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Late Pulmonary Valve Replacement in Patients With Pulmonary Atresia and Intact Ventricular Septum: A Case-Matched Study

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Abstract

Background—Pulmonary valve replacement (PVR) is a common therapy for chronic pulmonary regurgitation. However, the use of this strategy is mostly based on the studies performed on patients with tetralogy of Fallot (TOF) and not in patients with pulmonary atresia/intact ventricular septum (PA/IVS). The aim of this study is to evaluate our experience with PVR in patients with PA/IVS and compare them with a matched cohort of TOF patients.

Methods—Between 1995 and 2009, 13 patients with PA/IVS underwent a late PVR. Matched TOF control subjects were identified for 12 of these patients. Before and after PVR echocardiographic, magnetic resonance imaging, exercise test, Holter, and electrocardiographic data were compared between groups.

Results—There was no mortality in either group. The PVR improved pulmonary regurgitant fraction and right ventricular volumes in all patients. Patients with PA/IVS had more significant tricuspid regurgitation (TR [at least moderate]) by echocardiography and magnetic resonance imaging before PVR ($n = 11$ [85%] versus $n = 1$ [8%]; $p = 0.003$) and had more tricuspid valve repairs than TOF patients ($n = 9$ [69%] versus $n = 1$ [8%]; $p = 0.004$). Repair was undertaken by a combination of techniques. Although TR was improved early postoperatively, only 2 of 9 patients (22%) were free from significant TR at most recent follow-up (median 2.5 years; range, 0.1 to 10.9). No patient underwent reoperation at latest follow-up.

Conclusions—Patients with PA/IVS can undergo a late PVR with excellent results. Significant TR and repair are more commonly observed among patients with PA/IVS compared with TOF patients. Although tricuspid valve repair improves regurgitation early, TR tends to recur, suggesting the need for further refinement of current surgical techniques.

Pulmonary atresia with intact ventricular septum (PA/IVS) is a rare congenital heart disease, characterized by heterogeneity and varying degrees of right ventricle (RV) hypoplasia [1]. Classically, PA/IVS has been subdivided in two groups depending on the development of the RV: patients with mild hypoplasia of the RV who generally have a patent infundibulum, and patients with a severely hypoplastic RV, often with significant RV-coronary connections. The typical goal of the management for patients in the first group is to rehabilitate the RV and eventually establish a complete biventricular circulation [2]. Initial rehabilitation of the RV, however, frequently requires decompression using catheter techniques with or without a transannular patch [3, 4]. Significant pulmonary regurgitation

(PR) frequently follows these interventions, and the pressure load to the RV is converted to volume load. Previous studies on tetralogy of Fallot (TOF) patients but not PA/IVS patients undergoing a transannular patch confirm that the adaptive mechanisms of the RV can compensate for the volume load induced by PR for a number of years [5]. These compensatory mechanisms however, ultimately fail, leading to the development of late complications such as heart failure, arrhythmia, and death. Predictors of adverse clinical outcomes in TOF patients include moderate-severe RV dilatation, RV dysfunction, left ventricular dysfunction, QRS duration longer than 180 ms, syncope, positive programmed ventricular stimulations study, and sustained ventricular tachycardia [6]. However, the response of the RV in patients with PA/IVS to chronic volume load and the subsequent benefit/lack of pulmonary valve replacement (PVR) in this cohort of patients is unknown.

Severe chronic pulmonary regurgitation with associated RV dilation and dysfunction has been the main focus of several investigations in recent years [7, 8]. Current indications for PVR in TOF are multifactorial, with RV end-diastolic volumes serving as a major component [5]. In addition to PR, tricuspid regurgitation (TR) may also play an important role in providing a volume load to the RV, with as many as 30% of patients with TOF undergoing a PVR having significant TR [9]. In those cases, tricuspid valve (TV) repair is advocated at the time of PVR in patients with TOF. However, no previous report has studied the outcomes of TV repair in PA/IVS patients undergoing PVR for chronic PR.

We aim to compare PA/IVS patients with a similar group of TOF patients to evaluate their preoperative and postoperative features and outcomes after PVR. Our hypothesis is that the RV in the patients with PA/IVS will react similarly to volume load as seen in TOF patients, and that PVR can be undertaken in these patients with excellent early and late surgical results comparable to those seen in TOF patients.

