Association of Right Ventricular–to–Left Ventricular Diameter Ratio at End-Systole With Outcomes in Children Who Underwent Repair of Tetralogy of Fallot

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Abstract

RATIONALE: Tetralogy of Fallot (TOF) is a right-sided dominant cardiac lesion with a stenotic right ventricular (RV) outflow tract and hypertrophied RV, which could result in septal shift and RV dilation. This study evaluated the RV/left ventricular (LV) diameter ratio at end-systole in association with clinical outcomes in children who underwent repair of TOF. The main aim of this study was to determine the association of RV/LV diameter ratio at end-systole with the outcomes of TOF repair. The specific objectives were to determine whether the preoperative (demographic and echocardiographic data) parameters were associated with the clinical outcomes of TOF repair and to determine whether the intraoperative (cardiopulmonary bypass time and aortic cross-clamp time) parameters were associated with the clinical outcomes of TOF repair.

METHODOLOGY: This prospective cohort single-center study enrolled 112 TOF patients aged 1 to 18 years admitted for surgical repair. The RV/LV ratio was measured using echocardiography preoperatively, indexed to patient's weight and body surface area, and associated with its postoperative cardiac complications using logistic regression analysis.

RESULTS: Cumulative incidence of cardiopulmonary complications was at 28.7% (32 of 112). Reperfusion lung injury had the most cases (11.6%), followed by low cardiac output syndrome (9.8%) and postpericardiotomy syndrome (5.4%). Both RV and LV diameters, indexed to patient's weight and body surface area, ($P = 0.0051$, $P < 0.001$), RV/LV ratio ($P < 0.001$), and LV end-diastolic size with z scores ($P < 0.001$), showed statistically significant results. Increase in RV/LV ratio is associated with adverse postoperative clinical outcomes in pediatric patients who underwent repair of TOF ($P < 0.001$). Significant preoperative parameter showed that stunting is associated with complications postoperatively ($P = 0.017$), whereas for the intraoperative parameters, prolonged cardiopulmonary bypass time and aortic cross-clamp time were also associated with postoperative complications.

CONCLUSION: The increased value of RV/LV end-systolic diameter ratio at 1.63 (±0.256), which incorporates both pathologic septal shift and RV dilation, is associated with higher incidence of postoperative cardiac complications among patients with tetralogy of Fallot.

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease (CHD). A 2002 meta-analysis of the incidence of CHD, which included 41 studies pertaining to TOF, suggested that the best estimate of incidence would be 577 cases of TOF per million live births.[1] After surgery for TOF, patients may demonstrate progressive pulmonary regurgitation (PR), right ventricular (RV) enlargement, RV and left ventricular (LV) dysfunction, and exercise intolerance.[2] Studies have shown that PR or RV enlargement per se may predict impaired clinical status[1,3] in patients who underwent TOF repair. The effect of RV dilation on the interventricular septum leads to a septal shift toward the left ventricle in systole. This abnormal interventricular septal shift has been previously described in patients with TOF repair with ventricular dysfunction. In those with severe progression of PR, progressive RV dilation and dysfunction result in RV failure and death.[4]

Transthoracic echocardiography is a noninvasive method used to evaluate pulmonary hemodynamics and right-heart function.[5] It is cost-effective, accessible, and safe. Several echocardiographic indices have been described to postoperative recovery in children undergoing TOF surgery and its association with clinical outcomes.[6]

Locally in our institution, the surgical outcomes for the year 2017 showed 96.6% survival rate from 15 mortalities in 435 cases of TOF who underwent surgery. This study evaluated a new echocardiographic index, the RV-to-LV diameter ratio at end-systole (RV/LV ratio), as to the feasibility of this index and association between RV/LV ratio and clinical outcomes in children who underwent repair of TOF.

METHODS

This was a prospective cohort study conducted at a tertiary cardiovascular center from the period July 2017 to April 2018. Inclusion criteria were as follows: all pediatric patients aged 1 to 18 years admitted with TOF for total repair. Exclusion criteria were as follows: use of conduit in the repair of TOF, with previous surgery or other palliative procedure.

