Clinical Predictors of Right Ventricular Myocardial Fibrosis in Patients With Repaired Tetralogy of Fallot

Takashi Kido, MD; Takayoshi Ueno, MD, PhD; Masaki Taira, MD; Hideto Ozawa, MD; Koichi Toda, MD, PhD; Toru Kuratani, MD, PhD; Yoshiki Sawa, MD, PhD

Background: This study aimed to identify the clinical predictors of the degree of right ventricular (RV) myocardial fibrosis in patients with repaired tetralogy of Fallot (TOF) with special focus on the RV pressure load.

Methods and Results: From April 2004 to March 2017, 30 patients with repaired TOF underwent pulmonary valve replacement and concomitant RV myocardial biopsy. The stroke volume ratio (RV stroke volume/left ventricular stroke volume), RV end-diastolic volume index, and right-to-left ventricular systolic pressure ratio were evaluated with respect to their prognostic value for the degree of RV myocardial fibrosis. Significant positive linear correlations were detected between the stroke volume ratio and the degree of RV myocardial fibrosis (P=0.003, r=0.52). Patients with a right-to-left ventricular systolic pressure ratio >0.45 showed a significantly greater degree of RV myocardial fibrosis under an equivalent stroke volume ratio.

Conclusions: Under conditions of RV volume overload, a right-to-left ventricular systolic pressure ratio >0.45 was a predisposing factor for progression of RV myocardial fibrosis in patients with repaired TOF.

Key Words: Repaired tetralogy of Fallot; Right ventricular myocardial fibrosis; Right ventricular pressure

Chronic pulmonary regurgitation (PR) and resultant right ventricular (RV) dysfunction is the most common complication in adult patients with repaired tetralogy of Fallot (TOF).1 The timing of pulmonary valve replacement (PVR) in this patient population has been reported by several studies, which focused on RV volume overload.2–4 In addition to PR, a certain degree of RV outflow obstruction (RVOTO) is often associated with TOF and leads to RV pressure overload. The American College of Cardiology/American Heart Association guidelines recommend surgical intervention for RVOTO when the residual RVOT is >50 mmHg or the ratio of the RV systolic pressure to left ventricular (LV) systolic pressure (RVP/LVP) is >0.7.5 However, the optimal timing of PVR in patients with repaired TOF in the setting of chronic volume overload and concomitant RVOTO has not been thoroughly investigated.

RV myocardial fibrosis has been recognized as an adverse marker of clinical outcomes in patients with repaired TOF.6,7 The degree of RV myocardial fibrosis has the potential to predict late outcomes of RV function and should be considered when determining the indications for PVR. However, myocardial biopsy with cardiac catheterization is invasive and the results are inconsistent among the various examined regions.

The stroke volume ratio (SVR), which was originally calculated as the LV stroke volume/RV stroke volume, was initially reported as an index of LV volume overload in patients with aortic and mitral valve regurgitation.8 Our previous study revealed that the SVR is a sensitive predictor of both RV volume overload and the degree of RV myocardial fibrosis in patients with repaired TOF who exhibit PR and tricuspid regurgitation (TR) in the setting of normal RV pressure.9 Identification of the clinical predictors of RV myocardial fibrosis might help in determining the optimal timing of PVR; however, these clinical predictors in patients with residual RVOTO remain unclear.

The presented study aimed to identify the clinical predictors of the degree of RV myocardial fibrosis in patients with repaired TOF, focusing on the RV pressure load.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Osaka University Hospital (Approval no. 16105). From April 2004 to March 2017, 37 adult patients with repaired TOF underwent PVR at Osaka University Hospital. Among them, 30 patients (16 males; median age at PVR, 32 years) who agreed to participate in a histological analysis were included in this study. The median interval from corrective surgery was 29 years. The preoperative New York Heart Association class was I in 22 (73%)...
patients, II in 6 (20%), and III in 2 (7%). Atrial tachyarhythmia was observed in 2 (7%) patients. Cardiac catheterization was performed in all patients at a median of 125 days before surgery. Significant pulmonary stenosis (pressure gradient >50 mmHg) was found in 2 (7%) patients, and the median RVP/LVP was 0.4 (range, 0.2–0.9). Echocardiography was performed concurrently with cardiac catheterization, and greater than moderate TR was found in 13 (43%) patients. Cardiac magnetic resonance (CMR) imaging or computed tomography (CT) was performed in 21 patients. In 9 patients who had contraindications for CMR imaging, the ventricular volumes were evaluated with CT, which has been recognized as a modality comparable with CMR imaging for measurement of RV and LV sizes.\textsuperscript{10,11}

