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Clinical Investigation

The Value of Strain Echocardiography in Predicting Electrical Progression in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Background: Arrhythmogenic right ventricular (RV) cardiomyopathy is a progressive disease characterized by the replacement of the normal myocardium with fibrofatty tissue. This study aimed to determine the value of echocardiographic RV deformation parameters in predicting electrical progression as assessed by serial changes in RV lead sensing and threshold in patients with arrhythmogenic RV cardiomyopathy.

Methods: The present study recruited 40 patients with a definitive diagnosis of arrhythmogenic RV cardiomyopathy at a mean (SD) age of 38.6 (14.2) years between 2018 and 2020. All patients had received an implantable cardioverter-defibrillator for the primary or secondary prevention of sudden cardiac death. The patients underwent 2-dimensional (2D) and 3-dimensional (3D) transthoracic echocardiographic examinations and RV 2D and 3D strain analyses, comprising free-wall longitudinal strain, global longitudinal strain, and strain rate. They were then followed up for electrical progression.

Results: During a mean (SD) follow-up period of 20 (6) months, the RV lead amplitude decreased from 7.95 (IQR, 4.53-10.25) mV to 5.25 (IQR, 2.88-8.55) mV ($P < .001$), and the lead threshold increased from 0.75 (IQR, 0.50-0.79) V to 0.75 (IQR, 0.75-1.00) V ($P < .001$). Right ventricular 2D free-wall ($\rho = 0.56$, $P = .01$), RV 2D global ($\rho = 0.58$, $P = .007$), and RV 3D free-wall ($\rho = 0.65$; $P = .003$) longitudinal strain correlated with electrical progression.

Conclusion: Right ventricular 2D and 3D deformation parameters were found to be significant predictors of electrical progression during follow-up of patients with arrhythmogenic RV cardiomyopathy. These findings suggest that echocardiography has a pivotal role in predicting patients at high risk for electrical progression.

Keywords: Arrhythmogenic right ventricular cardiomyopathy; implantable cardioverter defibrillator; 3D echocardiography

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a right ventricular (RV) epicardial-to-endocardial disease process with the progressive loss of the RV myocardium and its replacement by fibrofatty deposition, predisposing patients to life-threatening ventricular arrhythmias and progressive ventricular dysfunction.[1] The establishment of an accurate diagnosis is challenging because the clinical manifestations of ARVC are highly variable. The pathologic gold standard for ARVC diagnosis is the histologic detection of the fibrofatty replacement of the RV myocardium from the epicardium or the midmyocardium extending intramurally to the subendocardium.[2] A diagnosis of ARVC is typically based on the Task Force Criteria of electrocardiographic (ECG) and

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mechanical structural changes in addition to manifest RV arrhythmias.[2-4] Echocardiography in patients with ARVC is helpful as a method to identify RV abnormalities and to establish prognoses in this group of patients.[5] New studies have shown that the use of relatively novel techniques, such as strain, can assist in the early diagnosis of the disease.[4] The natural history of ARVC is predominantly related to ventricular electrical instability, which may lead to arrhythmic death at any time during the disease course. Moreover, there is clinical and pathological evidence that ARVC is a progressive heart muscle disease.[6] An accurate prediction of electrical progression is crucial, because consequential events can be fatal. Information is limited on the predictive role of advanced echocardiography in determining electrical progression, and no study has been conducted on the role of myocardial deformation in predicting electrical progression.

The principal purpose of this study was to assess the extent of electrical progression as assessed by serial changes in RV lead sensing and threshold in patients with ARVC and its association with the echocardiographic RV free-wall strain and strain rate. We also sought to identify the indicators of electrical progression and to evaluate the occurrence of ventricular arrhythmias over time based on the hypothesis that the echocardiographic RV free-wall strain and strain rate at baseline are associated with future electrical progression in patients with ARVC.

