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Incremental Value of Cardiac Magnetic Resonance Imaging in Arrhythmic Risk Stratification of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers

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Objectives The aim of this study was to identify the incremental value and optimal role of cardiac magnetic resonance (CMR) imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)–associated desmosomal mutation carriers without histories of sustained ventricular arrhythmia.

Background Risk stratification of ARVD/C mutation carriers is challenging.

Methods Sixty-nine patients (mean age 27.0 ± 15.3 years, 42% men) harboring ARVD/C-associated pathogenic mutations (83% plakophilin 2) without prior sustained ventricular arrhythmias were included. Electrocardiographic and 24-h Holter monitoring findings closest to presentation were analyzed for electrical abnormalities per revised task force criteria. CMR studies were done to identify abnormal cardiac structure and function according to the revised task force criteria.

Results Overall, 42 patients (61%) presented with electrical abnormalities on the basis of electrocardiography and Holter monitoring, of whom 20 (48%) had abnormal results on CMR. Only 1 of 27 patients (4%) without electrical abnormalities at initial evaluation had abnormal CMR results. Over a mean follow-up period of 5.8 ± 4.4 years, 11 patients (16%) experienced sustained ventricular arrhythmias, exclusively in patients with both electrical abnormalities (electrocardiography and/or Holter monitoring) and abnormal CMR results.

Conclusions These results suggest that electrical abnormalities on electrocardiography and Holter monitoring precede detectable structural abnormalities in ARVD/C mutation carriers. Therefore, evaluation of cardiac structure and function using CMR is probably not necessary in the absence of baseline electrical abnormalities. Among ARVD/C mutation carriers, the presence of both electrical and CMR abnormalities identifies patients at high risk for events and thus patients who might benefit from prophylactic implantable cardioverter-defibrillator placement. (J Am Coll Cardiol 2013;62:1761–9) © 2013 by the American College of Cardiology Foundation

Arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by a high incidence of ventricular arrhythmias

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Abbreviations and Acronyms

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy

CI = confidence interval

CMR = cardiac magnetic resonance

ECG = electrocardiographic

ICD = implantable cardioverter-defibrillator

RV = right ventricular

TFC = task force criteria

VT = ventricular tachycardia

and an increased risk for sudden cardiac death (1,2). Over the past decade, pathogenic ARVD/C-associated mutations have been identified in 5 desmosomal genes (3–7), and clinical genetic testing is now routinely performed (8). Consequently, cardiologists will be more often confronted with the question of how to manage asymptomatic mutation carriers. Because familial ARVD/C is a clinically heterogenous disorder with incomplete penetrance and variable expressivity (9–11), management of mutation carriers remains challenging, and the optimal approach to risk stratification is yet to be elucidated.

Current guidelines recommend serial screening of genetically predisposed patients using a combination of electrocardiography, Holter monitoring, and imaging modalities (12). Many studies have shown that electrocardiography (13–15) and Holter monitoring (16) are useful in the risk stratification of patients with ARVD/C. Because of the anatomical, functional, and tissue-specific characteristics of ARVD/C, cardiac magnetic resonance (CMR) imaging is an ideal technique for the diagnostic workup (17). The incremental value and optimal timing of CMR in the prognostic workup of mutation carriers, however, are not well defined.

In patients with ARVD/C, both electrical uncoupling (18–20) and altered tissue architecture (3,6,20) are thought to contribute to arrhythmic propensity. We hypothesized that mutation carriers with both electrical and structural abnormalities on clinical evaluation are at particularly high risk for developing life-threatening arrhythmias and that CMR is a valuable tool to risk-stratify patients with abnormal electrical baseline test results.

Through prospective follow-up of ARVD/C mutation carriers with no histories of sustained ventricular arrhythmia, we sought to identify the optimal role of CMR within a risk stratification paradigm in these patients. As a secondary objective, we aimed to characterize the association between abnormal electrical test results (electrocardiography and Holter monitoring) and CMR abnormalities in ARVD/C mutation carriers.

