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Precordial T-Wave Inversions in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy Who Present with the Initial Features of Right Ventricular Outflow Tract Arrhythmia

Fa-Po Chung,[1,2] Cheng-I Wu,[1,2] Yenn-Jiang Lin,[1,2] Shih-Lin Chang,[1,2] Li-Wei Lo,[1,2] Yu-Feng Hu,[1,2] Chin-Yu Lin,[1,2] Ting-Yung Chang,[1] Tze-Fan Chao,[1,2] Jo-Nan Liao,[1,2] Ta-Chuan Tuan,[1,2] Ling Kuo,[1,2] Chih-Min Liu,[1,2] Chye-Gen Chin,[3] Ying-Chieh Liao[4] and Shih-Ann Chen[1,2]

Background: Precordial T-wave inversion (TWI) is an important diagnostic criterion for arrhythmogenic right ventricular cardiomyopathy (ARVC).

Objective: This study aimed to characterize the initial repolarization features of definite ARVC in patients who first presented with right ventricular outflow tract ventricular arrhythmia (RVOT-VA) and TWI.

Methods: Patients who presented with RVOT-VA and TWI $\geq V_2$ were retrospectively assessed. The initial characteristics of repolarization between patients with and without a final diagnosis of definite ARVC during follow-up were compared.

Results: TWI $\geq V_2$ was observed in 61 of 553 patients (mean age: 44.1 $\pm$ 14.7 years; 14 men) with RVOT-VAs. After an average follow-up time of 54.9 $\pm$ 33.7 months, 31 (50.8%) patients were classified into the definite ARVC group and 30 (49.2%) into the non-definite ARVC group. The disappearance of precordial TWI $\geq V_2$ was observed in eight (13.1%) patients after the elimination of RVOT-VAs. In a multivariate analysis of the initial electrocardiogram features, only fragmented QRS [odds ratio (OR): 15.45, 95% confidence interval (CI): 1.61-148.26, p = 0.02] and precordial V_2 TpTe interval (OR: 1.03, 95% CI: 1.01-1.06, p = 0.02) could independently predict definite ARVC during longitudinal follow-up. An initial V_2 TpTe cutoff value > 88.5 ms could predict the final diagnosis of definite ARVC, with a sensitivity and specificity of 74.2% and 78.6%, respectively.

Conclusions: Despite the high risk of ARVC in RVOT-VAs and TWI $\geq V_2$, "normalization" of TWI was observed after ventricular arrhythmia elimination in 13.1% of the patients. Fragmented QRS and longer V_2 TpTe interval were associated with definite ARVC during longitudinal follow-up.

Key Words: Arrhythmogenic right ventricular cardiomyopathy • Radiofrequency catheter ablation • Right ventricular outflow tract arrhythmia • Tpeak-Tend interval • T-wave inversion

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[1]Heart Rhythm Center and Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital; [2]Department of Medicine, National Yang-Ming University School of Medicine; [3]Division of Cardiovascular Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei; [4]Changhua Christian Hospital, Changhua, Taiwan.

Corresponding author: Dr. Fa-Po Chung, Heart Rhythm Center and Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan. Tel: 886-2-2875-7156; Fax: 886-2-2873-5656; E-mail: marxtaiji@gmail.com

The first two authors contributed equally to the work.

INTRODUCTION

Differentiating arrhythmogenic right ventricular cardiomyopathy (ARVC) from idiopathic right ventricular outflow tract ventricular arrhythmia (RVOT-VA) is important but it can be challenging, particularly in patients who present with subtle characteristics during the concealed phase of ARVC. The 2010 modified Task Force Criteria are currently used for the diagnosis of ARVC.[1] In

terms of repolarization abnormalities, T-wave inversion (TWI) of the right precordial leads in the absence of complete right bundle branch block (RBBB) is one of the diagnostic criteria for ARVC.[1-3] However, TWI in leads V_1 to V_2/V_3 has been observed in 6% of endurance athletes, and it has also been detected in patients with idiopathic ventricular arrhythmias (VAs),[4,5] which may confound the differential diagnosis. If patients present with frequent idiopathic RVOT-VAs and TWI $\geq V_2$ during sinus rhythm, their condition can be classified as borderline or possible ARVC, which would lead to clinical difficulties in risk stratification and further management.

Electrical disturbances, including repolarization and depolarization abnormalities, are commonly observed in patients with ARVC before the development of remarkable structural changes.[6] Therefore, distinguishing the pattern of precordial TWI between patients with idiopathic RVOT-VA and ARVC is of clinical significance. However, the proportion of patients presenting with the initial characteristics of RVOT-VA and precordial TWI and then finally being diagnosed as ARVC has not been well evaluated. Furthermore, whether radiofrequency catheter ablation (RFCA) would result in changes in precordial TWI remains unclear. Thus, this study aimed to elucidate the repolarization features in patients with the initial characteristics of RVOT-VA who were diagnosed with definite and non-definite ARVC during longitudinal follow-up. The results of this study may provide insight into clinical differential diagnosis, risk stratification, and prevention of erroneous diagnoses in patients with RVOT-VA.

