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Authors
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Pulmonary valve replacement in patients with repaired tetralogy of Fallot: early results for recovery of right ventricular dilatation and QRS duration

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Background/aim: Although pulmonary valve replacement (PVR) improves ventricular function and symptoms, the benefit and optimal timing of PVR are controversial. This study aimed to evaluate early response to PVR for right ventricle (RV) dilatation and QRS duration.

Materials and methods: Retrospective analysis was performed for 32 patients with repaired tetralogy of Fallot (TOF) between March 2005 and October 2017. The differences between preoperative and postoperative changes in echocardiographic parameters, clinical symptoms, and QRS duration were evaluated.

Results: There were no in-hospital or late deaths. Mean age at the time of PVR was 16.57 ± 7.97 years. The interval between TOF repair and PVR was 12.99 ± 7.06 years. Postoperative echocardiographic findings showed significant reduction in indexed RV end-diastolic diameter (RV-EDDI) and the ratio of RV/LV-EDDI (P = 0.001 and P = 0.001, respectively). Higher preoperative RV-EDDI was associated with decreased change in RV-EDDI after PVR (r = 0.63; P = 0.001). Normalization of RV diameters was found to be independent of age at PVR, interval between TOF repair and PVR, preoperative QRS duration, and preoperative RV-EDDI.

Conclusion: Significant improvement in RV diameter and symptoms could be obtained with PVR in patients with severe pulmonary regurgitation.

Key words: Tetralogy of Fallot, pulmonary regurgitation, pulmonary valve replacement, ventricular remodeling, QRS duration

1. Introduction
An increase in the number of tetralogy of Fallot (TOF) repair survivors led to an increase in surgical reintervention as relief of right ventricular (RV) outflow tract obstruction often results in severe pulmonary regurgitation (PR), especially in those repaired with a transannular patch (1). Chronic RV volume overload due to severe PR causes RV dilatation and dysfunction, right heart failure, ventricular arrhythmias, and death (2). Restoration of pulmonary valve competency via pulmonary valve replacement (PVR) can lead to improvement in symptoms of RV failure, reduction and normalization in RV volume, and reduction of QRS duration and ventricular arrhythmias (3,4).

The current indication for PVR is the presence of symptoms in patients with severe PR, but optimal timing of PVR in asymptomatic patients remains controversial (5,6). Cardiovascular magnetic resonance (CMR) has become the gold standard for evaluation of RV volumes and for deciding indications for intervention. We aimed to evaluate early response to PVR and early outcomes of PVR in patients with repaired TOF.

2. Materials and methods
Thirty-two patients who underwent PVR from March 2005 to October 2017 for chronic PR after total correction of TOF with transannular patching were included. Patients with other congenital heart disease-related severe PR were excluded from the study.

The diagnostic tools were transthoracic echocardiography (TTE) in all patients and CMR (3.0 T, Siemens Inc.) in 18 patients. The decision-making process for PVR includes symptoms of heart failure and evidence
of increased RV volume and diameter. Indexed RV end-diastolic diameter (RV-EDDI) according to TTE, indexed RV end-diastolic volume (RV-EDVI) of >170 mL, and RV ejection fraction (RV-EF) of <45% according to CMR were considered as an indication for PVR. RV diameters were indexed to body surface area. Normalization in RV-EDDI was defined by comparison with age-matched diameters obtained from the study of Koestenberger et al. (7).

Echocardiographic data and QRS duration before PVR were compared with data after PVR. Parameters of preoperative QRS duration, the interval between TOF repair and PVR, age at PVR, and preoperative RV-EDDI were studied to evaluate the response to PVR according to normalization of right ventricular diameters. Since 2009, we have performed cardiac CMR as a part of routine preoperative evaluation for PVR, and 18 patients (56.25%) have undergone the procedure. Therefore, preoperative CMR data were available for 18 patients. Moreover, the relationship between preoperative CMR parameters including RV-EDVI, RV-ESVI, PR fraction (PRF), RV-EF, and left ventricular (LV) EF (LV-EF) were analyzed.

