JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2016

ISSN 1936-878X

http://dx.doi.org/10.1016/j.jcmg.2016.06.011

Combination of ECG and Echocardiography for Identification of Arrhythmic Events in Early ARVC

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ABSTRACT

OBJECTIVES The aim of this study was to investigate early markers of arrhythmic events (AEs) and improve risk stratification in early arrhythmogenic right ventricular cardiomyopathy (ARVC).

BACKGROUND AEs are frequent in patients with ARVC, but risk stratification in subjects with early ARVC is challenging.

METHODS Early ARVC disease was defined as possible or borderline ARVC diagnosis according to the ARVC Task Force Criteria 2010. We performed resting and signal averaged electrocardiogram (ECG). Using echocardiography, we assessed right ventricular (RV) outflow tract diameter and right ventricular basal diameter (RV diameter). Global longitudinal strain and mechanical dispersion (MD) from strain echocardiography were assessed in both the right and left ventricle. AEs were defined as documented ventricular tachycardia, cardiac syncope, or aborted cardiac arrest.

RESULTS Of 162 included subjects with ARVC (41 ± 16 years of age, 47% female), 73 had early ARVC, including mutation positive family members not fulfilling definite ARVC diagnosis. AEs occurred in 15 (21%) subjects with early ARVC. Those with AEs in early disease had larger RV diameter (40 ± 4 mm vs. 37 ± 5 mm), more pronounced RVMD (39 ± 15 ms vs. 26 ± 11 ms), and more pathological signal averaged ECGs compared with those without AEs (all $p \leq 0.05$). Adding measurements of RV diameter and RVMD to electrical parameters improved identification of subjects with AEs compared with electrical parameters alone ($p = 0.05$).

CONCLUSIONS ECG parameters, RV diameter, and RVMD were markers of previous arrhythmic events in patients with early ARVC. A combination of electrical and echocardiographic parameters improved identification of subjects with AEs in early ARVC disease. (J Am Coll Cardiol Img 2016;■:■-■) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inheritable cardiomyopathy that predisposes to life-threatening arrhythmias and heart failure, and is one of the leading causes of sudden cardiac death (SCD) in young individuals (1). Ventricular arrhythmias are frequent in patients with ARVC and, importantly, arrhythmias may occur also in early stages of disease, making risk stratification challenging (2). Furthermore, the patients with ARVC seen in cardiological clinics have changed over the past decade. Fifteen years ago, patients were typically diagnosed with overt ARVC after they had survived a life-threatening arrhythmic event. Genetic family screening now identifies individuals at risk of developing ARVC before onset of symptoms of disease. Hence risk

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Manuscript received March 30, 2016; revised manuscript received June 27, 2016, accepted June 30, 2016.

ABBREVIATIONS AND ACRONYMS

AIC = Akaike information criterion

ARVC = arrhythmogenic right ventricular cardiomyopathy

CI = confidence interval

ECG = electrocardiogram

ICD = implantable cardioverter defibrillator

LV = left ventricular

LVEF = left ventricular ejection fraction

ROC = receiver operating characteristic

RV = right ventricular

RV FAC = RV fractional area change

RVOT = right ventricular outflow tract

SCD = sudden cardiac death

TFC 2010 = ARVC Task Force Criteria, revised in 2010

VT = ventricular tachycardia

stratification has moved from assessing obvious myocardial pathology to predicting the transition from asymptomatic, mutation positive ARVC to electrical disease with potential life-threatening ventricular arrhythmias (3). Of importance, outcome is favorable in patients detected early and treated according to guidelines (4). Tools are needed to detect early disease and to optimize medication and timing of implantation of a cardioverter defibrillator (ICD) to prevent SCD becoming the first symptom of ARVC.

The Task Force Criteria revised in 2010 (TFC 2010) improved sensitivity and specificity of ARVC diagnosis (5). Newer echocardiographic techniques, such as strain echocardiography, have shown promising results in ARVC risk stratification in previous studies (6,7). We aimed to explore early markers of ARVC disease and their association with previous ventricular arrhythmias. We hypothesized that a combination of electrocardiographic parameters and imaging parameters, including strain echocardiography, may improve risk stratification of arrhythmic events in subjects with ARVC.

METHODS

STUDY POPULATION. In this cross-sectional study, consecutive patients referred to the Department of Cardiology, Oslo University Hospital, Rikshospitalet, between 2008 and 2014 with suspected ARVC were evaluated for inclusion. Probands were genetically screened and family members of probands with disease-causing mutations were tested and included if mutation-positive. All patients fulfilling borderline, possible, or definite ARVC diagnosis by the TFC 2010 (5) at their visit were invited to participate. No patient refused consent to participate. Exclusion criteria were significant ischemic heart disease or coexisting heart disease of other origin. All participants underwent clinical examination. Arrhythmic events were reviewed retrospectively at inclusion and defined as documented nonsustained or sustained ventricular tachycardia (VT) by Holter monitoring, exercise test or ICD recordings, syncope of suspected cardiac origin, or aborted cardiac arrest. Medication use, ICD presence, and eventual prior ICD therapies at the time of the echocardiographic examination were recorded.