Abbreviations and Acronyms

2D	2-dimensional
3D	3-dimensional
A/a′	late
ARVC	arrhythmogenic right ventricular cardiomyopathy
E/e′	early
ECG	electrocardiography
EF	ejection fraction
FAC	fractional area change
ICD	implantable cardioverter-defibrillator
LV	left ventricular
RA	right atrium
RV	right ventricular
RVOT	right ventricular outflow tract
s′	septal
TAPSE	tricuspid annular plane systolic excursion

Patients and Methods

Patient Population

The present study enrolled 40 patients with a definitive diagnosis of ARVC based on the revised 2010 Task Force Criteria at a mean (SD) age of 38.58 (14.01) years between 2018 and 2020 (2-year period). All the participants underwent routine 12-lead ECG recording at baseline. Electrocardiograms were evaluated for the presence of depolarization criteria (epsilon waves and terminal activation duration ≥55 ms) and repolarization criteria (precordial T-wave inversion in leads V_1-V_6) according to the Task Force Criteria (Fig. 1).

Cardiac magnetic resonance was performed for all the patients to fulfill the criteria prior to device implantation. All patients had received an implantable cardioverter-defibrillator (ICD) for the primary or secondary prevention of sudden cardiac death. At the beginning with Philips EPIQ 7 (Philips EPIQ 7 Ultrasound Machine-2.5 MHz transducers). Thereafter, they were referred to the department of electrophysiology for further follow-up. The entire study population underwent a follow-up period of 14 to 26 months (median, 20 months), and they were monitored for electrical progression.

The study protocol was approved by the institution's ethics committee, and informed written consent was obtained from all patients.

Assessment of Electrical Progression

The patients were followed up in the outpatient clinic every 6 months routinely and promptly after ICD shocks. Appropriate ICD therapy was defined as antitachycardia pacing therapy or shock for ventricular tachycardias or ventricular fibrillations based on device-stored electrograms and clinical information. All the stored electrograms were assessed by an electrophysiologist and classified as appropriate or inappropriate. An electrical storm was defined as the occurrence of ventricular tachycardias or ventricular fibrillations resulting in device intervention 3 or more times within a 24-hour period. Electrical progression was defined based on ICD-lead analysis as a decrease in the R-wave amplitude and an increase in threshold over time and the occurrence of appropriate ICD therapy during the follow-up period. Ventricular lead parameters, comprising RV lead R-wave amplitude and RV lead threshold (voltage amplitude and pulse width), were determined at implant and subsequently every 6 months. Other causes that might influence the variation of R-wave amplitude,

