Right-Ventricular Enlargement in Arrhythmogenic Right-Ventricular Cardiomyopathy Is Associated with Decreased QRS Amplitudes and T-Wave Negativity

Robbert Zusterzeel, B.Sc.,* Rachel M.A. ter Bekke, M.D.,*
Paul G.A. Volders, M.D., Ph.D.,* Farah M.M. Leijten, B.Sc.,* Arthur van den
Wijngaard, Ph.D.,† Jan Serroyen, Ph.D.,‡ and Anton P.M. Gorgels, M.D., Ph.D.*

From the *Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands;
†Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands; and
‡Department of Methodology and Statistics, Maastricht University Medical Center, Maastricht, The Netherlands

Background: Arrhythmogenic right-ventricular cardiomyopathy (ARVC) can lead to RV dilatation. We hypothesized that electrocardiographic characteristics including QRS amplitudes in the extremity- and precordial leads, the S amplitude in lead V₁, and extent of T-wave negativity over the precordial leads are related to RV dilatation in this condition.

Methods: In 42 ARVC patients and 42 controls, we correlated total QRS amplitude in the extremity leads ($\sum QRS_{ext}$), precordial leads ($\sum QRS_{prec}$) and in all leads ($\sum QRS_{tot}$: summation of $\sum QRS_{ext}$ and $\sum QRS_{prec}$), S amplitude in lead V₁ and the extent of T-wave inversion in the precordial leads (V₁ vs. beyond V₁) with RV end diastolic diameter (RVEDD) by echocardiography.

Results: In the ARVC group, the mean age was 46 ± 14 years, 31 patients were male, 28 had an implantable cardioverter defibrillator (ICD), and 7 had a LV ejection fraction (EF) < 55%. The control group was age- and gender matched to the ARVC cohort. In contrast to controls, the $\sum QRS_{ext}$ (regression coefficient (RC), -0.29 ; $P = 0.020$), $\sum QRS_{prec}$ (RC, -0.20 ; $P = 0.015$), and $\sum QRS_{tot}$ (RC, -0.14 ; $P = 0.009$) were lower with RV dilatation in ARVC. S amplitude in lead V₁ was not related to RV diameter (RC, -0.98 ; $P = 0.088$). Precordial T-wave inversion beyond lead V₁ (V₂-V₆) was associated with a larger RV diameter (RC, 8.58 ; $P = 0.012$).

Conclusions: Summed QRS amplitudes in the extremity and precordial leads, and T-wave inversion beyond lead V₁ are associated with RV dilatation in patients with ARVC.

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ARVC; ECG; QRS; T-wave negativity; S amplitude

Arrhythmogenic right-ventricular cardiomyopathy (ARVC) is a genetically determined disease characterized by dilatation and dyskinesia of the RV and ultimately fibro-fatty replacement of RV myocardium. The cardinal manifestations are progressive RV malfunction and ventricular arrhythmias potentially leading to sudden cardiac death. Structural changes may also affect the LV.^{1,2} These changes may encompass regional or global wall-motion abnormalities, ultimately resulting in ventricular dilatation.

The presence of negative T waves in the precordial leads have been previously related to increased RV volume in ARVC and is part of the modified Task Force criteria for ARVC.^{1,3–5}

For the present study, we hypothesized that QRS amplitudes in the extremity leads and S amplitudes in lead V₁ are inversely related to RV enlargement in these patients. To this aim, we correlated these 12-lead electrocardiographic (ECG) measurements with echocardiographically

obtained RV dimensions, comparing ARVC patients and control subjects.

MATERIALS AND METHODS

Patient Population

ECGs and echocardiographies of 51 ARVC patients were analyzed in a retrospective cohort. ARVC was diagnosed according to the modified Task Force criteria for ARVC by Marcus et al.¹ This population was compared to a control group who had been evaluated because of unexplained dyspnea, palpitations or atypical chest complaints, showing a normal twelve-lead ECG and echocardiographic examination. The control group was gender- and age-matched to the ARVC cohort. Clinical descriptors included gender, age, LVEF and genetic mutations in desmosomal genes (both pathogenic and unclassified variants).

