Pulmonary Valve Replacement in Adult Patients With a Severely Dilated Right Ventricle and Refractory Arrhythmias After Repair of Tetralogy of Fallot

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**Background:** Refractory arrhythmias caused by right ventricular (RV) volume overload resulting from pulmonary regurgitation are the main concern in adult patients after repair of tetralogy of Fallot (TOF). Early pulmonary valve replacement (PVR) may prevent irreversible RV dysfunction and refractory arrhythmias, so the present study evaluated the PVR outcomes in adult patients with a severely dilated RV (d-RV) and refractory arrhythmias after TOF repair.

**Methods and Results:** Three TOF patients with a d-RV and tachyarrhythmias underwent PVR between the ages of 28 and 38 years. All had a d-RV (RV end-diastolic volume index (RVEDVI) >200 ml/m²) with a polymorphic nonsustained ventricular tachycardia (NSVT). Atrial tachycardia (AT) was identified in 2 patients and they underwent radiofrequency catheter ablation. The arrhythmias in all 3 were refractory to antiarrhythmic drugs. One year after PVR, the RVEDVI, left ventricular ejection fraction, right atrial pressure, cardiac index, cardiothoracic ratio, brain natriuretic peptide levels, and peak VO₂ improved in all, but without normalization. During the 2.6–3.8 year follow-up, all experienced tachyarrhythmias (NSVT or AT), which were controlled with medication.

**Conclusions:** PVR may be beneficial for refractory arrhythmias, even in TOF patients with a d-RV, but it is difficult to completely normalize the hemodynamics and resolve the arrhythmogenicity. (Circ J 2009; 73: 2135–2142)

**Key Words:** Arrhythmias; Pulmonary valve replacement; Right ventricular dysfunction; Tetralogy of Fallot

In the Japanese population, there is a lower prevalence of serious arrhythmias in patients after repair of TOF compared with Western countries, and so few reports regarding PVR in patients late after TOF repair exist. Therefore, in Japan the timing of PVR tends to be late in TOF patients with severe pulmonary regurgitation. In this study, we evaluated the PVR outcomes in Japanese adult patients after TOF repair with a severely d-RV (RVEDVI >200 ml/m²), RV dysfunction (RV ejection fraction (EF) <45%), and refractory arrhythmias, focusing on the clinical course of the arrhythmias.

**Methods**

**Patients**

From March 2005 to April 2006, 3 female patients (age range 26–38 years) with a d-RV and refractory tachyarrhythmias late after TOF repair underwent PVR at the National Cardiovascular Center in Japan. The clinical course...
of the tachyarrhythmias and of the hemodynamic changes before and after PVR were evaluated retrospectively.

**PVR**

Two patients received a porcine valve (27 mm) and 1 received a bovine valve (27 mm) (Table 1). During the PVR procedure, the resection of an RV outflow aneurysm caused by a RV patch that had been implanted during the initial intracardiac repair (ICR) was performed in 2 patients, and a right atrial (RA) maze procedure was performed in the third. In addition, RV aneurysm resection and RA maze procedure were scheduled in patient 1, but not carried out because of a huge RV and severe adhesions. A pacemaker was implanted in patient 3 because of sick sinus syndrome.

**Arrhythmias**

The tachyarrhythmias were diagnosed by surface ECG, 24-h ambulatory Holter monitoring or treadmill exercise tolerance test. Nonsustained tachyarrhythmias of more than 3 beats were included as the targets of treatment in this study. The percentage of premature ventricular contractions (%PVC) out of the total heart beats was measured by 24-h ambulatory Holter monitoring.

**Hemodynamics and Calculation of Ventricular Volumes**

Cardiac catheterization was performed before and 1 year after PVR in all 3 patients. We measured the pressures in the cardiac chambers and great vessels. We estimated the oxygen consumption from the age, gender, and heart rate (HR), and measured the cardiac index (CI: L · min$^{-1}$ · m$^{-2}$) using the Fick principle. We used Simpson’s rule to estimate the RV and left ventricular (LV) volumes. The end-diastolic and end-systolic volumes were divided by the body surface area to obtain the respective volume indexes (EDVI, ESVI), and the RV and LV EFs were calculated.

