Bradyarrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy

Erpeng Liang, MD[1], Lingmin Wu, MD, PhD[1], Siyang Fan, MD[1], Xiaofei Li, MD, Feng Hu, MD, Lihui Zheng, MD, PhD, Xiaohan Fan, MD, PhD, Gang Chen, MD, Ligang Ding, MD, PhD, and Yan Yao, MD, PhD*

Less is known about bradyarrhythmias in arrhythmogenic right ventricular cardiomyopathy (ARVC). This cross-sectional study aimed to assess the prevalence and clinical significance of bradyarrhythmias in ARVC. From May 1995 to December 2017, bradyarrhythmias including sick sinus syndrome, atrioventricular block, and intraventricular conductional block (ICB) were investigated in 522 ARVC patients. A total of 169 patients (32.4%) presented with bradyarrhythmias including sick sinus syndrome in18 (3.5%), atrioventricular block in 56 (10.7%), and ICB in 118 patients (22.6%). Multivariate analysis showed right atrial dilation increased the risk of bradyarrhythmias (odds ratio [OR] 1.641, 95% confidence interval [CI] 1.081 to 2.492, p = 0.020). Bradyarrhythmias were not associated with death and heart transplantation. In patients with bradyarrhythmias, female gender, left atrial diameter >40 mm, and New York Heart Association Ⅲ/Ⅳ increased the risk of death and heart transplantation (hazards ratio [HR] = 2.790, 95% CI 1.220 to 6.377, p = 0.015; HR = 4.913, 95% CI 2.058 to 11.730, p <0.001; HR = 3.223, 95% CI 1.246 to 8.340, p = 0.016). Among the 23 patients who underwent device implantation, left atrial diameter >40 mm was associated with death and heart transplantation (HR = 9.523, 95% CI 1.587 to 57.126, p = 0.014). In conclusion, bradyarrhythmias were commonly seen in ARVC, and ICB was the most common type. Female, left atrial diameter >40 mm, and NYHA class were associated with death and heart transplantation. **(Am J Cardiol 2019;123:1690−1695)**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by ventricular tachyarrhythmias, ventricular dysfunction, and sudden cardiac death.[1,2] Progressive loss of myocardium and its replacement by fibro-fatty tissue is the pathological hallmark of the disease,[3,4] which may not only lead to the lethal tachyarrhythmias but also bradyarrhythmias. Although a few studies have demonstrated the right bundle branch block in ARVC patients,[5,6] the results remain controversial and the long-term outcomes are unknown. Furthermore, other types of bradyarrhythmias such as sick sinus syndrome (SSS) and atrioventricular block (AVB) have been only reported in anecdotal ARVC cases.[7,8] This study aimed to investigate the real-world data of bradyarrhythmias in a large series of ARVC patients.

Methods

We reviewed all case records of patients in suspicion of ARVC referred to Fuwai hospital from May 1995 to December 2017. The diagnosis was established on the basis of the 2010 Task Force Criteria. All data were reviewed by 2 doctors independently, and inconsistencies were adjudicated by a third cardiologist. The study was approved by the institutional ethics committee.

All 12-lead electrocardiograms and at least a 24 hour-Holter data were analyzed in all patients. The diagnosis of bradyarrhythmia was made when bradyarrhythmias were appeared on ECG and/or Holter recording. SSS was defined as symptomatic sinus bradycardia, sinus arrest, or sinus exit block.[9] The 1° AVB block was given when the PR interval was more than 200 ms. The 2° AVB block includes Mobitz or Wenckebach block. The 3° AVB diagnosed was given when no correlation exists between P wave and QRS complex.[5]

Intraventricular conductional block (ICB) including incomplete right bundle branch block (iCRBBB) and complete right bundle branch block (CRBBB), left bundle brunch block, left anterior fascicular block (LAFB), and left posterior fascicular block was defined according to the AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram.[10]

Follow-up was carried out every 6 months after discharge via telephone or outpatient visit. For patients lost to follow-up, the long-term survival data were obtained from the database in Chinese Center for Disease Control and Prevention.

Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, PR China. Manuscript received December 12, 2018; revised manuscript received and accepted February 18, 2019.

Funding: This work was supported by the Beijing Municipal Science and Technology Commission grant Z161100000516022 and National Natural Science Foundation grant 81800300.[1]Contributed equally to this work.

See page 1695 for disclosure information.

*Corresponding author: Tel: +86-010-88322405; fax: +86-6024-1570.

