Tetralogy of Fallot in the Current Era

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Only few studies have reported long-term outcome of the transatrial-transpulmonary approach in the current era of management of tetralogy of Fallot (ToF). We investigated 15-year outcome of correction via a transatrial-transpulmonary approach in a large cohort of successive patients operated in the 21st century. All infant ToF patients undergoing transatrial-transpulmonary ToF correction between 2000 and 2015 were included ($N = 177$, 106 male, median follow-up 7.1 (interquartile range 3.0–10.9) years. Data regarding postoperative complications, reinterventions, development of atrial and ventricular arrhythmia, cardiac function, and survival were evaluated. Prior shunting was performed in 10 patients (6%). The transatrial-transpulmonary approach resulted in valve-sparing surgery in 57 patients (32%). Postoperative surgical complications included junctional ectopic tachycardia ($N = 12$, 7%), pericardial ($N = 10$, 6%) or pleural effusion ($N = 7$, 3%), chylothorax ($N = 7$, 4%), bleeding requiring reoperation ($N = 4$, 3%), and superficial wound infection ($N = 1$). Fifty-one patients underwent 68 reinterventions, mainly due to pulmonary restenosis (PS) ($N = 57$). ToF correction at age <2 months and double outlet or double-chambered right ventricle variants of the ToF spectrum were independent predictors for reintervention. Patients undergoing valve-sparing ToF correction had a significant longer PR-free survival than those with a transannular patch (8.5 [95% confidence interval 6.8–10.3] years vs 1.1 [95% confidence interval 0.8–1.5] years; $P < 0.001$). Overall mortality was 2.8%; mortality rates were higher in premature/dysmature newborns (0.7% vs 9.5%; $P < 0.001$). Although the 15-year outcome of the transatrial-transpulmonary approach in terms of postoperative complications and mortality rates is excellent, the high incidence of moderate and severe PR is worrisome. Valve-sparing surgery was associated with a substantially lower incidence of PR, yet was surgically not possible in the majority of patients.

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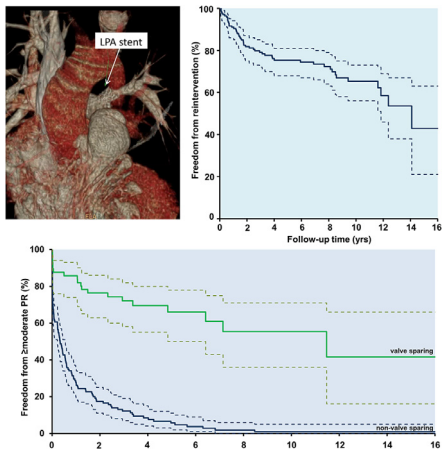
Keywords: congenital heart disease, tetralogy of Fallot, transatrial-transpulmonary correction, pulmonary stenosis, pulmonary regurgitation



Reintervention rate after total ToF correction.

Central Message

Current transatrial-transpulmonary ToF correction shows excellent survival, though residual PS or PR remain an area of concern often leading to RA and RV dilation or reintervention.

Perspective Statement

Only few studies reported outcome of the transatrial-transpulmonary approach, often with follow-up durations <5 years. We investigated long-term outcome of total transatrial-transpulmonary ToF correction in 177 patients operated since 2000. Differences between surgical approaches for reconstruction of the right ventricular outflow tract were assessed and risk factors for adverse outcome were analyzed.

Abbreviations: CAVSD, complete atrioventricular septum defect; DCRV, double-chambered right ventricle; DORV, double outlet right ventricle; HR, hazard ratio; IQR, interquartile range; JET, junctional ectopic tachycardia; LVEF, left ventricular ejection fraction; LVF, left ventricular function; max, maximum; min, minimum; MRI, magnetic resonance imaging; OR, odds ratio; PA, pulmonary atresia; PR, pulmonary regurgitation; PS, pulmonary stenosis; PV, pulmonary valve; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction; RVF, right ventricular function; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SVcouplet, supraventricular couplet; SVPB, supraventricular premature beat; SVrun, supraventricular run; TAP, transannular patch; ToF, tetralogy of Fallot; Vcouplet, ventricular couplet; VPB, ventricular premature beat; Vrun, ventricular run; VSD, ventricular septum defect

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INTRODUCTION

Over the past decades, surgical treatment for various congenital heart diseases has improved tremendously. Specifically, the introduction of the transatrial-transpulmonary approach for total tetralogy of Fallot (ToF) correction by Hudspeth et al in the early 60s lead to high expectations for long-term survival of ToF patients.[1] Previous studies in populations primarily operated between 1970 and 1990 identified several risk factors for late adverse outcome such as reoperation, arrhythmia development or death, including prior palliative shunting, early postoperative arrhythmias, use of a transannular patch (TAP), lower body temperature during surgery, and tricuspid insufficiency.[2–6]

Thus far, only a few studies reported on intermediate or late outcome of the transatrial-transpulmonary approach in the current era of surgical management, which often had follow-up durations less than 5 years.[4,7–9] Furthermore, the influence of additional comorbidities or syndromic diseases is rarely taken into account, hampering decision-making processes for these patients.

In this study, we investigated 15-year outcome of total ToF correction via a transatrial-transpulmonary approach in a large cohort of successive patients operated between 2000 and 2015. Differences between patients with and without comorbidities and between surgical approaches for reconstruction of the right ventricular outflow tract (RVOT) were assessed. In addition, risk factors for adverse outcome were analyzed.