Methods

Study population. The study population was identified from the Johns Hopkins ARVD/C registry. The Johns Hopkins ARVD/C registry, established in 1999, prospectively enrolls patients and their family members referred to the Johns Hopkins ARVD/C Center with possible histories of this disease. Participants are contacted, and updated medical records are collected annually. For the present study, 69 registry enrollees were included who: 1) harbored pathogenic ARVD/C-associated desmosomal mutations; 2) had no histories of sustained ventricular tachycardia (VT) or ventricular fibrillation at the time of enrollment; and 3) underwent CMR available for analysis. The majority of study subjects (n = 54 [78%]) were first-degree relatives of ARVD/C probands who were identified through family screening. The remainder (n = 15 [22%]) presented with syncope (n = 6), palpitations (n = 3), or chest pain (n = 1) that was not associated with a documented arrhythmia; 5 were incidentally discovered during routine medical examination. All registry participants provided written informed consent, and the study protocol was approved by the Johns Hopkins School of Medicine Institutional Review Board.

Clinical electrical baseline testing. Participants were evaluated as described previously (16,21). Medical records for each patient were obtained at enrollment. For the purpose of this study, 12-lead electrocardiograms and Holter results closest to presentation were obtained and carefully reviewed for the presence of electrical abnormalities per revised task force criteria (TFC) (22) (Online Table 1).

All 69 patients underwent routine 12-lead electrocardiography (recorded at rest, 10 mm/mV at a paper speed 25 mm/s). Electrocardiographic (ECG) results were classified as abnormal when repolarization (precordial T-wave inversion in leads V_1 and V_2 or beyond) and/or depolarization (epsilon waves or terminal activation duration $\geq$55 ms) criteria for ARVD/C were present. No patient was taking antiarrhythmic or other medications known to affect the QRS complex at the time of electrocardiography.

Overall, 54 patients (78%) underwent 24-h Holter monitoring. The Holter monitor was analyzed for ventricular ectopic activity, defined as isolated premature ventricular complexes exceeding 500 in 24 h and/or recorded runs of nonsustained VT ($\geq$3 consecutive premature beats at >100 beats/min).

Electrocardiography and Holter monitoring were combined to obtain a composite measure of electrical abnormalities at presentation. Any participant meeting at least 1 of the minor ECG or Holter TFC (22) was considered to have evidence of electrical abnormality.

CMR imaging. All 69 study participants underwent CMR, performed according to standard protocols for ARVD/C, which have previously been described in detail (23,24). All images were acquired using a 1.5-T scanner with a phased-array cardiac coil during breath-holds gated to the electrocardiogram. Cine images were acquired in axial and short-axis planes covering the entire right and left ventricles with a steady-state free precession technique. Fast spin echo (both fat-suppressed and non-fat-suppressed) images were acquired in both axial and short-axis planes with double inversion recovery blood suppression pulses. A gadolinium-based contrast agent was administered intravenously, and contrast-enhanced images were acquired on average 10 minutes after contrast administration using a phase-sensitive inversion recovery sequence in both axial and short-axis planes.

Table 1 Patient Characteristics

Variable	Overall (n = 69)	Normal Electrical Baseline Test Results (n = 27)	Abnormal Electrical Baseline Test Results (n = 42)	p Value
Men	29 (42%)	12 (44%)	17 (40%)	NS
Follow-up (yrs)	5.8 ± 4.4	7.0 ± 4.2	5.1 ± 4.5	NS
Age at presentation (yrs)	27.0 ± 15.3	24.2 ± 16.7	28.8 ± 14.2	NS
Symptomatic at presentation	22 (32%)	3 (11%)	19 (45%)	0.003
Syncope	9 (13%)	0 (0%)	9 (21%)	0.010
Presyncope	6 (9%)	0 (0%)	6 (14%)	0.040
Palpitations	16 (23%)	3 (11%)	13 (31%)	NS
Chest pain	3 (4%)	0 (0%)	3 (7%)	NS
ICD implantation during follow-up	26 (38%)	2 (7%)	24 (57%)	<0.001
Age at implantation (yrs)	29.7 ± 12.6	47.1 ± 10.5	28.1 ± 11.8	NS

Values are n (%) or mean ± SD.
ICD = implantable cardioverter-defibrillator.

CMR studies were analyzed for fulfillment of modified TFC (22), defined as the presence of an RV regional wall motion abnormality (akinesia, dyskinesia, or dyssynchronous contraction) combined with enlarged RV end-diastolic volume (≥100 ml/m^2 in men and ≥90 ml/m^2 in women) and/or reduced RV ejection fraction (≤45%) (Online Table 1).

CMR analysis was based on consensus agreement of radiologists with special interest in ARVD/C, who were blinded to all clinical data of included patients. CMR results were classified as abnormal if at least a minor task force criterion for ARVD/C was present. Additionally, the CMR analysts ascertained the presence of qualitative findings that were previously associated with ARVD/C (fatty infiltration and delayed gadolinium enhancement, as well as left ventricular involvement).