E-mail address: ianyao@263.net.cn (Y. Yao).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.02.032

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile). Categorical variables were presented as frequencies and percentages. Mann-Whitney U and Kruskal-Wallis H were used to compare continuous variables between groups if the variable was not normally distributed. Chi-square analysis was used to compare the categorical variables between groups. Cox regression analyses were performed to evaluate factors associated with the long-term outcomes in patients with bradyarrhythmias. The following variables including age, gender, New York Heart Association (NYHA) functional class, parameters of cardiac chambers, left ventricular ejection fraction (LVEF), degree of tricuspid regurgitation were analyzed. All tests were two-tailed and a statistical significance was established at a $p < 0.05$.

Results

Totally, 522 patients were diagnosed as ARVC among 551 suspected patients according to the 2010 criteria. Among which, 169 patients (32.4%) presented with bradyarrhythmias (Table 1 and Figure 1). Of note, there were 27 patients who underwent regular antiarrhythmic drug therapy before being enrolled and they were diagnosed as sinus arrest (1 case), 1° AVB (4 cases), RBBB (13 cases), iCRBBB (6 cases), and LAFB (3 cases). The remaining 142 patients did not receive antiarrhythmic drug therapy.

Table 1
Clinical characteristics of the study cohort (n = 522)

Age, (years)	39.0 ± 15.1
Male	373 (71.2%)
Syncope	184 (35.1%)
NYHA class	
Ⅰ	337 (64.6%)
Ⅱ	78 (15.0%)
Ⅲ	50 (9.6%)
Ⅳ	48 (9.2%)
Sick sinus syndrome	
Sinus bradycardia	13 (2.5%)
Sinus arrest	7 (1.3%)
Sinoatrial conduction block	2 (0.4%)
Atrioventricular block	
1°	38(7.3%)
2° Type 1	6 (1.1%)
2° Type 2	0 (0)
3°	12 (2.3%)
Intraventricular conductional block	
RBBB	
CRBBB	90 (17.2%)
iCRBBB	20 (3.8%)
LBBB	0 (0)
LAFB	21 (4.0%)
LPFB	1 (0.2%)

CRBBB = complete right bundle brunch block; iCRBBB = incomplete right bundle brunch block; LAFB = left anterior fascicular block; LBBB = left bundle brunch block; LPFB = left posterior fascicular block; NYHA = New York Heart Association; RBBBB = right bundle branch block.

SSS was observed in 18 patients (3.5%) (Table 1). All of the patients of sinus arrest were implanted permanent pacemaker. For patients with sinus bradycardia, 11 presenting with sustained ventricular tachycardia (VT) underwent radiofrequency catheter ablation [7 (1.3%)], dual-chamber implantable cardioverter defibrillator (ICD) [3 (0.5%)], and permanent pacemaker implantation with antiarrhythmic drugs prescribed [1 (0.2%)].

There were 56 patients (10.7%) who showed AVB. The 1° AVB was found in 38 patients (7.3%), among whom 32 patients combined with VT underwent radiofrequency catheter ablation [19 (3.6%)], catheter ablation combined ICD implantation [4 (0.8%)], and ICD implantation [8 (1.5%)]. There were 6 patients (1.1%) diagnosed as type Ⅰ 2° AVB, among whom, 3 patients showed sustained VT and 1 underwent ICD implantation whereas the rest underwent catheter ablation.

There were 12 patients (2.3%) diagnosed as 3° AVB (8 men and 4 women; mean age, 42.3 ± 10.2 years) of whom 6 presented initially with complete heart block with the rest deteriorated to 3° AVB. There were no differences in gender [male: 4 (66.7%) vs 4 (66.7%)], NYHA class severe than Ⅲ [3 (50%) vs 5 (83.3%), p = 0.545], age [44.7 ± 9.9 vs 45.2 ± 19.6, p = 0.956], and LVEF [(56.9 ± 4.0% vs 54.3 ± 16.4%, p = 0.715)]. Eight patients who were combined with sustained VT underwent ICD implantation [5 (1.0%)], cardiac resynchronization therapy with defibrillation (CRTD) [1 (0.2%)], pacemaker implantation combined with catheter ablation [2 (0.4%)]. The rest 4 patients underwent permanent pacemaker implantation.

