The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy

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ORIGINAL RESEARCH

The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the prognostic value of echocardiographic deformation imaging in arrhythmogenic right ventricular cardiomyopathy (ARVC) to optimize family screening protocols.

BACKGROUND ARVC is characterized by variable disease expressivity among family members, which complicates family screening protocols. Previous reports have shown that echocardiographic deformation imaging detects abnormal right ventricular (RV) deformation in the absence of established disease expression in ARVC.

METHODS First-degree relatives of patients with ARVC were evaluated according to 2010 task force criteria, including RV deformation imaging (n = 128). Relatives fulfilling structural task force criteria were excluded for further analysis. At baseline, deformation patterns of the subtricuspid region were scored as type I (normal deformation), type II (delayed onset, decreased systolic peak, and post-systolic shortening), or type III (systolic stretching and large post-systolic shortening). The final study population comprised relatives who underwent a second evaluation during follow-up. Disease progression was defined as the development of a new 2010 task force criterion during follow-up that was absent at baseline.

RESULTS Sixty-five relatives underwent a second evaluation after a mean follow-up period of 3.7 ± 2.1 years. At baseline, 28 relatives (43%) had normal deformation (type I), and 37 relatives (57%) had abnormal deformation (type II or III) in the subtricuspid region. Disease progression occurred in 4% of the relatives with normal deformation at baseline and in 43% of the relatives with abnormal deformation at baseline ($p < 0.001$). Positive and negative predictive values of abnormal deformation were, respectively, 43% (95% confidence interval: 27% to 61%) and 96% (95% confidence interval: 82% to 100%).

CONCLUSIONS Normal RV deformation in the subtricuspid region is associated with absence of disease progression during nearly 4-year follow-up in relatives of patients with ARVC. Abnormal RV deformation seems to precede the established signs of ARVC. RV deformation imaging may potentially play an important role in ARVC family screening protocols. (J Am Coll Cardiol Img 2019;12:446–55) © 2019 by the American College of Cardiology Foundation.

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy clinically characterized by ventricular arrhythmias and predominantly right ventricular (RV) dysfunction (1). Typical genetic features of ARVC are reduced penetrance and variable disease expressivity, which complicates family screening (2–4). Comprehensive cardiac screening of family members of patients with ARVC is routinely performed by electrocardiographic (ECG) assessment, Holter monitoring, and cardiac imaging and aims to detect typical ARVC-related abnormalities (3,5,6). However, early ARVC is characterized by a lack of overt structural abnormalities detected by conventional imaging approaches (3,7). Novel imaging techniques could be of incremental value in optimizing ARVC family screening protocols (8).

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Echocardiographic deformation imaging is a technique that enables the quantification of regional ventricular deformation and provides insight into mechanical synchrony and regional contractility (9,10). Previous reports suggest that this technique is capable of detecting subtle functional abnormalities in the absence of structural abnormalities by conventional imaging (11–13). We recently introduced a new approach that combines multiple deformation parameters into 3 distinct deformation patterns. A clear correlation between abnormal deformation patterns and disease severity among ARVC desmosomal mutation carriers was found (14). In addition, we were able to characterize the underlying electromechanical substrate of these patterns by dedicated computer simulation of deformation patterns. Abnormal deformation was typically seen in the basal area of the RV free wall (or subtricuspid region), which is recognized as 1 of the earliest affected areas in ARVC (12–15). Importantly, abnormal deformation in this specific area was seen during the earliest subclinical stage in which established phenotypic disease expression according to the 2010 task force criteria (TFC) was absent (5). Therefore, echocardiographic deformation imaging may potentially play a pivotal role in improving ARVC family screening.

Although all previously published data were obtained in a cross-sectional study design, this longitudinal study was conducted to explore the value of deformation imaging in screening family members of patients with ARVC. Our hypothesis is that distinct RV deformation abnormalities precede the conventional signs of disease during the early stages of ARVC and can therefore help stratify relatives at risk for disease progression.

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy
CI = confidence interval
CMR = cardiac magnetic resonance
ECG = electrocardiographic
LV = left ventricular
NPV = negative predictive value
PPV = positive predictive value
RV = right ventricular
TFC = task force criteria

METHODS

STUDY POPULATION. During a 10-year observational period (2006 to 2016), we performed echocardiographic examination according to our ARVC protocol in probands (all fulfilling definite diagnosis according to the 2010 TFC) and their relatives during their clinical work-up for ARVC (9,16). The study participants (n = 194, age >18 years) were derived from the Dutch national ARVC registry, with patients from University Medical Center Utrecht (n = 161), Academic Medical Center Amsterdam (n = 18), and University Medical Center Groningen (n = 15). Altogether, echocardiographic examinations with appropriate RV recordings for RV deformation imaging were available in 66 ARVC probands and 128 first-degree relatives. All participants were genetically tested for known ARVC-related pathogenic mutations: plakophilin-2, desmoglein-2, desmocollin-2, desmoplakin, and plakoglobin (5). Nondesmosomal analysis included transmembrane protein 43 and phospholamban (5,17).

