Realignment of the ventricular septum in tetralogy of Fallot using (partial) direct closure of the ventricular septal defect: Long-term follow-up and comparison to conventional patch repair

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ABSTRACT

Objectives : **Aortic dilatation and regurgitation after surgical repair of tetralogy of Fallot (TOF) is known, and beside other factors, mainly addressed to an intrinsic aortopathy. In 2011, we reported the influence of realingement of the left ventricular outflow tract (LVOT) by (partial) direct closure of the ventricular septal defect (VSD) in TOF on aortic structures and function. We now evaluated the further follow-up of this cohort and compared the results to a matched group of TOF patients with classical VSD patch closure.**

Patients and Methods : **Forty patients with TOF treated between 2003 and 2008 are included in the study, with 20 patients each in the VSD (a) (partial) direct closure and (b) patch closure group. Follow-up time after surgery was 12.3 years (11.3–13.0).**

Results : **Patient characteristics, echocardiographic measurements, and surgical and intensive care unit parameters were not significantly different between both groups. After surgery and during long-term follow-up, realignement of the LVOT, shown by the angle between the interventricular septum and the anterior aortic annulus in long axis view in echocardiography, was lower in Group A (34 vs. 45°, $P < 0.0001$). No differences in LVOT or aortic annulus size, aortic regurgitation, or dilation of the ascending aorta and right ventricular outflow tract gradients were found. Transient rhythm disturbances were found in 3 patients in each group, with only one persistent complete atrioventricular block in Group B.**

Conclusion : **(Partial) direct closure of the VSD in TOF leads to a better realignement of the LVOT and showed comparable short- and long-term results without higher risk for rhythm disturbances during follow-up.**

Keywords : Aortic angle, aortic dilation, realignment left ventricular outflow tract, tetralogy of Fallot, ventricular septal defect closure techniques

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INTRODUCTION

Standard treatment of the ventricular septal defect (VSD) during surgical correction of tetralogy of Fallot (TOF) patients is patch closure in addition to repair of the right ventricular outflow tract (RVOT), for which several techniques exist – in accordance to different types of obstructions.[1] This technique has shown favorable long-term results, nevertheless, during follow-up, remodeling processes of the left ventricular outflow tract (LVOT), especially with dilation of aortic valve, sinus aortae and ascending aorta have been described.[2-5] Reasons for dilation of these aortic structures seem to be multifactorial.[2,6-8] Beside others, it is assumed, that the unphysiological formation of the LVOT after VSD patch closure leads to an asymmetric blood flow with dilation of aortic structures over time.[9] In 2011, we published results of (partial) direct VSD closure in TOF patients, aiming to realign the LVOT with consecutive less problems of aortic structures like aortic insufficiencies and relevant aortic dilations.[10] In that study, with a follow-up time of 47 months, we were able to demonstrate, that this technique shows comparable results concerning rhythm disturbances, residual shunts of the VSD, obstructions in the RVOT, and re-interventions/operations. In this new study, we aimed to evaluate mid- and long-term follow-up of this cohort and compare the results to a matched group of TOF patients with similar follow-up time, treated by the same surgical team with classical VSD patch closure.

PATIENTS AND METHODS

Population and study design

In this retrospective study we included patients with TOF or Fallot-type double outlet right ventricle (DORV) operated between 2003 and 2008 at the Heart Center of the University Children's Hospital Zurich, Switzerland- a tertiary care hospital located in Zurich, Switzerland. Patients with missing informed consent were excluded from this study. Baseline characteristics included gestational age, gender, height, weight, genetic syndromes. Patients with relevant other cardiac findings were excluded from the analysis. Transthoracic echocardiography was performed using different ultrasound systems including Sonos 5500, IE 33 (Philips Co., Amsterdam, Netherlands), Vivid 7 or Vivid 9 (General Electric Company, Fairfield, Connecticut, US) by experienced consultant pediatric cardiologist on duty. Beside standard echocardiographic measurements, the angle between the intraventricular septum and the anterior margin of the aortic annulus in parasternal long axis view in early systole (just after opening of the aortic valve) according to Figure 1 was measured before and after surgery and at latest follow-up (so called "A Angle"