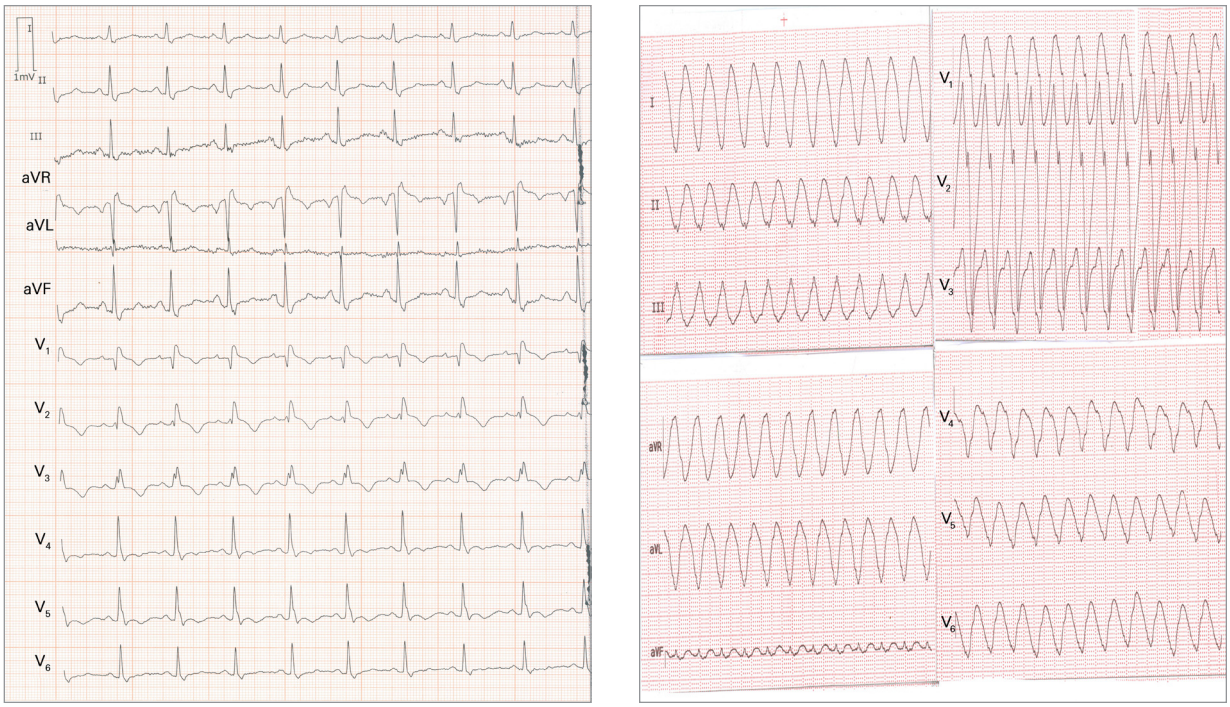

Fig. 1 Electrocardiograms illustrate electrocardiographic recording during sinus rhythm (note epsilon wave) **A**) and ventricular tachycardia **B**).

such as electrolyte disturbances, hypoxia, drugs, and ischemia, were excluded. Given the difficulty in finding a suitable location at the apex, ICD leads are typically placed in the RV septum at the study center.

Echocardiographic Findings

Conventional 2D Transthoracic Echocardiography. Standard left ventricular (LV) views were obtained from the parasternal long- and short-axis views and the apical 2-, 3-, and 4-chamber views. The function and diameter of the left ventricle were assessed via color-flow, pulsed-wave, and continuous-wave Doppler from the mentioned views based on the guidelines of the American Society of Echocardiography.[7] Right ventricular study was conducted in the parasternal window by measuring the dimension in the RV outflow tract (RVOT) (proximal long- and short-axis views to appraise ARVC criteria). Subsequently, through the RV-focused view, the dimension of the RV was measured at the base, at the mid-portion, and in the longitudinal direction at end-diastole (according to R-wave in ECG). The fractional area change (FAC) of the RV was calculated in this view as the difference between the end-diastolic and end-systolic areas divided by the end-diastolic area, and it was expressed as a percentage. Diastolic function was evaluated via the pulsed-wave Doppler of the mitral and tricuspid valve tips to measure early (E) and late (A) velocities. Moreover, tissue velocities were measured from the mitral annulus at the septal and lateral walls and the tricuspid annulus to obtain early (e′), late (a′), and septal (s′) velocities (all in cm/s).

Right Ventricular 2D-Strain ECG. Standard RV views were obtained from the 4-chamber and RV views. The captured images were examined offline by TOMTEC (TOMTEC Imaging System GmbH software) for the estimation of strain. Initially, the end-systolic and end-diastolic times were determined using the opening and closing times of the tricuspid valve. Then, specific zones of the endocardial margin of the RV were identified at end-systolic and end-diastolic times. The endocardial margin was traced automatically by the software at the end-systolic and end-diastolic cycles. At the final stage, these areas were adjusted manually, and the longitudinal strain of the RV free wall, the longitudinal strain of the RV septum, and the global longitudinal strain of the RV were calculated (Fig. 2).