METHODS

Study Population

Data of all infant ToF patients who underwent total surgical correction at our center from 2000 till 2015 were retrospectively retrieved. ToF patients with pulmonary atresia (ToF-PA) or with a complete atrioventricular septal defect (ToF-CAVSD) were excluded from our dataset, as these are considered a separate entity with a different surgical approach. ToF patients with a double-chambered right ventricle (DCRV) variant, that is, more extensive crossing muscle bundles at the RVOT resulting in the DCRV, and with a double outlet right ventricle (DORV) variant, that is, >50% overriding of the aorta, were included. This study is part of the DANARA-project, which primary aim is to examine the development of various dysrhythmias in CHD patients (MEC 2012-482); informed consent was not required.

Total ToF Correction

Transatrial-transpulmonary repair of ToF included closure of the ventricular septal defect (VSD) through the tricuspid valve with a Gore-Tex patch, while RVOT enlargement was performed by myotomy/myectomy through the tricuspid valve or, if necessary, through the pulmonary valve (PV). RVOT enlargement with TAP is considered in patients with a preoperatively echocardiographically assessed PV annulus z-score ≤2, indicated by the Boston z-score system, combined with a detailed intraoperative inspection of the pulmonary valve performed via an incision in the pulmonary truncus. In case the pulmonary valve is dysplastic or the annulus à vue is indeed too narrow as indicated by Hegar measurement, the incision in the pulmonary truncus was extended till the transitional border of the infundibulum at the discretion of the attending surgeon. A glutaraldehyde-pretreated pericardial patch was used for the TAP. Obstructive valve tissue was removed, whereas functional valve tissue was left in situ. In case of a pulmonary annulus of sufficient size and morphologically functional valvular leaflets, a valve-sparing approach is pursued, in which commissurotomy or Hegar dilation is performed if necessary, in addition to desobstruction of the infundibulum. Surgical success of RVOT desobstruction was assessed intraoperatively by echocardiographic Doppler flow <2 m/s and at maximum half systemic pressures in the RV.

Data Collection

Data regarding gestational age at birth were collected from digital patient files and premature/dysmature patients were distinguished from full-term newborns. Prematurity was defined as gestational age <37 weeks; dysmaturity was defined as ≤2 SD from the mean intrauterine growth curve.

Surgical and anesthetic reports were reviewed for documentation of (additional) cardiac anomalies, presence of palliative aortopulmonary shunts, description of surgical techniques used for total ToF correction, total cardiopulmonary bypass time, aortic crossclamp time, and height and weight of the patient prior to surgery.

Surgical complications occurring within 30 days after surgery were collected, including pleural effusion needing drainage, pericardial effusion needing drainage or drug therapy, chylothorax, severe renal insufficiency requiring hemodialysis, bleeding requiring reoperation and thromboembolic events, and prolonged intubation >2 days.

Early and late postoperative mortality was determined, defined as death ≤30 days and >30 days after total ToF correction, respectively.

Clinical data obtained at yearly outpatient follow-up visits were collected from electronic patient files. An ECG was made at each follow-up visit, and echocardiographic examination was done at least once every 2 years in stable patients and more frequently if indicated. Cardiac-MRI, 24-hour Holter recordings and exercise tests were performed on clinical indication. All echocardiographic results during follow-up were examined and the moment of first presentation with greater than moderate PR, PS, RV dilation and RA dilation was collected. At the latest follow-up moment, echocardiographic results of PR, PS, RV, and RA dilation and right ventricular function (RVF) and left ventricular function (LVF) were collected as well.

Medical correspondence, ECG, and Holter-recordings were reviewed for documentation of tachyarrhythmias including postoperative junctional ectopic tachycardia (JET), atrial fibrillation (AF), other supraventricular tachycardia (SVT),

ventricular tachycardia (VT), and ventricular fibrillation (VF); JET, AF, SVT, VT, and VF were defined according to the present guidelines.[10]

Statistical Analysis

Normally distributed data are described as mean ± SD (minimum-maximum) and analyzed with a Student's *t* test or a one-way ANOVA. Skewed data are described by median (interquartile range) and analyzed with Kruskal-Wallis test or a Mann-Whitney U test. Categorical data are expressed as numbers and percentages and analyzed with χ^2 or Fisher exact test when appropriate. Analysis of freedom from reintervention, freedom from PS, PR, RA, and RV dilation and overall survival was performed with the Kaplan-Meier Method. Univariate and multivariate predictors of reintervention and mortality were assessed with a Cox regression analysis, in which 10 events per included factor were required. Influence of mild, moderate, and severe PS within 1 year after total ToF correction was determined, using "no PS" as reference category.

RESULTS

Study Population

After exclusion of 25 patients with ToF-PA ($N = 12$, 6%) and ToF-CAVSD ($N = 13$, 6%), a total of 177 ToF children who underwent total ToF correction at our center were included. Table 1 displays characteristics of the included 177 ToF patients (median age last follow-up 8.3 [interquartile range (IQR) 4.4–11.6; min-max 0.3–17.0] years, 106 male [60%]), of whom 15 (8%) were diagnosed with a ToF-DORV variant and another 15 (8%) with a ToF-DCRV variant. Median follow-up time from total ToF correction was 7.8 (IQR 3.9–10.9; min-max 0.03–16.9) years.

A total of 42 patients (24%) were dysmature or prematurely born. Syndromic diseases occurred in 25 patients (14%) and nonsyndromic extracardiac abnormalities were present in 21 patients (12%, Table 1). At last follow-up, the vast majority of patients did not use any cardiovascular drugs or diuretics ($N = 173$, 98%).