**Exercise Protocol**

All patients underwent a symptom-limited treadmill exercise test before and 1 month and 1 year after PVR. The peak oxygen uptake (peak VO$_2$) (ml · kg$^{-1}$ · min$^{-1}$) and systolic blood pressure were measured. We used a 12-lead ECG to determine HR. Ventilation and gas exchange were measured by a breath-by-breath method using a hot-wire anemometer (Riko AS500, Minato Medical Science, Osaka, Japan) with a mass spectrometer (MG-300, Perkin Elmer, Waltham, MA, USA).

**Other Factors**

The cardiothoracic ratio (CTR) determined by X-ray, RA volume, QRS duration, and levels of brain natriuretic peptide (BNP) and α-human atrial natriuretic peptide (α-hANP) were compared before and 1 and 2 years after PVR. RA volume was estimated with a prolate ellipsoid formula, measuring the RA mediolateral and supero-inferior dimensions from the apical 4-chamber view on echocardiography.

**Electrophysiology Study**

An electrophysiological study (EPS) was performed in 2 patients with atrial tachycardia (AT) before PVR using an EPWorkMate® recording system (EP MedSystems Inc, West Berlin, NJ, USA) and the CARTO™ electro-anatomical mapping system (Biosense-Webster, Diamond Bar, CA, USA).
**Results**

**Patients’ Characteristics**

The patient characteristics are shown in Table 1. Patient 2 had a left pulmonary artery occlusion, and patient 3 had pulmonary atresia and major aortopulmonary collateral arteries (MAPCA). At the age of 3 years, patients 1 and 2 underwent ICR with a transannular patch, and patient 3 underwent ICR at the age of 31 with an external conduit following the unifocalization of both sides of the MAPCA. In patient 1, a second operation was performed 8 years after the first ICR for a residual ventricular septum defect, RV infundibular stenosis, and PV stenosis. An excessive muscle resection of the RV and re-RV outflow tract repair with a transannular patch was performed in the second operation.

All patients had a severely d-RV (RVEDVI ≥200 ml/m²) and RV systolic dysfunction (RVEF ≤45%) with multifocal nonsustained ventricular tachycardia (NSVT). Two patients had AT. The arrhythmias were refractory to sotalol, mexiletine, and β-blockers in all patients. The RVEF in patient 2 was measured at the beat following a PVC because of bigeminal PVCs.

**Tachyarrhythmias Before PVR**

**Patient 1** Patient 1 complained of palpitations and

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**Statistical Analysis**

Comparisons were made using the 2-tailed paired t-test. A P value <0.05 was considered statistically significant.
Figure 2. Tachyarrhythmias in patient 2. (A) Holter monitoring before pulmonary valve replacement (PVR). Frequent multifocal PVCs and non-sustained ventricular tachycardia (NSVT) are shown in the Holter monitoring. Only the second to last beat was her own QRS morphology, with sinus rhythm and bundle branch block. The maximum number of consecutive NSVT episodes was 6 and the cycle length was 320 ms. (B) Holter monitoring after PVR. The maximum number of consecutive NSVT episodes and cycle length improved (maximum 3 beats, cycle length 480 ms). The 1st, 4th, 6th, 10th, and 11th beats were her own QRS morphology.

Figure 3. (A) Tachyarrhythmias in patient 3. Twelve-lead surface ECG of an intra-atrial reentrant tachycardia (IART): 2 types of IARTs were detected clinically. IART 1 (cycle length 280 ms) had a negative P wave in leads I, II, III, and aVF and positive P wave in lead V1. IART 2 (cycle length 250 ms) had a positive P wave in leads I, II, III, aVR, and a negative P wave in lead V1. (B) Electrophysiological study (EPS): activation map of IART 1. Both IARTs were induced during the EPS, but IART 2 had only a short duration. The activation map during IART 1 exhibited a double loop reentry (circuit around the double potential line and around the tricuspid valve). The ablation was performed between the scars near the inferior vena cava (IVC) and tricuspid annulus (TA)–IVC isthmus line. Neither of the IARTs was induced by rapid atrial pacing after the ablation.
faintness during the tachycardia. Holter monitoring revealed 2 types of ATs with different cycle lengths (280 ms, 420 ms). The P wave morphology of both ATs was unclear on the 12-lead surface ECG because of a wide QRS morphology (220 ms). NSVT appeared during AT with a cycle length of 420 ms (Figure 1A). Also, frequent polymorphic PVCs (%PVC: 15.7%) were revealed by Holter monitoring and did not decrease during a treadmill exercise test.

