

# Circulation

## Arrhythmia and Electrophysiology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

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*Circ Arrhythm Electrophysiol* 2010;3;126-133; originally published online March 9, 2010;

DOI: 10.1161/CIRCEP.109.927202

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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# Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Diagnostic Task Force Criteria

## Impact of New Task Force Criteria

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**Background**—Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) Diagnostic Task Force Criteria (TFC) proposed in 1994 are highly specific but lack sensitivity. A new international task force modified criteria to improve diagnostic yield. A comparison of diagnosis by 1994 TFC versus newly proposed criteria in 3 patient groups was conducted.

**Methods and Results**—In new TFC, scoring by major and minor criteria is maintained. Structural abnormalities are quantified and TFC highly specific for ARVD/C upgraded to major. Furthermore, new criteria are added: terminal activation duration of QRS  $\geq 55$  ms, ventricular tachycardia with left bundle-branch block morphology and superior axis, and genetic criteria. Three groups were studied: (1) 105 patients with proven ARVD/C according to 1994 TFC, (2) 89 of their family members, and (3) 39 patients with probable ARVD/C (ie, 3 points by 1994 TFC). All were screened for pathogenic mutations in desmosomal genes. Three ARVD/C patients did not meet the new sharpened criteria on structural abnormalities and thereby did not fulfill new TFC. In 62 of 105 patients with proven ARVD/C, mutations were found: 58 in the gene encoding Plakophilin2 (*PKP2*), 3 in *Desmoglein2*, 3 in *Desmocollin2*, and 1 in *Desmoplakin*. Three patients had bigenic involvement. Ten additional relatives (11%) fulfilled new TFC: 9 (90%) were female, and all carried *PKP2* mutations. No relatives lost diagnosis by application of new TFC. Of patients with probable ARVD/C, 25 (64%) fulfilled new TFC: 8 (40%) women and 14 (56%) carrying pathogenic mutations.

**Conclusions**—In this first study applying new TFC to patients suspected of ARVD/C, 64% of probable ARVD/C patients and 11% of family members were additionally diagnosed. ECG criteria and pathogenic mutations especially contributed to new diagnosis. Newly proposed TFC have a major impact in increasing diagnostic yield of ARVD/C. (*Circ Arrhythm Electrophysiol.* 2010;3:126-133.)

**Key Words:** cardiomyopathy ■ diagnosis ■ criteria ■ arrhythmogenic right ventricular dysplasia/cardiomyopathy ■ genetics

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is histopathologically characterized by fibrofatty replacement, primarily of the right ventricle.<sup>1-3</sup> The gold standard for ARVD/C diagnosis is demonstration of this alteration of ventricular myocardium, either postmortem or at surgery. However, to facilitate diagnosis in daily practice, a task force proposed a set of clinically applicable criteria (TFC) in 1994, based on ECG, structural, and histological

characteristics of the disease as well as arrhythmias and family history.<sup>4</sup> Abnormalities were subdivided into major and minor, according to the specificity for ARVD/C. Univer-

### Clinical Perspective on p 133

sally, these TFC were adopted as the clinical gold standard to diagnose patients with ARVD/C. However, because they were based on characteristics from symptomatic index cases,

Received December 9, 2009; accepted February 23, 2010.

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*Circ Arrhythm Electrophysiol* is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.109.927202

mainly in an advanced stage of the disease, TFC were highly specific for ARVD/C diagnosis, but lacked sensitivity.

Subsequent clinical research in ARVD/C families and the discovery of disease-causing mutations, primarily in genes encoding desmosomal proteins, increased insight in etiology and pathogenesis of the disease.<sup>5–13</sup> Desmosomal impairment followed by mechanical and electric uncoupling of cardiomyocytes leads to cell death with fibrofatty replacement.<sup>14–19</sup> Resultant activation delay is the essential mechanism for reentry and thereby ventricular tachycardia (VT).<sup>20–23</sup> The increased clinical and scientific knowledge led to the awareness that changes to diagnostic criteria were a challenge of highest priority. Therefore, a new task force recently introduced modifications to the 1994 TFC by implementation of new insights.<sup>24</sup> Criteria proven to be highly specific rose from minor to major and new criteria on activation delay, and VT morphology as well as genetic criteria were added. Furthermore, quantitative parameters for both imaging modalities and histopathology were newly introduced and were defined based on comparison with normal subject data.

