ORIGINAL ARTICLE

Determinants of QRS duration in patients with tetralogy of Fallot after pulmonary valve replacement

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Abstract

Background: Following the repair of TOF patients may be left with pulmonary regurgitation and a dilated right ventricle (RV), which in turn can lead to ventricular arrhythmias and sudden death. A prolonged QRS is a predictor of ventricular arrhythmias. However, whether subsequent pulmonary valve replacement (PVR) can reverse QRS-prolongation is controversial. We hypothesized that changes in QRS duration following PVR are determined by preoperative QRS-duration and RV volumes

Methods: A retrospective single-center cohort study was conducted on 142 post-TOF repair patients (mean age 25 ± 13 years) who underwent PVR between 1995 and 2019. Information on QRS duration and RV volumes measured by cardiac MRI (available in 83 patients) were collected. A linear mixed model was used to investigate the association between the preoperative QRS duration and RV volumes and the postoperative QRS duration.

Results: The QRS-duration following PVR continued to increase in all subjects with a prolonged preoperative QRS-duration(>160 ms, rate of increase of 0.87 msec ± 0.33 per year; $p = .01$), markedly raised RV end-diastolic volume (RVEDV; ≥166 ml/m2, rate of increase of 2.0 msec ± 0.37 per year; $p < .01$) or RV end-systolic volume (RVESV; ≥89 ml/m^2, rate of increase of 1.25 msec ± 0.43 per year; $p = .01$). In contrast, in patients with preoperative QRS-duration <160 msec ($p = .16$), RVEDV <166 ml/m^2 ($p = .14$), or RVESV < 89 ml/m2 ($p = .37$), the QRS-duration did not change significantly when compared to preoperative values.

Conclusions: In subjects with shorter QRS and smaller RV volumes, QRS duration did not show further prolongation following PVR. While markedly prolonged QRS and increased RV volumes were associated with a small but constant increase in QRS duration despite PVR.

KEYWORDS
arrhythmias, pulmonary valve replacement, QRS duration, tetralogy of fallot

1 | INTRODUCTION

Surgical repair of tetralogy of Fallot (TOF) in children is associated with excellent long-term outcomes.[1] However, a large proportion of patients develop pulmonary valve regurgitation (PR) after surgery, which can lead to right ventricular (RV) dilatation, symptoms of RV failure, and malignant arrhythmias, including sudden cardiac death.[2,3] The QRS duration is a simple marker for predicting cardiac mortality in several clinical conditions including post-TOF repair with RV failure. Intraventricular conduction delay results in abnormal electrical depolarization of the heart and mechanical ventricular dyssynchrony, which can predispose to malignant arrhythmias. QRS duration may increase by an average of 2 msec/year in TOF patients with secondary PR[3] and a QRS interval >180 msec has been reported to be predictive for sudden cardiac death in this population.[3–5]

Pulmonary valve replacement (PVR) is recommended to improve symptoms of RV failure and reduce RV dilatation.[6–8] It has also been suggested that PVR may prevent or reverse QRS complex prolongation, by means of preventing volume and pressure overload allowing mechanical re-synchronization.[9] However, data to support the last hypothesis are scarce and conflicting.[9–11] It has been suggested that marked preoperative QRS prolongation and RV dilatation can prevent QRS stabilization or reversal of prolongation following PVR. In the present study we aimed to investigate the relationship between preoperative QRS duration and RV volume, as assessed using cardiac magnetic resonance imaging (cMRI), and changes in QRS duration post-PVR in patients with repaired TOF.

2 | METHOD

The study complies with the Declaration of Helsinki. The present analysis was approved by the audit board at the University Hospital of Bristol. As this analysis came under clinical audit/quality of care assessment and all data were anonymized following the governance criteria of the NHS, the IRB agreed informed consent was not required.

2.1 | Patient and public involvement

This study was done without patient and public involvement.

2.2 | Primary and secondary endpoints

The primary endpoint of the present analysis was to describe long-term changes in QRS duration following PVR in relationship to preoperative QRS duration. As secondary endpoint, we looked at the relationship between RV volumes and long-term changes in QRS duration, in a subset of patients with information on preoperative RV volumes assessed by cardiac MRI.

2.3 | Data source

This is a single-center cohort study conducted at the Bristol Heart Institute looking at repaired TOF patients undergoing their first surgical PVR. Data were retrospectively collected from medical records and the cardiac MRI database. A total of 223 TOF patients underwent first time PVR between 1995 and 2019 in our Institution. The main indication for the first PVR intervention was symptomatic PR (exercise intolerance not explained by extracardiac causes, signs, and symptoms of heart failure or syncope attributable to arrhythmia) and/or severe right ventricle dilatation (RVEDV >150 ml/m^2). Information on preoperative QRS was not available for 81 patients who were excluded from the main analysis. Information on preoperative RV volumes from cMRI examination was available for 83 patients and this subgroup was used to investigate the predicted value of RV volume on postoperative QRS duration.

TABLE 1 Characteristics of patients stratified by preoperative QRS duration and in the overall sample

	QRS = < 160 (N = 111)	QRS > 160 (N = 31)	Overall (N = 142)
Age at PVR			
Mean (SD)	23.9 (13.0)	29.5 (12.4)	25.1 (13.1)
Sex			
Men	57 (51.4%)	4 (12.9%)	61 (43.0%)
Women	54 (48.6%)	27 (87.1%)	81 (57.0%)
Chromosomal abnormality			
No	99 (89.2%)	27 (87.1%)	126 (88.7%)
Yes	12 (10.8%)	4 (12.9%)	16 (11.3%)
Smoking			
No	91 (82.0%)	24 (77.4%)	115 (81.0%)
Yes	20 (18.0%)	7 (22.6%)	27 (19.0%)
BSA			
Mean (SD)	1.61 (0.387)	1.75 (0.308)	1.64 (0.374)
Age at first repair			
Mean (SD)	3.34 (3.38)	5.27 (6.18)	3.76 (4.21)
Preop NYHA Class			
1	31 (27.9%)	16 (51.6%)	47 (33.1%)
2	67 (60.4%)	14 (45.2%)	81 (57.0%)
3	13 (11.7%)	1 (3.2%)	14 (9.9%)
Preop QRS (msec)			
Mean (SD)	138 (22.1)	175 (7.28)	146 (25.1)
RBBB			
No	21 (18.9%)	0 (0%)	21 (14.8%)
Yes	90 (81.1%)	31 (100%)	121 (85.2%)
History of VT			
No	107 (96.4%)	27 (87.1%)	134 (94.4%)
Yes	4 (3.6%)	4 (12.9%)	8 (5.6%)