The following participants were eligible for this study: 1) first-degree relatives carrying the identical pathogenic ARVC mutation as identified in the probands; and 2) first-degree relatives of mutation-negative probands. These relatives (n = 128) were classified according to the presence of subsets of the 2010 TFC during clinical work-up at baseline (5,14): 1) structural stage: relatives fulfilling the 2010 TFC for structural abnormalities detected by echocardiography or cardiac magnetic resonance (CMR); 2) electrical stage: relatives without structural abnormalities fulfilling the 2010 TFC but with ECG abnormalities (repolarization and/or depolarization) and/or history of ventricular arrhythmias as defined by the 2010 TFC; and 3) subclinical stage: relatives without any electrical or structural TFC.

To investigate the value of echocardiographic deformation imaging during the early clinical ARVC

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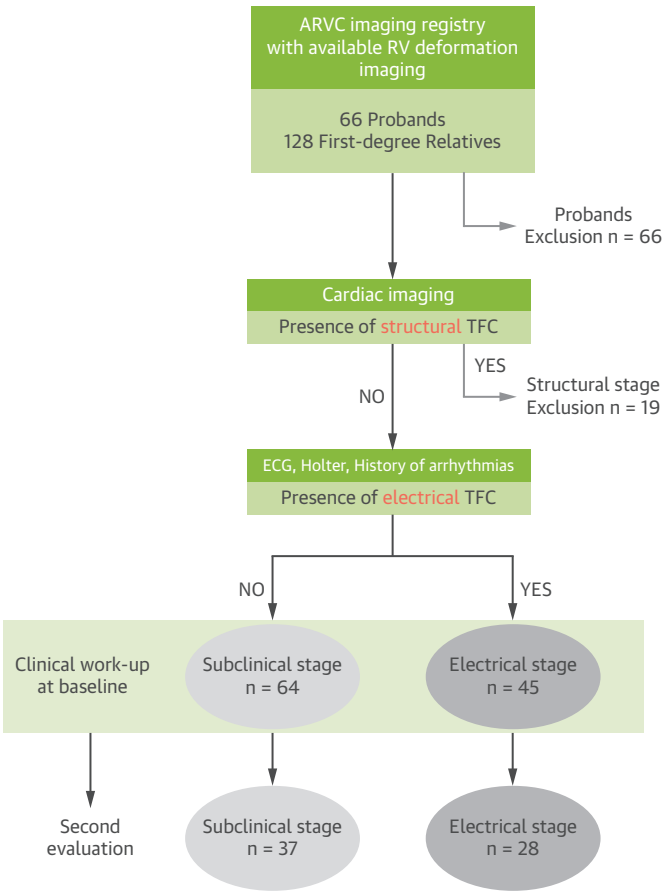
FIGURE 1 Study Design



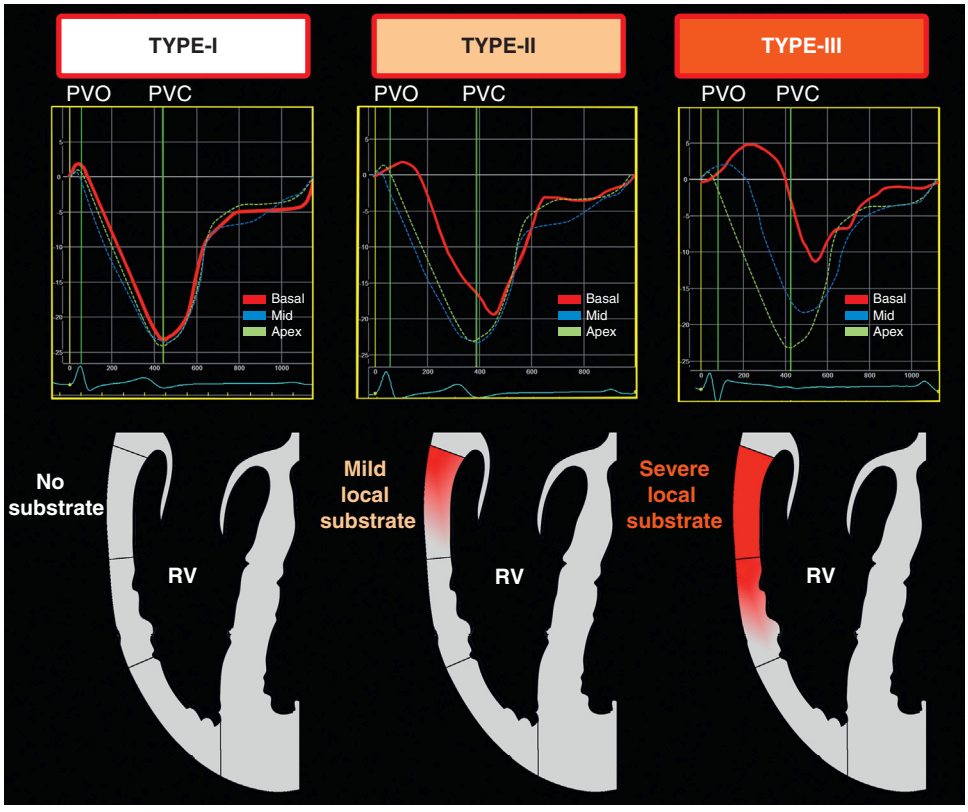
Relatives with available right ventricular (RV) deformation imaging were eligible for this study. The presence of structural abnormalities (as defined by 2010 task force criteria [TFC]) resulted in exclusion from the study. Only relatives in the early clinical stages (electrical stage and subclinical stage, n = 109) were included. Sixty-five relatives underwent a complete second cardiac evaluation. ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiography.

