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The long-term result of total repair for tetralogy of Fallot☆

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Abstract

Objective: The objective of this study was to evaluate the long-term outcome of total repair for tetralogy of Fallot. **Methods:** Between April 1986 and December 2007, a total of 734 patients underwent total repair for tetralogy of Fallot. There were 444 males and 290 females. The median age and weight were 17.2 months (0.4—329.6 months) and 9.5 kg (2.6—53.5 kg). The median follow-up duration was 150.2 months (1.9—356.2 months). **Results:** There were 27 early deaths (3.7%) and 13 late deaths. A longer cardiopulmonary bypass time and the use of total circulatory arrest were risk factors for early death. The overall survival rate was 94.8%, 92.8% and 92.8% at 10, 20 and 25 years, respectively. The presence of pulmonary atresia was a risk factor for long-term survival. Re-operation or re-intervention was required in 224 patients (31.7%). The most common causes of re-operation or re-intervention were pulmonary regurgitation in 109 patients and branch pulmonary artery stenosis in 127 patients. Freedom from re-operation or re-intervention rate was 81.5%, 68.9% and 46.6% at 5, 10 and 20 years, respectively. Reconstruction of the right ventricular outflow tract with other than non-trans-annular repair and branch pulmonary arterioplasty at the time of total repair were the risk factors for late re-operation or re-intervention. The use of a monocusp patch was not associated with early mortality or re-operation. At the latest follow-up, most patients were in the New York Heart Association functional class 1 or 2. **Conclusions:** The long-term outcome of total repair for tetralogy of Fallot was satisfactory. A longer cardiopulmonary bypass time and the use of deep hypothermic circulatory arrest were associated with early mortality. The patients with pulmonary atresia have poorer late survival. Preservation of the pulmonary annulus can reduce the re-operation rate. A small pulmonary artery that requires augmentation may increase the risk of re-operation. The use of a monocusp in patients who underwent trans-annular repair has no benefit for early survival, the postoperative recovery and avoidance of re-operation. Age was not a risk factor for early mortality and re-operation.

Keywords: Congenital heart disease; Long-term outcome; Tetralogy of Fallot

1. Introduction

Since the first successful repair of tetralogy of Fallot (TOF) in the 1950s, some authors have reported excellent long-term results [1—3]. However, the long-term survival rate for patients with repaired TOF was lower than that of the age- and gender-matched population [1], and late problems, including arrhythmia, unexpected sudden death, decreased functional capacity and re-operation for the right ventricular outflow tract (RVOT), are still concerns. Although numerous efforts have been made to overcome these problems over the decades, the ideal strategy regarding the optimal timing of total repair, the method for reconstruction of the RVOT, including the use of a monocusp patch and how to approach the ventricular septal defect (VSD), has yet to be established.

In this study, we investigated the long-term outcome after total repair of TOF, focusing on the above-mentioned controversial issues.

2. Material and methods

2.1. Patients

Our institutional review board/ethical committee approved this retrospective study and the informed consent was waived. We reviewed the medical records of all the patients who underwent total repair of TOF at our centre (Seoul National University Hospital) between 1986 and 2007. Patients who had absent pulmonary valve syndrome, major collateral arteries and a complete atrioventricular septal defect were excluded. A total of 734 patients were included and analysed. There were 444 males and 290 females, and their median age and weight at the time of operation were

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Table 1
Patients' characteristics.

		N (%)	Median (range)
Era	~1990	308 (42.0)	
	1991–2000	307 (41.8)	
	2001~	119 (16.2)	
Age (months)			17.2 (0.4–329.6)
Age category	<3 months	19 (2.6)	
	3–6 months	45 (6.1)	
	6–12 months	164 (22.3)	
	>12 months	506 (68.9)	
Weight (kg)			9.5 (2.6–53.5)
RVOT	Stenosis	704 (95.9)	
	Atresia	30 (4.1)	
Chromosomal anomaly[a]		27 (3.7)	
Strategy for total repair	Primary repair	580 (79)	
	Staged repair	154 (21)	
	Interval (months)		13.1 (1–245.1)
Follow-up duration (months)			150.2 (1.9–356.2)
CPB (min)			125 (62–408)
ACC (min)			68 (18–245)
DHCA (min)		33 (4.5)	27.0 (4–67)

RVOT: right ventricular outflow tract; CPB: cardiopulmonary bypass; ACC: aortic cross clamping; and DHCA: deep hypothermic circulatory arrest.
[a] Chromosomal anomaly included nine Down syndromes, nine CATCH 22s, three DiGeorge syndromes, one VACTERAL syndrome, one Noonan syndrome, and four others.

