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Evaluation of Structural Progression in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Thomas P. Mast, MD; Cynthia A. James, PhD; Hugh Calkins, MD; Arco J. Teske, MD, PhD; Crystal Tichnell, MGC; Brittney Murray, MS; Peter Loh, MD, PhD; Stuart D. Russell, MD; Birgitta K. Velthuis, MD, PhD; Daniel P. Judge, MD; Dennis Dooijes, PhD; Ryan J. Tedford, MD; Jeroen F. van der Heijden, MD, PhD; Harikrishna Tandri, MD; Richard N. Hauer, MD, PhD; Theodore P. Abraham, MD, PhD; Pieter A. Doevendans, MD, PhD; Anneline S. J. M. te Riele, MD, PhD; Maarten J. Cramer, MD, PhD

IMPORTANCE Considerable research has described the arrhythmic course of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). However, objective data characterizing structural progression, such as ventricular enlargement and cardiac dysfunction, in ARVD/C are relatively scarce.

OBJECTIVES To define the extent of structural progression, identify determinants of structural progression, and determine the association between structural progression and electrocardiographic (ECG) changes in patients with ARVD/C.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, first- and last-available echocardiograms of 85 patients with ARVD/C fulfilling 2010 Task Force diagnostic criteria (TFC) from a transatlantic ARVD/C registry were retrospectively compared to assess structural disease progression. Right ventricular (RV) size and systolic function between baseline and last follow-up were compared. The RV size was determined by RV outflow tract dimension, and RV and left ventricular (LV) systolic function were determined by RV fractional area change (RV-FAC) and LV ejection fraction (LVEF), respectively. Multivariable logistic regression was used to study associations between baseline characteristics and the occurrence of structural progression.

MAIN OUTCOMES AND MEASURES The main outcome was the change in variables indicating structural progression. Secondary outcomes were the correlation with electrical progression and identification of the association between baseline characteristics and occurence structural progression.

RESULTS Among the 85 patients with ARVD/C, mean (SD) age at baseline was 42.8 (14.4) years and 47 (55%) were men. After a mean (SD) follow-up of 6.4 (2.5) years, RV outflow tract dimension increased from 35 mm (interquartile range [IQR], 31 to 39) to 37 mm (IQR, 33 to 41) ($P < .001$), RV-FAC decreased from 39% (IQR, 33% to 44%) to 34% (IQR, 24% to 42%) ($P < .001$) (rate −3.3% per 5 years; IQR, −8.9% to 1.2%), indicating large interpatient variability. The LVEF decreased from 55% (IQR, 52% to 60%) to 54% (IQR, 49% to 57%) ($P = .001$) (rate, −0.2% per 5 years; IQR, −6.5% to 1.7%). Forty examinations were reanalyzed to establish the measurement error. Patients exceeding the measurement error by ±2 SDs were identified with significant progressive disease for RV, with a decrease in RV-FAC greater than 10% (n = 21) and, for LV, a decrease in LVEF greater than 7% (n = 23). Progression of RV disease was associated with depolarization criteria at baseline (odds ratio [OR], 9.0; 95% CI, 1.1-74.2; $P = .04$), whereas progression of LV disease was associated with phospholamban (*PLN*) mutation (OR, 8.8; 95% CI, 2.1-37.2; $P = .003$). There was no association between progressive RV/LV structural disease and newly developed ECG TFC.

CONCLUSIONS AND RELEVANCE Structural dysfunction in ARVD/C is progressive with substantial interpatient variability. Significant structural RV progression was associated with prior depolarization abnormalities, whereas LV progression is modified by genetic background. Structural progression was not associated with development of new ECG TFC. The results of this study pave the way for designing and launching trials aimed at reducing structural progression in patients with ARVD/C.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Thomas P. Mast, MD, Division of Cardiology, Room F.01.1.146, Department of Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (t.p.mast@umcutrecht.nl).

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Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy clinically characterized by ventricular arrhythmias and ventricular dysfunction.[1-3] Since the first major description of ARVD/C,[4] much has been learned about this condition. When viewed broadly, most research efforts have focused on developing optimal approaches for diagnosis,[5] defining the genetic basis of this condition,[6,7] and describing, predicting, and treating ARVD/C-associated ventricular arrhythmias.[7,8] Relatively little attention has been given to defining and characterizing the progressive nature of the condition, particularly for the issue of the extent to which ventricular enlargement and cardiac dysfunction progress in ARVD/C.

Although it is widely acknowledged that ARVD/C is progressive, as evidenced by the fact that it is not present at birth and emerges decades later,[8] no large studies have been performed to define the extent and rate of structural progression over time. This issue is emerging as the next critical research and clinical frontier in the field of ARVD/C. With increased awareness of this condition and improved strategies for preventing sudden cardiac death,[9,10] the remaining management question concerns whether structural progression occurs, in whom, and at what rate. Once these factors are defined, clinical trials can be designed to specifically test whether pharmacologic therapies or exercise restriction are useful in preventing progression.

Therefore, the main purpose of this study was to characterize the extent of structural progression of ARVD/C over time using data obtained from a unique transatlantic cohort of patients with ARVD/C from the United States and the Netherlands. Additional goals of this study were to identify determinants of structural progression of ARVD/C and determine the association between structural progression and electrical progression as assessed by electrocardiograms (ECGs) and Holter monitoring.