stages (i.e., subclinical and electrical stages), relatives fulfilling TFC for structural abnormalities (i.e., structural stage) were excluded from further analysis (n = 19). Of the remaining 109 early-stage first-degree relatives, a subset of 65 first-degree relatives (60%) who underwent a second complete cardiac evaluation during follow-up were included in the final study population (**Figure 1**). The other 44 subjects (40%) did not undergo a second complete evaluation with all diagnostic modalities during follow-up. Supplemental Table 1 provides a baseline comparison between subjects with follow-up and without complete follow-up. The local medical ethical committees of each participating center approved this study.

CARDIAC EVALUATION. A comprehensive description of the cardiac evaluation is found in the Supplemental Appendix. In brief, all subjects underwent standard 12-lead electrocardiography, which was scored for the presence of repolarization and depolarization abnormalities as defined by the 2010 TFC (5). Holter recordings for 24 h were analyzed for the presence of ventricular tachycardia and premature ventricular complexes (5). Structural abnormalities as defined by the 2010 TFC were primarily assessed by echocardiography according to standard ARVC protocols (5,9,16). Additionally, left ventricular (LV) involvement was assessed by visual wall motion analysis and measurement of LV ejection fraction using the Simpson biplane method. Additional CMR was performed at the discretion of the treating physician (typically in cases in which echocardiography was of insufficient quality or to verify new abnormalities seen by echocardiography). CMR studies were analyzed for fulfillment of TFC, and LV systolic function was assessed by measurement of LV ejection fraction (5,18). Contrast-enhanced images after administration of gadolinium were acquired to identify myocardial fibrosis in both the right and left ventricles. Definite diagnosis of ARVC was based on the presence of subsets of the 2010 TFC, which require 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria (5).

ECHOCARDIOGRAPHIC RV DEFORMATION IMAGING. All subjects underwent RV echocardiographic deformation imaging using a GE Vivid 7 or a GE Vivid E9 (GE Medical Systems, Milwaukee, Wisconsin) (9). Details on image acquisition and post-processing are extensively described elsewhere (9,16). In brief, a focused modified narrow-angle 2-dimensional image in the apical 4-chamber view was recorded to assess the RV. Frame rates between 55 and 110 frames/s were accepted for RV deformation imaging. GE EchoPac version 10.2 for PC (GE Healthcare, Little Chalfont, United Kingdom) was used to perform 2-dimensional speckle tracking. After manual tracing, the RV lateral free wall was divided automatically into the basal, mid, and apical segments. Pulmonary valve timing was assessed by Doppler traces in the RV outflow tract obtained in the parasternal short-axis view. The following deformation parameters were measured in the basal area: time to onset of shortening (13), systolic peak strain value (10,19), and post-systolic index (12) (for definitions, see Supplemental Figure 1). These deformation parameters can be combined into 3 distinct deformation patterns, as previously published (**Figure 2**) (14): type I, defined as normal deformation characterized by onset shortening ≤90 ms, systolic peak

FIGURE 2 **Right Ventricular Deformation Patterns**



Three distinct deformation patterns are observed in arrhythmogenic right ventricular cardiomyopathy. In a previous report by our group, we used a computer model to simulate type II **(middle)** pattern by the induction of a mechanical substrate (hypocontractility and increased passive wall stiffness) in the subtricuspid region (14). Type III **(right)** was simulated by aggravating this substrate. No local pathological electromechanical substrate was present in type I (normal deformation) **(left)**. PVC = pulmonary valve closure; PVO = pulmonary valve opening; RV = right ventricle.

strain ≥|−20%|, and ≤10% post-systolic shortening; type II, characterized by delayed onset of shortening (>90 ms), reduced systolic peak strain (<|−20%| and >|−10%|), and minor post-systolic shortening (>10%); and type III, characterized by predominantly systolic stretching (systolic peak strain <|−10%|) and major post-systolic shortening.

