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ORIGINAL ARTICLE

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Timing of pulmonary valve replacement in patients with corrected Fallot to prevent QRS prolongation

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CONGENITAL

Key question

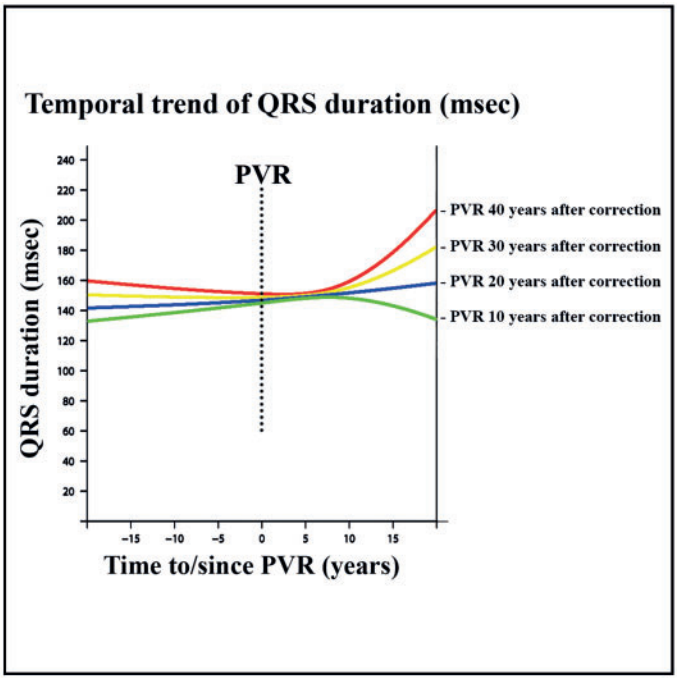
When should pulmonary valve replacement (PVR) be performed to prevent QRS prolongation in patients with corrected tetralogy of Fallot?

Key finding(s)

In patients with early correction of tetralogy of Fallot, QRS prolongation can be prevented if PVR is performed within 17 years after correction.

Take-home message

A longer time interval between ToF correction and PVR independently predicts QRS evolution after PVR.



Abstract

OBJECTIVES: Timing of pulmonary valve replacement (PVR) remains one of the most heavily debated topics in congenital cardiac surgery. We aimed to analyse the temporal evolution of QRS duration before and after PVR.

METHODS: We included 158 consecutive patients who underwent PVR after previous correction with transannular patch. All 3549 available serial standard 12-lead surface QRS measurements of 158 (100%) patients were analysed with linear mixed-effect modelling.

RESULTS: PVR was performed at a mean age of 28.0 ± 10.7 years, 23.4 ± 8.4 years after correction. Hospital survival was 98.1%. A longer time interval between ToF correction and PVR ($P < 0.001$), and an older age at correction ($P = 0.015$) were predictive of progressive QRS prolongation after PVR. Women on average had a shorter QRS duration ($P = 0.005$) after PVR. The model predicted that in patients corrected early (model age 0.5 years), PVR within 17 years after correction leads to narrowing or stabilization of QRS width. PVR beyond

17 years was associated with prolongation of QRS duration. In a patient corrected late (model age 5 years), PVR has to be performed within 15 years after correction to prevent prolongation. Finally, a longer time period between correction and PVR was associated with an increased hazard of cardiac death (hazard ratio 1.097, 95% confidence interval 1.002–1.200).

CONCLUSIONS: Prolongation of QRS duration after PVR was associated with a longer time between correction and PVR, older age at correction and male sex. Prevention of progressive QRS prolongation by earlier PVR can potentially reduce the hazard of adverse events after PVR.

Keywords: Tetralogy of Fallot • QRS • Pulmonary valve replacement • Allograft • Timing

ABBREVIATIONS

CI	Confidence interval
HR	Hazard ratio
PR	Pulmonary regurgitation
PVR	Pulmonary valve replacement
RV	Right ventricular
TOF	Tetralogy of Fallot

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease in life births and can be repaired safely at a young age [1]. However, long-term survival and freedom from reintervention are limited by the presence of ventricular arrhythmia, sudden death and heart failure [2, 3]. Ventricular tachyarrhythmia in repaired TOF patients is presumed to be the primary cause of sudden death. In the current paradigm, it is believed that chronic volume overload, caused by residual pulmonary regurgitation (PR), leads to right ventricular (RV) dilatation. This ultimately predisposes for electromechanical dissociation and heart failure [3–5]. Pulmonary valve replacement (PVR) treats PR and results in RV remodelling during the first postoperative years [6]. However, RV reverse remodelling does not occur in every patient and adverse events still occur frequently after PVR [7]. It is currently unknown how to define and determine the optimal time frame within which PVR should be performed.