ELECTROCARDIOGRAPHY. Twelve-lead electrocardiogram (ECG) was obtained at the time of the echocardiographic examination. Signal-averaged ECGs were performed (8) and patients with complete bundle branch block were excluded from signal-averaged ECGs analyses (5). S-wave upstroke was measured as the time from the nadir of the S-wave to the isoelectric line (9).

ECHOCARDIOGRAPHIC STUDIES. Two-dimensional echocardiographic studies were performed on a Vivid 7 or 9 (GE Healthcare, Horten, Norway) and data were analyzed with EchoPAC version 112 (GE Healthcare). Data analyses were performed blinded to patient clinical data.

From 2-dimensional echocardiography, we assessed proximal right ventricular outflow tract (RVOT) diameter in the parasternal short-axis view. We assessed right ventricular basal diameter (RV diameter) and right ventricular fractional area change (RV FAC) from the 4-chamber view (10). Left ventricular (LV) end-diastolic volume, LV end-systolic volume, and left ventricular ejection fraction (LVEF) were calculated by the modified Simpson biplane method.

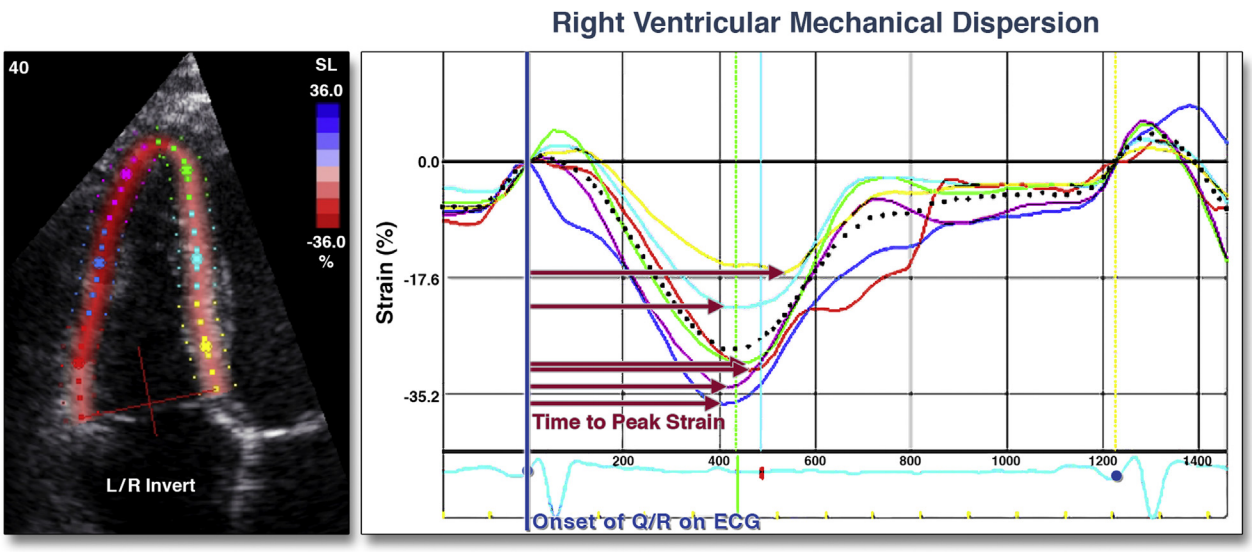
We assessed longitudinal strains by speckle tracking technique from the 3 apical views for LV global longitudinal strain (11) and from the 4-chamber view for right ventricular (RV) global longitudinal strain, all at frame rates >50/s. The endocardial border was traced in each view. The operator manually adjusted segments that failed to track; segments that subsequently failed to track were excluded. LV global longitudinal strain was defined as the average of peak negative longitudinal strain from a 16-segment LV model (11). LV mechanical dispersion was defined as the standard deviation of time from Q/R on the ECG to peak negative longitudinal strain in the same 16 segments. Peak negative longitudinal strain from 6 RV segments was averaged as a measure of RV function (RV global longitudinal strain) (6). RV mechanical dispersion was calculated as the SD of time from Q/R on ECG to peak negative longitudinal strain from 6 RV segments (**Figure 1**).

CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance was performed as previously described (12) and parameters for TFC 2010 were analyzed (5).

STAGING OF ARVC DISEASE. To assess the stage of ARVC disease (overt or early), we used the TFC 2010 criteria (5). Patients who fulfilled definite ARVC diagnosis (≥2 major or 4 minor criteria, or 1 major and 2 minor criteria) were defined as overt ARVC. Subjects fulfilling borderline ARVC (1 major + 1 minor or 3 minor criteria) and possible ARVC (1 major or 2 minor criteria) were defined as early ARVC.

GENETIC ANALYSES. Genetic testing was performed as previously described (12) as part of the diagnostic workup in subjects with suspected ARVC. Cascade genetic screening was performed in family members

FIGURE 1 Measurement of RV Mechanical Dispersion



Red horizontal arrows indicate time to peak strain, defined as time from onset of Q/R on ECG to peak negative strain. **Blue vertical line** indicates onset of Q/R on ECG. RV mechanical dispersion was defined as the standard deviation of contraction duration from 6 RV segments. ECG = electrocardiogram; RV = right ventricular.

of mutation-positive index patients. Only family members of ARVC patients with confirmed pathogenic mutations were included.

