Is the QRS duration useful for determining the optimal timing of pulmonary valve replacement after tetralogy of Fallot repair?

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Abstract

In pulmonary valve replacement (PVR) after tetralogy of Fallot (TOF) repair, it is recommended that PVR be performed before the right ventricular end-diastolic volume index (RVEDVI) reaches 170 ml/m^2 on cardiac magnetic resonance imaging (cMRI) to normalize the RV volume after PVR. We examined the utility of QRS duration, cardiothoracic ratio (CTR), and plasma brain natriuretic peptide (BNP) as markers of an enlarged RV volume to perform PVR at the optimal timing. We assessed the correlation of QRS duration, CTR, and BNP with RVEDVI and RVESVI on cMRI in 26 patients after TOF repair. Fifteen patients underwent PVR (age, 45.2 ± 11.4 years). The RV volume changes from before to after PVR were investigated. Twelve patients underwent post-PVR cMRI. QRS duration, BNP, and CTR were positively correlated with RVEDVI and RVESVI after TOF repair. The post-PVR QRS duration was also positively correlated with post-PVR RVEDVI ($p = 0.017$) and RVESVI ($p = 0.001$). From before to after PVR, in cases with QRS duration ≤ 160 ms, the QRS duration decreased from 110.4 ± 28.9 to 101.8 ± 30.5 ms ($p = 0.063$). Both RVEDVI and RVESVI decreased to the normal range in 4 of 5 cases. In contrast, in cases with QRS duration > 160 ms, the QRS duration decreased from 183.0 ± 17.4 to 160.3 ± 23.8 ms ($p = 0.013$); however, RVESVI did not normalize in 6 of 7 cases. A prolonged QRS duration is a useful marker of RVEDVI and RVESVI enlargement after TOF repair. A QRS duration of 160 ms is a sensitive cutoff value for predicting RV volume normalization after PVR.

Introduction

An increasing number of adult patients experience pulmonary regurgitation (PR) after tetralogy of Fallot (TOF) repair, and the resultant chronic volume overload can lead to right ventricular (RV) dilation, biventricular dysfunction, supraventricular or ventricular arrhythmias, and sudden death [1–3]. PVR should be performed while RV enlargement and functional deterioration are reversible. Many studies suggest the optimal timing of PVR in terms of the threshold of the preoperative RV end-diastolic volume index (RVEDVI) or RV end-systolic volume index (RVESVI) by cardiac magnetic resonance imaging (cMRI) for RV normalization after PVR [4–8]. Therrien et al. recommended that PVR be performed before RVEDVI reached 170 ml/m^2 or RVESVI reached 85 ml/m^2 to normalize the RV volume after PVR [4]. We investigated whether three parameters, the resting electrocardiogram (ECG) QRS duration, cardiothoracic ratio (CTR), and plasma brain natriuretic peptide (BNP) level, could be used as indicators of the appropriate timing of cMRI to assess the RV volume and function before PVR.

Methods

The present study included 26 patients who received TOF repair and who underwent cMRI between August 2013 and November 2019 at 38.9±14.0 years of age (range, 15.5-67.8 years) to consider PVR. Fifteen of the 26 patients underwent PVR between April 2016 and September 2020. The mean age at PVR was 43.1±11.4 years (range, 29.5-69.2 years), the mean interval after TOF repair was 37.6±9.2 years (range, 24.8–52.2 years), and the mean body weight at PVR was 71.5±32.5 kg (range, 40.4–168 kg). The mean age at TOF repair was 5.0±3.8 years (range, 0.8-17.0 years). Twenty-one cases were reconstructed

with a transannular monocusp patch and 5 cases received a pulmonary valve sparing procedure. Post-PVR cMRI was performed in 12 of 15 patients after PVR at a mean of 2.1±1.3 years (range, 0.6–4.1 years) after PVR (Table 1).

We considered PVR when RVEDVI assessed by cMRI approached approximately 160 ml/m^2.

The Institutional Review Board of Ehime University Hospital approved this retrospective study and waived individual informed consent. Data were obtained by review of medical records.