Study Maneuver

A prospective study was done on pediatric patients who underwent repair of TOF from July 2017 to April 2018. Data gathered were obtained from admitted pediatric patients scheduled for total repair of TOF. An informed consent or verbal assent was obtained from the participants (Appendices A–C), and this study was approved by the institutional ethics review board of our institution.

Patients were classified into two groups: those with postoperative cardiac complications and those without complications. A data collection form (Appendix D) was used in gathering the data. Information gathered included sample's baseline characteristics such as age, sex, weight, height, and body surface area (BSA). The age was grouped according to the stages in pediatric development: toddler stage (aged 1–3 years), preschool stage (aged >3–6 years), school-age stage (aged >6–12 years), and adolescent stage (>12 years).[7] Wasting refers to the low weight for height, where a child is thin for his/her height but not necessarily short. Stunting refers to the low height for age, where a child is short for his/her age but not necessarily thin. The World Health Organization database on child growth and malnutrition uses a z score cutoff point of 0 to −1, classifying under no to mildly wasting and stunting; z scores with <−2 were used to classify low weight for height and low height for age as moderate wasting and stunting, whereas <−3 signified severe wasting and stunting.[8] The type of operation done was also noted in the study such as infundibulectomy, transannular patching, RV outflow tract augmentation, and main pulmonary artery patching performed on the repair. Intraoperative parameters included cardiopulmonary bypass (CPB) time, aortic cross-clamp (AXC) time, and encountered intraoperative complications.

Echocardiography was performed in all pediatric patients with TOF admitted for total repair using an ACUSON SC2000 or iE33 (Philips Ultrasound, Bothell, Washington) ultrasound machine. Echocardiograms were acquired using a standard protocol with suitably sized transducers for patient size and age. This was performed in the resting and calm state, and all patients underwent routine echocardiography with simultaneous electrocardiographic monitoring. Right ventricle/left ventricle (RV/LV) ratios were measured from the parasternal short-axis two-dimensional view at the level of the papillary muscles with the RV free wall in view. Right ventricular and LV diameters were measured from the endocardial to endocardial surfaces at end-systole (Figure 1) and were indexed according to each patient's body weight and BSA. The RV/LV ratios were then calculated.

The LV end-diastolic diameter by M-mode was also noted, indexed according to patient's weight and BSA for each corresponding z score. The LV ejection fraction by M-mode, RV ejection fraction by fractional area change, and right and

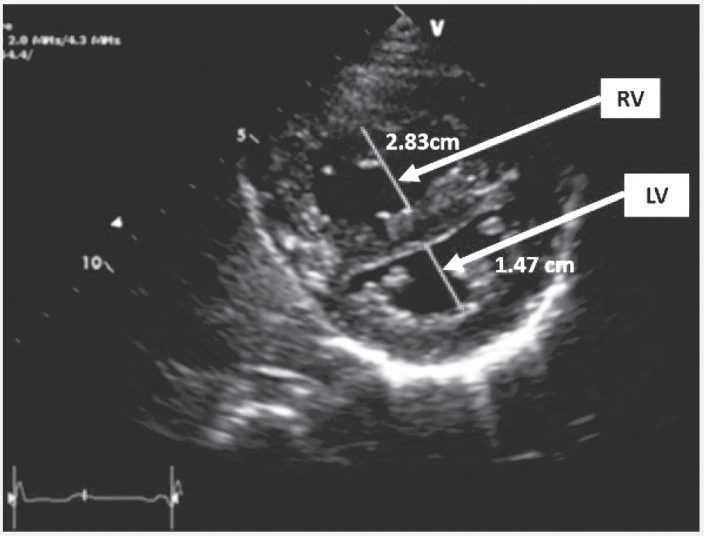

Figure 1. Parasternal short-axis view of the right and left ventricles and right ventricle/left ventricle ratio were derived from right ventricular and left ventricular diameter at end-systole

left pulmonary artery sizes with corresponding z scores and McGoon ratio were also measured. The CPB time and AXC time in minutes were also obtained.

