

The Association of Postoperative Right Ventricular Restrictive Physiology With Right Ventricular Systolic Dysfunction Among Pediatric Patients With Tetralogy of Fallot

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Background --- The increase in survival rate of Tetralogy of Fallot (TOF) patients lead to an increase in the number of post-op patients requiring critical follow-up. Abnormal Right Ventricular (RV) physiology is a significant long-term problem for these patients. Some studies show that RV restrictive physiology protects the development of RV dysfunction. This study aims to determine the association of Right Ventricular Restrictive Physiology with Right Ventricular Systolic Dysfunction in these patients.

Methods --- We conducted a cross-sectional study involving 69 post-op TOF patients at Philippine Heart Center from June 2012 to December 2012. We determined the following: age and sex, weight, body surface area, history and frequency of phlebotomy, and prior surgical procedure (Blalock Taussig shunt). We determined the presence of RV restrictive physiology based on antegrade pulmonary flow, TV dt, IVRT, E/A ratio and hepatic flow reversal. We also determined RV systolic dysfunction using the Tei index, TAPSE, resting QRS duration as well as the presence of arrhythmia. The results were analyzed using the Mann-Whitney, Fishers Exact Probability and Chi Square Test.

Results --- We enrolled 26 subjects with restrictive physiology, majority of which belonged to the 7-12 year old age group and 43 with non-restrictive physiology, with majority belonging to the 13-19 year old age group. Most of the subjects were males. Among those who underwent trans-annular patching (TAP), nine (13%) had restrictive physiology post-op whereas six (9%) had non-restrictive physiology. Among those who had non-TAP surgery, majority had nonrestrictive physiology. The timing of the appearance of RV restrictive physiology was noted between 1-2 years in majority of the subjects. RV dysfunction was noted in 11 out of 26 subjects with restrictive physiology, whereas, RV dysfunction was present in 29 out of 43 subjects with non-restrictive physiology (p=0.042).

Conclusions --- RV restrictive physiology occurs postoperatively in TOF patients who underwent total correction. TAP favors the development of RV restrictive physiology post-op versus non-restrictive physiology. RV systolic dysfunction is more evident in patients with non-restrictive physiology compared to those with restrictive physiology. The presence of RV restrictive physiology could offer a protective effect against RV systolic dysfunction. *Phil Heart Center J 2013;17(1):28-33.*

Key Words: Tetralogy of Fallot ■ RV Restrictive Physiology ■ Right Ventricular Systolic Dysfunction
■ Trans-annular patching

Tetralogy of Fallot (TOF) is the most common cyanotic congenital cardiac malformation. It occurs in three to six infants for every 10,000 livebirths.¹ In the Philippine Pediatric Society Registry from January 2007 to December 2011, there are 1603 admitted cases of TOF comprising 0.1% of the total pediatric admission nationwide for the last 5 years. At the

Philippine Heart Center, around 52 and 59 pediatric patients underwent TOF correction in 2010 and 2011 respectively. In the last decade, improvement in surgical technique and post-operative management resulted to decreased morbidity and mortality of TOF patients. With the increase in survival rate, there is an exponential increase of post-op TOF patient

requiring critical follow-up in the outpatient clinics.

Abnormal Right Ventricular (RV) physiology is a significant long-term problem for TOF patients. Pulmonary regurgitation is one of the major problems seen after corrective surgery for TOF, thus surgeons apply various surgical techniques to prevent or reduce this complication.² Chronic pulmonary regurgitation has been associated with RV dysfunction, exercise intolerance and ventricular dysrhythmias. Gatzoulis et al. describes restrictive RV dysfunction in 57% of patients.¹ Norgard et al however stated that the presence of RV restrictive physiology protects the development of pulmonary regurgitation in the long term postoperative period and that the presence of early restrictive RV physiology predicts the occurrence of RV dysfunction later in life.³

METHODOLOGY

This is a cross-sectional study done at the Philippine Heart Center from June 2012 to December 2012. The study was approved by the Institutional Ethics Review Board and consent/assent was obtained from the participants and their parents/guardians. We enrolled from the Out Patient Department consecutive TOF subjects, aged 1 to 18 years old at the time of surgery and at least one year had passed from the corrective surgery. Excluded were those subjects with residual shunts, with other associated congenital heart disease and with residual Right Ventricular Outflow Tract (RVOT) gradient >40mmHg. We noted the baseline characteristics of the patients in terms of age and sex, weight, body surface area, history and frequency of phlebotomy, prior surgical procedure (Blalock Taussig shunt).

Determination on RV Restrictive Physiology. We determined the RV diastolic function by 2d-Echocardiogram with Color Flow Doppler Studies (2D-CFDS) using the Phillips IE33 machine with the S8-/S5-1 transducer depending on the patient's weight. We determined the presence of an antegrade pulmonary arterial flow in late diastole and a residual RVOT gradient using the parasternal short axis view focusing on the pulmonary valve. We determined the Tricuspid E and A velocity and the

E/A ratio. We determined the Tricuspid Valve (TV) deceleration time and Isovolumic Relaxation Time (IVRT) using the doppler examination via the 4-chamber view. We used the subcostal approach for determining the presence of hepatic diastolic flow reversal. We classified the subjects as having restrictive or nonrestrictive physiology depending on the echocardiographic findings. The mean of 3 measurements was obtained. We reviewed the charts to check the operative procedure of the patients.