Table 1. Patient Characteristics

ToF patients	177
ToF-DORV variant	15 (8)
ToF-DCRV variant	15 (8)
Male	106 (60)
Age at ToF correction (months)	3.5 (IQR: 2.6–5.2; min-max: 0.2–49.5)
Weight at ToF correction (kg)	5.8 ± 2.2 (2–15.7)
Premature/dysmature	42 (24)
Associated cardiac anomalies	163 (92)
Atrial septal defect	151 (85)
Patent ductus arteriosus	45 (25)
Aberrant coronary artery	5 (3)
Persistent left superior caval vein	5 (3)
Branch pulmonary artery coarctation	2 (1)
Systemic-to-pulmonary collaterals	0 (0)
Additional syndromic disease	25 (14)
Trisomy 21	8 (4)
22q11-deletion	11 (6)
VACTERL	1 (0.7)
Rubinsteijn-Taybi	1 (0.7)
Opitz	1 (0.7)
Mowat-Wilson	1 (0.7)
Turner	1 (0.7)
Cornelia de Lange	1 (0.7)
Nonsyndromic extracardiac abnormalities	21 (12)
Gastrointestinal	5 (3)
Cerebral	9 (5)
Urogenital	8 (4)
Surgical approach	
Transatrial-transpulmonary correction	177
Prior palliative shunt	10 (6)
Valve-sparing surgery	57 (32)

DCRV, double-chambered right ventricle; DORV, double outlet right ventricle; VACTERL, association of various malformation including Vertebral defects, Anorectal malformation, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb anomalies.

Total ToF Correction

Ten patients (6%) underwent prior palliative shunting before undergoing total ToF correction at a later stage, including 5 patients with severe cyanotic spells, 3 with a complex RVOT, 1 who had an intercurrent infection leading to delay of the total ToF correction, and 1 patient underwent prior palliative shunting abroad. Transatrial-transpulmonary total ToF correction was performed at a median age of 3.5 months (IQR 2.6–5.2; min-max 0.2–49.5 months). Mean height and weight at total ToF correction were 62 ± 10 (40–106) cm and 5.8 ± 2.2 (2–15.7) kg, respectively. Valve-sparing surgery was performed in 57 patients (32%). Median cardiopulmonary bypass time was 111 minutes (IQR 76–151; min-max 50–398), and median aortic cross clamp time was 70 minutes (IQR 48–102; min-max 34–167). Patients were extubated within 2 days in the majority of cases ($N = 150$, 85%); 27 patients (15%) required prolonged intubation for a median of 5.5 days (IQR: 4–10.5, min-max: 2–76).

Early Surgical Outcome

Postoperative surgery-related complications are listed in Table 2 and included pericardial ($N = 10$, 6%) or pleural effusion ($N = 7$, 3%) requiring drainage, chylothorax ($N = 7$, 4%), bleeding requiring reoperation ($N = 4$, 3%), and a superficial wound infection in 1 patient. Postoperative JET occurred in 12 patients (7%).

During hospital admission, acute renal failure requiring temporary dialysis occurred in 1 patient and positive blood cultures were observed in 10 patients (6%) for which antibiotic treatment was started under the suspicion of venous catheter septicemia; pneumonia did not occur in our cohort. Temporary pacemaker wires were placed preoperatively in 12 patients

Table 2. Postoperative Complications

Postoperative complication	36 (20)
Pericardial effusion requiring drainage	10 (6)
Pleural effusion requiring drainage	7 (3)
Chylothorax	7 (4)
Bleeding requiring reoperation	4 (3)
Superficial wound infection	1 (1)
Junctional ectopic tachycardia	12 (7)

(7%) due to atrioventricular conduction system disorders, which recovered spontaneously before discharge in all cases.

Echocardiographic Follow-Up

Figure 1 displays the echocardiographic follow-up of the RVOT. Moderate or severe PS occurred in 78 patients (44%) during follow-up. Mean freedom from atleast moderate PS was 9.1 years (96% confidence interval [CI] 7.8—10.4 years) and, against expectation, was better in patients who underwent valve-sparing ToF correction (11.6 years, 95% CI 9.7—13.5 years) compared to those receiving TAP (8.0 years, 95% CI 6.5—9.5 years; $P = 0.008$), as displayed in Figure 2.

