



The effects of pulmonary valve replacement on QRS duration in repaired tetralogy of Fallot patients with pulmonary regurgitation



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ABSTRACT

Introduction: Chronic pulmonary regurgitation (PR) following surgical correction in Tetralogy of Fallot (TOF) leads to right ventricular (RV) dysfunction, arrhythmias and sudden cardiac death (SCD). Pulmonary valve replacement (PVR) decreases PR and improves RV function, but data regarding QRS duration reduction remain scarce.

Methods: All adult TOF patients undergoing transcatheter PVR or surgical PVR from 2010 to 2016 were included. Clinical characteristics and QRS duration were measured and compared to post-intervention QRS duration using an institutional software and manually verified. Significantly wide QRS was defined as QRS >140 ms.

Results: Of 133 PVR patients, 85 had TOF and 27 (21.1%) had QRS > 140 ms (14 transcatheter, 13 surgical) and were included in this analysis. A 6 ms decrease in QRS duration was seen at 3-year follow-up (168.0 ± 3.5 ms vs. 161.8 ± 3.5 ms, $p = .04$). There was a significant decrease in the median RV size (defined as RV/LV diameter ratio) pre-intervention to 3-year post-intervention: (0.96 vs 0.89, $p = .03$).

The median PR decreased significantly from moderate-severe to mild post-intervention ($p < .0001$).

Conclusions: Replacement of the pulmonary valve in high risk TOF patients reduces QRS duration at 3 years. Further study is needed to assess whether this QRS duration reduction may identify patients at lower risk of ventricular arrhythmias.

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Introduction

Congenital heart disease (CHD) is the most common birth defect, marked by an incidence of 1–2% of live births [1]. Tetralogy of Fallot (TOF) accounts for nearly 10% of all CHD and is a significant cause of cyanosis and morbidity in neonates [2]. TOF is characterized by obstruction of the right ventricular outflow tract (RVOT), ventricular septal defect (VSD), an overriding aorta, and right ventricular hypertrophy [2]. Without surgical intervention, patients show significant decrease in survival [2]. Advances in diagnosis and treatment have drastically improved outcomes, with >90% of TOF neonates expected to reach into adulthood [2,3]. Despite these advances, TOF patients have a

lower long-term survival than the general population, partly due to long-term complications of the initial cardiac repair. The surgical repair, which relieves the RVOT obstruction and decreases right ventricle afterload, results in significant pulmonary regurgitation (PR) [4]. Long standing chronic PR results in right ventricular dilation, which leads to biventricular dysfunction, exercise intolerance, arrhythmias, and increased risk of sudden cardiac death (SCD) [5]. During long-term follow-up, approximately 43% of TOF patients have ventricular or supraventricular arrhythmias [6,7] and incidence of SCD is nearly 1.8% at 8-year follow-up [8]. Patients may also develop progressive exercise intolerance and heart failure, thus contributing to the overall morbidity and mortality of TOF [6].

Identifying risk factors for ventricular tachycardia (VT) and SCD can aid in the management of TOF patients. QRS duration >180 ms is associated with high risk ratios for ventricular tachycardia and sudden cardiac death [9]. In a large multicenter study with a mean follow-up period of 21 years, severe right ventricle volume overload correlated with QRS prolongation [10]. Additionally, pulmonary insufficiency was found in 95% of patients who experienced VT (4.2%) or SCD (2%) [10]. Pulmonary valve replacement (PVR) has been shown to improve symptoms and functional status by decreasing PR, RV size, and RV dysfunction [11]. However, the degree to which PVR may reverse QRS prolongation and decrease the risk of ventricular arrhythmia remains unknown [4,12]. It

Abbreviations: CHD, Congenital Heart Disease; ECG, Electrocardiogram; EDV, End Diastolic Volume; LV, Left Ventricle; LVEF, Left Ventricular Ejection Fraction; Post-OP, Postoperative; PR, Pulmonary Regurgitation; Pre-OP, Preoperative; PVR, Pulmonary Valve Replacement; RV, Right Ventricular; RVEF, Right Ventricular Ejection Fraction; RVOT, Right Ventricular Outflow Tract; SCD, Sudden Cardiac Death; SPVR, Surgical Pulmonary Valve Replacement; TOF, Tetralogy of Fallot; TPVR, Transcatheter Pulmonary Valve Replacement; VSD, Ventricular Septal Defect; VT, Ventricular Tachycardia.