Follow-up and outcome measure. Patient management was performed at the discretion of the treating physician. According to ARVD/C registry protocol, patients were prospectively followed at yearly intervals. The primary outcome measure was the occurrence of a sustained ventricular arrhythmia (a composite measure of the occurrence of spontaneous sustained VT, aborted sudden cardiac death, sudden cardiac death, or appropriate implantable cardioverter-defibrillator (ICD) intervention for a ventricular arrhythmia; definitions are provided in Online Table 2). In patients without ICDs, the primary outcome was adjudicated on the basis of reviewing electrocardiograms and medical records; in patients with ICDs, the device-stored electrocardiograms were reviewed for the appropriateness of ICD therapy. In patients with multiple endpoints, the first event was considered the censoring event.

Statistical analysis. All continuous data are expressed as mean ± SD and categorical variables as number (percent). Continuous variables were compared using independent Student *t* tests or Mann-Whitney *U* tests and categorical data using chi-square or Fisher exact tests. Cumulative freedom from the composite arrhythmic outcome since presentation was determined using the Kaplan-Meier method. Differences in survival among groups were evaluated using a log-rank test. A p value <0.05 was considered significant. Statistical calculations were performed using SPSS version 19.0 (IBM, Chicago, Illinois).

Table 2 Electrical Baseline Test Results in ARVD/C Mutation Carriers Without Prior Ventricular Arrhythmia

Abnormal ECG results	39 (57)
Negative T waves in leads V_1 and V_2	7 (10)
Negative T waves leads V_1 to V_3 or beyond	28 (41)
Negative T waves in leads V_4 to V_6 in the presence of RBBB	0 (0)
Epsilon waves	1 (1)
Terminal activation duration ≥55 ms	13 (19)
Abnormal results on Holter monitoring*	14 (26)
>500 PVCs/24 h	13 (24)
Nonsustained VT recorded	9 (17)
Electrical abnormalities†	42 (61)

Values are n (%). *Fifty-four patients underwent Holter monitoring. †Defined as the presence of ≥1 abnormal ECG and/or Holter monitoring parameter.
ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; ECG = electrocardiographic; PVC = premature ventricular complex; RBBB = right bundle branch block; VT = ventricular tachycardia.

Results

Clinical characterization. The study population comprised 69 patients from 40 families who were identified as harboring pathogenic ARVD/C-associated desmosomal mutations (83% plakophilin-2) (Online Table 3).

Characteristics of study participants are shown in Table 1. Mean age at presentation was 27.0 ± 15.3 years, and 42% were men. Of 69 subjects, 47 (68%) were asymptomatic at presentation; the remainder (n = 22 [32%]) had histories of syncope, presyncope, palpitations, or chest pain.

Overall, 42 patients (61%) had abnormal baseline electrical test results, defined as at least 1 minor criterion for ARVD/C on the basis of evaluation of ECG and Holter monitoring results (Table 2). In the total cohort, abnormal ECG results were observed in 39 patients (57%), and abnormal Holter findings were observed in 14 of 54 patients (26%). Overall, 35 patients (51%) fulfilled repolarization criteria for ARVD/C (28 major and 7 minor), 13 patients (19%) fulfilled depolarization criteria for ARVD/C (1 major and 12 minor),

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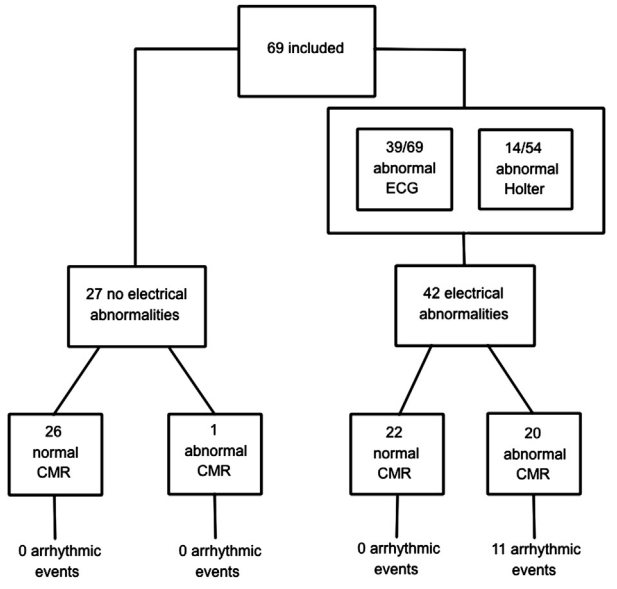

Figure 1 Patient Flowchart

Patient flowchart showing prognostic workup and arrhythmic events in the study population. CMR = cardiac magnetic resonance; ECG = electrocardiography.

and 14 patients (26%) fulfilled arrhythmia criteria for ARVD/C (all minor criteria). ICDs were implanted in 26 patients (38%), of whom the majority (n = 24 [92%]) had abnormal ECG and/or Holter results at baseline (Table 1). Prognostic workup for the study population is shown in Figure 1.

