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ORIGINAL ARTICLE

Prognostic Significance of PR Interval Prolongation in Adult Patients With Total Correction of Tetralogy of Fallot

Yoshitaka Kimura, MD
Koji Fukuda, MD, PhD
Makoto Nakano, MD, PhD
Yuhi Hasebe, MD, PhD
Kyoshiro Fukasawa, MD
Takahiko Chiba, MD
Keita Miki, MD
Shunsuke Tatebe, MD, PhD
Satoshi Miyata, PhD
Hideki Ota, MD, PhD
Masato Kimura, MD, PhD
Osamu Adachi, MD, PhD
Yoshikatsu Saiki, MD, PhD
Hiroaki Shimokawa, MD, PhD

BACKGROUND: Several studies have demonstrated the importance of mechanoelectrical interaction in patients with surgically corrected tetralogy of Fallot. However, the significance of atrioventricular conduction disturbance, that is PR interval prolongation, on adverse cardiac events in those patients remains to be elucidated.

METHODS: We examined electrocardiograms at baseline and their temporal change in a total of 176 patients with repaired tetralogy of Fallot (49% men; median age, 17.4 years). Then, we evaluated their correlation with right ventricular volume and function measured by cardiac magnetic resonance and the significance as a risk factor of adverse cardiac events: lethal ventricular arrhythmias, atrial arrhythmias, heart failure hospitalization, complete atrioventricular block (AVB), and all-cause death.

RESULTS: First-degree AVB was noted in 25 patients (14%). During a median follow-up of 10.0 (5.0–14.2) years, there was a progressive prolongation of PR interval (2.00±3.99 ms/y). Importantly, there were significant correlations between PR interval prolongation and right ventricular enlargement or right ventricular dysfunction. In contrast, in patients who underwent pulmonary valve replacement (n=23), significant shortening of PR interval by pulmonary valve replacement was noted (204±32 versus 176±34 ms; P=0.007). Cox regression analysis showed that first-degree AVB was an independent risk factor for lethal ventricular arrhythmias (hazard ratio, 5.479; 95% CI, 1.181–25.42; P=0.030) and complete AVB (hazard ratio, 27.67; 95% CI, 4.152–184.3; P<0.001) and had a tendency for heart failure hospitalization (hazard ratio, 3.301; 95% CI, 0.864–11.80; P=0.069). In addition, PR interval prolongation >2 ms/y was also a significant risk factor for lethal ventricular arrhythmias, regardless of the presence or absence of first-degree AVB at enrollment (hazard ratio, 24.18; 95% CI, 2.080–281.1; P=0.011).

CONCLUSIONS: These results indicate that progressive atrioventricular conduction disturbance is correlated with right ventricular enlargement and could be a useful predictor for increased risk of lethal ventricular arrhythmias in patients with repaired tetralogy of Fallot.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrioventricular block ■ electrocardiography ■ heart failure ■ sudden cardiac death ■ Tetralogy of Fallot ■ ventricular tachycardia

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WHAT IS KNOWN?

- Adult patients with repaired tetralogy of Fallot are at risk for various adverse cardiac events, including lethal ventricular arrhythmias and sudden cardiac death.
- Severe prolongation of QRS duration has been widely recognized as an important risk factor for lethal ventricular arrhythmias in tetralogy of Fallot, yet it has several limitations.
- PR interval prolongation on standard 12-lead ECG has been reported to be a risk factor for cardiac adverse outcomes in various populations, such as community-based cohorts, patients with ischemic heart disease, and those with heart failure.

WHAT THE STUDY ADDS?

- PR interval prolongation is significantly correlated with right ventricular end-diastolic and end-systolic volume enlargement and lower right ventricular ejection fraction in patients with tetralogy of Fallot.
- First-degree atrioventricular block and temporal prolongation of PR interval >2 ms/y are independent risk factors for lethal ventricular arrhythmias. Thus, more attention should be paid to the patients with PR interval prolongation.

Tetralogy of Fallot is one of the most common types of adult congenital heart disease.[1] Despite improved surgical techniques and subsequent survival, adult patients with repaired tetralogy of Fallot (rTOF) still remain at risk for lethal ventricular arrhythmias (LVAs) and sudden cardiac death.[2–4] Moreover, atrial arrhythmias,[4,5] atrioventricular block (AVB),[4] and heart failure (HF)[6] are also clinical problems because they can decrease quality of life and potentially lead to death.[4,6,7] Severe prolongation of QRS duration has been widely recognized as an important risk factor for LVAs in rTOF,[8–11] yet it has several limitations. First, the sensitivity of QRS duration >180 ms for mortality is low.[9,11] Second, QRS duration does not provide sufficient information about subsequent atrial arrhythmias or HF. Third, the prognostic significance of time-dependent changes in ECG parameters other than QRS duration has not been fully evaluated.[12]

Atrioventricular conduction disturbance is recognized as PR interval prolongation on standard 12-lead ECG. Recently, it has been reported to be a risk factor for cardiac adverse outcomes in various populations, such as community-based cohorts,[13] patients with ischemic heart disease,[14] and those with HF.[15] Moreover, we have previously reported that first-degree AVB is a risk factor of HF in patients with arrhythmogenic right ventricular (RV) cardiomyopathy.[16] In the present study, we thus examined whether first-degree AVB and temporal changes in ECG parameters could be risk factors for cardiac events in patients with rTOF.