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has been reported that PVR combined with cryoablation can maintain QRS duration and decrease the incidence of atrial and ventricular tachyarrhythmia; other studies suggest that PVR decreases QRS duration with a corresponding decrease in RV end-diastolic volume [12,13]. In contrast, another study of TOF patients with late PVR for RV dilation did not show a decrease in QRS duration to matched controls [4]. Thus, the impact of PVR on QRS duration remains unanswered. Interestingly, Koyak et al. demonstrated that for every 10 ms increase in QRS duration there is a 1.34 increased odds ratio for SCD [14].

The aim of this study was to observe the effect of PVR on medium-term follow up in patients with significant QRS duration, defined as >140 ms. We hypothesized that such an intervention would confer a significant narrowing of the QRS interval.

Patient and methods

This single center retrospective cohort study from the Ahmanson/UCLA Adult Congenital Heart Disease Center examined congenital heart disease (CHD) patients undergoing transcatheter pulmonary valve replacement (TPVR) or surgical pulmonary valve replacement (SPVR). In the present study, 293 CHD patients were evaluated between October 2010 and September 2016. An institutional database was accessed to collect data including age of procedure, sternotomies, pre-operative and post-operative pulmonary regurgitation, and QRS duration. Pre-operative QRS duration was defined as the most recent ECG recording, going back to one year before PVR. Serial QRS measurements occurred at the temporally most proximate ECG to 8, 12, and 36 months post PVR. The study was approved by the local institutional review board. Patients with insufficient echocardiographic or ECG pre-operative or follow-up data were excluded from the study.

Imaging data

Ventricular dilation, function, and PR severity was determined with Doppler echocardiography. RV size was defined as RV/LV diameter ratio, measured at the base at the end of diastole from RV-focused apical 4-chamber view, in accordance with current guidelines [15]. RV/LV ratio <0.8 = normal, 0.8–1 = mildly enlarged, 1–1.4 = moderately enlarged, >1.4 cm severely enlarged [15]. Left ventricle (LV) size, and ventricular dysfunction (both RV and LV), was defined as none = 0, mild = 1, moderate = 2, or severe = 3 based on gender, ejection fraction or ventricular diameter, based on established criteria and current guidelines [16]. Similarly, PR severity was defined as none = 0, mild = 1, moderate = 2, or severe = 3 based on proximal jet width, color jet area and jet length, in accordance with current guidelines [17]. All echocardiographic images were obtained with the use of a Philips iE33 ultrasound machine (Philips USA, Andover MA).

ECG

All ECGs were digitally stored and reviewed at pre-operative and post-operative intervals. All ECGs were standard 12-lead recordings with sample frequency of 500 Hz. Institutional software (MUSE, Version 8.0 SP2, General Electric USA, Boston MA) was implemented to analyze ECGs and QRS duration, which was defined as the first Q wave deflection in any lead until the last S wave deflection in any lead. Manual verification was performed in the study group for quality control.

Statistical analysis

Data are presented as median (25th–75th percentile) or as a percentage (number) where appropriate. Two-sided paired *t*-tests were used to compare pre and post-operative data. Linear regression analysis was performed to assess the relation between changes in QRS duration with time. All data were analyzed using SPSS 25 (IBM, Armonk NY) and a probability value of $p < .05$ was considered significant.

Results

Baseline characteristic and clinical outcomes

Of the 293 patients who underwent PVR, there were 133 patients who had sufficient data for analysis, of which 85 (63.9%) had TOF and 28 (21.1%) had initial QRS >140 ms (14 transcatheter, 13 surgical). A cut off of QRS > 180 ms did not yield a significant number of patients in this cohort, hence we selected a more inclusive QRS duration (>140 ms) in order to capture a larger number of patients with wide QRS. One patient was excluded from the study due to ventricular cryoablation, which can significantly affect the QRS duration, at time of surgical valve replacement (Fig. 1).

Baseline demographic, and echocardiographic characteristics of pre-intervention and post-intervention are presented in Table 1. There was no statistical difference in left ventricular size and dysfunction, or in right ventricular function between pre- and post-intervention. There was a significant decrease in the median (25th, 75th percentile) RV size defined as RV/LV diameter ratio from pre-intervention to 3-year post-intervention: 0.96 (0.83, 1.02) vs. 0.89(0.8, 0.9), $p = .03$. The median (25th, 75th percentile) PR severity decreased significantly post-intervention from moderate-severe to mild PR: 2.5(2,3), vs. 1 (0,1) ($p < .0001$). It should be noted that when the TPVR group and SPVR group were analyzed separately, there was no significant differences in baseline demographic and clinical data (not shown).