QRS duration assessed through standardized 12-lead electrocardiogram may potentially be a prognostic electrocardiographic biomarker for adverse cardiac events. A QRS duration exceeding 170–180 ms has repeatedly been indicated as independent predictor for malignant ventricular arrhythmia and sudden cardiac death [3, 8]. Furthermore, prolonged QRS duration is associated with regional wall motion abnormalities, RV dilatation [5], increased biventricular wall mass [9] and decreased left ventricular ejection fraction [9]. QRS duration can, therefore, be a potentially meaningful surrogate marker reflecting the impact of chronic severe PR and RV dilatation. A better understanding of the temporal evolution of QRS duration in patients with corrected TOF before and after PVR could improve timing of PVR.

We determined the temporal evolution of QRS duration before and after PVR in a consecutive cohort of corrected TOF patients.

METHODS

All consecutive patients ($N = 158$) who underwent surgical PVR in the Erasmus University Medical Center Rotterdam between August 1987 and November 2017 after complete correction of ToF with a transannular patch were included retrospectively. Gore-Tex transannular patches were used without monocusp reconstruction. Patients with pulmonary atresia, ventricular septal defects and systemic collateral arteries were excluded. The institutional review board approved this study and waived individual informed consent (MEC 12-477).

Indication and surgical technique

All patients were discussed in structured multidisciplinary meetings (congenital heart team meeting) including congenital cardiologists, congenital cardiac surgeons and radiologist, prior to interventions. All indications for PVR were severe PR with signs of progressive RV dilatation or reduced function with or without cardiac-related symptoms. PVR was generally performed through median sternotomy, using standard cardiopulmonary bypass as previously described. In our centre, cryopreserved homografts have been and still are exclusively used for RV outflow tract reconstruction, given their excellent results in terms of structural valve deterioration, and low rates of endocarditis and valve thrombosis [10].

Study design

After discharge, patients were followed though our outpatient clinic at 1 week, 6 weeks, 6 months and annually thereafter. Standardized 12 lead (25 mm/s, 10 mm/mV) surface electrocardiograms (ECGs) were acquired during every visit to our outpatient clinic regardless of symptomatology. Valve-related events and mortality were reported according to the guidelines for reporting valve-related mortality and morbidity [11]. Follow-up within 2 years of study closing (February 2018) was available for 151 (97.4%) patients discharged alive after PVR. Four patients were lost to follow-up after PVR due to emigration ($n = 3$) and unknown reasons ($n = 1$). QRS duration as marker of ventricular depolarization was extracted from computerized calculations based on the VERITAS^{TM} ECG algorithm (Mortara Instrument, 2018, Milwaukee, WI, USA). Paced rhythms were excluded from the analysis and ECGs were censored in case of re-PVR. Sixteen (10.1%) patients underwent pacemaker implantation 22.0 ± 10.8 years after correction of which 4 before PVR, 10 after PVR and 2 concomitantly to PVR. An integrated assessment of the severity and physiology of PR was based on a multi-window perspective using transthoracic colour flow and pulsed-wave Doppler echocardiography and qualitatively graded from none, light, moderate and severe. Significant regurgitation was defined as moderate or severe regurgitation [12].