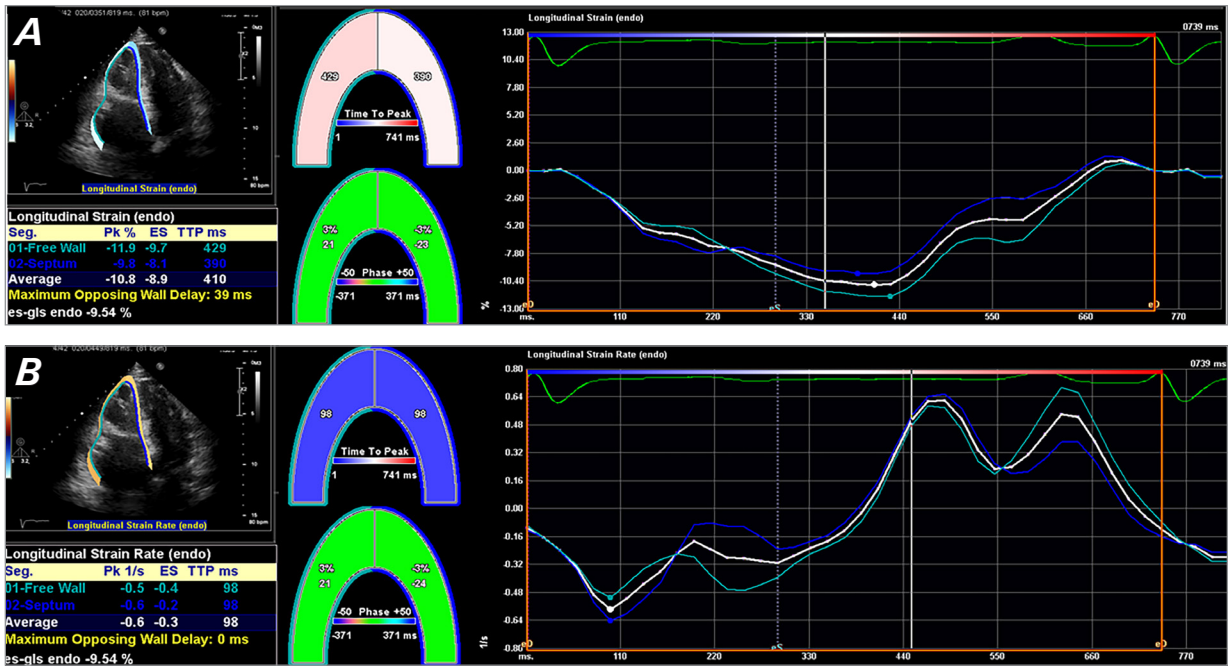

Fig. 2 Strain echocardiograms depict the speckle-tracking "strain" **A**) and strain rate **B**) analyses of RV systolic function using TOMTEC software for the estimation of global longitudinal strain and free-wall longitudinal strain. Mean frame rates were approximately 70 to 90 frames/second. The images were digitally stored for 3 to 5 cardiac cycles. The endocardial margin was traced automatically by the software at the end-systolic and end-diastolic cycles. Tracking quality was visually verified. At the final stage, these areas were adjusted manually, and the longitudinal strain of the RV free wall, the longitudinal strain of the RV septum, and the global longitudinal strain of the RV were calculated.

gls, global longitudinal strain; endo, endocardial; ES, end-systole; Pk, peak strain; RV, right ventricular; Seg., segment; TTP, time to peak.

Right Ventricular 3D ECG.

With the aid of a matrix-array transducer, 3D images of the right ventricle were acquired. After the selection of high-quality images, 4-beat full-volume images were taken in the apical views during a breath-hold based on recommendations by TOMTEC. The data were analyzed offline. Following the determination of the systolic and diastolic end-phases, the endocardial border was drawn; then, the software automatically calculated RV 3D parameters, including the volume and function (RV 3D ejection fraction [EF]).

Statistical Analysis

The fitness of interval variables to normal distribution was investigated using the 1-sample Kolmogorov–Smirnov test. The data were described as means (SDs) for interval variables with normal distribution, medians (IQRs) for variables with skewed distribution, and frequencies (percentages) for categorical variables. The correlation between echocardiographic and electrophysiological parameters was assessed via Spearman correlation coefficient (ρ).

Variations of the parameters during the follow-up were assessed by Wilcoxon signed-rank test. Quantitative variables were compared between the 2 groups by using the Mann-Whitney *U* test.

The association of electrical progression and echocardiography indices was investigated by linear regression models. Binary logistic regression models were applied to determine the association between the presence of epsilon wave and other factors. $P < .05$ was considered statistically significant. The statistical analyses were performed with IBM SPSS Statistics, version 22, for Windows (IBM, Inc).

Results

The present study assessed 40 patients, at a mean (SD) age of 38.6 (14.2) years, with a definitive diagnosis of

ARVC based on the revised 2010 Task Force Criteria. The entire study population underwent cardiac magnetic resonance to fulfill the criteria. The patients underwent a mean (SD) follow-up of 20 (6) months and were evaluated for electrical progression. The patients' clinical characteristics are presented in Table I.