2.1. Surgical technique

The surgical approach to all presented patients was performed through median resternotomy on cardiopulmonary bypass with mild hypothermia. PVR was performed by on-pump beating heart technique in 22 patients and under aortic cross-clamping in 10 patients who required additional surgical procedures or depending on the surgeon's preference. The choice of the size and type of prosthetic pulmonary valves was dependent on the size of the right ventricular outflow tract and the surgeon's preference. All of the prosthetic valves were biological (Table 1). When considered necessary, RV aneurysm resection, plication, or RV remodeling was performed according to the surgeon's preference. RV remodeling was achieved with aneurysm resection in 13 patients, using bovine pericardium in 17 patients, and with RV aneurysm plication in two patients. Additional surgical procedures were performed concomitantly in patients with a residual ventricular septal defect and severe tricuspid regurgitation (Table 1).

2.2. Statistical analysis

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software program (Kaysville, UT, USA). The Mann–Whitney U test was performed for comparison of the nonnormal distribution of parameters between groups as well as descriptive statistical methods (mean, standard deviation, median, frequency, and ratio). The Wilcoxon signed ranks test was used for comparison of preoperative and postoperative parameters with nonnormal distribution. Spearman correlation analysis was used to evaluate intervariable relationships. The results were evaluated in a confidence interval of 95%, and a level of 0.05 was used to test for significance.

### Table 1. Operative data.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ± SD</th>
<th>Min–max (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC time (min)</td>
<td>10</td>
<td>104.00 ± 41.87</td>
<td>46–190 (105)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>32</td>
<td>113.66 ± 60.01</td>
<td>50–289 (97.5)</td>
</tr>
<tr>
<td>Being heart technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of prosthetic pulmonary valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorin Soprano Bioprosthesis</td>
<td>10</td>
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<td></td>
</tr>
<tr>
<td>St Jude Biocor Bioprosthesis</td>
<td>10</td>
<td>31.25</td>
<td></td>
</tr>
<tr>
<td>Sorin Mitrolow Bioprosthesis</td>
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<td>18.75</td>
<td></td>
</tr>
<tr>
<td>Edwards Magna Bioprosthesis</td>
<td>4</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Metronic Duran AnCore Bioprosthesis</td>
<td>1</td>
<td>3.125</td>
<td></td>
</tr>
<tr>
<td>Edwards Perimount Magna Bioprosthesis</td>
<td>1</td>
<td>3.125</td>
<td></td>
</tr>
<tr>
<td>Size of prosthetic pulmonary valve (mm) (mean/min–max)</td>
<td>32</td>
<td>24.5</td>
<td>20–29 (25)</td>
</tr>
<tr>
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<tr>
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<tr>
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<tr>
<td>PA reconstruction</td>
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<td>6.2</td>
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</tr>
<tr>
<td>Pacemaker implantation</td>
<td>4</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

3. Results
3.1. Patient characteristics
Demographic and other patient-related data were retrospectively reviewed from medical records of our center. The demographic and preoperative characteristics of patients are detailed in Table 2. Nine were female (28.1%) and 23 were male (71.9%). The mean age of the patients at the time of PVR was 16.57 ± 7.97 years (range: 5.5 to 40.8 years), and the mean interval between initial TOF repair and PVR was 12.99 ± 7.06 years (range: 1.5 to 35.8 years). The mean follow-up time after PVR was 49.03 ± 38.65 months (range: 6 to 148 months).

3.2. Echocardiographic findings
Table 3 summarizes the differences in echocardiographic parameters before and after PVR. LV-EDDI and LV-SF showed no significant differences (P = 0.52 and P = 0.18, respectively). However, there was significant reduction in RV-EDDI (P = 0.001). The difference in means for LV-EDDI and RV-EDDI is also shown in Figure 1. The ratio of RV/LV-EDDI was decreased significantly after PVR (P = 0.001).