STATISTICAL ANALYSES. Comparisons of proportions were performed by the chi-square test or Fisher exact test when appropriate. Continuous data were presented as mean ± SD and compared by unpaired Student *t* test (SPSS version 21.0, SPSS Inc., Chicago, Illinois). Multivariable logistic regression analyses were used to adjust for beta-blocker use, age, sex, and mutation status in the total ARVC population. Overfitting was tested with Akaike information criterion (AIC).

Correlations between continuous parameters were assessed by linear regression. The C-statistic was calculated by receiver operating characteristic (ROC) curves. The value closest to the upper left corner of the ROC curve was defined as giving optimal sensitivity and specificity. Comparisons of C-statistics were performed with the software Analyze-it (Analyse-it Software, Ltd., Leeds, United Kingdom). We used likelihood ratios test to evaluate if echocardiographic parameters could improve the model for identifying subjects with arrhythmic events compared with electrical parameters only. Two sided p values ≤0.05 were considered statistically significant. Intraobserver and interobserver variability analyses were performed in 10 random study patients and expressed by intraclass correlation values.

All participants gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics.

RESULTS

We included 162 subjects with ARVC, including 86 (53%) index patients and 76 (47%) mutation-positive family members (41 ± 16 years of age, 45% female) (Table 1). A definite diagnosis of ARVC was present in 89 (55%) subjects, defined as overt ARVC, while 31 (19%) had borderline and 42 (26%) had possible ARVC diagnosis (5), defined as early ARVC disease (n = 73, 45%). Of subjects with early ARVC, 58 (79%) were mutation-positive family members and 15 (21%) had clinically suspected ARVC in addition to fulfilling possible or borderline ARVC diagnostic criteria.

Arrhythmic events occurred in 84 (52%) subjects in total; 69 (78%) with overt and 15 (21%) with early ARVC. Median time from first arrhythmic event to echocardiography was 3.2 months (interquartile range: 0.1 months, 5.9 years). At time of echocardiography, 57 (35%) patients were treated with beta blockers, 10 (6%) with amiodarone, and 1 (1%) with flecainide. Also, 50 (31%) patients had or were implanted with an ICD at the time of study inclusion, including 4 subjects with early ARVC. Appropriate

TABLE 1 Clinical Characteristics in 162 Subjects With ARVC

	Subjects With ARVC (n = 162)
Age, yrs	41 ± 16
BMI, kg/m^2	25.5 ± 4.5
Cardiac arrest	17 (10)
Definite/borderline/possible	89/31/42
Female	76 (47)
Resting heart rate, beats/min	63 ± 13
Index patients	86 (53)
Syncope	47 (29)
Ventricular arrhythmias	84 (52)

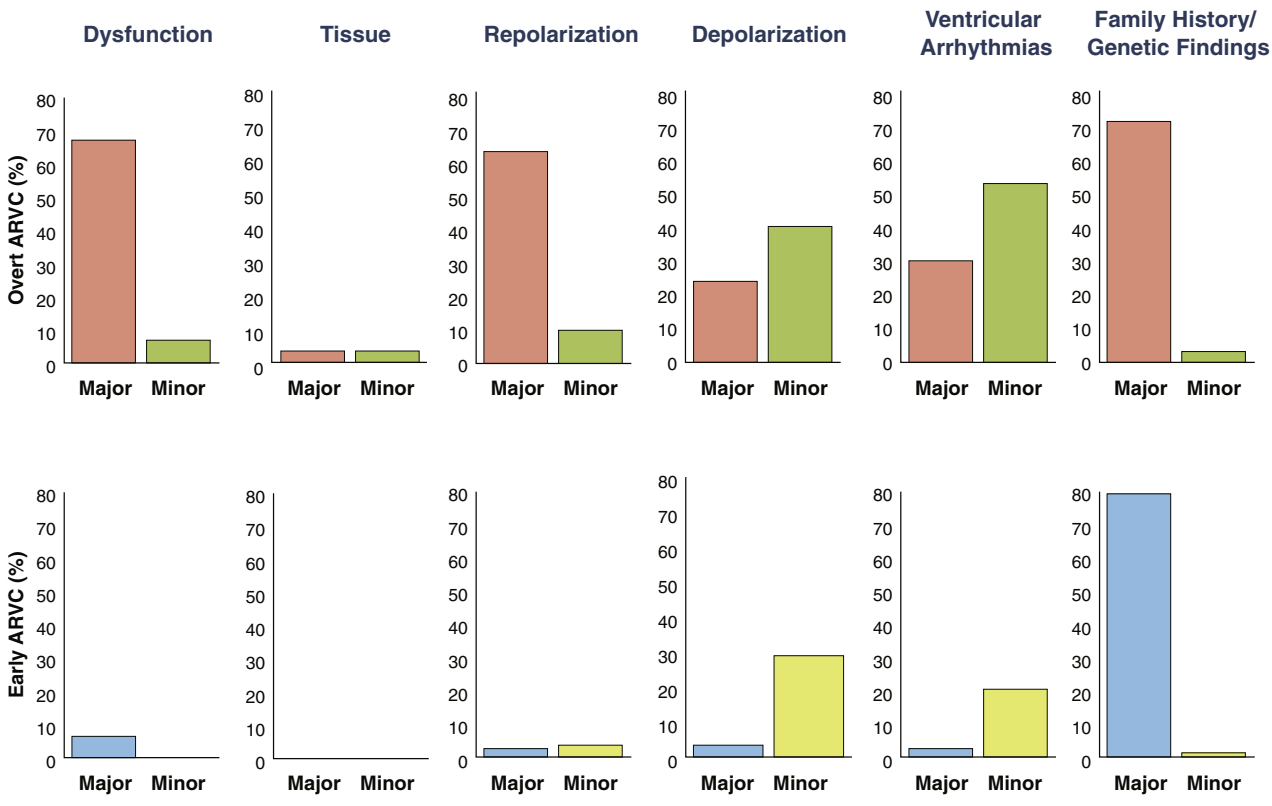
Values are mean ± SD, n (%), or n.
AVRC = arrhythmogenic right ventricular cardiomyopathy; BMI = body mass index.

