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Original Article

Outcomes of Tetralogy of Fallot repair performed after three years of age

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Abstract

Background The timing for Tetralogy of Fallot (ToF) repair is a subject of debate, however, in general repair before 3 years of age has resulted in good myocardial performance. Late repair has led to prolonged QRS duration, ventricular dysfunction in terms of myocardial performance index (MPI) and tricuspid annular plane systolic excursion (TAPSE), as well as longer intensive care unit (ICU) stays.

Objective To evaluate QRS duration, right ventricular function as measured by TAPSE, and ICU length of stay (LoS) after repair of TOF performed after three years of age.

Methods This retrospective cohort study was performed in children and adults who underwent ToF repair, with a minimum follow-up of 6 months. The TAPSE and QRS duration were evaluated during follow-up and compared between children who had the operation before vs. 3 years of age or older using Mann Whitney U and Chi-square tests.

Results We enrolled 52 subjects who underwent ToF repair from January 2007 to June 2013 (18 in the ≤3 years-old group and 34 in the >3 years-old group). Subjects' age at the time of repair ranged from 7 months to 25 years, with follow-up data at 24-30 months after discharge. Abnormalities of the right ventricle and left ventricle MPI were not significantly different between the two groups. However, we observed significant differences between the ≤3 years and >3 years groups in median ICU LoS [2 (range 1-9) days *vs.* 1.5 (range 1-46) days, respectively; (P=0.016)] and median QRS durations [118 (range 78-140) ms *vs.* 136 (range 80-190) ms, respectively; (P=0.039)]. The age at the time of repair did not increase the risk of having abnormal TAPSE (RR 0.85; 95%CI 0.26 to 2.79; P=0.798).

Conclusion Tetralogy of Fallot repair after 3 years of age appears to not increase ICU LoS or is associated with lower TAPSE, but it is associated with longer QRS duration. **[Paediatr Indones. 2016;56:176-83.]**.

Keywords: *tetralogy of Fallot; age at repair; ICU length of stay; QRS duration; TAPSE*

It has been more than five decades since the first repair of Tetralogy of Fallot (ToF) in 1955. With advances in surgical techniques and perioperative support, outcomes have substantially improved in the last 20 years. However, residual hemodynamic abnormalities are still common in many patients, with further re-intervention possibly required. Primary repair during early infancy has been advocated for the last ten years. The advantages of early repair include shorter duration of hypoxia, shorter duration of right ventricular hypertension, and potentially lower incidence of late arrhythmias. However, there are some concerns with early primary repair, including increased need for trans-annular patch (TAP) use, increased severity of pulmonary regurgitation (PR), and higher re-intervention and mortality rates.[1]

Choosing the appropriate timing for surgery may significantly decrease the risk of postoperative right ventricular failure.[2] Assessment of right ventricular function is a key point in the follow-up patients who have undergone ToF repair.[3] Late presentation after ToF repair shows conduction defects with PR and

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prolonged QRS in a high percentage of postoperative patients due to right bundle branch block (RBBB), which are inevitable because of the surgery. The function of the pulmonary and tricuspid valves are also affected due to the surgical procedure. Right ventricular (RV) function assessment shows decreased systolic function of the RV.[4] In patients < 3 years of age, repairs showed better myocardial characteristics than in older patients.[1] Tricuspid annular plane systolic excursion (TAPSE), as an echocardiographic index to assess right ventricular systolic function has been positively correlated to right ventricle ejection fraction (RVEF).[4] We aimed to compare the effect of age in outcomes after repair of ToF.

Methods

This retrospective, cohort study was performed at *The Integrated Cardiovascular Services*, Dr. Cipto Mangunkusumo Hospital in Jakarta from January 2014 to March 2014. From January 1st, 2007 until June 30rd, 2013, there were 358 patients who underwent ToF corrective surgery. Fifty-two subjects were eligible for the study. The inclusion criteria were children and adults who: (1) underwent ToF repair, (2) had a minimum follow-up of 6 months after the repair, (3) underwent all follow-up evaluations. The exclusion criteria consisted of: (1) ToF with absent pulmonary valve, or (2) ToF with Rastelli procedure. Subjects' symptoms, as well as pre-operative, peri-operative, and post-operative data were obtained from the medical records. The study was approved by Ethics Committees of the University of Indonesia Medical School and Dr. Cipto Mangunkusumo Hospital.