There were 118 patients (22.6%) diagnosed with intraventricular block. Right bundle brunch block was found in 110 patients (21.1%) including CRBBB (78 cases), CRBBB with LAFB (12 cases), iCRBBB with LAFB (2 cases), and iCRBBB (18 cases). Besides, LAFB (7 cases) and left posterior fascicular block (1 case) respectively. There was no left bundle brunch block found.

Right atrial dilatation was more commonly seen (70 [43.2%] vs 105 [32.0%], p = 0.015) and left atrial dimension is larger (33.8 ± 6.7 vs 32.5 ± 6.3, p = 0.040) in patients with bradyarrhythmias than in those without (Table 2). Multivariate analysis showed right atrial dilation was associated with increased risk of bradyarrhythmias (odds ratio [OR] 1.641, 95% confidence interval [CI] 1.081 to 2.492, p = 0.020).

Device implantation was conducted in 23 patients with bradyarrhythmias. Among whom, 14 patients were implanted permanent pacemaker (6 patients due to 3° AVB, 7 patients due to SSS, and 1 patient due to right bundle brunch block combined with LAFB). Eight patients who were referred due to VT were implanted ICD of whom 5 combined with 3° AVB and 3 combined with sinus bradycardia. One patient with 3° AVB and heart failure underwent CRTD therapy. Three patients with VT who refused ICD implantation for economic considerations underwent catheter ablation. For the patients who need device implantation to treat bradyarrhythmias, they showed larger left atrial diameter than those without (Table 3). What is more, right ventricular malfunction, right atrial dilatation, and severe tricuspid regurgitation were also more commonly seen (p = 0.023, 0.024, and 0.010; Table 3).

