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Severity of native pulmonary annular hypoplasia and late outcomes of tetralogy of Fallot: retrospective cohort study

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Summary

OBJECTIVE: Pulmonary annular hypoplasia and valvar dysplasia are key morphological features affecting long-term outcomes of tetralogy of Fallot. This retrospective study aimed to analyse factors affecting contemporary long-term outcomes with a focus on pulmonary annular growth and function over time.

METHODS: 131 consecutive isolated tetralogy of Fallot repairs performed between 2004 and 2014 at University Children's Hospital Zurich were included. Median age and weight at the time of repair were 4.8 (interquartile range [IQR] 3.2–6.3) months and 6.1 (IQR 5.1–7) kg, respectively. Based on the severity of native pulmonary annular hypoplasia, the cohort was divided into group 1 (preoperative pulmonary annular Z score < –4; n = 20), group 2 (Z score –2 to –4; n = 56) and group 3 (Z score > –2; n = 54). A transannular patch was used in 88/131 (67.2%) patients: 80%, 67.9% and 61.1% in groups 1, 2 and 3, respectively. The primary outcome was defined as right ventricular outflow tract (RVOT) reoperation or pulmonary valve replacement. Secondary outcome was composite pulmonary valve dysfunction defined as peak gradient >40 mm Hg or severe pulmonary regurgitation at follow-up. A multiple Cox regression model was used to quantify the association of age at tetralogy of Fallot repair, preoperative pulmonary annular Z score and RVOT approach with primary and secondary outcome. Follow-up was 98.5% complete, with a median follow-up duration of 9.6 (95% confidence interval [CI] 9–10.4) years.

RESULTS: All patients were alive at last follow-up resulting in 100% survival. 20/131 patients underwent pulmonary valve replacement (14 surgical and 6 catheter interventional) while 5/131 underwent RVOT reoperations other than valve replacement. The Kaplan-Meier 10-year freedom from primary outcome was 85% (95% CI 78–92%); 69% (46–100%), 91% (82–100%) and 84% (74–95%) for groups 1, 2 and 3, respectively (log rank p = 0.16). Composite dysfunction at follow-up was observed in 29.8% (overall): 45%, 28.6% and 25.9% for groups 1, 2 and 3, respectively (p = 0.12). The multiple Cox regression analysis for primary outcome indicated that the use of a transannular patch results in a Hazard Ratio (HR) of 3.3 (95% CI 0.7–14.7, p = 0.13). Additionally, the presence of composite dysfunction at discharge results in a HR of 2.1 (95% CI 0.8–5.4, p = 0.1). Age (in months) with a HR of 0.8 (95% CI 0.6–1, p = 0.06) and group 2 with a HR of 0.4 (95% CI 0.14–1.2, p = 0.11) showed a trend to being protective for the primary outcome. However, the 95% CI of all estimates included the HR of 1.

CONCLUSIONS: Transannular patch use and composite dysfunction at discharge, although not statistically significant at 5% level, may be associated with pulmonary valve replacement and RVOT reoperation. Avoiding the use of a transannular patch or using reconstructive techniques to achieve a better composite dysfunction at discharge could reduce the primary outcome. Large multicentre studies are needed to demonstrate more precisely the impact of pulmonary annulus Z scores on outcome.

Introduction

Repair of tetralogy of Fallot has come a long way since Walton Lillehei performed the first repair in 1954 [1]. While survival of repaired of tetralogy of Fallot beyond the perioperative period is the norm, the focus has shifted to the residual disease load and its impact on quality of life and longevity [2]. Long-term survival is excellent; however, it is worse when compared to the normal population. The late mortality is reported to be around 0.29 per 100 patient-years; most attributed to heart failure and arrhythmias [3]. The pathophysiology underlying late mortality and sudden cardiac death in a large proportion of repaired tetralogies of Fallot can be traced back to chronic severe pulmonary regurgitation and arrhythmogenicity (dilated right ventricle, surgical scars, prolonged QRS duration). The same factors also contribute to morbidity manifesting as decreased exercise tolerance, interventions and need for medications [4].

Many surgical initiatives in the last decades have involved prevention of modifiable causes adversely affecting long-term outcome, such as operating in early infancy and use of the transatrial approach to contain right ventricular hy-

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pertrophy, myocardial fibrosis and surgical scars. Transannular patch (TAP) has appeared as a predictor of all-cause late outcome in many studies [3]. Thus, early strategies involving overwhelming enlargement of the right ventricular outflow tract (RVOT) have given way to valve- and annulus-sparing approaches while accepting some residual obstruction. However, clarity about the limits up to which a non-transannular patch (n-TAP) approach could be pushed is lacking. Consequences of residual gradients in real-life conditions in the long run, in contrast to influence of evolving pulmonary monocusp techniques [5], the unknowns about timing pulmonary valve replacement [6–8] have left the strategies for optimal repair of tetralogy of Fallot subject to individual interpretation. A middle path, striving for good pulmonary valve competence using pulmonary valve reconstructive techniques, while allowing a peak-to-peak gradient of about 20 mm Hg is gaining acceptance.

The echocardiographically derived preoperative pulmonary annular Z score [9] serves as an important guiding parameter in surgical planning, communication with the family and prognostication of the early postoperative course as well as the long-term outcome. There is little data in the literature examining the prognostic value of the pulmonary annulus Z score. This retrospective cohort study of tetralogy of Fallot repair reports a long-term primary outcome (pulmonary valve replacement and RVOT reoperations) as well as a secondary outcome (pulmonary valve dysfunction) with a focus on the body size-adjusted growth of the pulmonary annulus (Z score).

Materials and methods

Methods

The study included 131 consecutive children undergoing tetralogy of Fallot and Double-Outlet Right Ventricle (Fallot type) repair at University Children's Hospital Zurich, Switzerland, between 2004 and 2014. The rationale for the cohort selection was to include patients who had at least five years of follow-up. Pulmonary atresia, tetralogy of Fallot with atrioventricular septal defect (AVSD) and tetralogy of Fallot repair involving primary right ventricle to pulmonary artery conduit were excluded. Data parameters were retrieved from the hospital database or actively sought from the referring cardiologists. Data acquired included demographic data, palliation (where applicable), perioperative data during repair of tetralogy of Fallot, follow-up echo and catheter-based/surgical interventions. Follow-up was 98.5% complete. A retrospective tabularised Excel sheet is available and can be provided on demand; while the study has been registered and approved by the appropriate agency as stated below.