The aim of the present study was to compare clinical diagnosis by new TFC with 1994 criteria, to test the impact on diagnostic yield. New TFC were applied to the largest cohort of index patients studied so far, and for the first time to family members as well.

## Methods

### Study Population

Newly proposed TFC were applied to 3 different groups of patients. First of all, we established whether 105 patients with clinically proven ARVD/C, according to the 1994 TFC, would also fulfill diagnosis with new TFC. In addition, 89 of their first- and second-degree family members were analyzed. Finally, 39 patients highly suspected of ARVD/C were included. These patients scored 3 points by fulfilling either 1 major and 1 minor or 3 minor criteria of the 1994 TFC and were therefore classified as “probable ARVD/C patients.”

For inclusion, at least a detailed history and family history, physical examination, copies of 12-lead ECG recordings, and original reports of 2D transthoracic echocardiograms were required. When performed, outcomes of exercise tests, 24-hour Holter monitoring, signal-averaged ECG (SAECG) and electrophysiological studies (EPS), as well as additional imaging by MRI and/or RV cineangiography were also included in the analyses. All quantitative analyses were performed in the different academic medical centers. The results and reports were collected in the core laboratory in Utrecht, where final scoring of TFC was performed. Tissue characterizations after biopsies were not taken into account because histomorphometric tissue analyses or estimations, as defined in new TFC, had not been performed, and biopsies were all taken from the interventricular septum instead of the RV free wall.<sup>24</sup> ARVD/C patients who had only been diagnosed after autopsy were excluded.

Seven Dutch University Medical Centers participated in patient screening. All data were collectively stored and analyzed in the University Medical Center Utrecht.

### New TFC

Compared with the 1994 TFC, modifications are:<sup>24</sup> (1) reclassification from minor to major of criteria highly specific for ARVD/C: negative T-waves in  $V_1$ - $V_3$  and ARVD/C in a first-degree relative, according to TFC; (2) quantification of RV structural abnormalities and dysfunction and tissue characterization by RV biopsy; (3) newly introduced criteria: negative T-waves in  $V_1$ - $V_2$  or  $V_4$ - $V_6$ ; negative T-waves in  $V_1$ - $V_4$  with right bundle-branch block (RBBB); terminal activation duration (TAD) of QRS  $\geq 55$  ms in  $V_1$ - $V_3$ ; VT of left

**Table 1. Additional Examinations Performed in the 3 Groups**

	Patients With Proven ARVD/C (n=105) n (%)	Family Members (n=89) n (%)	Patients With Probable ARVD/C (n=39) n (%)
24-Hour Holter monitoring*	105 (100)	55 (62)	38 (97)
Exercise test	81 (77)	46 (52)	30 (77)
Late potentials			
SAECG	35 (33)	15 (17)	6 (15)
Mapping during EPS	19 (18)	1 (1)	4 (10)
EPS	82 (78)	11 (12)	18 (46)
MRI	64 (61)	26 (29)	33 (85)
RV cineangiography	45 (43)	3 (3)	10 (11)

\*Either ambulatory or during admission.

bundle-branch block (LBBB) morphology with superior axis; pathogenic mutation associated with ARVD/C; and (4) adaptations: late potentials by SAECG in at least 1 of 3 parameters (was 2 of 3); >500 premature ventricular complexes/24 hours on Holter (was >1000).

Both in the 1994 and new TFC, major criteria count as 2 points and minor criteria as 1 point, with at least 4 points required for ARVD/C diagnosis.

All ECG parameters were studied in 12-lead ECGs, obtained using the conventional recording technique at a paper speed of 25 mm/s with low-pass filter set at 100 Hz. Depolarization and repolarization parameters were assessed with patients in sinus rhythm, while off drugs. Epsilon wave was defined as a distinct deflection after the end of the QRS complex, that is, after the QRS complex had returned to the isoelectric line.<sup>25</sup> TAD was determined as the longest value in  $V_1$ - $V_3$ , from the nadir of the S wave to the end of all depolarization deflections.<sup>26</sup> VT morphology and axis were considered only when 12-lead ECG recording of the VT was available. VT axis was called superior when the QRS complex was negative or indeterminate in II, III, and aVF and positive in aVL, and called inferior in the case of positive QRS in II, III, and aVF and negative in aVL.