An EPS was performed for the tachyarrhythmias. A slower AT was induced by RA burst pacing. The RA...
mapping during the slower AT exhibited a focal activation pattern. The earliest atrial activation was detected below the double potential line of the RA lateral site. After ablating that earliest atrial activation point 14 times, the AT could no longer be induced (Figure 1B-1). Furthermore, sustained VT could not be induced by programmed ventricular stimulation without isoproterenol.

There was a relapse of the AT the day after the first EPS session, and a second EPS was performed 2 months later. A faster AT (cycle length 220 ms) was induced with atrial pacing under isoproterenol infusion. The RA mapping during the AT revealed a focal activation pattern and the earliest atrial activation was detected along the tricuspid annulus (TA) (Figure 1B-2). Ablating that site 8 times, the AT was no longer induced with or without isoproterenol.

**Patient 2** Patient 2 had no history of any ATs or syncope; however, he had frequent polymorphic PVCs with frequent episodes of NSVT (%PVC: 28.8%) (Figure 2A). A treadmill exercise test decreased the polymorphic PVCs, but did not suppress them completely. An EPS was not performed, because the PVCs and NSVT exhibited various morphologies with different coupling intervals. We administered mexiletine and a β-blocker, but they were ineffective.

**Patient 3** Patient 3 complained of palpitations and fatigue. Clinically, she had 2 types of incessant intra-atrial reentrant tachycardias (IART 1 and IART 2), and cardioversion was performed several times (Figure 3A). Holter monitoring also detected polymorphic PVCs (%PVC: 0.04%) and NSVT. A treadmill exercise test did not decrease the polymorphic PVCs, but induced an IART.

An EPS was performed for the IARTs. Mapping during sinus rhythm revealed a double potential line at the RA free wall and 2 scar areas next to the inferior vena cava (IVC). Atrial rapid pacing induced both IARTs, but IART 2 had only a short duration. The activation map during IART 1 exhibited a double loop reentry (circuit around the double potential line and around the tricuspid valve) (Figure 3B). Ablation was performed between the scars and the TA–IVC isthmus line. Neither of the IARTs could be induced by rapid atrial pacing after the ablation. No programmed ventricular stimulation was performed during the session, because no frequent polymorphic PVCs occurred. IART 2 relapsed 9 days after the EPS and was uncontrollable with sotalol and verapamil.

**Changes Before and After PVR**

Figure 4 shows the changes in the hemodynamic parameters and other factors before and after PVR. The RVEDV1 decreased, LVEF and CI increased, and BNP decreased in all 3 patients. The RA pressure and CTR decreased, and the peak VO2 increased significantly, even in this small group of patients (P<0.05). Interestingly, the CTR decreased after the 1-year follow-up in patient 3. The RA volume, QRS duration and a-hANP did not change before or after PVR.

**Clinical Status After PVR (Table 2)**

During the 2.6–3.8-year follow-up, the tachyarrhythmias decreased in all 3 patients. Patient 1 had NSVT with complaints of faintness on exertion after PVR, but it was controllable with sotalol. No ATs were detected after PVR. Patient 2 had a multifocal NSVT after PVR, but the maximum number of consecutive NSVTs decreased, the cycle length was prolonged (Figure 2B), and %PVC decreased from 28.8% to 4.0% (Figure 4). In patient 3, IART 2 relapsed after the RA maze procedure during PVR, but was controllable with sotalol. She declined another EPS session after PVR. No NSVTs were detected, but postoperative PVCs did occur.