Since pulmonary annulus (PA) Z score > –2 is normal, this group was expected to undergo a non-transannular repair, while a PA Z score < –4 is likely to require a transannular repair. The intermediate group represents a grey zone where other factors such as number and quality of valve leaflets would determine the type of repair. This was the rationale for dividing the cohort into three groups stratified by the preoperative pulmonary annulus Z score.

Group 1: Z score < –4 (n = 20)

Group 2: Z score –4 to –2 (n = 57)

Group 3: Z score > –2 (n = 55)

Table 1 depicts the demographic features of the cohort.

Surgery

The surgical strategy involved palliation when the child presented with blue spells during the first 6 weeks of life. Elective total correction was undertaken at around 6 months of age. Transatrial and transinfundibular was our preferred approach; ventricular septal defect (VSD) was closed conventionally. The pulmonary annulus Z score served as a guiding parameter for RVOT reconstruction. The aim was to achieve a Z score of about –2. A dysplastic valve or an additional stenosis at the site of ductus arteriosus / shunt insertion site weighed against a valve-sparing approach for borderline pulmonary annulus. If a transannular patch was necessary, a monocusp was created or not created based on surgeon preference. The infundibulotomy was routinely closed using a xenopericardial patch.

Endpoints

The primary outcome was defined as RVOT reoperation or pulmonary valve replacement (surgical/catheter interventional), whichever appeared first. Secondary outcome was composite pulmonary valve dysfunction defined as peak gradient >40 mm Hg or severe pulmonary regurgitation at follow-up.

Statistical analysis

For descriptive analyses, we report median and interquartile range (IQR) for continuous variables and count and percentage for categorical variables. The standardised mean difference (SMD) was calculated between all pulmonary annulus Z score groups and averaged across all pairwise comparisons between the three groups.

The difference in the rate of growth of QRS from discharge to follow-up between the three pulmonary annulus Z score groups was compared with a one-way test assuming non-equal variances [10]. Potential differences between pulmonary regurgitation at discharge and follow-up were investigated with the McNemar test with continuity correction.

Kaplan-Meier curves were used to visually investigate RVOT reoperations, catheter interventions and the primary endpoint between the three pulmonary annulus Z score groups. The log-rank test was used to quantify potential differences between the survival curves.

The Cox proportional hazards model for the primary endpoint was calculated using age at repair of tetralogy of Fallot in months, RVOT approach (TAP/n-TAP), composite dysfunction at discharge (yes/no) and pulmonary annulus Z score groups 1–3 as explanatory variables assuming random censoring. The decision to include these variables was based on clinical knowledge and a consensus among clinical authors. Proportional hazard assumption was checked with Schoenfeldt residuals and a test for proportional hazard assumption by Grambsch and Therneau [11].

No adjustment for multiple testing was done and no subgroup analysis was conducted. Complete case analysis was

Table 1:
Baseline characteristics. Groups stratified by preoperative pulmonary annulus Z score: group 1: Z < –4; group 2: –4 < Z ≤ –2; group 3: Z > –2.