METHODS

Study population

A total of 553 patients who underwent RFCA for RVOT-VA from January 2007 to December 2016 at a single tertiary referral center was retrospectively assessed. Patients with TWI $\geq V_2$ were retrospectively enrolled in this study. Patients with complete RBBB morphology during sinus rhythm were excluded from the study. Baseline characteristics, including structural abnormalities, electrocardiogram (ECG) features, VA presentation, family history and genetic mutations were assessed in detail. The patients were free from antiarrhythmic drugs for at least five half-lives, and then ECG characteristics such as depolarization/repolarization abnormalities and VA features before ablation were assessed using standard 12-lead ECG, signal-averaged ECG (SAECG), and 24-hour Holter monitoring. Prior to RFCA, echocardiography and/or cardiac magnetic resonance imaging (CMR) were performed to assess structural abnormalities of the right ventricle. We excluded patients with a Brugada ECG pattern involving the anterior precordial leads or those diagnosed with Brugada syndrome either spontaneously or after a drug provocation test. The diagnosis of definite/borderline/possible ARVC initially and during longitudinal follow-up was assessed according to the 2010 modified Task Force Criteria.[1]

Electrocardiographic assessments

All patients underwent a standard 12-lead ECG while in the supine position. The ECG paper speed was 25 mm/s.[7] The following parameters/features were measured using 12-lead ECG during the initial presentation.

1. PR interval, QRS duration, RR interval, QT interval, and corrected QT interval (QTc interval, corrected using Bazett's formula).[8,9]
2. Fragmented QRS: The presence of deflections at the beginning of the QRS, on top of the R wave, or in the nadir of the S wave in either ≥ 1 right precordial lead or in > 1 lead in all remaining standard ECG leads.[10]
3. Peripheral low voltage: QRS amplitude $\leq$ 0.5 mV in each peripheral lead.[11]
4. Precordial QRS dispersion: Difference between the longest and shortest QRS durations in all leads.[11]
5. Terminal activation duration: Longest duration from the nadir of the S wave to the end of all depolarizations in V_1-V_3.[12,13]
6. Precordial TpTe interval (TpTe): The interval between the earliest Tpeak and the latest Tend in precordial leads.[13]
7. Precordial TpTe dispersion: Difference between the longest and shortest precordial TpTe interval.[13]
8. T-wave inversion in the inferior leads: T-wave inversion in ≥ 2 of 3 inferior leads.

All ECGs were performed by nationally accredited cardiac technicians. All ECG images were reviewed and measured by two independent cardiologists.

Electrophysiological study, mapping, and radiofrequency catheter ablation

The details of the electrophysiological study (EPS), substrate mapping, and ablation have been described in our previous work.[14-21] Briefly, after obtaining informed consent, all patients underwent a standardized EPS under fasting status. Rapid ventricular pacing and programmed stimulation up to three extra stimuli were performed at the RV apex and/or RVOT to induce VA with and without intravenous isoprenaline (1-5 μg/min). The QRS morphologies and cycle lengths of spontaneous and/or induced VAs were compared to those of clinical VAs. Activation mapping and/or entrainment mapping,[22] if needed, was used to localize the VA origin/circuit, and this information was incorporated to the findings obtained from pacemapping (12/12 matches) if ventricular premature complex (VPC) burden was limited. Endocardial mapping and ablation were initially performed, and the epicardial approach was considered in patients with failed endocardial ablation during the procedure or previous unsuccessful endocardial ablation despite adequate endocardial energy delivery.[19,23] In the current study, all patients underwent successful ablation of RVOT-VAs.

Follow-up and reappraisal of the Task Force Criteria

All of the patients underwent 12-lead ECG examinations, 24-hour Holter monitoring, SAECG, echocardiography, and/or cardiac magnetic resonance imaging during clinical visits after ablation. The patients were followed-up at our cardiology outpatient clinic or at our affiliated institutions every 3-6 months. The "disappearance" of precordial TWI after ablation was defined as the absence of TWI $\geq V_2$ in at least three sets of consecutive 12-lead ECGs during follow-up. The diagnosis of definite/borderline/possible ARVC was reappraised every 3-6 months. Recurrence was defined as the presence of sustained ventricular tachycardia (VT), non-sustained VT $\geq$ 3 beats,[24] or VPC burden > 1000 based on 24-h Holter monitoring during follow-up.[25] The date of recurrence was documented.[25]

The patients were classified into two groups: those with and without fulfilling the diagnosis of definite ARVC based on the latest reappraisal of the diagnosis. The initial depolarization and repolarization features of the 12-lead ECGs were measured and compared between the two groups.

