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Late management of the aortic root after repair of tetralogy of Fallot: A European multicentre study

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Abstract

Objectives: We sought to determine the indications, type, and outcomes of reoperations on the aortic root after repair of tetralogy of Fallot (TOF).

Methods: Eleven centers belonging to the European Congenital Heart Surgeons Association contributed to the data collection process. We included 36 patients who underwent surgical procedures on the aortic root, including surgery on the aortic valve and ascending aorta, between January 1975 and December 2017. Original diagnoses included TOF-pulmonary stenosis (n = 18) and TOF-pulmonary atresia (n = 18). The main indications for reoperation were aortic insufficiency (n = 19, 53%), aortic insufficiency and dilatation of the ascending aorta (n = 10, 28%), aortic root dilatation (n = 4, 11%), and ascending aorta dilatation (n = 3, 8%).

Results: The median age at reoperation was 30.4 years (interquartile range 20.3-45.3 years), and mechanical aortic valve replacement was the most common procedure performed. Five patients died early after reoperation (14%), and larger ascending aorta diameters were associated with early mortality ($P = .04$). The median age at the last follow-up was 41.4 years (interquartile range 24.5-51.6 years). Late death

occurred in five patients (5/31, 16%). Most survivors (15/26, 58%) were asymptomatic at the last clinical examination (New York Heart Association, NYHA class I). The remaining patients were NYHA class II (n = 7) and III (n = 3). The most common symptoms were fatigue (n = 5), dyspnea (n = 4), and exercise intolerance (n = 3).

Conclusions: Reoperations on the aortic root are infrequent but may become necessary late after TOF repair. The main indications for reoperation are aortic insufficiency, either isolated or associated with a dilatation of the ascending aorta. The surgical risk at reoperation was high and the presence of ascending aorta dilation is related to higher mortality.

KEYWORDS

aortic root, cardiac surgery, congenital, reoperations, tetralogy of Fallot

1 | INTRODUCTION

Tetralogy of Fallot (TOF) repair is now a routine practice and can be achieved with a very low surgical risk at many pediatric cardiac centers.[1-4] Despite excellent early and long-term survival after TOF repair,[1-4] it is now evident that the vast majority of these patients will require additional interventions for pulmonary valve regurgitation.[5-8] Very little is known about the need for reoperations on the aortic root,[9-13] which is frequently dilated in this subset of patients.[14-18] With the aim of giving more consistent data on this topic, we have embarked on a multicentre study within the European Congenital Heart Surgeons Association (ECHSA) to evaluate indications, type and outcomes of reoperations on the aortic root after TOF repair.

2 | MATERIALS AND METHODS

The Clinical Investigation Committee of the University Hospital of Padua, the coordinating center, approved the retrospective review of medical records in accordance with the protection of patient confidentiality and consented the use of the data for publication (ID number 4172/AO/17); patients were not identified and individual consent was not obtained. This study is a retrospective evaluation and was conducted on the behalf of the ECHSA. We included all patients with tetralogy of Fallot (either with pulmonary stenosis [TOF/PS] or pulmonary atresia [TOF/PA]) who required reoperations on the aortic root after TOF repair between January 1975 and December 2017. We defined reoperations on the aortic root as any reoperation performed on the aortic root, the aortic valve and/or the ascending aorta (Figure 1). We analyzed the demographics, palliation and correction data, surgical variables at reoperation on the aortic root, and outcomes and clinical status at the latest follow-up, dating 12 months or less. One patient was lost to follow-up. We excluded patients who underwent reoperation following TOF repair for isolated right-sided lesions and patients with a diagnosis of double outlet right ventricle TOF-type (DORV TOF-type).

We arbitrarily divided the reoperations on the aortic root, regardless of any concomitant intervention to the right heart, into the following five subgroups: (a) aortic valve replacement (AVR), (b) aortic valvuloplasty (AVP), (c) valve-sparing root replacement, (d) Bentall operation, and (e) isolated interventions on the ascending aorta (AA). Other surgical procedures in association with aortic root surgery were also described. Aortic diameters at the time of reoperation were obtained from 2D-echo images and included measurement of the following: the aortic annulus, sinuses of Valsalva (SoV), sino-tubular junction (STJ), and ascending aorta. Data were considered as absolute values in millimeters and relative Z-scores.[19] Aortic dilation was considered when the absolute diameters were above reference values[20] or when the Z-score was > 2.

