New ECG Criteria in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Background—Desmosomal changes, electric uncoupling, and surviving myocardial bundles in fibrofatty tissue characterize arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). Resultant activation delay is pivotal for reentry and thereby ventricular tachycardia (VT). Current task force criteria (TFC) for diagnosis have limited sensitivity. The aim of this study was to assess the diagnostic value of additional criteria on activation delay and VT to improve identification of affected individuals.

Methods and Results—ECG criteria were studied, while off drugs, in 50 index patients with proven ARVD/C according to TFC (TFC 4 points) and 33 patients with probable ARVD/C (TFC 3 points, or TFC3), being 21 index patients and 12 family members of proven ARVD/C patients. Newly proposed additional criteria are (1) prolonged terminal activation duration in V1–V3, an indicator of activation delay, (2) VT with left bundle-branch block morphology and superior axis, and (3) multiple VT morphologies. All index patients were screened for mutations in ARVD/C-related genes encoding desmosomal proteins. Altogether, 23 of 33 (70%) TFC3 patients fulfilled ARVD/C diagnosis when newly proposed criteria were applied additionally to current TFC. VT with left bundle-branch block morphology and superior axis or multiple VT morphologies were recorded in 12 and 9 of 33 TFC3 patients, respectively, all being index patients. When applying prolonged terminal activation duration additionally to TFC on depolarization/conduction abnormalities, 14 (42%) TFC3 patients fulfilled ARVD/C diagnosis. Results were not significantly different between mutation carriers and noncarriers.

Conclusions—Adding the newly proposed criteria to current TFC for ARVD/C will improve identification of affected individuals importantly, independent of outcome of DNA analyses. (Circ Arrhythmia Electrophysiol. 2009;2:524-530.)

Key Words: cardiomyopathy ■ electrocardiography ■ diagnosis ■ ventricular tachycardia ■ arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) is characterized by progressive loss of predominantly right ventricular (RV) myocardium, which is replaced by fibrofatty tissue.1–3 The gold standard for ARVD/C diagnosis is demonstration of the transmural fibrofatty infiltration of the RV. However, this gold standard is only applicable during autopsy or cardiac surgery. To facilitate diagnosis in clinical practice, a task force established a set of criteria (TFC) in 1994.4 These universally used TFC have proven to be highly specific for ARVD/C diagnosis, but with limited sensitivity. Thus, patients are often not recognized until a late stage of the disease. Clinical research in ARVD/C families and the discovery of disease-causing mutations, primarily in genes encoding desmosomal proteins, increased insight in disease development and behavior.5–13 Desmosomal impairment followed by mechanical and elec-
tric uncoupling of cardiomyocytes leads to cell death with fibrofatty replacement. 14–19 Eventually, this results in activation delay, which is the pivotal mechanism for reentry and thereby ventricular tachycardia (VT). 20–23

This increased knowledge was translated into new ECG criteria, which were previously studied in ARVD/C patients. 24 First is prolonged terminal activation duration (TAD), which reflects RV activation delay. In addition, new parameters of VT with left bundle-branch block (LBBB) morphology and superior axis and multiple VT morphologies reflect the location and extension of the disease process. Compared with current TFC, these criteria were highly specific for ARVD/C as well, and in addition appeared to be more sensitive. 24

In the present study, we aimed to establish whether the previously proposed additional ECG criteria would improve diagnosis in patients highly suspected of ARVD/C but who do not fulfill current TFC for ARVD/C diagnosis.

Methods

Study Population

ECG parameters were analyzed in 50 unrelated index patients with proven ARVD/C diagnosis according to the current TFC. 4 Furthermore, 33 patients with probable ARVD/C were evaluated. These patients fulfilled either 1 major (2 points) plus 1 minor (1 point) criterion or 3 minor criteria of left bundle-branch block (LBBB) morphology and superior axis and multiple VT morphologies in V1–V3. For each patient, current TFC were scored after at least: detailed history and family history, physical examination, 12-lead ECG recording, exercise testing, and 2D transthoracic echocardiography. Additionally, MRI and/or left ventricular and RV cine-angiography was performed in 39 (78%) index and 26 (79%) TFC3 patients, respectively. For 7 proven ARVD/C index patients and 4 TFC3 patients, structural abnormalities were visualized only after additional imaging. In the case that no VT had been recorded, 24-hour Holter monitoring was performed as well. Five Dutch University Medical Centers collaborated in patient screening.