Statistical analysis

Data were expressed as mean ± standard deviation for normally distributed continuous variables and proportions for categorical variables. The continuous variables of the ECG features between the two groups were analyzed using the Mann-Whitney U test. Discrete variables were compared using the chi-square ($\chi 2$) test. Logistic regression analysis was performed to evaluate the predictors of definite ARVC. Variables with a p value < 0.05 in the univariate models were included in the multivariate analysis. The Statistical Package for the Social Sciences software version 22.0 (IBM Corporation, Armonk, NY) was used for all analyses. A p value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 553 patients with RVOT-VA who underwent RFCA was retrospectively assessed, and TWI $\geq V_2$ was observed in 61 (11.0%) patients (mean age: 44.1 ± 14.7 years; 14 men). Regarding the initial characteristics, structural abnormalities were identified in 21 (34.4%) patients, and depolarization abnormalities were observed in 11 (18.0%) patients according to the 2010 revised Task Force Criteria. The clinical characteristics of RVOT-VAs included sustained VT in 21 (34.4%), non-sustained VT/VPC in 11(18.0%), and VPC in 29 (47.5%) patients. Multiform VPCs were observed in 32 (52.5%) patients. The average VPC burden was 26.1 ± 11.1% per 24 h. Of the 61 patients, the initial characteristics in 26 (42.6%), 19 (31.4%), and 16 (26.2%) patients fulfilled the diagnosis of definite, borderline, and possible ARVC, respectively (Figure 1). Of CMR assessments, the ratios of RV end-diastolic volume to body surface area were 76.9 ± 4.4, 80.3 ± 8.3, and 101.7 ± 14.5 ml/m^2 (p < 0.001), and the RV ejection fractions were 48.3 ± 3.5, 46.8 ± 4.9, and 38.9 ± 9.5% (p < 0.001) in the patients initially categorized as possible, borderline, and definite ARVC, respectively. Regional RV akinesia or dyskinesia or dyssynchronous RV contraction was observed in 20 of 26 (95.2%) patients with definite ARVC, one of 19 (4.8%) patients with borderline ARVC, and 0 of 16 (0%) patients with possible ARVC (p < 0.001).

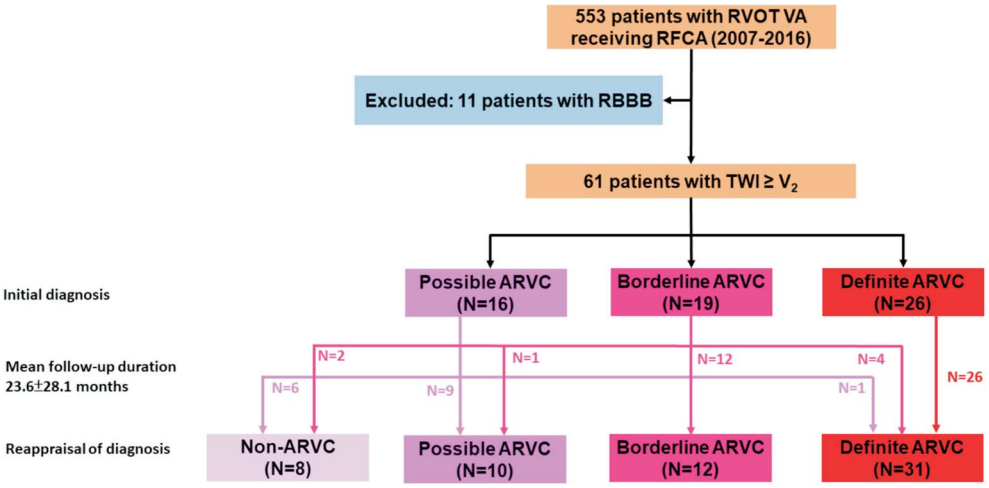

Figure 1. *Flow chart showing the classification of definite/borderline/possible arrhythmogenic right ventricular cardiomyopathy initially and after reappraisal during the longitudinal follow-up in patients who presented with right ventricular outflow tract arrhythmias and T-wave inversion ≥ V_2. See text for details. ARVC, arrhythmogenic right ventricular cardiomyopathy; RBBB, right bundle branch block; RFCA, radiofrequency catheter ablation; RVOT VA, right ventricular outflow tract arrhythmia.*

RFCA of RVOT-VA, follow-up and reappraisal of the Task Force Criteria

During the EPS, sustained VT, non-sustained VT/VPC, and VPC were observed in 33 (54.1%), three (4.9%), and 25 (41.0%) patients, respectively.

After a mean follow-up period of 19.1 ± 18.7 months, 16 (26.2%) patients had VA recurrence, including three (18.8%) who presented with a similar morphology of recurrent RVOT-VA and 13 (81.2%) with different morphologies. In the patients with VA recurrence, the average VPC burden after RFCA was 5.2% ± 7.6% (p = 0.012). All patients with recurrence underwent repeat RFCA with successful ablation.