We assessed the correlation of QRS duration of resting 12-lead ECG, CTR on chest radiography, and plasma BNP level with RVEDVI, RVESVI, and RVEF on cMRI in 26 patients who had received TOF repair. We also assessed the correlation of the post-PVR QRS duration, CTR, and plasma BNP level with post-PVR RVEDVI, RVESVI, and RVEF on cMRI in 12 patients who received cMRI after PVR. Changes of the QRS duration, RVEDVI, RVESVI and RVEF before and after PVR were also investigated.

QRS duration

Electrocardiography was analyzed automatically using the ECAPS12C ECG program (NIHONKODEN, Tokyo, Japan). Standard (speed, 25 mm/s and 1 mV/cm standardization) resting 12-lead ECG was used. The QRS duration was defined as the maximal QRS length in any lead from the first inflection to the final sharp vector changing to gentle inclination.

BNP

Venous blood was withdrawn and immediately sent for centrifugation. The plasma BNP level was determined by chemiluminescent immunoassay (CLIA) with BNP-JP□Abbott reagent (Abbott Japan, Matsudo, Japan) within 4 hours after blood sampling under room temperature.

Cardiac MRI

All cMRI examinations were performed using a clinical 3 T MR scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). True fast imaging with steady state precession (true FISP) was used for the retrospective ECG-gated cine cMRI scans of all participants. Short-axis cine cMRI were obtained in a stack of eight contiguous slices spanning the entire ventricle from the base to the apex. The imaging parameters were as follows: repetition time, 36.6 msec; echo time, 1.4 msec; flip angle, 50°; section thickness, 6mm; field-of-view, 312×384 mm; and voxel size, 0.9×0.9×6 mm.

For quantitative measurements, the stack of eight contiguous short-axis slices of cine cMRI was assessed using a dedicated software package (SYNAPSE VINCENT; Fujifilm Corp., Ltd, Tokyo, Japan).

The epicardial and endocardial contours were automatically traced on short-axis images. Contours rendered by the automated analysis were reviewed and manually corrected, as necessary.

PVR

PVR was performed through median repeat sternotomy using standard cardiopulmonary bypass. We performed PVR on beating, in cases without concomitant mitiral valve plasty or a left atrial Maze procedure. The concomitant procedures are shown in Table 1. The bioprosthetic valves included INSPIRIS RESILIA (size, 21-27 mm; Edwards Lifesciences Corporation, California, USA) in 8 cases, Carpentier-Edwards PERIMOUNT (size, 25 mm; CEP, Edwards Lifesciences Corporation, California, USA) in 3 cases, CEP Magna Ease (size, 23–25 mm) in 3 cases, and Mosaic (size, 25 mm; Medtronic, Dublin, Ireland) in 1 case.

Statistical Analysis

The data were expressed as the mean and standard deviation with range. Differences between parameters before and after surgery were analyzed using a paired Student's t test. The association between 2 continuous variables was assessed by a linear regression analysis. As plasma BNP levels showed a skewed distribution, logarithmically transformed BNP values were used in correlation and regression analyses. P values of <0.05 were considered statistically significant.

Results

Parameters correlated with RV volume or RVEF after TOF repair

In all 26 cases, the QRS duration, log BNP, and CTR showed good positive correlations with RVEDVI and RVESVI after TOF repair (Fig. 1, Table 2). The QRS duration and log BNP also showed a good negative correlation with RVEF (r=0.56, p=0.003; r=0.55, p=0.003, respectively, Fig. 2, Table 2) long after TOF repair.

Parameters correlated with RV volume or RVEF after PVR

In 12 cases in which cMRI was performed after PVR, the post-PVR QRS duration also showed a good positive correlation with post-PVR RVEDVI and RVESVI (r=0.67, p=0.017; r=0.81, p=0.001, respectively, Table 3). The post-PVR log BNP showed a good positive correlation with post-PVR RVEDVI (r=0.64, p=0.025; r=0.47, p=0.13, respectively). Post-PVR CTR did not show any correlation with post-PVR RVEDVI or RVESVI (r=0.40, p=0.20; r=0.34, p=0.27, respectively). The post-PVR QRS duration, log BNP, and CTR did not show any correlation with post-PVR RVEF (Table 3).