ECG Analysis

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. Parameters related to activation delay and altered repolarization were analyzed on the earliest recorded 12-lead ECG during sinus rhythm while off drugs and were only scored in absence of right bundle-branch block (RBBB). Furthermore, we collected 12-lead recordings of all VT episodes, both spontaneous and during electrophysiological studies (EPS), from before diagnosis and during follow-up. Patients with VT episodes recorded only by ICD interrogation were not included because an accurate VT axis could not be established. During EPS, programmed electric stimulation (PES) was performed according to a predefined protocol, as described previously. 24 From 50 of the entire population of 104 proven ARVD/C patients as well as from all 33 TFC3 patients, all 12-lead ECGs required for inclusion were available.

For ECG parameters assessed, see Table 1. ε wave was defined as a distinct deflection clearly separated from the previous QRS complex. 25 TAD was introduced in our previous study as a new parameter to convey total RV activation delay. 24 TAD was determined as the longest value in V1–V3, from the nadir of the S wave to the end of all depolarization deflections, thereby including not only the S-wave upstroke but also both late fractionated signals and ε waves (Figure). TAD was considered prolonged if ≥55 ms. 24 Prolonged TAD only counted for ARVD/C diagnosis in the absence of all other TFC on activation delay. T-wave inversions in at least V1, V2, and V3 are a minor criterion of the current TFC. VT morphologies were defined as different when the difference in frontal plane axis was ≥30°.

Table 1. Assessed ECG Parameters

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<thead>
<tr>
<th>Sinus rhythm</th>
<th>Activation delay</th>
<th>Repolarization abnormalities</th>
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<tr>
<td>Epsilon waves in V1–V3</td>
<td>Localized prolongation (&gt;110 ms) of QRS complex in V1–V3</td>
<td>T-wave inversion in V1–V3</td>
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<tr>
<td>Prolonged TAD ≥55 ms in V1–V3</td>
<td>VT with LBBB morphology and axis of −30° to −150°</td>
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Figure. Examples of measurements of TAD (in ms) in TFC3 patients: 2 family members (A and B) and 1 index patient (C). RV activation delay was present in all, as indicated by prolonged TAD (≥55 ms).
ECG analysis was carried out in randomized sequence and after blinding for all other results. Each measurement was performed twice by 2 physicians independently (M.G.P.J.C., R.N.W.H.) and in at least 2 consecutive QRS complexes in each lead. In case of discrepancy, agreement was reached by convention for final analyses.

DNA Analysis
In all proven ARVD/C and TFC3 index patients, DNA was screened for mutations in the plakophilin-2 (PKP2) gene, by direct sequencing and multiple ligation-dependent probe amplification (MLPA). In the case that a PKP2 mutation was found in the index patient, family members were only screened for the mutation concerned. A mutation was considered pathogenic when causing changes in charge or predicted major rearrangements of the protein and when occurring either in highly conserved residues or within a (predicted) functionally important domain. Furthermore, the mutation was not found in at least 150 ethnically matched control subjects.

The PKP2 gene was analyzed because pathogenic PKP2 mutations occur most frequently in Dutch ARVD/C patients, observed in at least 43%. Furthermore, mutations in genes encoding the desmosomal proteins desmoglein (DSG2), desmocolin (DSC2), and desmoplakin (DSP) are known to cause ARVD/C as well. Therefore, all TFC3 index patients were additionally screened for mutations in these genes in the case that no PKP2 mutation was found, in an attempt to confirm the association with ARVD/C.