ARVC DISEASE PROGRESSION. In the final study population of 65 first-degree relatives who underwent 2 separate complete cardiac assessments, disease progression was defined as the presence of a new major or minor task force criterion (structural, depolarization, repolarization, or arrhythmic) that was absent at baseline. RV deformation patterns in the basal area at baseline were evaluated for the predictive value for disease progression.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD or as median (interquartile range) as appropriate. Normal distribution was tested using the Shapiro-Wilk test. Mean group values were compared using independent Student's *t*-tests or Mann-Whitney *U* tests as appropriate. Distributions of proportions were performed using Fisher exact tests. Predictive values were expressed as positive predictive value (PPV) and negative predictive value (NPV) with the 95% confidence interval (CI) calculated using the Clopper-Pearson method. For interobserver analysis, a second operator performed RV deformation analysis in 20 random subjects. For determination of intraobserver agreement, this sample was reanalyzed by the first observer 6 weeks after the first analysis. Interobserver and intraobserver agreement were determined using linear weighted kappa statistics. Values of $p < 0.05$

TABLE 1 Baseline Characteristics of 65 First-Degree Relatives With 2 Complete Cardiac Evaluations

	Subclinical Stage (n = 37)	Electrical Stage (n = 28)	p Value
Age, yrs	26.4 ± 13.9	39.0 ± 17.4	0.003
Male	13 (35)	11 (39)	0.798
Pathogenic ARVC mutation	29 (78)	25 (89)	0.325
PKP2	24 (65)	21 (75)	0.258
DSG2	3 (8)	1 (4)	0.637
DSP	0 (0)	1 (4)	0.413
PLN	2 (5)	2 (7)	1.00
Symptomatic	4 (11)	4 (14)	0.707
Palpitations	3 (8)	4 (14)	0.452
Cardiac syncope	1 (3)	0 (0)	1.00
ARVC definite diagnosis	0 (0)	11 (39)	<0.001
ARVC borderline diagnosis	0 (0)	17 (61)	<0.001
2010 task force criteria			
Structural TFC (major/minor)	0 (0)	0 (0)	1.00
Depolarization TFC (major/minor)	0 (0)	20 (71)	<0.001
TAD	0 (0)	20 (71)	<0.001
Epsilon wave	0 (0)	0 (0)	1.00
Repolarization TFC (major/minor)	0 (0)	9 (32)	<0.001
T-wave inversion, leads V_1–V_2	0 (0)	3 (11)	0.075
T-wave inversion, leads V_1–V_3	0 (0)	4 (14)	0.030
T-wave inversion, leads V_4–V_6	0 (0)	1 (4)	0.431
T-wave inversion, leads V_1–V_6	0 (0)	1 (4)	0.431
T-wave inversion, leads V_1–V_4, with RBBB	0 (0)	0 (0)	1.00
Arrhythmia TFC (major/minor)	0 (0)	13 (46)	<0.001
(Non)sustained VT with superior axis	0 (0)	0 (0)	1.00
(Non)sustained VT with inferior or unknown axis	0 (0)	2 (7)	0.182
PVCs >500/24 h	0 (0)	12 (43)	<0.001
Family history of TFC (major)	37 (100)	28 (100)	1.00
Echocardiography			
RV WMA	1 (3)	0 (0)	1.00
PLAX RVOT, mm/m^2	15.2 ± 2.5	15.3 ± 2.2	0.870
PSAX RVOT, mm/m^2	16.3 ± 2.8	15.7 ± 2.4	0.464
RV FAC, %	46.4 ± 6.2	45.7 ± 7.1	0.691
LVEF, %	58.7 ± 4.6	59.9 ± 6.2	0.432
CMR	(n = 23)	(n = 19)	
RV WMA	2 (9)	2 (11)	1.00
RVEDV, ml/m^2	95.9 ± 14.9	91.9 ± 8.1	0.055
RVEF, %	53.0 ± 7.2	53.4 ± 7.6	0.890
LVEF, %	56.9 ± 5.7	56.2 ± 8.4	0.749
LGE	2 (9)	1 (5)	1.00

Values are mean ± SD or n (%). Definite ARVC diagnosis is defined as the presence of 2 major, 1 major and 2 minor, or 4 minor TFC. Borderline diagnosis of ARVC is defined as the presence of either 1 major and 1 minor or 3 minor TFC.

ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; *DSG2* = desmoglein-2; *DSP* = desmoplakin; FAC = fractional area change; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; *PKP2* = plakophilin-2; PLAX = parasternal long-axis view; PLN = phospholamban; PSAX = parasternal short-axis view; PVC = premature ventricular complex; RBBB = right bundle branch block; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVOT = right ventricular outflow tract; TAD = terminal activation duration; TFC = task force criteria; VT = ventricular tachycardia; WMA = wall motion abnormality.

were considered to indicate statistical significance. All statistical analyses were performed using commercially available software (SPSS Statistics for Windows version 21.0, IBM, Armonk, New York).