17.2 months (range: 0.1–329.6 months) and 9.5 kg (range: 2.6–53.5 kg). The patients' characteristics are described in Table 1.

The age at the time of total repair decreased during the progression of the study period (Fig. 1A) and, for the last decade, the percentage of patients who underwent total repair in infancy increased. One hundred sixty-six palliative procedures (three palliations in three, two palliations in six and one palliation in 145) were performed prior to total repair in 154 patients (21%) and total repair was performed at a median of 13.1 months (range: 1 day–245 months) after the palliation.

2.2. Operative technique

In most patients (701/734, 95.5%), total repair was performed under moderate hypothermic cardiopulmonary bypass without circulatory arrest. The median cardiopulmonary bypass time and median myocardial ischaemic time were 125 min (range: 62–408 min) and 68 min (range: 18–245 min), respectively. Deep hypothermic circulatory arrest (DHCA) was used in 33 patients. The mean duration of DHCA was 27.6 ± 15.2 min (range: 4–67 min). DHCA had been used until 1996.

The VSD was repaired through the tricuspid valve in 280 patients (38.1%) and through ventriculotomy in 380 patients (51.8%). The approach for repair of VSD was not documented in the remaining patients. The percentage of patients who underwent the right atrial approach for repairing a VSD has recently increased (Fig. 1B). The RVOT was reconstructed with a trans-annular patch in 413 patients (56.3%) and the annulus was preserved in 224 patients (30.5%). The percentage of patients who underwent non-trans-annular repair of the RVOT increased during the course of the study period (Fig. 1C). In the other patients, a conduit or Lecompte procedure was used to restore the continuity between the right ventricle and the pulmonary artery. A monocusp using a variety of materials was created to reduce the immediate pulmonary insufficiency in 130 patients among the patients who underwent RVOT reconstruction with a trans-annular patch (130/413, 17.7%).

2.3. Follow-up

A total of 605 patients (82.4%) were included in the recent follow-up, and the median follow-up duration was 150.2 months (range: 1.9–356.2 months). The information regarding the functional status and symptoms was obtained from the medical records. Late death was confirmed with an aid of the Korean Statistical Information Service in the National Statistical Office.

2.4. Statistical analysis

The data are presented as the mean ± standard deviation or the median with the range. To compare variables between groups, the unpaired *t*-test or Wilcoxon rank-sum method was used for the continuous variables and Pearson Chi-square test or Fisher's exact test was used for the categorical variables. Kaplan–Meier methods with the log-rank test and Cox proportional hazards regression analysis were used to analyse the long-term survival and freedom from re-operation or re-intervention. Multiple logistic regression analysis was used for the risk-factor analysis regarding early mortality.