Statistical Analysis
Continuous variables are expressed as mean±SD. Discrete variables are shown as percentages. Continuous variables were compared with the use of the Student t test. Categorical variables were analyzed by use of contingency tables and the Pearson χ2 method. In case the expected value was <5, the Fisher exact test was used instead. A value P<0.05 was considered statistically significant. SPSS 15.0 software (SPSS Inc, Chicago, Ill) was used for calculations.

Results
Of the 50 proven ARVD/C patients (40 men), age at time of first symptoms was 35±13 years. Age at diagnosis was 39±13 years on average, with a mean duration of follow-up of 12±9 years. For the 21 TFC3 index patients (13 men), both mean age at first symptoms and at first clinical evaluation were 38±15 years, and follow-up was 9±8 years. The 12 TFC3 family members (2 men) had first been screened at age 34±16 years and followed for 6±5 years on average. EPS were performed in 40 of 50 patients with proven ARVD/C and 11 of 33 TFC3 patients, all 11 being TFC3 index patients.

Table 2 shows prevalence of ECG parameters measured in patients with proven ARVD/C and TFC3 patients.

Patients With Proven ARVD/C
In patients with proven ARVD/C, the activation delay parameters ε waves and prolonged QRS duration were recorded in a minority of cases (8% and 22%, respectively). However, prolonged TAD indicated presence of RV activation delay in the majority (66%; mean, 63 ms; median, 60; range, 40 to 140). The large majority of patients (94%) had shown any VT with LBBB morphology spontaneously. The new VT parameter occurring most frequently was the recording of >1 different VT morphology when both spontaneous and PES-induced VT episodes were taken into account. In 34 of 40 (85%) ARVD/C patients who underwent EPS, >1 VT morphology had been induced by PES. In 15 ARVD/C patients in whom only 1 VT morphology occurred spontaneously, EPS was of additional value to obtain multiple VT morphologies.

TFC3 Index Patients
These 21 patients had mainly come to cardiothoracic attention because of VT with LBBB morphology (n=15; 71%). Of the remaining 6 patients, 2 had presented with palpitations caused by multiple ventricular premature complexes and 4 with ventricular fibrillation. Because during follow-up 2 of these patients also showed VT with LBBB morphology, in total 17 patients had this arrhythmia (Table 2). With respect to RV activation delay, none had ε waves or QRS duration >110 ms. However, 7 (33%) showed prolonged TAD (Figure 1C; mean, 47 ms; median, 45; range, 40 to 60) and would therefore fulfill ARVD/C diagnosis when this criterion is applied additionally to current TFC. Ages at first and last clinical evaluation did not differ significantly between TFC3 index patients with or without a prolonged TAD (P=0.42 and 0.78, respectively).

More than 1 different VT morphology was induced in 6 of 11 patients who underwent EPS. In 4 of these 6, only a single VT morphology had been recorded spontaneously and 1 had presented with VF. In 12 of 21 patients, VT with LBBB morphology and superior axis was recorded, either spontaneously or during EPS. When multiple VT morphologies were recorded, this always included 1 VT with LBBB morphology and superior axis. In total, 12 of 21 TFC3 index patients (57%) met at least 1 of the new criteria on VT morphology, in 4 cases only after EPS. Results were independent of age. Furthermore, fulfillment of 1 of the VT-related criteria measured was not related to a prolonged TAD.
Altogether, 16 (76%) of 21 TFC3 index patients did fulfill at least 1 of the newly proposed additional criteria on TAD and VT.

In Table 2, index patients with proven and probable ARVD/C are compared statistically with respect to prevalence of current and newly proposed ECG criteria. Obviously, most criteria were observed more frequently in the more severely diseased index patients with proven ARVD/C.

### TFC3 Family Members
From a total number of 126 family members of patients with proven ARVD/C, all data required for inclusion in this study were available. Of these 126, 14 family members fulfilled ARVD/C diagnosis and 12 had 3 points according to current TFC. These 12, included in this study, belonged to 10 different families, and all had initially been asymptomatic and underwent cardiological evaluation only because of family screening.