Echocardiographic Data

All recordings were made at the Maastricht University Medical Center, Maastricht, The Netherlands, between April 1994 and September 2012. Echocardiographic examinations were performed according to standard-operating procedures including measurement of RVEDD, LVEDD, and LVEF. RVEDD and LVEDD were determined using the two dimensional parasternal long axis (PSLAX) view.

ECG Data

The 12-lead ECG in time closest to the echocardiographic examination was selected. The selected ECGs were all available in high-quality pdf format. The ECG was magnified digitally to 1200% using Adobe Acrobat Reader (version 9.4.0, 2011, Adobe Systems Inc., San Jose, CA, USA). Measurements were performed using the on-screen measuring program Cardio Calipers (version 3.3, 2006, Iconico Inc.).

For the purpose of this study patients with right bundle branch block ($n = 9$) were excluded, because the variables of interest are influenced by this conduction defect.⁶ Eventually, 42 patients with ARVC and 42 healthy controls met the inclusion criteria.

For measurement of QRS-complex amplitudes in the extremity and precordial leads and S waves in lead V_1 , three sequential sinus-rhythm-dictated/anterogradely conducted QRS complexes were measured and the mean values were used. Mean sum of the QRS amplitudes in the extremity leads ($\sum QRS_{ext}$), precordial leads ($\sum QRS_{prec}$), and total QRS ($\sum QRS_{tot}$) were calculated. Also, the extent of T-wave inversion over the precordial leads was visually assessed and subsequently divided in lead V_1 versus beyond V_1 .

Terminal activation duration (TAD), determined as the maximum activation delay measured from the nadir of the S wave to the end of the QRS complex in lead V_1 , V_2 or V_3 , was also measured.⁷

In Figure 1, a representative example is given, showing the measurement of the QRS-complex and S amplitudes, respectively. Also, T-wave negativity from V_1 - V_6 can be seen in this ARVC patient with increased RVEDD of 48 mm.

Statistical Analyses

The data were analyzed using SPSS for Windows (version 17.0.0, 2008, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation. For comparing means between groups a Student's *t*-test was used. For the analysis of QRS amplitudes, S amplitudes and TAD in relation to RVEDD and LVEDD separately, multiple linear regression was used. RVEDD and LVEDD were defined as independent variables, sum of QRS amplitudes in the extremity leads, sum of QRS amplitudes in the precordial leads, total QRS and TAD were defined as dependent variables. The presence of T-wave inversion was arbitrarily split into two categories: V_1 versus beyond V_1 (V_2 - V_6). These two categories were included as a dependent variable in a logistic regression analysis. In addition, multivariate analyses including age and gender were conducted. Statistical tests were two-sided and a P value of < 0.05 was considered statistically significant. In addition, regression models for the same comparisons by group were compared using multiple linear regression including an interaction term.

Figure 1. Top left: shows measurement of the QRS-amplitude between the top of the R-wave and the nadir of the S-wave. **Bottom left:** shows measurement of the S-amplitude in lead V₁. The S-amplitude is measured between the nadir of the S-wave and the baseline. The baseline is determined by extending the line between the end of the T wave and the beginning of the P wave of the next sinus rhythm beat. **Right:** Precordial leads recordings of an ARVC patient with 48 mm RV end diastolic diameter. Negative T waves are present in all precordial leads.

Results

Figure 2 shows an example of the longitudinal decline in QRS and S amplitude, as well as the progressive negative T-wave evolution over a 16-year-period in an ARVC patient, diagnosed with a plakophilin-2 (*PKP2*) gene mutation.

