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# The left heart after pulmonary valve replacement in adults late after tetralogy of Fallot repair

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ABSTRACT

*Background:* Adverse ventricular-ventricular interactions have been recognized in those with repaired tetralogy of Fallot (TOF) and severe pulmonary regurgitation.
*Objective:* We aimed to examine the impact of pulmonary valve replacement (PVR) on the left heart late after TOF repair.
*Methods and results:* Left ventricular (LV) volumes and ejection fractions (EF) were analyzed in adults with severe pulmonary regurgitation after TOF repair with cardiac magnetic resonance imaging (CMR) before and after PVR. Thirty-nine patients (median age 33[20–65] years) were reviewed. Post-PVR, LVEF improved significantly in the entire cohort ($50 \pm 9\% \rightarrow 54 \pm 7\%$, $p<0.001$) and in those with moderately impaired (defined as LVEF ≤45%) preoperative LVEF ($38 \pm 5\% \rightarrow 47 \pm 6\%$, $p<0.0001$), but was not statistically different in those with relatively preserved (defined as LVEF >45%) preoperative LVEF. By multivariate linear regression analysis to evaluate independent CMR predictors of improved LVEF post-PVR for the entire cohort, the only CMR variable to emerge was preoperative LVEF ($p=0.012$, regression coefficient −0.54, SE 0.13). Whereas PVR resulted in increased LV filling in patients with relatively preserved preoperative LVEF reflected by an increase in LV end-diastolic volumes ($77 \pm 10 \rightarrow 82 \pm 16$ mL/m$^2$, $p=0.05$), LV end-systolic volumes decreased after PVR in patients with impaired preoperative LVEF ($65 \pm 12 \rightarrow 54 \pm 10$ mL/m$^2$, $p=0.001$) but LV end-diastolic volumes were not significantly changed.
*Conclusion:* When LVEF is decreased after TOF repair, PVR appears to have a salutary effect on postoperative LVEF, thereby supporting the concept of recovery of adverse right–left heart interactions. Mechanisms of left heart improvement post-PVR differ depending on degree of preoperative LV systolic dysfunction.


Much of the existing literature examining the impact of pulmonary valve replacement (PVR) in adults after tetralogy of Fallot (TOF) repair focuses predominantly on right heart form and function [1–5]. There is an emerging awareness, however, of the effect of biventricular systolic dysfunction on late outcomes. A strong correlation between right ventricular (RV) and left ventricular (LV) ejection fraction (EF) exists after TOF repair [6] and the deleterious effect of severe pulmonary regurgitation (PR) on LV systolic function attributed to ventricular-ventricular interaction has been described [7]. The presence of left heart dysfunction in the context of significant right heart disease has been linked to adverse events, including progressive heart failure and death [8–10].

The impact of PVR on the left heart in adults has not been well studied to date. Recently, in a prospective study of a relatively young cohort reported by Frigiola and co-workers [11], PVR was associated with normalization of right heart size and improvement of biventricular systolic function, with the greatest benefits demonstrated in the pediatric age group. However, there was no apparent attempt to stratify for the degree of preoperative LV dysfunction, or to examine differential modes of ventricular recovery. Thus, in this study, we sought to examine the mechanism of recovery of adverse right–left heart interactions after PVR in an exclusively adult population of patients late after TOF repair.

## 1. Methods

### 1.1. Study population

Adults with repaired TOF were included for analysis if: (1) they had undergone PVR for significant PR (in the absence of important pulmonary stenosis) after 2003 (2) they

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had cardiac magnetic resonance imaging (CMR) studies before and after valve replacement. Patients were excluded if the CMR dataset was incomplete or insufficient for analysis. Our institutional Research Ethics Board approved the study.