Correlations Between Echocardiographic and Electrophysiological Parameters

The relationships between baseline echocardiographic findings and electrophysiologic data during the follow-up period were evaluated. A significant relationship was detected between the occurrence of electrical

TABLE I. Demographic and Electrophysiologic Parameters of the Study Participants

Variable	Value
Sex, No. (%)	
Male	32 (80)
Female	8 (20)
Age, mean (SD), y	38.6 (14.2)
Family history of ARVC, No. (%)	22 (45)
Documented ARVC in first-degree relatives	6 (12.2)
SCD in first-degree relatives aged >35 y	4 (4.1)
ARVC in second-degree relatives	3 (6.1)
Electrocardiographic parameters and Holter monitoring, No. (%)	25.8 (5.1)
Normal sinus rhythm	44 (89.8)
AF rhythm	3 (6.1)
RBBB	11 (22.4)
Negative T wave in leads V_1-V_3 and later in the absence of RBBB	20 (40.8)
Negative T wave in leads V_1-V_2 or V_4-V_6 in the absence of RBBB	4 (8.2)
Epsilon wave	11 (22.4)
PVC >500/24 h in Holter monitoring	10 (20.4)
Types of ventricular tachycardia, No. (%)	
NSVT with RBBB morphology and superior axis	5 (10.2)
Sustained VT with RBBB morphology and superior axis	6 (12.2)
NSVT with RBBB morphology and inferior axis	1 (2.0)
Sustained VT with RBBB morphology and inferior or unknown axis	26 (53.1)
Detected arrhythmias in ICD programming, No. (%)	
NSVT	5 (10.2)
Supraventricular tachycardia	3 (6.1)
VT	18 (36.7)
VF	1 (2)
Electrical storm	9 (18.4)

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular tachyarrhythmia; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; RBBB, right bundle branch block; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

storms and RV systolic function parameters (RV 3D EF [ρ = 0.55, *P* = .01], RV 2D strain [*P* = .01], and RV 3D strain [*P* = .04]) and LV diastolic markers (LV septal e′ [*P* < .001] and a′ [*P* = .03]). A significant relationship was also revealed between a right bundle branch block pattern on electrocardiography and larger RV (*P* = .03) and RA dimensions in echocardiography (*P* = .004). Furthermore, the epsilon wave in ECG was associated with arrhythmic events (*P* = .02).

In patients with epsilon waves in ECG, the univariate regression analysis demonstrated the predictive role of the presence of the epsilon wave with the echocardiographic criteria of RV 2D tricuspid annular plane systolic excursion (TAPSE), RV 2D FAC, RVOT short-axis diameter, right atrium (RA) volume and area, and RV isovolumic contraction time (Table II).

Electrical Progression and Its Association With Echocardiographic Parameters

During a mean (SD) follow-up period of 20 (6) months, the RV lead amplitude fell from 7.95 (IQR, 4.53-10.25) mV to 5.25 (IQR, 2.88-8.55) mV (*P* < .001), and the lead threshold increased from 0.75 (IQR, 0.50-0.79) to 0.75 (IQR, 0.75-1.00) V (*P* < .001).

As is shown in Table III, in the univariate analysis, the dimension of the right ventricle at baseline and the presence of decreased RV systolic function based on 2D and 3D echocardiographic parameters were associated with electrical progression during the follow-up period. The absolute values of strain and strain rate were predictors of electrical progression. In the stepwise multivariate regression analysis, RV 3D EF remained an independent predictor of electrical progression during the follow-up period (*P* = .001; ρ = 0.86; coefficient [SD] = 0.32 [0.07]). In the multivariate regression analysis, the presence of the epsilon wave was not a significant predictor of arrhythmic events (*P* = .048; odds ratio, 7.55; 95% CI, 1.02-56.04).

Discussion

The results of the present study underscore the predictive role of echocardiographic markers in determining electrical progression over time in patients with ARVC. In patients with an ICD, we assessed lead parameters at multiple points during the follow-up period for each patient to ensure reliability of the recorded data. To our knowledge, this is the first study to assess the value of RV deformation parameters in predicting electrical progression in patients with ARVC.