Baseline Characteristics

The average age of the 42 patients in the ARVC group in this study was 46 (± 14) years. Thirty-one patients were male (74%) and twenty-eight (67%)

had received an ICD. Seven patients had a LVEF $< 55\%$. The control group was age- and gender-matched to the ARVC group (Table 1).

In the ARVC group, 25 patients had a genetic mutation associated with ARVC, of which *PKP2* was the most common affected gene, consistent with previously published data from the Dutch literature⁸ (Table 1).

The median temporal difference between echocardiography and electrocardiography was 4.5 days (interquartiles 1–30 days) in the ARVC group, and 6.2 days (interquartiles 0–43 days) in the control group.

Figure 2. Longitudinal observation in a patient with ARVC. Panels A–D show 12-lead serial ECGs at first diagnosis and after 10-, 14- and 16-years follow-up, respectively. There is a decrease in QRS-amplitude in the extremity and precordial leads; the S-amplitude in lead V₁ diminishes and there is progression of T-wave negativity in the precordial leads (lead V₁ in A, leads V₁–V₂ in B, leads V₁–V₂ and biphasic T wave in C, and eventually lead V₁–V₃ in D). **Bottom left** shows the relation between the $\sum QRS_{ext}$ and RV diameter over a time period of 16 years. **Bottom right** shows the relation between the $\sum QRS_{prec}$ and RV diameter over a time period of 16 years. Also shown is ventricular conduction delay in D represented by broadening of the QRS-complex. TAD increased from 50 to 85 ms. ARVC = arrhythmogenic right-ventricular cardiomyopathy; TAD = terminal activation duration.

Table 1. Characteristics of the Study Population

	ARVC (n = 42)	Control (n = 42)
General		
Age in years, mean ($\pm$ SD)	46 $\pm$ 14	46 $\pm$ 14
Male	31 (74)	31 (74)
ICD	28 (67)	
LVEF < 55%	7 (17)	
Genetics/Mutations		
PKP2	14 (17)	
DSG2	6 (14)	
SCN5A	2 (5)	
DSC2	1 (2)	
DSP	1 (2)	
JUP	1 (2)	

All numbers are n (%).

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; PKP2 = plakophilin-2; DSG2 = desmoglein-2; SCN5A = sodium channel, voltage-gated, Type 5, alpha subunit; DSC2 = desmocollin-2; DSP = desmoplakin; JUP = junction plakoglobin.

Table 2. ECG/Echocardiographic Characteristics

	ARVC (n = 42)	Control (n = 42)	P value
Echocardiogram			
RVEDD	44 (10)	33 (3)	<0.001
LVEDD	50 (5)	48 (5)	0.201
LVEF	59 (9)	63 (5)	0.072
ECG			
$\sum$ QRS extremity	36 (13)	52 (22)	<0.001
$\sum$ QRS precordial	70 (24)	91 (28)	0.036
QRS amplitude total	106 (34)	143 (47)	<0.001
S-amplitude lead V ₁	6 (3)	8 (4)	<0.001
TAD	72 (15)	52 (6)	<0.001

All numbers are mean ($\pm$ SD) mm (ECG: 1 mV is 10 mm); P values represent differences between ARVC and Control groups using multiple *t*-tests for independent measures.

TAD = ($\pm$ SD) ms; RVEDD = right-ventricular end-diastolic diameter; LVEDD = left-ventricular end-diastolic diameter; LVEF = left-ventricular ejection fraction; TAD = terminal activation duration.

Table 2 shows the ECG and echocardiographic characteristics of both cohorts, including mean QRS and S amplitudes, TAD and mean RV and LV diameters. Compared to the control group, ARVC patients had a significantly larger RVEDD, TAD and smaller $\sum$ QRS_{ext}, $\sum$ QRS_{prec}, QRS total amplitude and S amplitude in lead V₁.