Statistical analysis

Continuous outcomes are reported as means ± standard deviations or medians with range, as appropriate. Continuous variables

Table 1: Cox proportional hazards model for cardiac death

Variables	Univariable		Multivariable	
	HR	*P*-value	HR[a]	*P*-value
Cardiac death				
Sex	0.204 (0.042–0.989)	0.048	0.130 (0.016–1.085)	0.058
Age at correction	1.111 (1.030–1.198)	0.006		
Time correction-PVRb	1.119 (1.034–1.211)	0.005	1.097 (1.002–1.200)	0.005
Age at PVR	1.095 (1.043–1.150)	<0.001		
Length at PVR	1.058 (0.996–1.123)	0.069		
Weight at PVR	1.053 (1.009–1.098)	0.017		
Creatinine (mmol/l)	1.032 (0.988–1.079)	0.160		
QRS-duration pre PVR	1.004 (0.981–1.027)	0.733		

[a]Because of the correlations between the covariates and linear dependency between age at correction, time-between correction and PVR, age at PVR, length and weight at PVR, only 1 (i.e. time between correction and PVR) was entered in the multivariable part of the analysis.
HR: hazard ratio; PVR: pulmonary valve replacement.

between groups were compared using independent samples *t*-tests, one-way analysis of variance (ANOVA) analysis, or Kruskal–Wallis tests, as appropriate. Frequencies were presented with percentages and compared using χ^2 tests. Correlations between continuous baseline variables were calculated using Pearson correlation, and reported with 2-tailed significance levels. Time-dependent outcomes were analysed using life tables and visualized with Kaplan–Meier plots as a function of time to or since PVR. Sex, age at correction, time interval between correction and PVR, age at PVR, length at PVR, weight at PVR, creatinine (mmol/l) at PVR and QRS duration at PVR were studied as potential risk factors by univariate and multivariate Cox proportional hazards models, using a backward stepwise elimination process with a threshold of ($P > 0.05$) (Table 1). Missing values were considered missing at random and not imputed due to the very small amount of missing values. Analyses were exploratory in nature and no adjustment for multiple testing was performed.

Continuous repeated measurements of QRS duration were analysed using linear mixed-effects modelling [13]. A random effects structure with time was used to account for correlations between repeated measurements in the same patient and irregularly timed measurements. QRS duration was modelled as a function of time to PVR, including fixed effects for sex and age at correction. Time in relation to PVR was entered as a natural cubic spline with 2 internal knots. Furthermore, potential interaction effects between age at correction, sex and time between correction and PVR, were explored. Effect plots were provided to illustrate the temporal evolution of QRS duration of an average patient. Given a significant trend towards earlier repair in our practice as well as contemporary surgical practice, early and late repair were defined as correction at the age of 6 months and 5 years, respectively.

Statistical analyses were performed with SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) and R (LME4 package) [R Core Team (2016)].

RESULTS

Baseline patients and surgical characteristics

A total of 158 consecutive patients underwent surgical PVR after previous ToF correction with a transannular patch. Median age at correction was 2.0 years (range 5 days–29.5 years) and 90 (57%) were males (Table 2). Mean time between correction and PVR was 23.4 ± 8.2 years (range 1.93–44.) at a mean age of 28.0 ± 10.7 years (range 2.1–66.4). Moderate or severe regurgitation were present in 155 (98.1%) patients before PVR. Supplementary Material, Fig. S1A–C shows the trend during the study period of age at ToF correction, at PVR and the time between correction and PVR. The figures indicate an increasingly younger age at correction and a relatively stable time interval between correction and subsequent PVR.

Clinical outcome

Hospital survival was 98.1% ($n = 155$). Three patients (1.9%) died shortly after PVR of sudden cardiac death presumably due to arrhythmia ($n = 1$), severe oesophageal bleeding and pulmonary infection after concomitant tracheal resection ($n = 1$) and repeated rhythm disturbances with severe biventricular heart failure ($n = 1$). All 3 patients had severe PR with RV dilatation and symptoms. Mean follow-up time after PVR was 10.0 ± 7.0 years (median 9.3, range 0.3–28.7 years, total 1555 patient years), during which 18 patients underwent a second PVR (6 surgically, 12 percutaneously), after a mean period of 7.9 ± 5.5 years. Freedom from re-PVR after 10 and 15 years was 84 ± 4% and 81 ± 5%, respectively.

