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Severe Pulmonary Regurgitation Late After Total Repair of Tetralogy of Fallot: Surgical Considerations

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Abstract. BackgroundAfter total repair of tetralogy of Fallot (TOF-R) with transannular patching (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). In this study, time-related progression of PR and right ventricular (RV) dilatation, and functional recovery of the RV after PVR are analyzed, and the possible causes of PR and timing of PVR are discussed. MethodsEighteen patients, who late after TOF-R with TAP underwent PVR for severe PR, were chosen for the study. NYHA class, QRS duration, RV dilatation index (RVDI = RVEDD/LVEDD), and RV–distal pulmonary artery (PA) peak systolic gradient were reviewed and retrospectively analyzed. ResultsTOF-R was performed at a mean age of 5.1 ± 3.9 years (range: 0.6–12.8 years); the mean time interval from TOF-R to PR grade 3 onset was 11.8 ± 7.0 years (range: 3.3–27.4 years), and from TOF-R to PVR was 18.5 ± 7.8 years (range: 8.7–37.1 years).At PVR, 11 patients were in NYHA class II–III, all patients had severe PR (grade 3/3) and severe RV enlargement, 4 patients had ventricular arrhythmias, 7 patients significant distal pulmonary artery stenosis, and 2 patients small nonrelevant residual VSD. The mean preoperative RVDI (normal: 0.5) was 0.99 ± 0.14 (range: 0.75–1.3), the mean QRS duration 170 ± 24 ms (140–220 ms), and the mean RV–distal PA peak systolic pressure gradient 33.3 ± 19.0 mmHg (range: 10–60 mmHg). Patients aged at TOF-R > 5 years had considerably longer redo-free intervals than their younger counterparts: mean 23.1 years (range 8.7–37.1 years) vs 14.8 years (range: 9.3–21.2 years), respectively. The redo-free intervals and the duration of severe PR correlated inversely with the RV-PA gradient.At a mean follow-up of 1.3 years (2 weeks–5 years), the mean RVDI decreased from 0.99 ± 0.14 to 0.69 ± 0.15, the mean validity class improved from 2.5 to 1.1. One patient died. ConclusionsAfter TOF-R with TAP, the progression of PR has very individual dynamics, resulting in extremely varying redo-free intervals. Concomitant pulmonary stenosis seems to exaggerate progression of PR. PVR results in effective reduction of diastolic dimensions of severely dilated RV and in improvement of validity class. Referred PVR in no-risk cases seems to be justified.

Keywords: Total repair of tetralogy of Fallot — Transannular patching — Pulmonary regurgitation

To avoid the adverse long-term effects of cyanosis and chronic hypoxia, operative correction of tetralogy of Fallot is now usually performed in early infancy with excellent long-term outcome [1, 3, 22]. The use of transannular patching of the right ventricular outflow tract (RVOT) as a part of the repair of TOF has increased to >90% in recent series [3, 5, 6]. As a consequence, variable degrees of PR are common after TOF-R [1, 18]. In a distinct subset of patients PR progresses, and being associated with severe deterioration of RV performance [5, 7, 8], may result in congestive heart failure or sudden death [9]. Since even severe PR and RV dysfunction do not generally result in diminished exercise capacity on the one hand, and pulmonary valve replacement is known to be associated with an increased morbidity and mortality on the other, controversies exist regarding the timing of PVR, especially for asymptomatic patients.

In this study, we analyze time-related progression of PR, factors potentially influencing RV dysfunc-

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tion, and functional recovery of RV after PVR. We also discuss the possible causes of PR and the timing of PVR.

Methods

The study was conducted retrospectively and evaluated consecutive patients, who late after TOF-R with TAP developed severe PR needing PVR.

In all patients, TOF-R was performed with the aid of cardiopulmonary bypass (CPB) and hypothermia, and at repair, VSD closure, an extensive infundibular resection, and a TAP with autologous pericardium for relief of RVOT obstruction and augmentation of pulmonary annulus, were carried out. Additionally, systemic-to-pulmonary shunt, if previously created, was taken down.