CMR findings. Structural and functional CMR abnormalities in the entire cohort are summarized in Table 3. Overall, 21 patients (30%) had abnormal CMR results fulfilling TFC for ARVD/C. The majority of patients with abnormal CMR results fulfilled major TFC (17 of 21 patients [81%]). Symptomatic patients were significantly more likely to fulfill TFC for CMR than asymptomatic patients (14 [64%] patients vs. 7 [15%] patients, $p < 0.001$). The mean time between presentation and CMR was 3.4 ± 3.9 years. There was no statistically significant difference in age at CMR for patients with normal versus abnormal CMR results (31.5 ± 16.6 years vs. 28.0 ± 11.7 years, p = NS).

Compared with patients with normal electrical baseline test results, those with electrical abnormalities on the basis of ECG and Holter evaluation were significantly more likely to have abnormal CMR results (20 [48%] patients vs. 1 [4%] patient, $p < 0.001$), with higher RV volumes and lower biventricular ejection fractions (Table 3). The only patient with normal electrical test results and abnormal CMR results had dyskinesia of the RV free wall and a mildly diminished RV ejection fraction (45%), fulfilling a minor task force criterion on CMR. This patient had isolated T-wave inversions in leads V_1 and V_3 on electrocardiography (Online Fig. 1) and 20 premature ventricular complexes on 24-h Holter monitoring, thus not fulfilling TFC for electrocardiography or Holter monitoring.

Arrhythmic outcomes. Over a mean follow-up period of 5.8 ± 4.4 years, 11 patients (16%) experienced sustained ventricular arrhythmias. Characteristics of patients experiencing arrhythmic events are shown in Table 4. Of 11 patients experiencing events, the majority were men and probands (both n = 8 [73%]). The mean age at first arrhythmic event was 25.2 ± 5.0 years (range: 17 to 32 years), and the mean cycle length of the event was 258 ± 42 ms (range: 188 to 323 ms). For 7 patients (64%), the first arrhythmic event was an appropriate ICD intervention; 4 patients had spontaneous VT or ventricular fibrillation. The cycle length of the tachyarrhythmia was similar for patients who experienced ICD interventions and those with spontaneous episodes of sustained VT or ventricular fibrillation (260 ± 37 ms vs. 255 ± 57 ms, respectively, p = NS). ICD details are provided in Online Table 4. ICD programming was not significantly different between ICD carriers with and without appropriate intervention (mean rate cutoffs 189 ± 12 beats/min and 191 ± 15 beats/min, respectively, p = NS). None of the study population required cardiac transplantation or died during follow-up.

All patients with arrhythmic events presented with electrical abnormalities (Fig. 2). Mean time between presentation and the arrhythmic event was 4.5 ± 4.3 years (range: 0.2 to 14.0 years). For both electrocardiography and Holter monitoring separately, event-free survival was significantly lower in patients with abnormal test results compared with those with normal test results ($p = 0.001$ and $p = 0.002$, respectively). Overall, event-free survival in patients with any electrical abnormality (on electrocardiography and/or Holter monitoring) was significantly lower than survival in patients without electrical abnormalities ($p = 0.001$). Among patients with electrical abnormalities, cumulative survival free from arrhythmic events after 1, 5, and 10 years was 95% (95% confidence interval [CI]: 87% to 100%), 76% (95% CI: 60% to 92%), and 66% (95% CI: 46% to 86%), respectively.

Sustained ventricular arrhythmias occurred exclusively in patients with abnormal CMR results (Fig. 3). All patients with arrhythmic events fulfilled a major task force criterion for CMR. Biventricular involvement was seen in 7 of 11 patients (64%) experiencing sustained tachyarrhythmias. Compared with patients with electrical abnormalities in isolation (n = 22), patients with both electrical and CMR abnormalities (n = 20) had a significantly higher propensity toward ventricular arrhythmia ($p < 0.001$). In this group, cumulative survival free from arrhythmic events after 1, 5, and 10 years was 89% (95% CI: 75% to 100%), 54% (95% CI: 29% to 79%), and 36% (95% CI: 9% to 63%), respectively.