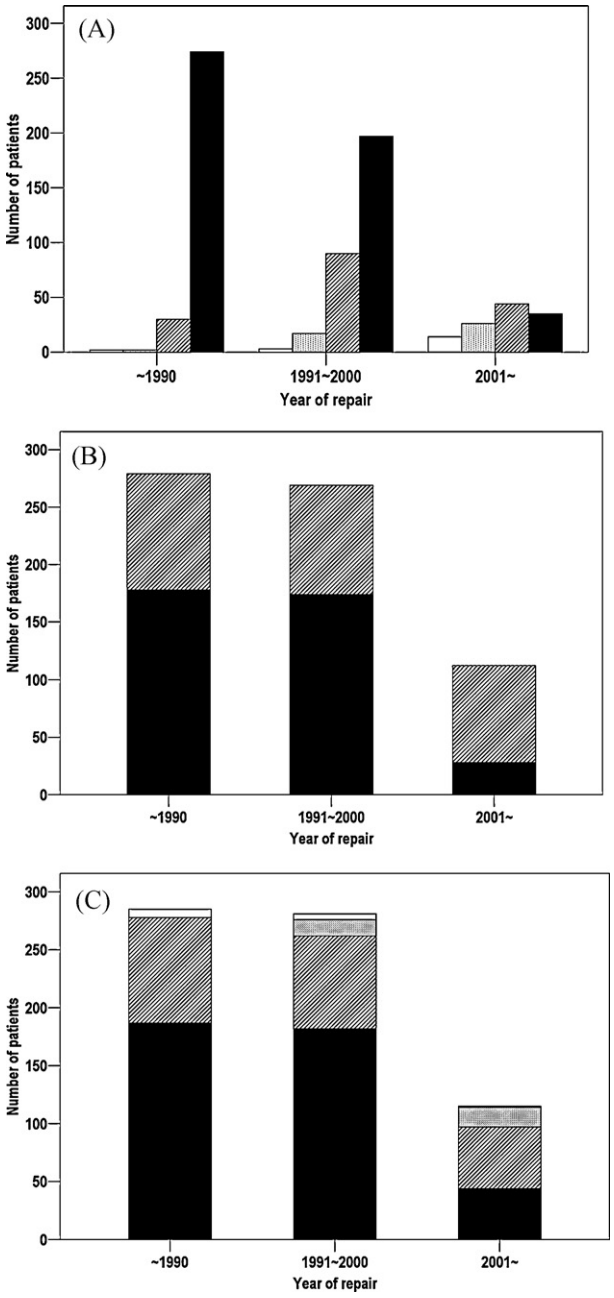

Fig. 1. Change in the patients' age and reconstruction of the right ventricular outflow tract during the study period. (A) the age distribution by decade (black, >12 months; oblique line, 6–12 months; dot, 3–6 months; white, 3 months); (B) changes in the approach for repair of ventricular septal defect (black, transventricular approach; oblique line, trans-atrial approach); and (C) changes in reconstruction of the right ventricular outflow tract (black, trans-annular repair; oblique line, non-trans-annular repair; dot, conduit; white, Lecompte procedure).

3. Results

3.1. Early mortality

Twenty-seven patients (3.7%) died within 30 days after the total repair or during the admission for total repair. The time period when the operation was performed and initial palliation prior to total repair were not risk factors for early death. On the univariate analysis, age < 1 year, combined pulmonary atresia and a longer cardiopulmonary bypass time, were related to early death. On the multivariate analysis, a longer cardiopulmonary bypass time and the use of DHCA were significant risk factors for early death (Table 2).

Table 2
Risk factors for early mortality.

	Univariate	Multivariate		
	p	*p*	OR	CI (95%)
Era (<2000)	0.70			
Age (>1 year)	0.032	0.63	0.63	0.10–4.12
Weight (kg)	0.11			
One-stage total repair	NS			
Other than non-trans-annular repair	0.17			
Trans-atrial VSD repair	0.13	0.50	1.85	0.31–10.91
CPB (min)	0	0.002	1.02	1.01–1.03
ACC (min)	0.60			
The use of DHCA	0.068	0.008	15.27	2.04–114.31
Chromosomal anomaly	0.26			

OR: odds ratio; CI: confidence interval; VSD: ventricular septal defect; CPB: cardiopulmonary bypass; ACC: aortic cross clamping; and DHCA: deep hypothermia circulatory arrest.

3.2. Survival

The overall survival rate at 10, 20 and 25 years was 94.8%, 92.8% and 92.8%, respectively (Fig. 2A). A difference in the survival distribution was observed for the TOF with pulmonary stenosis versus the TOF with pulmonary atresia ($p < 0.001$), non-trans-annular repair versus others ($p = 0.024$), and transventricular repair of a VSD versus trans-atrial repair of a VSD ($p = 0.019$) according to the log-rank test (Fig. 2B–D). However, the presence of pulmonary atresia was the only factor associated with reduced long-term survival on the Cox proportional hazards regression analysis ($p = 0.017$, hazard ratio (HR) = 8.14, 95% confidence interval (CI):1.45–45.79).

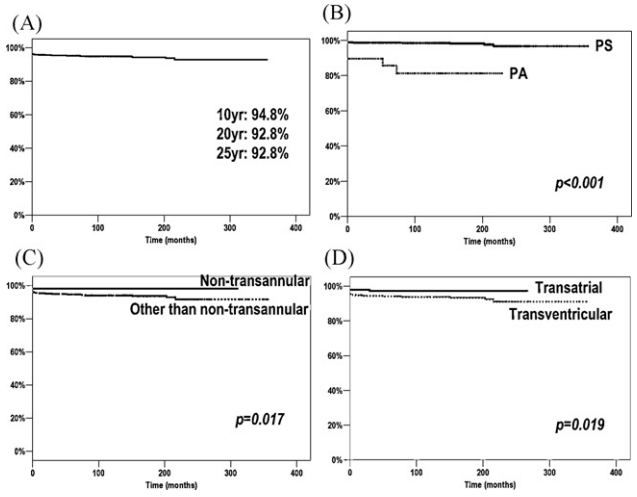

Fig. 2. Late survival. (A) Overall survival; (B) comparison between pulmonary stenosis and atresia; (C) comparison by reconstruction of the right ventricular outflow tract; and (D) comparison between trans-atrial and transventricular repair of the ventricular septal defect.

