Congenital Heart Disease

Long-Term Outcomes of Patients with Tetralogy of Fallot Repaired in Young Infants and Toddlers

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Background: Total repair of tetralogy of Fallot (TOF) during young infancy had been recently advocated, but recent outcomes leave this question undecided.

Methods: Between 1992 and 2002, 259 consecutive TOF patients received total repair in our hospital. To avoid confounding by previous shunt operations, we excluded those patients receiving staged shunt operation in the following analysis. Therefore, a total of 217 TOF patients who received one stage total repair before age 3 in our hospital were enrolled (early group: 38 patients 0-6 months old; late group: 179 patients 6 months-3 years old). We reviewed the medical records and confirmed the patients' survival status from the National Health Database.

Results: Baseline characteristics showed fewer emergent operations (1.7% vs. 13.2%, p = 0.005) and fewer transannular patches required (70.9% vs. 86.8%, p = 0.029) in the late group. However, the early group had longer intubation periods and intensive care stays. After the 1994 patient-years follow-up, the 10-year actuarial survival and reintervention-free survival rate was 97.4% and 89.4%, respectively in the early group, and 95.5% and 93.5% respectively in late group, which showed no statistically significant difference. The major risk factor for reintervention was small pulmonary artery size. Severe pulmonary regurgitation correlated with transannular patch, which tended to be higher in the early group.

Conclusion: Although patients with TOF repaired within first 6 months of life had prolonged postoperative recovery and an increased chance of transannular patch usage, outcomes were comparable to those patients with TOF repaired later. Therefore, symptomatic infants can receive total repair of TOF early to avoid the need for use of a palliative shunt. However, when total repair is undertaken on an elective basis, the procedure may be delayed until the patient is older than 6 months of age.

Key Words: Infant • Long-term outcome • Surgery • Tetralogy of Fallot

INTRODUCTION

It has been more than five decades since the first total repair of tetralogy of Fallot (TOF) by Lillehei et al. in 1955.[1] With advances in surgical techniques and perioperative support, outcomes have substantially improved in the last 20 years. However, residual hemodynamic abnormalities were still commonplace in many patients, with further reintervention possibly required. Primary total repair during early infancy had been advocated for the last ten years.[2] The advantages of early repair include shorter duration of hypoxia, shorter duration of right ventricular hypertension and a potentially lower incidence of late arrhythmias. However, there are some concerns regarding early primary repair, including elevated need for use of transannular patch, increased severity of pulmonary regurgitation (PR), and higher reintervention and mortality rate.[3-8] Though several reports

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had shown favorable early and mid-term results of primary repair during young infancy,[9-16] the data regarding long-term outcomes are still limited.[14,16-18] In our hospital, total correction of TOF during early infancy (within six months of birth) began in the early 1990s. With more than fifteen years experience, we have here investigated the benefits and risks of early total repair by comparing those patients with TOF repaired during the first six months of life with those repaired between six months and three years of age.

PATIENTS AND METHODS

From January 1992 to December 2002, 259 consecutive TOF patients who received total repair by the age of 3 years in this institution were studied. Patients with pulmonary atresia or absent pulmonary valve were excluded. The data collection was in accordance with regulations and approved by the institutional review board at National Taiwan University Hospital. Among these 259 patients, 42 of them received a shunt operation first. They had smaller initial pulmonary artery size, smaller initial operative age, and more commonly required emergent operation. Because staged shunt operation is an important risk factor of reintervention and late mortality, (Figure 1), and given that the procedure was gradually discarded as part of the current surgical strategy,[19,20] we also excluded those patients who received a previous shunt operation in the following analysis to avoid confounding. Therefore, a total of 217 patients who received one stage total TOF correction without previous shunt operation were enrolled in our study. They were further divided into two groups, an early group and a late group. The early group (n = 38) was defined as those who received total cardiac repair from 0 to six months of age, and the late group (n = 179) was defined as those who were repaired between the age of six months and three years. Preoperative echocardiography, cardiac catheterization, and operation data were reviewed. Right ventricular outflow tract (RVOT) reconstruction methods included RVOT transannular patch repair, RVOT patch without crossing pulmonary annulus, and transatrial-transpulmonary approach without RVOT patch (infundibulectomy only). For those patients who had surgery from 0 to 6 months of age, we further divided the group by elective, symptomatic and emergent operation. Symptomatic patients in our study were defined as those who have frequent blue spell attacks requiring beta blocker therapy, or those who were O2 or Prostaglandin E1 dependent. Emergent operation was defined as an operation performed either immediately during a hypoxic spell attack, or immediately after a hypoxic spell was medically controlled. Among these 217 patients, 198 had preoperative cardiac catheterization data for pulmonary size evaluation, 7 other patients had preoperative computed tomography results, and the remaining 12 patients had only preoperative echocardiography reports. The McGoon index was defined as the sum of the diameters of the left and right pulmonary artery divided by the diameter of the descending aorta at the diaphragm level.[21]