METHODS

The present study was approved by the University of Tohoku Institutional Review Board (2016-1-833, 2017-1-795), and informed consent was waived. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

We retrospectively examined 176 consecutive patients with rTOF, including 19 patients with surgically corrected double-outlet RV with subaortic ventricular septal defect, who were followed up at the Tohoku University Hospital or the Miyagi Children's Hospital from March 1996 to June 2017 (49% men; median age, 17.4 years; median age at initial repair, 4.4 years). Eligibility criteria for participation in this study included (1) availability of at least 2 ECGs recorded postoperatively after 15 years of age and (2) no atrial fibrillation or ventricular pacing rhythm at enrollment. A total of 223 patients with rTOF were followed at our institution, and 47 patients were excluded from the present study according to these criteria; 20 were <15 years of age, 17 had no available ECG or transthoracic echocardiography, 4 were not in sinus rhythm (3 atrial fibrillation and 1 ventricular pacing rhythm), and 6 were lost during follow-up. The remaining 176 patients were finally included in the present study.

ECG

The standard 12-lead ECGs (25 mm/s, 10 mm/mV) were taken at least 2×; one closest to 15 years of age and the other at the latest follow-up. In patients who underwent pulmonary valve replacement (PVR) during the follow-up, we took 2 more ECGs: one just before PVR and the other, 3 months after PVR. The rhythm, rate, morphology, and duration of PR, QRS, and JT were analyzed. Durations of PR interval were measured in lead II or other limb leads if necessary, and PR interval was defined as the interval from the onset of P wave (junction between the T-P isoelectric line and the beginning of the P-wave deflection) to the end of PR segment (junction with the QRS complex).[13] First-degree AVB was defined as a PR interval of ≥200 ms. To increase the accuracy of measurements, ECGs were enlarged 2× and were measured with digital calipers. The intervals were measured in 3 consecutive beats in each lead, and the mean value of the 3 beats was used. Each measurement was performed by a single observer (Y.K.) and was validated by at least 2 other physicians (T.C., K.M., and M.N.), all of whom were electrophysiologists blinded to the clinical data. A difference in measurement of ≤10 ms was accepted for agreement. In case of discrepancy, agreement was reached by convention for final analyses.

Imaging Studies

Transthoracic echocardiography was performed in all patients at enrollment. Left ventricular (LV) dimension, LV

ejection fraction, RV dimension, valve malfunction, and residual shunt were assessed by transthoracic echocardiography. RV dilatation was defined as an RV end-diastolic basal dimension >42 mm.[17] Cardiac magnetic resonance (CMR) images were obtained at least once in 113 patients (64%) using the standard CMR protocols at our institution on a 1.5-T imager (Intera Achieva 1.5T Nova Dual; Philips Healthcare, Best, the Netherlands) with a 5-channel cardiac coil. Two reviewers, including one with 12-year experience of CMR imaging, evaluated CMR images through consensus reading. We traced the LV and RV endocardial contours in end-diastolic and end-systolic frames of stacks of short-axis slices using workstation dedicated for CMR evaluation (CMR42; Circle Cardiovascular Imaging, Inc, Calgary, Canada), and measured RV end-diastolic volume, RV end-systolic volume, and RV ejection fraction.

End Points

Follow-up duration was defined as the period between the initial and the last ECG. In patients who underwent PVR, the last follow-up day was defined as the day of the PVR procedure because PVR strongly affects ECG parameters.[18]

End points included LVAs, atrial arrhythmias, complete AVB, hospitalization for HF, and all-cause death. LVAs were defined as composite major arrhythmic events, including ventricular fibrillation, sustained ventricular tachycardia, and sudden cardiac death. Sudden cardiac death was defined as an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours.[19,20] Atrial arrhythmias were defined as the first composite atrial arrhythmic events, such as atrial fibrillation, atrial tachycardia, and atrial standstill during the follow-up period. Hospitalization for HF was defined as an unplanned hospitalization without following ventricular tachycardia/ventricular fibrillation episodes because of sudden or gradual onset of the signs or symptoms of New York Heart Association class 3 or 4 HF.

Statistical Analysis

Results are presented as mean (SD) or median (interquartile range) for continuous variables and as n (%) for categorical variables. Categorical differences between groups were evaluated by the χ^2 test or Fisher exact test when appropriate. Continuous variables were compared using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Changes in means were compared using the paired *t* test or the Wilcoxon signed-rank test. The box-and-whisker plots were used to display the numerical data through their 5-number summary (minimum, first quartile, median, third quartile, and maximum) of the distribution of the observations. The association between ECG measurement and RV volume or RV function was presented by scatterplots and analyzed by linear regression and correlation analysis. Subjects were censored at the time of their first event or the time of their last clinical follow-up. Survival distribution during the follow-up was calculated using Kaplan-Meier curves for LVAs, atrial arrhythmias, complete AVB, hospitalization for HF, or all-cause death as the end points. The effects of covariates on the time to each end point were investigated using a Cox proportional hazards model. The hazard ratio (HR) and 95% CIs are always shown. A significant *P* value of 0.05 from a univariable Cox model, age at enrollment, age at intracardiac repair (ICR), era of ICR, and medications were required for variables to be candidates for the multivariable model. The proportional hazards assumption of a Cox regression model was confirmed by Schoenfeld residuals test for non-zero slope in a scaled Schoenfeld residuals versus each covariate. A $P<0.05$ was considered to be statistically significant. All analyses were performed using JMP Pro 13.2.1 (SAS Institute, Inc, Cary, NC) and R, version 3.5.0.[21]