Key Points

Question To what extent is arrhythmogenic right ventricular dysplasia/cardiomyopathy a structural progressive disease?

Findings In this cohort study of 85 patients with 6 years of follow-up, one-third of the patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy showed significant progressive structural dysfunction, with marked interpatient variability in the rate of progression.

Meaning The results of this study pave the way for designing and launching trials to further study progression in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy.

Methods

Study Population

The study population comprised 85 patients with ARVD/C (22 from the Johns Hopkins ARVD/C Registry [http://ARVD.com] and 63 from the University Medical Center Utrecht ARVD/C registry). All patients were diagnosed with ARVD/C based on the 2010 Task Force Criteria (TFC).[5] For the purpose of this study, we included individuals who underwent at least 2 separate echocardiographic evaluations at a minimum of 2 years apart at their home institution (The Johns Hopkins University or University Medical Center Utrecht). In addition, serial echocardiographic examinations had to be performed and digitally available for complete re-evaluation at their home institution. The first echocardiographic examination after fulfillment of the definite diagnosis was considered the baseline echocardiogram.[5] The last available clinical echocardiogram during follow-up was used as the follow-up echocardiogram, which was performed at least 2 years after the baseline echocardiogram.

The study was approved by the Johns Hopkins Medicine Institutional Review Boards. The Johns Hopkins University Registry participants provided written informed consent. The study protocol was submitted for approval to the Medical Research Ethics Committee of University Medical Center Utrecht and found that it was not subjective to the Dutch act on medical research involving human subjects. Therefore, the Medical Research Ethics Committee waived the need for informed consent. The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and good clinical practice.[11] The participants received no compensation.

Clinical Characterization

Fulfillment of the TFC at baseline and last follow-up was assessed for each participant. By study design, echocardiography was available for all patients at baseline and at last follow-up. All echocardiographic examinations were evaluated for the presence of regional right ventricular (RV) wall motion abnormalities (ie, akinesia, dyskinesia, or aneurysm), RV outflow tract (RVOT) dimension in both the parasternal long-axis (PLAX) and parasternal short-axis (PSAX) views, and RV fractional area change (RV-FAC) as described in the TFC.[5,12] In addition, left ventricular ejection fraction (LVEF) by the Simpson biplane method was assessed.[13]

All participants underwent routine 12-lead ECG recording at baseline and last follow-up. The ECG was evaluated for the presence of depolarization criteria (ε waves and terminal activation duration ≥55 milliseconds) and repolarization criteria (precordial T-wave inversion, V_1-V_6) as described in the TFC.[5] Definitions of ECG variables and arrhythmias are provided in eTable 1 in the Supplement. Signal-averaged ECG was evaluated for the presence of late potentials as defined in the TFC.[5] Signal-averaged ECG was not performed routinely in the Netherlands. Holter monitoring was evaluated for premature ventricular complex count that, according to the TFC, was abnormal if more than 500 were recorded in 24 hours.[5]

Genetic testing was performed in all index patients by molecular genetic screening of 5 ARVD/C-associated desmosomal genes: plakophillin-2 (*PKP2*; OMIM 609040), desmoglein-2 (*DSG2;* OMIM 610193), desmocollin-2 (*DSC2*; OMIM 610476), desmoplakin (*DSP*; OMIM 607450), and plakoglobin (*JUP*; OMIM 611548). Nondesmosomal analysis included transmembrane protein 43 (*TMEM43*; OMIM 604400) and phospholamban (*PLN*; OMIM 609909). Only affected relatives who were genotyped and found to carry the same mutation as the probands or were a first-degree family member of a mutation-negative proband were included in this study.

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Cardiac magnetic resonance examinations were performed according to standard protocols for ARVD/C, which are described elsewhere.[14] Cardiac magnetic resonance examinations were used for initial diagnosis of ARVD/C and were analyzed for the presence of major and minor structural TFC.

Measurement of Structural Disease Progression

To assess structural progression, we compared RV systolic function determined by RV-FAC, LV systolic function determined by LVEF, and RVOT dimension measured in the PLAX and PSAX views between baseline and follow-up for each patient. For each structural variable, structural progression was normalized in absolute percentage change over a 5-year period in each of the 85 patients. All 170 (2 × 85) echocardiogram examinations were analyzed by 1 operator (T.P.M.) to exclude interobserver variability. Measurements were performed blinded for clinical data as well as previous echocardiographic measurements.

We next characterized each patient based on the presence or absence of significant structural progression for RV and LV separately. To do so, we used a cutoff value of differences in RV-FAC (for RV progression) and LVEF (for LV progression) between baseline and last follow-up. Cutoff values were established based on the measurement error, which we determined by reanalyzing RV-FAC and LVEF in a random sample of 40 participants by the same observer (T.P.M.). The mean (±2 SDs) difference between the 2 measurements was used to determine cutoff values indicating significant structural progression. By this method, we aimed to correct for the measurement error inherent to echocardiographic measurements.[15] The mean difference for RV-FAC measurements was 1.0% (5.2%) and 0.7% (3.4%) for RV-FAC and LVEF, respectively. These differences resulted in a cutoff value for RV-FAC of 10% and for LVEF, 7%. The difference between first and second measurements fulfilled the definition for normal distribution, implying nonsystematic errors. Thus, *significant RV structural progression* was defined as an absolute value decrease of more than 10% in RV-FAC, and *significant LV structural progression* was defined as an absolute value decrease of more than 7% in LVEF.