After TOF-R, the postoperative follow-up evaluation consisted in all patients of a complete physical examination, an electrocardiogram (ECG), and, when needed, 24-h Holter monitoring, chest roentgenogram, two-dimensional and color Doppler echocardiography, and cardiac catheterization.

At clinical examination, capacity class according to the functional classification of the New York Heart Association was defined. ECG was evaluated for arrhythmias and QRS duration. QRS complex was measured manually over all leads, and was defined as the maximal QRS width in any lead from the first to the last sharp vector crossing the isoelectric line. For ventricular arrhythmias, ECG results were graded according to the Lown criteria [13]. For analysis of arrhythmia, electrophysiological studies were performed. From standard posteroanterior chest roentgenograms, cardio-thoracic ratios were calculated. At echocardiographic examinations, end-diastolic dimensions of both ventricles were measured by M-mode, performed in parasternal short axis views obtained just below the level of the tips of the mitral valve leaflets to exclude the dilation of the RVOT. For assessment of the degree of enlargement of the RV, the right ventricular end-diastolic diameter (RVEDD) was indexed to the left ventricular end-diastolic diameter (LVEDD), finally given as right ventricle dilatation index (RVDI = RVEDD/LVEDD). RV size was classified as normal when RVDI was equal or less than 0.5. The severity of PR was assessed by pulse-wave Doppler characteristics and color flow mapping, and was graded by the cardiologist as mild (grade 1), moderate (grade 2), or severe (grade 3). Tricuspid regurgitation was assessed on a scale from 1 to 3, grade 1 for trivial, grade 2 for mild, and grade 3 for severe. At cardiac catheterization, hemodynamic data with pressure and oxygen saturation measurements were obtained, pressure gradients and residual intracardiac shunts calculated. To delineate the pulmonary artery anatomy and to assess the degree of PR and the right ventricular performance, ventriculogram of the RV and pulmonary angiogram were done. PR was graded by the cardiologist, and the severity of PR was rated according to criteria published by Kobayashi [15]: mild (grade 1), moderate (grade 2), and severe (grade 3). Ejection fraction of the RV was not evaluated because data were not obtained from all patients.

At PVR, in all cases, standard CPB with bicaval cannulation and moderate systemic hypothermia were used during the operative procedures. Crystalloid cardioplegia was preferred in most cases; aortic cross-clamping was dependent mainly on concomitant procedures rather than surgeon's preference. In all patients, cryopreserved pulmonary homografts were used, and inserted in the orthotopic position with one proximal and one distal end-to-end running suture. Most of the pulmonary homografts required prosthetic extension with GoreTex material toward the right ventricle. Concomitant pulmonary artery stenosis were relieved by incising and patch enlargement of the stenotic region using an extension of the homograft and/or GoreTex material. If, at preoperative electrophysiological studies, ventricular arrhythmia was inducible and the reentry mechanism confirmed, intraoperative mapping and cryoablation of an arrhythmogenic focus concomitant with PVR was performed. Tricuspid regurgitation (TR), if necessary, was corrected with the de Vega technique.

All surviving patients were evaluated postoperatively; the evaluation consisted of a complete physical examination, an ECG analysis, and, when necessary, 24-hl. Holter monitoring, and two-dimensional and color Doppler echocardiography.

For analysis, the redo-free time intervals, as well as the time intervals between TOF-R and the onset of severe PR, and the duration of severe PR, as well as the RV–distal PA peak systolic gradients, QRS duration, RVDI, and the grade of TR were calculated. The relations between redo-free time intervals and RV-PA gradient, duration of severe PR, QRS, and RVDI, as well between RV-PA gradient and QRS, RVDI, and duration of severe PR, were examined. Relation between QRS and RVDI was also analyzed. Finally, the functional recovery of the RV, as expressed by the degree of reduction of the RVDI and of the validity class, was also assessed.

For statistical analysis, Student's t tests were used; regression analysis was performed using the method of least squares. The null hypothesis was rejected when $p < 0.05$.