Parameter changes before and after PVR related to QRS duration

In our data, the correlation between RVEDVI (X) and QRS duration (Y) was demonstrated by the following regression equation: Y = 0.42X + 85.0 (Fig. 1A). Therrien et al. reported that the cutoff value of RVEDVI for RV normalization after PVR 170 ml/m^2 [4]. This cutoff value was applied to our regression equation (QRS duration: 157 ms [Y]).

We found that a standard QRS duration of >160 ms after TOF repair could identify patients with RVEDVI >170 ml/m^2 with 88.9% sensitivity and 70.6% specificity, and patients of RVESVI >85 ml/m^2 with 91.7% sensitivity and 85.7% specificity.

According to the QRS duration, we divided the patients into the W group (QRS duration >160 ms) and the N group (QRS duration ≤ 160ms).

Post-PVR cMRI was performed in 7 of 9 patients in the W group, and 5 of 6 patients in the N group. Parameters before and after PVR were compered in these 12 cases (N group, n=5; W group, n=7).

From before to after PVR, the QRS duration decreased from 110.4±28.9 to 101.8±30.5 ms in all 5 cases in the N group (p=0.063), and the QRS duration decreased from 183.0±17.4 to 160.3 ±23.8 ms in all 7 cases but 1 in the W group (p =0.013, Fig. 4A).

In the N group, RVEDVI decreased from 136.9±58.5 to 76.7±23.4 ml/m^2 (p=0.076), normalized (<108ml/m^2) in all 5 cases after PVR, whereas in the W group, RVEDVI decreased from 188.0 ± 50.1 to 112.4 ± 44.7 ml/m^2 (p<0.001), normalized in 4 of 7 cases (Fig. 4B).

In the N group, RVESVI decreased from 71.6±27.1 to 43.2±15.6 ml/m^2 (p=0.081), normalized (<47 ml/m^2) in 4 of 5 cases after PVR. However, in the W group, RVESVI did not normalize in 6 of 7 cases, in spite of decreasing from 132.6±48.3 to 71.3±24.7 ml/m^2 (p=0.003, Fig. 4C).

RVEF did not change significantly from before to after PVR in either the N group (from 43.2 ± 8.0% to 43.7 ± 8.5%, p=0.93) or the W group (from 30.9±9.6% to 34.9±9.6%, p=0.51, Fig. 4D). In the N group, the post-PVR RVEF was >40% in 4 of 5 cases, whereas in the W group, it was <40% in 6 of 7 cases.

QRS duration changes and RVEDVI changes after TOF repair

The QRS duration changed simultaneously with the RVEDVI in each case after TOF repair. The QRS duration of TAP cases tended to be wider in comparison to pulmonary valve sparing cases in each generation after TOF repair. In Figure 5, the dashed line indicates the PSR cases with an RVOT pressure gradient of ≥25 mmHg; the QRS duration of PSR cases was larger than that of PR cases. However, most

PSR cases were older than the other cases of PR, the influence of RVOT stenosis was not obvious (Fig. 5).

Discussion

It is not practical to perform frequent cMRI to determine the optimal timing of PVR to normalize the RV volume and prevent RV dysfunction in patients after TOF repair. We considered it ideal that parameters measured in the daily clinical setting can indicate the optimal timing of cMRI as the gold standard for the evaluation of the RV volume and function.

In chronic PR, the RV systolic function is initially preserved, and many cases remain relatively free of symptoms. Once the compensatory mechanisms cannot be maintained, the RV mass-to-volume ratio decreases, then the RVESV increases, RVEF decreases, and patients finally fall into RV dysfunction. The RV dysfunction is also associated with RV wall stress due to RV afterload from RVOT obstruction, RV fibrosis, RVOT aneurysm at the site of transannular patch, an impaired RV diastolic function, and left ventricular (LV) dysfunction [1–3, 9–11] .

In order to increase the chances for the patient to reach a normal RV volume after the repair, Therrien et al. recommended PVR be undertaken before the RVEDVI reaches 170 ml/m^2 or the RVESVI reaches 85 ml/m^2 [4]. PVR is recommended to be performed under the condition that the RVEDVI is <160-170 ml/m^2 and the RVESVI is <80-90 ml/m^2, as thresholds for the normalization of the RV volume after PVR [4–8].