CMR studies were conducted using a 1.5-T system (Gyroscan NT: Philips Healthcare, Amsterdam, The Netherlands) and CMR analysis was performed on an offline workstation (View Forum: Philips Medical Systems, Best, The Netherlands). The ventricular volumes were calculated by tracing the end-diastolic and end-systolic ventricular slice contours and using the modified Simpson rule method. The end-diastolic and end-systolic volumes were defined as the largest and smallest ventricular cavity, respectively. CT examinations were performed using a 320-row CT scanner (Aquilion ONE: Toshiba Medical Systems, Otawara, Japan) at 150–550 mA according to body weight, a tube voltage of 120 kVp, and a slice collimation of 0.5 mm. The gantry period was 0.35 s. Intravenous landiolol (Ono Pharmaceutical, Osaka, Japan) was administered as tolerated for a baseline heart rate of 60 beats/min. After obtaining noncontrast localization images, the iodinated contrast agent (Iopamiron 300 mg/mL; Bayer Healthcare, Osaka, Japan) was administered intravenously at a rate of body weight (kg)×0.07 mL/s using the bolus-tracking technique. An ECG was recorded during a breath-hold examination for retrospective reconstruction. Axial images were then reconstructed at multiple phases covering the cardiac cycle in increments of 10% of the R-R interval from 5% to 95%. The reformatted images were

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>M/F</td>
<td>16/14</td>
</tr>
<tr>
<td>Age at PVR [years, median, (range)]</td>
<td>32, (14–52)</td>
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<tr>
<td>Additional procedure [n, (%)]</td>
<td></td>
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<tr>
<td>Tricuspid annuloplasty</td>
<td>19, (63%)</td>
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<tr>
<td>Right-side MAZE</td>
<td>6, (20%)</td>
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<tr>
<td>PMI</td>
<td>1, (3%)</td>
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<tr>
<td>Age at initial repair [years, median, (range)]</td>
<td>2, (0.6–9)</td>
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<tr>
<td>Type of repair [n, (%)]</td>
<td></td>
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<tr>
<td>No patch</td>
<td>9, (30%)</td>
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<tr>
<td>Transannular patch</td>
<td>21, (70%)</td>
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<tr>
<td>RV/LV systolic pressure [median, (range)]</td>
<td>0.4, (0.2–0.9)</td>
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<td>PG through RVOT [mmHg, median, (range)]</td>
<td>10, (0–83)</td>
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<tr>
<td>Atrial tachycardia [n, (%)]</td>
<td>2, (7%)</td>
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<tr>
<td>Greater than moderate TR [n, (%)]</td>
<td>13, (43%)</td>
</tr>
<tr>
<td>RVEDVI [mL/m\textsuperscript{2}, median, (range)]</td>
<td>157, (93–254)</td>
</tr>
</tbody>
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LV, left ventricle; PG, pressure gradient; PMI, pacemaker implantation; PVR, pulmonary valve replacement; RV, right ventricle; RVEDVI, right ventricular end-diastolic volume index; RVOT, right ventricular outflow tract; TR, tricuspid regurgitation.

Concomitant procedures included tricuspid annuloplasty in 19 patients, the right-sided Maze procedure in 6, and pacemaker implantation in 1. The baseline and surgical characteristics of the patients are shown in Table 1.