Determinants of Significant Structural Progression

To explore the association of clinical characteristics with significant structural progression, we studied the association between age, sex, genetic background, and proband status with the occurrence of significant structural progression. Baseline variables were also tested for determinant value, including echocardiographic structural factors, presence of arrhythmic TFC, presence of depolarization TFC, and presence of repolarization TFC abnormalities. In addition to the TFC, the extent of T-wave inversions in the inferior leads (II, III, and aVF) was included in this analysis. Follow-up duration was included as a determinant to assess the potential influence of interpatient differences in follow-up duration. All analyses were performed separately for significant RV structural progression and significant LV structural progression.

Correlation With Electrical Progression

To study the association between electrical progression and structural progression, we assessed the correlation between the fulfillment of new electrical TFC in follow-up and the occurrence of significant structural RV and LV progression. Electrical progression was defined by newly developed depolarization, repolarization, or arrhythmic TFC (minor or major). In addition, the association was assessed between the first appropriate implantable cardioverter defibrillator (ICD) therapy and the occurrence of structural progression.

Statistical Analysis

Continuous data are presented as mean (SD) or median (interquartile [IQR] range) as appropriate. Categorical variables are presented as numbers (percentages). Categorical data were compared by the Fisher exact test. The paired *t* test or Wilcoxon signed rank test was used to evaluate differences in continuous variables between baseline and last follow-up. The McNemar test without Yates correction for continuity was used for paired proportional data. Differentiation between normally and nonnormally distributed data was assessed by the Shapiro-Wilk test. A 2-sided *P* value <.05 was considered significant.

Univariable logistic regression was performed to identify determinants of progressive RV and LV disease. Univariable determinants with significance levels of $P < .10$ were included in multivariable logistic regression analysis. A backward, stepwise elimination selection procedure was used. Indicators with an odds ratio (OR) (95% CI) not including 1 were considered significant. All calculations were performed by SPSS Statistics for Windows, version 21.0 (IBM Corp).

Results

Study Population

The study population included 85 patients (61 probands and 24 affected family members) with ARVD/C from 70 families; clinical characteristics are reported in **Table 1**. All participants fulfilled the TFC for definite ARVD/C diagnosis. The mean (SD) age at baseline was 42.8 (14.4) years, and 47 (55%) were men. Genetic testing was performed in all patients, excluding 4 first-degree family members of mutation-negative probands because it had already been proven that there was no desmosomal or *PLN* mutation segregating in the family. A pathogenic ARVD/C-related mutation was found in most of the study population (64 [75%]).[5,8,16] All but 1 mutation carrier were single heterozygous mutation carriers. An overview of the mutations represented in the study population is provided in eTable 2 in the Supplement. Mutations in *PKP2* were most common. At baseline, 47 patients (55%) had a history of sustained ventricular tachycardia with left bundle-branch block morphology. An ICD was implanted at baseline in 49 patients (58%).

Structural Progression

Shown in **Figure 1** are the changes in RV-FAC, LVEF, RVOT-PLAX, and RVOT-PSAX observed over time. During a mean (SD) follow-up of 6.4 (2.5) years, the RV-FAC fell from 39% (IQR, 33%-44%) to 34% (IQR, 24%-42%) ($P < .001$) and the LVEF decreased from 55% (IQR, 52%-60%) to 54% (IQR, 49%-57%) ($P = .001$). The RVOT dimension measured in the PLAX view increased from 35 mm (IQR, 31-39) to 37 mm (IQR, 33-41)

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Table 1. Clinical Characteristics

Characteristic	No. (%) Baseline (n = 85)	Last Follow-up (n = 85)[a]	*P* Value
Demographics			
Age, mean (SD), y	42.8 (14.4)	49.2 (14.1)	
Males	47 (55)		
Race/ethnicity			
White	83 (98)		
Mongoloid	2 (2)		
Probands	61 (72)		
ICD	49 (58)	69 (81)	<.001
Follow-up duration, mean (SD), y		6.4 (2.5)	
Genetics			
Pathogenic mutation	64 (75)		
PKP2	44 (52)		
DSG2	3 (4)		
DSP	2 (2)		
DSC2	1 (1)		
PLN	14 (16)		
No pathogenic mutation	21 (25)		
Task Force Criteria			
Structural			
Major	57 (67)	64 (75)	.008
Minor	7 (8)	9 (11)	NS
Depolarization			
ε Waves (major)	9 (11)	15 (18)	.01
Depolarization minor TFC[b]	62 (73)	67 (79)	.03
Terminal activation duration ≥55 ms	42 (49)	53 (62)	<.001
Repolarization			
T-wave inversion V_1-V_3 (major)	52 (61)	55 (65)	NS
T-wave inversion V_1-V_2 (minor)	11 (13)	10 (12)	NS
T-wave inversion V_4-V_6 (minor)	5 (6)	6 (7)	NS
T-wave inversion V_1-V_4 in presence of RBBB (minor)	1 (1)	2 (2)	NS
Arrhythmias			
VT, superior axis (major)	29 (34)	30 (35)	NS
VT, inferior or unknown axis (minor)	48 (56)	52 (61)	.046
PVC count >500/24 h (minor)[c]	41 (54)	53 (70)	.001
Family history			
Pathogenic ARVD/C mutation carrier (major)	50 (59)		
ARVD/C confirmed			
First-degree relative (major)	33 (39)		
Second-degree relative (minor)	4 (5)		
SCD <35 in a first-degree relative owing to suspected ARVD/C (minor)	8 (9)		NA

Abbreviations: ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; *DSC2*, desmocollin-2; *DSG2*, desmoglein-2; *DSP*, desmoplakin; ICD, implantable cardioverter defibrillator; NA, not applicable; NS, nonsignificant; *PKP2*, plakophillin-2; *PLN*, phospholamban; PVC, premature ventricular complexes; RBBB, right bundle-branch block; SCD, sudden cardiac death; TFC, Task Force Criteria; VT, ventricular tachycardia.