Postoperative data were the in-hospital cardiac complications encountered such as low cardiac output syndrome, ventricular dysfunction, significant pericardial effusion with need for drainage, reperfusion lung injury, transient heart block, transient rhythm abnormalities, insertion of permanent pacemaker for complete heart block, and cardiopulmonary resuscitation. A favorable outcome was defined as a patient discharged with no cardiac complications as defined previously.

Statistical Analysis

A minimum of 108 subjects are required for this study based on 95% confidence interval, a 0.53 SD[8] of RV/LV ratio with a desired half width of confidence interval of 10%, as noted from the reference article by Śpiewak et al.[9] From this study, a total of 155 pediatric TOF patients were admitted at the Philippine Heart Center for total repair from July 2017 to April 2018. From these subjects, only 112 patients were eligible for the study (Figure 2).

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and interquartile range for ordinal variables, and mean and SD for interval/ratio variables. Independent-sample *t* test, Mann-Whitney *U* test, and Fisher exact/χ^2 test were used to determine the difference of mean, median, and frequency, respectively, between with and without complications. Intraclass correlation coefficients (ICCs) for reliability research[10] was used to determine the variability between and within observers in terms of RV/LV ratio. Ten subjects were randomly selected, and RV/LV measurements were performed by two echocardiography technicians as well as the author to determine the ICC for reliability research. Missing variables will neither be replaced nor estimated. Null hypothesis was rejected at the 0.05 α level of significance. STATA 13.1 (StataCorp, College Station, Texas) was used for data analysis.

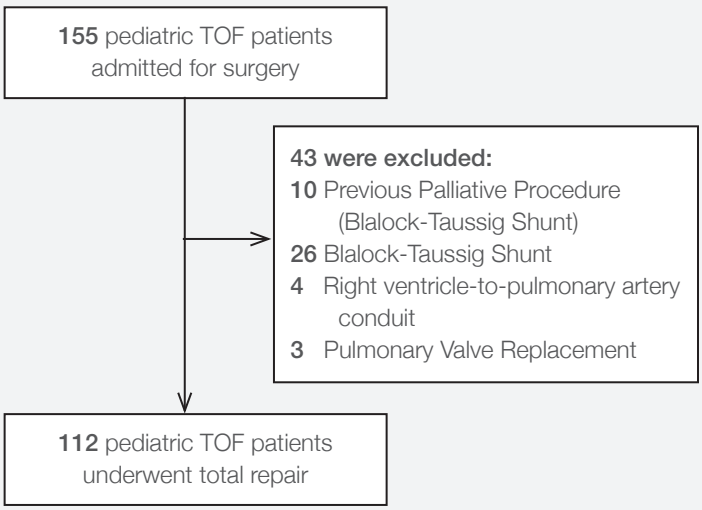

FIGURE 2. Patient flow

RESULTS

A total of 112 pediatric patients who underwent TOF repair from July 2017 to April 2018 were included in this study. Patients older than 1 to 3 years (toddlerhood) were noted to have higher complications (53.12%) as compared with those aged 3 to 6 years (preschool period); however, age-group period was not significant ($P = 0.414$). There was male preponderance on both patients with and those without complications, 18% and 52%, respectively. In patients with complications, the mean weight was at 14.4 (±5.22) kg, whereas in those without complications, the weight was at 16.13 (±7.49) kg. The mean height (in centimeters) among patients with complications was at 97.19 (±12.60) cm, and that among those without complications was 99.92 (±18.53) cm. The stunting category was statistically significant ($P = 0.017$). No significant differences were noted on BSA ($P = 0.287$) and type of TOF repair done (Table 1).

The mean CPB time was at 225 ± 63.12 minutes, and AXC time at 161.78 ± 49.83 minutes was longer among patients with complications ($P < 0.001$).

The cumulative incidence of cardiopulmonary complications among pediatric patients who underwent TOF repair in our institution was at 28.7% (32 of 112), whereas 71.42% (80 of 112) did not have any complications. Table 2 shows the list of postoperative cardiopulmonary complications encountered. Reperfusion lung injury occurred in 11.6% (13 of 112), followed by low cardiac output syndrome (9.8% [11 of 112]) and postpericardiotomy syndrome (5.4% [6 of 112]).