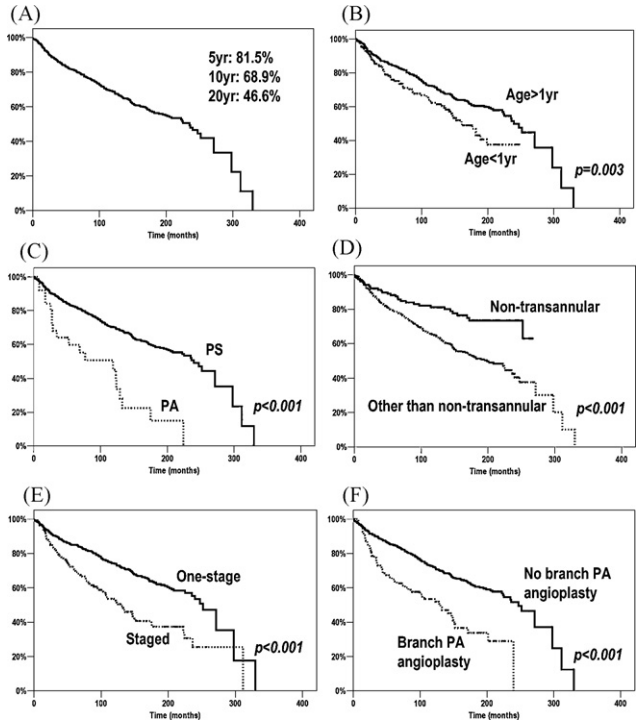

Fig. 3. Freedom from re-operation or re-intervention. (A) Overall freedom from re-operation or re-intervention; (B) comparison between an age younger than 1 year old and an older age; (C) comparison between pulmonary stenosis and atresia; (D) comparison by reconstruction of the right ventricular outflow tract; (E) comparison between one-stage and staged repair of tetralogy of Fallot; and (F) comparison between the patients who underwent concomitant branch pulmonary arterioplasty and those who did not.

3.3. Re-operation

Among the 707 early survivors, re-operation or re-intervention was required in 224 patients (31.7%) at a median of 71.9 months (range: 1—329.8 months) after the total repair. Among these patients, catheter-based re-intervention was performed in 47 patients at a mean interval from total repair of 53.4 months and re-operation was performed in 177 patients at a mean interval from total repair of 90.3 months. The most common causes of re-operation or re-intervention were pulmonary regurgitation in 109 patients and branch pulmonary artery stenosis in 127 patients. Stenosis of the branch pulmonary artery occurred at the left pulmonary artery (LPA) in 82 patients, at both pulmonary arteries in 33 and at the right pulmonary artery in 12. Rate of freedom from re-operation or re-intervention rate was 81.5%, 68.9% and 46.6% at 5, 10 and 20 years, respectively (Fig. 3A). Age $<$ 1 year versus older ($p = 0.003$), the presence or absence of pulmonary atresia ($p < 0.001$), non-trans-annular repair versus others ($p < 0.001$), one-stage repair versus staged repair ($p < 0.001$), transventricular repair of a VSD versus trans-atrial repair of a VSD ($p = 0.027$) and concomitant angioplasty of a branch pulmonary artery versus not performed ($p < 0.001$) showed a difference for freedom from re-operation (Fig. 3B—F). RVOT reconstruction with other than non-trans-annular repair ($p = 0.006$, HR: 0.53 and 95% CI: 0.34—0.84) and concomitant angioplasty of a branch pulmonary artery ($p = 0.011$, HR: 0.99 and 95% CI: 0.99—1.00) were the risk factors associated with later re-operation or re-intervention, as assessed by Cox proportional hazards regression analysis.