We also obtained clinical and echocardiographic follow-up data. We mailed questionnaires to or had telephone interviews with those patients who were lost to follow-up for more than 2 years. In addition, we linked to the National Health database for death records of those patients to check and confirm the survival status for all patients.

The echocardiography machines used during the study period include the Acuson Sequoia C256 (Acuson, Mountain View, CA, USA) and the Hewlett Packard Sonos iE33 (Philips Medical Systems, Andover, MA,

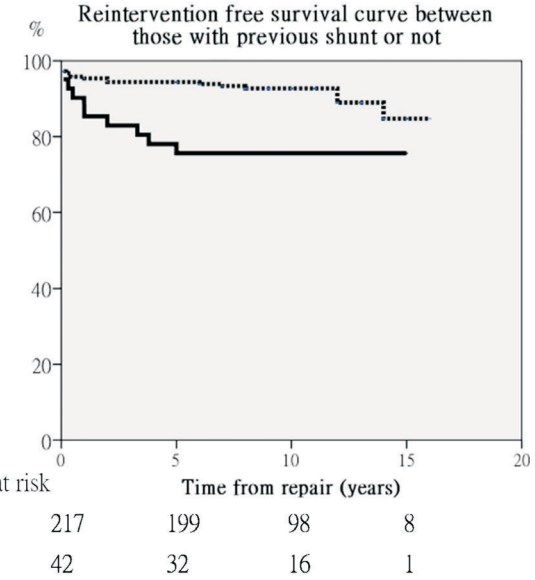

Figure 1. *Reintervention-free survival curve between those who did and did not receive previous shunt operation. Solid line: those with previous shunt operation. The p value comparing these two groups by log-rank analysis is 0.006.*

USA). We reviewed the videotape records of the echocardiography evaluation of each patient, and rechecked the left ventricular function, PR and pulmonary stenosis severity to assure consistency. The PR was graded as severe degree if regurgitated flow was from branch pulmonary artery, moderate degree if regurgitated flow was from distal half main pulmonary artery, and mild degree if regurgitated flow was from proximal half of pulmonary artery.[22] For left ventricular function assessment, we defined left ventricular ejection fraction (measured by M mode method) $\geqq$ 55% as normal.[23] However, because paradoxical septal motion is common in repaired TOF patients, we also used Simpson's biplane method. To evaluate echocardiographic accuracy, we also compared the results from magnetic resonance imaging (MRI) with echocardiography data in 36 of our patients. The RVOT and pulmonary stenosis were graded as severe degree if the pressure gradient across RVOT and the main pulmonary artery was greater than 60 mmHg, or further intervention was necessary. Severe peripheral pulmonary stenosis was defined as pressure gradient across one branch pulmonary artery that was greater than 50 mmHg, with marked preferential pulmonary flow to one lung, or estimated right ventricular pressure greater than 60 mmHg. Large residual ventricular septal defect was defined as pulmonary versus systemic shunt (Qp/Qs) greater than 1.5 upon cardiac catheterization, or further necessary intervention. RVOT aneurysm was defined as aneurysmal formation occurring at RVOT.

Statistics

The statistics used in our study included use of the chi-square test and Fisher's exact test for comparisons of clinical characteristics between groups. The Wilcoxon rank sum test was applied for comparisons of the duration of ventilator use, intensive care unit stay and length of admission. Independent Student's t-test was used for other numeric data comparisons. Log-rank test was used for comparisons in Kaplan-Meier event-free survival curves, and logistic regression and Cox regression were applied for regression analysis. Statistical significance was defined as a p value less than 0.05.

