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Original Article

Reassessment for the Late Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy in Patients With Ablated Premature Ventricular Contractions or Ventricular Tachycardia in the Right Ventricle

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ABSTRACT

Background: Premature ventricular contractions (PVCs) from a right ventricular outflow origin are the first clinical presentation of an underlying arrhythmogenic right ventricular cardiomyopathy (ARVC). The association between PVCs from the other parts of the right ventricle (RV) and an underlying ARVC is unclear. This study focused on the ARVC risk in patients with PVCs originating from the RV.

Methods: This cross-sectional study enrolled 69 patients undergoing PVC ablation to remove the arrhythmogenic cores of the RV. Data regarding ventricular arrhythmias, symptoms, and antiarrhythmic drug consumption were gathered. The subjects were recalled for follow-up evaluations using electrocardiography and echocardiography to diagnose cases affected by ARVC. The data were analyzed using SPSS, version 20.

Results: Among the participants, 5.8% of the cases were diagnosed with suspected ARVC. The origins of the arrhythmogenic foci were as follows: the right papillary muscles in 11 patients, the moderator bands in 2, the right ventricular outflow tract (RVOT) free wall in 23, the RV low septal wall in 2, and the tricuspid annulus in 31. RVOT dimensions exhibited a meaningful increase over time (P =0.01). The severity of tricuspid regurgitation also increased meaningfully over time (P =0.04).

Conclusions: Many patients undergoing ablation therapy on the RV for the treatment of arrhythmogenic foci are at an increased risk of ARVC, and they could exhibit PVCs originating from the other parts of the RV, necessitating robust observation. Increased RVOT dimensions and worsening tricuspid regurgitation should be an alarming sign in these cases. ***(Iranian Heart Journal 2021; 22(3): 44-52)***

KEYWORDS: Arrhythmogenic right ventricular cardiomyopathy, Premature ventricular contraction, Ventricular tachycardia, Right ventricle

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Arrhythmogenic ventricular dysplasia, also known as arrhythmogenic right ventricular cardiomyopathy (ARVC), is a condition that targets the cardiac muscles. The right ventricle (RV) is principally affected by this condition, compared with the other cardiac chambers. [1] The characteristic changes in ARVC include the loss of the myocardium (mostly) in the RV and subsequent replacement with fibro-fatty tissue. By delaying intraventricular signal conduction, this fibro-fatty tissue promotes the occurrence of arrhythmias. [1]

Overt ARVC usually affects individuals between the second and fourth decades of life. However, the onset of the disease precedes the overt phase. During this preclinical phase, none to minimal insult is induced upon the cardiac muscle. [2] Signs heralding the occurrence of ARVC include, but are not limited to, palpitations or exertional syncope associated with T-wave inversions throughout the precordial leads V_1 to V_4, ventricular arrhythmias exhibiting a left bundle branch block (LBBB) pattern, and irregularities in the RV in obtained cardiac images. [3, 4] Further, unusual depolarization represents abnormal signal conduction throughout the affected myocardium of the RV. [3, 4] The clinical progression of ARVC spans 4 patterns: 1) concealed, 2) overt electrical disorders, 3) RV failure, and 4) biventricular pump failure. [5]

Although the ectopic rhythm of the ventricles occurs more frequently with increasing age, in people younger than 50 years of age, a count of greater than 200 premature ventricular beats in 24 hours is indicative of underlying cardiomyopathies. [6] Ventricular arrhythmias that usually have LBBB configuration (originating from the right ventricular outflow tract [RVOT]) can be the early sign of ARVC in a number of cases. [7, 8] Therefore, the primary presentation of ARVC in an affected individual may be a premature ventricular contraction (PVC) originating from the RVOT. [7] The sign of RVOT-PVC is the presence of LBBB, which causes abnormal conduction in the V_1 lead, as well as late precordial transition and inferior axis deviation. [7] Progression to ventricular failure is observed amongst a percentage of those with seemingly healthy hearts with numerous PVCs. [9] Individuals affected by ARVC may have normal electrocardiograms (ECGs) in the concealed stage. Nonetheless, they may also exhibit palpitations and episode(s) of syncope as well as showing signs of PVC on their ECGs[9]. According to the Task Force Criteria, commonly occurring PVCs of the RVOT origin are considered a minor criterion in the diagnosis of ARVC. [9] As ARVC progresses into the overt phase, arrhythmias become more apparent and symptomatic. [5] Additionally, conventional imaging techniques are able to pick up on the structural abnormalities of the RV. Further along the course of the disease, biventricular heart failure may be expected, regardless of the absence or presence of arrhythmias. [2, 5] Such arrhythmias may have different presentations, from commonly occurring PVCs to ventricular tachycardia (VT), with the latter being more likely to convert into ventricular fibrillation. [2, 5]