QRS Amplitudes

In the ARVC group, smaller $\sum$ QRS_{ext}, $\sum$ QRS_{prec} and $\sum$ QRS_{tot} correlated significantly with in-

creased RVEDD but not with LVEDD (Table 3). Figure 3 shows the $\sum$ QRS_{ext} and $\sum$ QRS_{prec} in relation to RV diameter in the ARVC and control group. There was a significant difference among ECG parameters between both groups (*P* < 0.001). Multivariate analyses adjusted for age and gender did not change results in the ARVC group illustrated by a *P* value for RVEDD of 0.037, 0.012 and 0.016 for $\sum$ QRS_{ext}, $\sum$ QRS_{prec}, and $\sum$ QRS_{tot}, respectively. In addition, in the control group there was a significant association between LVEDD and $\sum$ QRS_{ext}, $\sum$ QRS_{prec} and $\sum$ QRS_{tot} (Table 3). Adjustments for age and gender in multivariate analyses in controls did not change these results (*P* value for LVEDD of 0.039, 0.046 and 0.040 for $\sum$ QRS_{ext}, $\sum$ QRS_{prec} and $\sum$ QRS_{tot}, respectively).

S Amplitude

S amplitude in lead V₁ was not significantly associated with increased RVEDD (RC, -0.98; CI, -2.11 to 0.15; *P* = 0.088), nor with LVEDD (RC, 0.02; CI, -0.51 to 0.55; *P* = 0.932) in both the ARVC and the control group (Table 3). Multivariate analysis including age and gender had no effect on the association between S amplitude in lead V₁ and RVEDD (*P* = 0.107 in the ARVC group and *P* = 0.433 in controls).

T-Wave Inversion in the Precordial Leads

In the ARVC group, the T wave was negative in leads V₁-V₂ in 1 (2.4%), in leads V₁-V₃ in 5 (11.9%), in leads V₁-V₄ in 6 (14.3%), in leads V₁-V₅ in 5 (11.9%) and in leads V₁-V₆ in 4 (9.5%). In controls, no T wave inversion beyond lead V₁ was present.

Precordial negative T waves beyond lead V₁ (V₂-V₆) were significantly associated with RV enlargement (RC, 8.58; CI, 2.07 to 15.10; *P* = 0.012), but not with LVEDD (RC, -1.51; CI, -5.11 to 2.08; *P* = 0.398). In the control group, there was no association between negative T waves and RVEDD or LVEDD (Table 3). Adjustment for age and gender did not influence the association between T-wave negativity in the precordial leads and RVEDD (*P* = 0.030 for the ARVC group and *P* = 0.636 in controls).

Terminal Activation Duration

In the ARVC group, TAD was generally prolonged when the RV was enlarged, although TAD was not significantly associated with RV diameter or LVEDD in the ARVC group (RC, 0.26; CI, -0.28 to 0.80 ; $P = 0.339$ for RV-diameter and RC 0.60 , CI -0.50 to 1.70 , $P = 0.276$ for LVEDD), and neither in the control group (Table 3) in both univariate and multivariate analysis including age and gender. Multivariate P values for RVEDD were 0.272 in the ARVC group and 0.602 in controls. However, there was a significant difference in TAD between the two groups ($P < 0.001$) (Fig. 3).

Discussion

ECG changes in patients with ARVC that have been previously identified include right QRS prolongation, poor R-wave progression in the precordial leads, decreased QRS amplitudes in the

precordial leads, incomplete right bundle branch block, prolonged TAD, epsilon waves, and ST-segment elevation in leads V_1 - V_3 .⁵

To the best of our knowledge, the current study is the first to evaluate the relationship between QRS amplitudes in the extremity leads, S amplitude in lead V_1 , TAD, and RVEDD and LVEDD in ARVC.