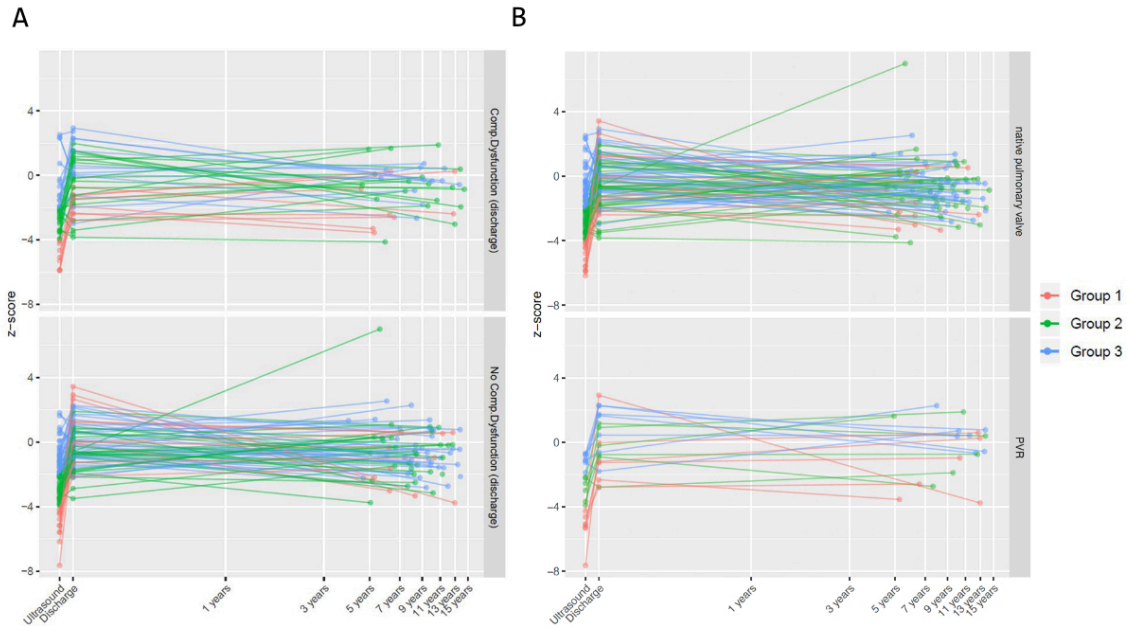
Baseline		Overall	Missing data in %	Group 1	Group 2	Group 3	Standardised mean difference*
n		131		20	56	54	
Female sex – n (%)		54 (41.2%)	0.0%	8 (40.0%)	23 (41.1%)	22 (40.7%)	0.015
Diagnosis – n (%)			0.0%				0.335
	Tetralogy of Fallot	116 (88.5%)		15 (75.0%)	52 (92.9%)	48 (88.9%)	
	DORV	15 (11.5%)		5 (25.0%)	4 (7.1%)	6 (11.1%)	
No genetic disorder – n (%)		107 (81.7%)	0.0%	18 (90.0%)	50 (89.3%)	38 (70.4%)	0.339
Number of palliations – n (%)		19 (14.5%)		3 (15.0%)	6 (10.7%)	10 (18.5%)	0.148
Age at palliation in days – median (IQR)		24.00 (9.00–39.00)	0.0%	9.00 (5.50–9.50)	29.50 (9.00–35.75)	31.50 (16.25–46.50)	0.985
Weight at palliation in kg – median (IQR)		3.10 (2.75–3.63)	5.3%	3.20 (3.04–3.20)	2.85 (2.62–3.75)	3.40 (2.90–3.70)	0.08
Age at tetralogy of Fallot repair in months – median (IQR)		4.77 (3.20–6.28)	0.0%	3.65 (2.54–5.47)	4.65 (3.09–6.14)	5.55 (3.62–6.62)	0.353
Weight at tetralogy of Fallot repair in kg – median (IQR)		6.13 (5.08–7.00)	0.8%	5.70 (4.84–6.60)	6.20 (5.08–7.15)	6.03 (5.10–6.80)	0.262
Preop pulmonary annulus in mm – median (IQR)		6.50 (5.50–8.15)	0.8%	4.25 (3.92–4.50)	6.00 (5.71–6.78)	8.40 (7.32–9.88)	2.311
Preop pulmonary annulus Z score – median (IQR)		−2.18 (−3.48 – −1.23)	0.8%	−5.18 (−5.65 – −4.44)	−2.92 (−3.45 – −2.32)	−1.04 (−1.54 – −0.28)	3.234
Preop RPA in mm – median (IQR)		5.20 (4.40–6.00)	1.5%	4.05 (3.40–5.08)	5.05 (4.07–5.70)	5.50 (5.00–6.50)	0.446
Preop RPA Z score – median (IQR)		−0.56 (−1.67–0.32)	1.5%	−1.65 (−2.67 – −0.76)	−0.72 (−2.29 – −0.01)	−0.16 (−0.82–0.70)	0.575
Preop LPA in mm – median (IQR)		5.00 (4.00–5.90)	1.5%	3.75 (3.22–4.75)	4.85 (3.70–5.82)	5.40 (4.50–6.00)	0.557
Preop LPA Z score – median (IQR)		−0.47 (−1.40–0.53)	1.5%	−1.95 (−2.35 – −0.50)	−0.72 (−1.69–0.39)	0.05 (−0.68–1.33)	0.654
RPA and/or LPA stenosis – n (%)		25 (19.1%)	0.0%	6 (30%)	11 (19.6%)	8 (14.8%)	0.467
Preop max RVOT gradient – median (IQR)		80.00 (68.50–92.55)	0.0%	75.00 (63.20–90.25)	86.50 (74.00–96.25)	79.50 (63.25–90.00)	0.425
Preop SaO2 – median (IQR)		91.50 (83.25–97.00)	0.8%	90.00 (82.50–94.50)	91.00 (82.00–97.00)	92.50 (85.00–97.00)	0.2
Number of pulmonary valve cusps – n (%)			29.8%				0.476
	1 leaflet	3 (2.3%)		0 (0.0%)	1 (1.8%)	2 (3.7%)	
	2 leaflets	70 (53.4%)		11 (55.0%)	32 (57.1%)	27 (50.0%)	
	3 leaflets	19 (14.5%)		1 (5.0%)	5 (8.9%)	13 (24.1%)	
	NA	39 (29.8%)		8 (40.0%)	18 (32.1%)	12 (22.2%)	
Quality of pulmonary valve cusps – n (%)			51.1%				0.599
	Normal pliable	29 (22.1%)		3 (15.0%)	7 (12.5%)	19 (35.2%)	
	Thickened less pliable	13 (9.9%)		1 (5.0%)	6 (10.7%)	6 (11.1%)	
	Dysplastic	22 (16.8%)		7 (35.0%)	10 (17.9%)	5 (9.3%)	
	NA	67 (51.1%)		9 (45.0%)	33 (58.9%)	24 (44.4%)	
Transannular patch versus non-transannular patch – n (%)							0.31
	Non-transannular	43 (32.8%)		4 (20.0%)	18 (32.1%)	21 (38.9%)	
	Transannular patch with monocusp	26 (19.8%)		6 (30.0%)	11 (19.6%)	9 (16.7%)	
	Transannular patch without monocusp	62 (47.3%)		10 (50.0%)	27 (48.2%)	24 (44.4%)	
Duration of mechanical ventilation – median (IQR)		2.00 (1.00–4.00)	0.0%	2.50 (1.00–5.00)	2.50 (1.00–4.00)	1.00 (1.00–2.75)	0.345
Duration of ICU Stay – median (IQR)		5.00 (3.00–7.00)	0.0%	7.50 (4.00–9.00)	5.00 (4.00–7.00)	4.50 (3.00–6.00)	0.269
Duration of hospital stay postop – median (IQR)		14.00 (11.00–21.00)	0.0%	19.00 (13.25–24.25)	14.00 (11.00–18.25)	13.00 (10.00–20.75)	0.237
Pulmonary annulus at discharge in mm – median (IQR)		8.00 (6.70–9.60)	72.5%	7.65 (6.60–8.40)	7.55 (6.85–8.77)	9.60 (8.45–9.65)	0.28
Pulmonary annulus at discharge Z score – median (IQR)		−0.38 (−1.28–0.72)	3.8%	−1.19 (−1.67–0.62)	−0.64 (−1.68–0.53)	0.03 (−0.88–0.81)	0.306
RPA at discharge Z score – median (IQR)		−0.31 (−1.36–0.60)	8.4%	−0.59 (−1.69–0.17)	−0.32 (−1.73–0.99)	−0.13 (−0.70–0.61)	0.349
LPA at discharge Z score – median (IQR)		0.10 (−0.96–0.99)	7.6%	−0.68 (−1.65–0.64)	−0.09 (−1.07–0.88)	0.31 (−0.36–1.08)	0.441
Max RVOT gradient at discharge – median (IQR)		20.00 (14.00–27.75)	0.8%	23.00 (15.00–30.00)	22.50 (16.75–32.00)	15.50 (10.22–25.75)	0.317
Pulmonary regurgitation at discharge – n (%)			0.8%				0.876
	≤mild	67 (51.1%)		4 (20%)	27 (48.2%)	35 (64.8%)	