RESULTS

The basic clinical characteristics of these TOF patients who received one stage total TOF repair are shown in Table 1. Basic data was also compared between 38 early repair patients and 179 late repair patients. A ge-

Table 1. Clinical characteristics of the 217 patients (38 in early group and 179 in late group) with tetralogy of Fallot operated on within the age of 3 years. p value less than 0.05 was typed as **bold** and *Italic*

	All (n = 217)	Subgroup analysis		p value
		Early group (n = 38)	Late group (n = 179)	
Operation age (months)	14.4 ± 8.1	4.6 ± 1.2	16.5 ± 7.3	< 0.001
Gender (M/F)	148/69	28/10	120/59	0.424
Emergent operation	8 (3.7%)	5 (13.2%)	3 (1.7%)	0.005
Syndrome combination	16 (7.4%)	1 (2.6%)	15 (8.4%)	0.316
PA size (McGoon index)				0.308
< 1.5	6 (2.9%)	1 (2.7%)	5 (2.9%)	
1.5-2	58 (27.6%)	14 (37.8%)	44 (25.4%)	
> 2	146 (69.5%)	22 (59.5%)	124 (71.7%)	
Presence of MAPCA	4 (1.8%)	0	4 (2.2%)	1.000
Surgical method				0.029
Transannular patch	160 (73.7%)	33 (86.8%)	127 (70.9%)	
RVOT patch only	34 (15.7%)	1 (2.6%)	33 (18.4%)	
Valve sparing surgery	23 (10.6%)	4 (10.5%)	19 (10.6%)	
Total follow-up (years)	9.2 ± 3.3	7.7 ± 2.3	9.5 ± 3.4	< 0.001
Echocardiography follow-up (years)*	8.0 ± 3.6	7.0 ± 3.1	8.3 ± 3.7	0.092

* include only those with data available more than 2 years after operation. MAPCA, major aortopulmonary collateral arteries; PA, pulmonary artery; RVOT, right ventricular outflow tract.

netic syndrome was found in 7.4% of TOF patients, including 1.9% with documented CATCH 22 syndrome, 0.9% with Down syndrome, 1.5% with VATER association, and the other 3.2% having other chromosomal anomaly or a combination with gastrointestinal or brain malformation. Patients in the early group were more likely to receive emergent total repair (13.2% vs. 1.7%, p = 0.005) and require transannular patch (86.8% vs. 70.9%, p = 0.029) for RVOT reconstruction. The total follow-up period was longer in the late group than in the early group. This may be related to the fact that relatively fewer patients received early repair in our institution in the early 1990s.

Survival status

The immediate outcomes of those patients receiving one stage repair in the early group and late group are shown in Table 2. We noted longer duration of intubation, prolonged stay in the intensive care unit, and a slightly elevated chance of delayed sternum closure or reoperation in the early repair group. There were 8 (3.7%) early deaths, which were all from the late group: 4 died of cardiopulmonary collapse within 5 days after operation, 2 died of neurological complications, and another 2 died of postoperative infection. Multivariate logistic regression (on those factors including sex, pulmonary artery size, major aortopulmonary collateral arteries existence, age at operation, syndromic combination, operation era, emergent operation, and transannular patch usage) showed operations conducted prior to 1997 as a significant risk factor for early mortality [odds ratio (OR) 0.55 for every increasing year, 95% confidence interval 0.38-0.80, p = 0.002]. The perioperative mortality rate before 1997 and after 1998 were 8/101 (7.9%) and 0/116 respectively (p = 0.002, Table 3).

There were only one late death (after discharge or more than 1 month after operation) in the whole study cohort. He died of cardiac tamponade due to post-

Table 2. Surgical results and follow-up data after total repair of the 217 Patients with tetralogy of Fallot. p value less than 0.05 was typed as **bold** and *Italic*

	All (n = 217)	Early group (n = 38)	Late group (n = 179)	p value
Short term outcome				
Total bypass time (mean ± SD)	108.9 ± 28.8	117.2 ± 28.5	107.0 ± 28.7	0.055
Aorta cross clamp (mean ± SD)	83.9 ± 24.6	87.3 ± 24.3	83.1 ± 24.7	0.380
Ventilator day (median)	2.0	3.5	1.0	< ***0.001***
Intensive care unit day (median)	3.5	5.5	3.0	< ***0.001***
Delay sternum closure or early reoperation	9 (4.1%)	4 (10.5%)	5 (2.8%)	0.052
Chylothorax	25 (9.7%)	3 (7.9%)	17 (9.5%)	1.000
Transient atrioventricular block*	12 (5.5%)	5 (13.2%)	7 (3.9%)	**0.039**
Severe infection	7 (3.2%)	2 (5.3%)	5 (2.8%)	0.354
Resuscitation early postoperatively	10 (4.6%)	2 (5.3%)	8 (4.5%)	0.688
Early mortality	8 (3.7%)	0	8 (4.5%)	0.356
Hemodynamics at follow-up				
Moderate or severe PR†	100 (69.9%)	22 (73.3%)	78 (69.0%)	0.823
Severe PR†	27 (18.9%)	8 (26.7%)	19 (16.8%)	0.292
Left ventricular ejection fraction (%)	69.4 ± 6.7	67.5 ± 7.0	69.9 ± 6.5	0.081
Significant residual VSD†	1 (0.7%)	0	1 (0.9%)	1.000
RVOT aneurysm†	13 (9.4%)	3 (10.0%)	10 (9.3%)	1.000
More than trivial AR†	8 (5.6%)	0	8 (7.1%)	0.204
Severe PS or peripheral PS†	16 (11.2%)	5 (16.7%)	11 (9.7%)	0.329
Reintervention	18 (8.3%)	4 (10.5%)	14 (7.8%)	0.528
Late mortality	1 (0.5%)	1 (2.5%)	0	0.182