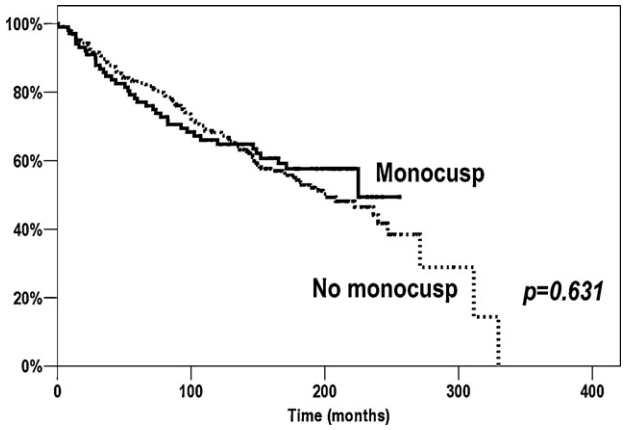

Fig. 4. Freedom from re-operation in the patients with trans-annular repair by the presence or absence of a monocusp patch.

3.4. Use of a monocusp in the trans-annular repair of the RVOT

Among the patients who underwent RVOT reconstruction with a trans-annular patch, there was no difference between the patients with a monocusp and the patients without a monocusp for age, body weight, the extubation time, the length of stay in the intensive care unit and the length of the hospital stay. Although the risk for early mortality was higher for the patients without a monocusp on univariate analysis ($p = 0.007$), multivariate analysis showed that this factor was not associated with early mortality ($p = 1.00$). There was no difference in freedom from re-operation with or without using a monocusp implantation in the log-rank test ($p = 0.63$; Fig. 4).

3.5. Adverse events: late cardiac deaths or symptoms

There were 13 late deaths. The causes of death included cardiac problems in nine patients (Table 3), pneumonia in two and sepsis of an unknown origin in one. During the follow-up period, cardiac symptoms related to heart failure or dysrhythmia developed in 23 patients. Among them, 15 patients suffered from dysrhythmia, including atrial arrhythmia in nine patients and ventricular arrhythmia in six. Arrhythmia intervention or surgery, including six implantations of a permanent pacemaker or a cardioverter defibrillator, was performed in 12 patients (Table 4). Most of the patients were in the New York Heart Association (NYHA) functional classes 1 or 2 at the latest follow-up.

4. Discussion

The early outcomes of total repair of TOF have improved since the procedure was first introduced in the 1950s. However, long-term studies have shown the development of pulmonary regurgitation, progressive right ventricular dysfunction, decreased functional capacity, arrhythmias and

Table 3
Cardiac-related late deaths.

	Age (months)[a]	RVOT reconstruction	VSD approach	Cause of death	Interval (months)[b]
1	26.8	Trans-annular	RV	Sudden	3.2
2	7.4	Trans-annular	RV	Intractable arrhythmia	216.2
3	15.2	Trans-annular	RA	Sudden	29.5
4	23	Trans-annular	RV	Sudden	151
5	13.1	N/A	N/A	Sudden	1.5
6	15.5	Trans-annular	RV	Sudden	79.4
7	13.3	REV	RV	Heart failure	52.2
8	8.2	Trans-annular	RV	After re-operation[c]	72.9
9	6.3	Rastelli	RV	Sudden	1.8

RVOT: right ventricular outflow tract; VSD: ventricular septal defect; REV: Réparation à l'Etage Ventriculaire; RV: right ventricle; RA: right atrium; and N/A: not available.
[a] Age at total repair.
[b] Interval from total repair to late death.
[c] After pulmonary valve replacement for pulmonary regurgitation.

Table 4
The patients who suffered from dysrhythmia late after total repair.

	Age (months)[a]	RVOT reconstruction	VSD approach	Mode of arrhythmia	NYHA Fc	Surgery or intervention for arrhythmia
1	211.2	Trans-annular	RV	Af	3	Right side Maze, PPM
2	4.5	Trans-annular	RA	Af	2	Right side Maze, PPM
3	3.5	Trans-annular	RV	VT	2	ICD
4	16.3	N/A	N/A	Af	3	–
5	10.2	Annulus preserved	RA	Af	2	–
6	42.0	REV	RA	VT	2	ICD
7	18.1	Trans-annular	RV	AFL	1	CTI cryoablation
8	18.5	Trans-annular	RV	SSS	2	PPM
9	16.9	Trans-annular	RV	SSS	2	PPM
10	31.8	Trans-annular	RV	NSVT	2	Cryoablation
11	118.2	Trans-annular	RV	AFL	2	Right side Maze
12	8.0	Trans-annular	RV	NSVT	2	Cryoablation
13	9.3	N/A	N/A	NSVT	1	–
14	15.3	Trans-annular	RV	NSVT	2	Cryoablation
15	28.7	Annulus preserved	RA	AFL	1	CTI cryoablation