	moderate	43 (32.8%)		10 (50.0%)	16 (28.6%)	17 (31.5%)	
	severe	20 (15.3%)		5 (25.0%)	13 (23.2%)	2 (3.7%)	
	NA	1 (0.8%)		1 (5.0%)	0 (0.0%)	0 (0.0%)	
Composite dysfunction at discharge – n (%)			0.8%				0.347
	No composite dysfunction	88 (67.2%)		11 (55.0%)	36 (64.3%)	40 (74.1%)	
	Presence of composite dysfunction	42 (32.1%)		8 (40.0%)	20 (35.7%)	14 (25.9%)	
	NA	1 (0.8%)		1 (5.0%)	0 (0.0%)	0 (0.0%)	
Duration of follow-up – median (IQR)		8.44 (6.32–10.84)	1.5%	6.44 (5.97–11.64)	8.20 (6.13–10.68)	9.15 (7.92–10.82)	0.196

DORV: double outlet right ventricle; LPA: left pulmonary artery; NA: Not available; RPA: right pulmonary artery.

* Standardised mean difference (SMD) is a measure of effect size. The higher the value of SMD, the more the groups differ. (It is calculated by taking the mean difference and dividing it by the standard deviation.) Some interpret SMD values of 0.2, 0.5 and 0.8 as small, medium and large imbalance. Groups with SMD estimates below 0.1 are considered more or less balanced.

Figure 1: Pulmonary annulus (PA) Z score over time. (**A**) Stratified by presence (above) or absence (below) of composite dysfunction at discharge. (**B**) Stratified by no pulmonary valve replacement (above) and need for pulmonary valve replacement (below).



performed assuming missingness completely at random for follow-up and baseline variables.

Ethics

The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland vide BASEC-Nr. 2017-01321. Need for consent was waived.

Results

Table 1 details the baseline demographic and perioperative data while table 2 documents the long-term outcomes.

Palliation

Modified Blalock Taussig Shunt, RVOT patch or RVOT / Persistent Ductus Arteriosus Botalli stent palliation was performed in 19 (15%) children (15%, 11% and 19% in groups 1, 2 and 3, respectively). Details are enumerated in table 1. All of them survived the total correction.

Native pulmonary valve cusps

Due to the retrospective character of the data harvest, information about the number and quality of native pulmonary leaflets was available only in 64 cases, thus precluding a statistical analysis. On descriptive analysis, 36 (55%) leaflets were documented as thickened, dysplastic and less pliable. The prevalence of abnormal leaflets was highest in group 1 and lowest in group 3. The number of pulmonary valve leaflets was evenly spread across groups.

Transannular versus non-transannular patch

Overall a transannular patch was used in 88 (67.2%) children; in 16 (80%), 38 (67.9%) and 33 (61.1%) children in groups 1, 2 and 3, respectively. While 62/131 (47.3%) received a simple transannular patch, 26 (19.8%) received a transannular patch with monocusp.

Perioperative results

There were no perioperative deaths. The duration of ventilation and ICU stay were longer in group 1, but there was no evidence that the hospital stay differed between groups (table 1). One patient received a pacemaker due to congen-

ital complete AV block; 4 (2.3%) patients received a pacemaker due to a iatrogenic complete AV block post-repair of tetralogy of Fallot.

Outcome at discharge

The pulmonary annulus Z score normalised at discharge: median –1.2 (IQR –1.7; 0.6), –0.6 (–1.7; 0.5) and 0.03 (–0.9; 0.8) for groups 1, 2 and 3, respectively. The preoperative distinctly smaller Z scores of right pulmonary artery and left pulmonary artery between groups normalised after total correction. The left pulmonary artery Z score remained borderline smaller in group 1 compared to the rest (table 1). The repair involved correction of side branch stenosis in 25 (19%) children. The postoperative peak RVOT gradient was a median of 20 (14–28) mm Hg. It was greater in group 1 >2 >3, with a standardised mean difference of 0.32 (an SMD below 0.1 indicates very balanced data). Severe pulmonary regurgitation at discharge was noted in 20 patients (15%): 25%, 23% and 4% in

Table 2:
Long-term outcome data. Groups stratified by preoperative pulmonary annulus Z score: group 1: Z < –4; group 2: –4< Z ≤–2; group 3: Z > –2.