ICD therapies had been given in 15 patients, none of whom had early disease.

Overt ARVC subjects had changes in all TFC 2010 (5) diagnostic categories, with the exception of tissue characterization by endomyocardial biopsy, which was missing in the majority of subjects (Figure 2). The diagnosis of early ARVC was mainly based on family mutations (n = 58), minor depolarization abnormalities (n = 22), and minor criteria for ventricular arrhythmias (n = 15) (Figure 2). Cardiac magnetic resonance was performed in 121 (75%) subjects with ARVC, including 50 (68%) with early ARVC.

TOTAL ARVC POPULATION. In the total ARVC population, RV and RVOT diameters were markers of arrhythmic events (both $p < 0.001$) (Table 2). RV function by RV FAC and RV global longitudinal strain were decreased in subjects with arrhythmic events (both $p < 0.01$) (Table 2) and RV mechanical dispersion was more pronounced ($p = 0.001$). By ROC analyses, RV diameter had a marginally higher C-statistic to detect subjects with arrhythmic events compared with RVOT diameter (0.78 [95% confidence interval (CI): 0.71 to 0.85] vs. 0.70 [95% CI: 0.62 to 0.78];

FIGURE 2 Distribution of Parameters for ARVC Diagnosis From the Task Force Criteria in 89 Overt and 73 Subjects With Early ARVC



In patients with overt ARVC, diagnosis was based on findings from all categories from the Task Force Criteria revised in 2010, with the exception of tissue characterization (missing data). Diagnosis in patients with early ARVC was mainly based on genetic mutations, minor depolarization abnormalities, and minor arrhythmias. Depolarization: Epsilon waves (major) or abnormal signal-averaged ECG (minor). Repolarization: ECG T-wave inversions (V1-V2 [minor], V1-V3 or beyond [major]). ARVC = arrhythmogenic right ventricular cardiomyopathy; other abbreviations as in Figure 1.

p = 0.06). An RV diameter of 41 mm and an RVOT diameter of 34 mm optimally detected subjects with arrhythmic events. RV and LV dimensions were larger and RV function and LVEF were lower in those with arrhythmic events (all p ≤ 0.05) (Table 2), also when adjusted for beta-blocker use, age, sex, and mutation status in multivariable analyses (all p ≤ 0.05).

QRS duration did not differ between ARVC with and without arrhythmic events, whereas T-wave inversions were more prevalent in subjects with arrhythmic events (p < 0.001) (Table 2). All 3 parameters from signal-averaged ECGs were markers of arrhythmic events (all p < 0.001) (Table 2).

PATIENTS WITH OVERT ARVC. In patients with overt ARVC, 69 (78%) had experienced arrhythmic events (17 aborted cardiac arrests, 40 sustained VTs, 11 nonsustained VTs, and 1 cardiac syncope without documented ventricular arrhythmia). Of the remaining 20 (22%) with overt ARVC and no arrhythmic events, 18 (90%) were ARVC-mutation positive. As expected, increased RVOT diameter and decreased RV FAC were markers of arrhythmic events. Interestingly, also the new parameters RV diameter and RV global longitudinal strain were arrhythmic markers, with a similar ability to identify patients with arrhythmic events (C-statistic, 0.75 [95% CI: 0.61 to 0.88] and 0.68 [95% CI: 0.54 to 0.82], respectively; p = 0.36). Parameters from signal-averaged ECGs were abnormal in overt patients with ARVC, but were not markers of arrhythmias (Online Table 1).

