Cardiology in the Young

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Pulmonary valve replacement in tetralogy of Fallot – who and how?

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Abbreviations:
QRS, complex QRS; PV, Pulmonary valve; TAVI, Transcatheter Aortic Valve Implantation

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Abstract

Background and Aim: Pulmonary regurgitation is the most common complication in repaired tetralogy of Fallot patients. Severe chronic pulmonary regurgitation can be tolerated for decades, but if not treated, it can progress to symptomatic, irreversible right ventricular dilatation and dysfunction. We investigated clinical associations with pulmonary valve replacement among patients with significative pulmonary regurgitation and how interventional developments can change their management. *Methods:* All adult patients with repaired tetralogy of Fallot who were followed at an adult CHD Clinic at a single centre from 1980 to 2022 were included on their first outpatient visit. Follow-up was estimated from the time of correction surgery until one of the following events occurred first: pulmonary valve replacement, death, loss to follow-up or conclusion of the study. *Results:* We included 221 patients (116 males) with a median age of 19 (18–25). At a median age of 33 (10) years old, 114 (51%) patients presented significant pulmonary regurgitation. Among patients with significant pulmonary regurgitation, pulmonary valve replacement was associated with male gender, older age at surgical repair, and longer QRS duration in adulthood. Pulmonary valve replacement was performed in 50 patients, including four transcatheter pulmonary valve implantations, at a median age of 34 (14) years. *Conclusion:* Pulmonary regurgitation affects a large percentage of tetralogy of Fallot adult patients, requiring a long-term clinical and imaging follow-up. Sex, age at surgical repair and longer QRS are associated with the need of PVR among patients with significative pulmonary regurgitation. Clinical practice and current literature support TPVI as the future gold standard intervention.

Tetralogy of Fallot is one of the largest cohorts of patients with moderate-severe defect complexity followed in adult CHDs centres. Tetralogy of Fallot surgical repair, which includes enlarging the right ventricular outflow tract, allows for an actuarial survival rate of nearly 90% at 30 years.[1] However, significant pulmonary regurgitation affects one-third of patients following surgical repair, in consequence of right ventricular outflow tract enlargement and loss of pulmonary valve integrity.[2–5]

Severe chronic pulmonary regurgitation typically develops during the third decade of life and may be well tolerated for decades.[1] However, if not treated, pulmonary regurgitation causes symptomatic right ventricular dilatation and dysfunction, left ventricle dysfunction, exercise intolerance, life-threatening arrhythmias and sudden death.[6] Surgical pulmonary valve replacement, the standard treatment for severe pulmonary regurgitation, avoids the downward spiral while improving quality of life and longevity;[7,8] unfortunately, it carries the burden of redo cardiac surgery every 10–15 years thereafter, with increasing complexity due to adhesions, fibrosis and scarring.[9]

The optimal timing for pulmonary valve replacement is unknown.[4,10] Clinicians have to balance the need to avoid progressive RV dilation with the risk of bacterial endocarditis or prosthesis dysfunction that are associated with PVR.[4,9,11,12] Transcatheter pulmonary valve implantation is now a well-established percutaneous procedure that has the potential to significantly alter the management of pulmonary regurgitation in repaired tetralogy of Fallot.

Considering that significant pulmonary regurgitation affects a large number of tetralogy of Fallot adult patients and represents the main indication for reoperation, we decided to investigate if clinical data could associate with pulmonary valve replacement among patients with significant pulmonary regurgitation and how technology developments can change their management.

Materials and method

Patients and clinical data

Adult (over 18 years old) patients with repaired tetralogy of Fallot who were followed at an adult CHD single centre from January 1, 2000 to December 15, 2022 were included on their first outpatient visit. Individual data, such as patient demographics (date of birth, sex and race), clinical history, arrhythmic events, comorbidities, genetic abnormalities, electrocardiographic and imaging data and surgical or catheter interventions were collected anonymously. Echocardiography was used to access tricuspid regurgitation, end-systolic RV pressure estimation and RV/PA peakgradient. Cardiovascular magnetic resonance (CMR) was used to acess diastolic and systolic RV and LV volumes, LV mass and pulmonary regurgitation fraction and volume; calculations included biventricular stroke volumes and ejection fraction (EF). Significant PR was considered if pulmonary regurgitation fraction was above 30% by CMR, as stated on current guidelines.[6] The imaging (echocardiogram and CMR) data described were the closest in time to the PVR procedure. Measurements were adjusted to body surface area using the Dubois and Dubois formula.[11] Indications for PVR according to the ESC Guidelines were followed[6] and death and reoperation during follow up were obtained.

Follow-up

Patients were censured at the time of death, date of PVR, date of loss to follow-up and on the date of study ending, 15/12/2022. Data were recorded until the date of censure. Patients were deemed lost to follow-up if they had not been seen in our centre for more than 3 years.