In this study, each resting QRS duration, plasma BNP level, and CTR demonstrated good positive correlations with RVEDVI and RVESVI long after TOF repair. The QRS duration and plasma BNP level also showed good negative correlations with RVEF long after TOF repair. Many studies have reported that the resting QRS duration reflects progressive RV dilatation (increased RVEDVI and RVESVI), and RVEDVI or RVESVI have been reported to be correlated with the RVEF [1, 6, 11–13].

Some studies reported that BNP and NT-pro BNP reflected the RVEDVI and RVEF of patients after TOF repair [14, 15]. In present study, the plasma BNP level was also correlated with the RV volume in patients after TOF repair. However, the use of the plasma BNP level for the estimation of RV volume during outpatient follow-up was thought to be complex as it requires logarithmic transformation. Moreover, Eindhoven et al. reported that NT-pro BNP was correlated with the systolic RV function, but more strongly correlated with the systolic LV function and dimensions. They said that the likelihood that NT-pro BNP will be released from the right ventricle is generally lower in comparison to left ventricle [16].

In the present study, only the post-PVR QRS duration showed good correlations with both post-PVR RVEDVI and RVESVI. This indicates that the QRS duration is a good marker of the RV volume both before and after PVR in patients after TOF repair [13].

In their report of 26 cases, Huysduynen et al. noted that the change in the QRS duration (ΔQRS duration) from before to after PVR is also correlated with the change in RVEDVI (ΔRVEDVI). They considered that

RV dilatation may increase the QRS duration by increasing the distance that the electrical activation front has to move in the right ventricle, and they considered that the relationship between RVEDVI and the QRS duration also applies to the ΔRVEDVI and the ΔQRS duration before and after PVR [17].

The positive correlation between RVEDVI and the QRS duration in our data yielded a cutoff value of the QRS duration of 160 ms when RVEDVI 170 ml/m^2 was used as the threshold for RV normalization by Therrien et al.. QRS duration >160 ms could detect patients with RVEDVI >170ml/m^2 and RVESVI >85 ml/m^2 with high sensitivity and high specificity.

In the present study, both RVEDVI and RVESVI normalized after PVR in most patients (RVEDVI, all 5 patients; RVESVI, 4 of 5 patients) in the N group, although RVESVI did not normalize in 6 of 7 patients in the W group. Because RVESVI has been reported to have a better relationship with RVEF than RVEDVI [1, 6, 12], our results are considered to have clinical significance. The post-PVR RVEF was maintained at >40% in 4 of 5 patients in the N group; however, the post-PVR RVEF was maintained at <40% in 6 of the 7 patients in the W group.

Geva et al. also used a cutoff value of QRS duration of ≥160 ms to predict persistent post-PVR RV dilatation and dysfunction, and suggested that a QRS duration of <140 ms was associated with a normal RV size and function after PVR [8]. Cocomello et al. reported that patients with a QRS duration approaching 160 ms or those with RVEDVI ≥ 166 ml/m^2 or RVESVI ≥ 89 ml/m^2 should be considered for PVR to prevent a gradual increase of RV volume after PVR [18]. These 2 studies support the validity of our results regarding the cutoff value of QRS duration (160 ms) after TOF repair.

Scherptong et al. reported that a severely prolonged QRS duration (>180ms) was associated with an increased incidence of adverse outcomes, and PVR should be performed before severe QRS prolongation occurrs [19].

Romeo et al. reported that the QRS duration could be used as a biomarker for RV volumetric and functional change, and as a risk factor for late adverse outcomes, and that if PVR can be performed early enough to prevent the progression of QRS prolongation, it may reduce the incidence of adverse events after PVR [20].