SUBJECTS WITH EARLY ARVC. In subjects with early ARVC, 15 (21%) had experienced arrhythmic events (5 sustained VT, 9 nonsustained VT, and 1 cardiac syncope without documented VT). RV diameter was larger in subjects with arrhythmic events (p = 0.05, Table 3) and RV mechanical dispersion was more pronounced (p = 0.003). By ROC analyses, RV mechanical dispersion and RV diameter had similar ability to detect arrhythmic events (C-statistic, 0.74 [95% CI: 0.59 to 0.90] and 0.62 [95% CI: 0.47 to 0.78, respectively; p = 0.20; optimal cutoffs were ≥37 ms and ≥40 mm, respectively). Neither standard parameters of RV function (RV FAC, RV global longitudinal strain) nor parameters of LV function were markers of arrhythmic events in early ARVC (Table 3), whereas all parameters from signal-averaged ECG were arrhythmic markers (all p < 0.05) (Table 3) with comparable discriminative ability (p > 0.59 for all comparisons). Optimal cutoff values were ≥115 ms for filtered QRS, ≥33 ms for high-frequency low-amplitude signal and ≤32 μV for RMS (sensitivity, specificity, and C-statistics, Online Table 2). Interestingly, mechanical dispersion correlated with the electrical parameter filtered QRS duration from signal averaged ECG (R = 0.38, p = 0.009) (Figure 3). There were no significant differences in QRS duration or presence of T-wave inversions (p = 0.27) between subjects with and without arrhythmic events (Table 3). Only 1 subject had S-wave upstroke >55 ms (Table 3).

TABLE 2 Comparison of Subjects With ARVC Without and With Arrhythmic Events in the Total ARVC Population

	No Arrhythmic Events (n = 78)	Arrhythmic Events (n = 84)	p Value
Definite/borderline/possible	20/21/37	69/10/5	
Female	45 (58)	31 (37)	0.008
Echocardiography			
RV diameter, mm	38 ± 6	46 ± 9	<0.001
RV FAC, %	44 ± 9	35 ± 10	<0.001
RV GLS, % (6 segments)	-24.1 ± 3.4	-21.1 ± 5.7	0.001
RV mechanical dispersion, ms (6 segments)	30 ± 16	45 ± 27	0.001
RVOT sax, mm	32 ± 5	38 ± 9	<0.001
LVEDV, ml	110 ± 26	121 ± 45	0.07
LVESV, ml	47 ± 13	58 ± 36	0.02
LVEF, %	58 ± 4	54 ± 9	0.001
LV GLS, % (16 segments)	-20.4 ± 2.4	-19.2 ± 4.1	0.03
LV mechanical dispersion, ms (16 segments)	34 ± 13	48 ± 34	0.002
Electrical parameters			
Filtered QRS, ms	111 ± 9	125 ± 24	<0.001
HFLA, ms	34 ± 9	46 ± 25	<0.001
RMS, μV	36 ± 16	24 ± 18	<0.001
Epsilon waves	4 (5)	19 (23)	0.001
T-wave inversions	15 (19)	55 (65)	<0.001
QRS, ms	93 ± 14	97 ± 18	0.13

Values are n, n (%), or mean ± SD. p by independent Student *t* test or chi-square test.

GLS = global longitudinal strain; HFLA = high-frequency low-amplitude signals; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RMS = root-mean-square voltage of terminal 40 ms; RV diameter = right ventricular basal diameter; RV FAC = right ventricular fractional area change; RV GLS = right ventricular global longitudinal strain; RVOT sax = right ventricular outflow tract diameter from parasternal short-axis view.

EARLY ARVC ARRHYTHMIC RISK ASSESSMENT. To assess arrhythmic risk in subjects with early ARVC, we evaluated the presence of major and minor electrical abnormalities as given by the TFC 2010 (5) (depolarization: epsilon waves in V1 to V3, pathological signal-averaged ECG; repolarization: T-wave inversions). In patients with early ARVC and arrhythmic events, 67% had abnormal electrical parameters (8 [54%] depolarization and 2 [13%] repolarization abnormalities by TFC 2010 [5]) and 67% had abnormal echocardiographic findings by the early parameters (RV diameter ≥40 mm and/or RV mechanical dispersion ≥37 ms). Interestingly, 87% of those with arrhythmias had at least 1 of the electrical or echocardiographic abnormalities. We tested the ability of major and minor electrical abnormalities to detect subjects with arrhythmic events in a logistic regression model (Figure 4). The model's ability to detect

TABLE 3 Comparison of 73 Subjects With Early ARVC Without and With Arrhythmic Events

	No Arrhythmic Events (n = 58)	Arrhythmic Events (n = 15)	p Value
Female	32 (55)	6 (40)	0.29
Echocardiography			
RV diameter, mm	37 ± 5	40 ± 4	0.05
RV FAC, %	45 ± 8	43 ± 6	0.45
RV GLS, % (6 segments)	-24.2 ± 3.3	-23.8 ± 2.9	0.69
RV mechanical dispersion, ms (6 segments)	26 ± 11	39 ± 15	0.003
RVOT sax, mm	32 ± 5	35 ± 5	0.09
LVEDV, ml	112 ± 28	115 ± 31	0.75
LVESV, ml	48 ± 14	50 ± 15	0.69
LVEF, %	58 ± 4	57 ± 4	0.43
LV GLS, % (16 segments)	-20.5 ± 2.4	-20.1 ± 1.7	0.57
LV mechanical dispersion, ms (16 segments)	33 ± 14	39 ± 31	0.28
Electrical parameters			
Filtered QRS, ms	109 ± 7	115 ± 8	0.005
HFLA, ms	32 ± 7	37 ± 5	0.02
RMS, μV	38 ± 14	27 ± 13	0.02
Epsilon waves	0 (0)	2 (13)	0.04
Incomplete RBBB	2 (3)	1 (7)	0.59
QRS, ms	92 ± 13	94 ± 8	0.43
S-wave upstroke, ms	39 ± 7	38 ± 8	0.59
S-wave upstroke >55 ms	1 (2)	0 (0)	1.00
T-wave inversions	3 (5)	2 (13)	0.27