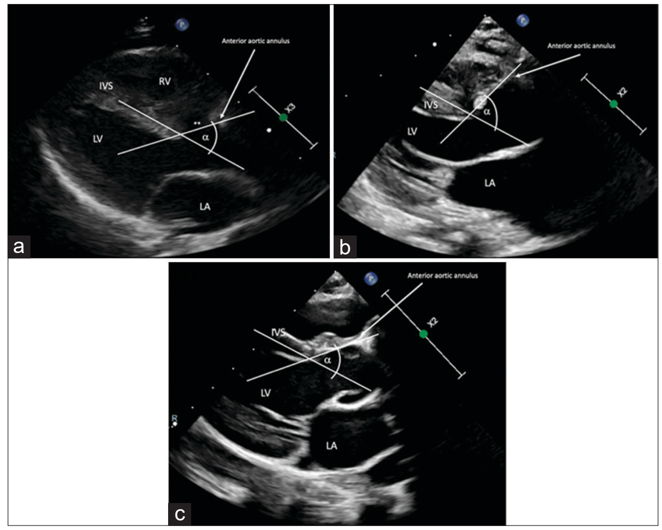

Figure 1: (a-c) Long axis view in echocardiography: (a) before surgical repair, (b) after VSD patch closure, (c) after VSD (partial) direct closure. IVS: Interventricular septum, LV: Left ventricle, LA: Left atrium, RV: Right ventricle, **: VSD; α: aortic angle ("A Angle"), VSD: Ventricular septal defect

= aortic angle), as a possible risk factor for aortic dilation or regurgitation. Intra- and perioperative data, including operation techniques, information about extra corporal circulation time, aortic cross-clamp time, duration of surgery, mechanical ventilator support, inotropic support, total intensive care unit (ICU) stay, total hospital stay, and postoperative complications were collected from the medical records of the patients. Follow-up data include parameters of last echocardiography concerning cardiac function, RVOT/LVOT dimensions and function, rhythm-disorders and number and type of re-interventions.

Operation techniques

According to the surgical procedure performed, patients were divided into the following two groups:

- A: (partial) direct closure of the VSD (n = 20).
- B: Classical patch closure of the VSD (n = 20).

Surgical techniques including operative images are described and shown in detail in the study by Till *et al.*[10] After establishing moderately hypothermic aorto-bicaval cardio-pulmonary bypass and administering antegrade cold blood cardioplegia, right atriotomy was performed, and a left-sided vent placed through the fossa ovalis. While the VSD closure was performed trans-atrially after detaching the anterior leaflet of the tricupid valve, a small infundibulotomy was often performed to transect the dense RVOT musculature. In the course of this, the conal septum was mobilized to aid direct approximation at the far end of the VSD. VSD direct closure was begun at the far end, often with suture buttressed by a strip of pericardium. The near end of the VSD was augmented by a small xenopericardial patch, mimicking the perimembranous septum (therefore called "partial" direct closure).

Statistical analysis

Descriptive data were expressed as mean and standard deviation, median, and interquartile range or percentages, as appropriate. Statistical analysis was performed with IBM SPSS statistics software (Version 27.0, IBM, USA) using t-tests, two-tailed Fisher's exact test and multivariate linear regression models. The level of statistical significance was set to $P < 0.05$.

Ethics

The local ethics committee approved this study (KEK No. 2017–01321).

RESULTS

Patient baseline characteristics

In total, 40 patients with TOF or Fallot-type DORV were operated between 2003 and 2008. According to the group definition above, 20 of these patients were operated using (partial) direct closure technique of the VSD (Group A), while the other 20 patients were operated using patch closure technique of the VSD (Group B) by the same surgical team.

In Group A, 19 patients were diagnosed with TOF, one with DORV whereas in Group B 15 patients were diagnosed with TOF and 5 with DORV. Mean age at surgery and mean weight were not significantly different between Groups A and B (age: group A: 143 days [98–237 days] vs. Group B: 155 days [95–203 days], $P = 0.92$; weight: group A: 6.15 kg [5.3–7.5 kg] vs. Group B: 5.7 kg [4.9–6.9 kg], $P = 0.47$). Baseline characteristics of the study population are shown in Table 1.