Patients and Methods

A retrospective review of our institutional and departmental medical records was conducted to identify patients with PA/IVS who had undergone late PVR, defined as 5 years after primary repair. Our institutional policy for indications of PVR has been previously published [5]. This protocol was approved by the Institutional Review Board at Children's Hospital Boston, and parental consent was waived.

Demographic, Surgical, and Electrophysiologic Data

The following demographic, surgical and electrophysiologic data were recorded: age at PVR, age at initial surgery, time between initial surgery and PVR, presence of arrhythmia on Holter monitor, and QRS duration. In addition, the operative notes were reviewed to collect data about the PVR implantation, status of the atrial septum, and technique used for TV repair. The QRS duration was provided by the automated analysis performed by the General Electric Marquette Electronics Mac 5000 platform (Fairfield, CT) and confirmed by manual inspection. All data were collected at latest study before PVR and at most recent follow-up.

Exercise Test

Data were recorded from studies performed before and after PVR. These tests were done with a ramp protocol on an electronically braked cycle ergometer. Data recorded included peak oxygen consumption ($\text{VO}_2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), peak heart rate at maximal exercise, and peak O_2 pulse (Peak $\text{VO}_2/\text{heart rate}$) were recorded. Peak VO_2 consumption, peak heart rate, and peak O_2 pulse for each patient were compared with age, sex, and size-adjusted normal values to produce percent of predicted normal values. These percentage predicted

values were used for analysis. The O₂ pulse was used as a surrogate for stroke volume at peak exercise.

Echocardiography

Echocardiographic data included qualitative assessments of left and right ventricular function on the latest evaluation before PVR. Qualitative dysfunction or dilation was characterized as none or trivial, mild, moderate, or severe. In addition, TR was measured by the vena contracta, defined as the smallest regurgitant flow area immediately beyond the flow convergence region and before expansion of the turbulent regurgitant jet, and which corresponds hydrodynamically with the effective regurgitant orifice area. The vena contracta was categorized as none or trivial (0 to 2 mm), mild (2 to 4 mm), moderate (4 to 6 mm), or severe (>6 mm).

Magnetic Resonance Imaging

The magnetic resonance imaging (MRI) data recorded were left and right ventricular ejection fraction, the pulmonary and tricuspid regurgitant fraction, and the RV end-diastolic volume (indexed to body surface area).

Matched Control Group

Control subjects were selected from the pool of patients in our databases with TOF initially repaired with a transannular patch who had a late PVR during the same timeframe as our PA/IVS population. For each PA/IVS patient, a paired control was identified in a two-step fashion. First, potential control subjects were matched by age at the time of PVR (at least 5 years after primary repair). Then, within the group of prospects, the first patient having the most robust set of preoperative and postoperative data was selected: electrocardiogram, Holter monitor, exercise test, echocardiography, and MRI at most 6 months before PVR and the most recent through follow-up.

Statistics

The Student *t* test or Mann-Whitney *U* test were used for categorical variable comparison between the two groups. The paired *t* test, McNemar test, or Friedman's two-way analysis of variance were used for intragroup continuous variables. The χ^2 test was used for categorical variables. A *p* value less than 0.05 was considered significant.

Results

At the time of database review (June 2009), 13 PA/IVS patients had undergone PVR for RV dilation. There was no perioperative or follow-up mortality in either group. Twelve TOF patients having a PVR during the same timeframe were identified and matched to the PA/IVS patients by age at PVR. Thus, difference in median age at PVR was not statistically significant between PA/IVS and TOF patients (15.5 versus 16.7 years, respectively; *p* = 0.43). As expected, median age at transannular patch was quite different between PA/IVS and TOF patients (0.14 versus 7 months, respectively; *p* = 0.00). Both groups were similar in terms of median duration of follow-up after PVR (2.5 versus 2.8 years; *p* = 0.07) and the degree of PR and RV dilation before PVR (Table 1). Significant TR was more frequent in the PA/IVS patients than in the TOF patients by either echocardiography (*p* = 0.003) or MRI (*p* = 0.03). Median preoperative QRS interval was significantly longer in the TOF patients (108 ms versus 162 ms; *p* = 0.006). In addition, the preoperative exercise test showed a significantly higher median O₂ pulse predicted in TOF patients (90% versus 74%; *p* = 0.04).