Values are n (%) or mean ± SD. p by independent Student *t* test or chi-square test.
RBBB = right bundle branch block; other abbreviations as in Table 2.

arrhythmic events increased significantly when adding the 2 early echocardiographic markers of arrhythmic events, RV diameter and RV mechanical dispersion, both in early ARVC (chi-square increased from 4.7 to 10.0, p = 0.05 [Figure 4A]; AIC 58 and 57, respectively) and in the entire ARVC population (chi-square increased from 28.1 to 48.1, p < 0.001 [Figure 4B]; AIC 155 and 139, respectively).

FEASIBILITY AND VARIABILITY ANALYSES. LV and RV strain analyses could be performed in 89% and 82% of patients and 88% and 96% of segments could be analyzed, respectively. Intraobserver and interobserver intraclass correlation for LV global longitudinal strain and LV mechanical dispersion, were 0.98 (95% CI: 0.92 to 0.99) and 0.94 (95% CI: 0.77 to 0.99) and 0.95 (95% CI: 0.81 to 0.99) and 0.91 (95% CI: 0.67 to 0.98), respectively, and for RV global longitudinal strain and RV mechanical dispersion, values were 0.98 (95% CI: 0.92 to 0.99) and 0.83 (95% CI: 0.40 to 0.95), respectively, and 0.87 (95% CI: 0.53 to 0.97) and 0.81 (95% CI: 0.35 to 0.95), respectively.

DISCUSSION

Risk stratification of arrhythmias and SCD in subjects with ARVC is difficult and most challenging in the early stages of ARVC. In this study, 21% of ARVC subjects with early disease had experienced arrhythmic events, underlining the importance of identifying early markers of arrhythmias. This study showed that both electrical parameters by signal-averaged ECGs and parameters from echocardiography were markers of arrhythmic events in early ARVC disease. Of importance, the addition of a few echocardiographic parameters to electrical measures improved identification of subjects with a history of arrhythmic events.

RV STRUCTURAL AND FUNCTIONAL CHANGES. In the total ARVC population, RV function was worse and RV dimensions were larger in those with a history of arrhythmic events, reflecting the well-known RV affection in ARVC and its relation to ventricular arrhythmias. Interestingly, RV diameter was a good marker of arrhythmic events, a parameter easily obtained and not included in the current TFC 2010 (5). However, the TFC 2010 is a diagnostic score and was not intended for identifying subjects with arrhythmic events. Our study may imply that RV diameter ≥41 mm might be associated with increased arrhythmic risk. RVOT diameter, which is included in the TFC 2010, was also a marker of arrhythmic events. Interestingly, the optimal RVOT diameter to detect patients with arrhythmic events was 34 mm and therefore even lower than the TFC 2010 diagnostic value (36 mm) (5).

Importantly, echocardiographic parameters were also arrhythmic markers in early ARVC with larger RV diameter and more pronounced RV mechanical dispersion in subjects with a history of arrhythmic events. These findings may indicate that dilation without visible affection of ventricular function may be the first RV changes and may imply a patient's transition to a level of higher risk of ventricular arrhythmia, although the retrospective study design inhibits interpretation of cause and effect. Mechanical dispersion, reflecting inhomogeneous contraction, has previously been shown to be a marker of arrhythmias in ARVC and other cardiac diseases (7,12–15). In ARVC, structural changes, and fibrosis in particular, are likely substrates for the increased mechanical dispersion. RV mechanical dispersion in ARVC detects segments with subtle dyskinesia in early disease and may reflect the start of fibrosis and arrhythmic risk. We have previously shown that asymptomatic ARVC mutation-positive family members also had more pronounced RV mechanical dispersion than healthy controls, indicating a continuum of risk (7). The current study included a large cohort and focused on arrhythmias in early disease

and showed the additive effect of imaging to electrical parameters in detecting high risk individuals.

LV STRUCTURAL AND FUNCTIONAL CHANGES. LV affection in ARVC is now commonly recognized (16). In the total ARVC population, parameters of LV function and timing, including LVEF, were markers of previous arrhythmic events. These findings support that overt ARVC disease commonly include the left ventricle and that LV dysfunction is an important risk factor of cardiac death (17). The relatively small difference in LVEF between those with and without arrhythmic events may be explained by the high proportion of patients with early disease, with no affection of LV parameters. Our results may indicate that onset of LV dysfunction occurred later compared with RV dysfunction in our population. This study cannot answer if the relatively preserved LV function was due to a future RV-predominant ARVC type in our population. Future studies should investigate if LV dysfunction precedes early RV dysfunction in patients who develop LV-predominant ARVC disease. However, in early ARVC, the future predominant ventricle of disease remains unknown and both ventricles should therefore be assessed carefully.