RESULTS

Baseline Patient Characteristics

The baseline clinical characteristics of the 176 patients with rTOF are shown in Table 1. About half of the patients (n=87; 49%) were men, and the median age at enrollment and the median age at initial repair was 17.4 (interquartile range, 15.6–27.2) and 4.4 (interquartile range, 2.8–6.2) years, respectively (Table 1). All patients were surgically corrected. The surgical techniques including RV outflow tract reconstruction were clearly documented in 163 patients (93%), whereas the exact technique remained unclear in 13 patients because operation notes were no longer available. LV ejection fraction was preserved (67.7±10.1%) in most of the patients, and RV dilatation (>42 mm in right ventricular diastolic dimension) was noted in 39 patients (22%). On standard 12-lead ECGs, the mean PR interval and QRS duration were 167.4±30.7 and 132.1±33.3 ms, respectively. In addition, at enrollment, first-degree AVB and QRS duration >180 ms were noted in 25 (14%) and 12 (7%) patients, respectively (Table 1).

Temporal Changes in ECG Parameters

A median follow-up period was 10.0 (interquartile range, 5.0–14.2) years. The follow-up ECG data and temporal changes in ECG parameters are summarized in Table 2. To improve the precision of the analysis of the temporal changes, 7 patients who were not followed up for >1 year were excluded in Table 2. At the latest follow-up, first-degree AVB was detected in 42 patients (24%), and QRS duration >180 ms was noted in additional 2 patients (Table 2). Annual prolongation of PR interval, QRS duration, and QTc interval was 2.00±3.99, 0.97±2.62, and 1.60±6.23 ms/y, respectively (Table 2).

Correlation Between ECG Parameters and RV Volume

We evaluated the correlation between the follow-up ECG parameters and RV volume assessed by CMR. Because CMR was not fully performed before 2006, we only analyzed a subgroup of 113 patients with rTOF

Table 1. Baseline Characteristics

n	176
Men	87 (49)
Age, y	17.4 (15.6–27.2)
Time from ICR, y	13.9 (12.2–20.4)
BSA, m^2	1.55±0.21
Characteristics of initial repair	
Age at ICR, y	4.4 (2.8–6.2)
Transannular patch	97 (55)
Nontransannular patch	30 (17)
RV-PA conduit	13 (7)
Pulmonary valvotomy or infundibular resection	23 (13)
Unknown	13 (7)
Previous palliation	
BT shunt	63 (36)
Others	9 (5)
None	104 (59)
TTE	
LVDd	43.1±5.9
LVDs	28.5±5.5
LVEF	67.7±10.1
RV dilatation	39 (22)
Moderate-to-severe TV regurgitation	63 (35)
Moderate-to-severe PV regurgitation	75 (43)
Residual VSD	20 (11)
ECG	
Hear rate, bpm	70±11
CRBBB	118 (68)
First-degree AVB	25 (14)
PR interval, ms	167.4±30.7
QRS duration, ms	132.1±33.3
QRS ≥180, ms	12 (7)
Fragmented QRS	93 (53)
QTc interval, ms	449.1±32.4

Results are expressed as n (%), mean±SD, or median (IQR). AVB indicates atrioventricular block; bpm, beats per minute; BSA, body surface area; BT, Blalock-Taussig; CRBBB, complete right bundle branch block; ICR, intracardiac repair; IQR, interquartile range; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PV, pulmonary valve; RV, right ventricle; TTE, transthoracic echocardiography; TV, tricuspid valve; and VSD, ventricular septal defect.

in whom both the follow-up ECG and CMR were performed at an interval of <1 year. ECG parameters at the latest follow-up are shown in Table 2 and CMR parameters in Table I in the Data Supplement. As shown in Figure 1, the prolongation of all 3 ECG parameters, PR interval, QRS duration, and QTc interval, was positively correlated with the increase in both RV end-diastolic volume index and RV end-systolic volume index and the decrease in RV ejection fraction by CMR.

Table 2. Follow-Up ECG Data and Temporal Change in ECG Parameters

Latest follow-up (all patients, n=176)	
CRBBB	127 (72)
First-degree AVB	42 (24)
PR interval, ms	180.8±33.3
QRS duration, ms	139.1±33.0
QRS ≥180, ms	14 (8)
QTc interval, ms	461.3±34.4
Change of ECG parameters (follow-up >1 y, n=169)	
ΔPR interval, ms	14.1±18.6
ΔPR per y, ms	2.00±3.99
ΔQRS duration, ms	7.41±15.24
ΔQRS per y, ms	0.97±2.62
ΔQTc interval, ms	12.47±29.52
ΔQTc per y, ms	1.60±6.23

Results are expressed as n (%) or mean±SD. AVB indicates atrioventricular block; and CRBBB, complete right bundle branch block.

Furthermore, we measured the changes in ECG parameters by PVR. Twenty-three patients underwent PVR during the follow-up. In 1 of the 23 patients, PR interval change could not be evaluated because of permanent atrial fibrillation rhythm before PVR, and in another patient, PR interval, QRS duration, and QTc interval were not evaluated because of persistent RV pacing by pacemaker after PVR. PR shortening by PVR was noted in 17 of 21 patients (81%), and a representative case is shown in Figure 2A. The degree of PR shortening by PVR was statistically significant (204±32 versus 176±34 ms; *P*=0.007), but there was no significant shortening in QRS duration or QTc interval (QRS duration, 166±26 versus 155±25 ms; *P*=0.143; QTc interval, 476±29 versus 496±29 ms; *P*=0.031; Figure 2B).