* all resolved within two weeks after operation although one received permanent pacemaker one week after operation; † include only 175 patients with echocardiography data available more than 2 years after operation.

AR, aortic regurgitation; PR, pulmonary regurgitation; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

Table 3. Perioperative mortality rate according to operation year

Operation year	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Mortality number	0	3	2	1	2	0	0	0	0	0	0
Operation volume	8	19	17	13	22	22	33	27	18	20	18
Mortality rate	0	15.8%	11.8%	7.7%	9.1%	0	0	0	0	0	0

pericardiotomy syndrome 2 months postoperatively after successfully repaired at 5 month of age. The 10-year actuarial survival rate by Kaplan-Meier analysis was 97.4% in the early group, and 95.5% in the late group (Figure 2A, $p = 0.60$). Regression analysis showed no specific factors for late mortality.

Late outcomes: hemodynamics and reintervention

There were no significant differences in hemodynamic parameters between the early and late groups (Table 2). Through echocardiographic follow-up, we found the percentage of severe PR and moderate PR was 18.9% and 69.9% respectively, after 8.0 ± 3.6 years of follow-up. Severe PR was common in early repair patients, but not significantly different from the late group (26.7 vs. 16.8%, $p = 0.292$). In our study, there were 36 patients receiving concomitant MRI examination for PR study. We found a good correlation between the PR degree by echocardiography and the PR index by MRI study, with a correlation coefficient of 0.581 ($p < 0.001$, Figure 3). None of our patients had impaired left ventricular function during follow-up, both in the early and late group (Table 2). None of those patients who underwent MRI imaging had impaired left ventricular function. Using multivariate regression analysis, we found that use of the transannular patch at repair was the major risk factor for severe PR (OR 10.1, 95% confidence interval 1.31-77.5, $p = 0.026$). The usage of a transannular patch was significantly more common in those who underwent early repair than in the late repair group (86.8% vs. 70.9%, $p = 0.029$).

The 10-year reintervention-free survival rate was 89.4% and 93.5% in early and late groups, respectively ($p = 0.314$, Figure 2B). Reintervention included transcatheter intervention in 12 patients, primarily for pulmonary or peripheral pulmonary stenosis. Multivariate Cox regression analysis on those factors noted above showed small pulmonary artery size as the independent risk factor for reintervention (OR 2.25, $p = 0.027$).

DISCUSSION

From this study cohort, we had two major findings: (1) early total repair of TOF in patients from 0 to six months of age was associated with slower postoperative recovery and a higher risk of transannular patch use, but that late outcomes, including reintervention rate, were comparable to those repaired between six months and three years of age; and (2) small pulmonary arterial size was the most important risk factor for reintervention. Therefore, we advocate direct total repair for symptomatic young infants with TOF because of the favorable long-term outcome. However, because of the higher risk of transannular patch usage, total repair surgery on an elective basis in early infant stage may be delayed until late infancy.

In the early 1990s, Sousa et al. reported that the mortality rate of primary TOF repair in patients from 0 to 6 months of age was comparable to the sum mortality rate from both staged initial palliation and later repair.[2] Since then, several studies had described favorable early results of primary repair of TOF in young infants.[9-16] In the present study, although the postoperative course, including sternum closure, ventilator support and intensive care unit stay, was relatively prolonged in the early group as compared to the late group, the total cardiopulmonary bypass time and aortic cross clamp time were similar. This implies that the surgical technique may not be the problem, but that young infant postoperative care was more complicated.[6,12,13] Nonetheless, postoperative morbidity, such as by chylothorax, severe infection, or severe cardiopulmonary compromise requiring resuscitation, was similar in both groups. Therefore, prolonged hospital stay may infer only a delayed recovery of cardiopulmonary function after operation rather than higher complication rate in the early group. With improved operative technique and postoperative care, early infant repair is no longer considered as a risk of early mortality.