According to the presented arguments, it has been established that PVCs from the RVOT region may be the first clinical presentation of an underlying ARVC. Nevertheless, the association between PVCs originating from the other parts of the RV and an underlying ARVC is unclear. In this study, we will focus on the risks of ARVC in patients with PVCs originating from the RV (other than the septal part of the RVOT).

METHODS

This cross-sectional study, conducted between April 2010 and March 2017,

enrolled all patients who had undergone PVC ablation therapy for the removal of arrhythmogenic cores in their RV, especially in the vicinity of the tricuspid annulus, the right papillary muscles, the moderator bands, and the RV free wall. We carried out an extensive clinical examination of all the participants at the time of enrollment to obtain an inclusive medical history and to gather information regarding symptom evaluation, antiarrhythmic drug consumption, and the presence of ventricular arrhythmias. In this study, we defined ventricular arrhythmias as syncope(s) of an assumed arrhythmic origin, coupled with documented non-sustained/sustained VT and aborted cardiac arrests. In addition, ECG and echocardiography were performed. Since ARVC is a progressive cardiomyopathy, we called all patients with a history of PVC or VT ablation for repeated echocardiography to evaluate the progression of their echocardiography findings. We decided not to perform cardiac magnetic resonance imaging (CMR) in all the participants because of financial reasons. In the case of any alterations in our plan, we planned to perform CMR. The study was approved by the Medical Research Ethics Committee of Iran University of Medical Sciences.

Follow up

All the subjects were recalled to the center for their follow-up evaluations up until June 2018. Our main goal during this evaluation was to diagnose cases affected by ARVC. In order to establish a diagnosis of ARVC, a multitude of diagnostic modalities are required. However, our study relied on ECG and echocardiographic evaluations.

ECG

To perform ECG, we used the DAVINSA COPMP 10 Electrocardiogram. The Task Force project regards an array of abnormalities in ECGs as minor and major criteria for the diagnosis of ARVC. [9] In accordance with these criteria, we aimed to track as many changes as possible in the obtained ECGs as part of our 2-step evaluation process. Anomalous finds that were closely monitored during our evaluations included T-wave inversions in the precordial leads, QRS morphology in the inferior and precordial leads, the presence of Epsilon waves, right bundle branch block (RBBB), transition zone manifestation, and the presence of arrhythmias such as PVCs and VT.

Echocardiography

All the patients underwent echocardiographic evaluation (GE, Vivid 3 Echocardiogram). In order to achieve reliability, the results were interpreted by a single clinician, blinded to every other clinical characteristic of the subjects. The Task Force guideline also suggests a series of echocardiographic aberrations as major and minor criteria in the diagnosis of ARVC. [9] Of such abnormalities, tricuspid regurgitation (TR); regional RV akinesia, dyskinesia, or aneurysm; and synchronous RV contractions were monitored closely in our evaluation process. Additionally, the ejection fractions of the left and right ventricles (LVEF and RVEF, respectively) were measured.

Statistical analyses

Quantitative variables were reported as the mean ± the standard deviation (SD) and qualitative data as frequencies and percentages. The Student *t* test and one-way ANOVA were employed in the comparison of quantitative variables, whilst the χ^2 (McNemar) test and the Fisher exact test (if needed) were used for that of qualitative data. Also in nonparametric conditions, we

used Wilcoxon and Friedman tests for continuous variables. Two-tailed *P*-values less than 0.05 were considered statistically significant. The statistical analyses were performed using SPSS, version 20, (IBM Co, Armonk, NY).