Clinical Characteristics and Prognosis of Patients With rTOF and First-Degree AVB

As a next step, we analyzed the clinical characteristics of the patients with first-degree AVB and its impact on their prognosis. We divided the patients with rTOF into 2 groups: patients with normal PR interval (PR, <200 ms) and those with first-degree AVB at enrollment. Their clinical characteristics are shown in Table 3. There was a predominance of male patients among those with first-degree AVB, whereas there was no significant sex difference in those without it. Age at enrollment was positively correlated with PR interval (R=0.38; *P*<0.01; Figure I in the Data Supplement), and the era of ICR was different between the 2 groups (Table 3; Figure II in the Data Supplement). Meanwhile, age at ICR and type of repair did not significantly differ between the 2 groups. Heart rate was comparable between the 2 groups

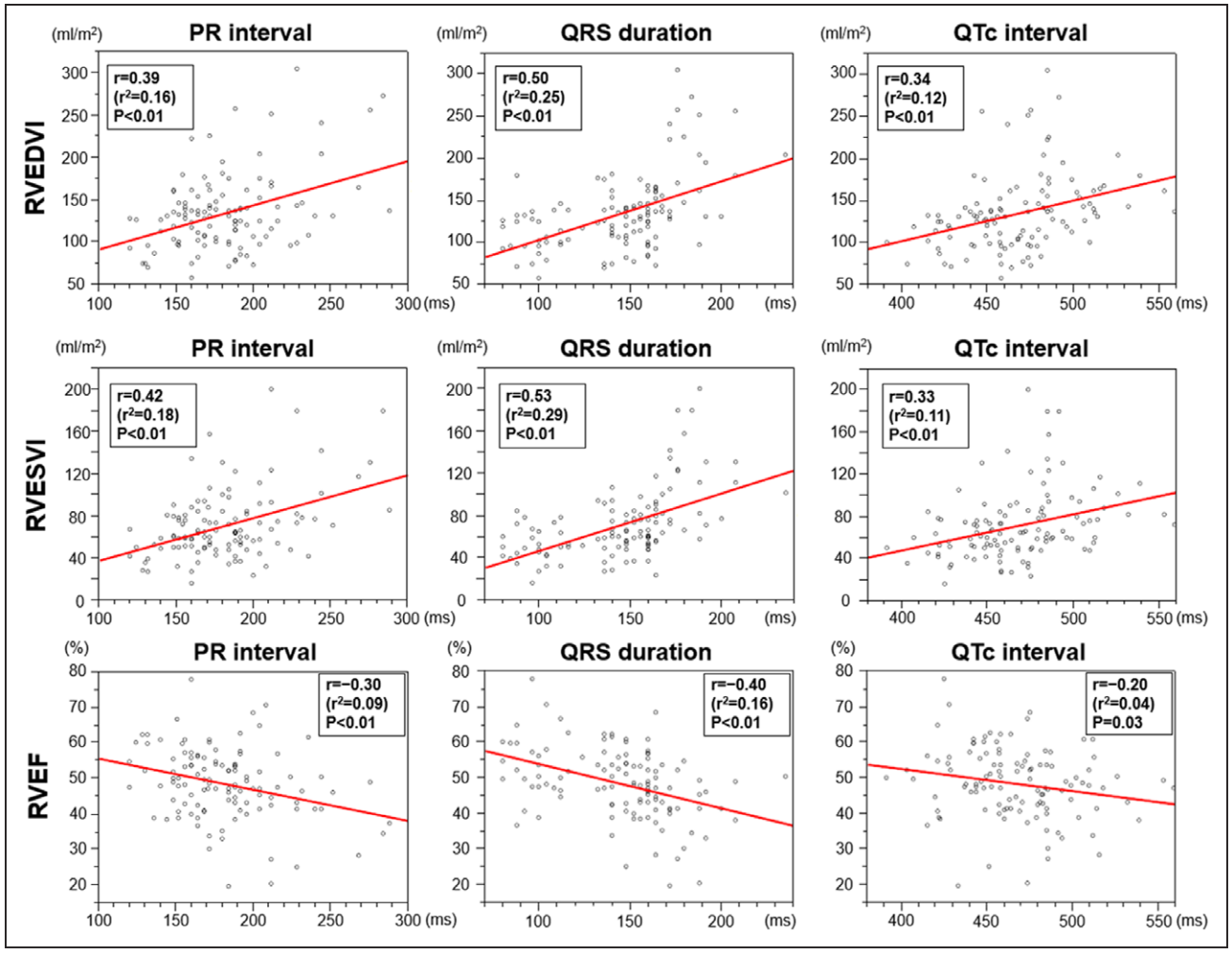

Figure 1. Correlation between ECG parameters and right ventricular volume and function.
All ECG parameters were positively associated with the increases in right ventricular end-diastolic volume index (RVEDVI; **A**) and right ventricular end-systolic volume index (RVESVI; **B**) and negatively associated with right ventricular ejection fraction (RVEF; **C**) by cardiac magnetic resonance.