Late cardiac death was observed in 9 patients, of whom 3 (33%) were also classified as having an extremely prolonged QRS duration (>230 ms) post-PVR (Table 3). The relative risk of cardiac death in patients with an extremely prolonged QRS duration was 7.25 [95% confidence interval (CI) 2.48–8.74; $P = 0.002$]. The 9 patients who died of cardiac causes were corrected at an average age of 12.4 ± 5.4 years (median 12.7, 4.5–23.0) and underwent PVR 28.6 ± 5.6 years later (median 29.2, range 18.4–36.8). They died 11.0 ± 4.2 years after PVR, at an average age of 52.0 ± 8.9 years. Cumulative freedom from cardiac death of all hospital survivors after 10 and 15 years post-PVR was 90 ± 4% and 83 ± 6%, respectively (Fig. 1).

QRS duration over time

In all but 1 patient, ECGs were available (Table 2). One patient underwent correction in 1976 and subsequent PVR in 1991 after which he died 14 days later due to severe rhythm disturbances. No ECGs could be retrieved from this patient.

Table 2: Baseline, surgical and diagnostic characteristics

	Overall	Interval <10 years	Interval 10–20 years	Interval 20–30 years	Interval >30 years	*P*-value[a]
Patients, *n* (%)	158 (100)	11 (7.0)	42 (26.6)	73 (46.2)	32 (20.3)	
Male gender, *n* (%)	90 (57.0)	7 (63.6)	19 (45.2)	41 (56.2)	23 (71.9)	0.140
Shunt before correction, *n* (%)	43 (27.2)	3 (27.3)	15 (35.7)	15 (20.5)	10 (31.3)	0.330
Age at correction (years), mean ± SD	4.6 ± 5.5	3.1 ± 5.5	4.9 ± 7.0	3.7 ± 3.8	6.9 ± 6.0	0.035
Time correction-PVR (years), mean ± SD	23.4 ± 8.2	6.7 ± 2.3	16.3 ± 2.9	25.0 ± 2.8	34.5 ± 3.3	<0.001
Age at PVR (years), mean ± SD	28.0 ± 10.7	9.8 ± 5.9	21.1 ± 7.2	28.8 ± 5.7	41.5 ± 7.8	<0.001
Haemodynamic indication, *n* (%)						
Severe regurgitation	137 (86.7)	7 (63.6)	38 (90.5)	64 (87.7)	28 (87.5)	0.264
Severe stenosis	3 (1.9)	1 (9.1)	1 (2.4)	1 (1.4)	0 (0)	
Mixed	18 (11.4)	3 (27.3	3 (7.1)	8 (11.)	4 (12.5)	
RVOT peak gradient (mmHg) (*n* = 145), mean ± SD	18.1 ± 20.7	46.1 ± 53.3	20.0 ± 17.5	14.9 ± 13.7	13.7 ± 11.0	<0.001
BSA[b] (*n* = 139) mean ± SD	1.78 ± 0.27	1.15 ± 0.35	1.61 ± 0.21	1.84 ± 0.20	1.94 ± 0.17	<0.001
Previous heart operations[C] (%), *n* (%)						
1	101 (63.9)	7 (63.6)	24 (57.1)	48 (65.8)	22 (68.8)	0.640
2	46 (29.1)	3 (27.3)	13 (31.0)	22 (30.1)	8 (25.0)	
3	9 (5.9)	1 (9.1)	3 (7.1)	3 (4.1)	2 (6.3)	
4	2 (1.3)	0 (0)	2 (4.8)	0 (0)	0 (0)	
Pre-PVR QRS duration[d] (*n* = 132), mean ± SD	150 ± 31	141 ± 32	147 ± 31	150 ± 30	155 ± 35	0.674
Elective (>24 h), *n* (%)	147 (93.0)	10 (90.9)	38 (90.5)	69 (94.5)	30 (93.8)	0.855
Diuretic use (*n* = 156), *n* (%)	15 (9.6)	1 (9.1)	4 (9.8)	8 (11.1)	2 (6.3)	0.895
Sinus rhythm (*n* = 156), *n* (%)	137 (87.8)	11 (100)	38 (92.7)	63 (87.5)	25 (78.1)	0.154
Creatinine (mmol/l) (*n* = 153), mean ± SD	70 ± 19	43 ± 16	63 ± 17	74 ± 14	79 ± 20	<0.001
Cross-clamp time (*n* = 141), mean ± SD	22 ± 43	47 ± 34	29 ± 42	17 ± 41	31 ± 48	0.101
Perfusion time (*n* = 147), mean ± SD	111 ± 63	106 ± 50	125 ± 62	101 ± 66	115 ± 58	0.296
Pulmonary allograft[e] (*n* = 154), *n* (%)	154 (97.5)	11 (100)	40 (95.2)	72 (98.6)	31 (96.9)	0.665
Diameter of allograft (mm) (*n* = 157), median (range)	24 (15–28)	22 (15–25)	24 (21–28)	24 (21–28)	24 (21–28)	0.440
Hospital mortality, *n* (%)	3 (1.9)	0 (0)	1 (2.4)	1 (1.4)	1 (3.1)	0.889
ECG						
Total number available, *n*	3549	137	809	1816	787	
Pre-PVR (%), *n* (%)	323 (9.1)	11 (8.0)	49 (6.1)	185 (10.2)	78 (9.9)	0.242
Unique patients, *n* (%)	157 (99.4)	11 (100)	41 (97.6)	73 (100)	32 (100)	
ECGs/patient, *n*	22.5	12.5	19.7	24.9	24.6	0.142
Echocardiography						
Total number available, *n*	1747	130	472	821	324	
Pre-PVR (%), *n* (%)	533 (30.5)	29 (22.3)	85 (18.0)	282 (34.3)	137 (42.3)	0.151
Unique patients, *n* (%)	156 (98.7)	11 (100)	41 (97.6)	73 (100)	31 (96.9)	
Echos/patient, *n*	11.1	11.8	11.5	11.2	10.1	0.242
Follow-up duration (years), mean ± SD	9.6 ± 9.6	12.3 ± 10.8	12.3 ± 8.0	9.3 ± 5.3	7.3 ± 6.2	0.010
Max post-PVR QRS duration, mean ± SD	158 ± 37	142 ± 35	153 ± 34	159 ± 32	168 ± 48	NA

