoidosis, endomyocardial fibrosis), and the recognition of myocyte loss with fibrous or fibrofatty replacement can be a valuable diagnostic feature.<sup>46</sup>

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 ventricular tachycardia with right bundle-branch block morphology and epicardial or midmyocardial late enhancement by MRI.<sup>4,7,38,39,41</sup> The importance of familial disease highlights a role for mutation

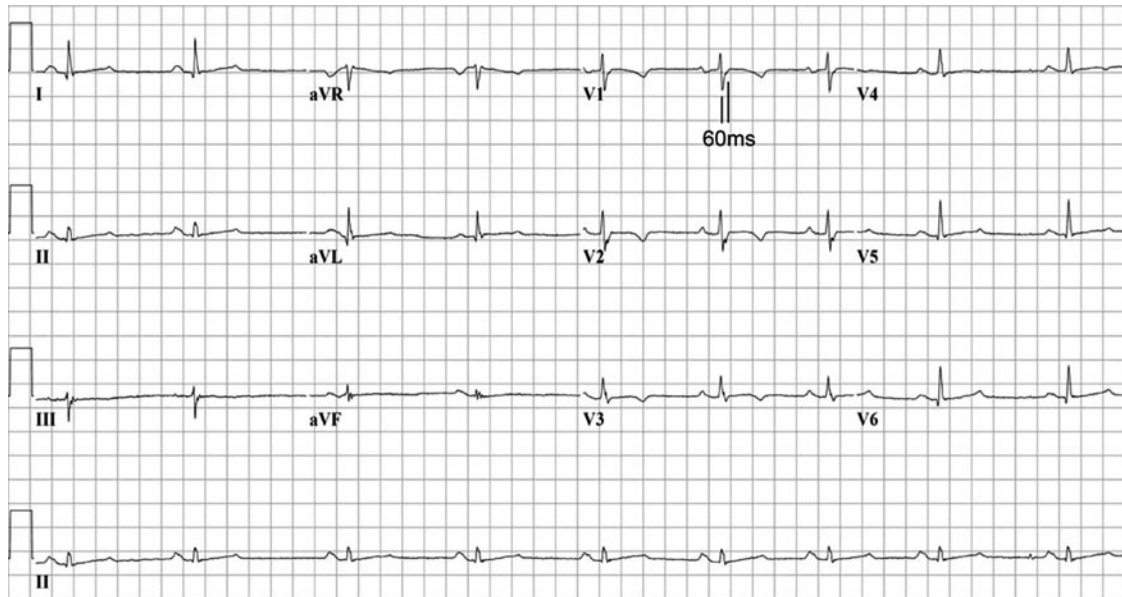
analysis of probands with cascade screening of relatives that offers an alternative strategy to serial noninvasive cardiovascular evaluation of families. A positive diagnosis in a family member changes the probability of disease in an individual suspected of the disease to 1:2 from 1:1000 to 1:5000. Thus, confirmed disease in a first degree relative is a major criterion for diagnosis.<sup>42</sup>

## 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 2-dimensional echocardiography 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<sup>47</sup> (Table 2). Previous diagnostic reliance on subjective assessment of RV wall thinning, wall motion abnormalities, and fatty infiltration of the myocardium by MRI has proven problematic.<sup>48,49</sup> 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 LV. It can be difficult to be certain of late enhancement for characterization of RV myocardium because of the thin wall of the RV and possible confusion with fat.<sup>50</sup>

There also have been recent developments to quantify the extent of RV wall motion abnormalities by angiography with computer-based analysis, as well as to determine RV volumes.<sup>51,52</sup> In addition, commercial software is available to determine RV volumes and ejection fraction.<sup>53</sup> The RV 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, RV angiogram, and MRI) are available on [www.arvd.org](http://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 >14 years of age who are otherwise healthy is observed in only 4% of healthy women and 1% of men. Therefore, it is reasonably specific in this population and considered a major diagnostic abnormality in ARVC/D.<sup>54</sup> Depolarization delay in right precordial leads is also common in ARVC/D.<sup>33,34</sup> Evaluation of the duration of terminal QRS activation (Figure 3) incorporates slurring of the S wave, as well as  $R'$ , into a single measure of terminal activation duration.<sup>34</sup> Depolarization abnormalities



**Figure 3.** ECG from proband with T-wave inversion in  $V_1$  through  $V_4$  and prolongation of the terminal activation duration  $\geq 55$  ms measured from the nadir of the S wave to the end of the QRS complex in  $V_1$ . Contributed by M.G.P.J. Cox, Utrecht, the Netherlands.

cannot be evaluated in the presence of typical complete right bundle-branch block with terminal delay in leads I and  $V_6$ . However, T-wave inversion in  $V_1$ ,  $V_2$ ,  $V_3$ , and  $V_4$  is uncommon in patients with right bundle-branch block who do not have ARVC/D and is seen frequently in those who do have the disease. Conventional definitions are used for ventricular arrhythmias. An abnormal SAECG is based on time domain criteria with cutoffs generated from receiver operating characteristic curves.<sup>55,56</sup> 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 is proposed as a criterion for this modality. The presence of left bundle-branch block ventricular tachycardia with an inferior axis (R wave positive in leads II and III and negative in lead aVL) is typical of focal RV outflow tract tachycardia.<sup>57</sup> 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  $<50$  years of age suggests underlying myocardial disease.<sup>58</sup>