The principal findings of this investigation are as follows:

1. RV 2D and 3D deformation parameters (strain and strain rate) are predictors of electrical progression.

2. Multiple echocardiographic RV 2D and 3D parameters have a predictive role in determining electrical progression. These parameters include RV 2D TAPSE, RV 2D FAC, RV free wall s′, RV 3D EF, RV end-diastolic diameter at the base and the midportion, and RVOT long-axis diameter.

The multivariate regression analysis demonstrated that RV 3D EF was the strongest predictor of electrical progression.

TABLE II. Univariate Logistic Regression Analysis to Identify the Association Between the Presence of the Epsilon Wave on Electrocardiography and Echocardiographic Parameters

Variable	*P* value[a]	OR (95% CI)
RVOT SAX	.05	5.46 (1.01-29.60)
2D TAPSE	.03	0.68 (0.48-0.97)
2D FAC	.03	0.86 (0.85-0.99)
RA volume	.03	1.03 (1.00-1.05)
RA area	.03	1.14 (1.01-1.29)
RV IVCT	.03	1.02 (1.00-1.05)

2D, 2-dimensional; FAC, fractional area change; IVCT, isovolumic contraction time; OR, odds ratio; RA, right atrium; RVOT SAX, right ventricular outflow tract short axis; TAPSE, tricuspid annular plane systolic excursion.

[a]*P* < .05 was considered statistically significant.

TABLE III. Linear Regression Analysis Between Electrical Progression and Echocardiographic Data[a]

Variable	ρ	Coefficient (SD)	*P* value
LV EF	0.38	–0.005 (2.88)	.04
Septal a′	0.57	–1.57 (2.30)	.001
Septal s′	0.47	–3.14 (3.39)	.009
RVEDD mid	0.423	15.32 (3.85)	.02
RVEDD base	0.55	18.03 (3.52)	.002
RVOT LAX	0.46	14.13 (2.93)	.009
2D TAPSE	0.42	0.27 (2.46)	.02
2D FAC	0.46	1.10 (2.47)	.04
RA volume	0.57	9.95 (1.16)	.001
RA area	0.60	12.27 (1.65)	.001
RV free wall s′	0.36	1.67 (2.22)	.05
RV 2D FWLS	0.56	1.34 (1.87)	.01
RV 2D GLS	0.58	0.27 (2.09)	.007
RV 2D FWLS rate	0.58	2.99 (1.31)	.008
RV 2D GLS rate	0.54	1.89 (1.78)	.01
RV 3D ESVI	0.52	12.88 (2.55)	.03
RV 3D EF	0.55	0.58 (2.45)	.01
RV 3D FWLS	0.65	0.94 (1.86)	.003
RV 3D GLS	0.50	1.71 (2.23)	.03

2D, 2-dimensional; 3D, 3-dimensional; EF, ejection fraction; ESVI, end-systolic volume index; FAC, fractional area change; FWLS, free-wall longitudinal strain; GLS, global longitudinal strain; LV, left ventricle; RA, right atrium; RV, right ventricle; RVEDD, end-diastolic diameter; RVOT LAX, right ventricular outflow tract long axis; TAPSE, tricuspid annular plane systolic excursion.

[a] Data were calculated using the Pearson correlation coefficient (*r*). $P < .05$ was considered statistically significant.

Malik et al[4] recognized echocardiographic strain as a useful technique to predict the structural progression of the disease in ARVC. Their findings suggest that echocardiographic strain and strain rate could be useful in the identification of patients at risk of disease progression who may require closer follow-up and treatment. Prior studies have evaluated RV and LV mechanical dispersion in addition to RV strain to predict arrhythmias in ARVC and to differentiate early ARVC from RVOT-ventricular tachycardias.[8,9] Lie et al[10] concluded that whereas RV longitudinal strain was associated with malignant ventricular arrhythmias, an even stronger relationship existed between such arrhythmias and LV mechanical dispersion parameters. Herman et al[11] reported that in their patients with ARVC, the amplitude of intracardiac electrograms recorded at the RV apex from ICD leads deteriorated significantly during a medium-term follow-up period. The concept that ARVC is a progressive disorder could not only influence treatment plans but also explain the unfavorable outcomes. The association between ARVC and the subsequent development of ventricular arrhythmias has been proven. The value of ICD therapy depends on the selection of patients, careful implantation, and meticulous follow-up. The R-wave amplitude is crucial to the performance of ICDs. A fall in the R-wave amplitude (electrical progression) and poor sensing may prevent optimal defibrillator therapy.[12] The concern in this regard assumes an even greater significance in the treatment of patients with ARVC. Previous studies have reported a remarkable decrease in the R-wave amplitude in patients with ARVC with ICDs during long follow-