Two-dimensional echocardiographic examination was performed in all patients using a commercially available system (*Vivid 7*, General Electric Healthcare). Echocardiographic measurements were performed by way of the standard para-sternal (long- and short-axis) and apical (4- and 5-chambers) images. Right ventricular systolic function was estimated from TAPSE. Two-dimensional echocardiography-guided m-mode recordings from the apical four-chamber view were used to measure TAPSE with the cursor placed at the free wall of the tricuspid annulus, as previously recommended.[4] Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the lowest point of descent during ventricular systole. TAPSE findings were compared to age-adjusted *z*-score charts.[5] Subjects were classified as having RV systolic dysfunction based on abnormal TAPSE < -2SD. The RV dimensions were evaluated by measuring the RV diameter on the two-dimensional images in the four-chamber view at the end of the diastolic phase. The degree of PR was evaluated semi-quantitatively using color Doppler and continuous-wave Doppler mapping. PR was classified to be severe (retrograde diastolic flow into the branch pulmonary arteries), moderate (retrograde diastolic flow in the main PA), or mild (regurgitant jet detectable in the RV outflow tract, but no retrograde diastolic flow in the pulmonary trunk).[6] The RV myocardial performance index (Tei index) was calculated by the following formula: (duration of tricuspid regurgitation – duration of pulmonary ejection)/duration of pulmonary ejection.[4]

All patients had a 12-lead surface electrocardiogram at a speed of 25 mm/s and 1 mv/cm standardization. The maximum QRS duration in any lead was measured from the first to the last sharp vector crossing the isoelectric line. A single investigator evaluated electrocardiograms at the same time as echocardiography measurements were performed.

Variables were expressed as mean (standard deviation) or median (range min-max), and categorical variables were expressed as percentages. Bivariate analysis was performed with the Mann-Whitney U test. Categorical variables were compared by the Chi-square test and the relative risk. Values of $P<0.05$ and 95%CI were considered to be statistically significant.

Results

We reviewed the medical records of all patients who underwent repair of ToF at our Centre (*Integrated Cardiovascular Services*, Dr. Cipto Mangunkusumo Hospital) from January 2007 to June 2013 to obtain pre-, peri-, and post-operative information. A total of 52 patients were included and divided into two groups according to age at the time of the procedure: 18 in the ≤ 3 years of age group and 34 in the > 3 years of age group. Gender distribution was similar between groups, and subjects' ages at the time of the operation ranged from 7 months to 25.5 years. The median follow-up duration was 24.5 (range 6-79) months in the ≤ 3 years group and 30 (range 6-112) months in the > 3 years group. Subjects' characteristics are shown in **Table 1**. Cardiac variations were right aortic arch (7/52 subjects), patent ductus arteriosus (PDA) (5/54 subjects), bicuspid pulmonary valves (5/52 subjects), atrial septal defect (ASD) (4/52 subjects), doubly committed subarterial ventricular septal defect (DCSA VSD) (2/52 subjects), persistent left superior vena cava (2/52 subjects), major aortopulmonary collateral arteries (MAPCAs) (1/52 subjects), and vegetation at right ventricular outflow tract (RVOT) (1/52 subjects). Peri-operative complications were AV block (1/18 subjects) in the ≤ 3 years group and 1/34 subjects in the > 3 years group, difficult found BT shunt (1/34 subjects), residual VSD (1/34 subjects), and bleeding (1/34 subjects).

The short-term outcomes until discharge are shown in **Table 2**. There were no differences between two groups on duration of ventilator, chest tube used, peritoneal dialysis, inotropic agent use (dopamine, milrinone, and/or epinephrine), low cardiac output syndrome (LCOS), organ dysfunction, or arrhythmias. The postoperative complications of pleural effusion, chylothorax, systemic inflammation response syndrome (SIRS), and wound infection were not different between the two groups, but a total of 3 (1/18 and 2/34) subjects needed re-intervention for drain reinsertion, wound debridement, or chest re-opening because of bleeding.