In the present study, we have identified that the major risk factor for reintervention was small pulmonary

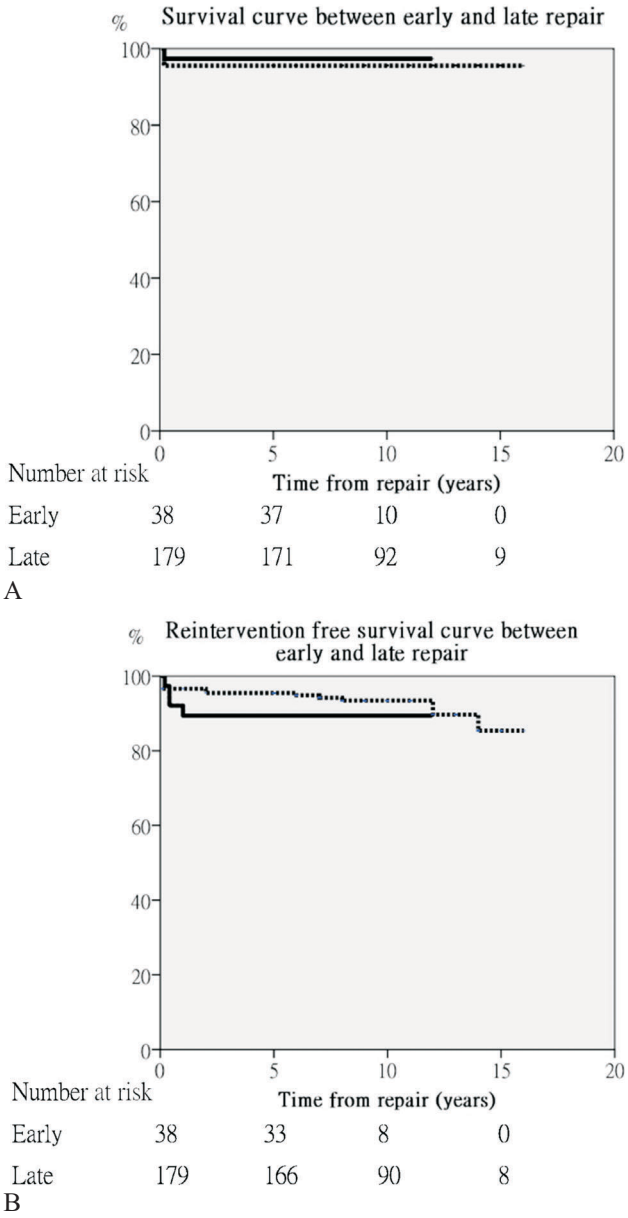

Figure 2. *(A) Kaplan-Meier survival curve and (B) reintervention-free survival curve between early and late repair group. There were no statistically significant differences when comparing these two events between early and late groups. Sold line: early repair group, dash line: late repair group.*

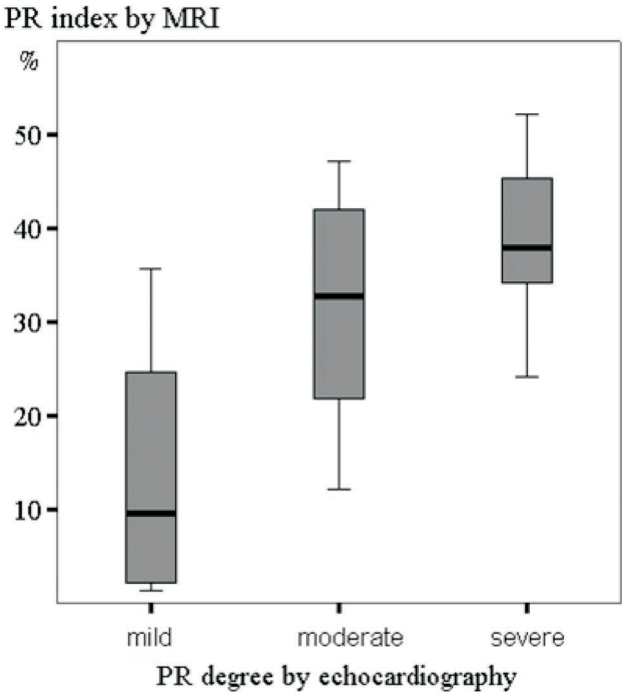

Figure 3. *Pulmonary regurgitation index by magnetic resonance imaging compared with pulmonary regurgitation grading by echocardiography. Using Pearson correlation method, we can find good a correlation between these two methods with correlation coefficient 0.581 and p value less than 0.01. The upper and lower margin of the box indicates the upper and lower quartile, and the line within the box indicates the median. Abbreviations: MRI, magnetic resonance imaging; PR, pulmonary regurgitation.*