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 Institutes of Health. They had been carefully evaluated, including assessment of diagnostic tests by expert core laboratories.<sup>43</sup> 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’s fulfilling only minor criteria in one and only mild hypokinesia in the angiogram of the other. Of the 28 probands classified as borderline (met some but not all of the original Task Force criteria—ie, 1 major and 1 minor or 3 minor), 5 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 7 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 2 different sets of phenotyped–genotyped cohorts (N. Protonotarios et al and M.D.G.J. Cox et al, unpublished data). In both studies, sensitivity increased without loss of specificity. Additionally, the ECG criteria have been applied to known ARVC/D cohorts and have shown an increase in diagnostic value.<sup>59</sup>

The proposed modifications of the original Task Force criteria represent a working framework to improve the diagnosis and management of ARVC/D. Awareness is growing that ARVC/D as such is the most 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 block morphology, subepicardial or midmyocardial late gadolinium enhancement of the LV myocardium, and global or regional LV dysfunction in patients presenting with arrhythmia rather than heart failure. With the identification of disease-causing genes, the potential exists for diagnostic mutation analysis and improved pedigree evaluation, with better understanding of natural history and 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 normal subjects have been determined from select populations from centers with expertise in the diagnostic test (online-only Data Supplement) because data on a large cohort of normal subjects studied by all the modalities were not available from any one center. Therefore, the reference values may not apply to all ethnic populations or those <12 years of age.

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### Disclosures

None.

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## SUPPLEMENTAL MATERIAL

### Normal values

Data from 398 normal subjects who had analysis of the number of PVCs per 24 hours by Holter monitor were contributed by Dr. S. DePaula, University Sao Paulo Medical School, Brazil.

Holter normals n = 398: 181 males, 217 females, age  $43.5 \pm 12.2$ , range 15 to 83

Holter ARVD probands n = 68: 37 males, 31 females, age  $37.1 \pm 13.3$ , range 15 to 63

There were 462 normal subjects who were the basis for the MRI data. These were provided by Drs. D. Bluemke and H. Tandri of Johns Hopkins Hospital, Baltimore, MD.

MRI data normals n = 462

263 males: age  $60.2 \pm 10$

RVEDV/BSA  $63.6 \pm 11 \text{ ml/m}^2$

RVEF  $61.9 \pm 8.4 \%$

199 females: age  $60.6 \pm 10$

RVEDV/BSA  $72.8 \pm 14.2 \text{ ml/m}^2$

RVEF  $68.5 \pm 7.5 \%$

MRI data ARVC/D probands n = 44

Males: age  $41.3 \pm 13.9$

n = 27 RVEDV/BSA  $96.6 \pm 37.6 \text{ ml/m}^2$  n = 28 RVEF  $42 \pm 12.3 \%$

Females: age  $39.6 \pm 11.5$

n = 14 RVEDV/BSA  $98 \pm 38.2 \text{ ml/m}^2$  n = 16 RVEF  $44 \pm 13.1 \%$

Echocardiographic data from 150 normal subjects were provided by Drs. M. Picard and D. Sanborn of the Massachusetts General Hospital, Boston, Massachusetts and 300 normal echocardiograms by Drs. A. Nava and B. Bauce from the University of Padua, Italy.

Echo normals: n=450, 241 males, 209 females, age  $32 \pm 12.8$

RVOT (PLAX)  $25.8 \pm 4$                       RVOT (PSAX)  $28.9 \pm 4.3$ ,                      FAC  $47.2 \pm 10.3$

Echo data ARVC/D probands: n = 69, 38 males, 31 females, age  $37.17 \pm 13.7$

RVOT (PLAX)  $36.5 \pm 6.8$ .                      RVOT (PSAX)  $37.5 \pm 5.2$ .                      FAC  $33.3 \pm 8.3$

Dr. W. Zareba of the University of Rochester provided information on the signal averaged ECGs from 20 normals and Dr. W. McKenna of the Heart Hospital, London, UK contributed data on 83 normal signal averaged electrocardiograms.

SAECG normals n = 103: 44 males 59 females  $33 \pm 14$ , range 10 to 73

SAECG ARVC/D probands n = 69: 37 males, 32 females, age  $37 \pm 13$ , range 15 to 62

## Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task Force Criteria

Frank I. Marcus, William J. McKenna, Duane Sherrill, Cristina Basso, Barbara Bauce, David A. Bluemke, Hugh Calkins, Domenico Corrado, Moniek G.P.J. Cox, James P. Daubert, Guy Fontaine, Kathleen Gear, Richard Hauer, Andrea Nava, Michael H. Picard, Nikos Protonotarios, Jeffrey E. Saffitz, Danita M. Yoerger Sanborn, Jonathan S. Steinberg, Harikrishna Tandri, Gaetano Thiene, Jeffrey A. Towbin, Adalena Tsatsopoulou, Thomas Wichter and Wojciech Zareba

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