QRS Amplitudes

In ARVC, the summed QRS amplitudes in the extremity leads are diminished in case of RV enlargement, for one unit mm increase in the RVEDD, the sum of the QRS amplitudes decreases with the amount of the RC. Similarly, summed QRS amplitudes in the precordial leads are lower in RV dilatation, consistent with previous observations.⁵ Our combined data indicate that the lower QRS amplitudes are solely based on

Table 3. Statistical Analysis of QRS-Amplitudes, S-Amplitude, T-Wave Inversion and TAD

		RV-Diameter (RVEDD)					LV-diameter (LVEDD)				
		Correlation	RC	95% confidence interval for RC		P value	Correlation	RC	95% confidence interval for RC		P value
ARVC	$\sum$ QRS extremity	-0.350	-0.287	-0.527	-0.047	0.020^a	-0.069	-0.025	-0.139	0.090	0.665
Control	$\sum$ QRS extremity	0.072	0.003	-0.044	0.039	0.883	0.271	0.072	0.003	0.140	0.042^a
ARVC	$\sum$ QRS precordial	-0.370	-0.201	-0.361	-0.041	0.015^a	0.010	0.003	-0.075	0.080	0.948
Control	$\sum$ QRS precordial	0.153	0.015	-0.018	0.048	0.370	0.359	0.059	0.005	0.113	0.034^a
ARVC	QRS total	-0.394	-0.141	-0.245	-0.037	0.009^a	-0.041	0.006	-0.058	0.045	0.800
Control	QRS total	0.106	0.004	-0.015	0.024	0.644	0.349	0.037	0.005	0.069	0.026^a
ARVC	S-amplitude V_1	-0.261	-0.980	-2.114	0.154	0.088	0.014	0.023	-0.506	0.551	0.932
Control	S-amplitude V_1	0.250	0.140	-0.107	0.387	0.258	0.210	0.329	-0.092	0.750	0.122
ARVC	T-wave inversion precordial	-0.438	8.583	2.070	15.096	0.012^a	0.084	-1.51	-5.11	2.08	0.398
Control	T-wave inversion precordial	-0.126	-0.307	-1.359	0.744	0.567	-0.238	-0.533	-1.469	0.403	0.264
ARVC	TAD	0.153	0.258	-0.282	0.799	0.339	0.172	0.601	-0.498	1.700	0.276
Control	TAD	-0.138	-0.079	-0.248	0.090	0.351	-0.134	-0.092	-0.359	0.175	0.489

Describes univariate regression models for ECG parameters (first column) correlated with RVEDD (second column) and LVEDD (third column), respectively, in ARVC and Control groups. Univariate logistic regression analysis was used for correlating T-wave inversion in the precordial leads to RVEDD and LVEDD. RVEDD = right-ventricular end diastolic diameter; LVEDD = left-ventricular end diastolic diameter; RC = regression coefficient; ARVC = arrhythmogenic right-ventricular cardiomyopathy; TAD = terminal activation duration. RC represents the relation between predictor and outcome.

^a $P < 0.05$.

Figure 3. Top: left: shows the relation between $\sum QRS_{ext}$ and RV-diameter in ARVC/control groups, r values were -0.350 and 0.072 for the ARVC group and the Control group, respectively, **right:** shows the relation between $\sum QRS_{prec}$ and RV-diameter in ARVC/control groups, r values were -0.370 and 0.153 for the ARVC group and the Control group, respectively. **Bottom: left:** shows the relation between TAD and RV diameter in ARVC/control groups, r values were 0.153 and -0.138 for the ARVC group and the Control group, respectively, **right:** shows the range and mean of TAD in ARVC/control groups. P values for difference between regression slopes of the ARVC and control groups were all $P < 0.001$, in the bottom right figure; $P < 0.001$ for difference in TAD using t -test for independent measures. When RV diameter increases, the QRS-amplitudes in the extremity and precordial leads diminish in the ARVC group, whereas this is not the case in the control group. ARVC = arrhythmogenic right-ventricular cardiomyopathy; TAD = terminal activation duration.