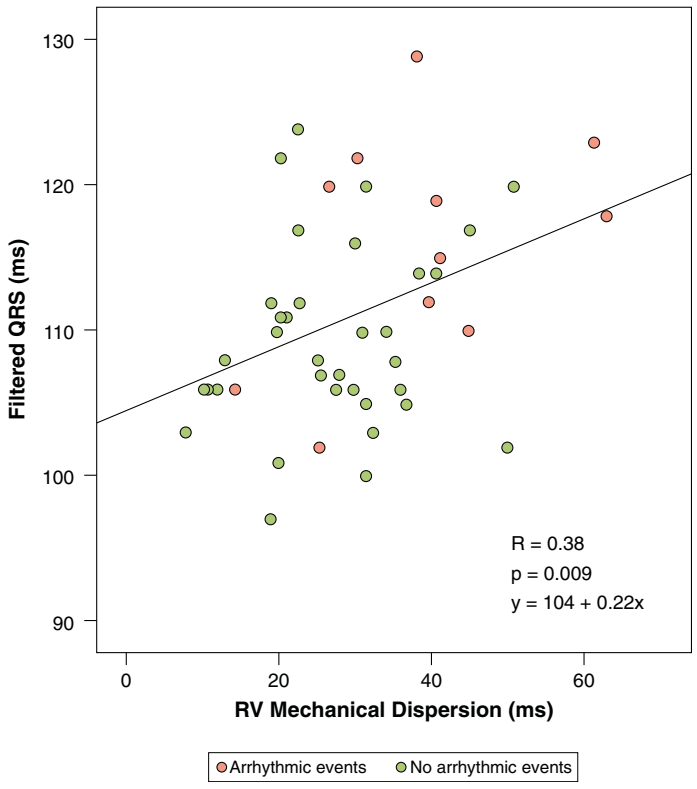
ELECTRICAL PARAMETERS. Pathological signal-averaged ECGs are common in early ARVC (18). Our study supports this finding, with one-third of patients with early ARVC showing pathological signal-averaged ECGs. However, the value of signal-averaged ECG in risk stratification of arrhythmias is less clear. Some studies have reported signal-averaged ECG parameters to be associated with arrhythmic risk and to relate to the extent of myocardial fibrosis (19,20). In our study, these parameters were markers of arrhythmic events in early ARVC, emphasizing the importance of this assessment in early disease. In patients with overt ARVC, signal-averaged ECGs were clearly pathological, but were not markers of arrhythmic events, indicating a threshold value for arrhythmic risk. In the total ARVC population, also the presence of T-wave inversions and epsilon waves were markers of arrhythmic events.

EARLY ARVC ARRHYTHMIC RISK ASSESSMENT. Current risk stratification of SCD and hence ICD indications are based on the presence of previous syncope, VT or aborted cardiac arrest, and RV/LV dysfunction, proband status, accumulated athletic activity, and a definite ARVC diagnosis by TFC 2010 (6,21-24). However, these markers are most useful in overt ARVC. We suggest including both electrical and echocardiographic parameters to assess arrhythmic risk in early ARVC. The addition of RV diameter and RV mechanical dispersion improved the ability to identify patients with arrhythmic events compared with the electrical changes given by the TFC 2010 alone (Figure 4), both in early ARVC and in the total ARVC population. Interestingly, mechanical dispersion was related to electrical parameters, indicating that pronounced mechanical dispersion may reflect early electromechanical interactions important for arrhythmogenicity.

In a recent paper, time from onset of QRS to start of regional shortening in the sub-tricuspid area was a marker of ventricular arrhythmias in asymptomatic ARVC mutation carriers (25), emphasizing the role of echocardiography in risk stratification. Alterations in s′ have also been described in ARVC, including early ARVC (26,27).

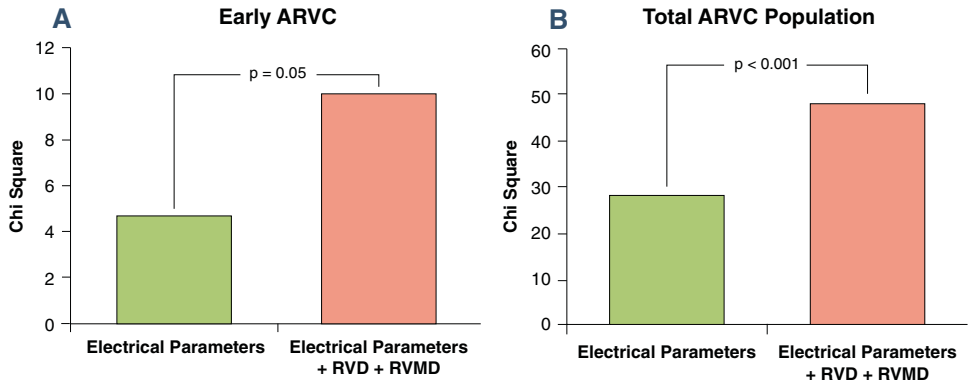
In our population, only 1 subject with early ARVC had an S-wave upstroke >55 ms, which has previously been described as a common and early finding in ARVC (9,25) and a predictor of arrhythmic events (25).