The association between preoperative RV-EDDI or QRS duration and the changes in LV-EDDI, LV-SF, and RV-EDDI after PVR are shown in Table 4. Higher preoperative RV-EDDI was associated with decreased change in RV-EDDI after PVR (r = 0.63; P = 0.001). There was no significant association between preoperative QRS duration and LV-EDDI, LV-SF, or RV-EDDI changes after PVR. However, significant correlation was observed between TOF repair-PVR interval and change in RV-EDDI (r = 0.47; P = 0.008) (Figure 2).

Normalization of right ventricular diameters after PVR was not found to be associated with age at PVR, the interval between TOF repair and PVR, preoperative QRS duration, or preoperative RV-EDDI (Table 5). RV shortening fraction became normal in all patients after PVR, which were moderately reduced in 13 patients and severely reduced in 2 patients preoperatively.

3.3. Patients with preoperative CMR
Preoperative CMR findings are detailed in Table 6. Higher RV-EDVI was strongly associated with higher RV-ESVI, as shown in Figure 3 (r = 0.95; P = 0.001). PRF was found to be strongly associated with RV-EDVI (r = 0.75; P = 0.001). Increasing RV-EDVI and RV-ESVI were correlated with lower RV-EF (r = –0.59, P < 0.01; r = –0.75, P = 0.001, respectively). Moreover, positive correlation between RV-EF and LV-EF was detected (r = 0.51; P < 0.05). However, preoperative QRS duration was not associated with RV-EDVI (r = –0.33; P = 0.17).

3.4. Comparison between echocardiography and cardiac CMR
There was a positive relationship between preoperative RV-EDVI and preoperative RV-EDDI, but this relationship was not significant (r = 0.290; P = 0.243).

3.5. Clinical outcome and early-term follow-up
There were no in-hospital deaths. The mean length of intensive care unit and hospital stays was 1.08 days (range: 0.7 to 2.1 days) and 7.62 days (range: 5 to 13 days), respectively. In follow-up, more than mild tricuspid insufficiency was not observed in patients who underwent tricuspid annuloplasty due to severe regurgitation. Two patients underwent redo PVR during follow-up due to valve endocarditis and valve degeneration 4 and 10 years after initial PVR, respectively. One patient needed balloon valvuloplasty 6 years after PVR. There was only one patient with more than NYHA class II symptoms, and all patients had NYHA I (26 patients) or II (5 patients) symptoms after PVR. In follow-up, atrial fibrillation was observed in 1 patient, and there were no significant rhythm abnormalities among the other patients. There was a significant reduction in QRS duration.
after operation (141 ± 23 ms vs. 97 ± 21 ms; P = 0.001), and no patient had values of >140 ms. However, preoperative RV-EDDI was found not to be associated with change in QRS duration (r = −0.25; P = 0.164).

4. Discussion

Because of the lack of consensus, the question of when to perform PVR is controversial in patients with repaired TOF who develop severe PR. Chronic severe PR results in progressive right ventricular dilatation, RV dysfunction, propensity towards arrhythmias, and sudden death (8,9). This raises the questions of whether patients should have undergone earlier PVR and whether such a management strategy would lead to better outcomes. However, the conservative approach to avoid early reoperation contradicts with the idea of more aggressive PVR for preserving right ventricular function.

Our study demonstrated a close relationship between RV-EDVI and RV-ESVI, PRF and RV-EDVI, and RV-EDVI and RV-EF, as reported by previous studies (10). It is reported that the echocardiographically measured RV-EDDI correlated modestly with the CMR-calculated RV-EDVI (11). Although we found a positive relationship between the two methods, it was not significant. This reconfirmed that the pathophysiological process caused by pulmonary regurgitant flow resulted in ventricular dilation and eventually ventricular dysfunction. Longer QRS duration was not found to be associated with larger RV volumes, and this finding reflects that the ventricular conduction system was affected by the pathophysiological process in the ventricular wall without reaching high RV volumes.

