Evaluation of Pulmonary Regurgitation Following Tetralogy of Fallot Repair

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Abstract

Background- Pulmonary regurgitation (PR) is the most important residual lesion remaining after the repair of Tetralogy of Fallot (TOF). Through a thorough review of the data, statistics of patients undergoing pulmonary valve replacement following total correction for TOF and analyzing these data, the following study was performed and presented below.

Methods- Database search for medical records of patients undergoing pulmonary valve replacement following total correction for TOF was performed and the data gathered, analyzed, and presented.

Results- The age of the patients (22.21±6.98 years old), time elapsed between the two operations, right ventricular ejection fraction (mildly decreased, 18.6%; moderately decreased, 67.9%; and severely decreased, 12.2% of cases), aneurysm in the outflow tract of the right ventricle (20.8%), tricuspid regurgitation (56.6%), tricuspid stenosis (1 case), valve type used for pulmonary valve replacement (biologic, 86.6%; metallic, 11.2%; and homograft, 1.9%), pulmonary artery pressure [<25mmHg, 34 cases (64.2%); 25mmHg - 50mmHg, 7 cases (13.2%); 50mmHg - 75mmHg, 1 case (1.9%), and > 75mmHg, 1 case] were evaluated.

Conclusions- Although right ventricular volume overload due to severe pulmonary regurgitation after repair of TOF can be tolerated for years, there is now evidence that the compensatory mechanisms of the right ventricular myocardium ultimately fail and that if the volume overload is not eliminated or reduced, this dysfunction may be irreversible. In light of those data and with better understanding of risk factors for adverse outcomes late after TOF repair, many centers are now recommending early pulmonary valve replacement before symptoms of heart failure develop***(Iranian Heart Journal 2010; 11 (2):14-24).***

Keywords: Tetralogy of Fallot ■ pulmonary regurgitation ■ pulmonary valve replacement

The number of adults with Tetralogy of Fallot (TOF) now exceeds the number of children with the disorder due to childhood surgical successes. After total correction of TOF, however, most patients are left with pulmonary regurgitation (PR), which over time results in right ventricular volume overload, enlargement, and dysfunction.

Usually well tolerated for 20 years or more, ongoing pulmonary insufficiency is at the core of late complications that include right ventricular failure, exercise intolerance, atrial and ventricular arrhythmias, myocardial scarring, and sudden death.

Though late pulmonary valve replacement appears to attenuate this risk, prostheses have a finite life span.

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Thus, the timing of surgery must be carefully considered, weighing the risks of surgery and possible repeat surgery against the risk of ongoing pulmonary regurgitation.

The diagnostic modalities pertaining to the failing right ventricle, the timing for eventual re-intervention, and the various surgical reconstruction possibilities of the right-ventricular outflow tract are still controversial and evolving.[1-6] The wide variability in clinical status, extent of RV dilatation, and dysfunction at the time of presentation for surgical intervention has resulted in disparate surgical results after pulmonary valve insertion. As no systematic analysis of patients with TOF that are presenting with PR has been conducted in our country, we have assessed and analyzed the data of patients in our center for the first time and we think this must be a beginning for a better understanding of this problem in our country.

In our center, we have performed total correction of TOF since 1980; and since about 3 years ago, cases of severe PR have been referred for pulmonary valve replacement. We have not had any systematic analysis of these patients in our country, but needless to say, as in other parts of world, it is a problem that we will encounter in the near future and many questions and controversies remain to be answered. It seems a multidisciplinary approach and protocol is needed to care for these patients. To solve the problem of decision making for these patients, we have performed the following analysis of data of the patients in our center, whom following total correction for TOF, have been referred for PVR. We hope this report is a trigger for beginning clinical trials to determine different aspects of treatment modalities for these patients.

Methods

From 2003 to 2007, there were 53 cases referred for PVR following total correction for TOF. In this case series retrospective analysis, the data of these patients obtained from their medical records are presented and discussed. The variables recorded and analyzed were age, time interval between the two operations, types of primary operation, presence of aneurysm in the outflow tract of right the ventricle, presenting symptoms and signs, presence of symptoms and signs following PVR, type of prosthesis used (biologic versus mechanical), other operations performed during PVR, and some echocardiographic findings of these patients.