FIGURE 3 Correlation Between Filtered QRS Duration and RV Mechanical Dispersion in Early ARVC



Pink dots: subjects with arrhythmic events; **green dots**: subjects without arrhythmic events. Subjects with arrhythmic events had a longer filtered QRS duration and more pronounced RV mechanical dispersion. RV = right ventricular; other abbreviations as in Figures 1 and 2.

FIGURE 4 Chi-Square Statistics for Models to Identify Subjects With Arrhythmic Events in Early ARVC (n = 73) and the Total ARVC Population (n = 162)



Electrical abnormalities were defined according to the Task Force Criteria revised in 2010 as epsilon waves in V1 to V3, pathological signal-averaged ECG, and T-wave inversions in V1-V2 or beyond. RV diameter and RV mechanical dispersion were included as continuous variables. Chi-Square statistics were used a measure of the ability to detect arrhythmic events and showed that the model for identifying subjects with arrhythmic events was improved both in early ARVC **(A)** (chi-Square increased from 4.7 to 10.0; $p = 0.05$) and in the total ARVC population **(B)** (chi-Square increased from 28.1 to 48.1; $p < 0.001$) when adding measurements of RV diameter and RV mechanical dispersion to the presence of electrical abnormalities alone. RVMD = right ventricular mechanical dispersion; other abbreviations as in Figures 1 and 2.

This discrepancy may be explained by the different definitions of S-wave upstroke (9,25).

CLINICAL IMPLICATIONS. ARVC mutation-positive family members with no apparent or only early disease constitute a substantial proportion of current ARVC populations seen in cardiomyopathy clinics. Risk stratification of SCD in these individuals has not been sufficiently addressed and they are currently followed every 1 to 2 years from age 15 with Holter monitoring, signal-averaged ECG, and echocardiography (28). The retrospective nature of arrhythmic events in relation to the echocardiography did not allow for causal interpretation, but there seemed to be an association between arrhythmias and echocardiographic alterations. We suggest that in subjects with pathological signal-averaged ECG, the presence of RV diameter ≥40 mm and mechanical dispersion ≥37 ms might incline the clinician to more frequent arrhythmia monitoring to detect episodes of arrhythmias and support the evaluation of ICD implantation.

STUDY LIMITATIONS. This study was cross-sectional in design with the inherent limitations. The limited number of patients with early ARVC makes the model for identifying subjects with arrhythmic events vulnerable to overfitting. Our analyses may be confounded by inclusion of mutation-positive family members who will remain ARVC nonpenetrant. Future and larger studies should prospectively follow subjects with early ARVC disease to confirm our results.

All echocardiographic analyses were performed in a blinded fashion; however, the presence of an ICD lead might have demasked arrhythmic status in a few cases.

Cardiac magnetic resonance imaging scans were lacking in 32% of early ARVC subjects, hence the TFC 2010 score may have been underestimated in a few subjects.

CONCLUSIONS

Subjects with ARVC and arrhythmic events had increased RV diameters and decreased RV and LV function by echocardiography. In patients with early ARVC disease, electrical parameters from signal-averaged ECGs and the 2 RV echocardiographic parameters RV diameter and RV mechanical dispersion, were markers of arrhythmic events. The addition of early structural changes increased the ability to detect subjects with arrhythmic events compared with electrical parameters alone. We suggest including measurements of RV diameter and RV mechanical dispersion when evaluating arrhythmic risk in subjects with ARVC.

ACKNOWLEDGMENTS The authors thank all of the study participants.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ARVC is characterized by structural and functional changes. Electrical changes are shown to occur prior to structural changes included in the 2010 TFC. However, this study showed that 2 novel RV parameters by echocardiography, RV mechanical dispersion and RV diameter, were also markers of arrhythmic events in early ARVC. These measures, not included in the 2010 TFC, may be important for risk stratification of arrhythmias in early disease.

TRANSLATIONAL OUTLOOK: Risk stratification of ventricular arrhythmias in ARVC is challenging, particularly in early disease. Genetic family screening has resulted in a substantial proportion of mutation-positive family members in ARVC clinics with no apparent or early ARVC disease in whom risk stratification for ventricular arrhythmias is not fully addressed. In this study, we showed that including novel RV measures by echocardiography was superior to electrical parameters alone in identifying subjects with a history of arrhythmic events, both in the total ARVC population and in patients with early ARVC disease. This might imply that in asymptomatic mutation-positive family members with pathological signal-averaged ECGs, the findings of RV diameter ≥40 mm and mechanical dispersion ≥37 ms should lead the clinician to more frequent arrhythmia monitoring to detect episodes of ventricular arrhythmias.

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KEY WORDS arrhythmic risk, arrhythmogenic right ventricular cardiomyopathy, echocardiography, signal averaged ECG, ventricular arrhythmias

APPENDIX For supplemental tables, please see the online version of this article.