The overall mortality among all patients was 8% (9 of 112). Low cardiac output syndrome had the highest incidence of mortality (5 of 11) followed by reperfusion lung injury (4 of 13).

Table 3 shows the preoperative echocardiographic parameters. The RV and LV diameters, as well as the LV end-diastolic (LVED) size, were indexed to patient's weight and BSA. Both RV and LV diameters ($P = 0.0051$, $P = 0.00001$), RV/LV ratio ($P = 0.00001$), and LVED size and z score ($P = 0.00001$) showed statistically significant results. However, the LV ejection fraction ($P = 0.255$), RV ejection fraction ($P = 0.971$), right pulmonary artery size ($P = 0.06$), z score ($P = 0.39$), left pulmonary artery size ($P = 0.922$), z score ($P = 0.347$), and McGoon ratio ($P = 0.554$) did not differ significantly.

Linear regression (Table 4) shows that increase in RV/LV ratio is associated with adverse postoperative clinical outcomes in pediatric patients who underwent repair of TOF ($P < 0.001$).

The RV/LV ratio measured in the parasternal short-axis views at end-systole was highly reproducible with good to excellent reliability between interobserver measurements. The ICCs for reliability research showed statistically significant results ($P < 0.001$). The ICC estimates and their 95% confidence intervals were calculated using SPSS statistical package version 13 (SPSS Inc, Chicago, Illinois) based on a mean rating ($k = 3$), absolute agreement, two-way mixed-effects model.

Table 1. Demographic and Clinical Characteristics of the Patients

	With Complications	No Complications	*P*
	Frequency (%); Mean ± SD		
Age	n = 32 (28.57%); 4.76 (±3.54)	n = 80 (71.43%); 4.19 (±2.83)	0.414
>1–3 y	17 (53.12%)	36 (45%)	
>3–6 y	10 (31.25%)	20 (25%)	
>6–12 y	5 (15.62%)	22 (27.5%)	
>12 y	0	2 (2.5%)	
Sex			0.257
Male	18 (56.25%)	52 (65%)	
Female	14 (43.75%)	28 (35%)	
Wasting weight, kg	14.4 (±5.22)	16.13 (±7.49)	0.237
None to mildly wasted	16 (50%)	42 (52.5%)	
Moderately wasted	6 (18.75%)	24 (30%)	0.22
Severely wasted	10 (31.25%)	14 (17.5%)	
Stunting height, cm	97.19 (±12.6)	99.92 (±18.53)	0.445
None to mildly stunted	11 (34.43%)	26 (81.25%)	
Moderately stunted	11 (34.43%)	41 (51.25%)	0.017*
Severely stunted	10 (31.25%)	13 (16.25%)	
BSA, kg/m^2	0.615 (±0.146)	0.658 (±0.207)	0.287
Cardiopulmonary bypass time, min	225 (±63.12)	181.26 (±47.13)	<0.01*
Aortic cross-clamp time, min	161.78 (±49.83)	118.26 (±31.95)	<0.01*
Type of TOF repair done			
Infundibulectomy	30 (93.75%)	74 (92.50%)	0.588
Ventriculotomy	4 (12.5%)	6 (7.5%)	0.307
Transannular patch	20 (62.5%)	42 (52.5%)	0.227
RVOT augmentation	10 (31.25%)	16 (20%)	0.152
MPA patch augmentation	9 (28.13%)	16 (20%)	0.245
Others	5 (15.63%)	11 (13.75%)	0.504

BSA=body surface area; MPA=main pulmonary artery; RVOT=RV outflow tract; TOF=tetralogy of Fallot.

Table 2. Frequency and Percentage of All Postoperative Cardiopulmonary Complications in Pediatric Patients Who Underwent TOF Repair, Philippine Heart Center, July 2017–March 2018

Cardiopulmonary Complications	n = 112	%
Reperfusion lung injury	13	11.6
Low cardiac output syndrome	11	9.8
Postpericardiotomy syndrome	6	5.4
Supraventricular tachycardia	2	1.8
Transient complete heart block	1	0.83
Transient junctional ectopic tachycardia	1	0.83

TOF=tetralogy of Fallot.