Regarding the question of whether the QRS duration can be used as a preoperative assessment of the RV volume in outpatients after TOF repair, there was a tendency for the QRS duration to change simultaneously with the RV volume in each case after surgery, although this was only observed in a small number of cases. In other words, RVEDVI increased in patients with a prolonged QRS, while RVEDVI did not change in patients with a steady QRS duration (Fig. 5). Such a change in QRS is essential for the continuous use of the QRS duration as an indicator of RV volume progression long after TOF repair. To the best of our knowledge, limited studies have focused on the QRS duration as an indication for PVR for RV enlargement due to PR [8,18].

Considering additional factors of QRS prolongation, right bundle branch block (RBBB) due to RV infundibular resection or RVOT incision in TOF repair influences the QRS prolongation. In this study, the QRS duration of TAP cases tended to be wider than that of pulmonary valve sparing cases in each generation after TOF repair (Fig. 5). In our study, 14 of the 15 PVR cases (the one exception had a narrow QRS duration of 92 ms) showed RBBB before PVR. RBBB due to infundibular resection will progress with RV dilatation from PR after TOF repair.

The QRS duration was a useful marker of the RV volume and RVEF; however, this study lacked sufficient power to determine whether the QRS duration can be used directly as a threshold to predict RV normalization after PVR. After TOF repair, we recommend that cMRI to evaluate the RV volume for the optimal timing of PVR be performed before the QRS duration reaches 160 ms.

Limitations

The present study was associated with some limitations, including its retrospective and monocentric design. The relatively small number of patients in this study resulted in a loss of statistical power. Not all patients could perform cMRI more than once after TOF repair, and a cMRI volume study could not be performed in all PVR patients. Our study requires validation by a further study of a larger population.

Conclusion

A prolonged QRS duration is a useful marker of the enlargement of RVEDVI and RVESVI. A QRS duration of 160 ms is a sensitive cutoff value for RV volume normalization after PVR. A QRS duration of 160 ms is a useful, simple, and non-invasive indicator of the RV volume, which may be used to determine the optimal timing of PVR.

Declarations

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This research was conducted independently without funding.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Ethics approval

This research was conducted after institutional ethical committee approval.

Author contributions

Conceptualization: JS, SU; Methodology: JS; Data collection: JS, AK, YA, HT, TH; Formal analysis and investigation: JS; Writing – original draft preparation: JS, MN; Writing – review and editing: JS, SU; Supervision: SU, TH, HI.

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Tables

Table 1 Patient and surgical characteristics

Variables	(n=26)
Male/female (n)	19/7
Age at TOF repair (y)	5.0±3.8
Type of RVOT reconstruction	
Transannular patch	21
Pulmonary valve sparing	5
Patients who received PVR (n)	15
Age at PVR (y, n=15)	43.1±11.4
Interval from TOF repair to PVR (y, n=15)	37.6 ± 9.2
Concomitant procedures	
Tricuspid valve plasty or ring annuloplasty (n)	12
Cryoablation to RVOT (n)	3
LA Maze procedure (n)	2
Mitral valve plasty or ring annuloplasty (n)	2
Pulmonary artery angioplasty (n)	1
RVEDVI (ml/m^2)	145.9±53.9
RVESVI (ml/m^2)	93.1±45.0
RVEF (%)	39.3±10.1
PR fraction (%)	48.1±20.4
QRS duration (ms)	149.7±39.4
CTR (%)	58.0±7.4
BNP (pg/ml)	64.4±76.1

TOF tetralogy of Fallot, *RVOT* right ventricular outflow tract, *PVR* pulmonary valve replacement, *LA* left atrium, *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *RVEF* right ventricular ejection fraction, *PR* pulmonary regurgitation, *CTR* cardiothoracic ratio, *BNP* brain natriuretic peptide

Table 2

Linear regression among QRS duration, BNP, CTR after TOF repair and the cardiac function

	RVEDVI (n=26)		RVESVI (n=26)		RVEF (n=26)	
	r	p value	r	p value	r	p value
QRS duration	0.58	0.009	0.69	<0.001	-0.56	0.003
log BNP	0.52	0.006	0.55	0.004	-0.55	0.003
CTR	0.50	0.009	0.41	0.03	-0.35	0.080

BNP brain natriuretic peptide, *CTR* cardiothoracic ratio, *TOF* tetralogy of Fallot, *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *RVEF* right ventricular ejection fraction