### 1.2. Patient data

Clinical data were retrospectively abstracted from hospital medical records including date of birth, gender, anatomic diagnosis, surgical history, date of PVR and date of CMR acquisition. Functional status, QRS duration and QRS axis on electrocardiography (ECG) were reviewed before and after PVR and were contemporaneous with the CMR examinations. The severity of valvular insufficiency outside of the pulmonary valve was assessed on echocardiography and graded as mild, moderate or severe [12].

### 1.3. Cardiac magnetic resonance imaging

The CMR protocols and technical acquisition parameters utilized at our institution for the evaluation of global ventricular systolic function, ventricular volumes, and PR have been recently published in detail [13]. Briefly, studies were performed using a commercially available 1.5 T scanner. Steady-state free-precession imaging of the ventricles in two- and four-chamber planes was performed followed by prescription of contiguous short-axis slices (8–10 mm thick) oriented perpendicular to the long-axis of the LV as well axial imaging to cover the heart from base to apex. End-diastolic volumes (EDV) and end-systolic volumes (ESV), stroke volumes, and EF were obtained using a commercially available software package (MASS, Medis, Leiden, The Netherlands). All volumes were indexed ($_i$) to body surface area. Pulmonary regurgitation fraction was quantified using phase contrast flow analysis as well as comparison of stroke volume differentials between right and left ventricles. Gadolinium was not consistently administered therefore myocardial fibrosis and/or scar could not be excluded. Additional volumetric data were acquired for "full heart volumes", a novel measure, to look for elements of pericardial constraint with contours drawn around the visceral pericardium in the axial plane in ventricular diastole for all patients before and after PVR; atrial volumes in end-diastole and end-systole were similarly acquired as a marker of elevated ventricular filling pressures.

### 1.4. Statistical analysis

Data analysis was performed using SPSS software (version 17.0, SPSS Inc., Chicago, Illinois). Data are described as medians with ranges or means with standard deviations, as appropriate. Comparisons of continuous or categorical variables were performed with Student's *t* test or Mann–Whitney test, and Chi-squared tests or Fisher exact test, as appropriate. Statistical significance was set at $p<0.05$. Comparisons were made between subgroups of patients with moderate impairment of LV systolic function preoperatively, previously determined as LVEF ≤45% [14] and relatively preserved preoperative LV systolic function (defined as LVEF >45%), as determined by CMR. Pearson correlation coefficients were used to determine associations between ventricular size, ventricular function and QRS duration, before and after PVR. Linear regression analysis with backwards selection was used to determine CMR parameters that were independently associated with improvement in LVEF after PVR. Only variables defined as $p<0.1$ on univariate analysis were entered into the model. Receiver–operator curves were constructed to determine whether magnitude of change in RVEDV or RVESV related to PVR (expressed as Δ z-score [15]) could discriminate between those with and without improvement in LVEF post-operatively.

## 2. Results

### 2.1. Patient data

A total of 44 patients met the inclusion criteria, as described above. Five patients were excluded due to incomplete/insufficient CMR datasets, leaving 39 patients for analysis. Baseline demographics, surgical history and clinical data are summarized in Table 1. Pulmonary valves implanted at our institution were all bioprosthetic in nature (Hancock n = 23 [59%], mosaic n = 14 [36%], allograft or others n = 2 [5%]). Pulmonary valve diameter (mm) was 27 (n = 6 [15%]), 29 (n = 19 [49%]), 31(n = 13 [34%]), and 33 (n = 1 [3%]). Surgical variables were explored for the entire population, including cardiopulmonary bypass time, cross clamp time, mean pulmonary valve diameter and effective orifice area of the implanted pulmonary valve indexed to body surface area. When the population was stratified based on preoperative LV systolic function there were no statistically significant differences between groups with impaired versus preserved preoperative LVEF with respect to the aforementioned surgical parameters.