(Table 3), and it was confirmed by linear regression and correlation analysis (Figure III in the Data Supplement). In terms of echocardiographic data, LV ejection fraction was similar, but RV dilatation and moderate-to-severe tricuspid valve regurgitation were more prevalent in patients with first-degree AVB. Moreover, as in the case of PR interval, QRS duration was also significantly longer in patients with first-degree AVB (153±33 versus 129±32 ms; *P*=0.0008), whereas there were not significant differences in the prevalence of complete right bundle branch block, fragmented QRS, and QTc interval (Table 3). In terms of medications, patients with first-degree AVB were more often treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and amiodarone at enrollment.

Nonpharmacological treatments and adverse clinical outcomes during the follow-up are summarized in Table 4. The follow-up period was comparable between both groups ([+] first-degree AVB, 9.7 years [3.4–14.6] versus [–] first-degree AVB, 10.0 years [5.4–14.1]; *P*=0.283). Patients with first-degree AVB more frequently underwent catheter ablation and device implantation compared with those without it.

During the follow-up, LVAs occurred in 13 patients (7%); 9 had ventricular tachycardia , 2 ventricular fibrillation, and 2 sudden cardiac death. Moreover, atrial arrhythmias and HF hospitalization were noted in 25 and 15 patients, respectively. Kaplan-Meier analysis revealed that patients with first-degree AVB had higher incidence rates of LVAs, atrial arrhythmias, HF hospitalization, complete AVB, and all-cause death compared with those without it (Figure IV in the Data Supplement).

Prognostic Factors of Cardiac Adverse Outcomes

We performed Cox regression analysis to identify the risk factors for cardiac adverse outcomes. We defined significant temporal prolongation of PR interval or QRS

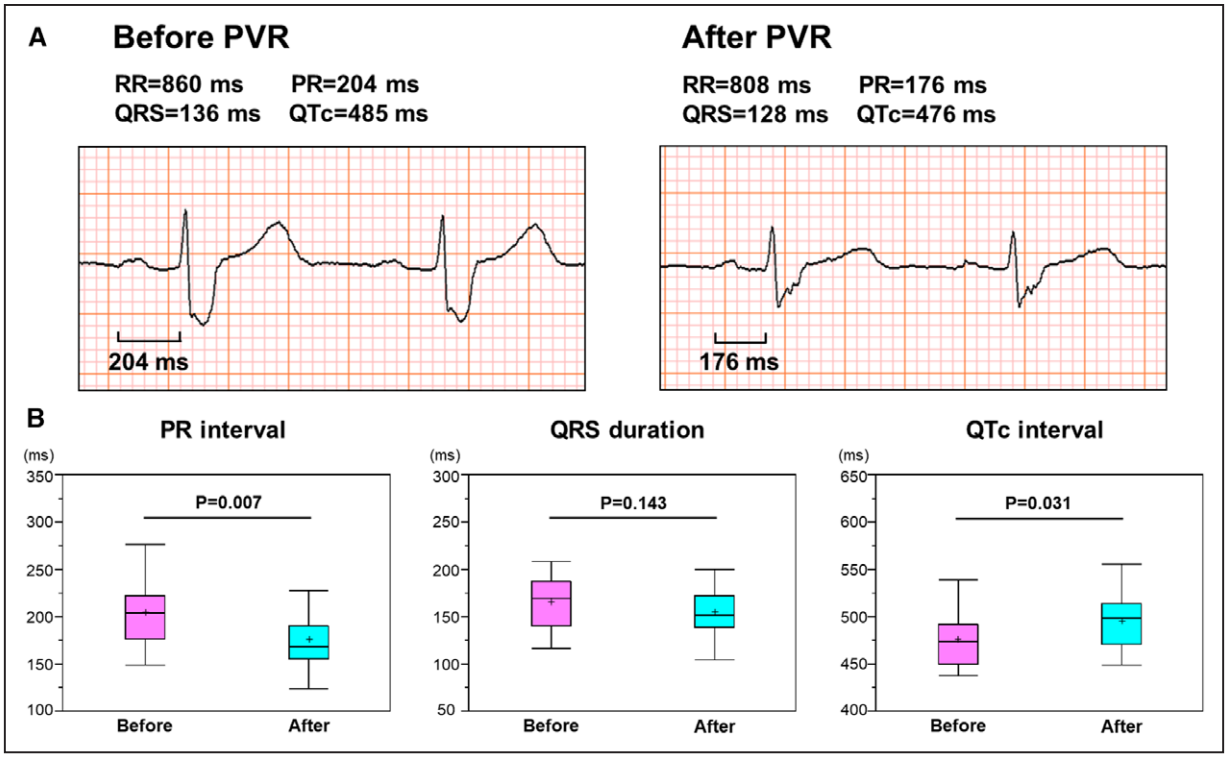

Figure 2. Changes in ECG parameters by pulmonary valve replacement (PVR).
A, A representative case is shown. PR interval was shortened by 28 ms by PVR, but QRS duration was only slightly shortened. **B**, The degree of PR shortening by PVR was statistically significant (**left**), but there was no significant shortening in QRS duration (**middle**) or QTc interval (**right**). The plus symbol in the box interior indicates the group mean.

duration as those exceeded their means (PR, ≥2 ms/y; QRS, ≥1 ms/y). The results of univariable analysis are shown in Table II in the Data Supplement. Multivariable analysis showed that first-degree AVB was an independent risk factor for LVAs (HR, 5.479; 95% CI, 1.181–25.42; *P*=0.030) and complete AVB (HR, 27.67; 95% CI, 4.152–184.3; *P*<0.001) and had a tendency for HF hospitalization (HR, 3.301; 95% CI, 0.864–11.80; *P*=0.069; Table 5). In addition, PR interval prolongation >2 ms/y was also a significant risk factor for LVAs, regardless of the presence or absence of first-degree AVB at enrollment (HR, 24.18; 95% CI, 2.080–281.1; *P*=0.011). The proportional hazards assumption was satisfied in terms of all significant covariates (Table III in the Data Supplement).