Discussion

During the past decade, understanding of the genetic basis of ARVD/C has evolved greatly (3–7). Genetic screening of patients with ARVD/C identifies pathogenic mutations in

Table 3 Quantitative and Qualitative CMR Findings in the Study Population

Variable	Overall (n = 69)	Normal Electrical Baseline Test Results (n = 27)	Abnormal Electrical Baseline Test Results (n = 42)	p Value
Fulfillment of TFC for CMR	21 (30%)	1 (4%)	20 (48%)	<0.001
Major criterion	17 (25%)	0 (0%)	17 (41%)	<0.001
Minor criterion	4 (6%)	1 (4%)	3 (7%)	NS
Quantitative parameters				
RV EDV/BSA (ml/m^2)	84.5 ± 21.2	77.6 ± 16.1	90.6 ± 24.0	0.012
RV ESV/BSA (ml/m^2)	46.0 ± 18.7	37.3 ± 8.7	52.6 ± 22.5	0.006
RV EF (%)	47.2 ± 10.1	52.0 ± 5.2	43.2 ± 11.9	0.002
LV EDV/BSA (ml/m^2)	80.2 ± 14.9	76.2 ± 14.5	82.3 ± 14.7	NS
LV ESV/BSA (ml/m^2)	37.4 ± 10.2	32.7 ± 8.1	40.2 ± 10.5	0.004
LV EF (%)	53.8 ± 6.8	57.7 ± 4.6	51.4 ± 6.7	<0.001
LV EDV/RV EDV	0.97 ± 0.17	0.99 ± 0.07	0.95 ± 0.20	NS
Qualitative parameters				
Global RV dilation	16 (23%)	0 (0%)	16 (38%)	<0.001
Global RV hypokinesia	12 (17%)	0 (0%)	12 (29%)	0.002
Global LV dilation	2 (3%)	0 (0%)	2 (5%)	NS
Global LV hypokinesia	4 (6%)	0 (0%)	4 (10%)	NS
RV regional wall motion abnormalities	24 (35%)	3 (11%)	21 (50%)	0.001
RV regional aneurysm	6 (9%)	1 (4%)	5 (12%)	NS
RV regional fatty infiltration	9/68 (13%)	1/27 (4%)	8/41 (20%)	NS
RV regional delayed enhancement	2/61 (3%)	0/24 (0%)	2/37 (5%)	NS
LV regional wall motion abnormalities	6 (9%)	0 (0%)	6 (14%)	0.040
LV regional aneurysm	0 (0%)	0 (0%)	0 (0%)	—
LV regional fatty infiltration	13 (19%)	1 (4%)	12 (29%)	0.010
LV regional delayed enhancement	7/61 (11%)	1/24 (4%)	6/37 (16%)	NS
Involvement				
RV involvement only	12 (17%)	2 (7%)	10 (24%)	NS
LV involvement only	3 (4%)	1 (4%)	2 (5%)	NS
Biventricular involvement	15 (22%)	1 (4%)	14 (33%)	0.004

Values are n (%), mean ± SD, or n/N (%).

BSA = body surface area; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; RV = right ventricular; TFC = task force criteria.

approximately one-half of individuals (8–10,25–27). Once a pathogenic mutation is identified in a proband, downstream genetic testing of family members is recommended (12,26). Although many studies have assessed noninvasive modalities for risk stratification in patients with ARVD/C (13,14,16,28–30), several uncertainties remain in the evaluation and management of these patients. For example, it is unclear what minimal initial testing should be performed in mutation-positive patients. Although conventional wisdom suggests that patients at risk for developing ARVD/C on the basis of the presence of a pathogenic mutation should undergo complete ARVD/C screening, including CMR, at regular intervals, there is little objective evidence to demonstrate the necessity of this approach. Also, with regard to CMR, it is important to recognize that many imaging centers have little or no experience with clinical evaluation of ARVD/C and that nonspecific findings such as fatty infiltration alone or minor wall motion abnormalities are often overinterpreted as providing evidence of ARVD/C (17,31–34). Our study provides data that help address some of the clinically important questions relating to ARVD/C mutation carriers without histories of prior arrhythmic events.