Results

In this study, conducted from 2003 to 2007, 53 patients having been affected by pulmonary regurgitation leading to pulmonary valve replacement after total correction for TOF were assessed and their data were analyzed. The mean age of the patients at the time of pulmonary valve replacement was 22.21±6.98 years old, with the youngest patient being 7 years old and the oldest 41 years old.

The mean age at the time of the primary operation was approximately 8.5±3.61 years old, with the oldest at 18 years and the youngest at two years old. The mean time interval between the two operations was approximately 12±6.6 years, the range being between 8 months and 32 years (Table I).

Table I. Age at the first and second operations and time interval between the two operations

	Mean±standard deviation (yrs)	Maximum (yrs)	Minimum (yrs)
Age at total correction	8.5±3.61	18	2
Age at second operation(PVR)	22.21±6.98	41	7
Interval between two operations	12±6.6	0.7	32

The types of primary operation performed were ventricular septal defect closure + pulmonary stenosis correction with patch in

39 (73.6%) patients, ventricular septal defect closure and pulmonary stenosis correction with patch combined with closure of primary shunt in 11 (20.8%) patients, ventricular septal defect closure and pulmonary commissurotomy in 2 (3.8%) patients, and pulmonary valvotomy in only 1 (1.9%) patient (Table II).

Table II. Type of primary operations

VSD closure + commissurotomy	2 (3.8%)
VSD closure + pulmonary valvotomy	1 (1.9%)
VSD closure + RVOT patch repair	39 (73.6%)
VSD closure + RVOT patch repair+ shunt closure	11 (20.8%)
Total	53 (100%)

In 8 cases, repair of residual ventricular septal defect was done (15%), but in only 3 of these cases was there a significant left-to-right shunt (Qp/Qs more than 1.8) and in the others repair was done when the RVOT and previous VSD patch were examined via the right ventricle. Right ventricular ejection fraction had decreased mildly in 18.6% of the cases, moderately in 67.9%, and severely in 12.2% (Table III).

Table III. Cardiac ejection fraction at the time of PVR

	Normal	Mildly reduced	Moderately reduced	Severely reduced	Sum
RVEF	0	10 (18.9%)	36 (67.9%)	7 (13.2%)	53 (100%)
LVEF	24 (44.4%)	29 (53.7)	0	0	53 (100%)

In 11 patients, aneurysm was found at the outflow tract of the right ventricle (20.8%), and in 42 cases, no aneurysm was seen (79.2%) (Table IV).

In 7 patients, decreased exercise tolerance, and in 1 patient, dyspnea was the only presenting symptom, and both of these were the presenting symptoms in 38 (71.7%) patients. Arrhythmia was seen in only 5 cases and symptoms and signs of right-sided heart failure such as ascites and peripheral edema were the presenting symptoms in 1 patient, and syncope was seen in 1 patient as well (Table V). In 30 (56.6%) patients, tricuspid regurgitation was seen during the second operation, and in 1 patient, tricuspid stenosis was detected. However, only 2 patients needed tricuspid repair, and in 1 patient tricuspid valve replacement was necessary (Table VI).

Table IV. Concomitant cardiac lesions at the time of PVR

Residual VSD	8	15%
RV aneurysm	11	20.8%
Tricuspid Regurgitation	30	56.6
Tricuspid Stenosis	1	19%

Table V. Symptoms at the time of PVR

Decrease exercise tolerance test	7	13.2%
Right Heart Failure	1	1.9%
Arrhythmia	5	9.4%
Dyspnea	1	1.9%
Dyspnea+ Decrease exercise tolerance	38	71.7%

Six months after pulmonary valve replacement, 22 (41.5%) cases were symptom-free and marked improvement in symptoms was seen in 30 (56.6%) cases. One patient was excluded from the study because he did not take part in the follow-up programs (Table XI).

The valve used for pulmonary valve replacement was biologic in 46 (86.6%) cases, the sizes used were from 21 to 27mm, and in 6 (10.4%) cases metallic valve was utilized. The sizes employed were from 23 to 27mm, and in only 1 case was valve conduit used (Table VII). Other operations performed during pulmonary valve replacement were patent foramen oval (PFO) closure in 2 (3.8%) cases, closure of residual VSD in 8 (15%), repair of aneurysm of the right ventricle in 9 (17%), tricuspid repair in 2

(3.8%), patch closure of the right ventricular outflow tract in 7 (13.2%), and tricuspid valve replacement in 1 (1.9%) (Table VI).

