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Heart rate-adjusted PR as a prognostic marker of long-term ventricular arrhythmias and cardiac death in ICD/CRT-D recipients

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Abstract

Objective To evaluate the PR to RR interval ratio (PR/RR, heart rate-adjusted PR) as a prognostic marker for long-term ventricular arrhythmias and cardiac death in patients with implantable cardioverter defibrillator (ICDs) and cardiac resynchronization therapy with defibrillators (CRT-D). **Methods** We retrospectively analyzed data from 428 patients who had an ICD/CRT-D equipped with home monitoring. Baseline PR and RR interval data prior to ICD/CRT-D implantation were collected from standard 12-lead electrocardiograph, and the PR/RR was calculated. The primary endpoint was appropriate ICD/CRT-D treatment of ventricular arrhythmias (VAs), and the secondary endpoint was cardiac death. **Results** During a mean follow-up period of 38.8 ± 10.6 months, 197 patients (46%) experienced VAs, and 47 patients (11%) experienced cardiac death. The overall PR interval was 160 ± 40 ms, and the RR interval was 866 ± 124 ms. Based on the receiver operating characteristic curve, a cut-off value of 18.5% for the PR/RR was identified to predict VAs. A PR/RR ≥ 18.5% was associated with an increased risk of VAs [hazard ratio (HR) = 2.243, 95% confidence interval (CI) = 1.665–3.022, $P < 0.001$) and cardiac death (HR = 2.358, 95%CI = 1.240–4.483, $P = 0.009$) in an unadjusted analysis. After adjustment in a multivariate Cox model, the relationship remained significant among PR/RR ≥ 18.5%, VAs (HR = 2.230, 95%CI = 1.555–2.825, $P < 0.001$) and cardiac death (HR = 2.105, 95%CI = 1.101–4.025, $P = 0.024$. **Conclusions** A PR/RR ≥ 18.5% at baseline can serve as a predictor of future VAs and cardiac death in ICD/CRT-D recipients.

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Keywords: Implantable cardioverter defibrillator; PR interval; RR interval; Ventricular arrhythmias

1 Introduction

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality. Ventricular arrhythmias (VAs) are the main cause of SCD and account for 75% to 80% of these deaths.[1,2] Thus, it is important to identify high risk factors for VAs. Previous studies have found that faster heart rates (shorter RR intervals) were associated with SCD and other adverse outcomes in the general population as well as in patients with implantable cardioverter defibrillators (ICD).[3,4]

The classification of the PR interval as a risk factor for clinical outcomes is controversial. Previous studies demonstrated that PR interval prolongation is associated with an increased risk of arrhythmia events and heart disease and therefore a poor prognosis.[5,6] Recent studies focusing on the association between the PR interval and cardiac resynchronization therapy (CRT) also concluded that PR interval prolongation can be a marker of heart failure hospitalization and death.[7–9] However, most recently, Senfield, *et al*.[10] demonstrated that the baseline PR interval did not affect clinical outcomes or reverse remodeling with CRT in mild heart failure. In an analysis from the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, Olshansky, *et al*.[11] demonstrated that as a continuous variable, the PR interval did not predict outcomes. Outcomes after CRT were similar in the groups with normal and prolonged PR intervals.[11] Notably, the PR in-

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terval was not adjusted for heart rate in these studies, as previous studies have not examined the predictive ability of heart rate-adjusted PR. Therefore, this study evaluates the PR to RR interval ratio (PR/RR, heart rate-adjusted PR) as a prognostic marker for long-term VAs and cardiac death.

2 Methods

We retrospectively analyzed archived HM transmissions data from the Study of Home Monitoring System Safety and Efficacy in Cardiac Implantable Electronic Device-Implantable Patients (SUMMIT) registry in China. All participants provided written informed consent, and the study protocol was approved by the hospital ethics committees.

2.1 Study population and device settings

We studied 428 patients who underwent ICD/CRT-D implantation between February 2009 and August 2014 and met the selection criteria. Before ICD/CRT-D implantation, a standard 12-lead resting electrocardiograph (ECG) at a paper speed of 25 mm/s was performed on each patient. The PR and RR intervals were transcribed from the computer interpretation of the ECG. All the measurements were validated by an investigator. Baseline PR and RR interval data from ECG were collected, and the PR/RRs was then calculated. The recorded demographic characteristics included age, sex, and body mass index (BMI). Before ICD/CRT-D implantation, baseline characteristics were obtained from the patients' medical records. The program settings were as follows: the basic lower rate was 40–70 beats/min, the ventricular tachycardia (VT) detection rate was 140 beats/min, the ventricular fibrillation (VF) detection rate was 200 beats/min, and the therapy parameters were programmed according to the patient's condition. To provide continuous patient monitoring, all devices were programmed to HM "on". The data manager collected follow-up data. VAs were identified from the stored transmitted data. The clinicians assessed intracardiac electrograms to confirm the occurrence of VAs. All the VAs were validated by adjudicating the investigator again. The data manager, clinicians and adjudicating investigator were blind to the study. Mistaken identification events were excluded.