At a mean follow-up period of 54.9 ± 33.7 months, definite ARVC was confirmed in 31 (50.8%) patients, borderline ARVC in 12 (19.7%) patients, possible ARVC in 10 (16.4%) patients, non-ARVC in eight (13.1%) patients, and non-definite ARVC in 30 (49.2%) patients (Figure 1). The condition of 14 (23.0%) patients was re-classified as either definite/borderline/possible/non-ARVC after reappraisal of the Task Force Criteria. Figure 2 shows the details of 22 (36.1%) patients with changes in the fulfilled criteria. Notably, the disappearance of precordial TWI ≥ V_2 was observed in eight (13.1%) patients after a successful ablation of RVOT-VAs after a mean follow-up period of 15.4 ± 23.9 months. Figure 3 depicts the patients with and without disappearance of precordial TWI ≥ V_2 after the elimination of RVOT-VAs.

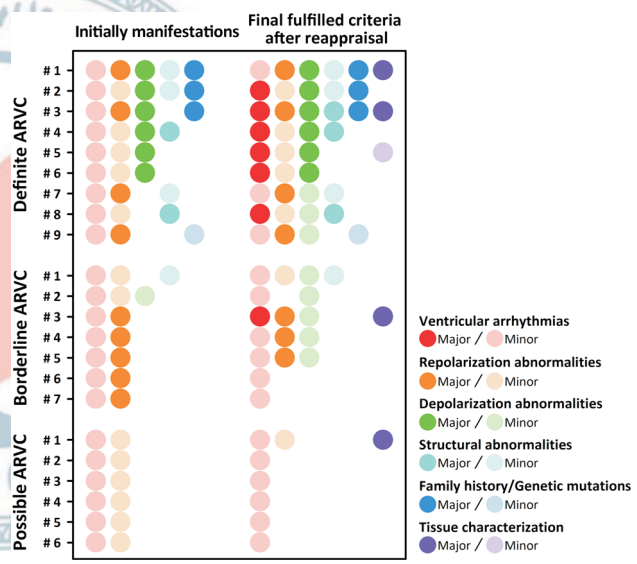

Figure 2. *Major/minor criteria for patients with changes in the fulfilled Task Force Criteria after reappraisal during the longitudinal follow-up. Left column showing the initially fulfilled Task Force Criteria, and the right column depicting the fulfilled Task Force Criteria after reappraisal during the longitudinal follow-up. The classification of definite/borderline/possible arrhythmogenic right ventricular cardiomyopathy was based on the initial characteristics of the patients. See text for details.*

Comparison of the initial baseline characteristics and electrocardiographic features between the patients with and without definite ARVC

Compared to the patients who met the diagnosis of definite ARVC after reappraisal during longitudinal follow-up, there were more women (96.7% vs. 58.1%, p <

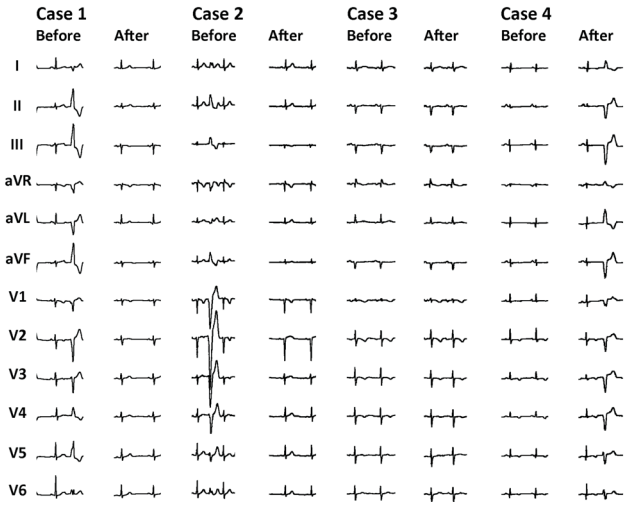

Figure 3. *Representative cases with and without changes in precordial T-wave invasion (TWI) before and after the elimination of right ventricular outflow tract arrhythmia (RVOT-VA). (A and B) Two patients who presented with RVOT-VA and TWI ≥ V_2 were initially diagnosed with possible and borderline ARVC, respectively. The disappearance of TWI ≥ V_2 was observed after the successful elimination of RVOT-VA [case 1: TWI in V_{1-2} before radiofrequency catheter ablation (RFCA) and TWI in V_1 after RFCA; case 2: TWI in V_{1-3} before RFCA and TWI in V_1 after RFCA]. Of note, TWI before and after ventricular premature complex (VPC) involved different precordial leads, thereby emphasizing the importance of VPC on repolarization remodeling. (C and D) Two patients initially presented with sustained RVOT-VA and precordial TWI and were diagnosed with borderline and definite ARVC, respectively (case 3: TWI in V_{1-4} before RFCA and TWI in V_{1-3} after RFCA; case 4: TWI in V_{1-6} before RFCA and TWI in V_{1-6} after RFCA). Persistent TWI ≥ V_2 was observed in both patients who fulfilled the diagnosis of definite ARVC during the longitudinal follow-up. Notably, VPC with left bundle branch block and superior axis was observed during follow-up.*