RESULTS

The study population comprised 69 patients (42.8 ± 13.96 years old, 47 females vs 22 males). Assessments performed prior to treatment initiation revealed that 2.9% of them had a history of syncope and 98.6% had previously experienced palpitations. All the subjects reported a negative family history of sudden cardiac death. Amongst them, 15 subjects had a history of an underlying disease, 2 (2.9%) had noncompaction LV, 6 (8.7%) had dilated cardiomyopathy, and 3 had ischemic cardiomyopathy. In addition, 4 patients (5.8%) were diagnosed with suspected ARVC due to the presence of 1 major criterion based on the Task Force guideline. Two of the subjects affected by a suspected ARVC had a report of VT in their medical records. Regretfully, these patients expired before the completion of the follow-up phase. Sudden cardiac death in 1 of these individuals and arrhythmia in the other were determined as the cause of death. In summary, 12 patients had implantable cardio inverter-defibrillators (ICDs): 4 of them had ICDs prior to ablation and an additional 8 subjects required the implantation of ICDs after ablation therapy.

The origins of arrhythmogenic foci in the study population, as well as their respective prevalence rates, are as follows: the right papillary muscles in 11 patients, the moderator bands in 2 patients, the RVOT free wall in 23 patients, the RV low septal wall in 2 patients, and the tricuspid annulus in 31 patients. In the latter group, the arrhythmogenic foci had formed in the anterior region of the annulus in 5 patients, the posterior region in 6 patients, the lateral section in 5 patients, the posterolateral region in 10 patients, and the anterolateral region in 4 patients. These data are presented in Table 1.

On average, the subjects were followed up for 44.57 (±23.6) months. As was mentioned before, 2 patients failed to complete the follow-up process due to their demise.

The ECGs obtained at baseline as well as the second visit as part of the follow-up protocol were evaluated for QRS-wave morphology during PVCs, in V_1, and the inferior leads of II, III, AVF. The data corresponding to this assessment are presented in Table 2. In addition, the cardiac axis during a sinus rhythm was determined. This axis was normal in 85.5%, left-superior in 13%, and right superior in 1.3% of the subjects, at baseline.

Prior to performing ablation therapy and at follow-up, transitional zones during PVCs were observed in the V_5, V_4, V_3, V_2 V_6, and V1 leads, which are demonstrated in Table 3. Following therapy, 86.6% of the subjects maintained a sinus rhythm. Amongst the 13.4% of the subjects with persistent PVCs, one-third exhibited transitional zones in lead V_5. RBBB was noted in the ECG assessment of 5.8% at baseline. This prevalence increased to 7.2% at the time of the second follow-up (Table 3).

The assessment of repolarization irregularities in ECGs revealed that T-inversion was present in 62.3% of the patients at baseline. This aberration, which was observed in the different leads, is shown in Table 4. The assessment for signs of depolarization abnormalities such as the epsilon wave and partial blocks was also performed. None of the subjects exhibited any abnormality in their ECGs, at baseline. However, 2 patients exhibited epsilon waves and another 2 exhibited partial blocks. The nadir of S to the isoelectric line decreased from 46.5 ± 12.8 ms at baseline to 44.7 ±

10.6 ms during the follow-up period; the differences, however, were not statistically significant (*P* =0.199).

The mean LVEF, as assessed by echocardiography, had no significant differences between the baseline and the follow-up time (*P* =0.07) (Table 5). RVOT dimensions were 27.07 mm (±12.6) and 28.3 mm (±4.7) at baseline and at the time of follow-up, respectively, exhibiting a meaningful increase throughout time (*P* =0.01). In addition, the alterations of RVEF over time were not statistically significant (*P* =0.10) (Table 5). The echocardiographic assessment of TR revealed that the severity of regurgitation increased meaningfully as time progressed (*P* =0.04) (Table 5).

The kinetic assessment of the RV revealed that none of the patients suffered from RV akinesia at baseline. However, 2 patients developed RV akinesia throughout the course of the study. Although RV akinesia was reported in 2 subjects, re-evaluation ruled out 1 instance and established the condition in the other. Additionally, evidence of RV aneurysms was found in none of the patients, neither at baseline nor at the time of follow-up.