2.2 Selection criteria

The inclusion criteria were (1) patients aged ≥ 18 years, patients with an ICD/CRT-D device (Biotronic, Germany) equipped with HM that could transmit data daily, and (3) patients with recorded PR and RR intervals prior to ICD/CRT-D implantation.

The exclusion criteria were patients with atrial fibrillation (AF), liver failure, significant renal impairment, and grade III atrioventricular block.

2.3 Endpoints

The primary endpoint was appropriate ICD/CRT-D therapy of VAs. Routine follow-up was carried out, and if the patient's transmission was disrupted, the condition of the patient was evaluated by follow-up phone calls. If the patient died, the date and cause of death were confirmed by contacting the patient's family or reviewing the death certificate. The secondary endpoint was cardiac death.

2.4 Statistical analysis

We used the mean ± SD as the descriptive statistics for continuous variables and the number and percentage as the descriptive statistics for categorical variables. Differences between each group were compared using Student's *t*-test for continuous variables and Pearson's X^2 test for categorical variables as appropriate. The *P* value was calculated when comparing two groups. A two-sided *P* value < 0.05 was considered statistically significant. To evaluate the discriminatory ability of the PR/RR for VAs, we plotted receiver operating characteristic curves and obtained a cut-off value for quantitative variables. The categories of PR/RR ≥ 18.5% and PR/RR < 18.5% were used for the calculations performed. We used Kaplan-Meier survival curves to assess the survival time from the date of ICD/CRT-D implantation to the dates of VAs and cardiac deaths. The log-rank test (univariate analysis) was performed to test the significance of differences between the survival curves. We used univariate binary Cox regression analysis to examine the relationship between baseline characteristics and endpoints. Hazard ratios (HRs) and 95%CIs were calculated for each variable. For the multivariate Cox model, variables that had a statistical significance at a *P* value < 0.05 were chosen. The covariates included for adjustment were age, PR interval, QT interval, QRS duration, heart rate, CRT-D presence, New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), β-blocker and amiodarone use, diabetes mellitus and hypertension.

All statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, New York) and GraphPad Prism software version 6.0 (GraphPad Software, La Jolla, California).

3 Results

3.1 Baseline characteristics

A total of 428 patients (320 males) with an average age of 58.6 ± 14.1 years were analyzed. The overall PR interval was

160 ± 40 ms, and the RR interval was 866 ± 124 ms. All eligible patients were grouped by PR/RR with a cut-off value of 18.5%. Cumulative hazard functions were significantly different between patients with a PR/RR ≥ 18.5% and those with a PR/RR < 18.5% ($P < 0.001$) (Figure 1). Baseline demographic and clinical characteristics between the two groups are detailed in Table 1. Compared with patients with a PR/RR < 18.5%, those with a PR/RR ≥ 18.5% were more likely to be male ($P = 0.035$) and have an implanted CRT-D ($P = 0.001$), lower LVEF ($P < 0.001$), shorter QT interval ($P < 0.001$), longer QRS duration ($P = 0.001$) and worse NYHA classification ($P < 0.001$). Hypertension ($P = 0.016$), diabetes mellitus ($P = 0.002$) and dilated cardiomyopathy ($P < 0.001$) were more prevalent in patients with PR/RR ≥ 18.5%.

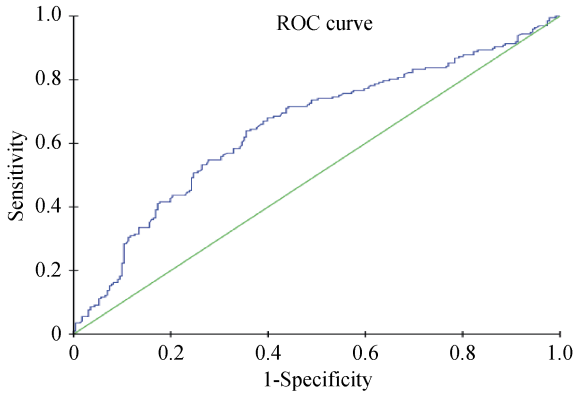

Figure 1. ROC curve with a cut-off value of 18.5% for PR/RR to predict VAs, $P < 0.001$. ROC curve: receiver operating characteristic curve; VAS: ventricular arrhythmias.