A total of 6 patients needed pacemakers in our series (3 in the PA/IVS group and 3 in the TOF group). All pacemakers were implanted electively. In the PA/IVS group, all patients

had an epicardial pacer at PVR: 1 for history of sick sinus syndrome, 1 for history of recurrent flutter and with an automated implanted cardioverter-defibrillator; and 1 with progressive heart block before surgery. In the TOF group, 1 patient with a history of ventricular tachycardia had an epicardial automated implanted cardioverter-defibrillator at PVR; 1 had symptomatic bradycardia 3 years after PVR and got a pacemaker in the catheterization laboratory; and 1 had progressive heart block 3 years after PVR and also received a pacemaker in the catheterization laboratory.

The PVR was undertaken successfully with no mortality. Of the 13 PA/IVS patients, 7 had an intact atrial septum and 6 an atrial septal defect or persistent foramen ovale before PVR. Five of those 6 later patients had the atrial septal defect/persistent foramen ovale closed at surgery; and therefore, only 1 patient had a fenestration left in the interatrial septum after PVR. Nine PA/IVS patients underwent TV repair at the time of PVR because of moderate or severe TR. By echocardiography, movement of the septal leaflet of the TV was restricted in 7 of 9 patients, and the TV annulus was dilated (z score >2) in 3 of 9 patients. Visual inspection of the TV in the operating room showed some degree of thickened and dysplastic leaflets, and the septal leaflet was tethered down by secondary chordae in most cases. The techniques of repair entailed a combination of commissuroplasties (n = 4), annuloplasties with or without a ring (n = 5), or release of the tethered septal leaflet by resection of secondary chordae (n = 3).

The last 2 patients in our series underwent a cone repair. In those 2 patients, the TV looked dysmorphic and with significant tethering of the septal leaflet by secondary chordae. The anterior leaflet was somewhat prolapsing at inspection. The abnormal chordae were resected, and the papillary muscles delaminated. In addition, the anterior leaflet of the TV was deinserted from the annulus, rotated clockwise, and sutured to the TV annulus. Both patients had an annuloplasty ring. No heart block developed, although 1 patient had an epicardial pacemaker for preexisting and progressive first-degree heart block.

All patients had an improvement in TR early after repair; however, in spite of surgical repair, only 2 patients (1 with commissuroplasty and 1 with an annuloplasty ring) showed a durable result through follow-up.

A MRI was not obtained postoperatively in all patients. In the PA/IVS group, MRI scans have not been obtained in 7 patients, owing to pacemakers (n = 2), patient has not yet received an MRI (n = 4), and patient is being followed up elsewhere (n = 1). Of the TOF patients, 3 did not have post-PVR MRI (1 owing to ICD, 1 scheduled in future, and 1 had significant artefacts). After PVR, RV volumes and PR significantly decreased in both groups. Specifically, MRI RV end-diastolic volumes decreased from 181.1 to 131.7 mL/m² and from 177.1 to 129.1 mL/m² in the PA/IVS and TOF patients, respectively. Thus, the response to PVR was similar in both groups. The TR remained significantly higher in the PA/IVS group despite TV repair in 9 patients. Median change in QRS duration was significantly higher in TOF patients ($p = 0.007$).

Preoperative and postoperative characteristics of PA/IVS patients compared with TOF patients are shown in Tables 1 and 2.

Comment

Although PVR is becoming increasingly common among patients with repaired TOF [10, 11], indications for this procedure and results of such approach in patients who had palliation of PA/IVS with perforation of their pulmonary valve have not been previously reported. In this study, we evaluated a series of 13 PA/IVS patients who underwent late PVR for chronic PR and RV dilation. All PA/IVS patients had undergone placement of a

transannular patch during initial repair and had either an intermediate or biventricular circulation. All patients but 1 had an intact atrial septum at or after PVR (complete septation of their circulation). Indications for surgery were based on degree of RV dilation and PR on MRI or echocardiography. All patients are alive and in good functional status after a median follow-up of 2.5 years after PVR. When compared with a similar cohort of 12 age-matched patients with TOF initially repaired with a transannular patch who underwent a late PVR during the same timeframe, no differences were found in preoperative versus postoperative RV volumes, PR fraction, and incidence of malignant arrhythmia. These findings are consistent with the observation that the RV responds similarly to volume load in PA/IVS patients and TOF patients. Patients with PA/IVS, however, had a higher prevalence of pre-PVR TR and underwent more TV repairs. Current surgical techniques failed to provide a durable competent TV.