Preoperative echocardiographic findings of TOF or DORV anatomy are described in Table 2, and showed no significant differences between both groups, except ascending aorta z-score values (Group A: 0.47 vs. Group B: 1.77, $P = 0.002$). The angle between interventricular septum (IVS) and anterior aortic annulus [Figure 1] showed no difference in both groups (Group A: 42.5° vs. Group B: 41.0°, $P = 0.30$).

Operation characteristics and postoperative course

To perform the extension of the RVOT, nontransannular patches were used in 5 patients (2 patients in Group A, 3 patients in Group B), transannular patches in

Table 1: Baseline characteristics of the patient population

Variable	Total	Direct (A)	Patch (B)	*P*
Gender				-
Male	28	14	14	
Female	12	6	6	
Body size at OP (cm)	62.0 (58.0-67.0)	64.0 (58.8-67.8)	61.0 (58.0-66.0)	0.48
Weight at OP (kg)	5.9 (5.0-7.1)	6.2 (5.3-7.5)	5.7 (4.9-6.9)	0.47
Age at OP (day)	147 (96-222)	143 (98-237)	155 (95-203)	0.92
Diagnosis (*n*)				
TOF	34	19	15	
DORV	6	1	5	

OP: Operation, TOF: Tetralogy of fallot, DORV: Double outlet right ventricle (fallot type)

Table 2: Preoperative echocardiographic findings and measurements

Variable	Direct (A)	Patch (B)	*P*
Age (day)	137 (83-230)	138 (81-184)	0.65
Weight (kg)	6.2 (4.9-7.2)	5.3 (4.5-6.4)	0.38
Height (cm)	63.3 (57.6-66.6)	59.0 (55.8-65.0)	0.40
RVOT gradient (maximum, mmHg)	80.0 (74.5-96.3)	77.0 (64.8-86.0)	0.14
RVOT gradient (mean, mmHg)	44.0 (39.0-48.0)	50.0 (39.0-86.0)	0.80
VSD size (mm)	8.0 (7.0-10.0)	7.0 (6.0-8.0)	0.11
IVS-anterior AoV annulus angle (°)	42.5 (38.3-49.0)	41.0 (39.0-42.0)	0.30
AoV annulus (mm)	13.5 (11.0-15.1)	12.0 (10.8-13.0)	0.19
AoV annulus (*z* score)	4.6 (3.6-5.3)	4.7 (4.0-5.1)	0.72
Sinus aorta (mm)	15.0 (14.0-16.0)	14.0 (13.0-15.0)	0.26
Sinus aorta (*z* score)	2.2 (1.8-2.6)	2.8 (1.7-2.9)	0.36
Ascending aorta (mm)	11.5 (10.3-12.9)	13.0 (11.0-13.0)	0.35
Ascending aorta (*z* score)	0.47 (−0.54-1.25)	1.77 (1.29-2.53)	0.0022
PuV annulus (mm)	6.8 (6.0-8.5)	6.1 (5.0-7.5)	0.33
PuV annulus (*z* score)	−1.8 (−2.5-−1.1)	−2.8 (−3.4-−1.3)	0.27
RPA (mm)	5.6 (4.4-7.0)	5.0 (4.5-6.0)	0.65
RPA (*z* score)	−0.84 (−2.07-0.72)	−0.32 (−1.24-−0.06)	0.54
LPA (mm)	5.8 (5.0-6.3)	5.0 (3.9-5.3)	0.13
LPA (*z* score)	−0.11 (−1.31-1.24)	−0.12 (−1.33-0.38)	0.92

RVOT: Right ventricular outflow tract, VSD: Ventricular septal defect, IVS: Interventricular septum, AoV: Aortic valve, PuV: Pulmonary valve, RPA: Right pulmonary artery, LPA: Left pulmonary artery

21 patients (10 in Group A, 11 in Group B) and transannular monocusp patches in 14 patients (8 in Group A, 6 in Group B). Parameters of the intraoperative and postoperative course are shown in Table 3. The surgical and postoperative characteristics including bypass time, aortic cross-clamp time, duration of ventilation, ICU stay and total hospital stay did not differ between the two groups.