DISCUSSION

The novel findings of the present study are as follows: (1) ≈14% of the adult patients with rTOF had first-degree AVB; (2) temporal prolongation of PR interval was noted during the long-term follow-up; (3) PR interval was significantly correlated with RV volume and function assessed by CMR; (4) first-degree AVB was one of the significant risk factors for LVAs and complete AVB; and (5) temporal prolongation of PR interval >2 ms/y was one of the significant risk factors for LVAs. These findings could provide a new approach for estimating the long-term prognosis of patients with rTOF.

Temporal Changes in Electrical Parameters

Progressive RV enlargement because of chronic severe pulmonary regurgitation as a sequelae of surgical procedure and the benefit of its surgical repair by additional PVR are well documented in patients with rTOF.[22] Similarly, several studies have reported that QRS duration is gradually prolonged after ICR of tetralogy of Fallot and is conversely shortened by PVR.[12,18,23] In contrast, only 1 report described a temporal prolongation of PR interval.[12] The present study supported these findings, and to the best of our knowledge, this is the first report to demonstrate the association between the temporal prolongation of PR interval and long-term prognosis of the adult patients with rTOF. Moreover, temporal change in PR interval might be a more sensitive marker of malignant arrhythmias compared with that in QRS duration.

The present study may raise questions about the association between the timing of PR prolongation and subsequent cardiac events. It is considered that PR prolongation seen after ICR is the combined influence of

Table 3. Baseline Characteristics in Patients With and Those Without First-Degree AVB

	Normal PR Interval (n=151)	First-Degree AVB (n=25)	*P* Value
Men	69 (46)	18 (72)	0.018
Age, y	16.8 (15.5–25.5)	20.9 (16.5–46.7)	0.013
Time from ICR, y	13.8 (11.8–19.3)	15.2 (12.9–30.4)	0.027
BSA, m^2	1.55±0.21	1.57±0.22	0.676
Characteristics of initial repair			
Age at ICR, y	4.3 (2.7–6.0)	5.8 (3.5–10.5)	0.119
Era of ICR			0.009
1960s	5 (3)	3 (12)	
1970s	13 (9)	6 (24)	
1980s	51 (34)	9 (36)	
1990s	72 (48)	4 (16)	
2000s	10 (7)	3 (12)	
Transannular patch	83 (55)	14 (56)	0.635
Nontransannular patch	29 (19)	1 (4)	0.635
RV-PA conduit	11 (7)	2 (8)	0.635
Pulmonary valvotomy or infundibular resection	19 (13)	4 (16)	0.635
Unknown	9 (6)	4 (16)	0.635
Previous palliation			
BT shunt	55 (36)	8 (32)	0.664
Others	8 (5)	1 (4)	0.664
None	88 (58)	16 (64)	0.664
TTE			
LVDd	42.7±5.7	45.9±7.0	0.018
LVDs	28.2±5.0	30.9±7.6	0.029
LVEF	68.1±9.8	65.3±12.1	0.228
RV dilatation	28 (18)	11 (44)	0.083
Moderate-to-severe TV regurgitation	47 (31)	14 (56)	0.022
Moderate-to-severe PV regurgitation	60 (40)	15 (60)	0.080
Residual shunt	16 (11)	4 (16)	0.493
ECG at baseline			
Heart rate, bpm	70±11	69±11	0.649
CRBBB	99 (66)	19 (79)	0.245
PR interval, ms	158.8±21.6	219.4±25.7	<0.0001
QRS duration, ms	128.8±32.1	153.0±33.3	0.0008
QRS duration ≥180, ms	6 (4)	6 (25)	0.002
Fragmented QRS	76 (50)	17 (68)	0.101
QTc interval, ms	448.2±32.2	455.3±33.9	0.338
Medications			
β-Blockers	12 (8)	4 (16)	0.266
ACE inhibitors/ARBs	10 (7)	8 (32)	0.001
Antiarrhythmic drugs	8 (6)	4 (16)	0.084
Verapamil	1 (1)	0 (0)	1.000
Class I antiarrhythmic drugs	7 (5)	2 (8)	0.625
Amiodarone	0 (0)	2 (8)	0.022

Results are expressed as n (%) or mean±SD. ACE indicates angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; AVB, atrioventricular block; BSA, body surface area; bpm, beats per minute; BT, Blalock-Taussig shunt; CRBBB, complete right bundle branch block; ICR, intracardiac repair; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PV, pulmonary valve; RV, right ventricle; TTE, transthoracic echocardiography; and TV, tricuspid valve.

immediate lengthening because of surgical injury on the myocardium and late lengthening relating to right atrial/RV dilation. We cannot conclude whether early or late PR prolongation was more critical for the prognosis because we do not have sufficient data on the ECG soon after rTOF. However, our results indicate that the late prolongation of PR interval is clinically important in considering the risk of developing lethal arrhythmias in patients with rTOF (Table 5).