For imaging tests to be scored for new TFC, appropriate quantifications had to be performed.<sup>24</sup> During EPS, programmed electric stimulation was performed according to a previously described protocol.<sup>26</sup> Table 1 shows how many subjects underwent which additional diagnostic tests.

DNA of all proven and probable ARVD/C index patients was screened for mutations in genes encoding the desmosomal proteins plakophilin2 (*PKP2*), desmoglein2 (*DSG2*), desmocollin2 (*DSC2*), and desmoplakin (*DSP*), as described earlier.<sup>9</sup> Mutations were considered pathogenic when occurring either in highly conserved residues or within a (predicted) functionally important domain, causing changes in charge or predicted major rearrangements of the protein and when not found in at least 150 ethnically matched control subjects. In the case a mutation was found in the proband, family members were only screened for this specific mutation.

The criterion of clinical ARVD/C diagnosis in first-degree relatives was only counted in nonindex patients.

### Statistical Analysis

Continuous variables are expressed as mean  $\pm$  1 SD. Discrete variables are shown as percentages. Continuous variables were compared with use of the Student *t* test. Categorical variables were analyzed by use of contingency tables and the Pearson  $\chi^2$  method. In the case that the expected value was <5, the Fisher exact test was used instead. In the case of repeated measurements, the Wilcoxon signed-rank test was used for continuous data and McNemar test for nominal data. A value  $P < 0.05$  was considered statistically significant. SPSS 15.0 software (SPSS, Chicago, Ill) was used for calculations.

## Results

The cohort comprised 125 patients with proven ARVD/C index, diagnosed according to the 1994 TFC. Twenty patients were excluded from this study: 7 were diagnosed only after autopsy, and of 13 no appropriate quantitative analyses of imaging tests were available. The 105 index patients who were included had a mean age at diagnosis of  $39 \pm 13$  years, with a mean duration of follow-up of  $10 \pm 8$  years. The 89 family members underwent first cardiological screening at age  $39 \pm 18$  years and were followed for  $5 \pm 3$  years on average. Finally, the 39 patients with probable ARVD/C were followed for  $10 \pm 9$  years after the first evaluation at age  $38 \pm 11$  years.

Table 2 shows prevalence of new TFC measured in the 3 different groups.

### Patients With Proven ARVD/C

These 105 patients had first presented with VT with LBBB morphology (n=86), ventricular fibrillation (VF, n=9), frequent premature ventricular complexes (PVC, n=8), or because of sudden death of a family member (n=2). In total, 55 patients carried 21 different *PKP2* mutations, whereas 3 patients had a *DSG2* and 1 a *DSC2* mutation. Furthermore, 3 patients had mutations in 2 genes: 2 in *PKP2* plus *DSC2* and 1 in *PKP2* plus *DSP*.

ECG abnormalities during sinus rhythm were the most prevalent abnormalities. As many as 103 of 105 patients did fulfill at least 1 of the criteria on depolarization and/or repolarization. The 1994 TFC of negative T waves in  $V_1$ - $V_3$  was already fulfilled by 70 patients (67%). However, 8 additional patients had T-wave inversions only in  $V_1$ - $V_2$  and 3 patients with a RBBB had negative T waves in  $V_1$ - $V_4$  and thereby fulfilled newly introduced criteria.

Structural abnormalities, both major and minor, were observed in 83 probands, in 24 cases only by MRI (n=15) and/or RV cineangiography (n=12).

With 1994 TFC, major structural abnormalities were observed in 79 patients. According to the new quantified definitions, 14 were categorized as minor and 3 as not abnormal. Because of this decrease, 3 patients scored only 3 points in new TFC and were thereby reclassified as "probable" patients. Two patients had akinetic areas with only mild dilation of the RV and 1 had RV dyskinesia only.

In 9 of 82 patients who underwent EPS, this produced VT with LBBB morphology and superior axis, which had not been recorded spontaneously.

Results of the scoring according to 1994 versus new TFC, for all 3 patient groups, are conveyed in the Figure.