DISCUSSION

In this study, RV/LV ratio was significantly higher in patients with cardiac complications compared with those with lower RV/LV ratios (1.63 [±0.256] vs 1.17 [±0.149]). The RV/LV ratios associated well with the postoperative cardiac complications, and increased RV/LV ratio was associated with adverse postoperative clinical events (P = 0.00001), thus signifying that this index can be used in the clinical setting as a sound noninvasive measurement to evaluate the severity of TOF and adverse postoperative clinical outcomes. As the RV/LV ratio increased, the risk for an adverse clinical event also increased in this study. As shown in Table 3, mean RV/LV ratio of more than 1.5 is more associated with cardiac complications. Thus, the echocardiographic study before a patient undergoes surgical repair of TOF becomes important in the patient's postoperative management and prognosis.

Table 3. Preoperative Echocardiographic Parameters of the Patients

	With Complications	No Complications	*P*
	Frequency (%); Mean ± SD		
RV diameter, cm	3.14 (±0.604)	2.77 (±0.628)	0.0051*
LV diameter, cm	1.93 (±0.33)	2.38 (±0.474)	<0.001*
RV/LV ratio, cm	1.63 (±0.256)	1.17 (±0.149)	<0.001*
LVED, cm	2.037 (±0.362)	2.43 (±0.501)	<0.001*
Below normal values	25 (78.13%)	37 (46.25%)	
Within normal values	7 (21.88%)	43 (53.75%)	
LVED (z score)			<0.001*
−6	1 (3.13%)	0	
−5	8 (25%)	0	
−4	8 (25%)	8 (10%)	
−3	7 (21.88%)	22 (27.5%)	
−2	2 (6.25%)	24 (30%)	
−1	1 (3.13%)	18 (22.5%)	
0	5 (15.63%)	6 (7.5%)	
1	0	2 (2.5%)	
LV ejection fraction, %	72.43 (±8.55)	74.53 (±9.27)	0.255
RV ejection fraction, %	49.46 (±8.11)	49.53 (±9.55)	0.971
Pulmonary artery sizes			
RPA, z score (cm)	0.71 (±0.13)	0.76 (±0.158)	
≤−2	14 (43.75%)	31 (38.75%)	0.063
>−2	18 (56.25%)	49 (61.25%)	0.390
LPA, z score (cm)	0.747 (±0.17)	0.75 (±0.176)	
≤−2	5 (15.63%)	17 (21.25%)	0.922
>−2	27 (84.38%)	63 (78.75%)	0.347
McGoon ratio	1.734 (±0.406)	1.774 (±0.282)	0.554

RPA=right pulmonary artery; LPA=left pulmonary artery; LV=left ventricular; LVED=left ventricular end-diastolic; RV=right ventricular.

Table 4. Regression Analysis of RV/LV Ratio Contributing to Postoperative Cardiac Complications, Analysis of 112 Pediatric Patients, July 2017–March 2018

Logistic Regression Log Likelihood = −32.540341				No. Observed = 112 LR χ^2_1 = 68.93 Prob > χ^2 = 0.0000 Pseudo R^2 = 0.5144		
Complications	Odds Ratio	Standard Error	z	*P* > |z|	95% Confidence Interval	
RV/LV ratio	9019.926	15,368.64	5.35–5.67	0.000	319.8005	254,405.7
_cons	1.68×10^{-6}	3.94×10^{-6}		0.000	1.7×10^{-8}	0.0001661

LR=likelihood ratio; LV=left ventricular; RV=right ventricular.