[a] Empty cells indicate that the data were unchanged from baseline.

[b] Depolarization minor criteria were scored if terminal activation duration was longer than 55 milliseconds on electrocardiogram (ECG) or late potentials by signal-averaged ECG. Signal-averaged ECG is not regularly performed in the Netherlands and therefore is not reported.

[c] Holter monitoring was performed in only 76 patients at baseline.

(P < .001) and in the PSAX view increased from 35 mm (IQR, 31-39) to 37 mm (IQR, 34-41) (P < .001).

Figure 2 shows the rate of change of each of the above factors observed in all study participants. As presented, the rate of RV-FAC change normalized to a 5-year period was −3.3% per 5 years (IQR, −8.9% to 1.2%). An absolute decrease in RV-FAC was observed in 50 of 75 (67%) of the patients (10 patients excluded because of insufficient image quality). This decrease in RV-FAC met our prespecified cutoff level for a significant decrease in RV-FAC of 10% or more in 21 of 75 (28%) of the patients (10 patients excluded because of insufficient image quality). In contrast, the rate of LVEF change was modest: −0.2% per 5 years (IQR, −6.5% to 1.7%), with an absolute decrease in LVEF observed in 39 of 78 (50%) of the patients (7 patients excluded because of insufficient image quality). This decrease in LVEF met our prespecified cutoff level for a significant decrease in LVEF of 7% or more in 23 of 78 (29%) of the patients (7 patients excluded because of insufficient image quality). The rate of RVOT-PLAX change was 1.4 mm per 5 years (IQR, 0.0-3.4). An increase in RVOT-PLAX was observed in 54 of 82 (66%)

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of the patients (3 patients excluded because of insufficient image quality). The rate of RVOT-PSAX change was 1.4 mm per 5 years (IQR, 0.0-3.9). An increase in RVOT-PSAX was observed in 54 of 81 (67%) of the patients (1 patient excluded because of insufficient image quality).

Determinants of Significant Structural Progression

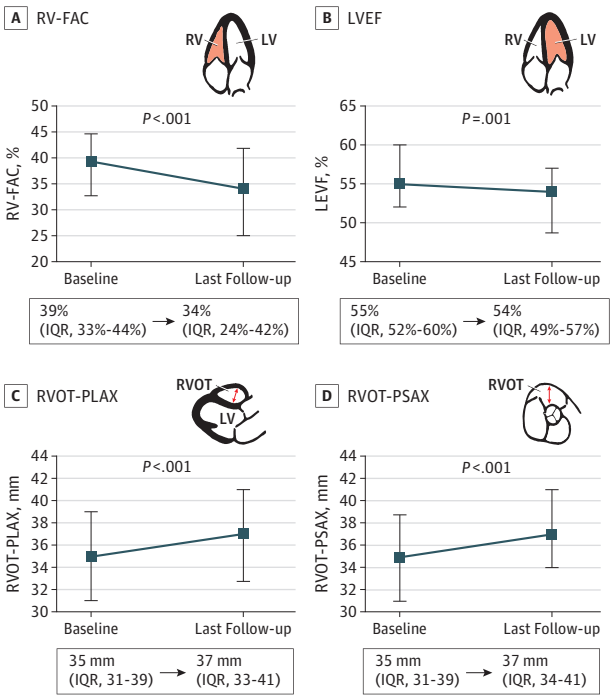
We next examined the association of demographic, genetic, and baseline clinical characteristics with the presence of significant RV and LV structural progression as defined by our prespecified cutoff values. Twenty-one of 75 (28%) of the patients (10 patients excluded because of insufficient image quality) met criteria for significant RV structural progression (absolute decrease in RV-FAC, >10%). As reported in **Table 2**, in univariable analysis, being a proband (P = .04), fulfilling depolarization criteria (P = .03), and RVOT dimension in the PSAX view (P = .046) at baseline were indicative of RV structural disease progression during follow-up. In the fully adjusted model and correcting for proband status and RVOT dimension, fulfillment of depolarization TFC at baseline (OR, 9.0; 95% CI, 1.1-74.2) remained significantly associated with significant RV progressive disease during follow-up.

Twenty-three of 78 (29%) patients with ARVD/C showed structural progressive LV disease as defined by an absolute decrease in LVEF of more than 7% (7 patients excluded because of insufficient image quality). As reported in Table 2, in univariable analysis, age at first echocardiographic evaluation (P = .08), baseline LV systolic function (P = .01), and harboring a *PLN* mutation (P = .009) were associated with LV progressive disease during follow-up. After adjusting for age, being a carrier of a *PLN* mutation (OR, 8.8; 95% CI, 2.1-37.2) and baseline LVEF (OR, 1.14; 95% CI, 1.04-1.24) remained independent determinants of progressive LV disease.