In Group A there were three cases of postoperative arrhythmias: one junctional ectopic tachycardia, one atrioventricular (AV)-Block II Mobitz, and one transient complete AV-Block which disappeared shortly after the procedure. In patients of Group B there were also three cases of postoperative arrhythmias: two transient complete AV-Block and one persistent complete AV-Block resulting in the necessity for pacemaker implantation.

Re-interventions

In 6 patients of Group A (30%) and 12 patients of Group B (60%), re-interventions were necessary, including catheter interventions and surgical procedures. In both groups, no LVOT intervention was necessary, but all interventions were needed due to residual findings in the RVOT or pulmonary arteries. Time to first re-intervention (either catheterization or surgery) was median 15 months (0–150 months) in Group A and median 8 months (0–118 months) in Group B ($P = 0.48$).

Follow-up

Mean follow-up for the whole study population was 12.3 years (range 11.3–13.0), with 11.9 years for Group A (range 11.2–13.4) and 12.7 years for Group B (11.4–13.2), $P = 0.95$. At follow-up, there was no difference between weight and size of patients in both groups [Table 4].

No residual VSD was detectable in both groups. Concerning residual stenosis of the RVOT during follow-up, echo gradient was 18.0 mmHg (15.0–24.0 mmHg) in Group A and 23.0 mmHg (14.0–35.0 mmHg) in Group B ($P = 0.24$). Moderate or severe pulmonary insufficiencies were found in 8 patients in Group A (40%) and 11 in Group B (55%) [Table 4].

Left ventricular outflow tract

We found no differences in dimensions of the aortic annulus, the sinus aortae and the ascending aorta between Groups A and B at last follow-up. Absolute and z-score values are shown in Table 4. While we found no differences in these dimensions, z-score values indicate, that dimensions are in the upper limit of normal (aortic annulus [z-score each 1.9] and ascending aorta [z-scores 1.0 and 0.7]) or slightly above (sinus aortae [z-scores each 2.1]). Aortic annulus z-score in comparison to preoperation was reduced from 4.6 (Group A) and 4.7 (Group B) to 1.9 (both groups). Aortic regurgitation was found in 17 patients in Group A (16 mild, 1 moderate) and 16 in Group B (16 mild). The angle between the IVS and the anterior margin of the aortic annulus was significantly lower in Group A (36° vs. 45°, $P < 0.0001$).

DISCUSSION

Several studies have addressed the fate of the aorta in patients after surgical TOF repair in the last years.[2,3,8] While the main focus of the surgical repair in TOF and Fallot-type DORV is initially the RVOT and surgical techniques needed for RVOT extension might determine the further course of the patients,[1] especially dilations of the aortic valve, sinus aortae and ascending aortae are common findings during follow-up.[5,11,12] In some reports even dissections of the ascending aorta due to progressive dilations have been described.[13] The etiology of a dilated aortic valve and supravalvular aortic structures seems to be multifactorial[10,14] and males seem to be at higher risk than females.[4] Histological abnormalities similar to Marfan patients have been

Table 3: Intra-and postoperative characteristics

Variable	Total	Direct (A)	Patch (B)	*P*
n	40	20	20	
Muscle bundle resection yes/no (*n*)	11/29	8/12	3/17	
RVOT extension (*n*)				
Nontransannular	5	2	3	
Transannular patch	21	10	11	
Transannular monocusp patch	14	8	6	
Bypass time (min)	161.0 (138.5-171.5)	162.0 (139.5-170.0)	149.5 (133.5-193.5)	0.58
X-clamp time (min)	58.5 (49.8–79.5)	53.5 (47.5–78.5)	69.5 (54.5–91.5)	0.057
Duration of ventilation (day)	3.0 (2.0–5.0)	3.0 (2.3–4.8)	3.0 (1.0–5.0)	0.47
ICU stay (day)	7.0 (5.5–8.5)	7.0 (6.0–8.0)	9.0 (3.8–11.5)	0.57
Time to release (day)	11.0 (8.0–14.3)	11.0 (6.0–14.3)	10.5 (8.3–14.8)	0.31
Rhythm problems yes/no (*n*)		3/17	3/18	
JET	1	1	0	
AV I	1	1	0	
AV III transient	3	1	2	
AV III persistent + PM	1	0	1	