Statistics

Statistical Analysis Categorical variables were summarized using frequencies and percentages, and the Fisher exact test was used to compare patients with and without the defined outcomes. Continuous variables were summarised using the mean and standard deviation, or the median and interquartile range (difference between the 75th and 25th percentiles), and compared using the unpaired *t*-test or the Wilcoxon rank-sum test. A 2-sided p value of 0.05 was considered statistically significant. SPSS 27 was used for statistical analysis (IBM, New York, EUA).

Results

Overall, 221 adult patients with repaired TOF were included on their first outpatient visit at our ACHD center between 1980 and 2022. One patient had been submitted to pulmonary valve replacement at the age of four. The median age of patients entering the study was 19 (20–18) years, and median follow-up was of 35 (16) years. One patient was lost to follow-up during the study period.

Demographic data and cardiac status at the time of entry in the study

Among all, 115 (53%) were male and 11 (5%) had Down syndrome. Ninety-nine patients (45%) had a previous palliative shunt. Patients were repaired at a median age of 4 (4) years in different centres (both national and international); 15 (7%) had correction during adulthood. At least 99 had a transannular patch (a descriptive surgical data were not available in 29 (13%) cases). See Table 1 for population characterisation.

Pulmonary regurgitation during follow-up

At a median age of 33 (10) years old, 114 (51%) patients presented significant pulmonary regurgitation. Of these, 50 patients were submitted to pulmonary valve replacement at a median age of 34 (14) years old. In this subgroup of patients, 27 patients (51%) had a previous palliative shunt at a median of 1 year of age. Tetralogy of Fallot repair was performed at 4 (5) years old, with a transannular patch in 31 patients (59%). At the time of pulmonary valve replacement, 50 patients (94%) were in NYHA class I or II. Median B type natriuretic peptide (BNP) concentration was 55 (58) pg/mL, and QRS duration was 171 ± 25 ms. Transthoracic echocardiography revealed that 11 (23%) patients had significant (moderate or severe) tricuspid regurgitation; mean end-systolic RV pressure estimation was 34±16 mmHg, and RV/PA peak gradient was 18 (22) mmHg. CMR was performed 12 (15) months before PVR: median pulmonary regurgitation fraction was of 42 (18) %, and the regurgitant volume was of 50 (53) mL. A right ventricular outflow tract aneurism was found in 18 (34%) patients. Nine patients (17%) had LV systolic function less than 50%, none with LV infarction/fibrosis detected by late hyperenhancement CMR study. In 10 patients, pulmonary stenosis coexisted with significant PR, but the peak gradient was 27±7 mmHg on average. More cardiovascular magnetic resonance is shown in Table 2.

Pulmonary valve replacement

Among the 50 patients submitted to pulmonary valve replacement, the median length of hospital stay was 8 (5) days. Concerning PVR type, 38 patients had a bioprosthetic heart valve (BHV), five had a TPVI, four had a homograft and three had a mechanical heart valve (MHV). The median size of the prosthesis was 25 (2) mm.

Four (7) years after pulmonary valve replacement, eight patients presented with either death or re-pulmonary valve replacement – two patients died (one during early re-pulmonary valve replacement) and six had at least a second pulmonary valve replacement (five after bioprosthetic heart valve dysfunction and one due to bioprosthetic heart valve endocarditis); among the four (initial) transcatheter pulmonary valve implantation patients, no complications were seen until the end of the study, though it was a shorter period of 12 (14) months. We highlight that among the six patients who had an re-PVR, five had more than one on a total of 16 re-operations (minimum 2 and maximum 4 interventions per person) until the end of the study. Considering TPVI in BHV (a valve in valve procedure), there were four patients in such conditions: two had no complications on a follow-up of three and six years respectively; the other two evolved with percutaneous prosthesisTPVI dysfunction after ten and two and had to have years.

Clinical associations for pulmonary valve replacement among patients with significant pulmonary regurgitation

Male gender (PVR vs no-PVR: 59% vs 41%; p=0.003), older age at surgical repair (4 (5) vs 2 (0.5); p=0.027), and longer QRS duration (mean 171±25 vs 157±22 ms; p=0.001) were all associated with PVR among patients with significant PR. Other variables such as prior palliative shunt (23% vs 76%; p=0.238), Down syndrome (18% vs 23%; p=0.520), and BNP level (55 (58) vs 46 (50) pg/mL;

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Table 1. Patients' characteristics at last evaluation or before PVR.