After PVR, 19 patients demonstrated improvement in their NYHA class, 20 remained unchanged and in no patient did NYHA functional class worsen (preoperative versus postoperative NYHA functional class for entire group, $p<0.001$). Medical therapy for the entire population consisted of low dose beta-blockade started in the context of postoperative arrhythmia (n = 3 in the subgroup with preserved preoperative LV function and n = 1 with impaired LV function). There was no statistically significant difference in resting blood pressure before or after PVR (for the entire population or for groups stratified by LV dysfunction). One patient had moderate mitral insufficiency (mild in 9, and absent or trivial in the remainder) and none had more than mild aortic insufficiency before PVR. None of the patients had documented coronary artery disease.

### 2.2. CMR Results

#### 2.2.1. CMR results for the entire population before and after PVR

The CMR results for the entire population before and after PVR are summarized in Table 2. Time interval between PVR and postoperative CMR was 2.4 ± 1.5 years (not statistically different for groups stratified by LV dysfunction). Lower preoperative LVEF was associated with lower preoperative RVEF ($r = 0.49$, $p = 0.002$). However, preoperative LVEF was not associated with preoperative $RVEDV_i$, $RVESV_i$ or PR fraction. After PVR, LVEF improved from 50 ± 9% to 54 ± 7% ($p<0.001$) without a statistically significant change in $LVEDV_i$ or $LVESV_i$. The correlation between preoperative LVEF and improvement in LVEF after PVR is illustrated in Fig. 1A. On univariate linear regression analysis, lower preoperative LVEF and larger preoperative $LVESV_i$ were associated with greater magnitude of improvement in LVEF after PVR (Table 3). Using multivariate linear regression analysis with backward selection applied to the entire cohort to evaluate independent determinants of improvement in LVEF after PVR, the only significant CMR variable was preoperative LV systolic function ($p = 0.012$, regression coefficient −0.54, SE 0.13). Using receiver–operator curves, neither change in $RVEDV_i$ nor change in $RVESV_i$ after PVR could be used to determine those with post-operative improvement in LVEF (AUC 0.59 and 0.63, respectively).

#### 2.2.2. CMR results stratified by LVEF before and after PVR

The CMR results in the subgroup of patients with impaired preoperative LV systolic function as compared with those with preserved preoperative LV systolic function are summarized in Table 4. Except for a notable gender difference, the 2 subgroups were not statistically different regarding baseline demographic data. A total of 11 patients had preoperative LVEF ≤45%. Preoperative LVEF in this particular subgroup ranged from 29% to 45% and preoperative $LVEDV_i$ and $LVESV_i$ were significantly larger than in the subgroup with preserved LV systolic function ($LVEDV_i$ 105 ± 17 versus 77 ± 10 ml/m$^2$, $p<0.001$ and $LVESV_i$ 65 ± 12 versus 35 ± 7 ml/m$^2$, $p<0.001$). Notably, the preoperative $RVEDV_i$ between the 2 subgroups did not differ statistically (226 ± 46 versus 204 ± 35 ml/m$^2$, $p = 0.1$). In patients with impaired preoperative LV systolic function, there was a statistically significant increase in LVEF after PVR whereas in the subgroup of patients with preoperative LVEF >45% there was no statistically significant improvement in LVEF after PVR (Fig. 1B). The magnitude of change in $LVEDV_i$ and $LVESV_i$ after PVR differed between the subgroups with preserved versus impaired preoperative LVEF (Fig. 2). Importantly, degree of change in RV size and function after PVR was not statistically different between the subgroups stratified by LV systolic function.

Full heart volumes and atrial volumes were derived to look for elements of pericardial constraint and elevated ventricular filling pressures. Specifically, the subgroup of patients with preoperatively impaired LV systolic function was compared with an age and gender-matched subgroup of 11 patients with preoperatively preserved LV systolic function (10 male, median age at PVR 33[range 21–58] years). Preoperatively, full heart volumes were significantly larger in patients with impaired systolic function as compared with those with preserved systolic function (560 ml/m$^2$ [378–1022] versus 455 ml/m$^2$ [359–587], $p = 0.02$). The magnitude of change after