The aim of this study was to investigate indications, type and outcomes of aortic root surgery after TOF repair. Outcomes included the frequency and type of postoperative complications following aortic root surgery, such as early and late mortality, the need for further reoperations on the aortic root and the clinical status at the

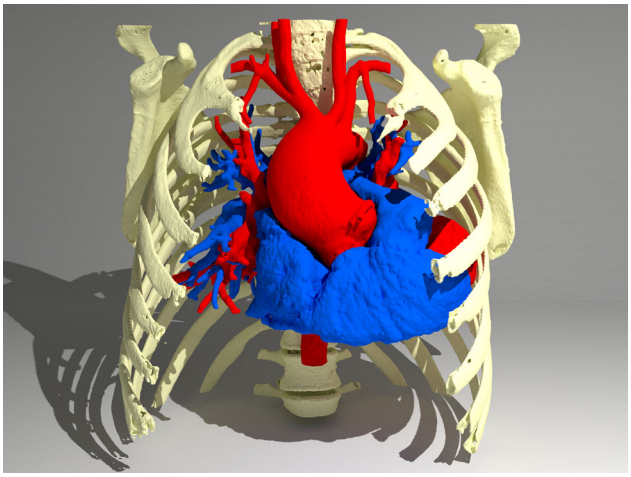

FIGURE 1 3D-reconstruction of a dilated aortic root in a 28-year-old patient who underwent repair of tetralogy of Fallot at 1 year of age

TABLE 1 Demographics and patients' characteristics at palliation and TOF repair

Variables	Total (n = 36)	TOF/PS (n = 18)	TOF/PA (n = 18)	*P* value
Males*	23 (64%)	11 (61%)	12 (67%)	1
Genetic syndromes* ‡‡	4 (11%)	1 (6%)	3 (17%)	.6
Right aortic arch*	8 (22%)	4 (22%)	4 (22%)	1
Bicuspid aortic valve*	7 (19%)**	3 (17%)	4 (22%)	.7
Palliation*	16 (44%)	3 (17%)	13 (72%)	**.002**
Age at palliation, y‡	0.9 (0.2-5.7)	6.8 (4.5-12.4)	0.5 (0.2-4.6)	.3
Age at correction, y‡	5.8 (3-14.8)	6.3 (4.3-15)	4.9 (2.8-8.7)	1
Palliation-to-correction interval, y‡	3.2 (1.5-6.5)	4 (2.9-7.7)	3.1 (1.4-5.7)	.7

Abbreviations: PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.
*Number of patients and percentage.
‡Median and interquartile range.
**One patient presented with a quadricuspid aortic valve.
‡‡Di George/Catch-22 syndrome (n = 2), peri-central inversion of chromosome 2 (n = 1), ring-chromosome 8, and microcephaly (n = 1).

last clinical evaluation. Early mortality was defined as any death occurring within the first 30 days after surgery or during hospitalization for aortic root surgery. Any other death following hospital discharge was defined as late mortality.

For the descriptive analysis of the data set, dichotomous nominal variables were expressed with the sample size and percentages; continuous variables were expressed as a median with the interquartile range (IQR) as a measure of the variability. Comparisons between the two groups were made using the Wilcoxon rank sum or Fisher's exact tests if the variables were continuous or dichotomous, respectively. The statistical significance was set at a familywise error rate of $P < .05$. We analyzed data with R-System statistical package using Harrell's RMS libraries.[21,22]

3 | RESULTS

Eleven out of 42 initially contacted centers contributed to the data collection. We included 36 patients who underwent elective aortic root surgery from an initial cohort of 6780 TOF repair surgeries (0.53%). The original diagnoses were TOF/PS (n = 18) and TOF/PA (n = 18). Patient characteristics at the time of TOF repair are listed in Table 1.

The median age at reintervention on the aortic root was 30.4 years (IQR 20.3-45.3) and was significantly lower in the TOF/PA group than in the TOF/PS group ($P = .002$). The main indications for aortic root-included aortic insufficiency (AI) (n = 19, 53%), followed by AI combined with dilatation of the ascending aorta (n = 10, 28%) (Video S1). Using univariate analysis, older age at reoperation was significantly associated with larger aortic diameters in both groups ($P = .04$). Other diagnoses that led to reoperation on the aortic root are listed in Table 2. The clinical and operative variables at reoperation are listed in Table 3.