The minimum follow-up duration was 6 months. There were no significant differences in median follow-up between the two groups. The long-term data taken at follow-up included physical examination, ECG, and echocardiography. Subjects had no complaints about their tolerance to activities. The outcome data are shown in **Table 3**. From the echocardiography examinations, most subjects showed mild to moderate free flow pulmonary regurgitation.

In comparing the ≤3 years group to the > 3 years group, we noted significantly that ToF repair

Table 1. Clinical characteristics of subjects

Characteristics	Repair ≤ 3 years (n = 18)	Repair > 3 years (n = 34)
Median age at operation (range), years	1.8 (0.7-3)	5.2 (3.1-25.5)
Mean body weight (SD), kg	9.2 (3.0)	21.0 (1.2)
Mean body height (SD), cm	79.1 (9.5)	113.8 (26.0)
Female gender, n (%)	8 (44)	16 (47)
Pre-operative data		
Cyanosis, n (%)	16 (67)	34 (100)
Mean saturation (SD), %	79.7 (21.1)	80.7 (9.5)
Cyanotic spell, n (%)	0 (0)	2 (6)
Echocardiography/catheterization parameters		
Mean PG RVOTO (SD), mmHg	74.1 (1.0)	71.2 (1.5)
Mean RPA diameter (SD), mm	9.0 (3.5)	10.6 (3.4)
Mean LPA diameter (SD), mm	8.6 (3.3)	10.8 (3.8)
Mean half size (SD, mm	7.1 (0.9)	9.8 (2.0)
Cardiac variations, n (%)	10 (56)	18 (53)
Laboratory parameters		
Mean hemoglobin level (SD), g/dL	15.2 (3.6)	17.2 (3.3)
Mean hematocrit level (SD), %	46.4 (9.5)	51.1 (13.7)
Palliative procedure, n (%)	0 (0)	7 (20,6)
Peri-operative data		
Mean cardiopulmonary bypass (SD), min	79.1 (27.5)	78.8 (28.7)
Mean aortic cross clamp (SD), min	35.6 (13.2)	34.7 (19.1)
TA-TP surgical approach, n (%)	18 (100)	34 (100)
TAP, n (%)	18 (100)	34 (100)
Complications, n (%)	1 (6)	4 (12)

PG=pressure gradient, RVOT=right ventricle outflow tract, RVOTO=right ventricle outflow tract obstruction, RPA=right pulmonary artery, LPA=left pulmonary artery, TA-TP=trans atrial–trans pulmonary, TAP=trans-annular patch

Table 2. Short-term outcomes post-TOF repair

Variables	Repair ≤ 3 years (n = 18)	Repair > 3 years (n = 34)	P value
Median ventilator use (range), days	1 (1-8)	1 (1-45)	0.149
Median chest tube use (range), days	3 (2-11)	3 (2-46)	0.620
Peritoneal dialysis, n (%)	2 (11)	0 (0)	0.050
Median inotropic agent use (range), days	2 (1-6)	2 (1-21)	0.811
LCOS, n (%)	6 (33)	10 (29)	0.773
Organ dysfunction, n (%)	0 (0)	2 (6)	0.199
Dysrhythmia , n (%)	4 (22)	10 (29)	0.317
Parameter of echocardiography			
Residual RVOTO, n (%)	8 (44)	7 (21)	0.074
Mean PG RVOT (SD), mmHg	25.5 (4.8)	29.4 (16.3)	0.232
Residual VSD, n (%)	0 (0)	1 (3)	0.417
Tricuspid regurgitation, n (%)	5 (28)	6 (18)	0.232
Normal left ventricle function, n (%)	18 (100)	34 (100)	0.134
Re-intervention/re-operation, n (%)	1 (6)	2 (6)	0.679
Median hospital stay (range), days	6 (4-17)	5 (4-55)	0.344
Complications, n (%)	11 (61)	22 (65)	0.800

LCOS=low cardiac output syndrome, RVOT=right ventricular outflow tract, RVOTO=right ventricle outflow tract obstruction, VSD=ventricle septal defect