Correlation Between Structural and Electrical Progression

We compared fulfillment of repolarization, depolarization, and arrhythmia TFC at baseline and follow-up and sought to establish whether these signs of electrical progression were associated with significant structural progression. As reported in Table 1, in the entire population, an increased proportion of participants met not only structural TFC but also depolarization TFC and arrhythmia TFC during follow-up. However, as given in **Table 3**, changes in electrical TFC were not disproportionately likely to occur in patients with significant structural progression. Presented in Table 3 are changes in electrical TFC for participants identified as having significant structural RV progression compared with those without significant structural RV progression during follow-up. In patients with significant structural RV progression, fulfillment of major depolarization TFC significantly increased during follow-up, with major depolarization TFC seen in 3 of 21 participants (14%) at baseline and in 7 of 21 individuals (33%) during follow-up (P = .046). However, new depolarization abnormalities also developed in patients without significant structural RV progression, with minor depolarization TFC fulfilled in 35 of 54 patients (65%) at baseline and in 39 of 54 individuals (72%) during follow-up (P = .046). Only patients with stable RV disease had a significant increase in the likelihood of meeting arrhythmia TFC; repolarization TFC did not significantly increase in either the stable or progressive group during follow-up.

Figure 1. Structural Progression in Patients With Arrhythmogenic Right Ventricular (RV) Dysplasia/Cardiomyopathy



Mean (SD) follow-up was 6.4 (2.5) years. A, Median RV fractional area change (RV-FAC) decreased from 39% (interquartile range [IQR], 33%-44%) at baseline to 34 (IQR, 24%-42%) at follow-up (P < .001). B, Median left ventricular ejection fraction (LVEF) decreased from 55% (IQR, 52%-60%) at baseline to 54% (IQR, 49%-57% at follow-up) (P = .001). C, Median RV outflow tract parasternal long axis (RVOT-PLAX) increased from 35 mm (31-39 mm) at baseline to 37 mm (33-41 mm) at follow-up (P < .001). D, Median RVOT parasternal short axis (RVOT-PSAX) increased from 35 mm (31-39 mm) at baseline to 37 mm (34-41) at follow-up (P < .001). The arrows indicate the RVOT dimension in the specific echo view.

Similarly, as presented in Table 3, patients with significant LV structural progression showed no increased likelihood of fulfilling depolarization, repolarization, and arrhythmia TFC during follow-up. In contrast, a greater proportion of patients with stable LV disease met major and minor depolarization TFC during follow-up (4 of 55 [7%] at baseline and 9 of 55 [16%]) during follow-up, P = .03; and 39 of 55 [71%] at baseline and 43 of 55 [78%] during follow-up, P = .046, respectively). Fulfillment of arrhythmic TFC for premature ventricular complexes count also significantly increased in the stable group (27 of 50 [54%] at baseline and 37 of 50 [74%] during follow-up; P = .002).

The presence of significant structural RV progression was associated with the occurrence of the first appropriate ICD therapy during follow-up. At baseline, 49 patients (58%) were already ICD carriers; 13 had received their first appropriate ICD therapy before baseline echocardiogram, and 15 had received this therapy during the follow-up period. The remaining 21 participants did not receive any appropriate ICD therapy after the implantation. In patients without appropriate ICD intervention, structural RV progression was less frequently seen com-

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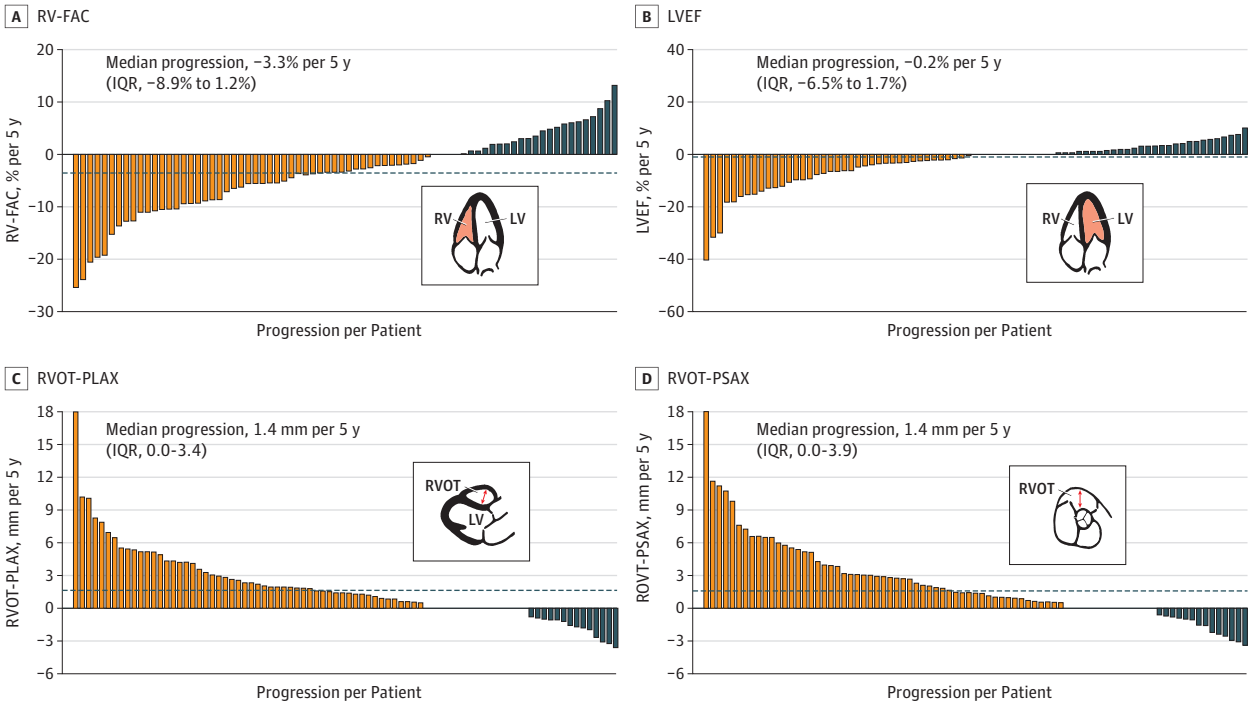
Figure 2. Distribution of Progression Rates for Right Ventricular Outflow Tract (RVOT) Dimension and Ventricular Systolic Function