Twelve out of 36 patients (33%) underwent an isolated procedure on the aortic root/valve. Surgeries were mainly performed on the aortic valve and included mechanical AVR (n = 15, 42%) followed by AVP (n = 13, 36%). Other surgical procedures on the aortic root and additional associated interventions on the right heart are listed in Table 4. One patient with a 61 mm ascending aorta had a contained, asymptomatic preoperative aortic rupture; none of the patients had aortic dissection.

3.1 | Early outcomes

Thirteen patients (36%) had postoperative complications following reoperation on the aortic root, most commonly of which were arrhythmias (n = 6, 17%) and low cardiac output syndrome (LCOS) (n = 6, 17%); postoperative ECMO support was required in four of the six patients with LCOS (Table 6). Using univariate analysis, the Bentall operation ($P = .003$), older age at reoperation ($P = .02$) and larger AA absolute diameters ($P = .04$) were significantly associated with a higher rate of postoperative complications.

TABLE 2 Main diagnosis leading to reoperation of the aortic root

Variables	Total (n = 36)	TOF/PS (n = 18)	TOF/PA (n = 18)	*P* value
Aortic insufficiency*	19 (53%)	8 (44%)	11 (61%)	.5
AI and AA dilation*	10 (28%)	6 (33%)	4 (22%)	.7
Aortic root dilation*	4 (11%)	3 (17%)	1 (6%)	.6
Ascending aorta dilation*	3 (8%)	1 (6%)	2 (11%)	1

Abbreviations: AA, ascending aorta; AI, aortic insufficiency; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.
*Number of patients and percentage.

TABLE 3 Clinical and operative variables of patients who underwent aortic root reoperation

Variables	Total (n = 36)	TOF/PS (n = 18)	TOF/PA (n = 18)	*P* value
Age at reintervention (y)‡	30.4 (20.3-45.3)	44.4 (32.7-51.6)	24.7 (19.1-29)	.002
LVEF %‡	55 (47.5-60)	51.5 (41.8-58.2)	57.5 (50-60.3)	.06
LV end-diastolic dimensions, mm‡	51 (46.5-57)	55 (49.3-58)	50 (41.2-53)	.1
AI at reoperation*	34 (94%)	16 (89%)	18 (100%)	.5
Mild	8 (22%)	4 (22%)	4 (22%)	1
Moderate/severe	26 (72%)	12 (67%)	14 (78%)	.7
Aortic annulus, mm‡	28 (21.8-35.3)	27 (21.5-28.5)	36(25-36)	.07
Aortic annulus, Z-score‡	4.3 (3.1-5.9)	3.7(2.7-4.3)	6.5 (4.9-7.8)	**.05**
Sinus of Valsalva, mm‡	46(39-50)	50 (40-50.5)	45(40-48)	.5
Sinus of Valsalva, Z-score‡	5.6 (4.5-6.3)	5.7 (5.2-6.3)	5.4 (4.1-6.5)	.7
Sino-tubular junction, mm‡	42(34-49)	47.5 (33.5-50.8)	41(35-45)	.3
Sino-tubular junction, Z-score‡	6.9 (5.4-7.5)	7.36-8	6.9 (5.1-7.4)	.4
Ascending aorta, mm‡	46 (38.5-52.8)	46 (37.5-54)	46 (39.5-50)	.8
Ascending aorta, Z-score‡	6.1 (4.3-7.1)	6.2 (4.3-7.6)	6.1 (4.9-6.7)	.9

Abbreviations: AI, aortic insufficiency; LV, left ventricle; LVEF, left ventricle ejection fraction; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.
*Number of patients and percentage.
‡Median and interquartile range.

TABLE 4 Types of reoperations on the aortic root and the associated surgical procedures