Table 3. Long-term outcomes post-TOF repair

Variables	Repair ≤ 3 years (n = 18)	Repair > 3 years (n = 34)	P value
Median age at follow-up (range), years	3.8 (2.1-8.8)	8.2 (4.5-30.5)	0.001
Median follow-up duration (range), months	24.5 (6-79)	30 (6-112)	0.100
RBBB, n (%)	15 (83)	30 (88)	0.626
Parameter of echocardiography			
Residual pulmonary stenosis, n (%)	0 (0)	3 (9.1)	0.204
Mean PG RVOT (SD), mmHg	6.7 (2.6)	10.8 (5.2)	0.110
Mean PG pulmonary regurgitation (SD), mmHg	11.0 (4.4)	13.9 (4.1)	0.095
Mean velocity pulmonary regurgitation (SD), m/s	1.6 (0.4)	1.7 (0.3)	0.280
Residual VSD, n (%)	0 (0)	2 (6)	0.299
Mean RV end-diastolic basal diameter (SD), cm	2.7 (0.6)	3.0 (7.7)	0.235
Mean RV end-diastolic mid-cavity diameter (SD), cm	2.9 (0.8)	3.2 (0.6)	0.168
Mean RV end-diastolic area (SD), cm^2	12.9 (4.1)	16.3 (6.1)	0.077
Mean RV length (SD), cm	4.5 (0.7)	5.5 (1.4)	0.110
Mean RVMPI (SD)	0.55 (0.2)	0.46 (0.18)	0.156
Mean LVMPI (SD)	0.62 (0.20)	0.64 (0.16)	0.537
Mean LVEF (SD), %	64.9 (11.9)	63.9 (8.6)	0.317
Tricuspid regurgitation, n (%)	10 (56)	19 (56)	0.190
Median PG tricuspid regurgitation (range), mmHg-	19.0 (10.0-27.2)	26.7 (13.0-78.0)	0.015

PG=pressure gradient, SD=standard deviation, RV=right ventricle, RVOT=right ventricle outflow tract, RVMPI=right ventricle myocardial performance index, LVMPI=left ventricle myocardial performance index, LVEF=left ventricle ejection fraction, TAPSE=tricuspid annular plane systolic excursion

at ≥3 years group has shorter median ICU LoS [2 (range 1-9) days *vs.* 1.5 (range 1-46) days, respectively; (P=0.016)] but prolonged QRS duration [median 118 (range 78-140) ms *vs.* median 136 (range 80-190) ms, respectively; (P=0.039)]. However, the ToF repair at > 3 years of age did not significantly increase the risk for RV systolic dysfunction (TAPSE) [RR 0.92; 95%CI 0.26 to 2.79; P=0.798].

Discussion

From this cohort study, we had three major findings: (1) repair of ToF in patients ≤ 3 years old was associated with shorter QRS duration; (2) repair at age > 3 years old did not increase the risk of having RV systolic dysfunction as shown by TAPSE; and (3) repair of ToF in patients ≤ 3 years old was associated with slower postoperative recovery in the ICU, but hospital stays were comparable between the two groups.

Tetralogy of Fallot as part of cyanotic heart diseases, are quite common. Most subjects in this study came with cyanosis and the saturation measurements by pulse oximetry were similar in the two groups. Most subjects received propranolol. Propranolol can eliminate hypoxic spells in 80% of children with ToF, and at least delay the need for surgical repair within 13 months.[7] The modified Blaylock-Taussig shunt was done in 7/34 subjects aged >3 years. The aims of these palliative procedures were to increase oxygenated blood to the lung, reduce cyanosis, and increase volume load of the left ventricle. Common indications for palliative procedures are infants with body weight <2.5 kg, infants aged <3-4 months with recurrent hypoxic spells, abnormal coronary arteries, hypoplastic pulmonary artery, hypoplastic pulmonary annulus requiring TAP, and infants with pulmonary atresia.[8]