PVR can be performed electively with low operative mortality, but patients are exposed to the risk of repeat PVR (3). While Lee et al. reported operative mortality as 1.2%, operative and 30-day mortality were not observed among our patients (10). The 4-year survival rate was satisfactory. Besides, the long-term survival benefit of PVR is not clear. No difference of death and VT between PVR and non-PVR patients was reported (12,13). Despite satisfactory results with respect to operative mortality having been obtained, long-term results of freedom from redo intervention are unsatisfactory due to the weakness of biological valve durability. In our study, freedom from redo PVR in 4-year follow-up was similar to that in the literature (14).
Previous studies provide significant knowledge about the response to PVR for those patients who: 1) present a defined reduction in PRF; 2) have normalization of RV dimensions; 3) have a decrease in QRS duration and incidence of symptomatic arrhythmias; 4) have an improvement of symptoms (12,15). Reduction in RV diameters, decrease in QRS duration, and improvement of heart failure symptoms have been reconfirmed by our study. Despite no significant increase being observed in LV-EDDI and LV-SF, the mean of the RV/LV-EDDI ratio showed significant reduction after PVR, as it did in the metaanalysis by Ferraz Cavalcanti et al (6). Frigola et al. documented an increase in LV-EDV after PVR, suggesting better LV filling due to improved pulmonary flow and right ventricular function (16). An improvement of LV systolic function was not observed in our study, unlike another study by Frigola et al. (17).

Therrian et al. reported an upper threshold (RV-EDVI of >170 mL/m²) beyond which optimal outcome

<table>
<thead>
<tr>
<th>Changes</th>
<th>Pre-op QRS duration</th>
<th>Pre-op RV-EDDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>LV-EDDI (mm/m²)</td>
<td>32</td>
<td>−0.009</td>
</tr>
<tr>
<td>LV-SF (%)</td>
<td>32</td>
<td>−0.072</td>
</tr>
<tr>
<td>RV-EDDI (mm/m²)</td>
<td>32</td>
<td>−0.159</td>
</tr>
</tbody>
</table>

r: Spearman’s correlation coefficient

*P < 0.05

**P < 0.01

LV-EDDI: Indexed left ventricular end diastolic diameter, LV-SF: left ventricular shortening fraction, RV-EDDI: indexed right ventricular end diastolic diameter.

Figure 2. Correlation between TC-PVR interval and change in RV-EDDI (TC-PVR: total correction-PVR interval, RV-EDDI: right ventricular end-diastolic diameter).

Table 5. Evaluation of factors on normalization of RV-EDD.

<table>
<thead>
<tr>
<th></th>
<th>Nonnormalized RV-EDD</th>
<th>Normalized RV-EDD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>Age at PVR (years)</td>
<td>7</td>
<td>18.21 ± 6.69</td>
<td>24</td>
</tr>
<tr>
<td>TOF repair-PVR interval (s)</td>
<td>7</td>
<td>13.79 ± 5.43</td>
<td>24</td>
</tr>
<tr>
<td>Preop QRS duration (s)</td>
<td>7</td>
<td>1.48 ± 0.17</td>
<td>24</td>
</tr>
<tr>
<td>Preop RV-EDDI (mm/m²)</td>
<td>7</td>
<td>3.68 ± 1.21</td>
<td>24</td>
</tr>
</tbody>
</table>