Electrical abnormalities on electrocardiography and Holter monitoring. An important finding of this study is that ARVD/C mutation carriers who lack electrical abnormalities on ECG and Holter monitor evaluation have a very low risk for arrhythmia during a mean follow-up period of 7 years. These data suggest that the presence of a mutation itself does not necessarily confer risk for arrhythmia in these patients. These data are also in alignment with prior retrospective studies, which have shown that electrocardiography (13–15) and Holter monitoring (16) are useful tools in the risk stratification of patients with ARVD/C. Although included in the revised TFC, we did not use signal-averaged electrocardiography to define electrical abnormalities. In our cohort, signal-averaged ECG data were available in only a subset of patients, in whom they did not add to the risk stratification paradigm.

We determined electrical abnormalities based on the ECG and Holter examinations closest to presentation. It is possible that some of the patients with normal results on electrocardiography and Holter monitoring at presentation developed electrical changes during their clinical courses; however, this was not specifically investigated in our study.

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Table 4 Characteristics of Patients According to Arrhythmic Outcomes

Variable	No Arrhythmic Event (n = 58)	Arrhythmic Event (n = 11)	p Value
Men	21 (36%)	8 (73%)	0.024
Proband	7 (12%)	8 (73%)	<0.001
Symptomatic at presentation	15 (26%)	7 (64%)	0.014
Syncope	7 (12%)	2 (18%)	NS
Presyncope	4 (7%)	2 (18%)	NS
Palpitations	10 (17%)	6 (55%)	0.007
Chest pain	2 (3%)	1 (9%)	NS
Abnormal results on ECG	29 (50%)	10 (91%)	0.012
Negative T waves in leads V_1 and V_2	6 (10%)	1 (9%)	NS
Negative T waves in leads V_1 to V_3 or beyond	19 (33%)	9 (82%)	0.002
Epsilon waves	0 (0%)	1 (9%)	0.021
Terminal activation duration ≥55 ms	9 (16%)	4 (36%)	NS
Abnormal results on Holter monitoring*	10/49 (20%)	4/5 (80%)	0.004
>500 PVCs/24 h	9/49 (18%)	4/5 (80%)	0.002
Nonsustained VT recorded	6/49 (12%)	3/5 (60%)	0.006
Fulfillment of TFC for CMR	10 (17%)	11 (100%)	<0.001
Major TFC	6 (10%)	11 (100%)	<0.001
Minor TFC	4 (7%)	0 (0%)	NS
RV EDV/BSA (ml/m^2)	80.9 ± 19.2	109.9 ± 20.7	<0.001
LV EDV/BSA (ml/m^2)	78.6 ± 13.9	87.7 ± 17.6	NS
RV EF (%)	49.3 ± 9.2	32.6 ± 6.8	<0.001
LV EF (%)	55.2 ± 6.0	45.8 ± 4.9	<0.001
RV wall motion abnormalities	14 (24%)	11 (100%)	<0.001
RV fatty infiltration	7 (12%)	2 (20%)	NS
RV delayed enhancement†	0/52 (0%)	2/9 (22%)	0.001
LV wall motion abnormalities	4 (7%)	2 (18%)	NS
LV fatty infiltration	7 (12%)	6 (55%)	0.001
LV delayed enhancement†	5/52 (10%)	2/9 (22%)	NS
RV involvement only	8 (14%)	4 (36%)	NS
LV involvement only	3 (5%)	0 (0%)	NS
Biventricular involvement	8 (14%)	7 (64%)	<0.001

Values are n (%) or mean ± SD. *54 patients underwent Holter monitoring. †For 61 patients, delayed enhancement images were available.
Abbreviations as in Tables 2 and 3.

This leads to 2 possibilities: 1) ARVD/C mutation carriers without electrical abnormalities at baseline do not have disease expression and therefore have no long-term risk for arrhythmia; or 2) the more likely possibility that ARVD/C mutation carriers without electrical abnormalities are in the concealed phase of the disease before overt disease manifestation. The fact that none of the patients without electrical abnormalities developed sustained ventricular arrhythmias during almost 6 years of follow-up suggests that there may be a long latent concealed phase in most patients. It is important to note in this regard that we routinely advise mutation carriers to give up high-level athletics. It is certainly possible that the absence of arrhythmic events in patients with an initially negative electrical and CMR results may not be applicable to ARVD/C mutation carriers who do not restrict athletic activity.