Table 3

Linear regression among post-PVR QRS duration, BNP, CTR and the cardiac function

	RVEDVI (n=12)		RVESVI (n=12)		RVEF (n=12)	
	r	p value	r	p value	r	p value
post-PVR QRS duration	0.67	0.017	0.81	0.001	-0.47	0.13
post-PVR log BNP	0.64	0.025	0.47	0.13	0.32	0.32
post-PVR CTR	0.40	0.20	0.34	0.27	0.098	0.76

PVR pulmonary valve replacement, *BNP* brain natriuretic peptide, *CTR* cardiothoracic ratio, *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *RVEF* right ventricular ejection fraction

Figures

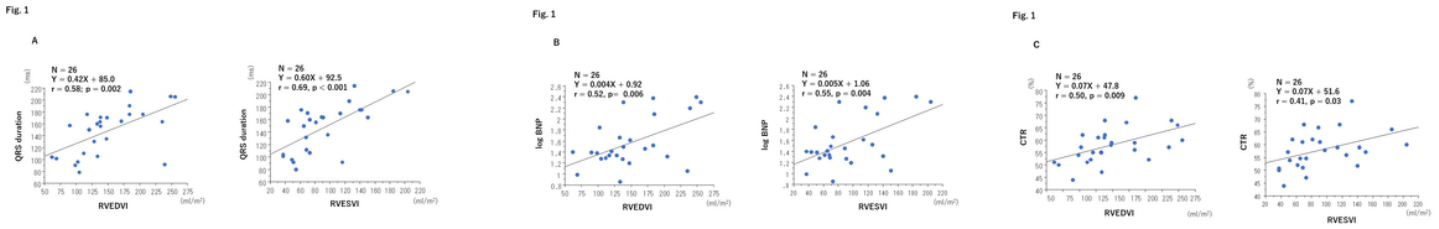

Figure 1

Correlation among 3 parameters (QRS duration: A, BNP: B, CTR: C) and RVEDVI or RVESVI after TOF repair. *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *TOF* tetralogy of Fallot, *BNP* brain natriuretic peptide, *CTR* cardiothoracic ratio

Fig. 2

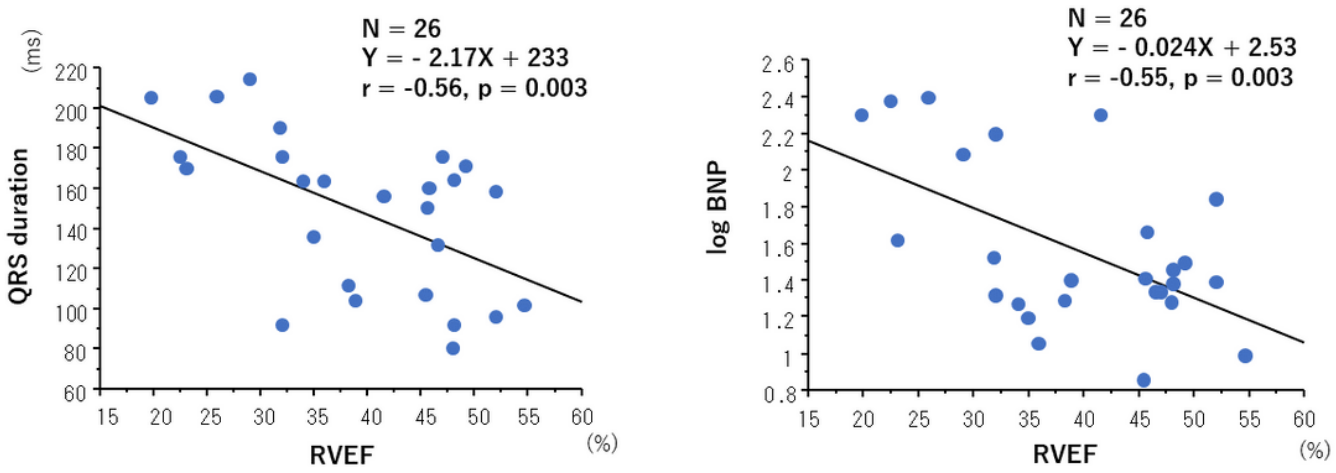

Figure 2

Correlation between the QRS duration or BNP and RVEF after TOF repair. *BNP* brain natriuretic peptide, *RVEF* right ventricular ejection fraction, *TOF* tetralogy of Fallot