[a]Continuous variables between groups are compared using one-way ANOVA analysis or Kruskal–Wallis tests.
[b]According to the formula of Mosteller.
[C]All previous open heart surgeries, including complete correction.
[d]QRS duration nearest in time but within 1 year prior to PVR.
[e]Pulmonary allograft or aortic allograft.
BSA: body surface area; NA: not applicable; PR: pulmonary regurgitation; PVR: pulmonary valve replacement; RVOT: right ventricular outflow tract; SD: standard deviation.

Patients are presented in different groups based on the time interval between ToF correction and PVR (interval between ToF correction and PVR <10 vs 10–20 vs 20–30 vs >30 years) (Table 2). The QRS duration prior to PVR was not associated with the time interval between correction and PVR ($r = 0.089$, $P = 0.311$), and was comparable among the 4 groups ($P = 0.674$). However, the time interval between correction and PVR showed significant correlations with other baseline factors. A longer time interval between correction and PVR was correlated with older age at correction ($r = 0.189$, $P = 0.017$), older age at PVR ($r = 0.864$, $P < 0.001$), higher creatinine ($r = 0.487$, $P < 0.001$), greater diameter of allograft ($r = 0.207$, $P = 0.009$), greater height at PVR ($r = 0.443$, $P < 0.001$) and higher weight at PVR ($r = 0.603$, $P < 0.001$).

Figure 2A and B provides a panel of effect plots of QRS duration over time before and after PVR. Temporal trends are depicted for male and female patients corrected early (Fig. 1A) and late (Fig. 1B). Different time intervals between correction and PVR are vertically depicted (10, 20, 30 and 40 years after correction, respectively). Our online application (https://cts-erasmusmc.shinyapps.io/fallotqrs/) provides results for any combination of choice. The figure illustrates that no major changes occur in QRS duration before PVR, and QRS duration is comparable right before PVR, regardless of duration since correction. However, important changes in the overall slope of the evolution of QRS duration can be observed in patients who undergo PVR beyond a certain period. After PVR, a longer time period between correction and PVR ($P < 0.001$), and an older age at correction

Table 3: Characteristics of patients with extreme QRS (>230) and/or late cardiac death