Correlation of electrocardiography and Holter monitoring with CMR. The second important result of our study is the very low incidence of abnormal CMR results in patients with normal results on electrocardiography and Holter monitoring at baseline. Interestingly, only 1 patient in the cohort fulfilled a minor task force criterion for CMR in the absence of electrical abnormalities at presentation. It is important to note that the ECG results in this patient were abnormal, with T-wave inversion in leads V_1 and V_3 but not lead V_2. Because T-wave inversion was not seen in consecutive precordial leads, TFC for ARVD/C were not fulfilled, and ECG results were classified as normal. It is also important to note that this patient, with an atypical ECG pattern and minor CMR abnormalities, did not experience an arrhythmic event during follow-up. These data lead us to believe that electrical abnormalities precede detectable structural changes in ARVD/C and that evaluation of cardiac structure and function using CMR may not be necessary in the absence of baseline electrical abnormalities. New CMR sequences such as high-resolution T1 mapping are promising tools to detect early, subtle changes in the right ventricle.

Arrhythmic events. The final important result of our study is that arrhythmic events occurred exclusively in patients

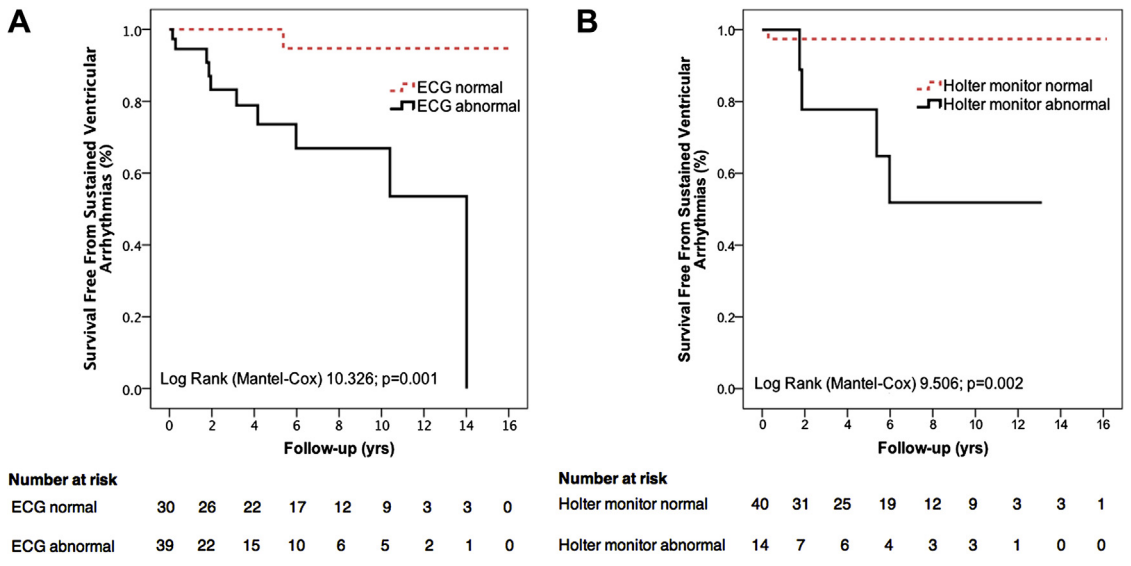

Figure 2 **Risk for Sustained Ventricular Arrhythmias on the Basis of ECG and Holter Monitoring**

Cumulative survival free from sustained ventricular arrhythmias among patients stratified according to the results of electrocardiography (ECG) **(A)** and Holter monitoring **(B)**. Event-free survival in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) mutation carriers who fulfilled at least 1 minor task force criterion for ARVD/C on ECG and/or Holter monitoring was significantly lower than survival in patients without electrical abnormalities.

who met both electrical (ECG and/or Holter monitoring) and structural (CMR) criteria for ARVD/C, suggesting that an abnormal electrical and structural substrate is required for arrhythmic occurrence. Our observation that patients with electrical abnormalities in isolation had a low risk for arrhythmic events in our study during 6 years of follow-up opens the path for the strategic implementation of CMR in patients with abnormal electrical baseline test results. This insight is critically important, because CMR might be able to identify those who may benefit from intensive screening, further clinical investigation, and consideration of prophylactic ICD implantation.