Long-term outcome		Overall	Missing data in %	Group 1	Group 2	Group 3	Standardised mean difference*
n		131		20	56	54	
Age at follow-up in years – median (IQR)		9.01 (6.78–11.50)	1.5%	6.82 (6.28–12.10)	8.63 (6.51–11.28)	9.96 (8.39–11.13)	0.221
Weight at follow-up in kg – median (IQR)		27.50 (20.50–34.58)	9.9%	22.50 (20.00–33.00)	26.60 (19.75–33.00)	31.00 (22.70–36.00)	0.165
Pulmonary annulus at follow-up – median (IQR)		16.00 (14.00–19.00)	10.7%	13.50 (12.00–17.50)	16.00 (14.00–19.00)	17.00 (16.00–20.00)	0.511
Pulmonary annulus Z score at follow-up – median (IQR)		−0.67 (−1.83–0.30)	12.2%	−1.92 (−2.91–0.09)	−0.67 (−1.64–0.24)	−0.57 (−1.42–0.40)	0.455
RPA Z score at follow-up – median (IQR)		−0.54 (−1.47–0.51)	16.0%	−0.78 (−2.14–0.45)	−0.39 (−1.20–0.71)	−0.69 (−1.32–0.49)	0.171
LPA Z score at follow-up – median (IQR)		0.34 (−0.57–1.09)	16.8%	0.34 (−1.21–0.60)	0.35 (−0.46–1.16)	0.08 (−0.56–0.91)	0.130
Max RVOT gradient at follow-up – median (IQR)		17.00 (10.75–24.00)	8.4%	23.00 (20.00–37.50)	17.00 (13.00–22.00)	12.00 (8.00–20.00)	0.653
Pulmonary regurgitation at follow-up – n (%)			9.9%				0.563
	≤ mild	55 (42%)		7 (35%)	21 (37.5%)	26 (48.2%)	
	moderate	27 (20.6%)		4 (20.0%)	18 (32.1%)	5 (9.3%)	
	severe	36 (27.5%)		8 (40.0%)	14 (25.0%)	14 (25.9%)	
	NA	13 (9.9%)		1 (5.0%)	3 (5.4%)	9 (16.7%)	
Composite dysfunction at follow-up – n (%)			10.7%				0.432
	No composite dysfunction	78 (59.5%)		10 (50.0%)	37 (66.1%)	30 (55.6%)	
	Presence of composite dysfunction	39 (29.8%)		9 (45.0%)	16 (28.6%)	14 (25.9%)	
	NA	14 (10.7%)		1 (5.0%)	3 (5.4%)	10 (18.5%)	
Catheter intervention at follow-up – n (%)			3.1%				0.393
	Catheter intervention	25 (19.1%)		6 (30.0%)	11 (19.6%)	8 (14.8%)	
	NA	4 (3.1%)		0 (0.0%)	0 (0.0%)	4 (7.4%)	
RVOT, native or replaced – n (%)			3.8%				0.466
	Replaced	20 (15.3%)		7 (35.0%)	6 (10.7%)	7 (13.0%)	
	Native	106 (80.9%)					
	NA	5 (3.8%)		0 (0.0%)	2 (3.6%)	3 (5.6%)	
Operation other than pulmonary valve replacement – n (%)			0.0%				0.542
	No reoperation	115 (87.8%)		16 (80.0%)	49 (87.5%)	50 (92.6%)	
	RVOT	5 (3.8%)		1 (5.0%)	0 (0.0%)	3 (5.6%)	
	PM-implantation	5 (3.8%)		1 (5.0%)	3 (5.4%)	1 (1.9%)	
	Diaphragm plication	2 (1.5%)		0 (0.0%)	2 (3.6%)	0 (0.0%)	
	Pleurodesis	1 (0.8%)		1 (5.0%)	0 (0.0%)	0 (0.0%)	
	Others	3 (2.3%)		1 (5.0%)	2 (3.6%)	0 (0.0%)	
Preop QRS duration in ms – median (IQR)*		64.00 (60.00–68.00)	11.5%	63.00 (60.00–74.00)	64.00 (56.50–68.00)	66.00 (60.00–68.00)	0.326
Discharge QRS in ms – median (IQR)*		96.00 (76.00–102.00)	10.7%	100.00 (94.00–110.00)	92.00 (72.00–102.00)	96.00 (79.00–102.00)	0.403
Follow-up QRS in ms – median (IQR)*		120.00 (94.00–134.00)	13.7%	130.00 (124.00–150.00)	120.00 (89.00–131.00)	118.00 (95.50–130.00)	0.452
Follow-up to discharge QRS slope – median (IQR)		2.30 (1.29–3.71)	20.6%	3.59 (1.47–5.25)	2.69 (1.60–3.76)	1.93 (0.87–2.89)	0.464

LPA: left pulmonary artery; ms: milliseconds; RPA: right pulmonary artery.

Standardised mean difference (SMD) is a measure of effect size. The higher the value of SMD, the more the groups differ. (It is calculated by taking the mean difference and dividing it by the standard deviation.) Some interpret SMD values of 0.2, 0.5 and 0.8 as small, medium and large imbalance. Groups with SMD estimates below 0.1 are considered more or less balanced.

* see appendix figure S1.

groups 1, 2 and 3, respectively. Composite dysfunction at discharge occurred in 42 patients (32%): 40%, 36% and 26% in groups 1, 2 and 3, respectively.

Late results

All patients were alive at a median follow-up of 9.6 (95% confidence interval [CI] 9–10.4) years. None of the patients suffered from severe left ventricular or right ventricular dysfunction at follow-up (table 2). Univariate analysis of long-term outcome data compared between groups are depicted in table 2.

Evolution of pulmonary annulus Z score over time

The median weight of the cohort increased from 6.1 (IQR 5.1; 7) kg at operation to 28 (21; 35) kg at follow-up. The median pulmonary annulus, right pulmonary artery and left pulmonary artery Z scores remained larger than –2; that is they grew proportionately with the growth of the child and did not differ between groups (table 2). Figure 1 (A–B) demonstrates the evolution of pulmonary annulus Z score on a log scale of time.

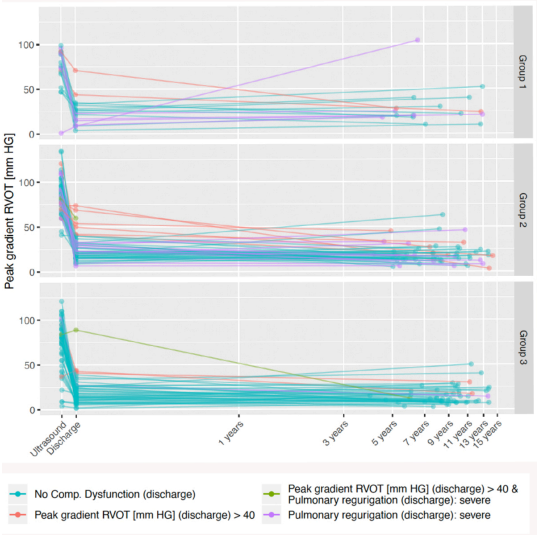
Composite dysfunction at discharge: evolution over time

Composite dysfunction at follow-up was prevalent in 31% (compared to 32% at discharge). Figure 2 depicts distribution of composite dysfunction at discharge, as well as its evolution over a log scale of time.

Kaplan-Meier survival

The time of discharge was considered time point 0. The three patients who had an event before discharge were deleted from this analysis. When event rate is so low so as not to reach the 50% mark, median event time cannot be estimated; this was the case for many of the outcomes addressed in this study.