RVOT: right ventricular outflow tract; VSD: ventricular septal defect; NYHA Fc: New York Heart Association functional class; REV: Réparation à l'Etage Ventriculaire; RV: right ventricle; RA: right atrium; Af: atrial fibrillation; VT: ventricular tachycardia; AFL: atrial flutter; SSS: sick sinus syndrome; NSVT: non-sustained ventricular tachycardia; PPM: permanent pacemaker; ICD: implantable cardioverter defibrillator; CTI: cavotricuspid isthmus; and N/A: not available.
[a] Age at total repair.

related sudden deaths [1–7]. Although many surgeons and paediatric cardiologists try to minimise the long-term problems by focussing on the optimal timing for surgery and the technique of repair of the RVOT or VSD, there continues to be controversy regarding these factors. Nevertheless, the age at which a total repair is performed continues to decrease worldwide since the introduction of the concept for early primary repair of TOF by Castaneda et al. [8] In our series, the age at which total repair was performed gradually decreased over the study period, and most of the patients (84/119, 70.6%) during the current decade (2001 onwards) were completely repaired in infancy, including 14 (11.8%) young infants (<3 months old). Additionally, trans-annular reconstruction of RVOT was less frequently performed in the recent decades, and the percentage of using the right ventricular approach for repairing a VSD also decreased in the recent decades.

The operative mortality rate has gradually fallen, and this is currently ~0% even in neonates and young infants [9–11]. The previous reports [2,12,13] that included the patients who underwent total repair in the earlier era demonstrated that a younger age at the time of operation, a lower body weight and trans-annular patch reconstruction of the RVOT were risk factors for early death. In our series, a longer cardiopulmonary bypass time and the use of DHCA were identified as risk factors for early mortality. As the mechanical properties and material used for cardiopulmonary bypass have been markedly improved [14], the adverse effects of cardiopulmonary bypass have been reduced, but these cannot be completely avoided. In the same context, the use of DHCA has harmful effects on human organs and especially on the brain. Although DHCA has the benefit of producing a clear operative field and some surgeons still routinely use DHCA in neonates [15], we have abandoned the use of DHCA since 1996. The overall survival in our cohort was excellent, but late survival was significantly poorer in patients with pulmonary atresia. This finding is concordant with those of the previous reports [7,13].

For many of the patients who underwent surgical reconstruction of the RVOT, re-operation or re-intervention is required for late pulmonary regurgitation. Although pulmonary regurgitation is well tolerated in some cases, the prolonged exposure to pulmonary regurgitation can lead to progressive right ventricular distension, increasing tricuspid regurgitation, dysfunction of both ventricles, ventricular arrhythmia and sudden death [16,17]. There are some reports

that showed poorer survival and an increased frequency of pulmonary regurgitation late after total repair using a trans-annular patch [18,19]. In our series, nearly one-half of the re-operations or re-interventions were performed for significant pulmonary regurgitation and there was a significant difference in the freedom from re-operation between the patients who underwent non-trans-annular repair and the patients who underwent surgery other than the non-trans-annular repair. The preoperative z-score of the pulmonary annulus, the intra-operative findings of the pulmonary valve or annulus and the pressure profile after discontinuation of bypass have been recently used in our centre to determine whether the pulmonary annulus could be preserved; z-score of the pulmonary annulus larger than -2, a non-dysplastic pulmonary valve leaflet and the pressure ratio between the right ventricle and systemic artery of <0.8 after discontinuation of bypass were considered factors that made it possible to preserve the pulmonary annulus. The percentage of annulus preservation increased during the recent decade. Another significant risk factor for late re-operation or re-intervention was performing branch pulmonary arterioplasty at the time of total repair. The factors that have been reported to contribute to re-operation or re-intervention for branch pulmonary artery stenosis were angulation or stenosis of the LPA, a ductal tissue extension into the LPA origin and a small-sized pulmonary artery at the time of total repair [1,7,20]. In our study, 127 patients underwent re-operation or re-intervention for branch pulmonary artery stenosis. It can be inferred that the patients that underwent branch pulmonary arterioplasty at the time of total repair might have a stenotic branch pulmonary artery. These findings are in agreement with those of the previous reports [1,7,20]. Freedom from re-operation or re-intervention rate was 81.5%, 68.9% and 46.6% at 5, 10 and 20 years, respectively. The patient age and initial palliation prior to total repair did not affect the freedom from re-operation.