Gender	Age at correction	Age at PVR	Time correction-PVR	Age at last follow-up/death	Late cardiac death	Extreme QRS	PM	Max QRS	PM	Max QRS before PM
Male	9.3	40.7	31.4	48.8	Heart failure	Yes	After PVR	336	After PVR	206
Male	13.4	48.4	35.0	64.3	Heart failure	Yes	Never	260	Never	260
Male	13.0	42.2	29.2	53.2	SUUD	Yes	Never	260	Never	260
Female	11.8	41.0	29.2	56.7	SUUD	No	Never	174	Never	174
Male	16.5	43.7	27.2	53.3	Heart failure	No	Never	142	Never	142
Female	12.7	38.8	26.1	51.6	Heart failure	No	Never	222	Never	222
Male	7.0	43.8	36.8	54.7	Heart failure	No	Never	194	Never	194
Male	4.5	28.9	24.3	31.2	SUUD	No	Never	178	Never	178
Male	23.0	41.4	18.4	54.3	Heart failure	No	Never	186	Never	186
Male	4.4	44.4	40.0	47.8	Alive	Yes	Never	250	Never	250
Male	8.4	41.7	33.2	60.8	Alive	Yes	Never	252	Never	252
Female	2.0	24.5	22.4	43.4	Alive	Yes	At PVR	299	At PVR	NA
Male	8.8	37.8	29.0	50.6	Alive	Yes	After correction	292	After correction	NA
Female	0.2	23.4	23.2	39.1	Alive	Yes	After PVR	226	After PVR	226
Male	10.5	43.8	33.2	56.4	Alive	Yes	After PVR	239	After PVR	234
Male	2.3	32.4	30.2	41.5	Alive	Yes	After PVR	233	After PVR	176

NA: not applicable; PM: pacemaker; PVR: pulmonary valve replacement; SUUD: sudden unexplained unexpected death.

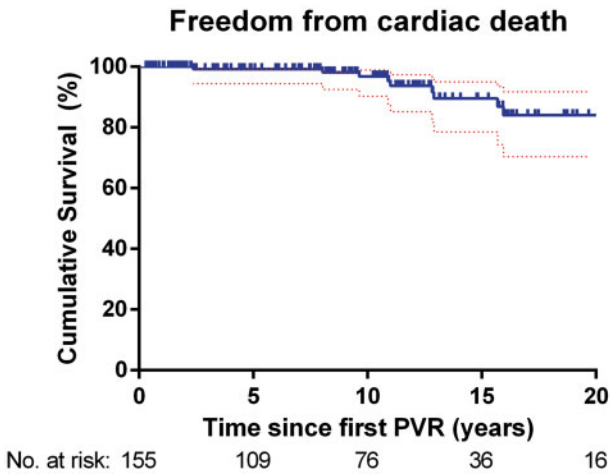


Figure 1: Kaplan–Meier curve depicting cumulative freedom from cardiac death after PVR (solid line) along with 95% confidence intervals (dotted lines). PVR: pulmonary valve replacement.

($P = 0.0185$) were both significantly and independently associated with progression of QRS duration.

Pacemaker and ICD

Among hospital survivors without a pacemaker, the time interval between correction and PVR was not associated with the hazard of late pacemaker implantation [hazard ratio (HR) 1.035, 95% CI 0.958–1.118; $P = 0.383$]. A longer time interval between correction and PVR was, however, associated with an increased hazard of late implantation of an implantable cardioverter-defibrillator (ICD) (HR 1.137, 95% CI 1.039–1.244; $P = 0.005$).

DISCUSSION

This study is the first to show an association between timing of PVR and QRS duration using innovative and advanced statistics to model the individual long-term evolution of QRS duration before and after PVR in a homogenous group of corrected ToF patients. QRS duration after PVR is significantly associated with a longer time interval between initial correction and PVR, a higher age at correction and sex. In patients who undergo early ToF correction, progressive QRS prolongation after PVR can be prevented by intervening within ∼17 years after correction. In patients with ToF correction at a later age, progressive QRS prolongation after PVR can be prevented by intervening within ∼15 years after correction. The time interval between ToF correction and PVR is therefore associated with postoperative QRS duration, cardiac death and the hazard of postoperative ICD implantation. QRS duration is an important risk factor before and after PVR in corrected ToF patients, and prevention of prolongation might improve the outcome of these patients.