Fig. 3

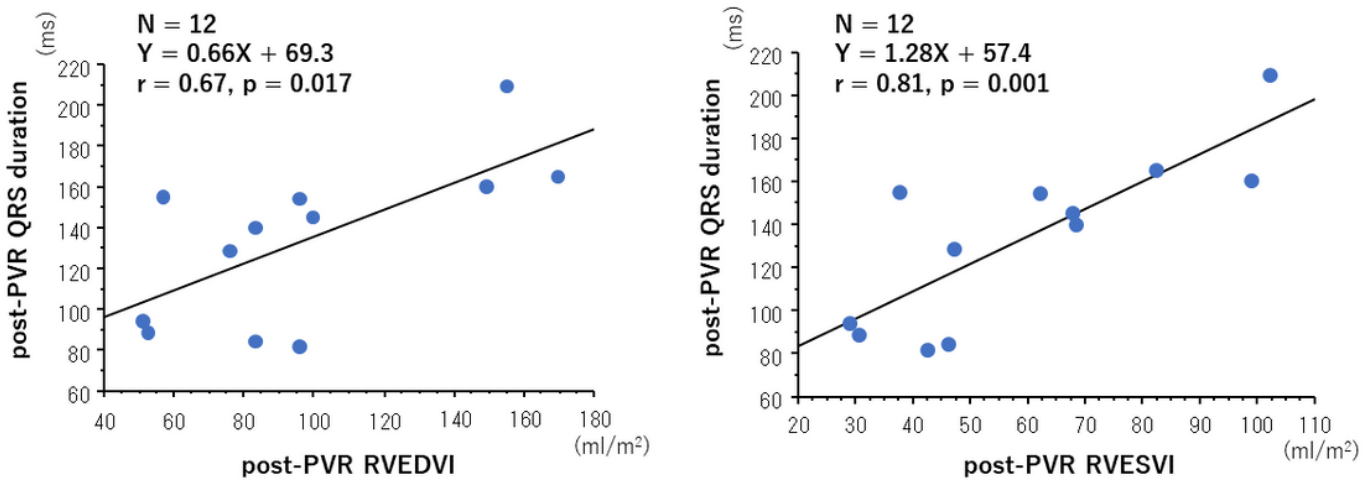

Figure 3

Correlation between the post-PVR QRS duration and post-PVR RVEDVI or RVESVI. *PVR* pulmonary valve replacement, *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index