Each bar represents individual progression rate ranked in ascending order. A, RV fractional area change (RV-FAC) decreased in 50 of 75 patients (67%); the median fall in RV-FAC was −3.3% per 5 years (dashed line). B, Left ventricular ejection fraction (LVEF) decreased in 39 of 78 (50%) patients; the median fall in LVEF was −0.2% per 5 years (dashed line). C, RVOT parasternal long axis (RVOT-PLAX) increased in 54 of 82 patients (66%); the median rise in RVOT-PLAX dimension was 1.4 mm per 5 years (dashed line). D, RVOT-parasternal short axis (RVOT-PSAX) increased in 54 of 81 patients (67%); the median rise in RVOT-PSAX dimension was 1.4 mm per 5 years (dashed line). IQR indicates interquartile range.

pared with patients with a history of appropriate ICD interventions or who received ICD therapy during follow-up (2 of 19 [11%] vs 10 of 23 [43%]; $P = .04$). This association was not observed between ICD therapy and significant structural LV progression.

Discussion

Overview and Main Findings

The main purpose of this study was to characterize the extent of structural progression of ARVD/C as assessed with echocardiographic imaging over time using data obtained from a transatlantic cohort of patients with ARVD/C. Additional goals were to identify indicators of structural progression and determine the association between structural progression and electrical progression as assessed by ECG and Holter monitoring.

There are 3 main findings of this study. First, the results provide definitive evidence of the structural progression in patients with ARVD/C. This study also defined the proportion of patients in whom structural progression is observed during a mean follow-up of 6.4 years and determined the overall rate of progression. Second, we identified several variables associated with structural progression, including the severity of ECG abnormalities at baseline and genetic background. Third, the results of this study reveal that structural disease progression is not reflected by the presence of new ECG TFC.

Prior Studies

Physicians who longitudinally care for patients with ARVD/C recognize that it is a progressive condition. Evidence for this progression can be derived from several sources and is reflected in the studies that have reported outcomes of patients with ARVD/C in the past 3 decades.[7,17,18] Perhaps the most compelling line of evidence that ARVD/C is a progressive disease is reflected by the fact that the mean age at presentation is 36 years, with virtually no patients being diagnosed with this condition before puberty.[8] Additional evidence of progression includes a study in patients with ARVD/C who underwent cardiac transplantation that was performed 16 years after disease presentation.[19] Although no prior studies have focused on structural progression, several studies contain evidence of progression based on serial echocardiograms.[18,20,21] For example, Nava et al[18] reported serial echocardiographic data on 132 patients with ARVD/C, with 7% of the patients showing increasing RV dimensions during almost 9 years of follow-up. Our data are in line with this study and extend the findings to a cohort fulfilling current diagnostic criteria. A more recent study in an ARVD/C cohort with limited sample size and follow-up also reported signs of decreasing RV function and increasing RV dimensions over time.[21]

Several studies have also examined ECG evidence of progression.[22-25] The largest of these, by Saguner et al,[24] reported that, in 77 patients with ARVD/C, depolarization abnormalities increased during follow-up. Another observation was that T-wave inversion may disappear during the disease course.

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Table 2. Indicators for Significant RV and LV Structural Progression Based on Univariable and Multivariable Logistic Regression