Table 1. Baseline characteristics *vs.* admission PR/RR.

	Total population ($n = 428$)	PR/RR ≥ 18.5% ($n = 224$)	PR/RR < 18.5% ($n = 204$)	*P* value
Demographics				
Male sex	320 (74.8%)	177 (79.0%)	143 (70.1%)	0.035
Age, yrs	58.65 ± 14.09	59.26 ± 13.34	57.97 ± 14.88	0.345
BMI, kg/m^2	23.49 ± 3.94	23.34 ± 3.87	23.66 ± 4.02	0.397
NYHA Class III-IV, %	188 (43.9%)	121 (54.0%)	67 (32.8%)	< 0.001
SBP, mmHg	123.87 ± 16.66	123.82 ± 16.56	123.93 ± 16.82	0.948
DBP, mmHg	76.63 ± 10.98	76.35 ± 10.89	76.95 ± 11.10	0.570
CRT-D	119 (27.8%)	78 (34.8%)	41 (20.1%)	0.001
Primary prevention	47 (11.0%)	26 (11.6%)	21 (10.3%)	0.757
ECG				
PR interval, ms	160.8 ± 40.4	186.4 ± 33.4	132.8 ± 26.4	< 0.001
RR interval, ms	865.9 ± 123.7	820.7 ± 109.8	915.6 ± 119.2	< 0.001
QT interval, ms	705.1 ± 128.1	634.3 ± 99.9	782.8 ± 109.4	< 0.001
QRS duration, ms	120.2 ± 32.9	125.4 ± 34.1	114.5 ± 30.5	0.001
Echocardiography				
LVEF, %	43.05 ± 15.80	40.42 ± 14.91	45.93 ± 16.28	< 0.001
LVEDD, mm	57.99 ± 13.89	59.14 ± 13.72	56.71 ± 14.01	0.073
Comorbidities				
CHD	100 (23.4%)	54 (24.1%)	46 (22.5%)	0.732
IHD	113 (26.4%)	56 (25.0%)	57 (27.9%)	0.511
HBP	134 (31.3%)	82 (36.6%)	52 (25.5%)	0.016
DCM	109 (25.5%)	79 (35.3%)	30 (14.7%)	< 0.001
Valvular disease	2 (0.5%)	1 (0.4%)	1 (0.5%)	1.000
Diabetes	38 (8.9%)	29 (12.9%)	9 (4.4%)	0.002
Stroke	105 (24.5%)	51 (22.8%)	54 (26.5%)	0.431
Meditation				
Beta-blockers	140 (32.7%)	86 (38.4%)	54 (26.5%)	0.010
Amiodarone	130 (30.4%)	81 (36.2%)	49 (24.0%)	0.008
ACEI or ARB	237 (55.4%)	132 (58.9%)	105 (51.5%)	0.144
Loop diuretic	114 (26.6%)	50 (22.3%)	64 (31.4%)	0.038

Data are presented as mean ± SD or *n* (%). ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI: body mass index; CHD: coronary heart disease; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; ECG: electrocardiograph; HBP: high blood pressure; IHD: ischemic heart disease; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SBP: systolic blood pressure.

3.2 A PR/RR ≥ 18.5% at baseline is a predictor of future VAs and cardiac death in ICD/CRT-D recipients

The clinical outcomes of patients depended on PR/RR, as shown in Table 2. During a mean follow-up of 38.8 ± 10.6 months, 197 patients (46%) experienced VAs, and 47 patients (11%) experienced cardiac death. The incidence rates of VAs in patients with PR/RR ≥ 18.5% and PR/RR < 18.5% were 58.9% and 31.9% ($P < 0.001$), respectively. In addition, there were more cardiac deaths in patients with a PR/RR ≥ 18.5% than in patients with a PR/RR < 18.5% (34, 15.2% *vs*. 13, 6.4%, $P = 0.005$).

Estimated Kaplan-Meier curves were plotted to determine VAs and cardiac death among patients based on PR/RR intervals. Compared with patients with a PR/RR < 18.5%, patients with a PR/RR ≥ 18.5% had an increased cumulative incidence of VAs ($P < 0.001$) and cardiac death ($P = 0.007$) (Figure 2).

Table 2. Clinical outcomes of patients dependent on PR/RR.