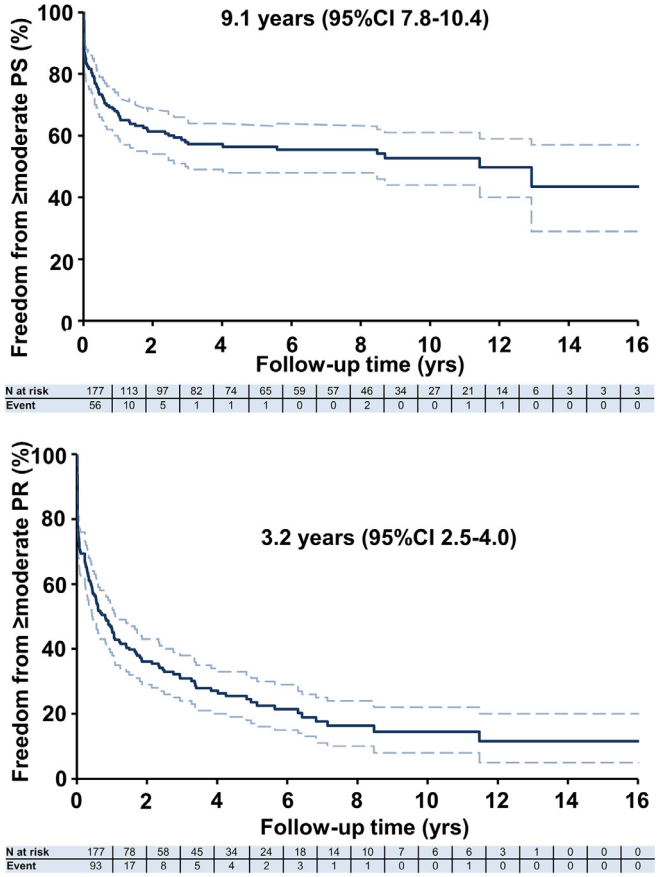


Figure 1. Freedom from pulmonary stenosis and pulmonary regurgitation.
Kaplan-Meier plot describing freedom from pulmonary stenosis (upper panel) and freedom from pulmonary regurgitation (lower panel). Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

As expected in a cohort mainly undergoing ToF correction with TAP, the overall incidence of atleast moderate PR was 76% ($N = 135$). Mean freedom from atleast moderate PR was 3.2 years (95% CI 2.5—4.0 years, Fig. 1). Patients undergoing valve-sparing ToF correction had a significant longer PR-free survival than those with TAP (8.5 [95% CI 6.8—10.3] years vs 1.1 [95% CI 0.8—1.5] years; $P < 0.001$, Fig. 2).

A total of 106 patients (60%) showed atleast moderate RV dilation and 80 patients (45%) showed atleast moderate RA dilation at some point during follow-up. Mean freedom of atleast moderate RV and RA dilation was, respectively, 6.3 (95% CI 5.3—7.4) years and 8.7 (95% CI 7.6—9.9) years.

As a consequence of less PR, patients undergoing valve-sparing correction also showed a far longer freedom from atleast moderate RA and RV dilation, as presented in Figure 2 (RA dilation: 12.5 [95% CI 10.6—14.6] years vs 7.3 [95% CI 6.0—8.6] years [$P < 0.001$] and 11.7 [95% CI 9.7—13.7] years vs 4.4 [95% CI 3.5—5.3] years [$P < 0.001$]).

At last follow-up, PS was present in 103 patients (58%), including mild PS ($N = 85$, 48%), moderate PS ($N = 14$, 8%) and severe PS ($N = 4$, 2%). PS was located subvalvular ($N = 27$, 15%), valvular (32, 18%), supravalvular ($N = 12$, 7%), combined subvalvular and valvular ($N = 17$, 10%), valvular and supravalvular ($N = 8$, 5%) or at all 3 sites ($N = 6$, 3%). Atleast moderate PS occurred in 13% ($N = 16$) of TAP patients vs 4% ($N = 2$) of valve-sparing patients at last follow-up ($P < 0.001$).

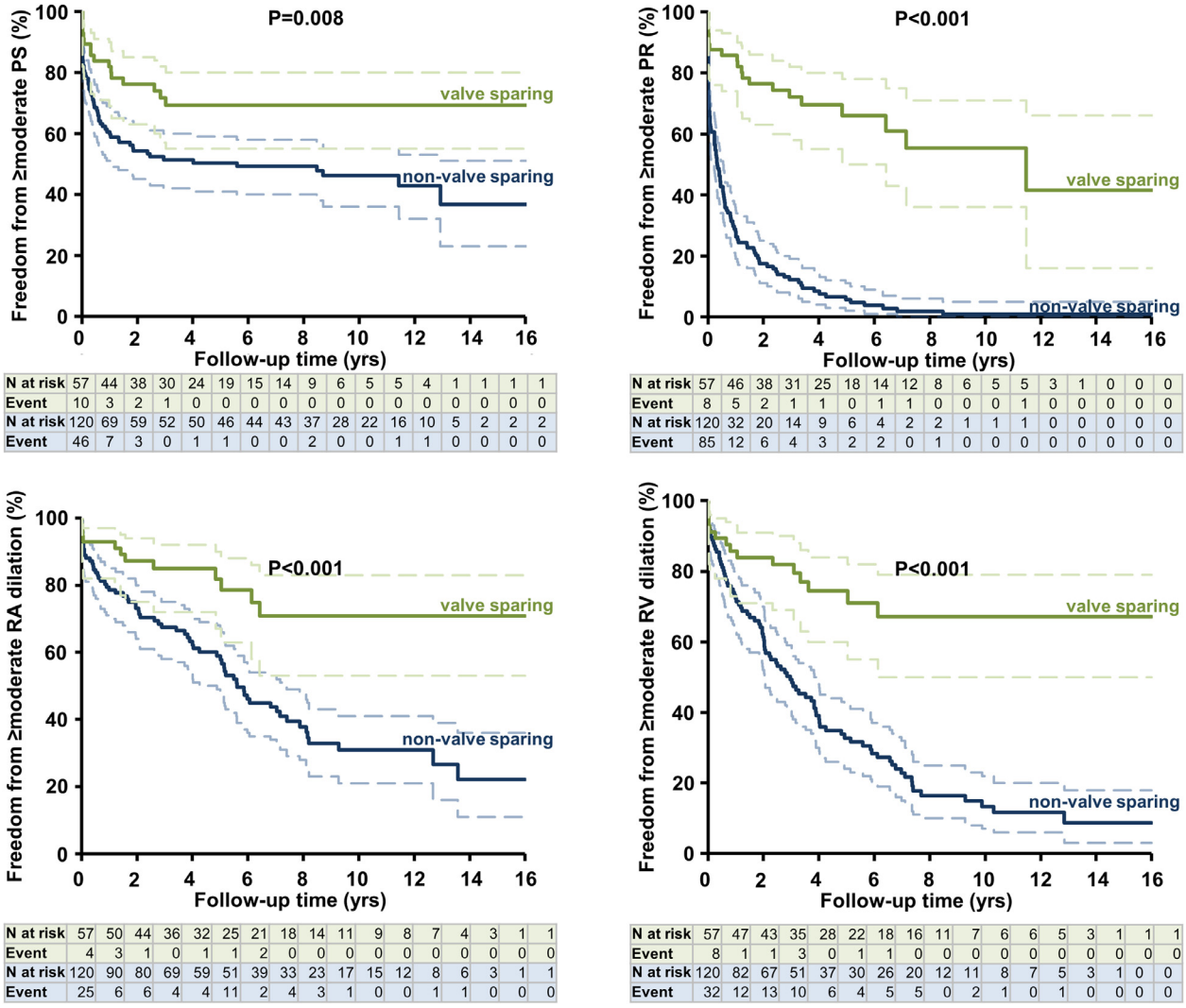
A total of 144 patients (81%) showed PR at last follow-up, which was mild in 26 patients (15%), moderate in 45 patients (25%) and severe in 72 patients (41%). At least moderate PR occurred in 85% ($N = 112$) of TAP patients vs 26% ($N = 15$) of valve-sparing patients at last follow-up ($P < 0.001$).