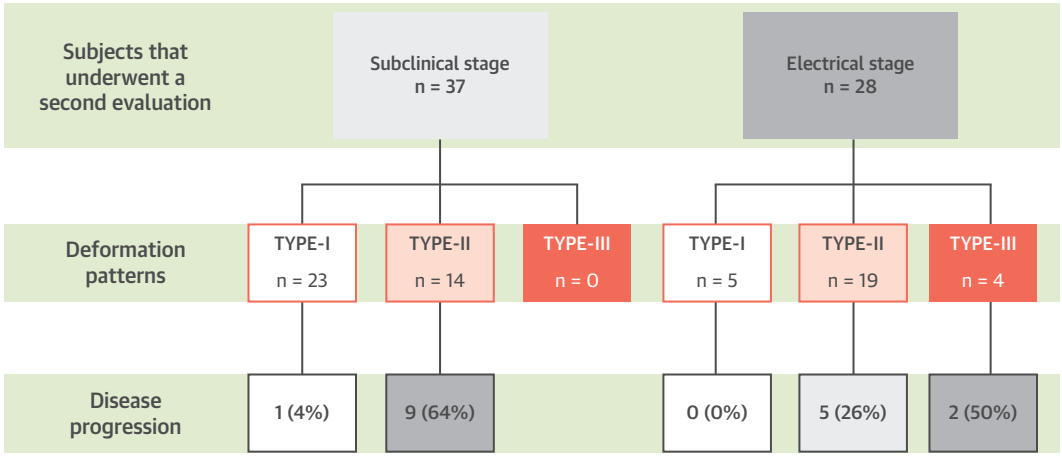
RESULTS

CLINICAL EVALUATION AT BASELINE. The final study population comprised 65 subjects with a mean age of 31.8 ± 16.6 years, of whom 24 (37%) were male. The majority carried pathogenic mutations (n = 54 [83%]), which mostly were considered desmosomal mutations (n = 50 [77%]). On the basis of baseline clinical evaluation, 37 subjects were assigned to the subclinical stage, and 28 subjects had electrical abnormalities according to the 2010 TFC (Figure 1). Subjects who showed electrical abnormalities at baseline were significantly older compared with subjects in the subclinical stage (26.4 ± 13.9 years vs. 39.0 ± 17.4 years; p < 0.001). Sex and the presence of a pathogenic mutation were not significantly different between subjects in the subclinical and electrical stages (Table 1). At baseline, CMR was available in 23 subjects (62%) in the subclinical stage and 19 subjects (68%) in the electrical stage. All mean values of the structural parameters (by CMR and echocardiography) were comparable between subjects in the electrical and subclinical stages (Table 1). At baseline, none of the subjects had signs of LV involvement by echocardiography or CMR. None of the included subjects had histories of sustained ventricular arrhythmias, and none were on antiarrhythmic medications. Eight subjects (12%) had implantable cardiac-defibrillators placed at baseline for primary prevention (3 in the subclinical stage and 5 in the electrical stage). No baseline differences were seen between subjects who underwent a second evaluation (n = 65) and those who did not (n = 44) (Supplemental Table 1).

RV DEFORMATION PATTERNS IN RELATIVES AT BASELINE. In the final study population, type I deformation was seen in 28 subjects (43%), type II deformation was seen in 33 subjects (51%), and type III deformation was seen in 4 subjects (6%). Abnormal deformation (types II and III) was more frequently seen in older subjects (36.6 ± 7.2 years vs. 25.5 ± 13.7 years; p = 0.005) and in pathogenic mutation carriers (92% vs. 71%; p = 0.045). Sex was equally distributed between subjects with normal and abnormal deformation patterns (male 36% vs. 38%; p = 1.00).

The 37 subjects in the subclinical stage were mainly characterized by deformation pattern type I (n = 23 [62%]), whereas deformation pattern type II was seen in the remaining 14 subjects (38%). The electrical stage was mainly characterized by deformation pattern type II (n = 19 [68%]). In the remaining subjects in the electrical stage, type I was seen in

FIGURE 3 Rate of Disease Progression Specified for Deformation Patterns and Clinical Stage at Baseline



These rates result in a negative predictive value (NPV) of 96% (95% confidence interval [CI]: 82% to 100%) and a positive predictive value (PPV) of 43% (95% CI: 27% to 61%) for abnormal deformation imaging in the subtricuspid region. For relatives in the subclinical stage, the NPV and PPV are, respectively, 96% (95% CI: 78% to 100%) and 64% (95% CI: 35% to 87%). For relatives in the electrical stage, the NPV and PPV are, respectively, 100% (95% CI: 48% to 100%) and 30% (95% CI: 13% to 53%).

5 (18%) and type III in 4 (14%). The distribution of baseline deformation patterns specified for the presence of ECG abnormalities as defined by the TFC is shown in Supplemental Table 2.

Inter-rater and intrarater reproducibility for RV deformation pattern classification was high, respectively 0.94 (95% CI: 0.81 to 1.00) and 0.93 (95% CI: 0.79 to 1.00).

DISEASE PROGRESSION. The mean follow-up duration was 3.7 ± 2.1 years and was equally distributed between subjects who showed signs of disease progression and those without signs of disease progression (respectively, 4.5 ± 2.0 vs. 3.5 ± 2.1 years; p = 0.09). Altogether, 17 relatives (26%) showed signs of ARVC disease progression.