### Family Members

Of the 89 relatives from 40 different families, 77 (87%) underwent cardiological evaluation because of family screening. The remaining 12 initially presented because of VT, syncope, or palpitations (4 individuals each). In total, 59 relatives carried 13 different pathogenic mutations in *PKP2* and 1 in *DSG2*.

Clinically, disease manifestation was mainly by ECG changes during sinus rhythm. In total, 39 family members met at least 1 of those criteria, with fulfillment of criteria both on depolariza-

**Table 2. Prevalence of New Diagnostic TFC in the 3 Groups**

	Patients With Proven ARVD/C (n=105)	Family Members (n=89)	Patients With Probable ARVD/C (n=39)
Age, y	48±12	44±17	48±12
Male, n (%)	81 (77)	34 (38)	21 (54)
Diagnosis according to			
1994 TFC, n (%)	105 (100)	22 (25)	0
New TFC, n (%)	102 (97)	32 (36)	25 (64)
New TFC, n (%)			
Depolarization abnormalities	78 (74)	28 (31)	19 (49)
Epsilon wave $V_1$ - $V_3$ *	11 (10)	3 (3)	0
QRS >110 ms*	23 (22)	1 (1)	0
Late potentials‡	29 (54)	5 (31)	5 (50)
Prolonged TAD	56 (53)	25 (28)	16 (41)
Repolarization abnormalities	81 (77)	20 (22)	21 (54)
Inverted T waves $V_1$ - $V_3$ *†	70 (67)	15 (17)	17 (44)
Inverted T waves $V_1$ - $V_2$	8 (8)	5 (6)	4 (10)
Inverted T waves $V_4$ - $V_6$	0	0	0
Inverted T waves $V_1$ - $V_4$ +RBBB	3 (3)	0	0
Arrhythmias	99 (94)	24 (27)	36 (92)
LBBB VT with superior axis*	45 (43)	2 (2)	14 (36)
LBBB VT+inferior/unknown axis	94 (90)	11 (12)	33 (85)
>500 PVCs on 24-h Holter‡	25 (24)	17 (31)	9 (24)
Structural alterations	83 (79)	23 (25)	22 (56)
Major	62 (59)	12 (13)	13 (33)
Minor	21 (20)	11 (12)	9 (23)
Family history			
Clinically confirmed ARVD/C in first-degree relative*†	NA	74 (83)	NA
Pathologically confirmed ARVD/C in first-degree relative*	6 (6)	13 (15)	0
Pathogenic mutation*	62 (59)	59 (66)	16 (41)
Sudden death <35 y	9 (9)	3 (3)	5 (13)

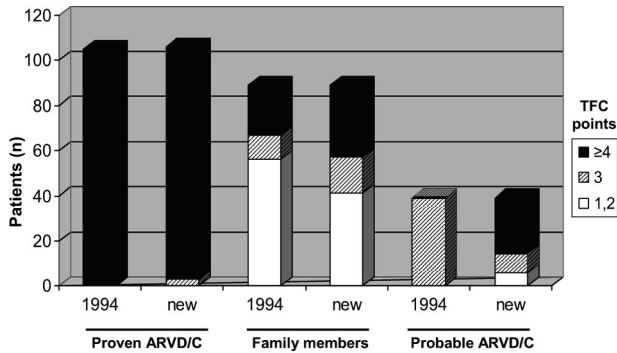
\*Major criterion.

†Minor in 1994 TFC, upgraded to major in new TFC.

‡In percentage of subjects measured.

tion and repolarization in 9 cases. Structural abnormalities were observed in 23 individuals, in 1 case only with MRI and in 1 case by RV cineangiography (Table 2). VTs with LBBB morphology were induced in 3 of 11 family members who underwent EPS, twice with inferior and once with superior axis.





**Figure.** Changes in score and diagnosis when applying 1994 and new TFC in the 3 groups.

According to the 1994 TFC, 22 (25%) members of 17 families had been diagnosed with ARVD/C. All carried pathogenic *PKP2* mutations. These 22 (mean age, 45±17 years, 8 men) all kept diagnosis when new TFC were applied.