Mild, moderate, and severe RA dilation occurred in, respectively, 69 (39%), 40 (23%), and 4 patients (2%), whereas mild, moderate, and severe RV dilation occurred in 66 (37%), 43 (24%), and 4 patients (2%) at last follow-up. Hence, severity of PS, PR, RA, ad RV dilation fluctuates during follow-up.

RVF and LVF remained well preserved in the majority of patients; mild RV dysfunction occurred in 15 patients (9%), who all had a normal LVF. Moderately and severely impaired RVF and LVF occurred in, respectively, 2 and 1 patient.

Late Surgical Outcome

During follow-up, reinterventions including redo surgery and percutaneous procedures were required in 51 patients (29%) (1 reintervention: $N = 37$ [73%]; 2 reinterventions: $N = 11$ [22%]; 3 reinterventions: $N = 3$ [5%]). As displayed in the upper panel of Figure 3, mean freedom from reintervention was 11.2 (95% CI 10.0—12.3) years.



N at risk	57	44	38	30	24	19	15	14	9	6	5	5	4	1	1	1	1
Event	10	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
N at risk	120	69	59	52	50	46	44	43	37	28	22	16	10	5	2	2	2
Event	46	7	3	0	1	1	0	0	2	0	0	1	1	0	0	0	0

N at risk	57	46	38	31	25	18	14	12	8	6	5	5	3	1	0	0	0
Event	8	5	2	1	1	0	1	1	0	0	0	1	0	0	0	0	0
N at risk	120	32	20	14	9	6	4	2	2	1	1	1	0	0	0	0	0
Event	85	12	6	4	3	2	2	0	1	0	0	0	0	0	0	0	0

N at risk	57	50	44	36	32	25	21	18	14	11	9	8	7	4	3	1	1
Event	4	3	1	0	1	1	2	0	0	0	0	0	0	0	0	0	0
N at risk	120	90	80	69	59	51	39	33	23	17	15	12	8	6	3	1	1
Event	25	6	6	4	4	11	2	4	3	1	0	0	1	1	0	0	0

N at risk	57	47	43	35	28	22	18	16	11	7	6	6	5	3	1	1	1
Event	8	1	1	3	0	1	1	0	0	0	0	0	0	0	0	0	0
N at risk	120	82	67	51	37	30	26	20	12	11	8	7	5	3	1	0	0
Event	32	12	13	10	6	4	5	5	0	2	1	0	1	0	0	0	0

Figure 2. Differences between valve-sparing and nonvalve-sparing surgery.
Differences in the development of pulmonary stenosis (upper left panel), pulmonary regurgitation (upper right panel), right atrial dilation (lower left panel), and right ventricular dilation (lower right panel) between patients undergoing valve-sparing surgery and patients undergoing nonvalve-sparing surgery. Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

Reinterventions ($N = 68$) mainly included reoperation for PS ($N = 36$, 53%; in 35 patients) and percutaneous pulmonary balloon dilation or stent placement for PS ($N = 19$, 28%; in 13 patients). In a minority of patients, reintervention consisted of homograft placement due to PR ($N = 7$, 10%; in 7 patients), residual VSD closure ($N = 3$, 4%; in 3 patients), or a combination of redo surgery for PS and residual VSD closure ($N = 3$, 4%; in 3 patients).

Median time interval from total ToF correction to reintervention was 0.1 (0.1–0.6) years for residual VSD closure, 0.5 (0.1–0.6) years for combined residual VSD and PS surgery, 1.9 (1.0–7.3) years for PS surgery, 2.6 (1.6–8.5) years for percutaneous treatment of PS, and 11.8 (5.9–14.1) years for PR surgery ($P < 0.001$). Freedom from reintervention due to PS was similar in patients undergoing valve-sparing surgery and patients undergoing correction with TAP ($P = 0.314$).