RVOT: Right ventricular outflow tract, ICU: Intensive care unit, JET: Junctional ectopic tachycardia, AV: Atrioventricular block

Table 4: Patient characteristics and echocardiographic variables at last follow-up

	Direct (A)	Patch (B)	*P*
Follow-up time (operation until follow-up) (year)	11.9 (11.2-13.4)	12.7 (11.4-13.2)	0.95
Age (year)	12.4 (11.7-13.8)	13.0 (11.8-13.6)	0.89
Weight (kg)	46.0 (34.0-58.0)	36.6 (32.58-44.9)	0.12
Height (cm)	154.1 (144.0-159.0)	147.0 (144.5-152.0)	0.45
Left ventricular variables			
IVS-anterior AoV annulus angle (°)	36 (34-38)	45 (43-53)	<0.0001
AoV annulus (mm)	22.0 (20.0-24.0)	20.0 (18.0-21.0)	0.08
AoV annulus (*z* score)	1.9 (1.3-3.7)	1.9 (0.9-2.4)	0.2
Sinus aorta (mm)	29.0 (28.0-31.0)	28.0 (27.0-30.0)	0.45
Sinus aorta (*z* score)	2.1 (1.4-2.6)	2.1 (1.5-2.6)	0.85
Ascending aorta (mm)	23.0 (20.0-26.0)	21.0 (20.0-23.0)	0.29
Ascending aorta (*z* score)	1.0 (0.5-2.4)	0.7 (−1.00-1.7)	0.32
Aortic insufficiencies, *n* (%)	17	16	
None/light	16 (94.1)	16 (100)	
Moderate	1 (5.9)	0	
Severe	0	0	
Right ventricular variables			
RVOT gradient (maximum, mmHg)	18.0 (15.0-24.0)	23.0 (14.0-35.0)	0.24
RVOT gradient (mean, mmHg)	10.0 (7.0-11.5)	12.5 (7.0-19.3)	0.08
PuV annulus (mm)	20.0 (19.0-21.0)	19.5 (17.0-21.3)	0.62
PuV annulus (*z* score)	−0.66 (−1.01-−0.19)	−0.48 (−1.86-−0.20)	0.89
RPA size (mm)	13.0 (11.0-16.0)	12.0 (11.0-13.0)	0.04
RPA size (*z* score)	−0.29 (−0.66-0.69)	−0.49 (−0.87-−0.09)	0.21
LPA size (mm)	13.0 (11.0-15.5)	11.0 (11.0-12.5)	0.06
LPA size (*z* score)	0.73 (−0.21-1.19)	0.09 (−0.42-0.99)	0.31
Pulmonary insufficiencies, *n* (%)	17	17	
None/light	9 (52.9)	6 (35.3)	
Moderate	5 (29.4)	6 (35.3)	
Severe	3 (17.6)	5 (29.4)	
Residual VSD (*n*)	0	0	-

IVS: Interventricular septum, AoV: Aortic valve, RVOT: Right ventricular outflow tract, PuV: Pulmonary valve, RPA: Right pulmonary artery, LPA: Left pulmonary artery, VSD: Ventricular septal defect

described, and genetic factors are assumed.[14] These wall structure abnormalities, among others, are caused by a media degeneration and reduced elastic capacity leading to increased aortic stiffness which seems to be related to aortic dilation.[6,7,12,15,16] In addition to genetic factors leading to wall abnormalities in the proximal aortic structures, mechanical factors like the volume overload to the LVOT before initial surgery, due to different degrees of stenosis in the RVOT, correspond to primary aortic dimensions[14,17] and can be observed already during fetal life.[18] Due to the overriding of the aorta in native TOF patients, even after patch closure of the VSD, the bayonet shape of the LVOT can lead to an asymmetric blood stream towards the aortic valve and the ascending aorta, a possible risk factor for dilations of structures in this area and for LVOT obstructions. To avoid these potential complications, our group started to realign the septum by a (partial) direct closure of the VSD. Although some concerns of possible AV-Block or tricuspid valve regurgitation existed, these complications did not occur and remained comparable to those observed in a more classical VSD patch closure.[10]