In addition, 10 more members of 9 families fulfilled ARVD/C diagnosis with new TFC (1 man and 9 women,

including 2 twin sisters). In 1994 TFC, 7 had scored 3 points, all by different combinations of criteria, and 3 only had a positive family history. All 10 carried a pathogenic *PKP2* mutation. Additional TFC points were scored by ECG changes: prolonged TAD, T-wave inversion in  $V_1$ - $V_3$  or  $V_1$ - $V_2$  (n=4, 3 and 2, respectively). None of the newly diagnosed relatives revealed VT with LBBB morphology and superior axis or between 500 and 1000 PVCs on 24-hour Holter monitoring.

Of 55 female relatives, 23 (42%) fulfilled new TFC for ARVD/C diagnosis, whereas 9 of 34 (26%) men were diagnosed. Both sex groups had similar age and percentage of mutation carriers. Difference of fulfilled criteria between individuals with and without ARVD/C diagnosis is conveyed in Table 3. In 32 of 59 (54%) relatives carrying a pathogenic mutation, ARVD/C was diagnosed. Of all 57 family members without diagnosis, 27 (47%) fulfilled at least 1 criterion, in addition to the positive family history, in another category. They all carried a pathogenic mutation (26 in *PKP2*, 1 in *DSG2*) (Table 3).

**Table 3. Prevalence of TFC in Individuals With Versus Without Diagnosis According to New TFC**

Diagnosis According to New TFC, n (%)	Family Members (n=89)		Patients With Probable ARVD/C (n=39)	
	Yes	No	Yes	No
Age, y	32 (36)	57 (64)	25 (64)	14 (36)
Male, n (%)	44±15	44±18	49±10	46±15
New TFC, n (%)	9 (28)	25 (44)	15 (60)	6 (43)
Depolarization abnormalities				
Epsilon wave $V_1$ - $V_3$ *	3 (9)	0	0	0
QRS >110 ms*	1 (3)	0	0	0
Late potentials‡	3 (60)	2 (25)	3 (43)	2 (67)
Prolonged TAD	15 (47)	10 (18)	10 (40)	6 (43)
Repolarization abnormalities				
Inverted T waves $V_1$ - $V_3$ *†	15 (47)	0	15 (60)	2 (14)
Inverted T waves $V_1$ - $V_2$	4 (13)	1 (2)	2 (8)	2 (14)
Inverted T waves $V_4$ - $V_6$	0	0	0	0
Inverted T waves $V_1$ - $V_4$ +RBBB	0	0	0	0
Arrhythmias				
LBBB VT with superior axis*	2 (6)	0	13 (52)	1 (7)
LBBB VT+inferior/unknown axis	9 (28)	2 (4)	23 (92)	10 (71)
>500 PVCs on 24-h Holter‡	17 (65)	0	4 (17)	5 (36)
Structural alterations				
Major	12 (38)	0	12 (48)	1 (7)
Minor	10 (31)	1 (2)	6 (24)	3 (21)
Family history				
Clinically confirmed ARVD/C in first-degree relative*†	28 (88)	46 (81)	NA	NA
Pathologically confirmed ARVD/C in first-degree relative*	6 (19)	7 (12)	0	0
Pathogenic mutation*	32 (100)	27 (47)	14 (56)	2 (14)
Sudden death <35 y	1 (3)	2 (4)	1 (4)	4 (29)

\*Major criterion.

†Minor in 1994 TFC, upgraded to major in new TFC.

‡In percentage of subjects measured.

**Table 4. Diagnosis in Individuals With Spontaneous VT and/or VF**

	VT/VF Recorded n (%) <sup>*</sup>	Diagnosis in Patients With VT/VF According to			
		1994 TFC		New TFC	
		Yes	No	Yes	No
Proven ARVD/C patients	97 (89)	97	0	94	3
Family members	13 (15)	9	4	11	2
Probable ARVD/C patients	37 (95)	0	37	25	12
Total		106	41	130	17

<sup>\*</sup>Percentage of total number in the specific patient group.

### Patients With Probable ARVD/C

The large majority of these patients highly suspected of ARVD/C initially presented with monomorphic VT with LBBB morphology (n=29, 74%). Four men had VF as a first symptom at mean age 22 years (range, 21 to 25). The remaining 6 patients' first symptoms were palpitations due to frequent PVCs (n=5) and syncope. Overall, age at first symptoms, current age, and sex were similar to proven ARVD/C patients. In total, 14 patients carried a pathogenic mutation in *PKP2*. Furthermore, 2 patients carried 2 pathogenic mutations each: 1 in *PKP2* and *DSG2* and the other in *DSC2* and *DSG2*.