Abbreviations: BSA, body surface area; PVR, pulmonary valve replacement; RBBB, right bundle branch block; VT, ventricular tachycardia.
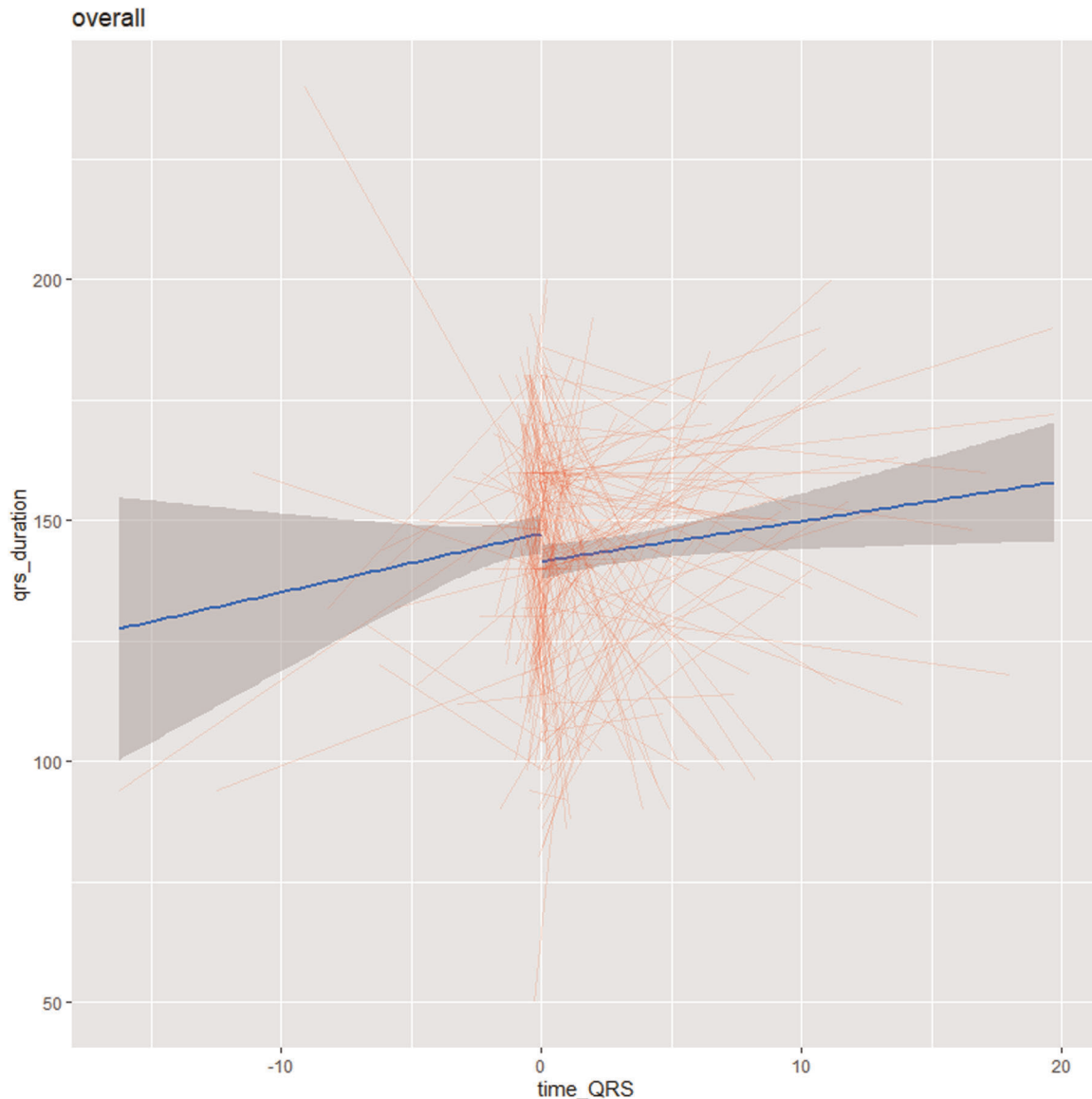
FIGURE 1 Graphical presentation of linear mixed model showing QRS changes over time before and after surgery. Blue line represents the overall changes with its 95% confidence interval, the red lines represent individual changes (long *x* axis: years from PVR). PVR, pulmonary valve replacement

Information regarding QRS duration was extracted from cardiology clinical letters in the medical records. cMRI data was used as it is considered the gold standard for quantification of RV volumes and systolic function because of its accuracy and reproducibility.[12,13] Right Ventricular volumes were indexed for body surface area.[14,15] We also reported the incidence of ventricular tachycardia (VT) before surgery defined as documented episode of spontaneous sustained VT (e.g., cardiac arrest); electrophysiology study with inducible VT and/or implantable cardioverter-defibrillator (ICD) implantation for ventricular arrhythmias.[11]