up periods. The change in the RV amplitude indices in this ARVC group is concordant with other published reports.[13] An observational study on the ICD lead electronic parameters of different cardiomyopathies showed that ventricular sensing was likely to deteriorate in patients with ARVC during a 5-year follow-up period.[14]

Challenging lead placement, which is a frequent complication, was reported in 18.4% of the patients in the current study. The structural and functional abnormalities of the right ventricle in patients with ARVC may hinder proper sensing and pacing and require repeated testing of the RV lead. There is a relationship between the extent of RV involvement revealed by angiography or endomyocardial biopsy and the need for testing the RV lead in at least 2 positions.[15]

Another advanced echocardiographic marker is RV 3D EF. Interestingly, the multivariate analysis in the present study showed that RV 3D EF was the strongest predictor of electrical progression. Among systolic function parameters, RV 2D TAPSE, RV 2D and 3D FAC, and RV free wall s′ could also predict electrical progression. Furthermore, a larger diameter of the RV at baseline echocardiography was also a predictor of worse R-wave amplitude over time, which is the indicator of electrical progression. In patients with electrical storms, there were lower LV septal tissue parameters (e′, a′, and s′) and greater RV and RA dimensions at baseline echocardiography. We also found a significant relationship between the occurrence of electrical storms and RV systolic function parameters such as RV 3D EF and RV 2D and 3D strain as well as diastolic markers.

The ECG assessment yielded a significant relationship between the right bundle branch block pattern and larger RV and RA dimensions in echocardiography. Also, in this subgroup of patients, RV 2D FAC and LV EF were significantly lower. This result reinforces the importance of ECG in determining the prognosis in patients with ARVC.

In this study, the strain parameters and their correlation with electrical progression have been analyzed in detail. The measurement of strain parameters can be done using 2D images, whereas 3D images are needed to measure the RV EF using echocardiography. Therefore, although the 3D RV EF is the strongest predictor, the strain parameters are more accessible and easier to measure.

It is worth mentioning that the purpose of this study was not to characterize the extent of structural progression of ARVC over time. The main goal of this study was to evaluate the use of echocardiography-based strain imaging in predicting electrical progression as a potential marker of disease progression. Therefore, both 2D and 3D strain parameters, as well as 3D EF, may all predict electrical progression, though without further documentation of worsening disease. The results of this study extend the current understanding of ARVC and its impact on implantable devices and pave the way for designing trials to further study progression in patients with ARVC.

Limitations

This study was conducted at a tertiary referral center with the possibility of assessing patients with longer standing and more advanced diseases. However, given the small sample size, the results of this study should be confirmed in a larger volume of patients.

Conclusions

In this study of patients with a definitive diagnosis of ARVC, worse 2D and 3D RV strain and strain rate at baseline were found to predict electrical progression over time, manifested as a significant reduction in the R-wave amplitude in the last follow-up.

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Author Contributions: All authors have read and approved the final version of the manuscript. Z.E. contributed article design, study planning, critical article revision, and analyses and played a major part in writing the manuscript. L.H. took part in planning the study, investigating all patients, and analyses and played a major part in writing the manuscript. N.R. contributed to data interpretation, drafting of the article, and review and discussion of the manuscript text. A.S. took part in planning the study and reviewing and discussing the manuscript. Z.A. and H.F. contributed to data acquisition and interpretation and to the analyses. S.A. and S.H. contributed to drafting the article and data interpretation. H.B. performed data analysis, statistical analysis, and data interpretation.

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