With respect to activation delay, 1 (8%) family member had an ε wave (Table 2). In contrast, RV activation delay appeared to be present in 7 more family members, according to a prolonged TAD (n=8, 67%; Figure 1, A and B). Mean TAD was 58 ms (median, 60; range, 40 to 80). Prolonged TAD occurred significantly more often than current TFC on activation delay (P=0.01). Thus, 7 family members (58%) fulfilled ARVD/C diagnosis when prolonged TAD was applied as an additional TFC. Moreover, occurrence of prolonged TAD was not significantly different between TFC3 index patients and TFC3 family members (P=0.06).

In 5 (42%) relatives, >1000 premature ventricular complexes were observed during 24-hour Holter monitoring, and in 2 women (17%) VT episodes originating from the RV outflow tract were recorded during follow-up. However, because none of the family members had had VTs with multiple morphologies and none underwent EPS, parameters on VT morphology did not contribute to ARVD/C diagnosis in this group.

### DNA Analysis
In 27 (54%) of patients with proven ARVD/C, a total number of 13 different pathogenic PKP2 mutations were identified. Nine of 12 TFC3 family members analyzed (75%) were PKP2 mutation carriers as well. Of 1 of 3 TFC3 family members without mutation, the corresponding ARVD/C index patient did have a PKP2 mutation. This patient did not fulfill any of the newly proposed additional criteria.

Contrarily, a pathogenic PKP2 mutation had been identified in only 7 of 21 (33%) TFC3 index patients. This comprised 5 different mutations, of which 4 occurred in index patients with proven ARVD/C. This strengthens the presumption that the individuals concerned are true ARVD/C patients, probably in an early stage of disease. In 4 other patients in this group, PKP2 mutations with uncertain pathogeneity were observed. The disease causing influence of these so-called “unclassified variants” is uncertain because they were located outside functional domains, were not located in highly conserved domains, or did not change the polarity of the amino acid involved. All 14 TFC3 index patients without pathogenic PKP2 mutations were screened for mutations in DSG2, DSC2, and DSP. No mutations with proven pathogeneity were identified in any of these genes.

All parameters analyzed showed no significant differences in prevalence between mutation carriers and noncarriers (P=0.23 to 1).

### Discussion
In this study, we assessed the diagnostic value of new additional ECG criteria in patients with probable ARVD/C, that is, 3 points according to the generally accepted TFC. Because during the past decade, clinical, genetic, and basic studies on ARVD/C increased insight in the disease and its underlying pathophysiologic mechanism, improvement of sensitivity of current TFC, as established in 1994, appeared to be a challenge of highest priority.

In total, 23 of 33 (70%) TFC3 patients fulfilled ARVD/C diagnosis when newly proposed criteria were applied additionally to current TFC. Results were not significantly different between mutation carriers and noncarriers.

### New Diagnostic Criteria
In a previous study, we demonstrated that TAD ≥55 ms, recording of VT with LBBB morphology and superior axis and multiple VT morphologies are all highly specific for ARVD/C and are observed more often than current TFC. Furthermore, reproducibility of TAD measurement was high. In this previous study, patients with proven ARVD/C were compared with a group of control subjects, consisting of 27 patients with idiopathic VT originating from the RV outflow tract. In this latter group, only 1 patient showed a prolonged TAD, and mean TAD was 41 ms (range, 25 to 60). Compared with this control group, TAD values were significantly longer in both TFC3 index patients and TFC3 family members from the present study (P=0.006 and 0.005, respectively). In the present study, high sensitivity of newly proposed criteria was confirmed in patients suspected of ARVD/C but who did not fulfill current diagnostic criteria. Hallmarks of ARVD/C could be observed in a majority of these patients, even when asymptomatic. This latter finding is in accordance with previous studies in which absence of symptoms appeared to be a poor index for disease severity, because ECG changes and structural abnormalities could be detected long before occurrence of the first VT episode.