2.4 | Statistical analysis

Data are presented as median (interquartile [IQR]), mean ± standard deviation, or as a percentage (number) where appropriate. The overall impact of surgery on QRS duration was assessed by means of linear mixed model using pre- versus postsurgery as fixed-term, time to evaluation as random slope, and patient-identifiable variable as a random intercept. To investigate the impact of preoperative QRS duration and RV volumes, marked QRS prolongation and marked RV volumes were defined as equal or higher than the 75th percentile of the variable distribution. Based on this definition, a preoperative QRS duration ≥160 msec was considered marked QRS prolongation, an indexed end-diastolic RV volume ≥166 ml/m^2 and an end-systolic RV volume ≥89 ml/m^2 were considered indexes of marked RV dilatation. Linear mixed model using time from surgery as fixed-term and individual patient as random effect was used to investigate whether QRS increased (time b-coefficient > 0), decreased (time b-coefficient < 0), or remained unchanged (time b-coefficient non-significant) following PVR. The analysis was then stratified according to preoperative QRS duration and RV volume cut-offs identified. For
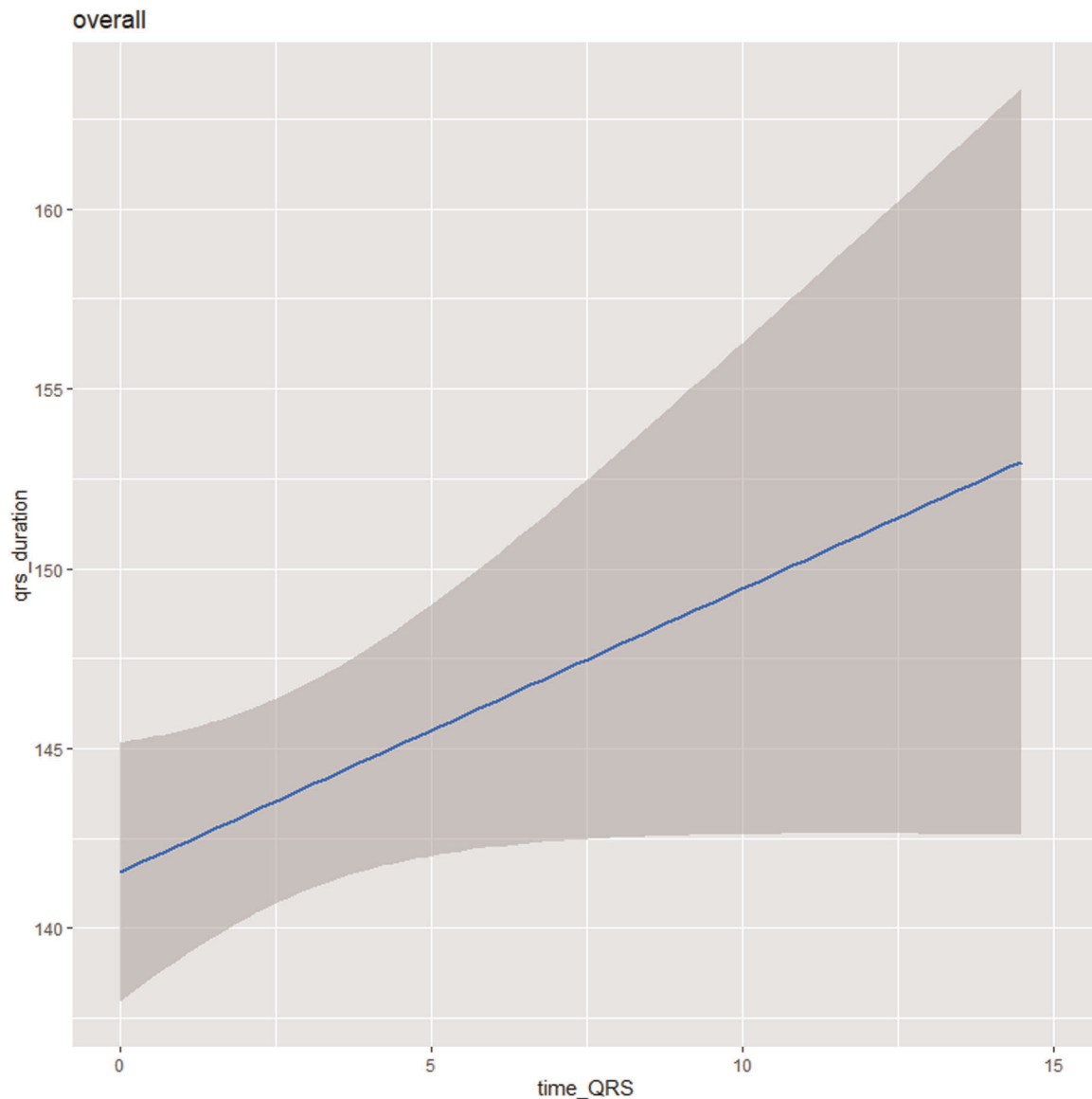
FIGURE 2 Graphical presentation of linear mixed model showing QRS changes after surgery in the overall population. Blue line represents the overall changes with its 95% confidence interval (long *x* axis: years from PVR). PVR, pulmonary valve replacement

each analysis, nonlinearity was checked by testing as 3-knots spline term based on Akaike information criterion (AIC) and χ^2. The trend in QRS duration across different subgroups was graphically presented as linear regression. R and lme4 and ggplot2 packages were used for statistical analysis.

3 | RESULTS

Patients characteristics overview in the overall sample and stratified by baseline QRS duration (<160 msec and >160 msec) is presented in Table 1. Patients with baseline QRS duration >160 were older at the time of PVR and were more likely to be older at the time of the first repair. Moreover, they were more likely to have experienced VT before surgery. The mean baseline QRS duration in

the overall sample was 146 (±25.1) msec. In patients with baseline QRS < 160 msec and >160 msec was 138 (±22.1) and 175 (±7.28) respectively.