As displayed in the lower panel of Figure 3, mean freedom from reoperation was 12.1 (95% CI 11.0–13.2) years. In total, redo cardiac surgery was required in 43 patients (24%), of whom 36 patients (84%) underwent 1 reoperation and a minority of 7 patients (16%) underwent 2 reoperations during follow-up.

Figure 4 displays freedom from reintervention based on age at the moment of total ToF correction. ToF correction at age <2 months had the shortest freedom from reintervention with a mean interval of 6.8 (95% CI 4.9–8.9) years ($P = 0.004$ and $P = 0.043$ compared to age 2–6 months and >6 months, respectively). Correction at 2–6 months and >6 months of age

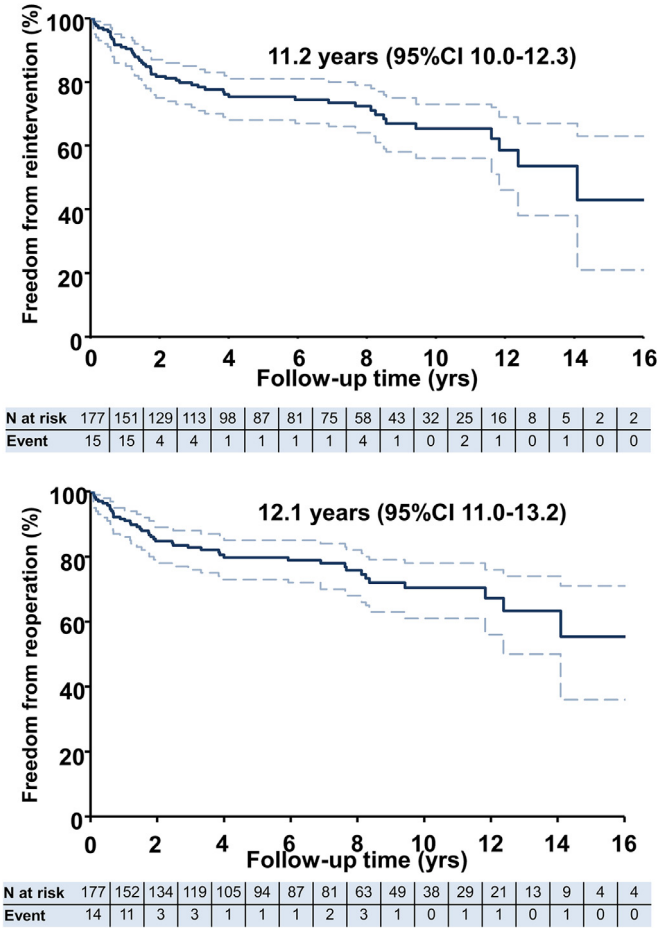


Figure 3. Freedom from reintervention and reoperation. Freedom from reintervention (upper) and freedom from reoperation (lower). Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

showed a similar freedom from reintervention with respective intervals of 11.7 (95% CI 10.3−13.1) and 11.9 (95% CI 9.2−14.6) years ($P = 0.923$).

As shown in Table 3, univariate analysis identified use of TAP, ToF correction at age <2 months, ToF-DORV/DCRV and lower body weight at ToF correction as possible predictors for future reintervention. Multivariate analyses identified ToF correction at age <2 months and DCRV/DORV as independent predictors for reintervention.

Tachyarrhythmias and Cardiac Function Tests

Holter monitoring was performed, on clinical indication, in 41 patients and showed supraventricular or ventricular ectopy in 27 patients, including supraventricular premature beats ($N = 23$), SVcouplets ($N = 2$), SVruns ($N = 2$), VPB ($N = 19$), Vcouplets ($N = 6$), and Vruns ($N = 1$). Only 8 patients had >100 episodes of supraventricular ectopy and 2 patients had >100 episodes of ventricular ectopy. None of the patients had sustained episodes of regular SVT, AF, or VT. One patient underwent ablative therapy for Wolf-Parkinson-White syndrome.

Nineteen patients underwent exercise testing at a mean age of 11.9 ± 2.1 (8.3−16.9) years, performing at a mean of 90 (60−110)% of their predicted value; 5 patients showed ventricular ectopy during exercise testing; no ST-T deviations were observed during exercise testing.

Cardiac MRI was performed in 42 patients at a median interval of 10.9 (8.4−13.0) years after total ToF correction. Twenty-three (55%) of them did not have PS, whereas mild, moderate, and severe PS was observed in, respectively, 12 (29%), 5 (12%), and 2 patients (5%). Median PR-fraction was 35 (27−43)%.

Mean BSA-indexed LVEDV and RVEDV were 81 ± 17 (24−116) ml/m^2 and 128 ± 31 (57−195) ml/m^2, respectively. Median LVEF and RVEF were, respectively, 56 (52−61)% and 53(48−58)%. Only 4 patients who underwent cardiac MRI had undergone valve-sparing total ToF correction; therefore, comparison of PR fraction, LVEF, and RVEF as assessed by MRI was not possible.

Early and Late Mortality

A total of 5 patients (3%) died during follow-up, of whom 2 patients died within the first postoperative month. Three patients died of cardiovascular cause (age 5 months, 5 months, and 9.3 years), 1 patient died of noncardiovascular cause (age 14.4 years) and in 1 patient, cause of death could not be identified. Both early and overall postoperative mortalities were similar between patients without ($N = 152$) and with additional syndromes ($N = 25$) ($N = 1$ [0.7%] vs $N = 1$ [4%], $P = 0.263$ and $N = 4$ [2.6%] vs $N = 1$ [4%], $P = 0.537$, respectively).