Table VI. Concomitant operations at the time of PVR

PFO closure	2	3.8%
VSD closure	10	18.9%
RV aneurysm repair	9	17%
TR repair	2	3.8%
TV replacement	1	1.9%
RVOT patch repair	7	13.2%
No	22	41.5%
sum	53	100%

Table VII. Kinds of valves used for PVR

Valve size	**21**	**23**	**25**	**27**
Biologic	6(11.3%)	15 (28.3%)	22(41.5%)	3 (5.7%)
Metallic	0	1 (1.9%)	3 (3.7%)	2 (3.8%)
Homograft	0	1(1.9%)	0	0

Table VIII. Preoperative PA pressure

	<25 mm Hg	**25-50 mm Hg**	**50-75 mm Hg**	**>75 mm Hg**
Preoperative pulmonary artery pressure	11 (20.8%)	34 (64.2%)	7 (13.2%)	1 (1.9%)

Complications after pulmonary valve replacement were complete heart block needing permanent pacemaker in 1 (1.9%) case, fever in 2 (3.8%), bleeding leading to re-exploration in 3 (5.7%), and mortality in 2 (3.8%) (Table X). During the follow-up, no necessity for redo pulmonary valve replacement was seen. Using echocardiography, pulmonary artery pressure during the operation was lower than 25mmHg in 34 (64.2%) cases, between 25mmHg to 50mmHg in 7 (13.2%), between 50mmHg and 75mmHg in 1 (1.9%), and more than 75mmHg in 1 (1.9%) (Table IX).

Table IX. Preoperative diameters and pressures by echocardiography

	Mean± SD	**Max.**	**Min.**	**Valid**	**Miss**
Ascending aorta diameter	2.50± 0.29 cm	3.16 cm	1.90 cm	39	14
Preoperative end-systolic LV diameter	3.01± 0.54 cm	4.10 cm	2.00 cm	39	14
Preoperative end-diastolic LV diameter	4.33± 0.55 cm	5.70 cm	3.05 cm	39	14
Preoperative pulmonary artery diameter	1.06± 0.42 cm	2.70 cm	0.7 cm	39	14
Preoperative end RV diameter	4.2073± 0.90 cm	7.61 cm	2.00 cm	39	14
Preoperative RV systolic pressure	44.83± 14.39 mmHg	80.00 mmHg	25.00 mmHg	39	14

Table X. Postoperative complications

Postoperative fever	2	3.8%
Reoperation for bleeding	3	5.7%
RBBB	19	33.8%
Complete heart block needs pacemaker	2	3.8%
Mortality	2	3.8%
Nothing	45	84.9%
sum	53	100%

Table XI. Symptoms 6 months after operation

Symptom-free	22	41.5%
Reduced symptoms	30	56.6%
Missed	1	1.9%

Right ventricular ejection fraction before the operation was normal in 24 (45.3%) cases, mildly reduced in 28 (52.8%), and not reported in 1 (1.9%) (Table III). Left ventricular end-systolic and diastolic diameters before the operation, measured by echocardiography, are shown in Table IX. Mean left ventricular end-systolic diameter before the operation was 3.01±0.044 (range: 2 – 4cm, Table IX). Mean left ventricular end-diastolic diameter before the operation was 3.31±0.55 (max. 5.70, min. 3.05 cm, Table IX). Pulmonary valve diameter before the operation was 1.06±0.42 (max. 2.70 and min. 0.7 cm, Table IX). Mean aortic diameter during pulmonary valve replacement was 2.50±0.29 (max. 3.16 and min.1.6cm, Table

IX). Mean right ventricular systolic pressure was 44.84±14.39 (max. 80 and min. 25mmHg, Table IX). Mean right ventricular diameter before the operation was 4.21±0.90 (maximum 7.61 and minimum 2 cm). Right bundle branch block (RBBB) was seen in 35.8%, and need for permanent pacemaker was seen in 2 (3.8%) of them.