Variables – N (%)	All patients 221 (100)	Significant PR* 114 (100)	Submitted to PVR 50 (100)
Male – N (%)	115 (53)	64 (56)	35 (70)
Down Syndrome – N (%)	11 (5)	2 (2)	2 (4)
Previous palliative shunt – N (%)	99 (45)	55 (48)	14 (51)
Previous transannular patch – N (%)	99 (45)	63 (55)	30 (59)
Age at surgical repair, years – median (IQR)	4 (4)	5 (5)	3 (5)
Repair at adult life – N (%)	15 (7)	10 (8)	6 (11)
Systemic arterial hypertension – N (%)	8 (4)	4 (4)	1 (2)
Diabetes mellitus – N (%)	5 (2)	0 (0)	0 (0)
Dyslipidemia – N (%)	14 (6)	4 (4)	5 (9)
NYHA class I or II – N (%)	215 (97)	111 (97)	46 (92)
QRS duration, ms – mean ± SD	159 ± 23	163 ± 24	175 ± 25
BNP, pg/mL – median (IQR)	45 (45)	47 (52)	55 (57)
None or mild tricuspid regurgitation– N (%)	179 (85)	57 (50)	31 (58)
End-systolic RV pressure, mmHg – median (IQR)	19 (16)	18 (16)	18 (22)
RV/PA gradient, mmHg – median (IQR)	28 (14)	28 (13)	33 (18)

BNP = B-type natriuretic peptide; PA = pulmonary artery; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RV = right ventricular.
*Significant PR was considered if pulmonary regurgitation fraction was above 30% by CMR.

Table 2. CMR measurements.

CMR measurements – N (%)	Significant PR* 114 (100)	Submitted to PVR 50 (100)
LVEF, % – median (IQR)	57 (7)	55 (5)
LVEDV index, mL/m^2 – median (IQR)	78 (18)	80 (21)
LVESV index, mL/m^2 – median (IQR)	33 (12)	38 (13)
LVSV index, mL/m^2 – mean ± SD	46 ± 8	45 ± 8
LV mass index, g/m^2 – mean ± SD	56 ± 18	59 ± 12
RVEF, % – mean ± SD	46 ± 8	40 ± 8
RVEDV index, mL/m^2 – mean ± SD	147 ± 34	160 ± 57
RVESV index, mL/m^2 – mean ± SD	77 ± 25	92 ± 34
RVSV index, mL/m^2 – mean ± SD	67 ± 19	64 ± 22
PR fraction, % – mean ± SD	45 ± 10	44 ± 10
PR volume, mL – mean ± SD	58 ± 27	61 ± 29
RVOT aneurysm – N (%)	32 (28)	17 (34)
Pulmonary stenosis– N (%)	18 (18)	9 (18)
Late gadolinium enhancement – N (%)	111 (98)	50 (100)

LVEDV = left ventricular end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular stroke volume; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVOT = right ventricular outflow track.
*Significant PR was considered if pulmonary regurgitation fraction was above 30% by CMR.
Continuous variables described as mean ± SD or median (interquartile range – IQR), accordingly.

p=0.073) showed no association with PVR in our cohort (see Table 1).

We also analysed the association between clinical data and cardiovascular magnetic resonance parameters as surrogates for pulmonary valve replacement. Previous transannular patch was associated with higher right ventricular end-diastolic volume index (138 (50) versus 122 (59) mL; p = 0.037), higher right ventricular end-systolic volume index (72 (36) versus 55 (47); p = 0.014), and lower right ventricular ejection fraction (46 (9) versus 50 (11)%; p = 0.027). The presence of RVOT aneurysm was associated as expected with a lower RV ejection fraction (43 (8) vs 49 (8); p=0.001) and a higher PR fraction (40 (13) vs 35 (31)%; p=0.013). Previous transannular patch was found to be significantly related to a higher pulmonary regurgitant volume (47 (48) versus 33 (53) ml; p = 0.022). Previous palliative shunt and Down syndrome were not linked to any of the cardiovascular magnetic resonance variables.

Discussion

Long-term follow-up and serial CMR evaluation is mandatory in repaired TOF patients, due to the possibility of late development of significant PR with PVR indication, which in this study occurred at a mean age of 34±14 years. In our cohort, significant PR and the indication for PVR were more frequent than what has been described in the literature (47% vs 33% and 23% vs 15%, respectively). This may be explained by the significant use of the transannular patch technique for TOF surgical repair (50%), since it is very frequently associated with late development of significant PR,[6,7] and by the presence of a RVOT aneurysm in a third of patients, a possible sequel of the transannular patch due to loss of PV integrity.[12] Efforts should be made to try to maintain PV competence, preferring limited RV incision and small stiff patches rather than extensive RV outflow resections,[1] though it depends on the native pulmonary and RVOT anatomy. Figure 1 is a representative scheme of the pulmonary regurgitation burden in our population at the end of the study.