In 10 of 35 patients who underwent MRI and/or RV cineangiography, structural abnormalities were thereby newly discovered. VT with LBBB morphology and superior axis was recorded only after induction by programmed electric stimulation in 7 of 18 patients who underwent EPS.

When applying new TFC, 25 (64%) patients were diagnosed with ARVD/C. Pathogenic mutations were found in 14 of these 25, all in *PKP2*. Thus, 14 of 16 (88%) patients with pathogenic mutations fulfilled new TFC. In 6 patients, carrying a mutation was essential for diagnosis. Besides mutations, diagnosis was mainly due to additional points newly scored by prolonged TAD, negative T waves in V<sub>1</sub>-V<sub>3</sub>, and VT with LBBB morphology and superior axis (Table 2). Eleven patients could have been diagnosed based on ECG parameters only.

On the contrary, fewer points were scored on structural abnormalities. Whereas initially major and minor structural abnormalities were observed in 20 and 8 patients, respectively, this was only 13 and 9, respectively, according to new definitions. Age and sex were not related to new diagnosis.

When all 3 groups studied are taken into account, a higher percentage of individuals with spontaneous VT and/or VF fulfilled new TFC than 1994 TFC (see Table 4;  $P<0.001$  for all individuals together,  $P<0.001$  and  $P=0.500$  for probands and family members, respectively).

### Discussion

In this study, we assessed the effect of newly proposed Task Force criteria on ARVD/C diagnosis. Application of new TFC additionally diagnosed ARVD/C in 35 individuals: 10 of 89 (11%) relatives and 25 of 39 (64%) previously classified as probable index patients. On the contrary, 3 of 105

ARVD/C patients previously classified as "proven" did not fulfill new TFC.

The gold standard for ARVD/C diagnosis is demonstration of transmural fibrofatty replacement in the RV at autopsy or after surgery. Of all patients included in this study, autopsy has been performed in 2 of 3 proven ARVD/C patients who died after diagnosis. Of the 7 ARVD/C patients diagnosed by autopsy, excluded from this study, no clinical cardiological data were available. Because new TFC could not be compared with the gold standard, it cannot be established what percentage of ARVD/C patients is truly identified by the new TFC. However, previous research results provided at least 3 arguments to support diagnostic superiority of new TFC to 1994 TFC.

### Improvement of Diagnosis

First of all, basic and genetic studies performed during the past decade provided insight into the pathophysiological mechanism of ARVD/C.<sup>5-19</sup> The pathognomonic RV fibrofatty replacement appears to be preceded by mutation-related desmosomal changes and associated gap junction remodeling. This is strongly supported by a recent study of Asimaki et al.<sup>27</sup> They showed that specifically in ARVD/C, altered localization of desmosomal and gap junction proteins occur in ventricular areas (still) without evidence of fibrofatty modifications. Resultant electric uncoupling and, at a later stage, the surviving myocardial bundles embedded in the fibrofatty infiltration forming communicating zigzag courses, all lead to lengthened conduction pathways and conduction slowing due to load mismatch.<sup>14,15</sup> These delays in activation are crucial in providing a substrate for reentry and thereby VT.<sup>20,21,28</sup> The 1994 TFC comprised 3 criteria on activation delay: epsilon waves, QRS prolongation, and late potentials. In our previous studies, confirmed by Marcus et al, we demonstrated that prolonged terminal activation duration in V<sub>1</sub>-V<sub>3</sub> is an indicator of RV activation delay more sensitive than epsilon waves and QRS prolongation and still highly specific for ARVD/C.<sup>26,29,30</sup>

Second, electric activation mapping and CARTO electro-anatomic voltage mapping provided advanced insight in the sites of the RV that were electrically affected.<sup>28,31</sup> These techniques demonstrated that loss of vital myocardium of inferior parts of the RV can result in reentry-based VTs with a LBBB morphology and superior axis. On the contrary, idiopathic VT from the RV outflow tract results in VT with nonsuperior axis. Therefore, recording of a LBBB VT with superior axis appeared to be more specific for ARVD/C.