3.1 | Relationship between preoperative and postoperative QRS duration

Mean follow-up time to postoperative QRS duration assessment was 3 years (range 1 month, 19 years). Mean QRS duration within the first year from surgery was 142 ± 23 msec. After the first year, mean QRS duration was 146 ± 25 msec. The early reduction in QRS duration soon after surgery was minimal but evident (−2.98 msec ± 1.11 msec; $p < .01$; Figure 1). However, we found a steady significant increase in QRS duration of 0.42 msec ± 0.19 every year ($p = .03$) afterward

FIGURE 3 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative QRS ≥ 160 msec. Blue line represents the overall changes with its 95% confidence interval (long *x* axis: years from PVR). PVR, pulmonary valve replacement
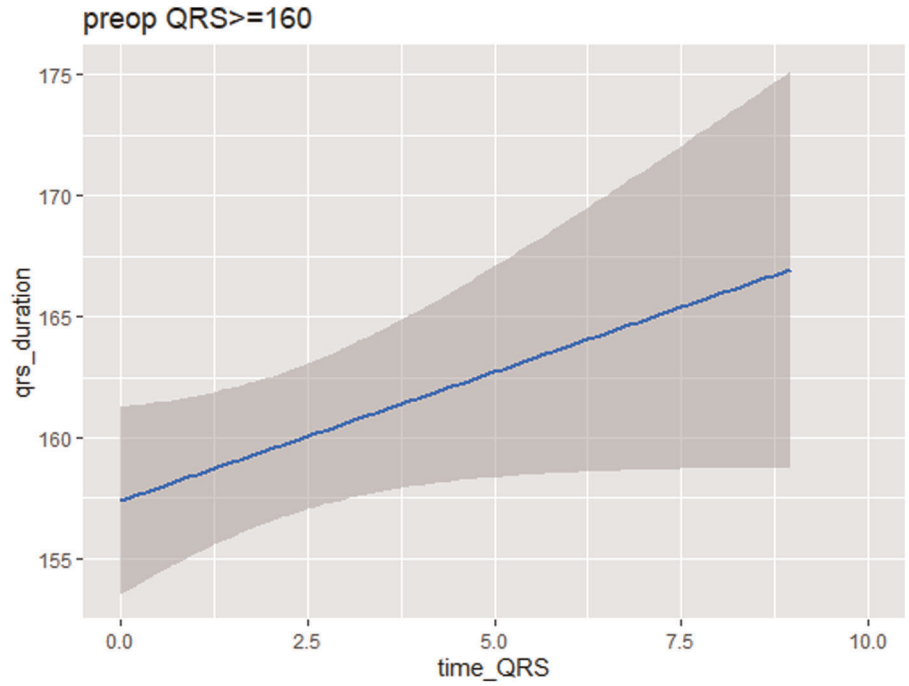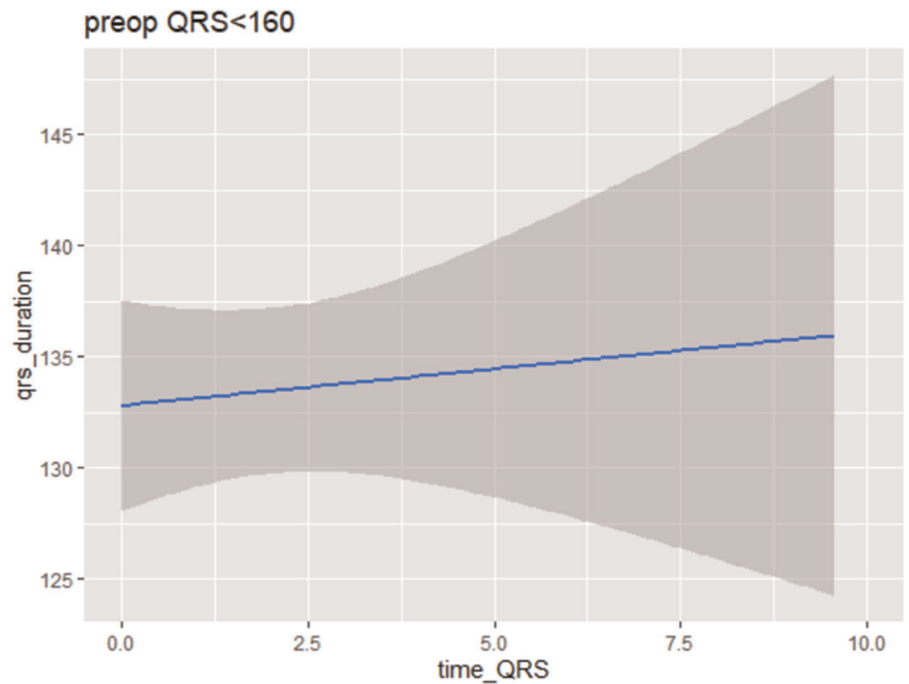

FIGURE 4 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative QRS < 160 msec. Blue line represents the overall changes with its 95% confidence interval (long *x* axis: years from PVR). PVR, pulmonary valve replacement

(Figure 2). When the analysis was stratified based on preoperative QRS duration, the QRS tended to increase over time in subjects with baseline QRS duration >160 msec ($p = .01$), with a rate of increase of 0.87 msec ± 0.33 per year; (Figure 3). However, there was no significant increase in the QRS duration in those with a baseline QRS duration <160 msec (rate of increase of 0.34 msec ± 0.24; $p = .16$) (Figure 4).