Results

Of a total of 160 patients with tetralogy of Fallot who had intracardiac repair, a subgroup of 18 patients (6 female, 12 male) developed severe PR needing PVR. All patients had ventriculo-arterial concordance, nonrestrictive VSD, pulmonary valve stenosis or atresia, and infundibular muscular obstruction of the RVOT.

Demographic, surgical, and clinical data of the whole study population are presented in Tables 1 and 2. The mean time interval from TOF-R to PVR for all patients was 18.5 ± 7.8 years and varied between 8.7 and 37.1 years. Sixteen patients had their reoperation more than 10 years after the primary repair; 11 of all operated patients reached their adult age at PVR. The mean time interval between TOF-R and onset of severe PR grade 3 and the mean duration of severe PR were 11.8 ± 7.0 years (range 3.3–27.4 years) and 6.9 ± 1.5 years (range 4.9–9.8 years), respectively (see Table 2).

Major indication criteria for PVR, as severe PR and progressive RV dilatation, were fulfilled in each patient, and all patients had at least three or more indications for PVR: 11 patients were in NYHA class II–III, 8 patients had QRS duration > 180 ms, 4 patients Lown 4a/4b class arrhythmia, 8 patients RV–distal PA peak systolic gradient > 30 mmHg, and 11 patients had tricuspid regurgitation grade 1 to 3.

Table 1. Demographic and surgical data

Patients (*n*)	18
Female gender (*n*)	6
Age at TOF-R (yr)	5.1 ± 3.9 (0.6–12.8)
Age at PVR (yr)	23.6 ± 11.1 (11.6–49.9)
Prior palliation (*n*)	12 (9xWAT, 1x BTS, 1x TAP, 1x BP)
TOF-R	VSD patch, TAP with autologous pericardium, WAT/BTS take-down
PVR (pulmonary homograft) (*n*)	18
Mean size	25 mm (20–27 mm)
Concomitant procedures	4x RPA plasty, 3x LPA plasty 1x De Vega tricuspid annuloplasty 2x residual VSD closure Ix cryoablation RV
Mortality (*n*)	1 (cardiac)

Values are expressed as the mean ± SD with ranges in brackets; BP, balloon angioplasty; BTS, Blalock-Taussig shunt; LPA, left pulmonary artery; PVR, pulmonary valve replacement; RPA, right pulmonary artery; RV, right ventricle; SD, standard deviation; TAP, transannular patchplasty; TOF-R, total repair of tetralogy of Fallot; VSD, ventricular septal defect; WAT, Waterston shunt.

Table 2. Clinical data

Redo-free interval (yr)	18.5 ± 7.8	(8.7–37.1)
Time interval TOF-R to PR3 (yr)	11.8 ± 7.0	(3.3–27.4)
Time interval PR3 to PVR (yr)	6.9 ± 1.5	(4.5 ± 9.8)
QRS (ms)	170 ± 24	(140–220)
RVDI	0.99 ± 0.14	(0.75 ± 1.3)
RV-PA gradient (mmHg)	33.3 ± 19.0	(10–60)
CTR	0.55 ± 0.1	(0.5–0.7)

Values are expressed as the mean ± SD with ranges in brackets; CTR, cardio-thoracic ratio; PR3, pulmonary regurgitation grade 3; PVR, pulmonary valve replacement; RVDI, right ventricular dilatation index (see text); RV-PA, right ventricular-to-distal pulmonary artery peak systolic gradient; TOF-R, total repair of tetralogy of Fallot.

In 7 of 8 patients with a significant RV–distal PA peak systolic gradient, pulmonary angiogram revealed stenoses in right and/or left PA main branch.

The mean values with SD and ranges for QRS duration, RVDI, RV-PA gradient, and CTR are presented in Table 2.

The redo-free time intervals correlated significantly with the age at TOF-R ($p = 0.0002$) (Fig. 1). There was an inverse relationship between the RV-PA gradients and the redo-free time intervals as well as the duration of severe PR (Fig. 2 and 3). No correlations were found between the redo-free time intervals and QRS, RVDI, as well as between the RV-PA peak systolic pressure gradient and QRS, RVDI. There was also no correlation between QRS and RVDI (Fig. 4).