However, prematurely/dysmaturely born patients showed an increased risk of postoperative mortality. During 16-year follow-up, mortality rate in á term newborns was 0.7%, whereas mortality rate was 9.5% in prematurely/dysmaturely born patients ($N = 4$, $P < 0.003$).

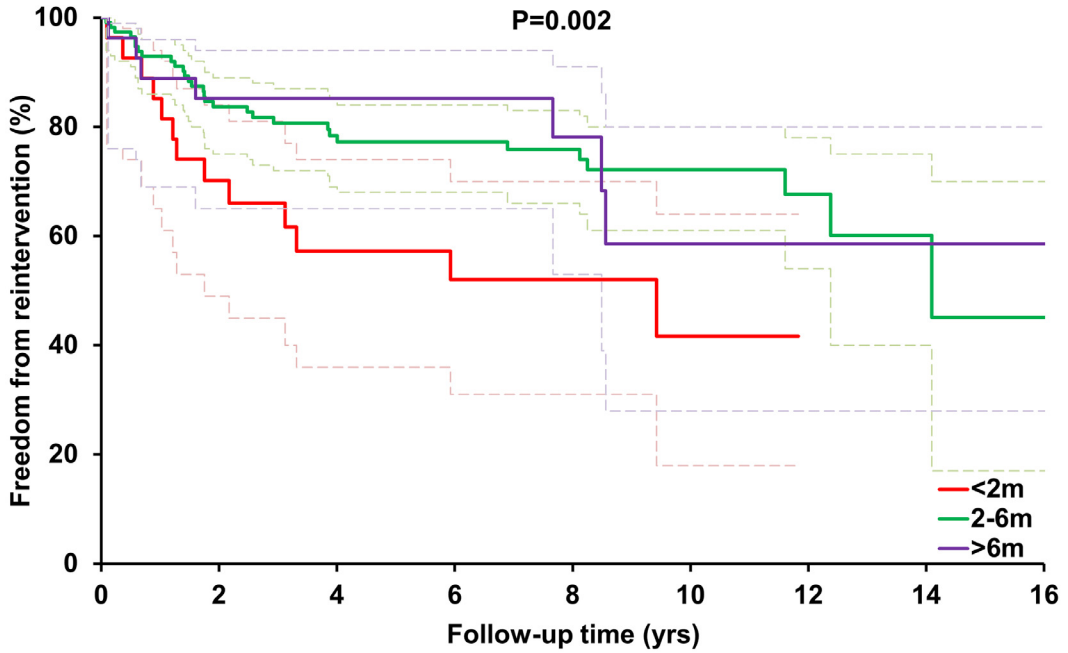
DISCUSSION

Key Findings

The present study reports on 15-year outcome of transatrial-transpulmonary total ToF correction in the current era of surgical and perioperative management. Our data reveal an excellent 15-year survival rate. Nevertheless, premature/dysmature newborns had a higher mortality risk.

Tachyarrhythmias in the early postoperative phase were observed in a minority of patients and none of the patients required permanent pacemaker implantation due to early postoperative conduction disorders.

During long-term follow-up, we observed a high rate of residual PS and PR, requiring reintervention in a substantial number of patients. Valve-sparing surgery resulted in a lower incidence of PR during follow-up. Particularly the high



N at risk	27	23	18	16	13	13	10	9	7	6	3	1					
Event	4	4	1	2	0	1	0	0	0	1	0	1					
N at risk	119	104	88	77	68	57	55	51	42	31	24	20	12	6	4	1	1
Event	8	10	3	2	1	0	1	0	2	0	0	1	1	0	1	0	0
N at risk	31	24	23	20	17	17	16	15	9	6	5	4	4	2	1	1	1
Event	3	1	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0

Figure 4. Freedom from reintervention according to age at total ToF correction.
Kaplan-Meier plot describing differences in freedom from reintervention according to age at the moment of total ToF correction. Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

incidence of PR is worrisome, as it may lead to RV and RA dilation and thereby deterioration of cardiac function and arrhythmia development over time. Prospective follow-up by cardiac MRI is recommended.

Table 3. Predictors for Reintervention

	OR	95% CI	*P* Value
Univariate analysis			
Transannular patch	1.75	0.874–3.511	0.114
ToF correction <2 m	2.50	1.340–4.654	0.004
Syndromic disease	1.06	0.499–2.266	0.873
Premature/dysmature	1.03	0.524–2.005	0.943
DORV/DCRV	2.16	0.120–4.153	0.021
Weight	0.89	0.754–1.042	0.145
Palliative shunt	0.97	0.235–3.990	0.964
Multivariate analysis			
Transannular patch	1.71	0.829–3.539	0.146
ToF correction <2 m	2.06	1.034–4.095	0.040
Syndromic disease	–	–	–
Premature/dysmature	–	–	–
DORV/DCRV	2.44	1.251–4.775	0.009
Weight	0.921	0.781–1.087	0.332
Palliative shunt	–	–	–

Management of the Right Ventricular Outflow Tract

Particularly in ToF patients, improved surgical and perioperative management lead to survival into adulthood. Yet, long-term survival is often characterized by the necessity of (multiple) reinterventions and development of tachyarrhythmias.