In another study, although the postoperative course (including sternum closure, ventilator support, and intensive care unit stay) was relatively prolonged in the early group compared to the late group, the total cardiopulmonary bypass time and aortic cross-clamp time were similar.[1] Based on our results, the similar short-term outcomes were achieved in 2 groups except for ventilator support, duration of inotropic agents were longer at ages > 3 years. Early extubation following heart surgery is associated with a shorter ICU length of stay in infants.[9,10] Nonetheless, postoperative morbidity, such as by pleural effusion, chylothorax, severe infection, or organ dysfunction were similar in both groups. This implies that the surgical technique (trans-annular patch and transatrial - transpulmonic approaches) may not be the problem, but the postoperative care of young infants may be more complicated. Modifications in perioperative care, such as surgical and anesthetic techniques, as well as postoperative sedation strategies, contributed to the decrease in the overall duration of mechanical ventilation.[11]

Electrocardiography revealed that conduction disturbances such as complete RBBB were similar between the two groups. Most RBBBs were complete. Arrhythmias are long-term complications, occurring in about 12% of patients 35 years after ToF repair. The prevalence of atrial and ventricular arrhythmias increase 5-10 years after surgery. The causes of arrhythmias are complex and multifactorial. Early repair decreases the arrhythmogenic substrates, but long-term study is needed.[12] In our study, the prevalence of arrhythmia was similar in the two age groups. Conduction disturbances after ToF repair are caused by surgical technique, pulmonary regurgitation, and loss of right ventricular restrictive physiology, leading to dilatation of the right ventricle as well as prolonged QRS duration.[13] Surgical technique was not much different between groups, as most patients underwent TA-TP with trans-annular patch. A previous study reported that the right ventriculotomy technique increased the risk of arrhythmia.[14] The change in surgical technique did not decrease the conduction disturbances. Technique differences may need to be a focus for another study.

Echocardiographic assessment on post-operative follow-up from a previous study showed the gradient on right ventricular outflow tract (RVOT) to be 26 (SD 1.9) mmHg,[15] similar to our short-term result. Residual pulmonary stenosis could be at the infundibulum, annulus, or pulmonary branch after to repair. Most of this residual RVOT was well-tolerated in infants. The RVOT gradient is dynamic and will decrease,[12] as shown in **Table 3**. In addition to the RVOT, the tricuspid valves should be examined after TOF repair. Post-repair echocardiography commonly shows tricuspid regurgitation (TR). The mechanisms of TR after surgery are multifactorial, such as the effect of the surgery itself, ventricle-remodeling post-operatively caused by annular dilatation, and decreased tricuspid chordae strength. Tricuspid regurgitation is usually accompanied by pulmonary regurgitation, prolonged QRS duration, and dilated right ventricle.[12]

In ToF repair subjects, a moderate to severe degree of pulmonary regurgitation is common and may be present in more than half of patients. This regurgitation commonly occurred after repair of ToF, consistent with other reports.[16,17] The PR severity is often related to trans-annular patch usage, valvulotomy, valvectomy, or other procedures that disturb the valves. These PR outcomes have very important long-term implications, may leading RV dilatation and subsequent ventricular arrhythmia from electromechanical interaction. Pulmonal regurgitation is defined to be present if the color jet Doppler shows a wide open or free pulmonary regurgitation with laminar flow and short velocity.[18] However, we observed similar gradients between the two groups, with free mild to moderate pulmonary regurgitation by color Doppler.

Pulmonary regurgitation causes right ventricular dilatation and ventricular dysfunction, decreased exercise performance, and increased risk of arrhythmia in the atrium and ventricle. Ventricular dilatations are shown from the area, basal diameter, mid-cavity diameter, and the length of right ventricle. These dimensions are difficult to interpret and especially challenging by echocardiography in a retrosternal position, as the highly variable geometry does not conform with standard geometry, and there are no normal ranges in children. Another study showed predictors of right ventricle dilation to be QRS duration > 160 ms, significant pulmonary regurgitation, and a high gradient between the right ventricle and pulmonary artery.[19] Compared with an adult range, we found normal values of right ventricle dimension,[20] revealing that the right ventricle may be dilated. In addition, echocardiography showed mild dilatation with variation on QRS duration and mild to moderate pulmonary regurgitation.