Variable	Univariable OR (95% CI)	*P* Value	Multivariable OR (95% CI)	*P* Value
Decrease in RV Function by Absolute Value of 10%[a]				
Age	1.02 (0.98-1.06)	NS	NA	NA
Male	1.59 (0.55-4.58)	NS	NA	NA
Proband	5.16 (1.08-24.60)	.04	4.1 (0.9-20.4)	NS
Follow-up duration, y	1.12 (0.91-1.38)	NS	NA	NA
Electrical criteria				
TFC (major or minor)				
Depolarization	10.90 (1.35-87.30)	.03	9.0 (1.1-74.2)	.04
Repolarization	1.90 (0.48-7.50)	NS	NA	NA
Extent of inferior leads T-wave inversion	0.80 (0.46-1.39)	NS	NA	NA
Arrhythmic TFC (major or minor)	1.42 (0.27-7.44)	NS	NA	NA
Baseline structural measurements				
RVOT, mm				
PLAX	1.07 (0.99-1.14)	NS	NA	NA
PSAX	1.07 (1.00-1.15)	.046	1.03 (0.96-1.11)	NS
RV-FAC, %	0.98 (0.93-1.04)	NS	NA	NA
LVEF, %	0.98 (0.91-1.05)	NS	NA	NA
Genetics				
Desmosomal mutation	1 [Reference]		NA	NA
Gene elusive	1.69 (0.51-5.63)	NS	NA	NA
PLN	1.37 (0.35-5.35)	NS	NA	NA
Decrease in LV Systolic Function by Absolute Value of 7%[b]				
Age	1.03 (1.00-1.07)	.076	1.03 (0.99-1.08)	NS
Male	0.72 (0.27-1.92)	NS	NA	NA
Proband	2.13 (0.63-7.20)	NS	NA	NA
Follow-up duration, y	0.95 (0.77-1.16)	NS	NA	NA
Electrical criteria				
TFC (major or minor)				
Depolarization	1.16 (0.39-3.48)	NS	NA	NA
Repolarization	0.71 (0.23-2.22)	NS	NA	NA
Extent of inferior leads T-wave inversion	0.94 (0.57-1.54)	NS	NA	NA
Arrhythmic TFC (major or minor)	1.29 (0.24-6.90)	NS	NA	NA
Baseline structural measurements				
RVOT, mm				
PLAX	1.03 (0.97-1.10)	NS	NA	NA
PSAX	1.06 (0.99-1.13)	NS	NA	NA
RV-FAC, %	1.00 (0.95-1.05)	NS	NA	NA
LVEF, %	1.11 (1.02-1.21)	.01	1.14 (1.04-1.24)	.005
Genetics				
Desmosomal mutation	1 [Reference]		1 [Reference]	
Gene elusive	2.06 (0.61-6.97)	NS	2.39 (0.63-9.05)	NS
PLN	5.48 (1.52-19.81)	.009	8.79 (2.08-37.16)	.003

Abbreviations: LVEF, left ventricular ejection fraction; NA, not applicable; NS, nonsignificant; OR, odds ratio; PLAX, parasternal long axis; *PLN*, phospholamban; PSAX, parasternal short axis; RV-FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; TFC, Task Force Criteria.

[a] Logistic regression was used to identify predictors for significant RV structural progression that was found in 21 (28%) of the patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). Fulfillment of depolarization criteria at baseline was associated with significant RV structural progression.

[b] Left ventricular (LV) structural progression was found in 23 (29%) of the patients with ARVD/C. Carriers of a phospholamban mutation showed more significant LV structural progression compared to desmosomal mutation carriers. High baseline values of LVEF at baseline were also associated with more decreases in LV systolic function during follow-up.

Structural and Electrical Progression in Patients With ARVD/C

The results of this study confirm and extend the results of the previous studies reviewed above. We observed a significant decline in RV systolic function and an increase in dilatation of the RV dimensions during 6.4 years of follow-up. A significant decline in RV function, which was defined as a decline of more than 10%, was observed in nearly one-third of the patients, and almost one-third of the patients showed a significant decline of more than 7% in LVEF. These findings underscore the presence of significant structural ARVD/C disease progression in both the RV and the LV. In previous studies, both decreased RV-FAC and LVEF were found to be associated with adverse outcomes in ARVD/C, which stresses the clinical importance of careful analysis of structural progression.[9,21,26]

Another important finding of this study is that the declines in RV and LV function were not uniform. Progression is

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Table 3. Structural Progression vs Electrical Progression by TFC

Characteristic	Progressive Structural Disease,[a] No. (%)			Stable Disease, No. (%)		
	Baseline	Follow-up	*P* Value	Baseline	Follow-up	*P* Value
RV Disease[b]						
Depolarization TFC						
ε Waves (major)	3 (14)	7 (33)	.046	4 (7)	6 (11)	.16
Depolarization minor TFC	20 (95)	20 (95)	>.99	35 (65)	39 (72)	.046
Repolarization TFC						
T-wave inversion V_1-V_3 (major)	16 (76)	18 (86)	.16	32 (59)	32 (59)	>.99
T-wave inversion V_1-V_2 (minor)	2 (10)	0	.16	8 (15)	9 (17)	.32
T-wave inversion V_4-V_6 (minor)	1 (5)	1 (5)	>.99	3 (6)	4 (7)	.32
T-wave inversion V_1-V_4 in presence of RBBB (minor)	0	0	>.99	0	1 (2)	.32
Arrhythmias TFC						
VT						
Superior axis (major)	8 (38)	9 (43)	.32	18 (33)	18 (33)	>.99
Inferior or unknown axis (minor)	15 (71)	16 (76)	.32	28 (52)	30 (56)	.16
PVC count >500/24 h (minor), No./No. (%)	12/19 (63)	14/19 (74)	.16	24/49 (49)	33/49 (67)	.003
LV Disease[c]						
Depolarization TFC						
ε waves (major)	3 (13)	4 (17)	.32	4 (7)	9 (16)	.03
Depolarization minor TFC	17 (74)	18 (78)	.32	39 (71)	43 (78)	.046
Repolarization TFC						
T-wave inversion V_1-V_3 (major)	14 (61)	15 (65)	.32	36 (65)	38 (69)	.16
T-wave inversion V_1-V_2 (minor)	1 (4)	0	.32	8 (15)	8 (15)	>.99
T-wave inversion V_4-V_6 (minor)	4 (17)	4 (17)	>.99	1 (2)	2 (4)	.32
T-wave inversion V_1-V_4 in presence of RBBB (minor)	0	1 (4)	.32	0	0	>.99
Arrhythmias TFC						
VT						
Superior axis (major)	9 (39)	9 (39)	>.99	17 (31)	18 (33)	.32
Inferior or unknown axis (minor)	14 (61)	14 (61)	>.99	31 (56)	34 (62)	.08
PVC count >500/24 h (minor), No./No. (%)	12/21 (57)	12/21 (57)	>.99	27/50 (54)	37/50 (74)	.002

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; PVC, premature ventricular complexes; RBBB, right bundle-branch block; RV, right ventricular; TFC, Task Force Criteria; VT, ventricular tachycardia.