The presence and severity of TR has been associated with increased RV volume and decreased effective ejection fraction [9], and is an independent risk factor for sustained ventricular or atrial tachycardia in TOF patients. Furthermore, a number of authors have reported as high as 35% pre-PVR significant TR [9, 12], requiring surgical address at the time of PVR in patients with repaired TOF. In our series, this incidence was 8%. This low incidence of significant TR could be due to the relatively low RV volumes before PVR, which would minimize regurgitation due to annular dilation. Moreover, in these patients, the mechanism of TR may be due to distortion of the valve by the ventricular septal defect patch or secondary to RV dilation. In patients with PA/IVS, however, the TV is thickened and dysplastic and may have abnormal tethering attachments as well. The dysmorphic features range from thickened and abnormally attached leaflets to the presence of an Ebstein's malformation with enlargement of the anterior leaflet and downward displacement of the septal leaflet. Freedom and colleagues [13], for example, have demonstrated structural abnormalities of the TV in PA/IVS in a series of 60 cases at autopsy. Anderson and coworkers [14] have argued for an Ebstein's-like arrangement of the valve with downward displacement of the "annular" attachment of one or more leaflets of the TV. In 5 of those cases, this later arrangement was associated with gross dilation of the right atrium and ventricle. When severe Ebstein's abnormality is present, it represents a risk factor for early mortality in patients with PA/IVS. However, mild forms are well tolerated. In our series, TR was significantly more common among patients with PA/IVS when compared with control subjects, whereas PR was very similar between groups. Furthermore, of the 13 patients with PA/IVS, 9 exhibited moderate or severe TR by vena contracta before PVR and underwent TV repair. The anatomic mechanism of regurgitation was some degree of tethering of the septal leaflet of the TV in 7 of these patients and annular dilation in 3 of them. Interestingly, none of these patients had a perinatal diagnosis of severe Ebstein's.

Recently, the "cone repair" has been introduced for repair of the TV in patients with Ebstein's disease, with promising early results [15]. Although our patients did not demonstrate the classic findings of the Ebstein anomaly, some of the repair techniques described for Ebstein's disease have been applied in some of our cases. In our series, 9 patients with PA/IVS underwent repair by a combination of commissuroplasties, annuloplasties, and release of abnormal secondary chordae, and 2 had a conelike repair. Regardless of the techniques employed, the ability to achieve a durable TV repair has been limited. In such cases, a competent pulmonary valve assumes even greater importance.

In conclusion, patients with PA/IVS and severe PR can undergo PVR late after initial repair with a significant reduction in PR fraction and RV end-diastolic volume and no mortality. The PA/IVS patients showed a similar RV response to chronic volume load compared with the TOF patients. Tricuspid regurgitation, however, was more common among the PA/IVS

group, and frequently recurred after surgical repair. These findings support continued efforts to refine current surgical techniques for TV plasty.

Abbreviations and Acronyms

MRI	magnetic resonance imaging
PA/IVS	pulmonary atresia with intact ventricular septum
PR	pulmonary regurgitation
PVR	pulmonary valve replacement
RV	right ventricle
TOF	tetralogy of Fallot
TR	tricuspid regurgitation
TV	tricuspid valve

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Table 1

Comparison Between Pulmonary Atresia With Intact Ventricular Septum (PA/IVS) and Tetralogy of Fallot (TOF) Controls: Baseline Characteristics and Before Pulmonary Valve Replacement (PVR) Variables