Electrical progression occurred more frequently compared with structural progression: 11 subjects showed only electrical progression, 4 subjects showed electrical progression along with structural progression, and 2 subjects showed structural progression on top of pre-existing electrical disease at baseline. None of the subjects experienced a sustained arrhythmic event or appropriate implantable cardioverter-defibrillator intervention during follow-up.

The progression rates among the carriers of different mutations are shown in Supplemental Figure 2.

PREDICTIVE VALUE OF ABNORMAL DEFORMATION IN EARLY ARVC. Of the 28 subjects with a normal deformation pattern (type I) at baseline, only 1 subject showed disease progression, expressed as an increased premature ventricular complex count of >500 over 24 h during second evaluation. In the 37 subjects with abnormal deformation patterns (types II and III) at baseline, disease progression was seen in 16 subjects (43%). The NPV of normal deformation at baseline for disease progression was 96% (95% CI: 82% to 100%). The PPV of abnormal deformation at baseline for disease progression was 43% (95% CI: 27% to 61%). The predictive values were similar in a subcohort consisting only of mutation-positive relatives (n = 54): NPV 95% (95% CI: 75% to 100%) and PPV 44% (95% CI: 27% to 62%).

Figure 3 shows a flowchart of the rate of disease progression specified for both deformation pattern and clinical stage at baseline. Among the 23 subjects in the subclinical stage with normal deformation at baseline, only 1 subject showed disease progression (NPV 96%; 95% CI: 78% to 100%). Among the 14 subjects in the subclinical stage with abnormal (type II) deformation, 9 (64%) showed disease progression (Figure 3). This resulted in a PPV of 64% (95% CI: 35% to 87%).

Among the 5 electrical-stage subjects with normal deformation at baseline, disease progression occurred in none (NPV 100%; 95% CI: 48% to 100%). Of the 19 subjects in the electrical stage with type II pattern at baseline, 5 (26%) showed signs of disease progression. Two of the 4 subjects (50%) in the electrical stage with deformation pattern type III showed

disease progression. The PPV of abnormal deformation (type II or III pattern) on disease progression in the electrical stage was 30% (95% CI: 13% to 53%).

DISCUSSION

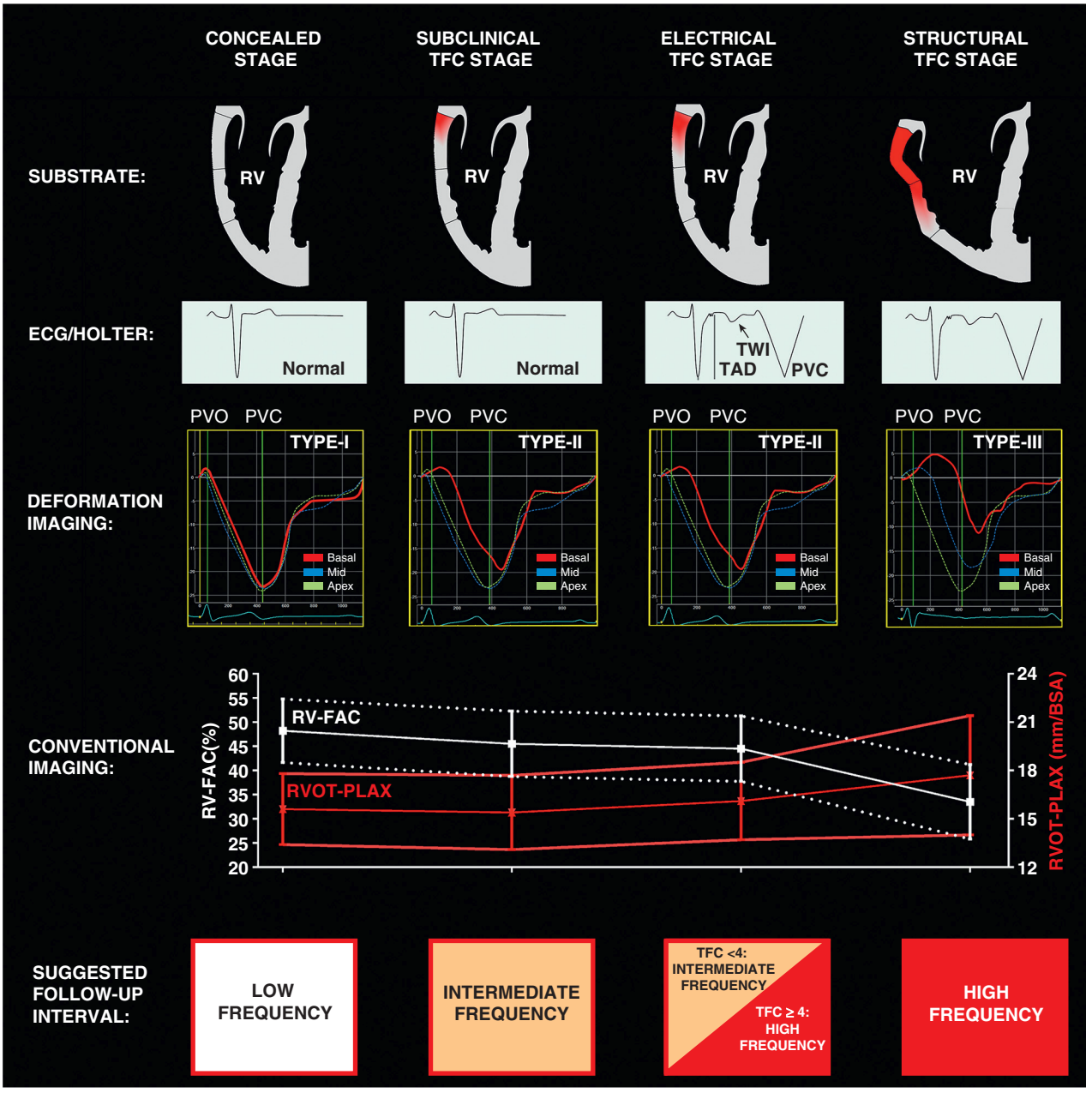
The main findings of our study are that in case of normal findings on conventional echocardiography and CMR: 1) first-degree relatives of patients with ARVC with normal deformation in the RV basal area did not show disease progression during a mean follow-up of nearly 4 years; and 2) the presence of abnormal deformation at baseline was associated with unequivocal signs of disease progression during follow-up in early ARVC. The results of this study might have implications for our follow-up strategy of relatives in clinical practice. Relatives with normal RV deformation on top of normal results during standard cardiac screening seem to have an excellent midterm prognosis, and less frequent cardiac screening might be equally effective.