Table 4. Nonpharmacological Treatments and Adverse Clinical Outcomes in Patients With and Those Without First-Degree AVB During Follow-Up

	All (n=176)	Normal PR Interval (n=151)	First-Degree AVB (n=25)	*P* Value
Treatment				
Catheter ablation, VT	8 (4)	3 (2)	5 (20)	<0.01
Catheter ablation, AT	12 (7)	6 (4)	6 (24)	<0.01
Pacemaker/ICD/CRTD	7 (4)/1 (1)/1 (1)	3 (2)/1 (1)/0 (0)	4 (16)/0 (0)/1 (4)	<0.01
Outcome				
All-cause death	6 (3)	2 (1)	4 (16)	0.02
PVR	21 (12)	16 (11)	5 (20)	0.18
LVAs	13 (7)	4 (3)	9 (36)	<0.01
VT	9 (5)	3 (2)	6 (24)	
VF	2 (1)	1 (1)	1 (4)	
SCD	2 (1)	0 (0)	2 (8)	
AT	25 (14)	14 (9)	11 (44)	<0.01
Complete AVB	7 (4)	2 (1)	5 (20)	<0.01
HF hospitalization	15 (9)	7 (5)	8 (32)	<0.01

Results are expressed as n (%). AT indicates atrial tachyarrhythmias; AVB, atrioventricular block; CRTD, cardiac resynchronization therapy defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVA, lethal ventricular arrhythmia; PVR, pulmonary valve replacement; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 5. Multivariable Cox Regression Analysis

	LVAs			Atrial Arrhythmias			Hospitalization for HF			Complete AVB		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Men	2.963	0.516–17.01	0.223									
Age at enrollment, y	1.197	0.936–1.530	0.152	1.118	0.951–1.310	0.172	1.061	0.940–1.212	0.363	0.996	0.860–1.154	0.961
Age at ICR, y	0.863	0.670–1.113	0.256	0.905	0.777–1.060	0.211	1.029	0.903–1.170	0.662	0.800	0.563–1.136	0.212
Year of ICR, y*	1.194	0.947–1.505	0.134	1.127	0.968–1.310	0.123	0.938	0.831–1.061	0.300	1.034	0.913–1.171	0.596
Palliation												
LVDd (1-mm increase)				0.986	0.899–1.078	0.760	0.925	0.811–1.049	0.232			
RV dilatation	0.749	0.127–4.430	0.750									
Moderate-to-severe TVR				1.465	0.441–4.778	0.524	4.858	1.096–28.04	0.037			
CRBBB				1.314	0.359–6.275	0.694						
First-degree AVB	5.479	1.181–25.42	0.030	2.727	0.676–9.944	0.153	3.301	0.864–11.80	0.069	27.67	4.152–184.3	<0.001
ΔPR ≥2 ms/y	24.18	2.080–281.1	0.011									
QRS ≥180 ms	2.017	0.268–15.20	0.496	1.857	0.357–8.133	0.446						
Antiarrhythmic drugs	4.587	0.629–33.47	0.133	4.838	1.479–16.30	0.009	0.111	0.001–0.789	0.025	Infinity	0.000 to infinity	0.998
ACE inhibitors/ARBs	1.357	0.216–8.524	0.745	3.724	0.999–13.36	0.051	3.452	0.886–12.55	0.073	8.865	1.458–53.90	0.018
β-Blockers	0.760	0.054–10.71	0.839	2.879	0.768–10.35	0.115	0.583	0.070–3.396	0.573	8.993	0.577–140.1	0.117

ACE indicates angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; AVB, atrioventricular block; CRBBB, complete right bundle branch block; HF, heart failure; HR, hazard ratio; ICR, intracardiac repair; LVA, lethal ventricular arrhythmia; LVDd, left ventricular diastolic dimension; RV, right ventricle; and TVR, tricuspid valve regurgitation.

*Reference year 1990.

Prognostic Electrophysiological Markers in Patients With rTOF

QRS prolongation >180 ms is a conventional simple marker for adverse outcomes in patients with rTOF.[10] In contrast, Bokma et al[24] recently reported that its sensitivity for mortality was only 28% and that fragmented QRS was rather superior to QRS prolongation in predicting mortality. However, several studies showed negative results of fragmented QRS for diagnosis and prognosis of various cardiac diseases.[25–27]

In the present study, first-degree AVB in patients with rTOF was the significant predictor for LVAs, and QRS duration or fragmented QRS was not a significant prognostic factor (Table 5; Table II in the Data Supplement). Although QRS prolongation >180 ms was also significantly associated with LVAs (HR, 8.300; 95% CI, 2.450–26.09; *P*<0.001; Table II in the Data Supplement, LVAs) in the univariable analysis, multivariable analysis revealed that first-degree AVB could be more sensitive marker for LVAs. The reason for the present negative findings for fragmented QRS in predicting cardiac adverse events is unclear. More detailed characterization may elucidate the prognostic value of fragmented QRS in patients with rTOF.

Conversely, in multivariable Cox regression analysis, first-degree AVB was not a significant predictor of other outcomes, namely, atrial arrhythmias, HF hospitalization, and all-cause death. However, it had a high tendency for atrial arrhythmias and HF hospitalization. In addition, for all-cause death, we were unable to obtain reliable data in multivariable Cox regression analysis because of the small event number of cases (n=6). Therefore, a larger sample size is needed to clarify the relationship between first-degree AVB and these adverse outcomes.