Third, in contrast to 1994 TFC, normal values for new TFC were based on comparisons to large numbers of healthy control subjects. Establishment of optimal cutoff points was performed scientifically by analyses of ROC curves.<sup>24</sup>

### Application of New TFC

In all 3 groups studied, patients lost points previously scored on structural abnormalities. Reasons for that are 2-fold. First, observation of either a-/dyskinetic area or major dilatation of the RV was sufficient to fulfill a major criterion in 1994. However, according to new TFC definitions, both a-/dyskinesia and RV dilatation are required for echocardiography

and MRI. Second, clear cutoff values for degrees of dilation are newly introduced to avoid subjective interpretations. Still, overlap between healthy and diseased cannot be excluded entirely. Especially in endurance athletes, physiological RV dilatation and deformation occur, which may mimic ARVD/C.<sup>32</sup>

Multiple studies on different cohorts demonstrated that ECG changes are the earliest and most sensitive indicators of ARVD/C.<sup>5-7,30</sup> This was acknowledged by the members of the new international task force. The contribution of ECG abnormalities, both with respect to depolarization and repolarization as well as arrhythmias, was increased importantly in new TFC. ARVD/C could already have been diagnosed in 62 (61%) proven, 11 (44%) probable ARVD/C patients, and 7 (22%) family members if only these ECG parameters would have been taken into account.

In the present study, prolonged TAD, as activation delay parameter, was observed in ARVD/C patients with similar frequency as late potentials. In 22 proven ARVD/C patients, 3 family members and 3 probable ARVD/C patients without a prolonged TAD, RV activation delay was observed as QRS >110 ms and/or late potentials. We speculate that this difference might be due to the fact that prolonged TAD is only measured in leads V<sub>1</sub>-V<sub>3</sub>. Because these leads face the RV outflow tract, activation delay in other parts of the RV is not detected. Further studies are needed to evaluate the applicability of prolonged TAD in all ECG leads to establish whether this criterion may be used as the sole criterion for depolarization abnormalities.

Despite ECG changes being considered the earliest and most sensitive abnormalities seen in ARVD/C, in this study, prevalence of ECG criteria in sinus rhythm was similar between probable ARVD/C patients with and without diagnosis according to new TFC.<sup>5-7,30</sup> However, all 14 nondiagnosed patients are clearly affected by some kind of disease. Longer follow-up will have to show whether they are in an early stage of ARVD/C or another kind of cardiomyopathy. Thereby, follow-up can also inform us about the TFC specificity.

The criterion of negative T waves in leads V<sub>4</sub>-V<sub>6</sub> was introduced because of the awareness of a left-dominant form of the disease.<sup>33</sup> These patients have fibrofatty alterations primarily in the left ventricle. None of the proven ARVD/C patients fulfilled this criterion, suggesting that either the left-dominant form was indeed not acknowledged by the 1994 TFC or that this form is a rare entity. However, in ARVD/C, desmosomal and gap junctional remodeling occur in both ventricles and the interventricular septum, also in the absence of fibrofatty alterations.<sup>27</sup> Why histological alterations are primarily found in the RV free wall is not yet completely understood. It is speculated this is related to increased wall stress affecting the thin RV free wall more than other structures.<sup>7</sup>

Identification of pathogenic mutations is newly included as diagnostic criterion. DNA analysis revealed mutations in the *PKP2* gene in 131 patients. This is in accordance with previous Dutch ARVD/C studies.<sup>9,34</sup> Due to founder mutations, *PKP2* appears to be the main genetic factor causing ARVD/C. Mutations in *DSG2*, *DSC2*, and *DSP* were found in

6, 4, and 1 of 233 subjects studied, respectively. For 6 probable ARVD/C patients and 2 second-degree family members, having a pathogenic mutation was crucial for ARVD/C diagnosis according to the new criteria.