0.01) and less sustained VT as the initial manifestation (16.7% vs. 51.6%, p < 0.01, Table 1) in the non-definite ARVC group. In addition, the numbers of patients in the non-definite ARVC group with structural abnormalities (0% vs. 67.7%, p < 0.01), depolarization abnormalities (6.7% vs. 29.0%, p < 0.01), and positive family history and/or genetic mutations (0% vs. 25.8 %, p < 0.01) were lower than in the definite ARVC group (Table 1).

Moreover, the initial depolarization features of the patients with definite ARVC had a more fragmented QRS than those of the patients with non-definite ARVC (35.5% vs. 3.3%, p < 0.01). With regards to repolarization, the patients with definite ARVC had a longer initial QTc interval (455.9 ± 43.2 vs. 426.2 ± 43.5 ms, p = 0.01), higher proportion of TWI in the inferior leads (48.4% vs. 23.3%, p = 0.04), and longer precordial TpTe interval in V_2 (98.7 ± 33.8 vs. 74.3 ± 22.4 ms, p < 0.01) than those with non-definite ARVC (Table 2).

Predictors of definite ARVC during follow-up in the patients who presented with the initial characteristics of RVOT-VAs andTWI ≥ V_2

As shown in Table 3, the univariate analysis showed that negative T wave in the inferior leads [odds ratio (OR): 3.08, 95% confidence interval (CI): 1.02-9.26, p = 0.04), fragmented QRS (OR: 15.95, 95% CI: 1.91-133.54, p = 0.01), and V_2 TpTe interval (OR: 1.03, 95% CI: 1.01-1.06, p = 0.01) were associated with definite ARVC during follow-up in the patients who presented with the initial characteristics of RVOT-VAs and TWI ≥ V_2. In the multivariate logistic regression analysis, only fragmented QRS (OR: 15.45, 95% CI: 1.61-148.26, p = 0.02) and precordial V_2 TpTe interval (OR: 1.03, 95% CI: 1.01-1.06, p = 0.02) could independently predict the final diagnosis of definite ARVC after reappraisal of the Task Force Criteria during longitudinal follow-up.

Based on receiver operating characteristic curve analysis of V_2 TpTe interval (Figure 4), the area under the curve was 0.717, and an initial V_2 TpTe cutoff value > 88.56 ms could predict definite ARVC during longitudinal follow-up, with a sensitivity of 74.2% and specificity of 75.9%. The interobserver correlation coefficient in the measurement of V_2 TpTe interval was 0.996 (95% CI: 0.989-0.998), and the interobserver agreement for fragmented QRS yielded an intra-class correlation coefficient of 0.795 (95% CI: 0.680-0.872, p < 0.01). In addition, the kappa statistics for classification agreement was 0.793 (p < 0.01).

DISCUSSION

Main findings

The present study has several important findings. First, TWI ≥ V_2 was observed in 11.0% of the patients who presented with the initial characteristics of RVOT-VA. Among them, 42.6% and 50.8% fulfilled the diagnosis of definite ARVC initially and during longitudinal follow-up, respectively. Second, 31.6% of the patients had changes in the fulfilled Task Force Criteria during follow-up. Of note, the successful ablation of RVOT-VA resulted in the disappearance of precordial TWI ≥ V_2 in 13.1% of the patients. Finally, in terms of the initial ECG