3.2 | Relationship between preoperative RV volumes and changes in QRS duration

Preoperative cMRI RV volumes were available in a subset of 83 patients. cMRI RV volumes in the overall sample and stratified by QRS duration are reported in Table 2. Patients characteristics stratified by baseline RV volumes are reported in Table S1. We found

	QRS ≤160 msec (N = 70)	QRS > 160 msec (N = 13)	Overall (N = 83)
RV ejection fraction			
Mean (SD)	48.2 (8.15)	47.6 (5.38)	48.1 (7.76)
RV end-diastolic volume (mml/m^2)			
Mean (SD)	145 (30.6)	175 (31.6)	150 (32.5)
RV end-systolic volume (mml/m^2)			
Mean (SD)	74.8 (19.0)	94.3 (16.8)	77.9 (19.9)
RV stroke volume (mml)			
Mean (SD)	70.5 (18.8)	86.5 (14.7)	73.1 (19.0)
PV regurgitant fraction (%)			
Mean (SD)	39.6 (11.6)	40.3 (11.5)	39.7 (11.6)

TABLE 2 Preoperative MRI volumes in patients with information from baseline cardiac MRI available (overall and stratified by baseline QRS duration)

Abbreviations: PV, pulmonary valve; RV, right ventricle.

FIGURE 5 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative right ventricular end-diastolic volume index (RVEDVi) ≥ 166 ml/m^2. Blue line represents the overall changes with its 95% confidence interval (long x axis: years from PVR). PVR, pulmonary valve replacement
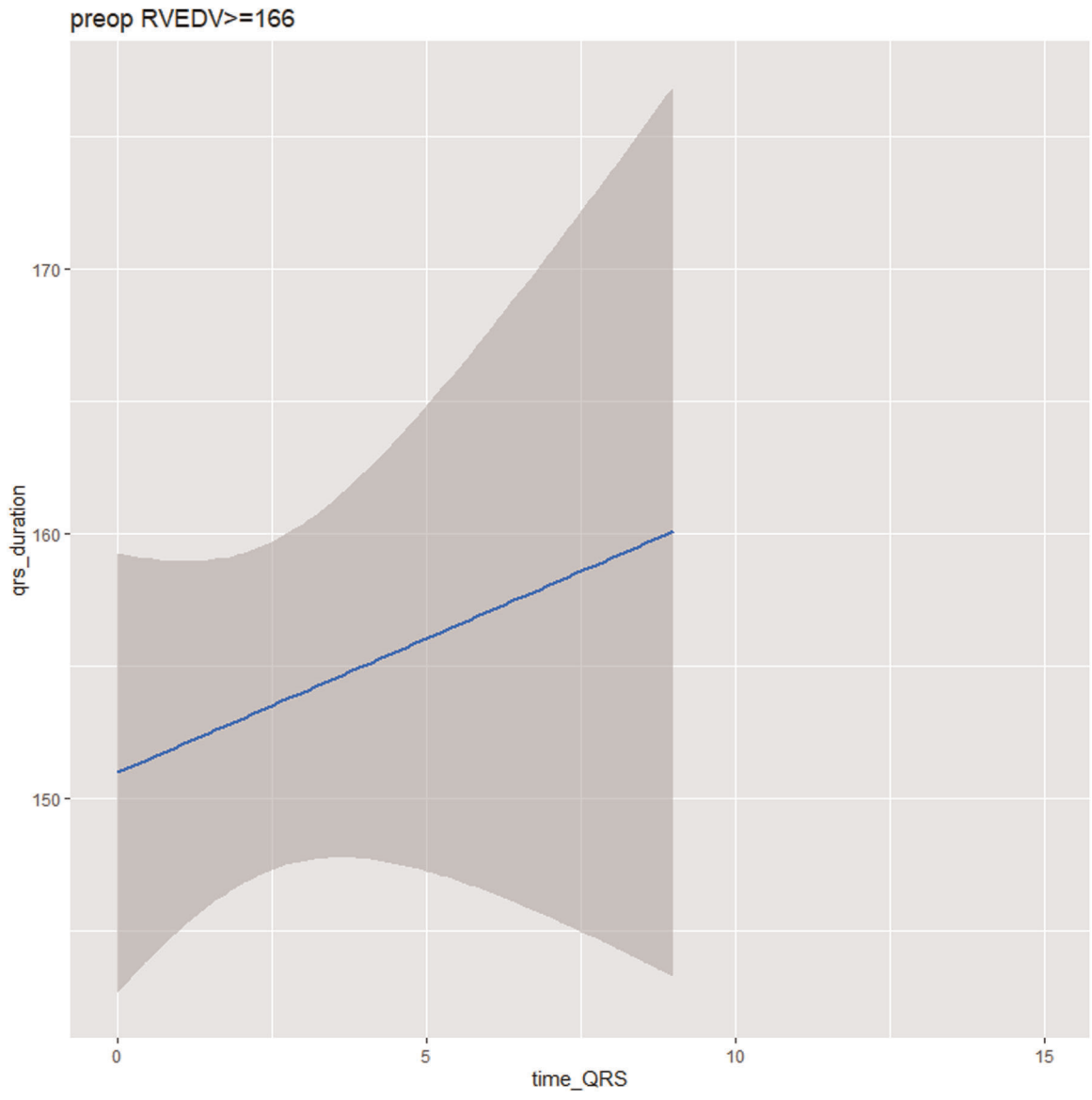
FIGURE 6 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative right ventricular end-diastolic volume index (RVEDVi) < 166 ml/m². Blue line represents the overall changes with its 95% confidence interval (long *x* axis: years from PVR). PVR, pulmonary valve replacement
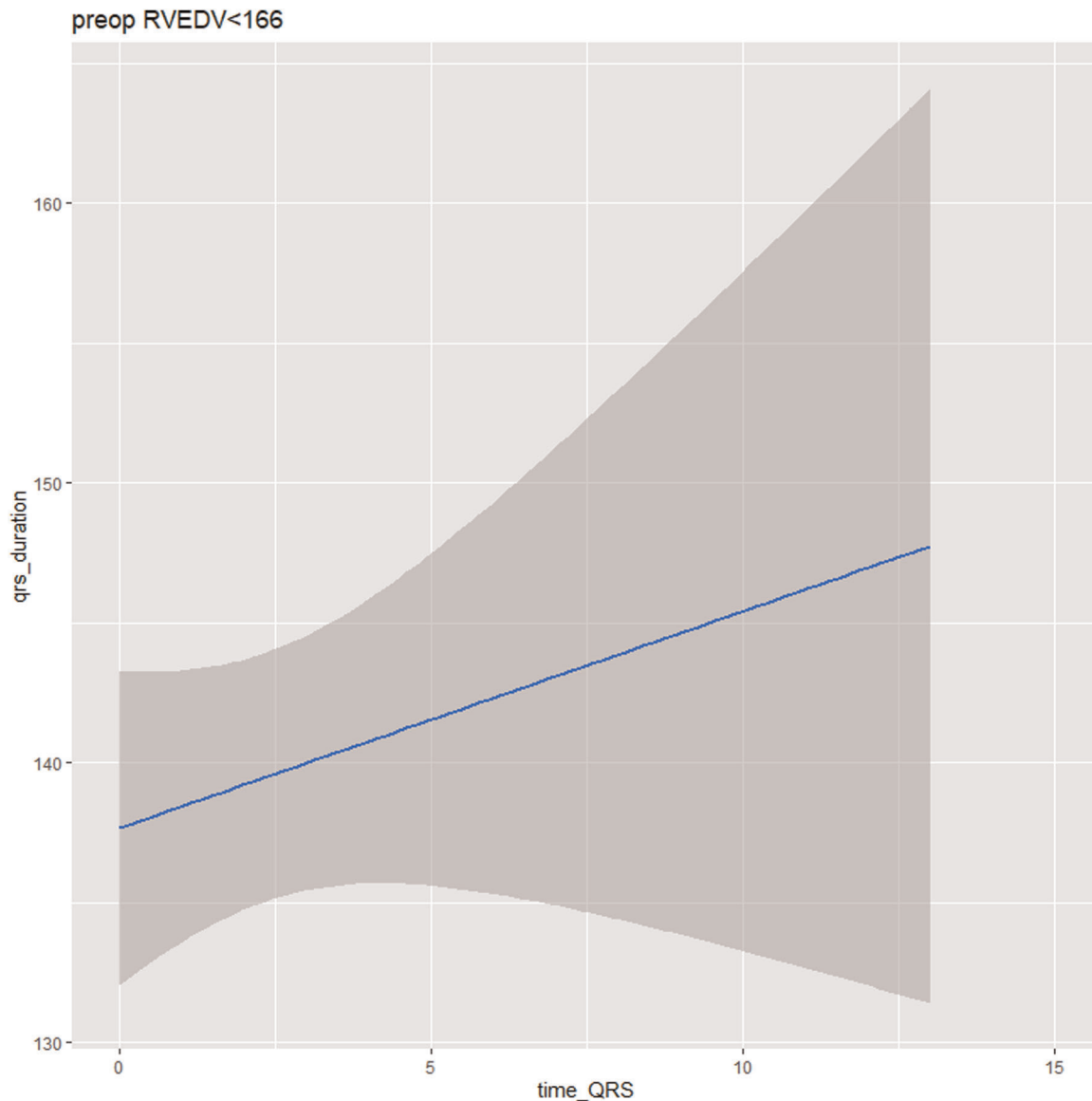
that QRS duration continued to increase postoperatively in patients with a preoperative RVEDV ≥ 166 ml/m² (2.0 msec ± 0.37 per year; $p < .01$, Figure 5), but not in those with RVEDV < 166 ml/m² (0.26 ± 0.33; $p = .14$, Figure 6). Furthermore, postoperative QRS duration tended to increase in subjects with large baseline RVESV (≥89 ml/m²) (1.25 msec ± 0.43 per year; $p = .01$, Figure 7), but not in those with smaller RVESV (<89 ml/m² (0.32 ± 0.36; $p = .37$, Figure 8).