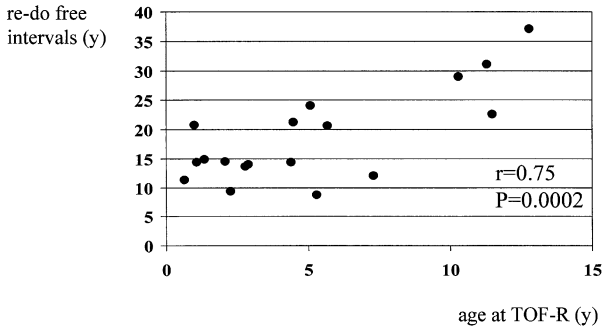

Fig. 1. Plot of correlation between age at TOF-R and redo-free time intervals.

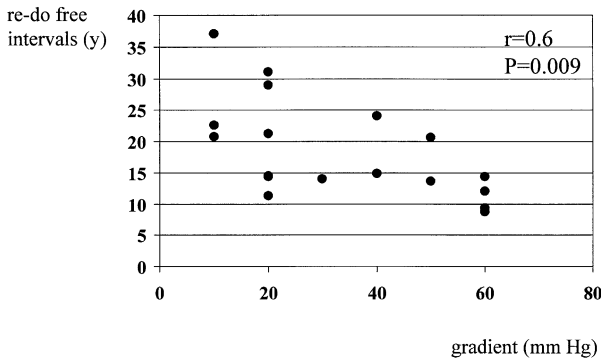

Fig. 2. Plot of correlation between RV-PA gradients and redo-free intervals.

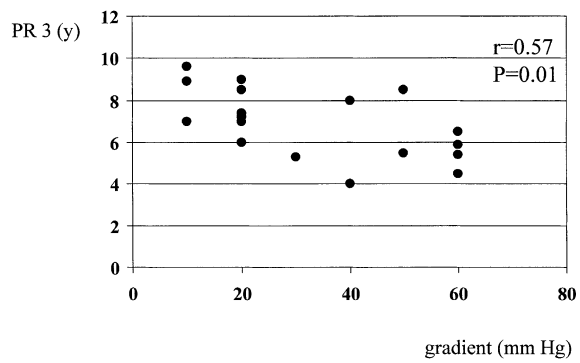

Fig. 3. Plot of correlation between RV-PA gradients and duration of pulmonary regurgitation grade 3 (PR 3).

At PVR, no serious perioperative complications were observed, except for one patient, who died immediately after repair from cardiac cause (low output). The one operative death occurred in a 15-year-old boy, who underwent PVR 8 years after TOF-R, receiving a 20-mm pulmonary homograft for severe PR, who presented with severely dilated and functionally compromized RV and a significant RV-PA gradient, being in NYHA functional class III.

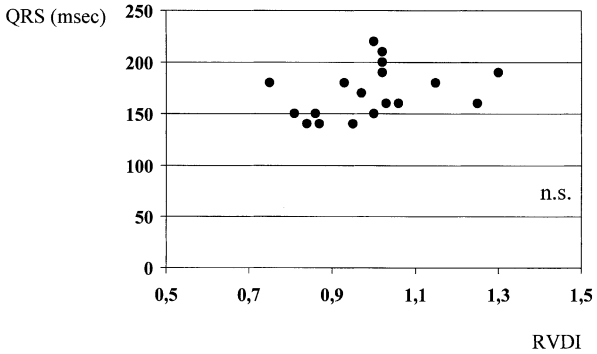

Fig. 4. Plot of correlation between RVDI and QRS.

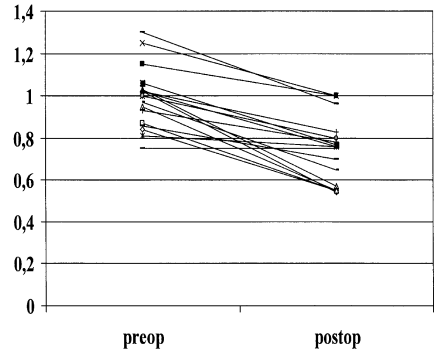

Fig. 5. RVDI at last follow-up before and after PVR.