Table 1. Comparison of initial baseline characteristics between two groups

	Non-definite ARVC (N = 30)	Definite ARVC (N = 31)	p value
Variable			
Age	43.6 ± 15.8	44.7 ± 13.9	0.77
Sex (female; %)	29 (96.7)	18 (58.1)	< 0.01
Hypertension (%)	3 (10.0)	7 (22.6)	0.33
Diabetes mellitus (%)	3 (10.0)	1 (3.2)	0.58
Clinical manifestation			
Palpitation (%)	23 (76.7)	22 (71.0)	0.77
Syncope/pre-syncope (%)	6 (20.0)	6 (19.4)	0.99
Sudden cardiac death (%)	1 (3.3)	3 (9.7)	0.63
Clinical characteristics of VA			
Sustained VT (%)	5 (16.7)	16 (51.6)	< 0.01
Non-sustained VT/VPC (%)	5 (16.7)	6 (19.4)	
VPC only (%)	20 (66.7)	9 (29.0)	
Monomorphic (%)	18 (60.0)	11 (35.5)	0.07
Polymorphic (%)	12 (40.0)	20 (64.5)	
VPC burden prior to RFCA (%)	27.9 ± 11.3	20.7 ± 11.4	0.15
Task Force Criteria			
Structural abnormalities (%)			< 0.01
Major	0	5 (16.1)	
Minor	0	16 (51.6)	
Tissue characterization (%)			-
Major	0	0	
Minor	0	0	
Repolarization abnormalities (%)			0.13
Major	13 (43.3)	20 (64.5)	
Minor	17 (56.7)	11 (35.5)	
Depolarization abnormalities (%)			< 0.01
Major	0	9 (29.0)	
Minor	2 (6.7)	0	
Ventricular arrhythmias (%)			0.99
Major	0	1 (3.2)	
Minor	30 (100.0)	30 (96.8)	
Family history/genetic mutations (%)			< 0.01
Major	0	6 (19.4)	
Minor	0	2 (6.5)	
Echocardiography			
LVEF (%)	58.0 ± 7.5	56.5 ± 9.8	0.51
RV FAC (%)	42.8 ± 9.7	30.6 ± 10.1	< 0.01
Use of anti-arrhythmic drug before RFCA			
Beta-blocker (%)	4 (13.3)	6 (19.4)	0.77
Class I (%)	7 (23.3)	8 (25.8)	0.99
Others (%)	2 (6.7)	1 (3.3)	0.98

ARVC, arrhythmogenic right ventricular cardiomyopathy; LVEF, left ventricular ejection fraction; RFCA, radiofrequency catheter ablation; RV FAC, right ventricular fractional area change; VA, ventricular arrhythmia; VPC, ventricular premature complex; VT, ventricular tachycardia.

features, we found that fragmented QRS and V_2 TpTe interval were surrogate markers for predicting definite ARVC during the longitudinal follow-up.

T-wave inversion ≥ V_2 in patients with RVOT-VA

The diagnosis of ARVC during the early phase can be challenging, particularly in patients with concealed char-

Table 2. Comparison of initial 12-lead ECG features between two groups

	Non-definite ARVC (N = 30)	Definite ARVC (N = 31)	p value
PR interval (ms)	171.2 ± 31.5	169.5 ± 25.3	0.81
QRS duration in V_2 (ms)	97.4 ± 15.3	100.6 ± 23.6	0.55
RR interval (ms)	846.5 ± 34.1	902.4 ± 38.0	0.28
QTc interval (ms)			
V_1	459.2 ± 65.6	467.9 ± 43.1	0.55
V_2	469.5 ± 73.0	477.2 ± 53.7	0.65
V_3	471.0 ± 68.8	468.2 ± 55.9	0.67
V_4	473.8 ± 70.1	488.6 ± 61.4	0.40
V_5	466.9 ± 64.4	478.0 ± 55.3	0.49
V_6	464.4 ± 63.3	478.3 ± 49.2	0.36
T-wave inversion			0.10
V_1 to V_2 (%)	17 (56.7)	11 (35.5)	
V_1 to V_3 (%)	7 (23.3)	8 (25.8)	
V_1 to V_4 (%)	2 (6.7)	3 (9.7)	
V_1 to V_5 (%)	0	6 (19.4)	
V_1 to V_6 (%)	4 (13.3)	3 (9.7)	
Negative T wave in inferior leads (%)	7 (23.3)	15 (48.4)	0.04
Fragmented QRS (%)	1 (3.3)	11 (35.5)	< 0.01
Peripheral low voltage (%)	0	1 (3.2)	0.32
Precordial QRS dispersion (ms)	27.0 ± 13.4	31.5 ± 15.7	0.23
Terminal activation duration (ms)	37.1 ± 8.2	41.2 ± 13.9	0.38
Precordial TpTe interval			
V_1 (ms)	80.1 ± 21.5	88.8 ± 25.1	0.15
V_2 (ms)	74.3 ± 22.4	98.7 ± 33.8	< 0.01
V_3 (ms)	89.6 ± 40.4	88.2 ± 31.9	0.89
V_4 (ms)	86.8 ± 39.9	101.7 ± 42.7	0.16
V_5 (ms)	89.1 ± 31.5	92.4 ± 42.8	0.74
V_6 (ms)	86.9 ± 31.5	93.5 ± 30.9	0.41
Precordial TpTe dispersion	63.6 ± 30.3	58.9 ± 35.5	0.58

ARVC, arrhythmogenic right ventricular cardiomyopathy; QTc, corrected QT; TpTe, T wave peak-to-end.