	Overall	PR/RR ≥ 18.5%	PR/RR < 18.5%	*P* value
VAs	197 (46%)	132 (58.9%)	65 (31.9%)	< 0.001
Cardiac Death	47 (11%)	34 (15.2%)	13 (6.4%)	0.005

Data are presented as *n* (%). VAs: ventricular arrhythmias.

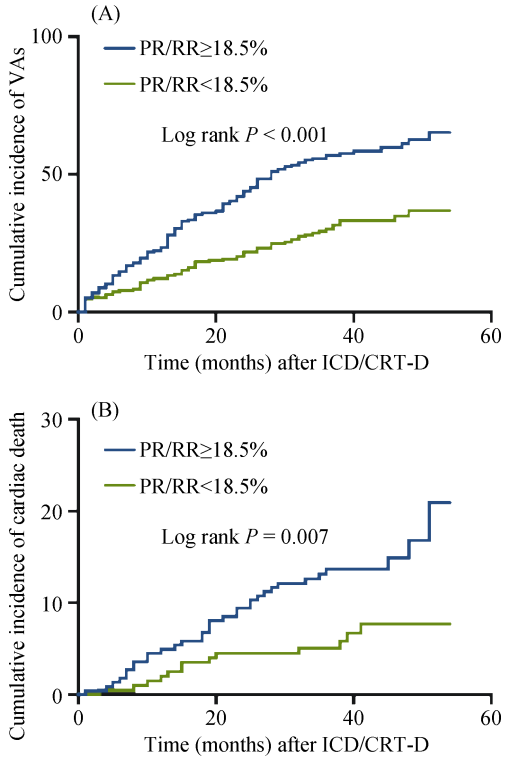

Figure 2. Kaplan-Meier estimates of the cumulative incidence of the outcomes. (A): VAs; (B): cardiac death. CRT-D: cardiac resynchronization therapy defibrillators; ICDs: implantable cardioverter defibrillators; VAs: ventricular arrhythmias.

In univariate Cox proportional hazard models, PR/RR ≥ 18.5% was associated with an increased risk of VAs (HR = 2.243, 95%CI = 1.665–3.022, $P < 0.001$) and cardiac death (HR = 2.358, 95%CI = 1.240–4.483, $P = 0.009$). Upon adjustment in a multivariate model, PR/RR ≥ 18.5% remained an independent predictor of VAs (HR = 2.096, 95%CI = 1.555–2.825, $P < 0.001$) and cardiac death (HR = 2.105, 95%CI = 1.101–4.025, $P = 0.024$) (Table 3). The covariates included for adjustment were age, PR interval, QT interval, QRS duration, heart rate, CRT-D presence, NYHA classification, LVEF, LVEDD, β-blocker and amiodarone use, diabetes mellitus, and hypertension.

3.3 Baseline heart rate, PR interval and long-term outcomes

In univariate Cox proportional hazard models, baseline heart rate was associated with an increased risk of VAs (HR = 1.019, 95%CI = 1.006–1.032, $P = 0.004$) and cardiac death (HR = 1.026, 95%CI = 1.002–1.051, $P = 0.031$). Upon adjustment in a multivariate model, baseline heart rate remained an independent predictor of VAs (HR = 1.018, 95%CI = 1.006–1.031, $P = 0.004$) (Table 3).

In univariate Cox proportional hazard models, the PR interval was associated with an increased risk of VAs (HR = 1.006, 95%CI = 1.002–1.009, $P = 0.002$) but not cardiac death (HR = 1.007, 95%CI = 1.000–1.014, $P = 0.062$). Upon adjustment in a multivariate model, the PR interval

Table 3. Univariate and multivariate Cox proportional hazard models according to PR/RR as a category.

	HR	95%CI	*P* value
PR/RR			
Univariate			
VAs	2.243	1.665–3.022	< 0.001
Cardiac death	2.358	1.240–4.483	0.009
Multivariate			
VAs	2.096	1.555–2.825	< 0.001
Cardiac death	2.105	1.101–4.025	0.024
PR interval			
Univariate			
VAs	1.006	1.002–1.009	0.002
Cardiac death	1.007	1.000–1.014	0.062
Multivariate			
VAs	1.006	1.003–1.010	< 0.001
Heart rate			
Univariate			
VAs	1.019	1.006–1.032	0.004
Cardiac death	1.026	1.002–1.051	0.031
Multivariate			
VAs	1.018	1.006–1.031	0.004

VAs: ventricular arrhythmias.

remained an independent predictor of VAs (HR = 1.006, 95%CI = 1.003–1.010, $P < 0.001$) (Table 3).