Variables ^a	PA/IVS	TOF/PS	<i>p</i> Value
Median age at TAP, months	0.14 (0.03, 8)	7 (1.2, 84)	0.00 ^a
Median age at PVR, years	15.5 (7, 27)	16.7 (7, 27)	0.43
Median duration follow-up after PVR, years	2.5 (0.01, 10.9)	2.8 (0.5, 7.8)	0.07
Tricuspid valve surgery required at PVR	9/13 (69%)	1/12 (8%)	0.004 ^a
Pacemaker placed during lifetime	3/13 (23%)	3/12 (25%)	1.00
Echocardiography			
RV size, moderate/severe	10/10 (100%)	8/10 (80%)	0.49
RV dysfunction, moderate/severe	1/12 (8%)	0/11 (0%)	0.56
LV dysfunction, moderate/severe	2/13 (15%)	1/11 (9%)	0.77
Pulmonary regurgitation, moderate/severe	13/13 (100%)	10/10 (100%)	1.0
Tricuspid regurgitation, moderate/severe	11/13 (85%)	1/12 (8%)	0.003
Magnetic resonance imaging			
Median RVEDVi, mL/m ²	181.1 (114, 232)	177.1 (125, 249)	0.60
RV dysfunction, moderate/severe	2/11 (18%)	1/12 (8%)	0.65
Median LVEDVi, mL/m ²	82.3 (74, 97)	90.1 (57, 119)	0.17
LV dysfunction, moderate/severe	2/11 (18%)	0/12 (0%)	0.22
Median PR fraction (%)	50 (21, 64)	50 (36, 61)	0.75
Tricuspid fraction severity, moderate/severe	8/11 (73%)	1/12 (8%)	0.03 ^a
ETT			
Median VO ₂ predicted (%)	61 (36, 88)	73 (51, 93)	0.44
Median O ₂ pulse predicted (%)	74 (58, 95)	90 (67, 105)	0.04 ^a
Median peak HR predicted (%)	85 (55, 101)	75 (66, 102)	0.34
Median pre PVR QRS, ms	108 (84, 194)	162 (100, 188)	0.006 ^a
Pre-PVR Holter			
VT	0/6 (0%)	1/8 (12.5%)	0.2
SVT	2/7 (28%)	0/8 (0%)	0.2

^aThe continuous variables are represented as median (minimum, maximum values).

ETT = exercise tolerance test; HR = heart rate; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; PR = pulmonary regurgitation; RV = right ventricular; RVEDVi = right ventricular end-diastolic volume index; SVT = supraventricular tachycardia; TAP = transannular patch; VO₂ = oxygen uptake; VT = ventricular tachycardia.

Table 2

Comparison Between Pulmonary Atresia With Intact Ventricular Septum (PA/IVS) Patients and Tetralogy of Fallot (TOF) Controls at Most Recent Follow-Up

Variables ^a	PA/IVS	TOF/PS	<i>p</i> Value
Echocardiography			
RV size, moderate/severe	4/10 (40%)	3/9 (35%)	0.76
RV dysfunction, moderate/severe	0/11 (0%)	2/12 (16%)	0.29
LV dysfunction, moderate/severe	1/11 (9%)	1/12 (8%)	0.47
Pulmonary regurgitation, moderate/severe	2/11 (18%)	2/12 (16%)	0.40
Tricuspid regurgitation, moderate/severe	8/13 (61%)	0/11 (0%)	0.003 ^a
Magnetic resonance imaging			
Median RVEDVi, mL/m ²	131.7 (115, 138)	129.1 (87, 168)	0.89
RV dysfunction, moderate/severe	1/6 (16%)	1/9 (11%)	0.20
Median LVEDVi, mL/m ²	89.2 (59, 112)	107.6 (53, 158)	0.15
LV dysfunction, moderate/severe	0/6 (0%)	1/9 (11%)	0.30
Median pulmonary fraction (%)	6 (2, 20)	2 (1, 6)	0.25
Tricuspid fraction severity, moderate/severe	4/5 (80%)	0/9 (0%)	0.03 ^a
Change in RVEDVi, mL/m ²	-61.6 (-94, -30)	-61.8 (-127, 43)	0.93
ETT			
Median VO ₂ predicted (%)	85 (46, 99)	70.5 (37, 93)	0.35
Median O ₂ pulse predicted (%)	83.5 (58, 125)	85 (59, 121)	0.84
Median peak HR predicted (%)	90.5 (69, 102)	77 (59, 105)	0.63
Median change in VO ₂ predicted (%)	1 (-10, 10)	-3 (-14, 14)	0.49
Median change in O ₂ pulse predicted (%)	0 (-37, 9)	-9 (-20, 16)	0.92
Median change in peak HR predicted (%)	1 (1, 17)	2 (-10, 8)	0.63
Holter			
VT	0/6 (0%)	0/9 (0%)	0.52
SVT	2/6 (33%)	1/9 (11%)	0.52
Median post-PVR QRS, ms	124 (84, 190)	153 (92, 180)	0.25
Median change in QRS, ms	6 (-14, 72)	-7 (-22, 0)	0.007 ^a

^aThe continuous variables are represented as median (minimum, maximum values).

ETT = exercise tolerance test; HR = heart rate; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; RV = right ventricular; RVEDVi = right ventricular end-diastolic volume index; SVT = supraventricular tachycardia; VO₂ = oxygen uptake; VT = ventricular tachycardia.