acteristics. A previous study demonstrated that the onset of electrical abnormalities commonly precedes the presence of structural remodeling.[24] Therefore, the recognition of depolarization and repolarization abnormalities, as well as co-existing VAs, can provide information that can be used in risk stratification, clinical follow-up, and recommendations.[20,26] Of note, the European consensus recommended that patients with anterior TWI in ≥ 2 contiguous leads, particularly in young athletes, must be further assessed.[27] However, precordial TWI, particularly in those with TWI in $V_{1\text{-}2}$, has been reported to be a normal variant in 2.3% of asymptomatic individuals.[4]

To date, studies about the prevalence of "benign" TWI in patients with idiopathic RVOT-VA are limited. Cases with idiopathic RVOT-VA with concomitant TWI ≥ V_2 are classified as borderline or possible ARVC.[1] In the present study, only 14.3% of the patients who initially had borderline or possible ARVC fulfilled the diagnosis of definite ARVC during the longitudinal follow-up. Furthermore, the disappearance of TWI ≥ V_2 after a successful ablation was observed in 13.1% of the patients, thereby indicating the importance of reassessing the Task Force Criteria in patients presenting with the initial characteristics of RVOT-VA and TWI ≥ V_2.

Distinguishing ARVC from idiopathic RVOT-VA in patients with TWI ≥ V_2: potential surrogate markers

The characteristics of several diseases including idiopathic RVOT-VA, myocarditis, sarcoidosis, amyloidosis, and endomyocardial fibrosis, can be similar to those of ARVC.[17] Thus, these diseases must be differentiated, and

Table 3. Logistic regression analysis for the initial electrocardiographic predictors of definite ARVC during longitudinal follow-up

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
PR interval (ms)	0.99	0.98-1.02	0.80			
QRS duration (ms)	1.03	0.98-1.08	0.23			
RR interval (ms)	1.01	0.99-1.01	0.28			
QTc interval (ms)	1.02	1.00-1.03	0.02			
V_1	1.00	0.99-1.01	0.55			
V_2	1.00	0.99-1.01	0.65			
V_3	0.99	0.99-1.01	0.86			
V_4	1.00	0.99-1.01	0.39			
V_5	1.00	0.99-1.01	0.48			
V_6	1.00	0.99-1.01	0.35			
Precordial leads with TWI*	1.32	0.90-1.93	0.15			
Negative T wave in inferior leads	3.08	1.02-9.26	0.04	3.10	0.81-11.96	0.10
Fragmented QRS	15.95	1.91-133.54	0.01	15.45	1.61-148.26	0.02
Precordial QRS dispersion	1.02	0.99-1.06	0.23			
Terminal activation duration	1.03	0.96-1.11	0.38			
Precordial TpTe interval						
V_1	1.02	0.99-1.04	0.15			
V_2	1.03	1.01-1.06	0.01	1.03	1.01-1.06	0.02
V_3	0.99	0.99-1.01	0.88			
V_4	1.01	0.99-1.02	0.16			
V_5	1.00	0.99-1.02	0.73			
V_6	1.01	0.99-1.02	0.41			
Precordial TpTe dispersion	1.02	0.99-1.06	0.23			

ARVC, arrhythmogenic right ventricular cardiomyopathy; CI, confidence interval; OR, odd ratio; QTc, corrected QT; TpTe, T wave peak-to-end.
* Numbers of precordial leads with TWI.

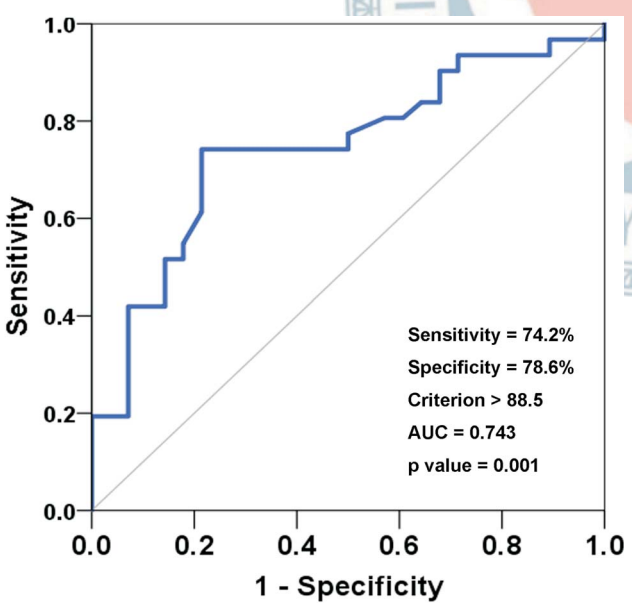

Figure 4. *Receiver operating characteristic curve of the V_2 TpTe interval to differentiate definite and non-definite arrhythmogenic right ventricular cardiomyopathy. A V_2 TpTe interval cutoff value > 88.56 ms could predict the final diagnosis of definite arrhythmogenic right ventricular cardiomyopathy (ARVC) during the longitudinal follow-up, with a sensitivity of 74.2% and specificity of 75.9%.*