[a] Progressive disease was defined as more than 7% absolute decrease in LVEF.

[b] Twenty-one patients with progressive disease and 54 with stable disease; 10 patients were excluded from this analysis owing to insufficient image quality.

[c] Twenty-three patients with progressive disease and 55 with stable disease; 7 patients were excluded from this analysis owing to insufficient image quality.

subject to high interpatient variability in a large cohort, which proves the nonuniformity of ARVD/C disease progression. This finding, while perhaps not surprising, makes it clear that several clinical variables must be involved. Previous studies have proposed that environmental factors, such as exercise, might be mediators of the severity of ARVD/C phenotype.[27,28] Other studies have proposed that superimposed myocarditis or inflammation may play an important role.[29] One could hypothesize that these environmental and inflammatory factors are the origin of the large interpatient variability in structural progression. Consistent with recent research[30,31] and in contrast to other cardiomyopathies,[32] age of onset does not appear to indicate the rate of progression.

Our data show that fulfillment of depolarization criteria at baseline is associated with progressive structural RV disease during follow-up. All but 1 patient with significant RV structural progression showed abnormal depolarization in the ECG at baseline. Another finding of our study is that patients with ARVD/C who had a *PLN* mutation demonstrated more progressive LV dysfunction compared with those without *PLN*-mediated ARVD/C. This finding is in line with a previous study that had already shown a higher prevalence of LV dysfunction among *PLN* mutation carriers than among carriers of desmosomal ARVD/C mutations.[7] Although these findings are intriguing, the limited statistical power of this study makes it difficult to draw firm conclusions regarding both indicators and moderators of structural disease progression. Larger studies, including those with exercise data, are needed to further elucidate the moderators of structural disease progression in patients with ARVD/C.

Another interesting observation was the association between first appropriate ICD therapy and significant structural RV progression. Although the numbers are small, this association demonstrates the clinical importance of assessing structural progression in ARVD/C. We observed no association between rapid structural disease progression and newly acquired

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ECG or arrhythmia TFC. Rather, fulfillment of new repolarization, depolarization, and arrhythmia criteria are as common among patients with stable structural disease. Therefore, both ECG and echocardiography are required to monitor overall disease progression in ARVD/C.

Limitations

Limitations of the study include its retrospective design with the associated variable follow-up interval. Furthermore, the use of echocardiography for the assessment of structural progression is associated with some limitations inherent to this technique. The complex RV geometry prevents volumetric assessment by echocardiography. Therefore, we used 2-dimensional methods for estimating the changes in RV function and RV size, which might be less sensitive to minor signs of structural progression. These limitations could be aggravated by the use of a single observer. The reason for this setting was that we aimed to exclude interoperator variability. Consequently, the echocardiograms used in this study had to be available for complete re-evaluation, which led to a reduction in our sample size. The modest sample size of 85 patients, one-third of whom showed the outcome definition, also affects the reliability of our results derived during the regression analyses. Therefore, the likelihood of overfitting is relatively high, and this factor should be taken into account when interpreting our results. Furthermore, detailed information concerning the exercise programs and medications taken by each of the patients during the time between echocardiograms was unavailable for many patients and hence not included in this analysis.

Conclusions

This study demonstrates that ARVD/C is a progressive cardiomyopathy with marked interpatient variability in the rate of progression. Because of the modest size of this investigation, further studies are needed to elucidate the progressive nature of ARVD/C. Nevertheless, the results of this study pave the way for designing and launching trials to further evaluate and ultimately reduce disease progression in patients with ARVD/C.

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Author Affiliations: Division of Cardiology, Department of Medicine, University Medical Center Utrecht, Utrecht, the Netherlands (Mast, Teske, Loh, van der Heijden, Doevendans, te Riele, Cramer); Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (James, Calkins, Tichnell, Murray, Russell, Judge, Tedford, Tandri, Abraham, te Riele); Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands (Velthuis); Department of Medical Genetics, University Medical Center Utrecht, Utrecht, the Netherlands (Dooijes); Netherlands Heart Institute, Utrecht, the Netherlands (Hauer, Doevendans, te Riele).

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Study concept and design: Mast, James, Calkins, Teske, Tichnell, Murray, Loh, Tedford, Tandri, Doevendans, Cramer.
Acquisition, analysis, or interpretation of data: Mast, James, Calkins, Teske, Tichnell, Murray, Russell, Velthuis, Judge, Dooijes, Tedford, van der Heijden, Hauer, Abraham, te Riele, Cramer.
Drafting of the manuscript: Mast, James, Calkins, te Riele, Cramer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Mast, James, te Riele.
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Study supervision: James, Calkins, Teske, Loh, Russell, Velthuis, Tandri, Hauer, Doevendans, Cramer.

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