After demonstration of specificity earlier, this study was particularly destined for validation of the new additional criteria to improve ARVD/C diagnosis. We strived only to evaluate ARVD/C patients who had not been diagnosed as such because of lack of sensitivity of current TFC and excluded patients with evidence of other diseases. Therefore, only patients with 3 points according to current TFC were included in this study. Moreover, this strategy enabled us to directly establish which patients would fulfill diagnosis, if these new criteria would be applied additionally to current TFC.
Hamid et al. previously suggested a modified set of diagnostic criteria for first-degree family members of patients with proven ARVD/C. However, because of a positive family history, these relatives already fulfill 1 of the current TFC (which can be major or minor, depending on type of history) and consequently need fewer of other criteria to be diagnosed with ARVD/C. However, this significant increase in sensitivity constitutes the potential hazard that family members will be stigmatized unnecessarily. Having a positive family history indicates a higher risk to develop ARVD/C but does not change the degree of disease. Therefore, we advocate that instead of applying different sets of diagnostic criteria for index cases and their family members, respectively, it seems favorable to improve diagnostic power of the current TFC by addition of new criteria. Thereby, not only affected relatives will be better identified but also identification of new index cases will be ameliorated.

Activation delay and loss of myocardial tissue can be recorded most directly and sensitively by RV mapping during EPS as late potentials and low voltage areas, respectively. However, the aim of our study was to present new ECG criteria universally applicable in every cardiological center. These new and more sensitive ECG criteria on activation delay facilitate diagnosing ARVD/C earlier, with noninvasive tools. Thereby, invasive EPS will be superfluous for diagnostic purpose in many patients. Still, EPS can be performed in equivocal cases to investigate activation delay and inducibility of multiple VT morphologies. Because RV mapping had been performed in a small minority of proven ARVD/C and TFC3 index patients and also not according to a specific protocol, these limited data have not been incorporated in the present study.

In total, 5 of 21 TFC3 index patients and 4 of 12 family members did not fulfill any of the newly proposed additional criteria. These patients had a mean age of 41 ± 16 years, and only 2 are men. Because age was similar to that in patients with proven ARVD/C, age alone cannot explain the difference in criteria fulfillment. Contrarily, sex may play a role. The patients not fulfilling any of the new criteria form a clinically very heterogeneous group because all acquired their 3 TFC points by fulfilling a different combination of criteria. Long-term follow-up will be needed to show whether these individuals are presently in an early stage of ARVD/C or if they have another disease entity currently not definable. The former is expected, especially in the 1 index patient and 2 family members carrying a pathogenic PKP2 mutation.

DNA Analysis
A single member of a family with PKP2 mutation did not carry this mutation herself. She was suspected for ARVD/C though, because in her brother, who had died suddenly at age 20, ARVD/C was proven on autopsy. In addition, an area of hypokinesia was observed echocardiographically in her RV free wall. However, diagnosis is doubtful in her case because the ECG shows no abnormalities and no arrhythmias have ever been recorded. Moreover, she did not meet any of the newly proposed criteria.

Position of New Criteria
In both TFC3 subgroups (index patients and family members), addition of prolonged TAD to current TFC as a minor criterion will increase the number of individuals recognized to have RV activation delay and ARVD/C diagnosis importantly, without loss of specificity. In contrast, new VT criteria are only applicable in subjects with spontaneous and/or inducible VT. Recording a VT with LBBB morphology and superior axis or multiple VT morphologies is sensitive and more specific for ARVD/C than current TFC. Therefore we advocate that these criteria should either outweigh or replace the current criterion of LBBB type VT, which is without definition of axis. However, for addition of new criteria, weighing should be performed in relation to all diagnostic parameters, including those on structural abnormalities and family history. In asymptomatic family members, the new VT criteria are not useful, at least in the absence of EPS.

Study Limitations
This study was limited by small numbers. This might explain part of the differences being nonsignificant.

The gold standard for diagnosis is demonstration of transmural fibrofatty replacement in the RV. Because biopsies have not been performed in any of the TFC3 patients, it cannot be established to what extent true ARVD/C is represented or discovered by implication of new parameters. However, from both technical and ethical perspectives, we used the best tools available to validate the newly proposed additional criteria for diagnostic purposes. Moreover, both prolonged TAD and VT morphology criteria are expressions of well-known and generally accepted ARVD/C characteristics, being activation delay and VT originating from multiple RV sites, respectively. The new ECG criteria form extensions and improvement of the already existing criteria including \( \epsilon \) waves, QRS widening, and VT with LBBB morphology.