Variable	Total (n = 36)	TOF/PS (n = 18)	TOF/PA (n = 18)	*P* value
Procedures on the aortic root (43 procedures on 36 patients)				
Mechanical aortic valve replacement*	15 (42%)	5 (28%)	10 (56%)	.2
Aortic valvuloplasty*	13 (36%)	8 (44%)	5 (28%)	.7
• **Valvular decalcification***	1 (3%)	1 (6%)	…	1
• **Leaflet perforation repair***	3 (8%)	2 (11%)	1 (6%)	1
• **Commissuroplasty***	4 (11%)	2 (11%)	2 (11%)	1
• **Annuloplasty***	2 (6%)	1 (6%)	1 (6%)	1
• **Other less common plasties***	3 (8%)	2 (11%)	1 (6%)	1
Bentall operation*	5 (14%)	3 (17%)	2 (11%)	1
AA intervention*	5 (14%)	2 (11%)	3 (17%)	1
• **AA replacement**	4 (11%)	2 (11%)	2 (11%)	1
• **AA reduction plasty**	1 (3%)	…	1 (6%)	1
Valve-sparing root replacement*	5 (14%)	4 (22%)	1 (6%)	.3
• **Yacoub operation***	3 (8%)	2 (11%)	1 (6%)	1
• **David operation***	2 (6%)	2 (11%)	…	.5
Other associated procedures at the time of aortic root surgery (47 procedures on 36 patients)				
RV-PA conduit replacement*	10 (28%)	2 (11%)	8 (44%)	.06
Pulmonary valve replacement*	7 (19%)	6 (33%)	1 (6%)	.09
• **Biological PVR**	6 (17%)	6 (33%)	…	**.02**
• **Mechanical PVR**	1 (3%)	…	1 (6%)	1
Residual VSD closure*	7 (19%)	5 (28%)	2 (11%)	.4
Pulmonary homograft replacement*	5 (14%)	1 (6%)	4 (22%)	.3
Other associated surgical procedures* †	18 (50%)	10 (56%)	8 (44%)	.7

Abbreviations: AA, ascending aorta; PA, pulmonary atresia; PS, pulmonary stenosis; PVR, pulmonary valve replacement; RV-PA, right ventricle to pulmonary artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*Number of patients and percentage. Procedure performed to remove calcifications on the non-coronary aortic cusp, causing moderate/severe aortic insufficiency.
†Listed in Supplementary File 1.

TABLE 5 Characteristics of patients who died after reoperation on the aortic root

No	Type of TOF	Mortality	Procedure on the aortic root	Cause of death
1	TOF/PA	Early	AA replacement	LCOS
2	TOF/PA	Early	Bentall operation	LCOS
3	TOF/PS	Early	Yacoub operation	Intracranial hemorrhage
4	TOF/PS	Early	AVR	LCOS
5	TOF/PS	Early	Bentall operation	LCOS
6	TOF/PA	Late	AVR	Septic shock
7	TOF/PA	Late	Aortic valvuloplasty*	Septic shock, AKI, and respiratory failure
8	TOF/PA	Late	AVR	Sudden cardiac death
9	TOF/PS	Late	Bentall operation	Intracranial hemorrhage
10	TOF/PS	Late	AVR**	Unknown

Abbreviations: AA, ascending aorta; AKI, acute kidney insufficiency; AR, aortic regurgitation; AVR, aortic valve replacement; ICD, internal cardioverter defibrillator; LCOS, low cardiac output syndrome; PA, pulmonary atresia; PS, pulmonary stenosis; PVR, pulmonary valve replacement; TOF, Tetralogy of Fallot; TVP, tricuspid valvuloplasty.

*Died late after a second reintervention including PVR, central pulmonary artery plasty, and ICD implantation.

**Died late after a second reintervention including PVR, TVP, ICD implantation, and repair of a paravalvular aortic leak. Patient is known for having an ascending aortic aneurysm (60 mm).

Five patients died in-hospital (14%), mainly from postoperative low cardiac output syndrome (Table 5). Patients who died were older at the time of reoperation than the overall TOF population (a median of 39.5 vs 30.4 years) and had larger aortic diameters at the SoV, STJ, and AA levels (medians of 53, 55, and 55 mm vs 46, 42, and 46 mm, respectively). Two of the patients had a preoperative depressed left ventricular ejection fraction, while one had a contained, asymptomatic aortic rupture. Three of the patients underwent a concomitant procedure on the right heart. The type of TOF was not related to higher early mortality or complications ($P = 1$). There was no significant difference in the mortality between patients who received isolated aortic root surgery or in association with other procedures ($P = 1$). Moreover, even though overall mortality by reoperation period decreased over time, the difference in surgical eras was not found to be associated to an increased mortality risk. Via univariate analysis, only the larger diameter of the AA correlated significantly with higher early mortality ($P = .04$).

3.2 | Follow-up

Follow-up was completed in 35/36 patients (97%). The median follow-up time after TOF repair was 32 years (IQR 16.9-40.9 years) and the median follow-up time after reoperation on the aortic root was 3.7 years (IQR 1-9.7 years).