Proposed Mechanism of Adverse Cardiac Events in Patients With rTOF With First-Degree AVB

Previous reports did not fully address whether PR interval prolongation is the cause of worse outcomes or merely the result of right atrium (RA) and RV dysfunction. In the present study, we demonstrated that patients with first-degree AVB had more severe phenotypes at baseline (Table 3). They were older compared with those without first-degree AVB. Moreover, other clinical parameters, such as RV dilatation, significant tricuspid valve regurgitation, and QRS widening, were more frequently noted in patients with first-degree AVB. These findings indicate that patients with first-degree AVB already had both electrical and mechanical abnormalities at baseline, suggesting that first-degree AVB was the result of the prognosis.

Meanwhile, we speculate that PR prolongation may also be the cause of worse outcomes. We were able to demonstrate that first-degree AVB at enrollment was an independent risk factor for LVAs, atrial arrhythmias, and all-cause death in multivariable analysis, even after adjusting for patients' age and other clinically significant parameters. There are several possible explanations for the close association between the presence of first-degree AVB and adverse cardiac events in patients with rTOF.

First, PR prolongation may have negative hemodynamic effects, such as shortening of blood filling time[28–30] and diastolic atrioventricular valve regurgitation.[31–33] In a subset of patients, the onset of atrial depolarization occurs immediately after the previous ventricular contraction, resulting in the shortening of blood filling time to the ventricle.[28–30] This could adversely affect RV and RA filling pressure, leading to RA and RV volume overload. Moreover, previous studies reported that in diastolic atrioventricular valves, both mitral and tricuspid valves, regurgitation is common in patients with AVB, regardless of their severity.[31–33] They occur in the setting of inappropriate atrioventricular coupling when the atrium contracts early after ventricular contraction, resulting in a prolonged LV filling period; it increases LV pressure toward end-diastole, despite a lower left atrial pressure.[31,33] The regurgitant volume is thought to be small and clinically insignificant in patients without structural heart disease.[32] Meanwhile, it may have significant effects on patients with RV or tricuspid valve annulus dilation, such as rTOF. Namely, diastolic tricuspid valve regurgitation can also induce RA and RV volume overload, leading to RA and RV remodeling. Consequently, first-degree AVB can cause both atrial and ventricular arrhythmogenesis.

Another possible mechanism is an effect of RV pacing because RV pacing may worsen RV function.[34] As shown in Figure IVD in the Data Supplement, the incidence of progression to complete AVB was higher in patients with first-degree AVB compared with those without it. As a result, the rate of pacemaker implantation was significantly higher in patients with first-degree AVB (Table 4). Thus, in patients with rTOF, we thought that first-degree atrioventricular block probably has 2 aspects: a precipitating factor of RV dysfunction and a general marker of a more severe phenotype. Furthermore, we need to demonstrate a positive efficacy of intervention to the first-degree AVB (eg, His pacing) to conclude its causative role.

Clinical Implications

Cardiac magnetic resonance imaging is a gold standard method for evaluation of cardiac function, although it is expensive for routine use when considering the long life of patients with rTOF. The present study showed that PR interval was significantly correlated with RV volume and function assessed by CMR. ECG parameters could be used as an index of RV function in patients with rTOF at routine follow-up. In addition, the presence of first-degree AVB increased LVAs and complete AVB in adult patients with rTOF. Moreover, PR interval prolongation >2 ms/y was also one of the risk factors for subsequent LVAs, regardless of the presence or absence of first-degree AVB at enrollment. Thus, more attention should be paid to the patients with PR interval prolongation in addition to other traditional markers, such as QRS widening.

Study Limitations

Several limitations should be mentioned for the present study. First, the present study is a retrospective cohort study. The patient characteristics, the type of initial surgery, and the indication of PVR may reflect referral bias and institutional preferences. In addition, many changes in therapy took place for each patient, and we were unable to evaluate the impact of changes in medications during the follow-up. Second, we did not have complete information on initial repair surgery in 14 (8%) patients, and CMR imaging was performed only in 113 (63%) patients. Third, there were significant differences in the backgrounds of patients with and those without first-degree AVB (Table 3). Thus, we should take into account the differences in baseline characteristics on the risk of the cardiac events. However, we consider that first-degree AVB is an independent risk factor for LVAs and complete AVB in patients with rTOF because it was one of the significant parameters on multivariable Cox regression analysis.

In conclusion, first-degree AVB, which is correlated with RV enlargement in adult patients with rTOF, could be a useful predictor for increased risk of LVAs and complete AVB in those patients. Besides, PR interval prolongation >2 ms/y could be also one of the risk factors for subsequent LVAs, regardless of the presence or absence of first-degree AVB.

ARTICLE INFORMATION

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Correspondence

Koji Fukuda, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980–8574, Japan. Email fukuda@cardio.med.tohoku.ac.jp

Affiliations

Department of Cardiovascular Medicine (Y.K., K. Fukuda, M.N., Y.H., K. Fukasawa, T.C., K.M., S.T., H.S.), Department of Evidence-Based Cardiovascular

Medicine (S.M., H.S.), Department of Diagnostic Radiology (H.O.), Department of Pediatrics (M.K.), and Department of Cardiovascular Surgery (O.A., Y.S.), Tohoku University Graduate School of Medicine, Sendai, Japan.

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Disclosures

None.

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