The RV/LV ratio was derived to combine RV size with septal shift secondary to elevated RV pressure from a stenotic RV outflow tract. The RV pressure overload then causes RV hypertrophy and dilation.[11] Coincident with RV dilation, there is a shift in the interventricular septum toward the left side causing changes in the LV geometry and decreased LVED. In this study, a reduced size in LVED, that is, below normal values, showed more patients with postoperative complications (25 of 32 [78.13%]; $P < 0.001$). As the LVED gets smaller in size (Table 4), more patients with cardiac complications were encountered. With LVED z scores less than −2, there were 24 patients out of 32 (75%) with complications ($P < 0.001$). Right ventricular dilation results in both diastolic and systolic dysfunction, which is associated with poor prognosis and increased mortality.[12] Davlouros et al[9,13] demonstrated that the RV end-systolic area rises significantly in nonsurvivors and reflects poor

RV systolic performance. As the right ventricle dilates, the geometry of the right ventricle is changed, and the inability of the right ventricle to adapt to increased afterload results in RV dysfunction.[9] Increases in RV pressure and RV dilation result in higher transseptal pressures, which result in abnormal septal shift. Abnormal septal motion was first described on echocardiography by Popp et al[14] in 1969. Subsequent studies have demonstrated interventricular septal shift in patients with surgically repaired TOF.[2,6] This results in interventricular septum bowing into the left ventricle, resulting in the characteristic "D-shaped" left ventricle. Right ventricular size has been shown to be a strong predictor of outcomes, with its effects on the left ventricle.[9,11–13] Our analysis demonstrates that increasing RV/LV ratio is associated with an increasing hazard for a clinical event, suggesting the prognostic value of this measurement (Table 3).

From previous studies in cases with RV remodeling, RV/LV ratio at end-systole was greatest because of increased RV afterload.[15] This was consistent in the leftward displacement and flattening of the interventricular septum, with increase in RV afterload and shift in the interventricular septum greatest at end-systole. Ryan et al[16] found that LV deformation of the interventricular septum was greatest at end-systole in patients with RV pressure overload. Interventricular septal shift impairs LV diastolic filling, which results in decreased LV function, and the RV/LV ratio measured in end-systole captured both RV dilation and the adverse ventricular–ventricular interaction.[17] The low cardiac output syndrome postoperatively cannot be solely defined as a result of the diminished LV size preoperatively as this condition could be multifactorial in the presence of prolonged bypass and ischemic time during open heart surgery or as a consequence from reperfusion lung injury.

High morbidity and mortality rates after prolonged CPB and AXC time in open heart surgery have been previously reported. Long procedures are often associated with complex surgical treatments, resulting in increased bypass and ischemic times, leading to upsurge in inflammatory responses.[18,19] One study showed that CPB should be kept as short as possible to prevent acute respiratory distress syndrome.[20] In patients who had reperfusion lung injury, a potential explanation could be that hydrostatic edema occurred as a consequence of overperfusion from a previously restricted vascular bed as this was first described by Landolt et al.[21]

In this study, stunting was statistically significant in patients who had postoperative complications. Malnutrition can be explained by several factors, including the distribution pattern of cardiac lesions, the presence of severe complications of CHD, and prolonged absence of surgical CHD correction. The prolonged duration of not surgically corrected CHD is more likely to be associated with chronic hypoxemia, chronic heart failure, and suboptimal dietary intake.[22]

RECOMMENDATIONS

This study focused on the RV/LV ratio in pediatric patients who underwent repair of TOF in association with its cardiac complications; the following are recommended:

(1) a validation of the RV/LV ratio limit to predict outcomes and
(2) a serial investigation of RV/LV ratio postoperatively.

This study showed that RV/LV ratio preoperatively were used to gauge clinical outcomes and to use this as an index to follow up patients over time.

LIMITATIONS

The limitations to this study are as follows:

(1) This study represents a single-institution experience that may not be applicable to other centers.
(2) Limited use of the RV/LV ratio in TOF patients as those who underwent palliation or had previous surgeries were excluded in this study.
(3) This study provided a comprehensive overview of postoperative cardiac complications, allowing more focused evaluation in future studies.

CONCLUSION

The increased value of RV/LV end-systolic diameter ratio at 1.63 (±0.256), which incorporates both pathologic septal shift and RV dilation, is associated with higher incidence of postoperative cardiac complications among patients with TOF.

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