Two patients (2/31, 6%) required a second reoperation on the aortic root. Both had initially undergone a mechanical AVR. The first patient (with TOF/PS) was reoperated on 6 years later for an aortic para-valvular leak associated with pulmonary valve replacement, tricuspid valve plasty and implantable cardioverter defibrillator insertion; an ascending aortic aneurysm (60 mm) was left untouched at reoperation. She died late after the second surgery of unknown

TABLE 6 Postoperative complications and mortality (29 postoperative complications in 13 patients)

Variable	Total (n = 36)	TOF/PS (n = 18)	TOF/PA (n = 18)	*P* value
Postoperative complications*	13 (36%)	7 (39%)	6 (33%)	1
Arrhythmias* ††	6 (17%)	3 (17%)	3 (17%)	1
LCOS*	6 (17%)	3 (17%)	3 (17%)	1
Neurological complications* ††	3 (8%)	1 (6%)	2 (11%)	1
Acute kidney insufficiency*	2 (6%)	1 (6%)	1 (6%)	1
Gastroenterological complications* ††	2 (6%)	1 (6%)	1 (6%)	1
Other less common complications* ††	10 (28%)	6 (33%)	4 (22%)	.2
Early mortality*	5 (14%)	3 (17%)	2 (11%)	1
Late mortality*	5 (16%)	2 (13%)	3 (19%)	1
Overall mortality*	10 (28%)	5 (28%)	5 (28%)	1

Abbreviations: LCOS, low cardiac output syndrome; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.

*Number of patients and percentage.

††Listed in Supplementary File 1.

causes. The second patient (with TOF/PA) underwent a reoperation 17 years later for replacement of the aortic root and ascending aorta (aortic sinuses dimensions were 58 × 75 mm and the AA was 47 mm).

Five patients died late after reintervention (16%); three of them underwent other cardiac surgeries following reoperation on the aortic root. The characteristics of the patients who died after the reoperation are listed in Table 5. Among the 26 survivors, most (15/26, 58%) were characterized as asymptomatic, New York Heart Association (NYHA) class I. The remaining patients were in NYHA class II (n = 7) and III (n = 3). The most common symptoms were fatigue (n = 5), dyspnea (n = 4), and exercise intolerance (n = 3).

4 | DISCUSSION

Primary TOF repair can currently be safely accomplished in early infancy with excellent early and long-term results.[1-4] Nonetheless, TOF patients are at risk of developing various long-term complications that are mostly determined by chronic pulmonary insufficiency.[5-8] Less is known about the indications and outcomes of surgery for late complications on the left side of the heart, mainly those involving aortic structures.[9-13]

Aortic dilation is commonly found in both uncorrected and corrected TOF patients with a prevalence ranging from 6.6% to 87%[17,23]; this is mostly because of the lack of a standard definition of aortic dilation between studies as well as the heterogeneity of various study cohorts. Risk factors for aortic dilation after TOF repair are male sex, a diagnosis of TOF/PA, right aortic arch, longer intervals between palliation and correction, older age at correction, a residual ventricular septal defect (VSD) and AI.[14]

The etiology of aortic dilation appears to be multifactorial, but mostly related to an increased aortic flow during fetal life and after birth until correction, creating an additional stress on the aortic wall, possibly leading to aortic dilation.[14] Some authors[24,25] have demonstrated that aortic diameters tend to normalize at approximately 7 years of age if TOF repair is performed in the first year of life, while they tend to remain larger than normal in TOF patients corrected after the first year. However, these studies have a relatively short follow-up and cannot exclude long-term aortic dilation due to the presence of histological abnormalities in the aortic media, even in patients who were corrected early in infancy. In fact, elastic fiber fragmentation, accumulation of ground substance, medial necrosis, disarray of smooth muscle cells, and a certain degree of fibrosis were all found in the aortic wall of TOF patients; and this was significantly correlated with larger aortic diameters and with an increased aortic stiffness, potentially leading to aortic dissection and rupture.[23,26-29]

The incidence of AI in operated TOF patients varies from 3.5% to 12.5%[17,18] and significantly correlates with AA dimensions. Other possible mechanisms for aortic valve insufficiency may be related to valve structural anomalies as well as traumatic or infective processes. It is also important to mention the mechanical distortion of the aortic cusps caused by the turbulent blood flow underlying the aortic valve in the overriding position, as well as the possible impairment of aortic valve function following repair, possibly due to surgical injury during the positioning of the VSD patch or to fibrosis and scarring related to the presence of the patch itself.