While in the early years of ToF correction PR was considered a benign condition which was well tolerated, it is now recognized that chronic PR leads to ventricular deterioration and increased arrhythmogenesis over time.[11–13]

To date, surgical approach of ToF correction is focused more and more on preservation of the pulmonary valve. A broad scala of valve-sparing surgical techniques exists, of which the most commonly used include infundibulectomy, commisurotomy, supra-annular pulmonary artery patch placement, Hegar dilation, and balloon dilation.[11,14] However, preservation of the native pulmonary valve is not always possible, and even if possible, the beneficial results of valve-sparing techniques are not ever-lasting.

Residual Pulmonary Regurgitation

In our cohort, incidence of greater than or equal to moderate PR in the first year after surgery was similar to previous reports by Sen et al[15] and Vida et al,[16] who observed greater than or equal to moderate PR in, respectively, 20% and 14% of

patients undergoing correction without TAP after, respectively, 9 months' and 2.8 years' follow-up.

However, even though valve-sparing surgery drastically reduced the rate of PR development compared to TAP correction, freedom of atleast moderate PR declined from 66% at 5-year follow-up to 55% at 10-year follow-up after valve-sparing surgery.

The progressive nature of residual PR even in patients with valve-sparing surgery was also confirmed in a study by Hickey et al.[17] In their population, atleast moderate PR occurred in 14% of patients undergoing valve-sparing surgery early after surgery, which progressed to 67% after 5.6 years' follow-up.

Similarly, in a recent study by Hofferberth et al, patients undergoing valve-sparing repair with intraoperative balloon dilation developed progressive PR over time.[18] Freedom of atleast moderate PR at 5-year follow-up was only 43%. It appeared that valve leaflet growth was not commensurate with annular growth. The authors hypothesized that although surgical intervention may lead to satisfactory short-term outcomes by altering valvular morphology, valve deterioration over time seems common even in patients with excellent early valvular function. Their findings suggest that long-term biological behavior is not altered by surgical intervention.

Residual Pulmonary Stenosis

Overall, freedom from atleast moderate PS was 50% and 46% after, respectively, 5- and 10-year follow-up after TAP correction and 69% and 69% after, respectively, 5- and 10-year follow-up after valve-sparing correction. Against our expectations, mean freedom from residual PS in our cohort was thus longer in patients with valve-sparing correction, which may indicate that these patients also had less initial RVOT obstruction and perhaps our criteria for valve-sparing correction could be expanded to inclusion of smaller annular sizes. Yet, keeping in mind that this is no guarantee of long-term freedom from PR or reintervention and that there is a substantial risk of intraoperative revision requiring additional cardiopulmonary bypass pump runs to achieve surgical success, as was reported in a recent study by Hickey et al.[17]

A compromise should be found between inclusion of smaller annular sizes versus the risk of intraoperative revision requiring additional pump runs.

However, it may also indicate that while pursuing an transannular incision as limited as possible in those undergoing TAP repair, muscle bundle resection in the RVOT is not sufficient enough even though intraoperative surgical success of RVOT desobstruction was assessed by echocardiographic Doppler flow <2 m/s and at maximum half systemic pressures in the RV. Subvalvular desobstruction of the RVOT may be performed more aggressively in both valve-sparing and nonvalve-sparing surgery to prolong the freedom of residual PS requiring reintervention.

Reintervention Rates During Long-Term Follow-Up

This high amount of residual PS also reflected in our reintervention rate, reaching 29% of the cohort during >10-year follow-up, which is comparable to the findings of recent studies, reporting reintervention rates between 10% and 20% during up to 5-year follow-up.[13,15–17] Reintervention mainly was due to residual RVOT stenosis; in correspondence to the reports of Bacha et al and Sen et al,[13,15] we observed no difference in reintervention rates between TAP and valve-sparing procedures.

An interesting finding, which was also recognized in previous reports, was the age dependency of the reintervention rates. Our results clearly showed worse freedom from reintervention when ToF correction was performed at age <2 months. In addition to higher reintervention rates with younger age at correction, previous studies also associated correction <3 months with increased postoperative morbidity including prolonged ventilation time, prolonged hospital stay, and prolonged lactate clearance.[19–21]

It is likely that the higher reoperation rate is for a great part due to the use of prosthetic materials with limited growth potential in combination with a complex neonatal anatomy. Moreover, as in our center age >2 months is preferred, correction at younger age is performed on indication usually due to severe cyanotic spells in patients with usually more severe obstruction and more complex anatomy, increasing the risk of reintervention.

Limitations

Since this study included patients undergoing ToF correction between 2000 and 2015, patients are still of relatively young age. As a result, none of the patients developed sustained tachyarrhythmias yet and comparison on arrhythmogenesis between valve-sparing and nonvalve-sparing surgery was therefore not possible. Furthermore, when interpreting results on the development of postoperative PR and PS, one must take into account that patients undergoing valve-sparing and nonvalve-sparing surgery show a spectrum of different morphologies and conclusions drawn should also be seen in this perspective.

CONCLUSIONS

Although the 15-year outcome of the transatrial-transpulmonary approach in terms of postoperative complications and mortality rates is excellent, the high incidence of moderate and severe PR is worrisome. Valve-sparing surgery is associated with a lower incidence of PR, yet was surgically not possible in the majority of patients. As arrhythmia development is largely influenced by ventricular function, which is in turn subject to the consequences of PR and use of transannular patches, improved surgical techniques with limited myocardial scarring can only reduce the arrhythmia burden to some extent. To allow a bright future, management of ToF patients should continuously focus on optimal preservation of ventricular function.

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