Table 1. Baseline characteristics of the study patients

Baseline Characteristics	Mean±SD / N (%)
Age at PVC ablation time	42.8(±13.96)
Sex (n)	
male(n)	47(68.1%)
female(n)	22(31.9%)
Syncope (n)	2(2.9%)
Palpitation (n)	1(1.4%)
Ventricular tachycardia (n)	11(15.9%)
Family history of SCD (n)	None
Arrhythmogenic Origin of PVCs (n)	
Moderator band	2(2.9%)
RVOT free wall	23(33.2%)
RV inferoseptal wall	2(2.9%)
Tricuspid annulus	32(46.4%)
Right papillary muscle	11(15.9%)
Underlying Diseases (n)	
noncompaction LV	2(2.9%)
DCM	6(8.7%)
ICMP	3(4.3%)
Questionable ARVC	4(5.7%)
ICD (n)	
Yes	12(17.4%)

PVC, Premature ventricular contraction; SCD, Sudden cardiac death; DCM, Dilated cardiomyopathy; ICMP, Ischemic cardiomyopathy; ARVC, Arrhythmogenic right ventricular cardiomyopathy; ICD, Implantable cardioverter-defibrillator

Table 2. QRS morphologies among inferior ECG and V_1 leads before PVC ablation and at the time of follow-up

QRS Morphologies	Before Ablation	Follow-up
QRS morphologies in lead II		
R	45(65.2%)	7(10.1%)
RS	7(10.1%)	-
QS	7(10.1%)	1(1.4%)
rS	9(13.0%)	-
rs	1(1.4%)	-
QRS morphologies in lead III		
R	34(49.3%)	7(10.1%)
RS	2(2.9%)	-
QS	28(40.6%)	1(1.4%)
rS	5(7.2%)	-
QRS morphologies in lead AVF		
R	36(52.2%)	7(10.1%)
RS	7(10.1%)	-
QS	24(34.8%)	1(1.4%)
rS	2(2.9%)	-
QRS morphologies in lead V_1		
RS	1(1.4%)	3(4.3%)
QS	55(79.9%)	4(5.8%)
rS	13(18.8%)	1(1.4%)
QRS axis (in the sinus rhythm)		
Normal	59(85.5%)	61(88.4%)
Left superior	9(13.0%)	5(7.2%)
Right	1(1.4%)	1(1.4%)

ECG, Electrocardiography; PVC, Premature ventricular contraction

Table 3. Transition zone in PVCs and RBBB before PVC ablation and at the time of follow-up

	Before Ablation	Follow-up
Transition Zone (in PVCs)		
V_1	1(1.4%)	1(1.4%)
V_2	2(2.9%)	2(2.9%)
V_3	8(11.6%)	1(1.4%)
V_4	24(34.8%)	2(2.9%)
V_5	32(46.4%)	3(4.3%)
V_6	2(2.9%)	-
RBBB		
No	65(94.2%)	62(89.9%)
Yes	4(5.8%)	5(7.2)

PVC, Premature ventricular contraction; RBBB, Right bundle branch block

Table 4. Repolarization and depolarization ECG abnormalities before PVC ablation and at the time of follow-up (* in lead V_1 and while the patients were in the sinus rhythm)

ECG Abnormalities	Before Ablation	Follow-up
Inversion of T-wave		
None	26(37.7%)	25(36.2%)
V_1	29(42.0%)	28(40.6%)
V_1-V_2	3(4.3%)	6(8.7%)
V_1-V_3	11(15.9%)	8(11.6%)
Nadir S to the isoelectric line*	46.4(±12.8)	44.7(±10.6)
Epsilon wave	None	2(2.9%)
Parietal block	None	2(2.9%)

ECG, Electrocardiography; PVC, Premature ventricular contraction

Table 5. Echocardiographic feature of the study population before PVC ablation and at the time of follow-up

Echocardiographic Abnormalities		Before Ablation	Follow-up	*P*-value
LVEF		46.7(±12.6)	47.4(±10.7)	0.078
RVOT dimension		27.1(±3.4)	28.3(±4.7)	0. 01
RVEF	Normal	47(68.1%)	38(55.1%)	0.102
	mild	14(20.3%)	18(26.1%)	
	moderate	7(10.1%)	10(14.5%)	
TR Severity	No	21(30.4%)	13(18.8%)	0.04
	trivial	5(7.2%)	1(1.4%)	
	mild	35(50.7%)	41(59.4%)	
	moderate	7(10.1%)	11(15.9%)	
	severe	1(1.4%)	1(1.4%)	