During the past decade, different echocardiographic techniques have been developed that allow a more detailed analysis of cardiac function. Right and left ventricle myocardial performance index (RV/LV-MPI) and left ventricle ejection fraction (LV EF) are important values to examine ventricular function after surgery. In general, the MPI examination reflects systolic and diastolic function as the global ventricular function. Complex ventricular geometry, especially in the right ventricle, makes it difficult to use 2D or m-mode echocardiography to diagnose ventricular dysfunction. Abnormalities of MPI are found in all patients after ToF repair and can be an early parameter of ventricular dysfunction. There is no correlation between RVMPI and LVMPI, but these parameters can show us if there is any valve insufficiency after repair.[21,22] RVMPI 0.3 has a 10% sensitivity and 74% specificity to predict RVEF < 35%.[3] Similarly, we found that all subjects had abnormal MPI values, but there were no significant differences between the two groups.

One predictor of ICU mortality is ICU length of stay. Intensive care has become a standard component of postoperative care for most patients who undergo cardiothoracic procedures.[10] The median ICU LoS was significantly longer in the $\leq$ 3 years group. We identified age as an independent predictor of length of ICU stay. Differences in centers, peri-operative care, anesthesia strategies, and post-operative sedation may lead to decreased days of ventilation and ICU LoS.[23] Other studies also found that patients with younger age had longer ICU stays compered to older patients.[24,15] The ICU LoS between subjects aged < 6 months and > 6 months - 3 years were significantly different because of age and duration of ventilation.[1] Another factor was the ratio between patient and nurse of about 1:1 and complications after surgery.[10] In our study, days of ventilation, inotropic duration, and post-surgery complications were not significantly different between the two groups, and the different ICU LoS due to age of operation or others reasons that were not evaluated in this study.

Long-term outcomes evaluated by ECG showed prolonged QRS duration. This result was significantly different between the two groups, with longer QRS duration in the > 3 years group than in the ≤ 3 years group. Prolonged QRS duration associated with ventricle arrhythmia. Causes of abnormal conduction may include anatomic modification or injury after surgery, ventricular dilatation and stretching, or abnormal fibrous tissue at the right or left ventricles.[25] Prolonged QRS duration in the > 3 years group was consistent with results with another study. The ECG and Holter studies showed 91% of subjects with RBBB and mean QRS duration was 137 (SD 29) ms.[26] Another study evaluated ECG parameters in patients aged 6-18 years who were operated on at the ages of 4-36 (median 7) months. They found 78% of subjects with RBBB, and their mean QRS duration was 132 (SD 26) ms.[27] These results suggest that prolonged QRS duration may be influenced of by age at the time of operation.

Echocardiography has become the most important non-invasive tool for follow-up after surgery in children. Echocardiography findings showed abnormalities of right ventricular systolic function (TAPSE) that did not correlate with age at the time of operation. Systolic and diastolic dysfunctions are common after ToF repair. Pre-operative hypoxia and hypertrophy, intra-operative myocardial injury, and pulmonary regurgitation after repair are the ethiopathogenesis of right ventricle dysfunction.[21] RBBB causes ventricular dyssynchrony, then ventricular dysfunction.[28] TAPSE, obtained in m-mode, reflects the base to apex shortening of the RV in systole. TAPSE is especially useful for the RV, because these measurements have the potential to assess ventricular contractile function independently of the shape of the ventricle.[4] Hence, this study showed 30% of subjects to have abnormal systolic function (mean TAPSE > 1.4 cm). This result may have been caused by diastolic dysfunction that occurred earlier then systolic dysfunction. Myocardial performance index values may allow early diagnosis of right ventricle diastolic dysfunction.[21]

A limitation of this study was the small number of subjects. Patient databases in our institution contained incomplete addresses and phone numbers that we needed for follow-up evaluation after ToF repair. In addition, the time between surgery and follow-up was too short, and the modality for follow-up examination was not the gold standard for right ventricle evaluations. Further study is needed to differentiate long-term outcomes in younger patients who undergo corrective ToF surgery. In conclusion ToF repair after 3 years of age appears to not increase ICU LoS or is associated with lower TAPSE, but it is associated with longer QRS duration.

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Conflict of interest

None declared.

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