Strategic use of CMR. Our study reveals the potential of CMR to identify desmosomal mutation carriers at high risk for arrhythmias, when used strategically in conjunction with the results of electrocardiography and Holter monitoring. Prior work by our group has demonstrated the utility of electrocardiography and Holter monitoring in the risk stratification of mutation carriers and highlighted the increased arrhythmic risk of probands compared with family members detected through cascade screening (15). In the present study, 8 of 11 patients (73%) experiencing arrhythmic events were probands, similar to prior findings. The present study builds on this risk stratification paradigm and suggests a strategy for optimizing the use of CMR to evaluate mutation carriers presenting without histories of arrhythmic events. On the basis of our results, the optimal approach would be to use CMR in patients with abnormal results on electrocardiography and/or 24-h Holter monitoring at initial evaluation. Evaluation of cardiac structure and function using CMR may be able to be deferred in the absence of baseline electrical abnormalities, at least among asymptomatic family members detected through cascade screening. The clinical follow-up evaluation of patients who have no electrical abnormalities at baseline and those who meet electrical criteria but do not have CMR abnormalities remains to be determined. Although further studies are needed to validate our data, these results suggest a strategy to optimize the use of CMR to detect ARVD/C-associated mutation carriers who are at significant risk for arrhythmic events, while limiting the use of this second-line test among those who are unlikely to derive benefit from its results.

Study limitations. Rate cutoff for therapy during ICD programming was not uniform. However, ICD programming was not different between ICD carriers with and without interventions, and ICD discharges were adjudicated as appropriate on the basis of ECG analyses. Studies of ARVD/C, in particular involving CMR, are typically small. Larger studies are needed to validate our findings and to determine optimal clinical follow-up recommendations for these high-risk patients. Also, our study sample was underpowered to assess the independent prognostic value of specific parameters. However, to our knowledge, we studied the largest cohort of asymptomatic ARVD/C mutation carriers using an integrated approach of both electrical and CMR investigations. This provided us with the unique possibility to assess the optimal role of CMR within the prognostic workup of these patients. The only imaging modality we used to define structural and/or functional

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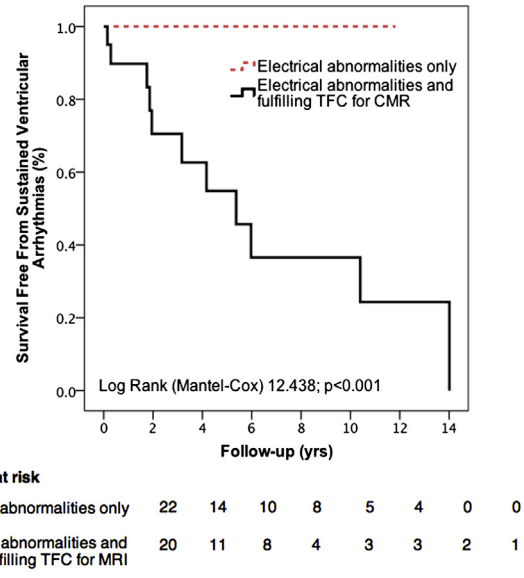

Figure 3 **Incremental Risk for Sustained Ventricular Arrhythmias With Abnormal CMR Results**

Mutation carriers who met both electrical (electrocardiographic and/or Holter monitoring) and cardiac magnetic resonance (CMR) criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy had significantly higher arrhythmic propensity compared with patients with abnormal results on electrocardiography and/or Holter monitoring in isolation. MRI = magnetic resonance imaging; TFC = task force criteria.

abnormalities was CMR. Yet, because CMR offers the unique possibility to assess cardiac morphologic, functional, and tissue characteristics in a single investigation, it is frequently used in the prognostic evaluation of ARVD/C mutation carriers. In our study, CMR was not performed at the time of initial presentation for all study participants. This represents clinical practice, in which CMR is often not considered a first-line test for ARVD/C. Our study results actually favor this approach, because all events occurred in patients with abnormalities detected on their electrical baseline tests, and electrical abnormalities appear to precede abnormal CMR findings. It would be interesting to see whether similar results can be obtained using echocardiography or angiography.

Conclusions

In this prospective cohort of 69 ARVD/C-associated pathogenic mutation carriers without prior sustained ventricular arrhythmias, we demonstrate that there is a strong association between electrical baseline abnormalities on electrocardiography and Holter monitoring and structural and functional abnormalities detected by CMR. Importantly, we show that CMR is a valuable tool to identify patients at high risk for ventricular arrhythmias, especially when used strategically in patients with abnormal electrical baseline test results.

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Key Words: cardiomyopathy ■ electrocardiography ■ magnetic resonance imaging ■ risk stratification ■ tachyarrhythmias.

APPENDIX

For supplemental tables and a figure, please see the online version of this article.