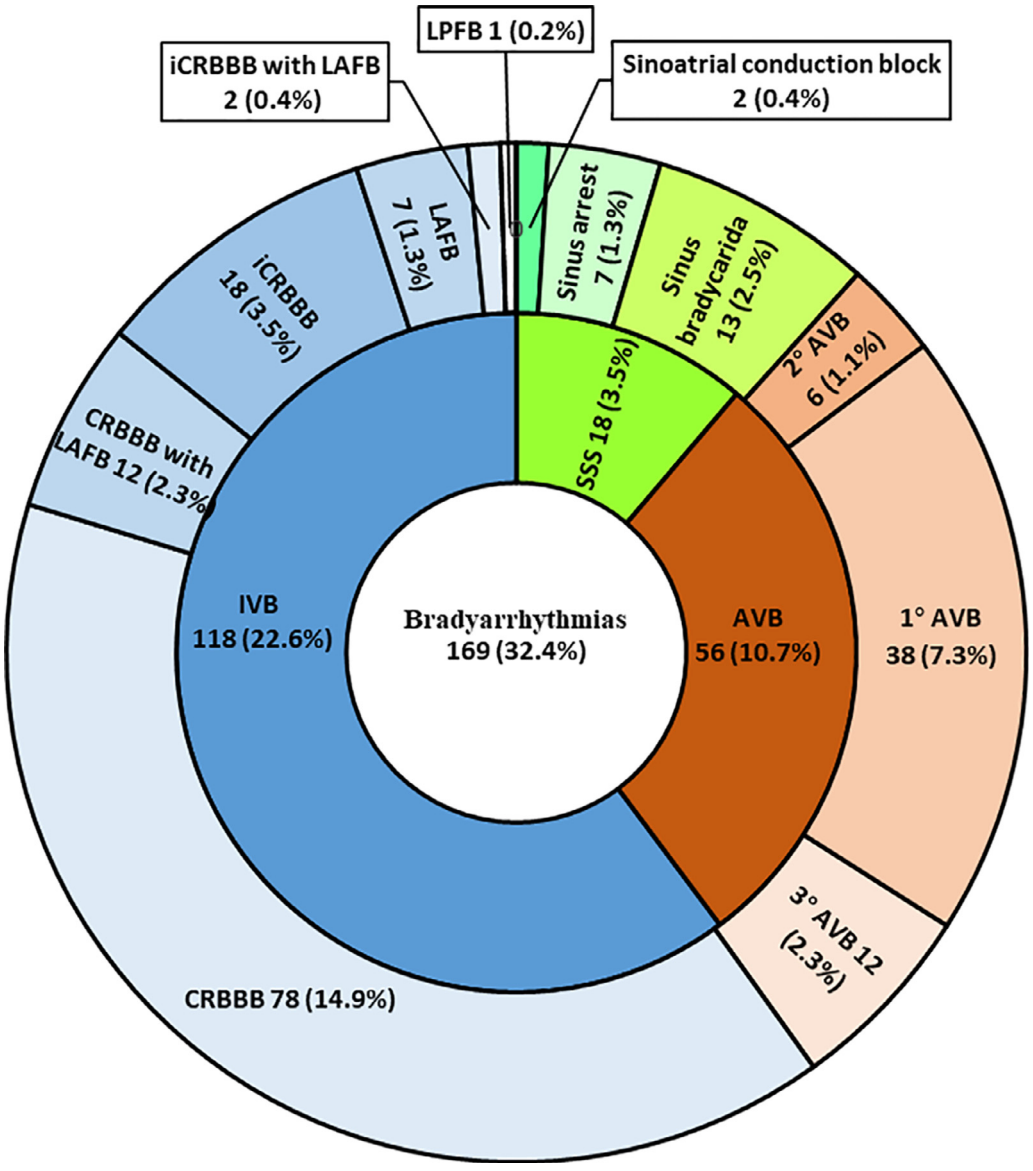

Figure 1. Bradyarrhythmias in ARVC patients.
ARVC = arrhythmogenic right ventricular cardiomyopathy; AVB = atrioventricular block; CRBBB = right bundle branch block; iCRBBB = incomplete right bundle branch block; IVB = intraventricular conductional block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; SSS = sick sinus syndrome.

After a median follow-up time of 51.4 (range 0 to 196) months, 62 patients died and 53 patients underwent heart transplantation. Cox regression analyses showed bradyarrhythmias were not associated with death and heart transplantation (p = 0.859; Figure 2). Of the 169 patients with bradyarrhythmias, after a median follow-up time of 62.0 (range 35.7 to 108.7) months, 9 patients died of heart failure, 14 died of sudden death, and 8 patients underwent heart transplantation. Different types of bradyarrhythmias were not associated with death and heart transplantation (Figure 2). Cox regression analyses showed female gender, left atrial diameter >40 mm, and NYHA Ⅲ/Ⅳ were associated with increased risk of death and heart transplantation (hazards ratio [HR] = 2.790, 95% CI 1.220 to 6.377, p = 0.015; HR = 4.913, 95% CI 2.058 to 11.730, p <0.001; HR = 3.223, 95% CI 1.246 to 8.340, p = 0.016; Figure 3).

For the 23 patients with bradyarrhythmias who need device implantation, the median follow-up time was 44.3 (25.0, 63.8) months. Three patients died of heart failure, 4 patients underwent heart transplantation. Cox regression analyses showed left atrial diameter >40 mm (HR = 9.523, 95% CI 1.587 to 57.126, p = 0.014) was associated with death and heart transplantation (Figure 4).

Discussion

In this study, data from a large series of patients revealed that bradyarrhythmias were commonly in ARVC. ICB was the most common type of bradyarrhythmias. Right atrial

Table 2
Comparison of clinical characteristics in patients with and without bradyarrhythmias

Variable	With (n = 169)	Without (n = 352)	p Value
Age, (years)	40.0 ± 15.1	38.5 ± 15.1	0.295
Male	122 (32.7%)	251 (67.3%)	0.797
From first symptom to enrolled, (months)	28.4 (9.7, 70.4)	24.3 (6.1,73.0)	0.277
Sustained VT	136 (83.4%)	291 (82.4%)	0.780
TTE			
LA dimension, (mm)	33.8 ± 6.7	32.5 ± 6.3	0.040
LV dimension, (mm)	48.6 ± 7.4	48.4 ± 7.1	0.703
RV dilatation	63 (38.4%)	105 (31.7%)	0.139
RV malfunction	51 (31.3%)	96 (29.1%)	0.616
LVEF (%)	55.5 ± 14.7	56.7 ± 14.1	0.391
RA dilatation	70 (43.2%)	105 (32.0%)	0.015
Severe TR	21 (12.9%)	39 (11.8%)	0.725

Disease course = time from first symptom onset to enrollment; LA = left atrial; LV = left ventricle; LVEF = left ventricular ejection fraction; RA = right atrial; RV = right ventricle; TR = tricuspid regurgitation; TTE = transthoracic echocardiography; VT = ventricular tachycardia.