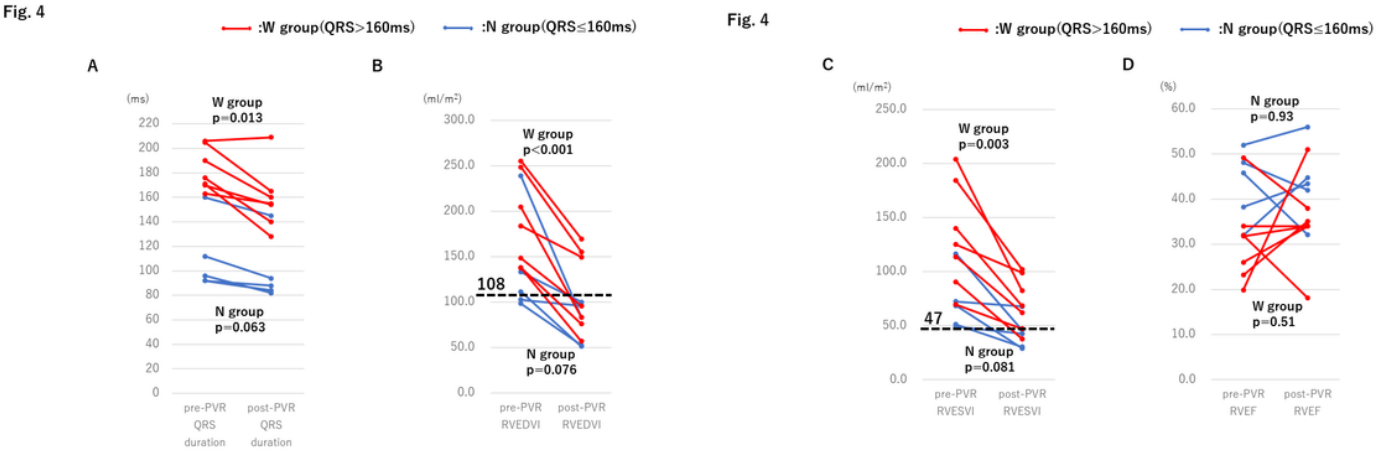

Figure 4

Changes of the QRS duration (A), RVEDVI (B), RVESVI (C), RVEF (D) before and after PVR. Red line represents the W group (QRS duration >160 ms). Blue line represents the N group (QRS duration ≤160 ms). In both the W and N groups, the QRS duration decreased after PVR (A). In the N group, RVEDVI

normalized in all 5 cases after PVR (B) and RVESVI normalized in 4 of 5 cases (C), whereas in the W group, RVEDVI normalized in 4 of 7 cases (B); however RVESVI did not normalize in 6 of 7 cases (C). There was no significant change in the RVEF from before to after PVR in either the N group or W group (D). *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *RVEF* right ventricular ejection fraction, *PVR* pulmonary valve replacement

Fig. 5

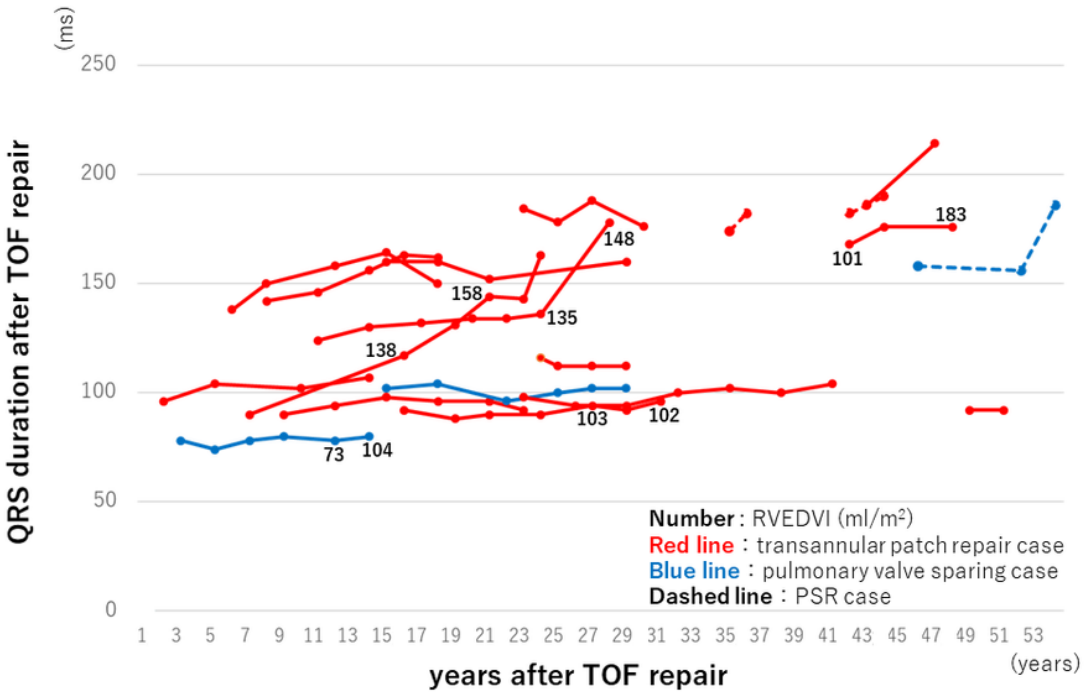

Figure 5

Changes in the QRS duration and RVEDVI after TOF repair. The QRS duration changed simultaneously with the RVEDVI in each case after TOF repair. *RVEDVI* right ventricular end-diastolic volume index, *TOF* tetralogy of Fallot