All surviving patients in the study were evaluated 2 weeks to 5 years (mean 1.3 years) after PVR. By the time of last follow-up, diuretic medication could be discontinued in all patients, while antiarrhythmic therapy was maintained. The RVDI changed significantly 0.99 vs 0.69 (30%). In 6 of 17 patients the RVDI reached almost normal values postoperatively, ranging between 0.55 and 0.65 (Fig. 5).

Functional capacity improved significantly; none of the patients was in NYHA class III. Three patients were in NYHA capacity class II, reporting symptoms of fatigue or premature heart beats (Fig. 6).

No significant RV–distal PA pressure gradient and no significant regurgitation of the conduit valve were observed.

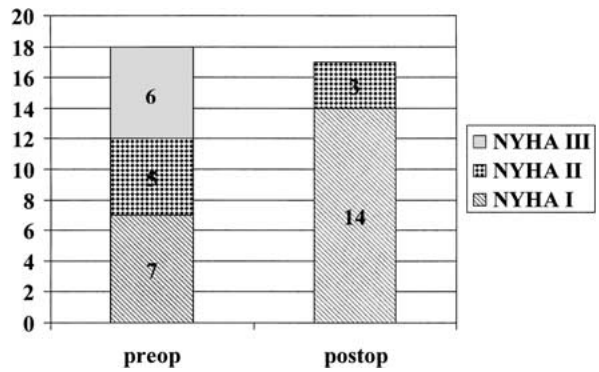

Fig. 6. NYHA functional class at last follow-up before and after PVR.

Discussion

The excellent overall immediate and long-term results support the concept of primary repair of TOF during infancy; however, early repair is reported to be associated with an increased need for TAP [24]. After TAP, chronic PR is universally present to some degree and generally well tolerated for many years, but in a subset of patients becomes severe and is associated with dilatation and dysfunction of RV, therefore leading to increased morbidity and mortality due to arrhythmia, sudden death, or congestive heart failure [21].

The reported incidence of severe PR after TAP ranged about 30% at 22 year follow-up, and the number is expected to grow with increasing age of patients [5, 8, 16]. To control the pulmonary regurgitation, PVR is necessary in at least 12% of patients at 20-years-follow-up [14], and the incidence will probably increase with time.

In an attempt to estimate the long-term fate of patients with PR after TOF-R with TAP, Shimazaki [20] investigated the natural history of isolated congenital pulmonary valve incompetence and concluded that 6% of patients develop symptoms within 20 years, and 29% of patients within 40 years. These data show that PR develops slowly over time but inexorably progresses, and TOF patients who underwent early repair will inevitably face serious problems, at best in their forties. However, the dynamics of the development of severe PR after TOF-R differs strongly from that of isolated PR, ranging from very slow to very fast. In our patient cohort, the time interval between TOF-R and the onset of severe PR varied between 3 and 27 years; similar differences were observed by other investigators [7, 11, 21, 27]. The mechanism of progression of PR and functional impairment of RV also still remains not elucidated. The fact that in some patients the RV is able to tolerate PR and in some other patients not, implies that long-term PR is not the only factor causing RV dilatation [8].

Weidemann [26] demonstrated some typical deformation properties after TOF-R in basal mid- and apical segments of RV, which may be attributable to the TAP and its detrimental effect on abnormal circular muscular middle layer in the RV [19].

D'Udekem [8] suggested that resection of parieto-septal and parieto-parietal muscle bundles may destabilize RV, and contribute to progressive RV

dilatation. Our observations may support this suggestion. In our patient cohort, all patients received an extensive infundibular resection and a TAP with autologous pericardium; most of them developed RVOT aneurysms, associated with a complete loss of contraction of the infundibular area.

In recent reports, emerging importance of restrictive RV physiology for development of RV dilatation and dysfunction, as well as protective effects of poorly compliant RV against detrimental effects of pulmonary valve incompetence, were stressed [10, 16, 17].