Table 3
Comparison of clinical characteristics in patients of arrhythmogenic right ventricular cardiomyopathy and bradyarrhythmias with and without device implantation

Variable	With n = 23	Without n = 147	p Value
Age, (years)	44.0 ± 14.3	39.4 ± 15.2	0.166
Male	15 (65.2%)	107 (73.3%)	0.422
From first symptom to enrolled, (months)	30.4 (12.2, 70.0)	28.4 (7.8, 73.0)	0.950
Sustained VT	12 (60.0%)	124 (86.7%)	0.003
TTE			
LA dimension, (mm)	38.7 ± 5.6	33.0 ± 6.6	<0.001
LV dimension, (mm)	50.4 ± 8.4	48.4 ± 7.2	0.292
RV dimension, (mm)	28.3 ± 11.2	28.5 ± 11.5	0.938
RV malfunction	12 (52.2%)	40 (28.4%)	0.023
LVEF (%)	51.6 ± 14.4	56.0 ± 14.8	0.187
RA dilatation	15 (65.2%)	56 (40.0%)	0.024
Severe TR	7 (30.4%)	15 (10.6%)	0.010

The abbreviations are the same as in Table 2.

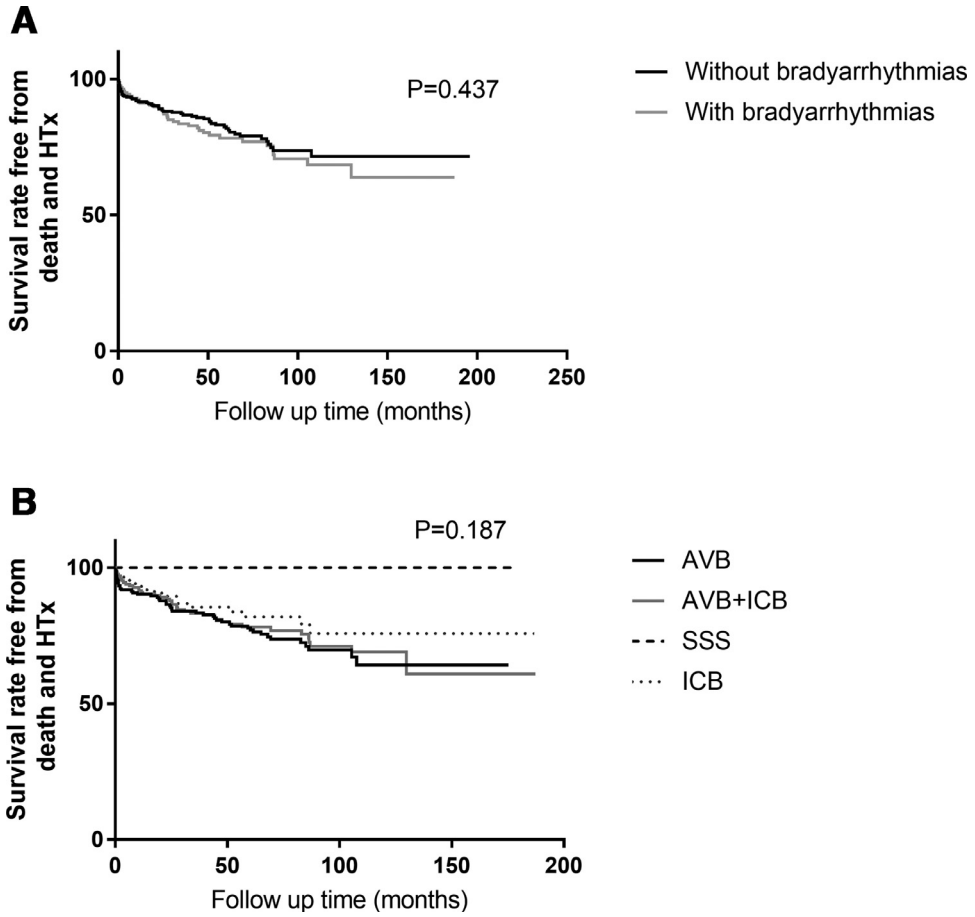

Figure 2. The relation of bradyarrhythmias with death and heart transplantation in ARVC.
(*A*) Survival curve of free from death and heart transplantation in ARVC patients with and without bradyarrhythmias; (*B*) Survival curve of free from death and heart transplantation within different kinds of bradyarrhythmias.
The abbreviations are the same as Figure 1.