RV, not LV, dilatation. In the control group, there is no association between RV diameter and QRS amplitudes, at least for the RVEDD values measured (range 22–42 mm). The effect of decreasing QRS amplitudes could be explained by loss of myocardial tissue due to replacement by fibrofatty tissue, RV intramyocardial conduction delay, and/or the fact that the LV rotates out of the frontal plane when the RV enlarges causing a decrease in electrical vector magnitude in the direction of the frontal electrodes. As opposed to the ARVC group, there was no significant association between

RV diameter and ECG parameters in controls due to the normal position of the RV (not enlarged) and thus of frontal plane electrical forces. In addition, there is a normal RV myocardial mass in controls.

Also, a positive correlation between QRS amplitudes and LVEDD was found in the control group indicating an increase in amplitudes when the LV enlarges. One of the reasons could be that this is caused by the possible LV-wall thickening associated with LV dilatation leading to increased frontal electrical forces.

S Amplitude

We hypothesized that the S amplitude in lead V₁ would decrease when the RV diameter increases, due to stronger opposing forces from the RV compared to the LV. Although the present study showed a trend towards decreased S amplitude in lead V₁ with RV enlargement, this was not statistically significant. This may be due to loss of myocardial tissue in the RV leading to less significant opposing forces compared to the LV.

T-Wave Inversion

T-wave inversion in the precordial leads beyond lead V₁ (V₂-V₆) is found in ARVC patients with RV dilatation. The presence of T-wave negativity is a well-recognized major criterium for clinical ARVC phenotyping.¹ Several hypotheses for this have been proposed. According to Fontaine et al.,⁴ T-wave inversion in ARVC can be attributed to RV-conduction defects and/or repolarization abnormalities secondary to prolonged episodes of ventricular tachycardia (VT). Although we did not regularly perform long-term ECG monitoring, in 67% of subjects ICD readouts excluded pacing-induced cardiac memory or sustained VT. Alternatively we, like others,^{3,5} found that T-wave inversion in the precordial leads in ARVC is associated with enlargement of the RV.

Terminal Activation Duration

Previously, it was demonstrated that a prolonged TAD is a strong diagnostic ECG criterion for ARVC.⁶ In this study, TAD increased when RV diameter increased, however this was not significant. There was a significant difference in TAD between the ARVC and the control group implicating significant conduction delay in the RV in patients with ARVC as compared to controls with normal RV diameters.

Limitations

This study has several limitations including the cross-sectional design, lacking serial ECGs, and echocardiographic examinations. Due to the retrospective character of this study we assessed echocardiographic data from 1994 to 2012. These measurements could have been influenced by a difference in the reliability of echocardiography

in 1994 as compared to 2012. As ARVC is a progressive disorder, it would be of interest to prospectively evaluate QRS amplitudes and T-wave inversion characteristics as RV enlargement evolves.

There was a large variation in QRS amplitudes in both the ARVC- and the control group, this study should therefore be seen as a pilot study. A prospective study with a greater sample size should be conducted to assess the clinical value of the included ECG parameters associated with RV enlargement in ARVC patients. Also, due to the small sample size T-wave inversion in the precordial leads was arbitrarily categorized in two groups (V₁ vs. beyond V₁) and no substudies in the genetic subpopulations could be done. Intra- and interobserver variability and measurements on potential confounders were not addressed in this study.

Clinical Implications and Future Research

A 12-lead ECG is a ubiquitous diagnostic tool with great diagnostic power based upon which clinical decisions are made. If diminished QRS amplitudes in the extremity and precordial leads and/or negative T-waves in the precordial leads are found in (suspected) ARVC individuals, attention should be given to potential underlying RV enlargement. Future research should confirm our results in larger cohorts, also to assess the predictive accuracy of the ECG to diagnose ARVC and RV enlargement in this setting. Also, confirmation in a longitudinal study with the inclusion of possible confounders would be desirable. Cardiac magnetic resonance imaging should preferably be used for more accurate assessment of RV geometry.

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