The total group of ARVD/C probands diagnosed with new TFC contains more men than women (n=95 versus 32). This is in accordance with previous clinical studies, which reported male:female ratios of approximately 3:1.<sup>8-10</sup> On the contrary, among family members included in this study, more women were diagnosed. All criteria occurred in similar frequencies in both sex groups. Negative T waves in V<sub>1</sub>-V<sub>3</sub> and mutations were observed more frequently in women than in men (in 41% versus 24% and 72% versus 59%, respectively), but the differences were not significant. These findings are in agreement with previous studies, in which no unequivocal conclusions on sex differences could be drawn.<sup>35,36</sup> However, these studies pointed out that although equally affected, male ARVD/C patients and/or mutation carriers are more often symptomatic than their female counterparts. Therefore, men are more likely to be the first in a family to be diagnosed and thereby become the proband.

Although debate on true sensitivity of the clinical diagnostic criteria for ARVD/C will continue, especially in case of asymptomatic relatives, multiple studies from various countries worldwide have repeatedly confirmed certain parameters to be highly specific for ARVD/C. The consensus reached by a group of experts in the field from all over the world translates state-of-the-art knowledge on ARVD/C into a set of criteria useful in daily clinical practice.<sup>24</sup> Modifications made on the 1994 TFC have provided an important increase in diagnosing ARVD/C. Further studies will have to prove the true value of the new TFC.

### Study Limitations

This study was hampered by the fact that not all diagnostic modalities had been performed in all patients, particularly with respect to RV imaging and late potential detection. In addition to 2D echocardiography, the majority of index patients underwent MRI and/or RV cineangiography. However, this was only performed in 31% of family members; thus, structural and functional abnormalities might have been missed. Similarly, 82 (78%) proven and 18 (46%) probable ARVD/C patients but only 11 (12%) family members underwent EPS. Furthermore, late potentials were measured in only 80 of 233 individuals included in this study because SAECGs are not performed in all participating hospitals and late potential mapping was rarely carried out during EPS. Holter monitoring was performed significantly more often in family members ultimately with diagnosis according to new TFC (81% versus 51%), due to already existing suspicion of abnormalities. Application of these diagnostic modalities in more subjects probably will increase the number of criteria fulfilled and thereby the number of patients diagnosed with ARVD/C.

Results of biopsies were not included in this study. However, biopsies had been taken from none of the family members and only from 1 probable ARVD/C patient, who already fulfills new TFC without biopsy taken into account. Therefore, the number of patients diagnosed in these 2 groups

would not have been influenced by inclusion of biopsy results.

### Conclusion

This is the first large study comparing ARVD/C diagnostic criteria from 1994 with the newly proposed TFC.<sup>4,24</sup> Newly proposed TFC increase ARVD/C diagnosis importantly, especially due to modifications on ECG and genetic criteria. This will result in ameliorated identification of affected individuals and thereby contribute to prevention of both ventricular tachyarrhythmias and sudden death.

### Sources of Funding

This study was supported by the Interuniversity Cardiology Institute of the Netherlands Project 06901, the Netherlands Heart Foundation Grant 2007B139, and the Van Ruyven Foundation.

### Disclosures

None.

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### CLINICAL PERSPECTIVE

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by progressive loss of predominantly RV myocardium, which is replaced by fibrofatty tissue. Typically, affected individuals present with ventricular tachycardia between the 2nd and 4th decades of life, but ARVD/C can also cause sudden death in adolescence. Clinical diagnosis is made according to generally accepted task force criteria (TFC). This initial set of criteria, dating from 1994, was highly specific but lacked sensitivity. Therefore, a modified set of TFC was recently proposed. In new TFC, scoring by major and minor criteria is maintained. Structural abnormalities are quantified and TFC highly specific for ARVD/C are upgraded to major. Furthermore, new criteria are added: terminal activation duration of QRS  $\geq 55$  ms, ventricular tachycardia with left bundle-branch block morphology and superior axis, and genetic criteria. In the present study, we applied new TFC to 3 groups: (1) 105 patients with proven ARVD/C according to 1994 TFC, (2) 89 of their family members, and (3) 39 patients with probable ARVD/C (ie, 3 points by 1994 TFC). In total, 35 individuals were newly diagnosed with ARVD/C: 10 of 89 (11%) relatives and 25 of 39 (64%) previously classified as probable index patients. On the contrary, 3 of 105 ARVD/C patients previously classified as “proven” did not fulfill new TFC. ECG criteria and pathogenic mutations especially contributed to new diagnosis. Therefore, newly proposed TFC have a major impact in increasing diagnostic yield of ARVD/C.