4 | DISCUSSION

The main finding of the present study was that there was no decrease in postoperative QRS duration in TOF-repair patients undergoing subsequent PVR. The subsequent trajectory in the following years was influenced by preoperative QRS duration and RV volumes. In particular, patients with baseline QRS duration>160 msec or markedly dilated RV volumes (RVEDV ≥ 166 ml/m² and RVESV ≥ 89 ml/m²) demonstrated a slow but steady increase in postoperative QRS duration despite surgical intervention. In patients with shorter preoperative QRS duration and smaller RV volumes, the QRS duration remained unchanged.

While the association between preoperative and postoperative QRS duration has previously been reported, to the best of our knowledge this is the first study that demonstrates a positive correlation between preoperative RV volume and duration of QRS postoperatively. This information can be used to further inform on optimal timing to PVR in TOF repaired patients with PR.

The increase in RV volumes is determined by a dynamic component (i.e. volume overload) and an anatomic component
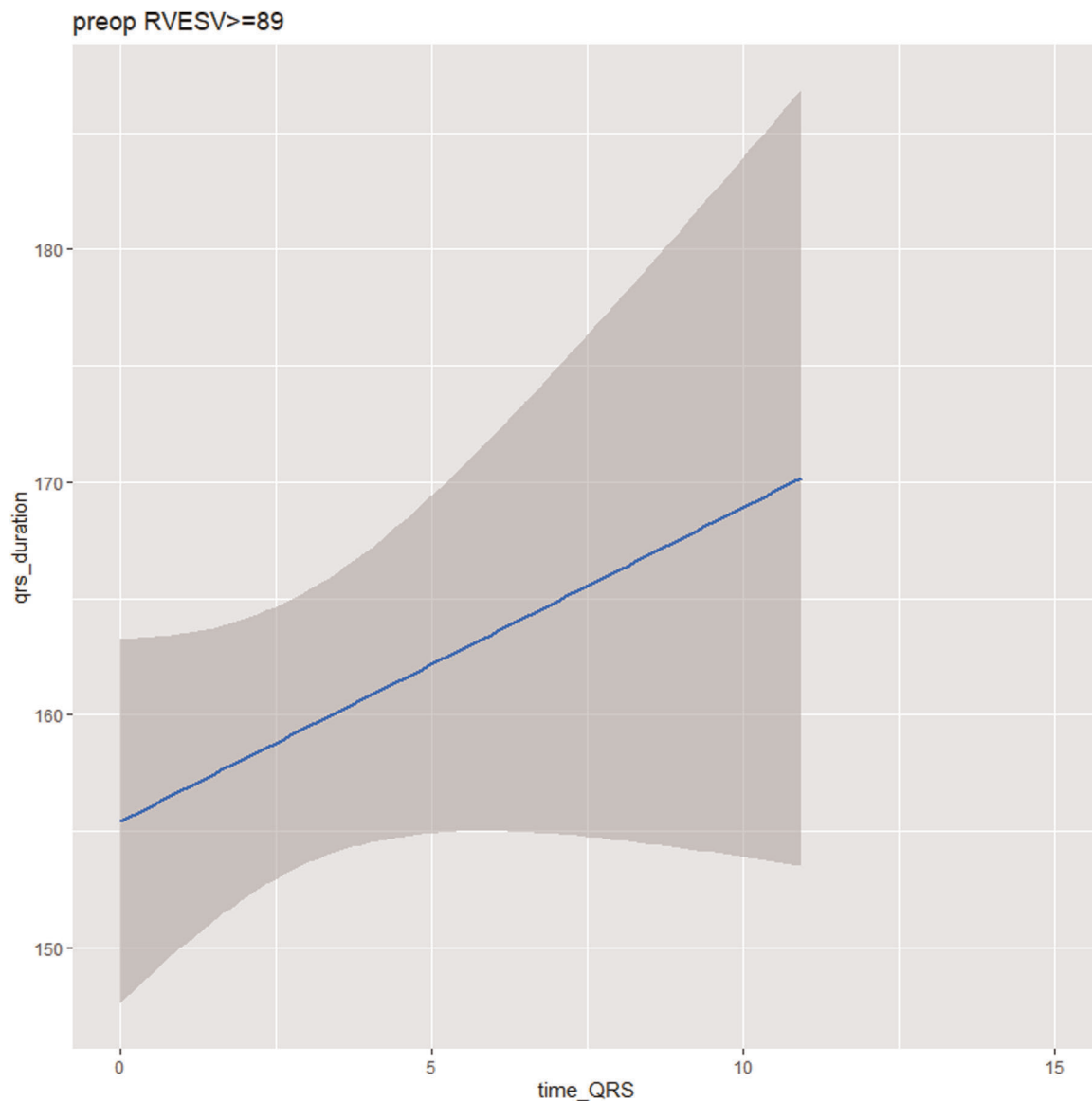
FIGURE 7 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative right ventricular end-systolic volume index (RVESVi) ≥ 89 ml/m^2. Blue line represents the overall changes with its 95% confidence interval (long *x* axis: years from PVR). PVR, pulmonary valve replacement

(hypertrophy and fibrosis). Even though the RV may have a degree of irreversible fibrosis and hypertrophy at the time of surgery, its volume will still decrease after PVR because of volume overload correction. However, fibrosis leads to irreversible anatomical damage to the intraventricular conduction system.[16] Once irreversible fibrosis is established, the electrical changes tend to persist and progress independent of postoperative changes in RV volume. This hypothesis represents the basis of the apparent mismatch between RV volume reduction in patients who do not show any improvement in QRS duration following PVR.[17] This hypothesis was confirmed by the present findings.