4 Discussion

The significant findings of this analysis are summarized as follows: patients with a baseline PR/RR value of ≥ 18.5% exhibited a higher incidence of VAs and cardiac death independent of baseline PR intervals and RR intervals. Moreover, baseline heart rate is associated with a higher incidence of VAs and cardiac death. Finally, the baseline PR interval is a significant risk factor for VAs but not cardiac death.

The inverse correlation between heart rate and PR interval is widely recognized, with PR intervals shortening as heart rates increase.[12,13] Without rate adjustment, PR intervals decrease progressively, and the differences in rate-adjusted PR intervals are 10 ms or more at higher and lower heart rates.[14] Therefore, the significance of rate-adjusted PR intervals is evident. The PR interval was an independent risk factor for VAs and a borderline significant risk factor for cardiac death ($P = 0.062$) in this study. However, after adjusting for heart rate, the PR interval was associated with a high risk of both VAs and cardiac death. There are at least two possible explanations for the relationship between high PR/RR ratios and the prevalence of VAs and cardiac death.

First, this relationship may be associated with PR interval prolongation. Two large community-based studies (the Framingham Heart Study and the Atherosclerosis Risk in Community Study) both showed that PR interval prolongation was associated with increased risks of arrhythmic events and death.[5,15] Prolongation of the PR interval can be caused by an organic lesion or a functional disorder related to the autonomic nervous system, and it is associated with a number of factors that have been proven to be associated with VAs and cardiac death (including ischemic heart disease, AF, diabetes mellitus, conduction tissue fibrosis and autonomic tone) and may be a marker for increased ventricular fibrosis and scarring.[5,8] Recently, Chan, *et al*.[16] demonstrated that prolongation of the PR interval is associated with endothelial dysfunction, which has already been demonstrated as one of the mechanisms of ventricular tachycardia[17] and other cardiovascular events.

Second, the ratio of PR to RR intervals was calculated with baseline PR and RR intervals. The higher the ratio is, the longer the PR interval and/or the shorter the RR interval. however, when the heart rate is faster, the RR interval is shorter. This study found baseline heart rate to be a significant predictor of VAs and cardiac death, which is similar to previous findings. There have been several reports that increased heart rate is associated with increased risks of VAs, mortality, and heart failure hospitalization.[3,4,18] The mechanisms involved in include greater heart rate increases, vascular oxidative stress, decreased endothelial function restoration and autonomic nervous system dysregulation.[4] A disassociation between the PR interval and RR interval may be an indicator of autonomic dysfunction. In most cases, a prolonged PR interval is due to prolonged conduction in the AV node, which is profoundly influenced by the autonomic nervous system. Sympathetic nervous activation results in a decrease in PR intervals, whereas parasympathetic nerve activation results in an increase in PR intervals.[19] Shortened RR intervals reflect sympathetic activation and/or vagal withdrawal at the sino-atrial node level.[20] The dissociation between the PR interval and RR interval may be a novel marker of cardiac autonomic dysfunction and, thus, a novel independent predictor of VAs and cardiac death. There are several significant implications of these findings; specifically, unlike previous studies, we examine the predictive ability of rate-adjusted PR intervals. Moreover, PR/RR ≥ 18.5% at baseline can serve as a predictor of future VAs and cardiac death in ICD/CRT-D recipients. This novel marker may provide an opportunity to manage ICD patients at risk for cardiac events. In clinical practice, optimal medication is needed to control heart rate more strictly for these patients. Additionally, dual chamber pacemaker or CRT may be more suitable for patients who need ventricular pacing to shorten the AV interval by programming. Finally, this information will be helpful in screening patients at a high risk for cardiac events and may help clinicians refer high-risk primary prevention patients for ICD or CRT-D.

4.1 Study limitations

Our study has several limitations. First, we used a single 12-lead ECG, not an average of multiple ECGs or data from a 24-h Holter. Due to the absence of baseline Holter data, we did not assess the relationship between heart rate variability and PR/RR. Furthermore, both the RR and PR intervals have circadian variation and may change with time. Many potential unknown confounding factors may be unaddressed in this study. Finally, this study was retrospective. Thus, a prospective analysis with a longer observational period should be performed to validate the results.

4.2 Conclusions

A PR/RR ≥ 18.5% at baseline can serve as a predictor of future VAs and cardiac death in ICD/CRT-D recipients. This marker may provide an opportunity to manage ICD patients at risk for cardiac events, and it will be helpful in screening patients at a high risk for cardiac events.

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