Late potentials, forming the third of current TFC on activation delay, have not been included in our analyses, because these had been measured in only a small minority of patients. Therefore, we considered comparison of prevalence between prolonged TAD and late potentials invalid. Notably, because this is a reflection of daily practice, in which a 12-lead ECG is available in every cardiological center, whereas a signal-averaged ECG is not, prolonged TAD is the parameter with potentially a more general applicability. For this same reason, recording of low-voltage areas and late potentials during EPS, although being more direct measurements of activation delay and myocardial loss, were not included in this study.

All individuals included in this study had been screened for mutations in the PKP2 gene. Other desmosomal genes known to be involved in ARVD/C, for example, Desmoglein-2, Desmocollin, and Desmoplakin, have been analyzed in all TFC3 index patients as well. For index patients with proven ARVD/C, this work is in progress. Analyses performed thus far have revealed in these genes...
mutations with uncertain pathogeneity in a small minority of the patients screened. Longer follow-up and analysis of larger numbers of patients will be crucial to establish whether prolonged TAD correlates with disease development and symptoms.

Conclusions
In the present study, we evaluated the diagnostic value of additional 12-lead ECG criteria in patients with probable ARVD/C (TFC3): (1) prolonged TAD, being a new indicator of activation delay, (2) recording of VT with LBBB morphology and superior axis, and (3) multiple VT morphologies. Prolonged TAD was observed in 45% of all patients with probable ARVD/C, thereby being the most sensitive indicator of activation delay. In total, 14 (42%) TFC3 patients, 7 (33%) index patients, and 7 (58%) family members fulfilled ARVD/C diagnosis when prolonged TAD was applied additionally to current TFC on activation delay. VT with LBBB morphology and superior-axis and/or multiple VT morphologies were recorded in 12 of 23 (52%) TFC3 index patients, but did not contribute to ARVD/C diagnosis in asymptomatic family members. PES contributed importantly to the yield of different VT morphologies. In total, 23 of 33 (70%) TFC3 patients fulfilled ARVD/C diagnosis when newly proposed criteria were applied additionally to current TFC.

In conclusion, adding the newly proposed additional criteria to current TFC for ARVD/C diagnosis will importantly improve identification of affected individuals. The observation that activation delay described as prolonged TAD has been identified in a high percentage of asymptomatic family members is a promising avenue toward early diagnosis of ARVD/C.

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Disclosures
None.

References
Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by progressive loss of predominantly right ventricular myocardium, which is replaced by fibrofatty tissue. Typically, affected individuals present with ventricular tachycardia between the 2nd and 4th decade of life, but ARVD/C is also a major cause of sudden death in adolescence. Clinical diagnosis was made according to generally accepted task force criteria (TFC). These criteria are highly specific but lack sensitivity. After demonstration of high sensitivity and specificity in a previous study, we showed that our newly proposed additional ECG criteria improved ARVD/C diagnosis. Patients highly suspected of ARVD/C, that is, with 3 points according to current TFC (TFC3), were studied, being 21 index patients and 12 family members of patients with proven ARVD/C. Prolonged terminal activation duration is a new parameter on right ventricular activation delay. Although only 1 of these patients had an epsilon wave, 15 (45%) showed right ventricular activation delay by prolonged terminal activation duration, mainly family members. The new parameters on ventricular tachycardia morphology, ventricular tachycardia with left bundle-branch block morphology and superior-axis and multiple ventricular tachycardia morphologies, were recorded in 12 of 21 (57%) TFC3 index patients but not in family members. Altogether, 70% of highly suspicious patients fulfilled ARVD/C diagnosis when newly proposed criteria were applied additionally to current TFC. Thus, adding our newly proposed ECG criteria would improve sensitivity of current TFC and thereby ARVD/C diagnosis. By this means, affected individuals can be recognized in an earlier stage of disease, and appropriate therapeutic measures can be taken to prevent arrhythmias and sudden death.
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