PVR and QRS duration

Few published studies have investigated the relation between PVR and QRS duration [14–29]. However, the results are heterogeneous with some authors reporting a stable QRS duration [17, 19, 20, 22, 28], some an increase [16] and some a decrease [6, 15, 18, 21, 25, 27] after PVR in corrected ToF patients. Therrien *et al.* [28] were the first to report a stabilization in QRS duration after PVR in corrected ToF patients compared to a control group who had not undergone PVR. van Huysduynen *et al.* [29] were the first to report a decline in QRS duration following PVR in 26 patients with corrected ToF with at least moderate regurgitation. Oosterhof *et al.* studied 99 corrected TOF patients who underwent a first PVR and reported an initial decline in mean QRS duration directly post-surgery. QRS duration increased, however, during a median follow-up of 5 years in patients with preoperative QRS >120 ms. In patients with a preoperative QRS <120 ms, no increase was reported [30]. The mixed results of QRS duration could potentially also be explained by undisclosed differences in time interval between correction and

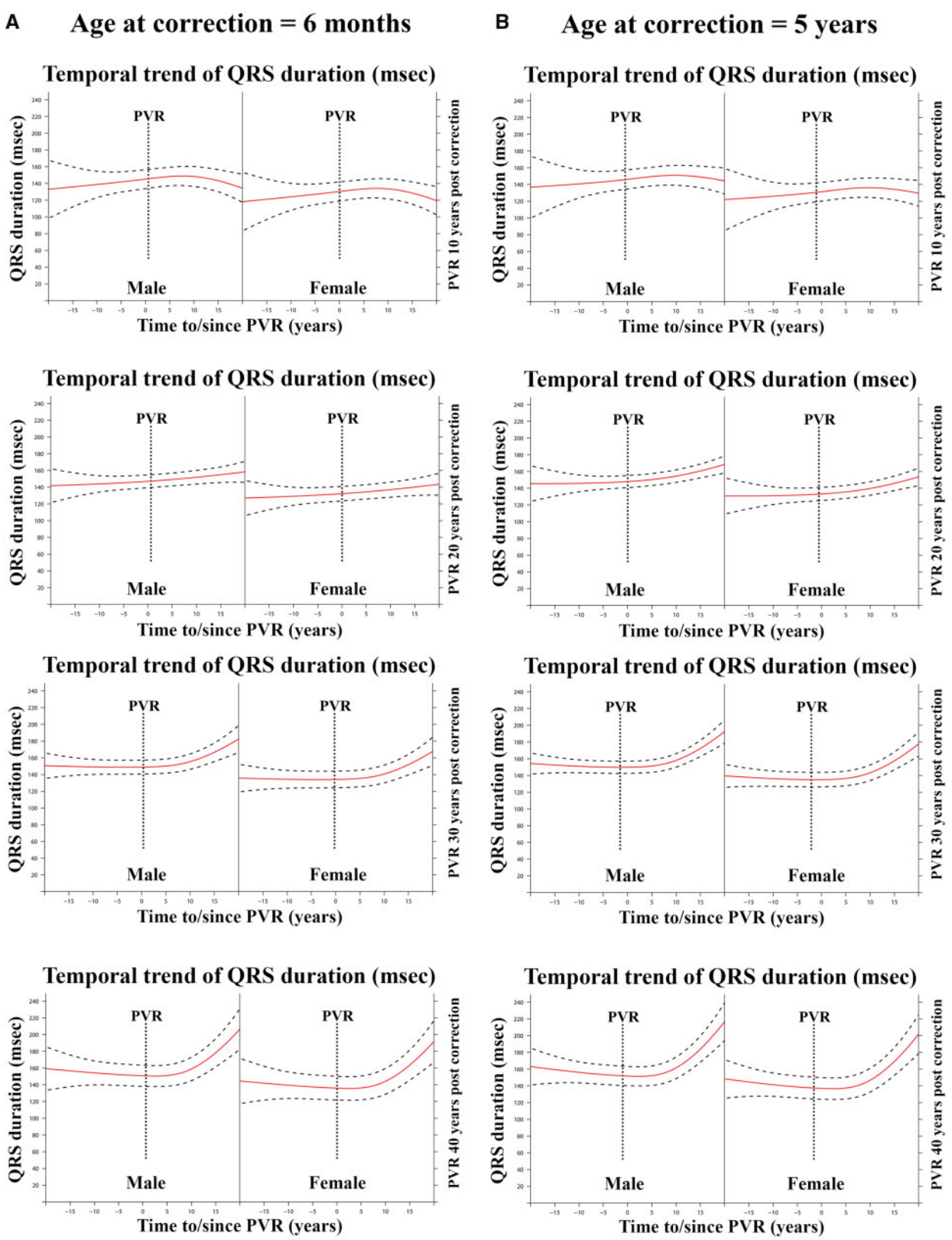


Figure 2: Panel figure of the longitudinal QRS (in ms) evolution for 2 fictional patients of both genders. Age at correction of 6 months (**A**) and 5 years (**B**) were chosen. Time between correction and PVR increases from 10 to 40 years (vertically). Thus, the figure indicates the longitudinal evolution of QRS duration for a child corrected at 6 months (**A**) and 5 years (**B**), for both males and females, given 4 different moments of PVR after correction (vertically depicted; 10, 20, 30 and 40 years, respectively). Post-PVR evolution of QRS duration shows a progressive prolongation in patients who underwent PVR 30 and 40 years after correction, despite comparable QRS durations right before PVR. PVR: pulmonary valve replacement.

PVR. Mixed-effect modelling enabled us to model the variability that is inherent to and only observable in a longitudinal design that considers irregularly scheduled and collected measurements and accepts a non-linear evolution.

QRS prolongation as risk factor

Prolongation of QRS duration has been reported despite successful PVR and is predictive of adverse outcome [16, 25, 29]. As multiple studies have demonstrated the malignant nature of QRS progression as a substrate for cardiac dysfunction and increasing depolarization disturbances, preventing this postoperative prolongation seems imperative [25, 29]. Scherptong *et al.* [25] reported that a post PVR QRS duration exceeding 180 ms was associated with a reduced freedom from a composite end point including death, re-PVR, ventricular tachyarrhythmia and symptomatic heart failure after 5 years. Stabilization of QRS duration after PVR has occasionally been associated with a reduced frequency of ventricular tachycardia [18]. Harrild *et al.