Discussion

Complete correction of TOF, the most common cyanotic congenital heart defect, has now become routine. However, late residual lesions, primarily chronic pulmonary valve insufficiency, may have a negative impact on right ventricular function, leading to the need for reoperation to insert a competent valve at the right-ventricular outflow.[10] Debate on the proper timing of PVR after repair of TOF is still continuing. Significant pulmonary regurgitation (PR) could result in right ventricular dysfunction, exercise intolerance, arrhythmia, and sudden death.[11] In PR following TOF repair, while there is a group of patients that responds favorably to pulmonary valve insertion, there is also a large subgroup that does not; this requires further analysis of the mechanisms responsible.[7] Early definitive repair of TOF can be performed safely on patients under six months of age. Age at surgery does not appear to affect the medium-term hemodynamic status.[8] Pulmonary valve replacement (PVR) has beneficial effects on RV size and function, provided it is performed early, before irreversible RV dysfunction ensues.[9] Cesnjevar et al., in a retrospective case series study, and by reviewing hospital records of patients operated on for TOF at their institution between 1960 and 2002 and interviewing the patients, concluded that obstructive lesions (right ventricular outflow tract obstruction and pulmonary artery stenosis) and residual defects were frequently observed in patients needing late PVR and might play a crucial role in the development of RV failure. Timely valve replacement with repair of all obstructive lesions proximal and distal to the implanted valve is the key to preserving RV function.[12] In order to maintain adequate RV contractility, pulmonary valve implant in these patients should be considered before RV function deteriorates.[14] Vliegen et al. used magnetic resonance imaging (MRI) to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of TOF in 26 adult patients. Cardiac MRI was performed at a median of 5.1±3.4 months before and 7.4±2.4 months after PVR. Their findings showed that in adult patients with PR and RV dilatation late after total correction of TOF, MRI measurements demonstrated remarkable hemodynamic improvement in RV function after PVR, and thus a trend towards earlier PVR compared to conservative management.

In our cases, the mean duration between the two operations was 138.47+-79.99 months, the range being between 8 months and 314 months. As significant PR could result in right ventricular dysfunction, exercise intolerance, arrhythmia, and sudden death,[11] whether or not earlier operation will be beneficial remains to be determined. In our series, in 7 patients decreased exercise tolerance and in 1 patient only dyspnea were the presenting symptoms, and in 38 cases both of these were the presenting symptoms of the patients (71.7%). Arrhythmia was seen in only 5 cases and symptoms and signs of right side heart failure such as ascites, peripheral edema in 1 patient and syncope in 1 patient were the presenting symptoms (Table V) In our series, mean right ventricular diameter before the operation was 4.20±0.90 (max. 7.61 and min. 2 cm), and we did not use other imaging modalities other than echocardiography for this measurement. In a recent research, Henkens et al. analyzed the influence of pulmonary regurgitation severity and RV size and function before PVR on the outcome of RV size and function after PVR in 27 adult Fallot patients who had cardiac MRI before and after PVR. The RV dimensions were indexed for body surface area. They

concluded that the timing of PVR should be based on indexed RV end-systolic volume and corrected RV ejection fraction rather than on the severity of pulmonary regurgitation.[16] This can be a point to ponder for future evaluations of our patients, i.e., using MRI and indexing RV size for measurements and follow-ups of patients. In order to facilitate the optimal timing of pulmonary valve replacement, Oosterhof et al. analyzed preoperative thresholds of right ventricular (RV) volumes above which no decrease or normalization of RV size takes place after surgery. Between 1993 and 2006, 71 adult patients with corrected TOF underwent pulmonary valve replacement in a nationwide, prospective follow-up study. Patients were evaluated with cardiovascular magnetic resonance both preoperatively and postoperatively. Overall, they could not find a threshold above which RV volumes did not decrease after surgery. Preoperative RV volumes were independently associated with RV remodeling and also when corrected for a surgical reduction of the RV outflow tract. However, normalization could be achieved when preoperative RV end-diastolic volume was <160 mL/m^2 or RV end-systolic volume was <82 mL/m^2.[19] Dave et al. showed that improvement in ventricular dimensions and functions directly correlated with the timing of pulmonary valve insertion. Early insertion leads to normalization and late insertion leads only to improvement. These observations, along with a low morbidity for these reoperations, justify earlier reintervention in cases of chronic pulmonary regurgitation. A RV end-diastolic volume index of 150 mL/m^2 seems to be a practical cut-off value to prescribe pulmonary valve insertion. They used PVR in 39 patients (aged 14 to 39 years) when the right ventricular end-diastolic volume index on MRI exceeded 150 mL/m^2. Changes in morphology and function of the RV were prospectively analyzed via MRI at 6 months postoperatively (available in 21 patients).[20] Tricuspid regurgitation is common in these patients and is related to both tricuspid annulus dilatation and structural valve abnormalities, which are potentially related to previous surgery. Even after adjusting for pulmonary regurgitation, tricuspid regurgitation is significantly correlated with right ventricular volume, suggesting that tricuspid regurgitation as well as pulmonary regurgitation may contribute significantly to progressive right ventricular dilatation in this population.[24] In our series, tricuspid regurgitation was seen in 30 (56.6%) patients during the second operation, and tricuspid stenosis was found in 1 patient; nevertheless, only 2 patients needed tricuspid repair, and tricuspid valve replacement was necessary in 1 patient (Table VI). Large right ventricular outflow akinetic and aneurysmal regions are frequent and further compromise RV function; therefore, resection during PVR should be attempted.[9,25,26] In our series, in 11 patients aneurysm was found in the outflow tract of the right ventricle (20.8%), and in 42 cases, no aneurysm was seen (79.2%).