PVC, Premature ventricular contraction; LVEF, Left ventricular ejection fraction; RVOT, Right ventricular outflow tract; RVEF, Right ventricular ejection fraction; TR, Tricuspid regurgitation

DISCUSSION

The results of this study describe patients undergoing PVC ablation therapy of the uncommon sites of the RV, who have the risk of ARVC development in the future. As was mentioned in previous parts, ARVC is divided into 4 levels, and each level can be characterized by several presentations. The presence of PVCs could be the first sign of early ARVC in fewer than 2% of affected individuals. [8] Although in our study, none of our patients was considered confirmed ARVC, some of them developed a group of clinical presentations, mentioned as the criteria of ARVC in the Task Force Criteria for diagnosing ARVC. As such, RVOT dimensions during the follow-up period are the most prominent criterion.

In the Task force Criteria, RVOT dimensions greater than 32 mm are regarded as a major criterion, while dimensions ranging from 29 mm to 32 mm are considered a minor criterion. [9] Although the mean RVOT dimension in our study did not fulfill the Task Force Criteria, the significant increase of this parameter (from 27.1 to 28.3 mm) showed a trend of changes toward ARVC. Given the nature of ARVC (eg, structural modifications of the RV), RV dilation and RV dysfunction are among the common presentations of this disorder. [10] Furthermore, TR may be seen as a result of this modification if other underlying causes are not present. [11] In this study, a progressive worsening of TR was observed, which may imply structural changes in favor

of ARVC or valve damage due to catheter manipulation because no other underlying causes such as pulmonary hypertension or left heart failure were found. On the other hand, the patients' LV showed improvements in function during the follow-up period and patients had higher LVEFs. Albeit not significant, it can be deemed a negative point for the diagnosis of ARVC. However, we observed an insignificant declining trend in the RVEF. Together with TR, these 2 factors would rationally imply RV dysfunction, which might be in favor of ARVC.

Among different ECG findings such as QRS morphologies, inverted T waves, and the epsilon wave, a small portion of our patients achieved the ECG features of ARVC based on the Task Force Criteria. [12] Owing to the progressive nature of ARVC, it is necessary to place patients who have undergone ablation therapy for the treatment of arrhythmogenic foci of the RV under close observation. Moreover, further monitoring can reduce the risk of sudden cardiac death and other complications of ARVC.

CONCLUSION

The results of the current study revealed that many patients who undergo ablation therapy of the RV for the treatment of arrhythmogenic foci are at an increased risk of ARVC and could manifest PVCs originating from the other parts of the RV. Although this study was unable to cover all required diagnostics for the proper evaluation of ARVC, changes such as increased RVOT dimensions were observed. Increased RVOT dimensions and TR worsening should be considered alarming signs.

Limitations

Due to the nature of a cross-sectional study, as well as the absence of appropriate control cases, we are unable to ascertain whether the changes observed in this study are specific to ARVC. Since only a limited number of patients fulfilled the inclusion criteria, our study population was not large enough to provide the possibility of assessing the various risk factors observed throughout the course of the research. Given that ARVC is a condition that reveals itself more with the progression of time, varying follow-up durations between the study population, as well as the insufficient allocated time of observation, could be considered further limitations of the performed study.

We faced many difficulties and restrictions during the course of observation and assessment. The diagnosis of ARVC based on the Task Force Criteria relies on an array of evaluations, of which the execution of many was not possible in this study. CMR is considered a major criterion in the diagnosis of ARVC; however, various economic and technical difficulties precluded us from performing this imaging modality for our patients. Amongst other diagnostic tools, we also excluded the use of signal-averaged ECG because the assessment was not carried out for all the participants. Since the study population was scattered throughout the country and many refused to be hospitalized or housed at our center, Holter monitoring could not be performed. On the other hand, due to these limitations in this study, we evaluated anatomical and electrocardiographic changes after PVC or VT ablation in the RV.

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