Figure 2: Distribution of composite dysfunction at discharge between groups 1–3 over a log of time. Please note the colour distribution demonstrating various types of composite dysfunction (below in the legends). RVOT: right ventricular outflow tract.



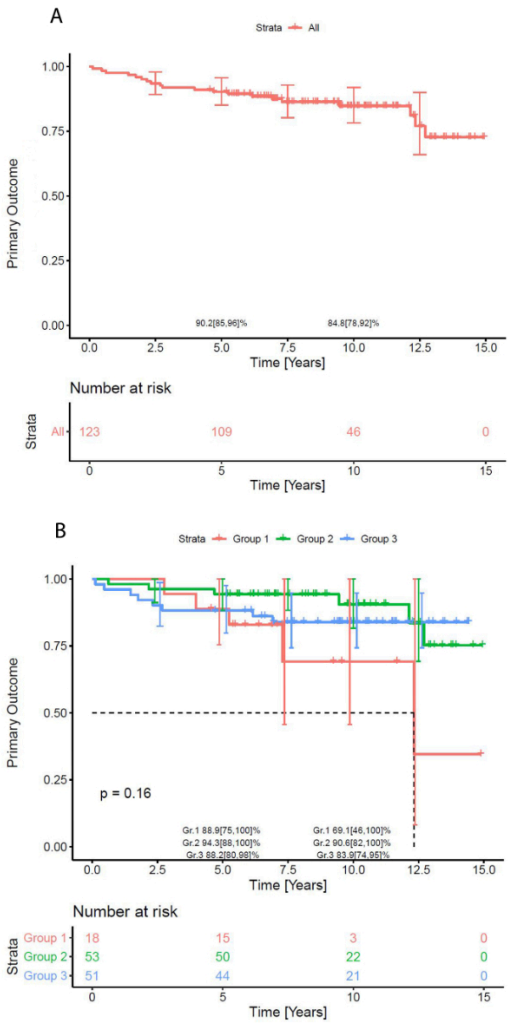
Freedom from primary outcome (RVOT reoperation or pulmonary valve replacement)

Overall median follow-up time for primary outcome was 9.6 (95% CI 9–10.4) years, median event time for group 1 was 12.3 (95% CI 7.3 to xx) years (upper bound of CI does not exist and median event time for group 2 and 3 does not exist). Freedom from primary outcome at 10 years was 69% (46–100%), 91% (82–100%) and 84% (74–95%) for groups 1, 2 and 3, respectively (log-rank p = 0.16), see figure 3.

Catheter intervention

Overall median follow-up time for catheter intervention was 9.5 (95% CI 9–10.3) years. Median event time for group 1 was 12.8 (95% CI 7.4 to xx) years (upper bound of CI does not exist). 10-year freedom from catheter intervention was 54% (27–100%), 81% (71–93%) and 83% (72–94%) for groups 1, 2 and 3, respectively (log-rank p = 0.2).

Figure 3: Freedom from primary endpoint (right ventricular outflow tract reoperation or pulmonary valve replacement). (**A**) Overall. (**B**) Stratified according to pulmonary annulus Z score groups.



Multiple Cox regression

The multiple Cox regression model estimates the hazard ratio (HR) associated with the event for the primary endpoint. In detail, this model (figure 4) estimated the following associations:

- Age (in months) at tetralogy of Fallot repair has a HR of 0.8 (95% CI 0.63–1, p = 0.06] and group 2 (compared to group 3) with a HR of 0.4 (95% CI 0.14–1.2, p = 0.11] displayed a trend to being protective for the event for the primary outcome.
- The transannular patch has a HR of 3.25 (95% CI 0.72–14.7, p = 0.13) as compared to non-transannular patch.
- Composite dysfunction at discharge has a HR of 2.1 (95% CI 0.82–5.4, p = 0.12] as compared to those without.

(Interpretation assumes holding all the other variables constant.)

Discussion

With increasing numbers of patients with tetralogy of Fallot repair surviving to adulthood, the focus has naturally shifted to their long-term survival and wellbeing. Late death after repair of tetralogy of Fallot has been attributed to cardiac causes (predominantly sudden cardiac death and congestive cardiac failure) in around two thirds of cases [2]. With studies indicating that pulmonary regurgitation may indeed be responsible for many of the late consequences in repair of tetralogy of Fallot [12], pulmonary valve- or annulus-preserving techniques have flourished [13, 14]. The impact of these strategies on late outcome may only become evident after decades of follow-up [15]. Recent MRI data has demonstrated the presence of diffuse myocardial fibrosis in repair of tetralogy of Fallot, which may be triggered by extreme volume overload or pressure overload, in addition to those resulting from surgical insults (patches, stitching scars, etc.) [16]. The intensity of myocardial fibrosis is impacted by the duration and intensity of volume, pressure or mixed overload. The natural variations in the severity and type of RVOT obstruction make it difficult to envisage a one-size-fits-all approach. Few studies have explored surgical decision-making based on the pulmonary annulus Z score [17–19]. Our study adds to this body of data about the prognostic value of preoperative pulmonary annulus size in long-term follow-up of repaired tetralogy of Fallot.

Age and weight

A recent study by Bosch et al. has shown greater age and weight at tetralogy of Fallot repair to be associated with lower mortality [20]. It is logical that the more severe the RVOT obstruction, the earlier the child needs repair. Despite early age at repair in group 1 of our study, their body weight was comparable to those of groups 2 and 3. This could be explained by the inverse relationship between pulmonary and systemic output. Older age at repair showed a tendency to be protective (HR 0.8). Whether delaying tetralogy of Fallot repair beyond 6 months of age would help late outcome is open to debate. Any such decision should be tempered by the fact that operating too late may lead to increased right ventricular hypertrophy and diastolic dysfunction. Indeed, while some reports do plead for later repair [20], there is an evolving consensus that repair not be delayed beyond 12 months of age [21].