the use of variables such as QRS duration in precordial leads and terminal activation duration of QRS ≥ 55 ms have been considered in distinguishing ARVC from idiopathic RVOT-VA.[28,29] In this study, initial fragmented QRS and V_2 TpTe interval > 88.56 ms were associated with the final diagnosis of definite ARVC during the longitudinal follow-up. These findings are in accordance with previous findings showing that the presence of electrical abnormalities can be observed in early-phase ARVC.[30,31] Fragmented QRS and prolonged TpTe in ARVC have been considered to be consequences of diseased substrates.[28,32,33] A previous study also demonstrated that fragmented QRS could be used to stratify risk in ARVC. Notably, the present study focused on patients who presented with RVOT-VA and precordial TWI. Therefore, the diseased substrate underlying RVOT in ARVC is responsible for ventricular arrhythmogenesis, and this could have contributed to the findings of the current study. Moreover, only V_2 TpTe interval could predict the final diagnosis of ARVC during the longitudinal follow-up, indicating that this surrogate marker may represent the

localized repolarization pattern of diseased substrate in RVOT. Moreover, Golcuk et al.[32] reported a similar finding that TpTe value could help to distinguish ARVC from RVOT-VA. In their report, the precordial lead selected for discrimination was V_1, and the cut-off value was 97 ms. This result is different from the current study, which may be due to difference in study populations in these studies. Future large-scale studies are needed to validate the abovementioned findings.

Precordial T-wave inversion and the potential repolarization effect of RVOT-VA

To the best of our knowledge, this study is the first to explore the occurrence of precordial TWI with concomitant RVOT-VA. Precordial TWI can be a normal variant, particularly in women and athletes, and it is usually confined to V_1-V_2, whereas TWI > V_2 has only been reported in 1% of women and 0.2% of men.[4] Importantly, in the study of Malhotra et al.,[4] none of the patients developed or were diagnosed with cardiomyopathies during follow-up, thereby emphasizing that TWI in V_1-V_2 can be a nonspecific feature, particularly in low-risk patients without the presence of other electrical features. However, if RVOT-VA with concomitant TWI $\geq V_2$ is observed, early-phase ARVC should be ruled out. The disappearance of TWI $\geq V_2$ was observed in 13.1% of patients in this study, indicating that TWI was not a variant in these patients. This can be attributed to cardiac memory caused by an adaptive reaction response to frequent VPC and different ventricular activation sequences, which can be found in the presence of accessory pathway or ventricular pacing.[34] Therefore, in spite of the initial categorization as borderline or possible ARVC owing to frequent RVOT-VAs and precordial TWI $\geq V_2$, the long-term prognosis was good and none of the patients were diagnosed with ARVC, emphasizing the importance of sequential follow-up of repolarization abnormalities, particularly for those receiving successful RVOT-VA ablation. However, a mechanistic investigation is warranted to validate these findings.

Limitations

The present study has several limitations. First, the study population was relatively small. Thus, a large-scale study, particularly in a prospective cohort, will be required for internal/external validation of the current findings. Second, depolarization and repolarization patterns were assessed in patients who had not taken antiarrhythmic drugs for at least five half-lives, and none of the patients received amiodarone. However, amiodarone was used in some patients after the confirmation of definite ARVC. Moreover, we did not compare the initial and follow-up repolarization patterns. Thus, further studies are needed to investigate the dynamic changes in repolarization patterns in these patients. Third, 52 of 61 patients received an initial myocardial biopsy due to concerns of early or concealed ARVC in the patients with RVOT-VAs and TWI $\geq V_2$. However, owing to the segmental involvement of fibrofatty infiltration, the histopathologic findings may have varied between initial and repeat myocardial biopsies. Furthermore, 61 patients did not undergo a systemic survey during longitudinal follow-up. However, all patients underwent at least electrocardiographic and echocardiographic examinations after ablation, which would have made the mis-diagnosis of definite ARVC as non-definite ARVC less likely. Finally, although RVOT-VA was eliminated, some patients were still classified as having borderline or possible ARVC after reappraisal of the fulfilled Task Force Criteria during the longitudinal follow-up. Whether a longer follow-up period is required to clarify the final clinical characteristics and the associated outcomes is unknown.

CONCLUSION

Approximately half of the patients who presented with the initial characteristics of RVOT-VA and TWI $\geq V_2$ fulfilled the diagnosis of definite ARVC during follow-up. Moreover, fragmented QRS and longer V_2 TpTe interval were considered to be surrogate markers in predicting definite ARVC. The successful elimination of RVOT-VA "normalized" the precordial TWI $\geq V_2$ in 13.1% of the patients, indicating the benign process of VA-related repolarization remodeling.

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CONFLICT OF INTERESTS

All the authors declare no conflict of interest.

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