Reduced diastolic compliance of RV was found in up to 50% of patients after TOF-R, and was more common in patients with TAP. Restrictive RV physiology correlated significantly with shorter QRS duration, smaller RV size, and better exercise capacity [10, 17].

Unfortunately, determinants for restrictive RV physiology could not be found, and intrinsic factors promoting myocardial restrictive processes are not known [10, 17].

Interestingly, some authors suggested, that early primary repair may reduce the risk for restrictive RV [10, 16]; others reported lower frequency of restrictive physiology if a previous shunt had been done [4]. In our patient cohort, we observed significantly longer redo time intervals in the oldest patient group; unfortunately, restrictive physiology of RV was not examined in our patients.

The role of associated lesions should also be emphasized. In our study, we found a significant inverse relationship between the degree of systolic RV–PA gradient and the redo-free intervals as well as the duration of severe PR, which implies that distal pulmonary stenosis may exaggerate the effects of PR on RV function. Our observations are congruent with those of other investigators. Ilbawi [12] reported that patients with residual pulmonary artery stenosis and a large transannular outflow patch are at risk for the development of right ventricular dysfunction and stressed the importance of repair of PA distortion stemming from palliative shunts at total TOF operation.

The timing and a specific indication strategy for PVR still remain subject of debate due to their complexity.

To delineate the optimal timing for PVR, conditions such as the risk for arrhythmia and sudden death associated with RV dilatation, the potential for functional recovery of severely dilated RV, as well as the increased morbidity and mortality after PVR, must be considered.

Due to possible mechanical interaction, a correlation between RV size and QRS duration exists. A QRS duration on the ECG of > 180 ms was found to be the most sensitive predictor of life-threatening arrhythmias and sudden death [10].

The literature reports regarding the effects of PVR on dilated RV are in part contradictory. The recent data presented by Hazekamp and Vliegen [11, 23] showed a significant reduction of right ventricular end-diastolic volume (RV-EDV) and RV end-systolic volume (RV-ESV), and no change in RV ejection fraction (RVEF), as measured by magnetic resonance imaging. The authors advocate a less restrictive management concerning PVR in these patients.

Therrien [21] in her recent work, demonstrated no change in RVEDV, RVESV, and RVEF after PVR, as measured by radionucleid angiography, and suggested that pulmonary valve implant should be considered before RV function deteriorates.

Using radionucleid angiography, D'Udekem [8] could demonstrate no significant improvement in RVEDD, but significant incease in the RVEDD/LVEDD ratio, whereas Bove [2] reported improvement in RVEF.

Using M-mode echocardiography, Warner [25] observed a significant reduction of RVEDD/BSA index, and Bove [2] significant diminution in RVEDD.

Regardless of the different results concerning the functional recovery of the RV, all authors reported unanimously a significant improvement of exercise capacity after PVR.

Although the ED and ES-RV dimensions may generally diminish after PVR, it seems that the RVEF with a value of 0.40, as reported by Therrien [21], is of predictive importance in the assessment of the postoperative outcome. However, Therrien's recommendation, to perform PVR before deterioration of RV function, could be of practical value only were a perfect pulmonary valve substitute available, or is more true for adult patients, in whom the long-term morbidity and mortality related to the biological, mechanical, or homograft valve are not as high as in children.

In conclusion, the progression of PR after TOF-R with TAP has very individual dynamics and results in strongly varying redo-free intervals. The causes are not yet exactly elucidated and may be of diverse nature. Our results and those of other investigators show that even severely enlarged, chronically volume-overloaded RV is capable of reducing its end-diastolic dimensions after PVR, resulting in considerable improvement of exercise performance. Therefore, in no-risk cases (QRS $<$ 180 ms, EF $>$ 40%), especially in pediatric patient populations, a deferred PVR seems to be justified, as the risks of PVR in terms of increased morbidity and mortality may exceed those associated with progressive RV dilatation. Finally, prospective stu-

dies are necessary to investigate the causes of RV dysfunction and to learn how to prevent it.

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