Preoperative pulmonary annulus Z score: Repair and outcome

Need for palliation

Preoperative RVOT gradient considerably differed between groups. Interestingly, despite greater severity of obstruction, the gradient was lower in group 1 compared to groups 2 and 3. This can be explained by presence of collateral flow or a Blalock Taussig shunt. This may also explain the similar incidence of palliation across groups. In fact, the need for palliation in group 3 with adequate pulmonary annulus may be explained by dynamic infundibular obstruction leading to blue spells. The Chicago group [19] showed that 50% of transannular patch patients (Z –4.8±1.7) as also 18% of non-transannular patch patients (Z –1.7±1.2) needed a shunt.

Incidence of transannular patch

The use of transannular patch in the contemporary era may range from 5–88% [14, 17]. Interoperator variability may be considerable, with use of transannular patch ranging from 55–79% in our own cohort. Various surgical strategies using a Z score cut-off of –1.3 to –4 have been followed [17, 22]. While the pulmonary annulus Z score provides a rough guide, pulmonary valve morphology also plays an important role in decision-making. Since transannular patch repairs represent the prognostically worse group, a higher risk of reoperation is to be expected. Various groups [23, 24] have argued that even if the transannular patch carries a higher risk of reoperation, it has no impact on late survival. This is counterintuitive and needs further long-term data.

Vida et al. [25] have described complex pulmonary valvuloplasty including delamination and balloon dilation to achieve nearly 100% freedom from transannular patch (excluding the monocuspid pulmonary valves).

Logoteta et al. [26], while pursuing a valve-sparing strategy for pulmonary annulus Z score > –4, reported a transannular patch in 32% of patients, and reoperations in 14% at a median follow-up of 13 years. They demonstrated that MRI-diagnosed pulmonary regurgitation fraction was significantly less (21% patients) and the right ventricular mass not any greater than those in a controlled nationwide German registry.

Using an aggressive approach, Kim et al. [14] performed valve-sparing repair in 95% of repairs of tetralogy of Fallot; their freedom from significant RVOT obstruction was 83% at 1 year. In their experience, peak systolic right ventricular/left ventricular pressure ratio (pRV/LV) >0.59 had a high probability of developing RVOT obstruction; every 0.01 increase in pRV/LV being associated with a slightly increased hazard (HR 1.12).

Indeed, while the push for valve-sparing repair is understandable, Bacha et al. have warned about the limits of valve-sparing repair [27] citing freedom from reoperation of 82% at 1 year [14]. The Alabama group reported RV/

LV pressure ratio of >0.85 to be associated with 2.5 times increased risk of death, and 7.3 times increased risk of re-operation [28]. Our pRV/LV ratio threshold of 0.65–0.7 and freedom from RVOT reoperation / pulmonary valve replacement of 84.8 (78–92) % at 10 years compares favourably with published reports.

With an incidence of transannular patch of 67% in our cohort, we have been more permissive compared to above-mentioned groups, while being careful to avoid overzealous pulmonary annulus enlargement. Body surface area-proportional PA enlargement was achieved across the three groups and their growth has remained stable over a median follow-up of 10 years (figure 1). Early reoperations were seldom required. Also, perioperative outcome parameters in terms of duration of hospital stay did not differ between severity groups.

Pulmonary valve and RVOT function

Variable time to reoperation, replacement and composite dysfunction can be attributed to the surgical strategy employed as also to the differences in native valve tissue available or to differences in reconstructive ability of the surgeon. The Osaka group [18], reporting results of their pulmonary annulus-sparing strategy, showed freedom from moderate-severe pulmonary regurgitation of 50% at 5 years and 36% at 20 years. Our freedom from moderate/severe pulmonary regurgitation of around 42% at 9 years compares well with the above study.

The functional outcomes of our cohort (figure 2) indicate that RVOT gradient and severe regurgitation at discharge contributed equally to late reoperations and replacements, indicating a balanced reconstructive strategy. Pulmonary valve function remained stable during 9+ years of follow-up, suggesting growth proportional to the 5-fold increase in the weight of the child. RVOT gradient was seldom the reason for reoperation or pulmonary valve replacement.

Most patients had less than moderate regurgitation. The deterioration to severe regurgitation in some can be attributed to the use of monocusp in only 29% of transannular patches; this suggests room for improvement.

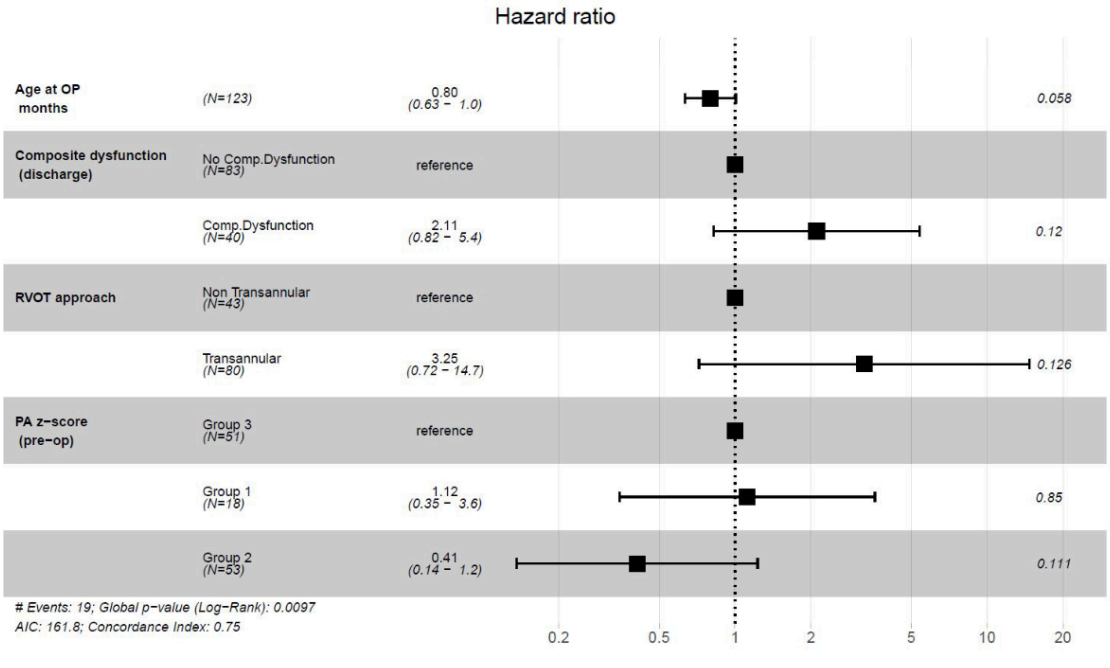
Survival and hazards for the primary outcome