NORMAL RV DEFORMATION IMAGING IN EARLY ARVC. Our study shows that deformation imaging is able to identify relatives at low risk for disease progression. This holds true particularly for relatives in the earliest stage without any established disease expression as defined by the TFC. Normal deformation in the RV basal area in addition to the absence of abnormalities detected by electrocardiography, Holter monitoring, and conventional cardiac imaging largely excludes disease progression for at least almost 4 years. Previously, we demonstrated with computer modeling that deformation pattern type I represents normal electromechanical properties of the RV myocardium such as seen in healthy subjects (14). We focused on the RV basal area (subtricuspid region) because previous studies have convincingly shown that this area is 1 of the first affected regions in ARVC (12,13,15). Our results suggest that relatives without any disease expression (including normal deformation in the subtricuspid region) are in a clinical stage that precedes the subclinical stage. Traditionally, a clinical stage without any disease expression in ARVC is often considered as the concealed stage (1). Our data show that deformation imaging helps discriminate between relatives who are in a true concealed stage and relatives with subtle local RV mechanical dysfunction not detected by conventional approaches (subclinical stage) (**Figure 4**). A recent consensus statement by an international task force recommends repeated clinical assessment in all family members of patients with ARVC every 2 to 3 years, even in those without any morphological or functional abnormalities (6). In the present study, we observed low progression rates in relatives of patients with ARVC in the true concealed stage (i.e., relatives with normal deformation in the subtricuspid region in addition to normal findings by conventional techniques). This allows us to speculate that the follow-up interval in this group might be extended beyond the current recommendations (6). However, further studies with longer follow-up and preferentially larger patient numbers, in which disease progression is accurately assessed by CMR, are needed to further substantiate our findings. Moreover, individual factors (e.g., cardiac symptoms and sports activity) should always be considered when determining individual follow-up intervals.

ABNORMAL RV DEFORMATION IMAGING IN EARLY ARVC. By definition, relatives in the subclinical stage lack any established disease expression as defined by the TFC. Interestingly, one-third of the included subclinical staged subjects in this study were identified with an abnormal deformation pattern (type II). In a recent study, we showed that this abnormal deformation pattern was present in almost one-half of the desmosomal mutation carriers in the subclinical stage, and the underlying electromechanical substrate seems to be regional hypocontractility and mildly increased passive wall stiffness (14). This finding was confirmed in the present study, in which abnormal deformation patterns were encountered in subclinical-stage subjects without any established disease expression, including the absence of ECG abnormalities (Supplemental Table 2). One of our main findings was that the presence of abnormal deformation actually precedes ECG abnormalities, as approximately one-half of the subjects in the subclinical stage with abnormal deformation developed unequivocal signs of disease progression during follow-up, primarily electrical disease progression. The association between the presence of abnormal deformation and the occurrence of established disease expression during follow-up supports our hypothesis that the observed deformation patterns are a functional representation of an underlying pathological electromechanical substrate.