Mann–Whitney U test

PVR: Pulmonary valve replacement, TOF: tetralogy of Fallot, TR: tricuspid regurgitation, RV-EDDI: indexed right ventricular end diastolic diameter.
Table 6. Preoperative CMR findings.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Min–max (median)</th>
<th>Mean ± SD</th>
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</thead>
<tbody>
<tr>
<td>RV-EDVI (mL/m²)</td>
<td>18</td>
<td>83.7–233.9 (157.5)</td>
<td>164.42 ± 45.2</td>
</tr>
<tr>
<td>RV-ESVI (mL/m²)</td>
<td>18</td>
<td>44.5–174.1 (98.5)</td>
<td>99.83 ± 36.54</td>
</tr>
<tr>
<td>PRF (%)</td>
<td>18</td>
<td>29–69 (49)</td>
<td>48.66 ± 11.22</td>
</tr>
<tr>
<td>LV-EDVI (mL/m²)</td>
<td>18</td>
<td>45.1–89.2 (74.3)</td>
<td>68.39 ± 14.65</td>
</tr>
<tr>
<td>LV-ESVI (mL/m²)</td>
<td>18</td>
<td>19–52.4 (35.4)</td>
<td>34.02 ± 9.77</td>
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<tr>
<td>LV-EF (%)</td>
<td>18</td>
<td>32.4–66.6 (51.6)</td>
<td>51.62 ± 8.9</td>
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<tr>
<td>RV-EF (%)</td>
<td>18</td>
<td>23–57.3 (40.5)</td>
<td>40.32 ± 7.87</td>
</tr>
<tr>
<td>RV-EDVI/LV-EDVI</td>
<td>18</td>
<td>1–3.6 (2.4)</td>
<td>2.35 ± 0.62</td>
</tr>
</tbody>
</table>

RV-EDVI: Right ventricular end diastolic volume index, RV-ESVI: indexed right ventricular end systolic volume index, PRF: pulmonary regurgitation fraction, LV-EDVI: left ventricular end diastolic volume index, LV-ESVI: indexed left ventricular end systolic volume index, LV-EF: left ventricular ejection fraction, RV-EF: right ventricular ejection fraction.

Figure 3. Associations between CMR findings (n = 18): A) Correlation between right ventricular (RV) end-diastolic volume index (EDVI) and RV end-systolic volume index (RV-ESVI); B) correlation between pulmonary regurgitation fraction (PRF) and RV-EDVI; C) correlation between RV ejection fraction (RV-EF) and RV-EDVI; D) RV-EF and RV-ESVI; E) left ventricular ejection fraction (LV-EF) and RV-EF.
Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, some authors (20,21), significant decrease was observed no reduction of QRS duration after PVR was reported by achieved even in patients with late intervention. While optimal results (normalized RV diameters) may be observed to be independent of age at PVR, the interval of TOF repair-PVR, preoperative QRS duration, and of RV diameters after PVR, these results suggest that right ventricular diameters lead to decrease in improvement preoperative RV-EDDI. Although increased preoperative normalization of right ventricular diameters has been better improvement in RV volumes (19). In our study, the postoperative period (6).

Büchel et al. showed that early PVR resulted in better improvement in RV volumes (19). In our study, normalization of right ventricular diameters has been observed to be independent of age at PVR, the interval of TOF repair-PVR, preoperative QRS duration, and preoperative RV-EDDI. Although increased preoperative right ventricular diameters lead to decrease in improvement of RV diameters after PVR, these results suggest that optimal results (normalized RV diameters) may be achieved even in patients with late intervention. While no reduction of QRS duration after PVR was reported by some authors (20,21), significant decrease was observed in our study, like those of other authors (22,23). Harrild et al. reported no change of QRS duration in enrolled patients with relatively longer baseline QRS duration and advocated the significance of aggressive surgical PVR before severe RV dilation to provide better results in terms of QRS duration (12). This speculation was not supported by our study and change of QRS duration was found to be independent of preoperative RV diameters.

In conclusion, PVR can be performed with low mortality rates in patients with repaired TOF who develop severe pulmonary regurgitation. Significant reduction of RV diameters and QRS duration and improvement in heart failure symptoms could be obtained. This study advocated that optimal results may be achieved even in patients with larger RV diameters.

We acknowledge that our study has several limitations. First, the retrospective study design is a limitation in itself. Larger series of patients and longer follow-up are required to clearly show indicators for better outcome, and there is a need for further studies with regard to these issues to further clarify the factors in RV normalization and for better outcomes. It is also unknown how residual defects (ventricular septal defect and tricuspid valve regurgitation) affect RV dilatation and the contribution of repair of residual defects on the recovery of RV.

References