QRS duration

In the significant widened QRS cohort (>140 ms), there was a 6 ms reduction in QRS duration at 3-year follow up (168 ± 3 ms vs. 162 ± 3 ms, $p = .04$), irrespective of the type of intervention for PVR. The

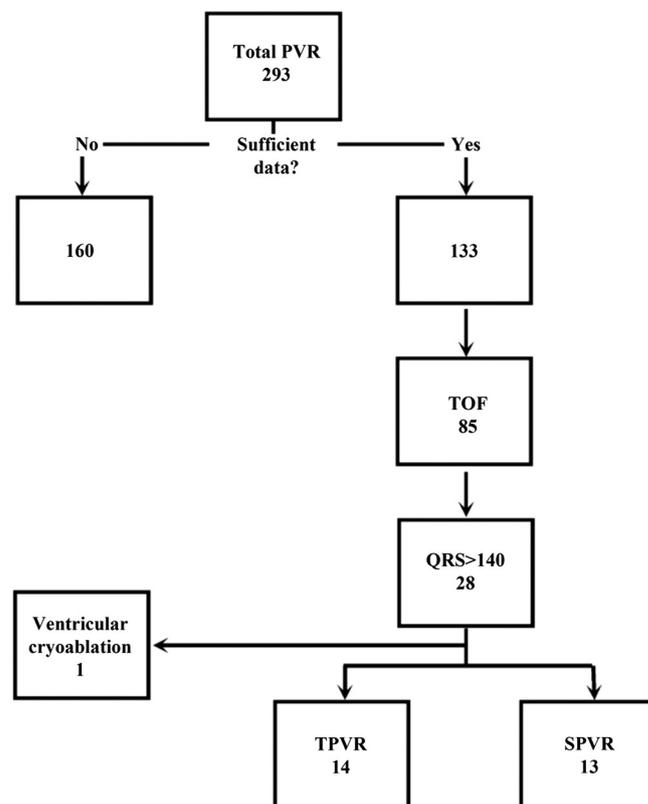


Fig. 1. Study design. One patient was excluded due to ventricular cryoablation at time of surgical valve replacement. PVR = pulmonary valve replacement; TOF = tetralogy of fallot; TPVR = transcatheter pulmonary valve replacement; SPVR = surgical pulmonary valve replacement.

Table 1

PR = pulmonary regurgitation, LV = left ventricle, RV = right ventricle. The severity of PR decreased significantly post-intervention: 2.5(2,3), vs. 1 (0,1) ($p < .0001$), 0 = none, 1 = mild, 2 = moderate, 3 = severe. There was a significant decrease in the median (25th, 75th percentile) RV size defined as RV/LV ratio from pre-intervention to 3-year post-intervention: 0.96 (0.83, 1.02), 0.89 (0.8, 0.9) ($p = .03$). RV/LV <0.8 = normal, 0.8–1 = mildly enlarged, 1–1.4 = moderately enlarged, >1.4 = severely enlarged.

Variable	Pre-intervention (n = 27)	Post-intervention (n = 27)	p Values
Age (25th, 75th percentile)	25 (16, 40)	n/a	n/a
Male gender - % (n)	52% (14)	n/a	n/a
Sternotomies (25th, 75th percentile)	2 (1,3)	n/a	n/a
Severity of PR (25th, 75th percentile)	2.5 (2,3)	1 (0,1)	<0.0001*
LV size (25th, 75th percentile)	0(0,0)	0(0,0)	1
LV function (25th, 75th percentile)	0(0,1)	0(0,1)	0.57
RV size (RV/LV ratio; 25th, 75th percentile)	0.96 (0.83, 1.02)	0.89 (0.80, 0.90)	0.03*
RV function (25th, 75th percentile)	1(0,2)	1(0,1)	0.14

overall mean QRS duration in the population with baseline QRSd >140 ms and a representative example of QRS duration reduction are shown in Fig. 2 Although there was an overall decrease in the QRS duration in the TPVR and SPVR cohorts, there was no significant difference in QRS duration reduction between TPVR and SPVR cohorts when analyzed separately (data not shown), suggestive that any reduction in PR improves QRS duration.