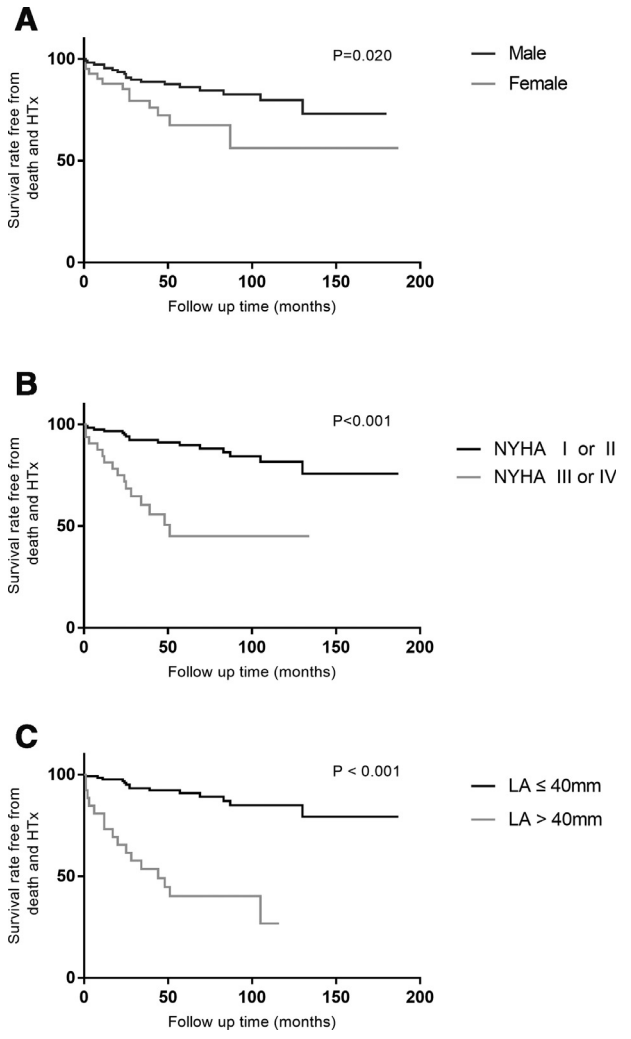

Figure 3. The survival curve of free from death and heart transplantation in ARVC patients with bradyarrhythmias.
(*A*) Impact of gender; (*B*) Impact of NYHA class; (*C*) Impact of left atrial dilation.

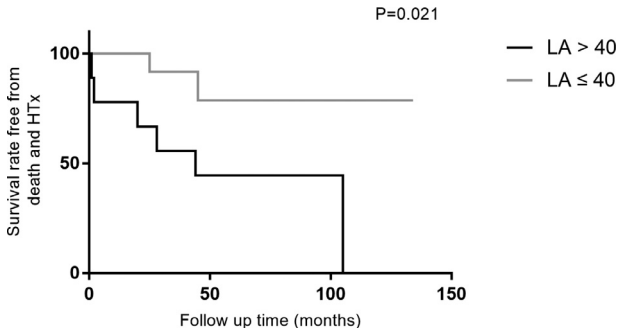

Figure 4. The survival curve of free from death and heart transplantation in ARVC patients with bradyarrhythmias who underwent device implantation.
HTx = heart transplantation; NYHA = New York Heart Association.

dilation in ARVC increased the risk of bradyarrhythmias. Female, left atrial diameter >40 mm, and NYHA Ⅲ/Ⅳ were associated with increased risk of death and heart transplantation in patients with bradyarrhythmias.

The data of bradyarrhythmias in ARVC remain limited. Tabib et al reviewed 200 forensic autopsies of ARVC patients and found that about 68% patients showed conductive tissue infiltrated by fibrosis (54.3%), adipose tissue (8.1%), and fibro-fatty (5.6%).[4] Disturbance of cell adhesion defects and alterations in gap junction localization which result in conduction disturbance and fibro-fatty replacement of cardiomyocytes may also occur in the conduction system.[11] Desmosomal and adherens junction components involved in connecting cardiomyocytes which were considered as the main reasons for ARVC can be found in adhering junctions of Purkinje fiber cells.[12]

However, there were few cases of ARVC with conduction abnormalities reported, especially for the patients of ARVC with VT and conduction abnormality.[13,14] Peters et al conducted a study regarding the conduction abnormality in ARVC finding that only 6% of the patients with complete right bundle branch block and any degree of AVB.[5] In this study, 169 patients (32.4%) showed abnormality of conduction system of whom 23 patients needed to be intervened by either ICD, permanent pacemaker, or CRTD. The conduction system abnormality was really not a rare phenomenon in ARVC. The possible reasons maybe the patients of 3° AVB referred to our center were in the severer stage. For the 12 patients of 3° AVB, half of them presented initially with 3° AVB with the rest deteriorated to complete AVB. Age, NYHA class, and LVEF were not significantly different between groups. Both directly involvement of conduction system and progressive deterioration maybe the reasons of 3° AVB.