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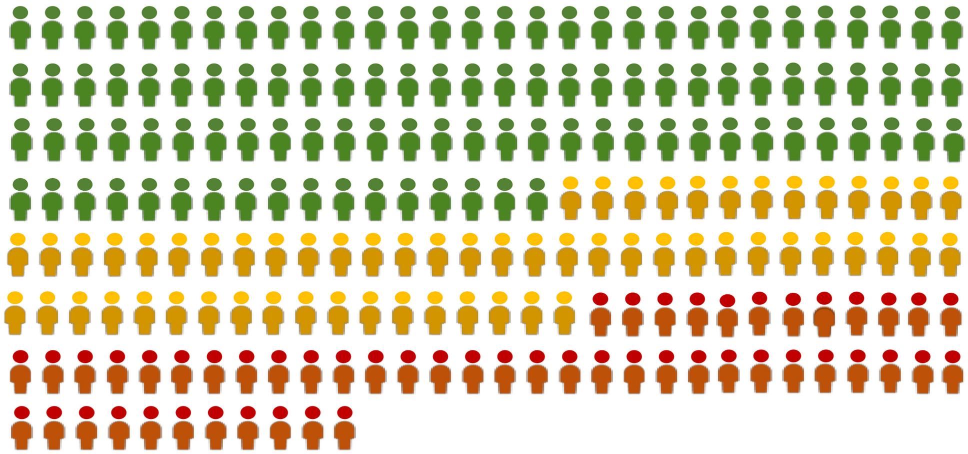

Figure 1. 221 patients were included in our study: 107 had no significant pulmonary regurgitation during follow-up (green people), whereas 114 evolved with significant pulmonary regurgitation; of these, 61 so far did not accomplish intervention criteria (yellow people) and 50 were submitted to valvular replacement (red people).

Clinical data that may alert physicians to a higher likelihood of PVR during follow-up are: male gender, older age at surgical TOF repair and longer QRS duration in adulthood. The relationship between late QRS prolongation, RV dilatation and the degree of PR has been described previously.[13] Larger studies are needed to evaluate the association between male gender and older age at surgical TOF repair with the need of future PVR. CMR parameters are valuable for the management of these patients, and we observed that previous transannular patch was associated with higher RV end-diastolic volume index, higher RV end-systolic volume index, lower RV ejection fraction and higher pulmonary regurgitant volume, all possible indicators for future PVR. Similarly, RVOT aneurysm was associated with a lower RV ejection fraction.

Nowadays BHV (homograft or porcine) in pulmonary position is considered the preferred option for PVR,given the lower complication rate when compared to mechanical prostheses.[14,15] However, more recently, TPVI emerged as a valuable non-surgical approach either in native valves or after BHV and,if eligible, it is first option in the no-native outflow tract.[6] TPVI allows a shorter hospital stay, eliminates the need for anticoagulation, and delays a potential reoperation. RVOT diameter, ideally measured by CMR, is the actual main limitation, as nowadays it is limited to a maximum of 32 mm diameter for transcatheter-stented valve implantation.[14] However, models are evolving to make a greater number of patients eligible. The focus is now on the development of percutaneous valves more suitable for RVOT implantation. There are procedural complications, such as stent fracture, disruption of noncompliant conduits, valve malposition or embolization, which may require urgent surgery. During follow-up, coronary artery compression and endocarditis are also possible complications.[9]

This paradigm shift may eventually change our PVR threshold in severe PR after TOF repair. A lower threshold for earlier PVR may be accepted since reinterventions may be catheter-based. As a result, repaired TOF patients may experience less RV volume overload and less long-term morbidity and mortality. So far, TVPI after BHV accounts for only 20% of all PVR interventions, but TPVI could be avaluable alternative to reoperation.[5] Lessons and expertise should be learned from Transcatheter Aortic Valve Implantation (TAVI) experience. Lessons and expertise should be learned from TAVI experience.

Assessment of the long-term effects of different types of interventions (either surgical or percutaneous) in a highly heterogeneous population (different native anatomic substrate) is a great challenge, and the scarcity of hard outcomes stifles high-quality scientific evidence surrounding the management of TOF.[3]

This single-center retrospective study has several limitations due to the study design, sample size and diverse patient population. However, it reflects a real-world population of adult patients after TOF repair, with a median follow-up of more than 30 years of a late appearing residual lesion, as is significant PR, that compromises survival.

In conclusion, PR is a common late complication after TOF repair requiring long-term clinical and serial CMR evaluation. Male gender, older age at surgical repair and longer QRS duration in adult age were associated with the need of PVR among patients with significant PR during follow-up. Clinical practice and current literature supports TPVI as the future gold standard intervention.

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Author contribution. All author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Competing interests. None.

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