The New York Heart Association class improved in patients 1 and 3. Diuretics were administered to all 3 patients, and an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker in 2 patients.

**Discussion**

This small study showed that PVR treatment is effective in patients with a severely d-RV and refractory arrhythmias after repair of TOF. Preoperative catheter ablation for ATs was effective in 2 patients and PVR improved the hemodynamics of all 3 patients. However, all 3 patients still required prudent medical follow-up and treatment for both RV dysfunction and arrhythmias.

The major problems in patients late after TOF repair are arrhythmias, exercise intolerance, heart failure, and death caused by RV volume overload from pulmonary regurgitation, residual atrial and/or ventricular septal defects, tricuspid regurgitation or RV outflow tract patch aneurysms.1–8 In particular, refractory arrhythmias because of RV volume overload caused by pulmonary regurgitation are a major concern late after TOF repair.1–3,9,10 The risk factors for sudden death and sustained VT are said to be older age at the time of the repair, QRS duration ≥180 ms, additional RV structural abnormalities (outflow tract aneurysms and pulmonary or tricuspid regurgitation), positive programmed ventricular stimulation studies, and severe RV dilatation with either LV or RV dysfunction.1,3,10,20,21

AT has also been associated with substantial morbidity, including congestive heart failure, reoperation, subsequent VT, stroke, and death, in patients after TOF repair.2,3 Harrison et al2 reported that the AT group in such patients had a higher mean RA volume and proportion of significant pulmonary regurgitation than the matched controls; however, the proportion of significant tricuspid regurgitation was not higher. They did not mention how the RA enlargement was related to the pulmonary regurgitation without any significant tricuspid regurgitation. In the present study,

| Table 2. Clinical Status of the Patients After PVR |
|-----------------|-----------------|-----------------|
| Patient no. | Follow-up period (years) | Arrhythmia | NYHA |
| 1 | 3.6 | NSVT | II |
| 2 | 2.5 | NSVT | II |
| 3 | 2.4 | IART | II |

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ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations see in Table 1.
the RA volume in all 3 cases was higher (82–175 cm³) than normal (range 49±22 cm³). 10 We assessed whether or not the mechanism of RA enlargement was similar to that of left atrial (LA) enlargement in patients with aortic regurgitation. In patients with aortic regurgitation, the degree of LA enlargement depends on the LV mass with LV concentric patterns, and chronic LV pressure overload, more than the volume overload, stimulates the LA and increases its workload. 22 Accordingly, we speculate that in a severely d-RV, the RV wall stress during exercise and emotional stress would increase the RA workload and enlarge the RA, resulting in induction of AT.

PVR is an alternative solution to RV volume overload because of pulmonary regurgitation associated with problems late after TOF repair. The benefits of PVR include improvement in the functional class and exercise capacity, reduction in the RV size, increase in the LV size and CI, and decrease in the QRS duration. 1,14–17 However, the timing of PVR is still controversial because of the surgical risk and lack of prosthetic valve longevity. 11–13 Calderone et al reported that freedom from valve replacement was 82% at 5 years and 58% at 10 years in all age groups (median age 6.2 years), and that PVR at an early age is associated with a higher rate of valve failure and early reoperation. 12 Moreover, Fiore et al reported that freedom from valve replacement was 92% for bovine pericardial valves and 78% for porcine valves at 5 years in older age patients late after an initial outflow tract reconstruction (median age 22.7 years). 13 Several reports suggest that early PVR with an RVEDVI <150–170 ml/m² prevents irreversible RV dysfunction and refractory arrhythmias and leads to normalization of the RV volumes. 1,14–16 In our study, all 3 patients had a severely d-RV and RV dysfunction with refractory arrhythmias. In previous reports, PVR was performed with a low operative mortality of 0–2%, 14,18,23–25 but the 5 patients who suffered perioperative death all had an advanced, severely d-RV and RV dysfunction, 23–25 suggesting that delaying the PVR may have contributed to the poor outcome. Moreover, the effectiveness of PVR for a severely d-RV is unknown. Therrien et al reported no improvement in the RV size or function after a PVR in patients with a severely d-RV (mean RVEDV, 227 ml; mean RVEF, 36%). 17 whereas Munecchi et al reported a significant decrease in the CTR and RV volume after PVR in a study in which 75% of the patients had a severely d-RV (RVEDVI ≥200 ml/m²). 18 Our 3 patients showed an improvement in the RVEDVI, LVEF, RA pressure, CI, CTR, BNP, and peak VO₂ at 1 year after PVR. Although PVR for patients with a d-RV might pose a high risk for perioperative death, it may still be effective for improving the hemodynamics without the expectation of normalization of the RV volume.