While paediatric cardiac care consortium data found the transannular patch approach to be a hazard (HR 3.76) for mortality/transplant [29], we had no mortality in our cohort. However, multiple Cox regression showed transannular patch (HR 3.25), composite dysfunction at discharge (HR 2.11) and Z score group 1 (HR 1.12) to be associated with the primary outcome in our study. This reinforces the need to reduce composite dysfunction at discharge with all means at one's disposal. The 10-year Kaplan-Meier freedom from primary outcome of 85 (78–92) % (with no evidence of difference between groups) compares well with 72% event-free survival from the Netherlands [20]. Logoteta et al. [26], pursuing an aggressive valve-sparing strategy, in contrast have reported excellent 10-year freedom from reoperation of 92%.

QRS duration

QRS duration [30] and fragmentation [31] have been proposed to be prognostic of ventricular arrhythmias in repair of tetralogy of Fallot [8]. Ventricular arrhythmias were found to occur in about 16% of subjects followed up for 30 years and correlated with QRS duration >160 ms. Marked fibrosis consequent to outflow stenosis as well as regurgitation is thought to underlie this finding. In our study, median QRS duration was 64 (60; 68), 96 (76; 102) and 120 (94; 134) milliseconds preoperatively, postoperatively and

Figure 4: Cox proportional-hazards model for primary endpoint (right ventricular outflow tract [RVOT] reoperation or pulmonary valve replacement). Cox proportional-hazards model for the primary endpoint was calculated using age at tetralogy of Fallot repair, RVOT approach (transannular patch versus non-transannular patch), presence or absence of composite dysfunction at discharge and pulmonary annulus (PA) Z score groups 1–3 as explanatory variables assuming random censoring.



at last follow-up, respectively. The median QRS duration was longer in group 1 and in patients with primary outcome (table 2). This progression should be seen in the context of the fact that QRS duration is in the range 70–85 ms in neonates and increases in a linear fashion to about 90–110 ms in adolescents [32]. Occurrence of right bundle branch block in repair of tetralogy of Fallot contributes to prolonged QRS in the first place. Correlating the slope of increase in QRS to morphology, surgical technique and late functional outcome would help place QRS duration in the right perspective. This was beyond the scope of the present study.

Summary

Comparing our outcomes with contemporary studies, a more aggressive valve-sparing approach using delamination, balloon dilation and leaflet augmentation is warranted; however, how small a pulmonary annulus Z score < –2 can be conserved is unclear. There is a worldwide tendency to set a ceiling of post-repair RV:LV pressure ratio of around 0.7. Pursuing an aggressive strategy may invite early reoperations. Even if this is acceptable, how high residual gradients can be accepted, and for how long a duration, remains unclear. Enough literature exists alluding to the damaging influence of chronic pulmonary regurgitation [6, 33]. Newer data, however, also suggests a possible damaging role of right ventricular afterload and mass. Geva et al. [34] from Boston, while investigating determinants of poor outcome post-pulmonary valve replacement, have demonstrated that right ventricular mass/volume ≥0.45 g/ml (HR 4.1), pulmonary valve replacement ≥28 years (HR 3.1) and right ventricular ejection fraction (RVEF) <40% (HR 2.4) are multivariable predictors of mortality and sudden cardiac death. Significantly, right ventricular systolic pressure ≥40 mm Hg (HR 3.4) also correlated with negative outcome. Latus et al. [35] in another MRI study have shown that while RVOT obstruction in the presence of pulmonary regurgitation appears to be protective with preserved RV strain and interventricular interaction, it is associated with decreased left ventricular strain and intraventricular synchrony. Peak RVOT gradient has also been proved to be a significant predictor of impaired exercise capacity [36]. While leaving mild residual gradients (peak-to-peak of around 20 mm Hg) could probably be advantageous [37], sound evidence should precede any idea of stretching these limits. Frigiola et al. [38] in their study characterising "good repair of tetralogy of Fallot" demonstrated that patients with repaired tetralogies of Fallot >35 years of age with normal exercise capacity, mild residual gradient and pulmonary annulus Z score <0.5 may probably be considered cured. It appears that the last word about an optimum RVOT strategy has yet to be written.

Limitations

This study has all the limitations inherent to a retrospective cohort observational study. It involves heterogeneous morphology of tetralogy of Fallot patients involving multiple surgeons over a time frame of nearly two decades. It is obvious that surgical strategies and perioperative care may have undergone static change which may introduce biases. Retrospective data acquisition means that available data about various standard variables, e.g. pulmonary valve morphology, is limited. A longitudinal dataset of the evolution of ECG, echocardiographic and exercise test parameters is not available for each patient. These shortcomings make it difficult to draw substantive conclusions from the study.

Conclusions

With gradually evolving surgical techniques, even extreme forms of tetralogy of Fallot continue to enjoy a growth-appropriate functioning pulmonary valve in the majority of cases of repaired tetralogy of Fallot during the first decade of life. Use of transannular patch and composite dysfunction at discharge, although not statistically significant at 5% level, may be associated with need of RVOT reoperation and pulmonary valve replacement. Considering this, a more aggressive pulmonary annulus-sparing approach is justified. Applying valve reconstructive techniques to achieve a better composite dysfunction at discharge, if transannular patch is necessary, could reduce the primary outcome. If clinically permissible, tetralogy of Fallot repair at an older age but within the first year of life, may be considered. A middle path aiming at a mild residual gradient and mild regurgitation appears achievable and best suited for an event-free survival in repair of tetralogy of Fallot.

Congress presentation
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Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: supplementary figure

Figure S1: Evolution of QRS duration in milliseconds (ms) over time stratified by groups. Red lines represent patients with composite dysfunction at discharge. Green lines represent patients not having composite dysfunction at discharge.