Whether the duration of QRS decreases after PVR remains controversial. Our series included patients who underwent surgery at an earlier stage where RV volumes were not severely affected but also patients who underwent surgery at an advanced stage with markedly dilated RV volumes and prolonged QRS, thus explaining the variability in QRS duration amongst our patients. Nevertheless, we found that regardless of the baseline characteristics, there were minimal changes in QRS duration after surgery. Any changes were subject to different trajectories according to baseline QRS. Our results are supported by a previous report from Oosterhof et al. showing that QRS duration decreased initially after surgery, but then slowly increased by 1.09 msec/years.[18] Contrarily, Therrien et al.[9] found no significant changes in QRS duration after surgery while other studies have reported a reduction in QRS duration. However, these studies had small sample sizes and limited follow-up.[10,19,20] A possible explanation of the discordant findings by the different groups may
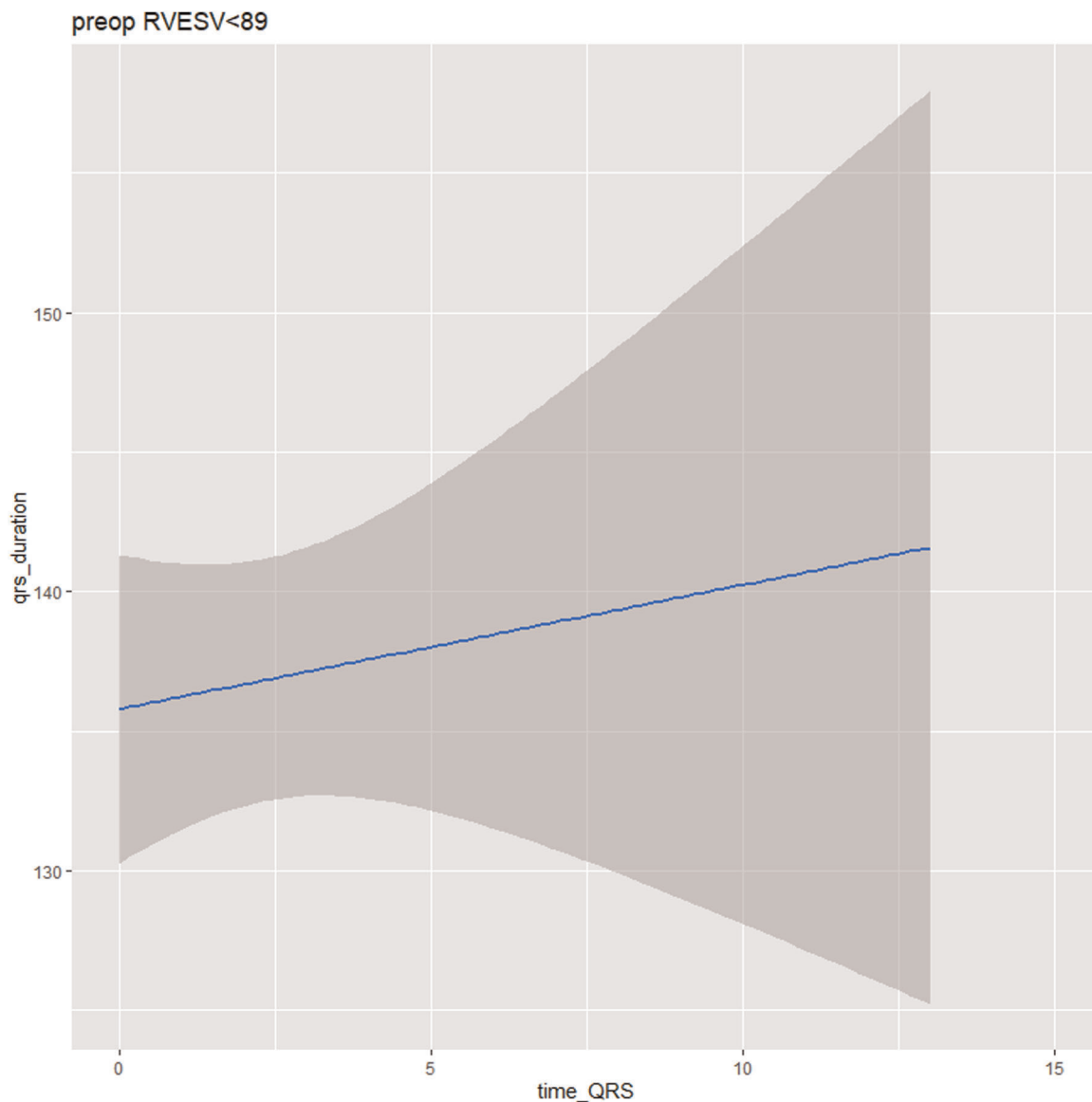
FIGURE 8 Graphical presentation of linear mixed model showing QRS changes after surgery in patients with preoperative right ventricular end-systolic volume index (RVESVi) < 89 ml/m². Blue line represents the overall change with its 95% confidence interval. (long *x* axis: years from PVR). PVR, pulmonary valve replacement

reside in the variability in the duration of follow-up between the series. We propose that those studies with a shorter follow-up are more likely to reflect a small initial reduction in the QRS duration, which is later neutralized by a progressive increase in QRS duration over an extended follow-up. Moreover, some of the previous studies did not account for longitudinal data which takes into consideration variation within the same subject.

It is well established that prolonged QRS duration can ultimately result in malignant arrhythmias and sudden death. Gatzoulis et al.[3] showed that patients with a QRS > 180 ms have a significant higher risk of developing sustained ventricular arrhythmias and sudden cardiac death during a 10-year follow-up. Other studies confirmed a direct relation between QRS duration and late arrhythmia presentation.[21,22] Ventricular tachycardias

and sudden cardiac death in TOF patients are solely determined by RV dilatation secondary to PR and therefore a timely correction of the valvular disease can dramatically improve clinical outcomes in these patients.[23] The optimal timing to perform the PVR remains controversial: when the surgery is performed later in life many patients experience irreversible damage to the RV, but, early surgery can lead to multiple re-operations over the years, which also increase global morbidity. However, in recent years, the impact of multiple surgeries has been mitigated by the novel techniques of percutaneous implantation of pulmonary valves. Therefore early surgery should not be denied solely on the basis of the risk of future reintervention. Indeed, a recent study from Romeo et al.[24] found that a longer period between repair and PVR is associated with the progression of QRS duration after PVR, and

seems to support early intervention. Our data support this finding that it is crucial to undertake PVR before the prolongation of QRS becomes irreversible.

5 | LIMITATIONS

The present study has limitations similar to any retrospective study. QRS duration information was obtained by clinical entry and letter from different clinicians over a long period of time and interobserver variability was not accounted for in the model. Secondly, the study sample was largely underpowered to investigate the effect of QRS prolongation on clinical outcomes (i.e., recurrence of VT) and therefore we can only speculate on long-term clinical consequences of prolonged QRS duration. Finally, the study population was enrolled for a long period of time and changes in patient management may have influenced the final results.

6 | CONCLUSION

The present analysis found that after PVR in post-TOF repair, in subjects with shorter QRS and smaller RV volumes, QRS duration remained unchanged after surgery. However, in those with prolonged QRS and dilated RV volumes, QRS tended to slowly but steadily increase after surgery. These findings provide guidance for clinicians on surveillance for patients with repaired TOF and PR. The QRS duration is a very practical and inexpensive variable to monitor, especially in primary care, and it can be used as an indication for further investigation and escalation of treatment. The present analysis supports the hypothesis of superior outcomes following the early intervention, that is, before QRS duration and RV volumes reach threshold values for nonreversibility. In particular, our analysis suggested that regardless of the presence of symptoms, patients with preoperative QRS approaching 160 msec or those with RVEDV ≥ 166 ml/m^2 or RVESV ≥ 89 ml/m^2 should be considered for intervention. Our results will need to be validated in other series.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Lucia Cocomello planned, conducted, and reported the work described in the article. Shubhra Sinha and Maria Cecilia Gonzalez Corcia reported the work described in the article. Mai Baquedano conducted the work described in the article. Umberto Benedetto and Massimo Caputo conducted and reported the work described in the article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.