**Study Methods**

The RV and LV volumes were evaluated with CMR imaging in 21 patients. In 9 patients who had contraindications for CMR imaging, the ventricular volumes were evaluated with CT, which has been recognized as a modality comparable with CMR imaging for measurement of RV and LV sizes.\textsuperscript{10,11}

Surgical Procedure

Our indication for PVR during the study period was the presence of symptoms or signs of RV volume overload, including palpitations, pedal edema, or atrial tachyarhythmia. For asymptomatic patients, we scheduled PVR when the RVEDVI as assessed by CMR imaging or CT approached 150 mL/m\textsuperscript{2} or the pressure gradient in the RV outflow tract was >50 mmHg. The indications for all PVR operations were symptoms of RV failure in 6 patients, RV dilatation with RVEDVI >150 mL/m\textsuperscript{2} in 22 patients, and significant pulmonary stenosis in 2 patients. PVR was performed through a median sternotomy using cardiopulmonary bypass with mild hypothermia. Cardiac arrest was conducted in 15 patients. A longitudinal incision was performed into the pulmonary trunk or a previously placed patch. Reduction plasty of the infundibulum and complete removal of a previously placed patch was performed, if necessary. To eliminate the effect of histological changes induced from the previous surgery, RV myocardial biopsy was obtained with a needle biopsy from the mid-portion of the RV free wall, which was sufficiently remote from the outflow tract (\textbf{Figure 1}). PVR was performed using a biological valve with a continuous suture in all of the patients.
For histopathological examination of the RV myocardium, samples were embedded in paraffin, cut into 5-m sections, and stained with Masson’s trichrome stain. The percentage of myocardial fibrosis was assessed with computerized imaging software (MetaMorph® 6.2: Universal Imaging Corp, Downingtown, PA, USA). Three fields of the subendocardial and mid-mural layers of the RV wall per slide were analyzed and averaged. The relationships between the degree of RV myocardial fibrosis and the preoperative RVEDVI, SVR and RVP/LVP were assessed. Additionally, the effects of the age at initial repair and the type of repair on the degree of RV myocardial fibrosis were assessed.

### Statistical Analysis

Measurements are reported as the mean and standard deviation. The Mann-Whitney U test was used to compare continuous variables and Fisher’s exact test was used to compare frequencies between groups. The relationships between the variables were assessed using Pearson’s cor-

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**Figure 2.** Representative photomicrographs (×400, scale bar=50µm) of Masson’s trichrome staining of right ventricular myocardium in patients with (A) severe myocardial fibrosis, (B) moderate fibrosis, and (C) mild fibrosis.

**Figure 3.** Correlation between amount of right ventricular (RV) myocardial fibrosis and (A) stroke volume ratio and (B) RV end-diastolic volume index. The open circles represent patients with significant pulmonary stenosis.
relation analysis. Multiple regression analysis was performed to identify the clinical predictors of RV myocardial fibrosis using SVR and RVP/LVP as explanatory variables. In order to find an appropriate cutoff point, a stepwise method was used.

We prepared the following candidates of explanatory variables (or cutoff points):

\[
\text{RVP/LVP}_X = \begin{cases} 
0 & \text{if } \text{RVP/LVP} < X \\
1 & \text{if } X \leq \text{RVP/LVP}
\end{cases}
\]

Here, \(X=0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65\).

These analyses were performed with JMP Pro 12 (SAS Institute, Cary, NC, USA). Statistical significance was defined as \(P<0.05\).

### Results

#### Overall Outcomes

Follow-up was completed in all patients and the median follow-up period was 5.5 years (range, 0.7–7.6 years). No early or late deaths were reported. No re-intervention was needed for the RVOT during the study period. All patients had New York Heart Association class I heart failure.

#### RV Myocardial Fibrosis

The mean percentage of RV myocardial fibrosis was 14.02±5.16% (range, 5.99–27.53%) and the mean preoperative SVR was 1.6±0.5 (0.8–3.0). Examples of severe RV myocardial fibrosis (Figure 2A) and moderate fibrosis (Figure 2B) are shown in comparison with examples of less pronounced fibrosis (Figure 2C). As an index of RV volume overload, the SVR showed a significant positive linear correlation with the degree of RV myocardial fibrosis (\(P=0.003, r=-0.52\)). In contrast, RVEDVI showed no significant correlation in the univariate analysis (Figure 3A,B). RVP/LVP, age at initial repair, and type of repair showed no significant correlation with the degree of RV myocardial fibrosis (Figure 4A–C). In the multivariate analysis,
the preoperative SVR and an RVP/LVP >0.45 showed a significant correlation between the degree of RV myocardial fibrosis (P=0.0006 and P=0.001, respectively) (Table 2). In other words, patients with an RVP/LVP >0.45 showed a significantly greater degree of RV myocardial fibrosis than did patients with an RVP/LVP <0.45 under conditions of an equivalent preoperative SVR (Figure 5).

