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Follow-Up After Pulmonary Valve Replacement in Adults With Tetralogy of Fallot

Association Between QRS Duration and Outcome

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Objectives The aim of this study was to analyze whether QRS duration, before and after pulmonary valve replacement (PVR), is related to long-term outcome in patients with tetralogy of Fallot (TOF).

Background Key factors that determine outcome after PVR in adult TOF patients are largely unknown. Recognition of such factors assists the identification of patients at increased risk of adverse events.

Methods Adults who previously underwent total correction for TOF (n = 90; age 31.4 ± 10.3 years) and required PVR for pulmonary regurgitation were included. The QRS duration was measured pre-operatively and 6 months after PVR. The post-operative changes in QRS duration were calculated. Adverse events (death, re-PVR, ventricular tachycardia, and symptomatic heart failure) were noted during follow-up.

Results During 5.5 ± 3.5 years of follow-up, 13 adverse events occurred. The 5-year event-free survival rate was 76% for patients with a pre-operative QRS duration >180 ms and 90% in patients with a QRS duration ≤180 ms ($p = 0.037$). For patients with a post-operative QRS duration >180 ms, 5-year event-free survival was 71%, whereas it was 91% for patients with a post-operative QRS duration ≤180 ms ($p = 0.004$). After multivariate correction, a post-operative QRS duration >180 ms (hazard ratio: 3.685, 95% confidence interval: 1.104 to 12.304, $p < 0.05$) and the absence of a reduction in QRS duration post-PVR (hazard ratio: 6.767, 95% confidence interval: 1.704 to 26.878, $p < 0.01$), was significantly associated with adverse outcome.

Conclusions Severe QRS prolongation, before or after PVR, and the absence of a reduction in QRS duration after PVR, are major determinants of adverse outcome during long-term follow-up of patients with TOF. (J Am Coll Cardiol 2010;56:1486–92) © 2010 by the American College of Cardiology Foundation

Progressive pulmonary regurgitation (PR) is a common complication after total surgical correction of tetralogy of Fallot (TOF) (1). Long-standing PR leads to right ventricular (RV) dilation, which in turn causes RV dysfunction and reduced exercise tolerance (2,3). Pulmonary valve replacement (PVR) provides an adequate surgical therapy for PR as it leads to improvement of RV function and the patient's functional class (4). Numerous studies have indicated the beneficial effects of PVR in terms of improvement of RV volume and ejection fraction shortly after PVR (5–7). In addition, it was demonstrated that RV depolarization and repolarization characteristics improve after PVR, partly in response to the reduction in RV volumes (8,9). Specifically, QRS duration, which is strongly associated with RV function and prognosis in TOF (10), tends to reduce after PVR (8). In addition, it is known that TOF patients with severely prolonged QRS duration (>180 ms) are at risk for adverse events (11). Nevertheless, it is unclear whether an association exists between, on the one hand, pre-PVR QRS duration and post-PVR changes in QRS duration and, on the other hand, long-term outcome after PVR. Consequently, the clinical relevance of pre- and post-PVR QRS duration, and of changes in QRS duration after PVR, is presently unknown. The current study aimed to assess how pre-operative QRS duration and post-

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operative changes in QRS duration are related to outcome during long-term follow-up after PVR in TOF patients.

Methods

Study population. In a prospective, multicenter cohort study, adult patients after prior total repair for TOF, who had undergone a PVR for PR, were followed up (12,13). In all patients, primary surgical repair was performed during childhood. The indications for PVR were moderate to severe PR in combination with RV dilation and impaired New York Heart Association (NYHA) functional class (4). A standard 12-lead electrocardiogram (ECG) was obtained immediately before and 6 months after PVR. If an ECG was not available at 1 of the time points, patients were excluded from further analysis. All patients were followed up annually at the out-patient clinic, and the occurrence of adverse events was noted during follow-up after PVR. Adverse events were defined as death due to any cause, reoperation for recurrent pulmonary regurgitation, symptomatic heart failure, and ventricular arrhythmias.