If the pulmonary annulus cannot be preserved during total repair of TOF, then the sudden haemodynamic change of the right ventricle due to pulmonary insufficiency causes delayed recovery of the right ventricular function [21]. The creation of a monocusp-RVOT patch was introduced as an attractive option to avoid this problem. In our centre, 130 patients of the 413 patients who underwent trans-annular repair underwent implantation of a monocusp patch, and the patches were made of different materials. On univariate analysis, there was no difference in age, body weight, the duration of ventilatory support, the length of stay in the intensive care unit and the length of the hospital stay between the patients with a monocusp patch and those without a monocusp patch. Although the use of a monocusp patch was a factor associated with early mortality on univariate analysis, it was not a risk factor for early mortality on multivariate analysis. In addition, there was no difference in freedom from re-operation between the patients with a monocusp patch and those without a monocusp patch. These results suggested that the use of a monocusp patch in the patients who underwent trans-annular repair had no benefit for early survival, the postoperative recovery and reducing the re-operation rate.

Although total correction of TOF offers a favourable long-term outcome, a significant proportion of patients with repaired TOF experience the deleterious consequences of progressive right ventricular dilatation [1,4—7]. On the recent follow-up, most of the patients were in the NYHA functional classes 1 or 2. However, 32 adverse events (32/707, 4.5%), including nine cardiac deaths and 23 cardiac-related symptoms, occurred during the follow-up period. More careful follow-up is required and more objective parameters must be defined to more reliably evaluate the long-term outcomes.

5. Limitation of this study

This study was limited by its retrospective methodology and the inclusion of patients who were operated on during a wide-ranging time period. Among the symptomatic patients who had undergone initial palliation, only the completely repaired patients were included in this study. The parameters used to evaluate the functional outcome in this study were subjective. In addition, the recent follow-up was completed for a rather small number of patients as compared to the number of patients included in this study. Although most of these limitations were corrected via statistical methods as much as possible, our study limitations must be considered when interpreting our results.

6. Conclusions

The long-term outcome of total repair for TOF was satisfactory. A longer cardiopulmonary bypass time and the use of DHCA were associated with early mortality. The patients with pulmonary atresia have poorer late survival. Preservation of the pulmonary annulus can reduce the re-operation rate. A small pulmonary artery that requires augmentation increases the risk of re-operation. The use of a monocusp in the patients who underwent trans-annular repair had no benefit for early survival, the postoperative recovery and avoidance of re-operation. Age was not a risk factor for early mortality and re-operation.

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Appendix A. Conference and discussion

Dr C. Mignosa (*Taormina ME, Italy*): This is a large series of tetralogy of Fallot that is well documented and has been statistically well analysed.

I've got two questions for you. Going through your manuscript, it appears evident that the need for trans-annular patch and PA reconstruction is a risk factor for late re-intervention. But we all know that when we have to perform these procedures in neonates, these two issues are compulsory.

So what is the message? Do you advise palliation of this subset of patients, the neonates I mean, and what is the policy in your centre?

And the second question is related to the timing for late re-operation when severe pulmonary incompetence occurs. Is it based on clinical status or on the echo or MRI? So what parameters do you consider for that?

Dr Lee: Regarding your first question, it is hard to make a conclusion because we have a very small number of patients who are in the neonatal period. But as we all know, the pulmonary annulus in these small babies is very flexible. We try to save the patient's own pulmonary valve if possible, although almost all of the patients don't have the intact pulmonary valve in the neonatal period. If pulmonary valve morphology and size are not optimal, it is desirable to defer the operation.

And the second question is related to the timing of late re-operation for pulmonary regurgitation. We have a little more number than the reported papers, because we included our initial period experience. At that time, we made a very long incision of the right ventricle to close the VSD which might cause the free pulmonary valve regurgitation.

Our indication to perform pulmonary valve replacement is pulmonary regurgitant fraction over 35% on MRI, right ventricular end-diastolic volume index of more than 170 ml/m^2 on MRI, increasing size of the right ventricle or newly formed tricuspid valve regurgitation.