Discussion

The main findings of the present study are follows. (1) The preoperative SVR was significantly associated with the degree of RV myocardial fibrosis in patients with repaired TOF with various degrees of residual RVOTO. (2) A preoperative RVP/LVP >0.45 was a predisposing factor for a high degree of RV myocardial fibrosis independent of the SVR.

The SVR was initially introduced in 1979 for quantitative assessment of aortic and mitral regurgitation. Theoretically, the SVR can be applied to right-sided valvular regurgitation in the absence of left-sided valvular abnormalities. Our previous study demonstrated that the SVR is a useful predictor of RV volume overload and RV myocardial fibrosis in patients with repaired TOF in the setting of normal RV pressure. By comparing RV stroke volume with LV stroke volume, the SVR might be a more sensitive predictor of the degree of PR and TR than the RVEDVI alone. The present study confirmed the reliability of the SVR as a predictor of RV myocardial fibrosis under various pressure-overload conditions. CMR imaging has been the most common method for evaluating the ventricular volume and function in patients with repaired TOF. In patients with contraindications for CMR imaging, CT is also a standardized tool for assessment of ventricular function. Regardless of which imaging modality is selected, the stroke volume can be easily calculated as the difference in the end-diastolic and end-systolic volumes. Some studies have demonstrated overestimation of ventricular volumes when using CT vs. CMR imaging. By comparing the RV stroke volume with the LV stroke volume, the SVR can minimize this bias and might be a more sensitive marker of the RV volume load than the RVEDVI or RVESVI alone.

Whereas RV myocardial fibrosis has been recognized as an adverse marker of clinical outcomes in patients with repaired TOF, the degree of RV myocardial fibrosis has not been well investigated. Pradegan et al reported that the degree of RV myocardial fibrosis was a median of 13.1% in the anterior wall and 12.7% in the inferior wall patients with repaired TOF (median age, 35 years), which was consistent of our results.

Several reports have demonstrated the beneficial effects of residual RVOTO in patients with repaired TOF in terms of reduced PR fraction, prevention of RV dilatation, and preservation of RV systolic function. RV pressure overload induces RV hypertrophy and promotes restrictive RV physiology. Decreased RV diastolic compliance with restrictive RV physiology has been considered the etiology of the protective effect on RV function by limiting PR.

However, unfavorable effects of residual RVOTO on long-term outcomes in patients with repaired TOF have also been reported. Valente et al demonstrated that elevated RV pressure and RV hypertrophy were independent risk factors for death or sustained ventricular tachycardia. Freling et al showed that residual RVOTO was significantly associated with decreased exercise capacity. Therefore, the optimal degree of RVOTO needs to be determined. We previously reported that the RV pressure load induced by RVOTO leads to the development of RV myocardial fibrosis and decreased RV diastolic function. Restrictive RV physiology might be closely related to RV myocardial fibrosis. Considering the unfavorable effect of RV myocardial fibrosis in patients with repaired TOF, an RVP/LVP >0.45 should not be clinically acceptable based on the present study.

Study Limitations

First, the number of patients was limited. Second, we could not completely eliminate bias, because of the inconsistent preoperative RV volumes and the effects of various surgeries that were concomitantly performed with PVR. Third, because all patients’ heart failure remained in New York Heart Association class I, the clinical significance of RV myocardial fibrosis was not demonstrated in the present study.

Conclusions

The preoperative SVR was significantly associated with the degree of RV myocardial fibrosis in patients with repaired TOF under various RV pressure-overload conditions who underwent PVR. A preoperative RVP/LVP >0.45 was a predisposing factor for progression of RV myocardial fibrosis independent of the SVR. In the setting of RV volume overload, PVR would be worth considering when the RVP/LVP is >0.45 in patients with repaired TOF.

Name of Grant

None.

References