In this study we now aimed to evaluate further follow-up of patients with (partial) direct VSD closure in TOF in comparison to matched patients with classical VSD patch closure, treated by the same surgical team. We are aware of the fact, that classical patch repair in TOF patients is a well-established treatment method in the last decades with good results in mid- and long-term follow up and therefore new techniques must be chosen carefully – nevertheless, it is always important to challenge established methods and techniques. During a median follow-up time of 12.3 years (range 11.3–13.0), we could show, that this technique – even in mid-to long-term follow-up – is not associated with a more complicative course during or after surgery. We found no differences in surgical time, bypass time, ICU and total hospital stay or the occurrence of rhythm disturbances. In contrast, even if not significant, the need for re-interventions (all in the RVOT/pulmonary arteries, none in the LVOT) were lower in the group with (partial) direct VSD closure (6 vs. 12 patients), which can only be assumed to be due to redressing the conal septum towards the LVOT, leading to more space in the RVOT. The only difference we found, as expected, was the significantly lower “A Angle” between the IVS and the anterior aortic annulus [Figure 1], potentially leading to a better blood flow pattern to the aortic valve and the ascending aorta. Despite the improvement in angle, tangible advantage of the realignment is limited to the normalization of the z score of the aortic annulus, sinus as well as ascending aorta. The normalization of all z scores was also visible in Group B, leading us to conclude that the early correction of TOF as in our case, positively impacts the dynamics of the aortic root. It can only be hypothesized that the reduction of the malalignment is still too low and the difference to classical patch closure too small (36° vs. 45°). The aortic valve is the most dilated part of the LVOT before corrective surgery with z score values of median 4.6 (Group A)/4.7 (Group B), while sinus aortae or ascending aortae only show mild or no dilations (z scores 2.2/2.8 and 0.47/1.77 respectively). Nevertheless, we found no differences between both groups in aortic function, especially aortic regurgitation, or dilation of the valve itself or the supravalvular structures postoperatively and at last follow-up, with normalization of aortic valve z score values till last follow up (1.9 in both groups), which was described before.[19] This supports the thesis, that especially volume overload before corrective surgery is responsible for initial dilation of the valve.[14,17] Due to missing investigations, we cannot compare these findings to other studies, as no other evaluations in TOF have been published to this topic to our knowledge, while (partial) direct closure of VSDs are performed on a routine base in regular VSDs,[20] depending on the size and exact location. Even though a different entity of LVOT disease, in studies focusing on bicuspid aortic valves (BAV), some similarities to the LVOT in TOF can be found: in BAV, progressive dilations of the aortic structures can be found in up to 60% of patients with an up to 9-fold increased risk for aortic complications.[21] In addition, in BAV, genetic and hemodynamic components for aortic dilation are discussed as well.[21,22] It could be shown, in four-dimensional (4D) flow MR studies, that altered blood flow and aortic valve dysfunction (stenosis or regurgitation) influence the aortic wall homeostasis by wall shear stress and can lead to progressive aortic dilation in comparison to normal tricuspid aortic valve.[22] These findings support the approach for a better alignment of the LVOT in TOF and Fallot-type DORV patients for risk reduction for aortic dilations over time.

In some studies in which dilations of aortic structures are evaluated after TOF repair during follow-up, follow-up time was longer than in our investigation.[5] This needs to be considered when looking at the results and the benefits of the different surgical techniques, as late onset dilations are possibly not assessed in our population yet.

CONCLUSIONS

Long-term follow-up of patients with (partial) direct closure of the VSD in TOF or Fallot-type DORV showed results comparable to classical patch closure. While the partial direct VSD closure resulted in a significantly better realignment of the IVS-Ao angle, no differences in aortic dilations or valve insufficiencies were observed. Longer follow-up with 4D flow MR studies might help better understand the flow kinetics in both surgical techniques and thus predict their influence on late aortopathies.

Author contribution statement

All authors are responsible for the article's content, have participated in its conception/analysis/interpretation, have been responsible for drafting or revising the manuscript, and have approved the submitted version.

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Conflicts of interest

There are no conflicts of interest.

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