The subjects in our cohort did not experience any life-threatening events such as sudden cardiac death, sustained ventricular arrhythmia, or appropriate implantable cardioverter-defibrillator intervention during follow-up. This could be explained by the fact that all relatives fulfilling structural TFC were excluded from our study, while especially this form of disease expression is seen in all relatives prior to

FIGURE 4 Suggested Follow-Up Strategy in Relatives Depends on Clinical Stage of Arrhythmogenic Right Ventricular Cardiomyopathy



In the concealed stage, right ventricular deformation imaging shows normal deformation (type I), suggesting the absence of electromechanical substrate. In the subclinical stage, right ventricular deformation imaging shows an abnormal pattern, but electrical and structural abnormalities (as defined by the task force criteria [TFC]) are not detectable. The electrical stage is characterized by electrical abnormalities, and deformation imaging in this stage shows a transition between type II and type III deformation patterns. In the structural stage, there are both electrical and structural abnormalities as defined by the TFC, and deformation imaging in this stage shows type III deformation, which is associated with a large right ventricular electromechanical substrate. Normal deformation (type I) without any other detected abnormalities excludes the presence of an electromechanical substrate, and follow-up intervals in this stage might be less frequent compared with the follow-up strategies recommended by current guidelines (6). BSA = body surface area; ECG = electrocardiography; FAC = fractional area change; PLAX = parasternal long-axis view; PVC = premature ventricular complexes; RV = right ventricle; RVOT = right ventricular outflow tract; TAD = terminal activation duration; TWI = T-wave inversion.

sustained arrhythmic events (3,4,7). Another explanation could be that this cohort was too small, and the lack of events was possibly a matter of chance. Although we were not able to prove any association between abnormal deformation and sustained arrhythmias, we do speculate that abnormal deformation is an early sign of structural changes. Considering the apparent low arrhythmic risk in patients with no structural expression, cardiac screening every 2 years in accordance with the current task force consensus statement seems to be sufficient and safe (6) (**Figure 4**).

TOWARD OPTIMIZATION OF FAMILY SCREENING PROTOCOLS. To our best knowledge, the present study is the first to prospectively investigate the prognostic value of RV deformation imaging in early ARVC. A recent retrospective study by Leren et al. (20) reported a multimodality approach in identifying subjects at risk for ventricular arrhythmias during early ARVC and thereby aiming at the use of deformation imaging in addition to conventional techniques. Our study is in line with their multimodality design during family screening and further highlights the additional value of RV deformation imaging in ARVC.

A recent expert consensus document of the European Heart Association supports the additional use of strain echocardiography in the echocardiographic assessment of ARVC, particularly in early ARVC, when the diagnosis is challenging (8). We may be entering a new era in which echocardiographic deformation imaging will participate in the field of clinical decision making in ARVC (21).

STUDY LIMITATIONS. On the basis of the rates of disease progression that were observed in our cohort after almost 4 years, we made suggestions for follow-up intervals for family members of patients with ARVC. However, these intervals may not be suitable for all family members. First, it is known that the disease behaves differently among the carriers of different mutations, while our cohort represented mainly plakophilin-2 and phospholamban mutation carriers (17). Additionally, in our proposed follow-up intervals, we did not take into consideration factors such as age, sex, presence of cardiac symptoms, and sports activity (4,22). These factors may have a significant influence on disease progression and thus should be taken into consideration in studies aiming to make recommendations for follow-up intervals. Even though the present study included a relatively large cohort of patients with this relatively rare disease, our study population was too small to correct for genetic profile and additional clinical factors in a multivariate analysis.

Forty percent of the baseline cohort could not be included in the study, because their second evaluation did not take place during our study period or because the second evaluation did not include all diagnostic modalities that are needed to adequately assess disease progression. On the basis of the baseline comparison between subjects with follow-up and without available follow-up (Supplemental Table 1), relevant selection bias seems unlikely.

Structural disease progression was primarily assessed using conventional echocardiography, and 25 subjects (38%) underwent additional CMR. However, the sensitivity of conventional echocardiography is known to be inferior to that of CMR, which could potentially lead to lower detection of structural abnormalities in subjects who did not undergo CMR (23). In future studies, disease progression should be accurately assessed using both CMR and echocardiography.

CONCLUSIONS

Echocardiographic deformation imaging is capable to identify relatives who are at low risk for disease progression during the early stages of ARVC. A normal RV deformation pattern at baseline is associated with an absence of disease progression during midterm follow-up in relatives of patients with ARVC, suggesting that a low-frequency follow-up strategy would suffice. Moreover, the presence of abnormal RV deformation in early ARVC is associated with unequivocal signs of disease progression. Therefore, our data suggest that echocardiographic deformation imaging may potentially be implemented in ARVC family screening protocols. Future studies including a larger study population are required to validate our data.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present study demonstrates that in the absence of structural TFC, normal echocardiographic deformation in the subtricuspid region identifies family members of patients with ARVC who are at low risk for disease progression. Abnormal echocardiographic deformation in this region is associated with unequivocal signs of disease progression.

TRANSLATIONAL OUTLOOK: Future studies including a larger number of family members of patients with ARVC and with longer follow-up are required to validate the predictive value of echocardiographic deformation imaging in risk stratification in early ARVC. Echocardiographic deformation imaging may become an important part of family screening protocols in ARVC. We should be heading in the direction of a predictive model in which a variety of clinical parameters are implemented, to create individual, tailor-made follow-up strategies for family members of patients with ARVC.

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KEY WORDS arrhythmogenic right ventricular cardiomyopathy, ARVD/C, deformation imaging, disease progression, family screening, strain imaging

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.