Discussion

Our study demonstrated a reduction in QRS duration in TOF patients with significantly widened QRS (defined in our study as >140 ms), who underwent PVR. Previous studies have shown stabilization of QRS duration after PVR, and reduction of QRS duration with PVR in TOF patients with QRS duration >180 ms [12,13]. In these previous studies QRS duration was attributed to reduction in RV end diastolic volume (EDV). Our observations further expands the findings from previous studies, by including TOF patients with lesser degrees of QRS widening. Although a 6 ms decrease in QRS duration appears to be of small magnitude, prior studies have suggested that for every 10 ms increase in QRS duration there is a 1.34 increased odds ratio for SCD [14].

Gatzoulis et al. has reported QRS duration >180 ms as a risk marker for development of malignant tachyarrhythmias, VT and SCD [9]. The relationship between QRS duration and late arrhythmias has been previously described [18]. Prolonged right ventricular volume overload leads to right ventricle dilation and fibrosis which is suggested to play

a direct role in distortion of myocardium electroconductivity, predisposing such patients to late arrhythmias and SCD. Therefore, a reduction of RV strain and dilation would lead to a reduction of these factors and likely a reduction of malignant arrhythmias. These findings suggest that TOF patients with pulmonary valve insufficiency and QRS duration >140 ms may benefit from either surgical or transcatheter PVR leading to reduction of QRS duration, and thereby possibly reduce incidence of ventricular tachycardia and SCD. Determining which TOF patients are considered higher-risk will help determine timing of pulmonary valve replacement and patients with wide QRS can potentially have a decrease on QRS duration after PVR.

There are several limitations to this study. First, due to the small number of patients these findings cannot be generalized to all patients with TOF undergoing PVR. Hence the relationship between PVR and QRS narrowing requires further analysis in a larger group of patients. Second, the stability or any further decreases of QRS duration over long term follow up will need to be assessed when long term data becomes available.

Conclusions

Our findings suggest that in at-risk TOF patients with significant pulmonary valve dysfunction and QRS duration >140 ms on baseline ECG, replacement of the pulmonary valve can lead to reduction of QRS duration, and thereby possibly reduce incidence of ventricular tachycardia and SCD. Further study is needed to assess whether this QRS duration reduction may identify patients at lower risk of ventricular arrhythmias.

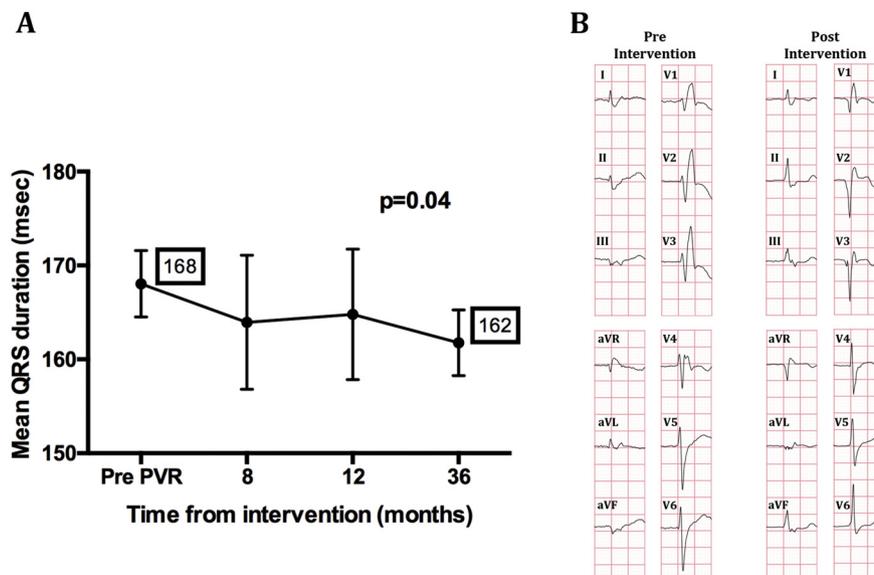


Fig. 2. Mean QRS duration changes over time. A. Mean pre-intervention QRS duration of 168 ms to 162 ms at 3 years post-intervention. $p = .04$. B. A typical example of QRS duration reduction is shown.

Conflict of interest

The authors do not have any disclosures of conflicts to report.

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