Nonetheless, aortic dilation and AI after TOF repair are common, while reoperations on the aortic root and the aortic valve appear to be infrequent, though data in the literature are scarce. Nagy et al[16] reported an incidence of 1.8% for aortic valve replacement and a 2.8% for aortic root and ascending aorta replacement. Current indications for aortic valve surgery in adult patients with corrected TOF are similar to those for acquired pathologies, and so far, there are no clear guidelines for aortic root surgery in this population. Other physicians, especially congenital surgeons, are well aware of the dilating potential of the aorta in patients with TOF and prefer to assume a more conservative approach to intervention.[11,12]

The aim of the present study was to provide some relevant information on the indications, type and outcomes of reoperations on the aortic root after primary TOF repair on a large scale offered by a multicentre study. Over a 42-year period, we collected data on 36 patients who underwent aortic root surgery after correction from a total of 6780 TOF repairs. Therefore, we can consider aortic root surgery after TOF repair to be relatively rare (overall incidence of 0.53%). The main indication for surgery was aortic valve insufficiency followed by AI combined with dilatation of the AA according to other similar single center studies.[9,11,12]

Reoperations on the right side of the heart after TOF correction carry a low surgical risk, especially in congenital centers.[7] In contrast, based on our data, we can affirm that the surgical risk at reoperation on the aortic root appears to be rather high in this subset of patients, with a high incidence of postoperative complications and significant early mortality (14%). Importantly, in our cohort, no patient was reoperated on for acute aortic dissection, and only one patient with a severely dilated ascending aorta had a contained, asymptomatic, preoperative aortic rupture. Late mortality after reoperation on the aortic root was also relatively high, and a second reintervention on the aortic root was occasionally required for residual aortic lesions.

Early mortality rates are variable and range from 1.9% to 25%.[11-13] We can speculate that older age at reoperation, and therefore larger aortic diameters, and the need for high-risk surgery (ie, nonvalve sparing aortic root procedures)[30] may in fact be related to the relevant surgical risk in our series, even though only larger AA diameters were significantly associated with higher early and overall mortality. A larger number of patients and a longer follow-up may help find additional data able to confirm and justify this important hospital mortality.

Surgical risk stratification for these patients is rather complex,[30] and we believe that currently available mortality risk scores should also consider the patient's basic diagnosis (ie, AVR in patients with repaired VSD may be different from AVR in patients with repaired TOF) and the hemodynamic setting in which the procedure is

performed to correctly evaluate these patients. Moreover, while indications for aortic valve replacement are relatively well established, we agree with Stulak et al[12] that in patients requiring isolated surgery of the aortic root and ascending aorta, a more conservative approach needs to be followed and additional follow-up gathered. The treatment of corrected TOF patients in specialized facilities for adults with congenital heart disease is mandatory for achieving better outcomes.

Our study has several limitations. First, this is a retrospective data examination over a long period of study, and inter- and intra-center variability on surgical treatment is expected. Second, we do not have any information about the characteristics of the overall population of patients who underwent TOF repair, so we cannot speculate about the impact of anatomical variables, time of surgery and different surgical techniques on the incidence of reintervention on the aortic root. Third, we were not able to determine an accurate frequency of reoperations on the aortic root after TOF repair. We suppose that some centers did not participate to the data collection process because they did not have any cases to report, but many corrected TOF patients could have been potentially lost at follow-up at the original pediatric cardiac center and could have undergone aortic root surgery in other institutions. In addition, given the small number of patients in our series, we could not consider the centers' effects in the mortality analysis, such as the relationship between mortality and the number of procedures performed at each center. Lastly, our follow-up observation after the initial repair is relatively short. A larger number of patients and longer follow-up times are necessary to reach any definitive conclusions.

Nonetheless, we were able to collect a consistent cohort focusing only on patients who underwent aortic root surgery after primary repair of TOF with or without PA. We concluded that reoperations of the aortic root may be required late after TOF correction, mostly for AI or AI combined with dilatation of the AA. The surgical risk at reoperation is high, and recurrent operations on the aortic root may occasionally be needed. Considering the high surgical risk in this selected subset of patients, a strict evaluation of the indications and timing of surgery on the aortic root is mandatory.

CONFLICT OF INTERESTS

The authors declares that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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