* studied 98 corrected ToF patients who underwent PVR 20 years after correction at a mean age of 5 years. In a later study, QRS duration did not change after PVR, and matched controls with significant PR and RV dilatation who did not undergo PVR showed no differences in reported ventricular tachycardia or death [17]. The average delay to PVR of 19.7 years is close to the time frame proposed by this study with regard to prolongation prevention. Similarly, the change rate of QRS prolongation and older age at correction have been associated with an increased incidence of ventricular tachyarrhythmia and sudden death [5]. These findings underline the clinical importance of QRS duration after PVR and the relevance of preventing progression.

It could be hypothesized that QRS duration is a reflection of RV remodelling, often shown by progressive RV end-diastolic volume [4, 5]. The relevance of preventing progressive QRS duration could be similar in that regard as well, aimed at preserving or even improving ventricular function, given that the correlation between QRS duration and RV end-diastolic volume persists after PVR. QRS duration could, therefore, act both as a biomarker for volumetric and functional change, as well as a risk factor for late adverse events. Unfortunately, no serial volumetric data, preferably by magnetic resonance imaging, were available of sufficient patients to conduct a similar analysis. The design of the current study can, however, be adapted with RV volume over time to potentially identify the pivot point to prevent further RV dilatation, heart failure and malignant arrhythmia.

CONCLUSION

The decision whether to intervene in corrected ToF patients should ideally depend on the combination of multiple biomarkers with the clinical state of the patient. QRS duration is an easily obtainable electrocardiographic biomarker with extensive prognostic capabilities in ToF patients suffering from chronic PR who undergo PVR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Jamie L.R. Romeo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft. **Johanna J.M. Takkenberg:** Supervision; Writing—review & editing. **Judith A.A.E. Cuypers:** Writing—review & editing. **Natasha M.S. de Groot:** Writing—review & editing. **Pieter van de Woestijne:** Investigation; Writing—review & editing. **Nico Bruining:** Data curation; Writing—review & editing. **Ad J.J.C. Bogers:** Supervision; Writing—review & editing. **M. Mostafa Mokhles:** Supervision; Writing—original draft; Writing—review & editing.

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