Patients of ARVC and bradyarrhythmias needed to be paid more attention. On the one hand, for the patients with VT and conduction abnormality including 3° AVB, sinus arrest and severe sinus bradycardia, dual-chamber ICD were suggested to implant. However, for the patients without VT, permanent pacemaker was proposed. Antiarrhythmic drug therapy was also suggested for sustained/nonsustained VT and frequent premature ventricular contractions.[15] In contrast, in terms of the patients of ARVC with atrial enlargement, more attention should be paid regarding the conduction system and the event of heart failure and cardiac death.

There are several limitations to note. First, only minority of patients underwent genetic test and myocardial histopathological examination. More data on genetic analysis, cardiac MRI, and histopathology could make the study more attractive. It is also of consideration that we only investigated the Chinese population, and racial differences are likely existed in such an inherited disease. These limitations must be taken into consideration when interpreting our results.

Bradyarrhythmias were commonly in ARVC of which ICB was the most common form. Female, left atrial diameter, and NYHA class were associated with death and heart transplantation. Due to the progressive nature of the disease, more attention should be paid on it and regular follow-up is needed especially in patients with enlarged atrium.

Disclosure

The authors have no conflicts of interest to disclose.

1. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010;31:806–814.
2. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation* 1982;65:384–398.
3. Thiene G, Basso C, Danieli G, Rampazzo A, Corrado D, Nava A. Arrhythmogenic right ventricular cardiomyopathy a still underrecognized clinic entity. *Trends Cardiovasc Med* 1997;7:84–90.
4. Tabib A, Loire R, Chalabreysse L, Meyronnet D, Miras A, Malicier D, Thivolet F, Chevalier P, Bouvagnet P. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation* 2003;108:3000–3005.
5. Peters S. Conduction abnormalities in arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiol* 2013;168:4920–4921.
6. Peters S, Trummel M, Koehler B. Special features of right bundle branch block in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Int J Cardiol* 2012;157:102–103.
7. Bruna V, Diez-Villanueva P, Martinez-Selles M, Datino T, Fernandez-Aviles F. Atrioventricular conduction disorder as a first manifestation of arrhythmogenic right ventricular dysplasia. *Rev Esp Cardiol (Engl Ed)* 2016;69:1222–1224.
8. Akazawa H, Ikeda U, Minezaki KK, Hayashi Y, Kuroki S, Shimada K. Right ventricular dysplasia with complete atrioventricular block: necessity and limitation of left ventricular epicardial pacing. *Clin Cardiol* 1998;21:604–606.
9. Adan V, Crown LA. Diagnosis and treatment of sick sinus syndrome. *Am Fam Physician* 2003;67:1725–1732.
10. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:976–981.
11. Pieperhoff S. Gene mutations resulting in the development of ARVC/D could affect cells of the cardiac conduction system. *Front Physiol* 2012;3:22.
12. Pieperhoff S, Borrmann C, Grund C, Barth M, Rizzo S, Franke WW. The area composite of adhering junctions connecting heart muscle cells of vertebrates. VII. The different types of lateral junctions between the special cardiomyocytes of the conduction system of ovine and bovine hearts. *Eur J Cell Biol* 2010;89:365–378.
13. Nogami A, Adachi S, Nitta J, Taniguchi K, Marumo F, Aonuma K, Iesaka Y, Hiroe M. Arrhythmogenic right ventricular dysplasia with sick sinus syndrome and atrioventricular conduction disturbance. *Jpn Heart J* 1990;31:417–423.
14. Morimoto S, Sekiguchi M, Okada R, Kasajima T, Hiramitsu S, Yamada K, Mizuno Y. Two autopsied cases of arrhythmogenic right ventricular dysplasia. *J Cardiol* 1990;20:1025–1036.
15. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, Tandri H, Paul M, Schmied C, Pelliccia A, Duru F, Protonotarios N, Estes NR, McKenna WJ, Thiene G, Marcus FI, Calkins H. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;36:3227–3237.