The effect of PVR on tachyarrhythmias has been reported previously. Therrien et al showed a decreased incidence of VT from 22% to 9%, but no decreased incidence of atrial flutter/fibrillation. 23 In contrast, a recent study that used a matched TOF group showed that PVR for symptomatic pulmonary regurgitation and RV dilatation did not reduce the incidence of VT or death. 26 In our 3 patients, the tachyarrhythmias after PVR were controlled with antiarrhythmic drugs. Two of the 3 patients suffered from ATs, which were successfully treated with catheter ablation before PVR. We believe that catheter ablation can reduce the arrhythmogenic substrate in the RA, but does not prevent the establishment of new arrhythmogenicity. The effect would be temporary without a reduction in the RA overload caused by the severely d-RV. PVR reduces the RA and RV overload; however, it was also not completely effective for the tachyarrhythmias in these 3 patients. We should not expect complete resolution of the arrhythmogenic substrate that has formed progressively for decades since the ICR, even after a satisfactory improvement in the hemodynamics following PVR. A multimodal approach, including PVR, catheter ablation, and antiarrhythmic drugs, should be considered for patients with a severely d-RV and refractory arrhythmias.

In Japan, there is a relatively low prevalence of serious problems late after TOF repair. The actuarial survival rate at 30 years was 98% in a Japanese multicenter study, 7 compared with 80% ² and 89% ³ in the large studies from Western countries. The incidence of sustained VT and AT/atrial fibrillation was 0.4% and 3%, respectively, in Japan, 7 compared with 4% and 4–12% in Western countries. 2,3,9 Nakazawa et al indicated that the effort to prevent complete right bundle branch block with a small or no right ventriculotomy using a small transannular patch that surgeons in Japan have been performing since the early 1970s ²²,²₈ contributes to preventing significant pulmonary regurgitation and results in fairly good postoperative RV function, preventing life-threatening tachyarrhythmias. Until recently, this has been the reason that Japanese surgeons and cardiologists considered an ICR for the curative treatment of TOF and to bring the PR to an acceptable level. This may be related to the fact that in Japan the timing of PVR tends to be late for patients with TOF and severe pulmonary regurgitation. In a report about PVR for patients after repair of TOF in Japan, 75% of the patients had a severely d-RV (RVEDVI >200 ml/m²). 18 PVR was effective in our 3 patients with a severely d-RV, but the size and function of their RA and RV did not normalize after PVR and they still had tachyarrhythmias and needed several medications. The possibility cannot be denied that earlier PVR may have produced better results. Once RV dysfunction symptoms or life-threatening tachyarrhythmias have appeared, it might be too late to normalize the RV after PVR. Therefore, prudent evaluation of the RV with various modalities, not only the symptoms, would enable us to perform PVR at the appropriate time.

Conclusion

PVR may be beneficial for treating the hemodynamics and refractory arrhythmias, even in adult patients with a severely d-RV after repair of TOF. However, delayed PVR does not normalize the RV volume or completely resolve the arrhythmogenic substrate. Therefore, a multimodal approach including PVR, catheter intervention, and antiarrhythmic drugs should be considered for patients with a severely d-RV and refractory arrhythmias. Moreover, prudent evaluation of the RV with various modalities will enable us to perform PVR at the appropriate time; namely, before progression of any irreversible RV dysfunction and refractory arrhythmias.

References