arterial size. In addition, previous shunt operation was also found to increase late reintervention rate, which is consistent with findings in previous reports.[19,20] Given the possibility of acute shunt occlusion and late reintervention, the use of staged shunt operation has gradually been discarded, and a one stage operation is now the preferred procedure.[24] For those receiving one stage operation, the risk of late reintervention in the early group was not higher than that in the late group. Reintervention in this study mainly involved dilatation and stenting of the pulmonary or peripheral pulmonary stenosis. The 10-year reintervention free survival rate after total repair was 92.7%, which was close to results obtained in previous reports (ranged from 76.6 to 94.2%).[3,10,11] Therefore, primary total repair in symptomatic young infants for appropriate candidates, instead of shunt palliation, may be preferred to avoid shunt-related morbidity and mortality.

As just mentioned, one of the advantages of early total repair is a shorter duration of hypoxia, which may cause reduced ventricular dysfunction.[3,6] However, in our study, we did not find any patients presenting left ventricle dysfunction by echocardiography in either group. In one large scale multicenter study, approximately 21% of adult TOF patients had more than a mild degree of left ventricle dysfunction measured by M

mode method, which is significantly higher than in our study.[23] In that earlier study, the significant risk factors for left ventricle dysfunction included operation age (mostly older than 10 years of age), duration of previous shunt operation, right ventricle dysfunction, prolonged QRS duration and arrhythmia status. Such discrepancy between their study and our study could be explained by different measurement methods and a different study population. In their study, they only used the M mode method, which can be biased by paradoxical septal motion in repaired TOF patients. Besides, we did not enroll staged shunt operation patients, and most patients in the earlier study underwent surgery at an older age (even older than 10 years old) which were all regarded as high-risk groups. As none of our patients had left ventricle dysfunction, we may speculate that total TOF repair before 3 years may carry a low risk of left ventricle dysfunction.[18]

In repaired TOF subjects, moderate to severe degree pulmonary regurgitation is common and may be present in more than half of the patients.[4,25] However, the influence of early repair on the PR status in these patients is still unclear.[10,12,13,20] Two mid-term follow-up results showed a high percentage of moderate to severe PR (more than moderate PR 53.4% and severe PR 22%) in these early repair patients.[9,26] However, long-term follow-up data is limited.[14] As the PR severity is often related to transannular patch usage, and the transannular patch is more often used in the early group patients, it may explain why PR is a common late problem in early repaired patients. PR in repaired TOF patients may lead to right ventricular dilatation and subsequent ventricular arrhythmia from electromechanical interaction.[7,8,25-28] Therefore, we suggest that total repair of TOF, on an elective base, may be delayed until late infancy to avoid the necessity of transannular patch usage, and subsequent PR.

Study limitation

The follow-up duration was longer for the late group, which may underscore some differences between the two groups such as PR severity, incidence of RVOT aneurysms, and QRS duration. In addition, we used echocardiography for pulmonary regurgitation measurement, but not MRI, which is the standard of PR measurement.[27-31] In previous studies addressing PR severity assessment by echocardiography, there was still no standard measurement. The jet width, length, and localization of regurgitant flow have all been used.[32] In recent studies, they found the branch pulmonary artery diastolic flow reversal had a good correlation with PR severity by MRI, which is also shown in our study.[31,33] Finally, we had not yet introduced transcatheter pulmonary valve implantation; therefore, reintervention arising from pulmonary regurgitation was underscored as some eligible patients for pulmonary valve implantation refused additional surgery.

CONCLUSION

This study demonstrated that TOF patients repaired from 0 to 6 months of age, though accompanied by a more complicated postoperative course and higher chance of transannular patch usage, had long-term outcomes comparable to those repaired between 6 months and 3 years of age. Therefore, symptomatic young infants could receive total TOF repair early, to avoid the complications of shunt operation. But for those to be repaired on an elective basis, total repair should be delayed until the infant is over six months of age, to avoid transannular patch usage and potentially severe PR.

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