The assessment of RV function is important in the management of these patients. RV function is notoriously difficult to quantify. There is still a lack of an adequate geometric model to quantify RV function by echocardiography.[27,28] Cardiovascular magnetic resonance is becoming an important tool in the clinical management of patients with congenital heart disease.[29] In these patients, the ejection fraction is decreased in both ventricles, whereas the size of the right ventricle is significantly increased. Reproducibility of the RVEF calculation is good, but in the case of volumes it is suboptimal.[30] Using echocardiography in our series, right ventricular ejection fraction had mildly decreased in 18.6% of the cases, moderately decreased in 67.9%, and severely decreased in 12.2%. In total repair of TOF with transannular patch (TAP), severe pulmonary regurgitation (PR) is reported to develop in up to 30% of patients at a follow-up of 20 years, and 10-15% or more need pulmonary valve replacement (PVR).[33] In our series, most patients operated on for PR had a

transannular patch at the first operation. Late pulmonary valve replacement after tetralogy repair significantly improves right ventricular function, functional class, and atrial arrhythmias, and it can be performed with low mortality. Subsequent re-replacement may be necessary to maintain functional improvement.[34,35] In our series, during the follow-up no necessity for redo pulmonary valve replacement was seen. Buechel et al. performed PVR in 20 children, when the RV end-diastolic volume exceeded 150 mL/m^2, as measured by cardiovascular magnetic resonance. The time interval between primary repair and PVR was 12±3 years. In our series, mean duration between the two operations was 138.47±79.99 months, the range being between 8 months and 314 months.

Conclusion

Surgical management of TOF results in anatomic and functional abnormalities in the majority of patients. Although right ventricular volume overload due to severe pulmonary regurgitation can be tolerated for years, there is now evidence that the compensatory mechanisms of the right ventricular myocardium ultimately fail and that if the volume load is not eliminated or reduced the dysfunction might be irreversible. In light of these data and with better understanding of risk factors for adverse outcomes late after TOF repair, many centers are now recommending early pulmonary valve replacement before symptoms of heart failure develop.[59] The decision to operate should be based on the balance between progressive RV dilatation, exercise intolerance, symptoms, arrhythmias, and the fact that further reoperations will be needed. Research on the ideal valve for RVOT reconstruction is ongoing. Prospective follow-up of patients with repaired TOF with exercise testing and assessment of RV size and function, preferably with magnetic resonance, will better define the natural history of the disease and will probably provide firm guidelines for PVR timing, especially in asymptomatic patients.[46] We suggest randomized controlled trials for answering many questions and controversies (like timing and indications for operations, type of prosthetic valve, etc.) regarding these patients. We suggest that other diagnostic modalities like MRI and radionuclide angiography be used for planning and decision making in these patients. It is also recommended to use valve-preserving operations in total correction for TOF, and leave patch repair in situations where there is no other choice.

Conflict of Interest

No conflicts of interest have been claimed by the authors.

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