Surgical procedures. The PVR was performed through median sternotomy. After release of adhesions, total cardiopulmonary bypass was started. A cryopreserved pulmonary homograft was implanted, usually on beating heart. If necessary, small residual ventricular septal defects were suture closed, and right ventricular outflow tract (RVOT) reconstruction was performed as described previously (12). In addition, when pre-operative assessment revealed significant tricuspid regurgitation, tricuspid annuloplasty was performed (14).

Electrocardiographic analysis. Electrocardiograms were stored digitally and exported from the ECG database management system for off-line analysis with the MATLAB-based (The MathWorks, Natick, Massachusetts) computer program LEADS (Leiden, the Netherlands). Details about the calculation methods used in LEADS have been reported previously (15). The software averages a digitized version of the standard 12-lead surface ECG into a representative single-beat ECG in which all 12 leads are superimposed. The software is equipped with a cross-hair editor interface that allows magnification of the ECG, and thereby facilitates accurate measurement of QRS duration according to the Minnesota criteria for population-based ECG studies (8). All ECGs were analyzed by a single observer blinded to the patient's clinical status and operation results. The cut-off for severely prolonged QRS duration was set at 180 ms (10,11).

Statistical analysis. The SPSS version 16.0.2 software (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. GraphPad Prism 4.00 for Windows (GraphPad Software, La Jolla, California) was used to obtain life tables and corresponding Kaplan-Meier survival curves.

First, pre- and post-operative QRS duration and NYHA functional class were compared using a paired *t* test. Second, the association between QRS duration and the occurrence of adverse events during post-operative follow-up was assessed using Cox's proportional hazards regression analysis. Univariate hazard ratios (HR) were calculated with corresponding 95% confidence interval (CI) for the following variables: 1) pre- and post-operative QRS duration as a continuous variable, in ms; 2) pre- and post-operative QRS duration as a categorical variable, ≤180 or >180 ms; 3) changes in QRS duration, from pre- to post-operative, as a continuous variable, in ms; and 4) changes in QRS duration, from pre- to post-operative, as a categorical variable, expressed as the presence or the absence of reduction in QRS duration. Afterward, the HRs were adjusted for age at PVR (below or above the median age of 30 years) and the presence of concomitant procedures during PVR, to obtain the multivariate HRs.

Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram
HR = hazard ratio
NYHA = New York Heart Association
PA = pulmonary artery
PR = pulmonary regurgitation
PVR = pulmonary valve replacement
RV = right ventricular
RVOT = right ventricular outflow tract
TOF = tetralogy of Fallot

Third, the annualized event rates were assessed in patient subgroups on the basis of the pre- and post-operative QRS durations (≤180 or >180 ms) in addition to the post-operative changes in QRS duration (reduction or no reduction). The number of observed events was normalized to 100 patient-years in each subgroup to facilitate comparison between groups. Afterward, the 95% CI of the observed event rate was calculated, and the difference in event rate was compared to the overall event rate by assuming that the number of observed events has a Poisson distribution.

Finally, to visualize the difference in event-free survival between different QRS duration patient categories, Kaplan-Meier curves were drawn and log-rank statistics were calculated for the following 3 patient subgroups: 1) pre-operative QRS duration ≤180 or >180 ms; 2) post-operative QRS duration ≤180 or >180 ms; and 3) changes in QRS duration, expressed as the presence or absence of a post-operative reduction in QRS duration. Separate Kaplan-Meier curves were obtained in which death, symptomatic heart failure, and ventricular arrhythmias were included as an end point and re-PVR was excluded.

Where appropriate, data are reported as mean ± SD, n (%), or as HR (95% CI). All p values <0.05 were considered statistically significant.

Results

Ninety-nine consecutive corrected TOF patients who underwent PVR at adulthood were considered for the study. Nine patients were excluded because of missing ECGs, and the remaining 90 patients were all included in the study (Table 1). The PVR was performed at an age of 31.4 ± 10.3 years, and pre-operative NYHA functional