Determination of RV Systolic dysfunction. After we classified the subjects as either having restrictive or non-restrictive physiology, we determined the presence or absence of RV dysfunction. The Tei index was taken using the Doppler technique in the four chamber view at the tips of the tricuspid valve. We encountered technical difficulty in acquiring the Tei index using the IVRT and Isovolumic Contraction Time (IVCT) in the RV. Tricuspid Annular Plane Systolic Excursion (TAPSE) was taken also from the apical 4 chamber view. It was acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole. Pulmonary regurgitation was taken using color flow doppler using the parasternal short axis view with the tip of the cursor just below the tip of the pulmonary valve. The mean of 3 measurements was obtained. Heart rate was measured using the R to R interval of a long lead II ECG. QRS duration was determined and identification of ventricular arrhythmia was checked. Predictors of postoperative RV dysfunction are the presence of any of the following: (1) TEI index of >0.4, (2) TAPSE of 16mm, (3) presence of significant PR, (4) resting QRS duration of >180msecs and presence of ventricular arrhythmia.

Sample Size and Statistical Analysis. The computed sample size is 91 based on 95% confidence level, 20% relative error and assumed restrictive physiology rate of 38% as presented in the paper of Gunnar Norgard about "The Relationship Between Type of Outflow Tract Repair and Postoperative Right Ventricular Diastolic Physiology in Tetralogy of Fallot" in 1996.³

The results were then tabulated and analyzed using the Chi Square Test. However, multiple/

logistic regression was applied to the data if there were probable confounders. A p value of ≤ 0.05 was considered significant.

Definition of Terms

1. *Restrictive RV physiology* – is a state of the RV characterized by diminished myocardial compliance⁴ evident by antegrade pulmonary arterial flow in late diastole,^{5,6} shortened tricuspid valve deceleration time ($<150\text{m/sec}$)⁸ and isovolumetric relaxation time (IVRT $<60\text{ms}$),⁹ decreased tricuspid peak A velocity, increased E/A velocity ratio (>2.1) and venous/hepatic diastolic flow reversal.⁷

2. *Right Ventricular Systolic Dysfunction* – physiologic state of the RV postoperatively characterized by the presence of a) Tei index >0.4 b) TAPSE $<16\text{mm}$ ⁸c) pulmonary regurgitation, d) resting QRS duration of >180 msec,⁴ and e) presence of ventricular arrhythmia.⁴

3. *Tei index (MPI, RIMP)* – ratio of isovolumic time divided by ET, or $[(\text{IVRT} + \text{IVCT})/\text{ET}]$. The MPI may be used for initial and serial measurements as an estimate of RV function complementing other quantitative and non-quantitative measures. The upper reference limit for the right-sided MPI is 0.40 using the pulsed Doppler method.¹⁰

4. *TOF Total Correction* - an open heart surgical procedure which includes repair of ventricular outflow tract from the infundibulum to the pulmonary arteries.

RESULTS

Table 1 shows that from a total of 69 subjects, 26 had restrictive physiology and 43 had non-restrictive physiology. Majority of the subjects with restrictive physiology belonged to the school age group (7-12 years old). On the other hand, majority of the subjects with nonrestrictive physiology were in the adolescent age group (13–19 years). The result was not statistically significant. There was almost an equal number of male and female subjects in the restrictive and non-restrictive group. The result was also not statistically significant.

More subjects with non-restrictive physiolo-

gy (16%) had a history of phlebotomy compared to those with restrictive physiology (9%). Moreover, more subjects with non-restrictive physiology (10%) had a history of phlebotomy compared to those with restrictive physiology (7%).

Majority of the surgery done for total correction did not involve transannular patching. Thirteen percent (13%) or 9 patients who underwent TAP had restrictive physiology post-op whereas 9% or 6 subjects who had TAP surgery had nonrestrictive physiology. On the other hand, among those who had non-TAP surgery, 34 subjects (50%) had nonrestrictive physiology compared to 14 subjects (20%) with restrictive physiology post-op. There were 6 subjects whose type of total corrective surgery was not specified comprising 8% of the population. Results are statistically significant. ($p=0.035$).

Among those with RV restrictive physiology, the timing of the appearance of RV restrictive physiology was noted between 1-2 years after surgery in 16% of subjects.

Table 2 shows that among the 69 subjects, 40 had RV dysfunction (58%) and 29 (42%) had no RV dysfunction. Among the 26 patients who had restrictive physiology post-op, 11 (42%) had RV dysfunction in contrast to 15 (58%) who had no RV dysfunction. Among the 43 subjects who had nonrestrictive physiology, 29 patients or 67% have RV dysfunction compared to only 14 patients or (33%) who have no RV dysfunction. The results are statistically significant ($p = 0.042$).

DISCUSSION

The study shows that RV restrictive physiology as determined by echocardiographic parameters occurs postoperatively in TOF patients who underwent total correction. The factor which achieved statistical significance was the type of surgical repair in which transannular patching favors the development of RV restrictive physiology post-op. The study also shows that RV systolic dysfunction was more evident in patients with non-restrictive physiology compared to those with restrictive physiology.

Majority of the subject population seen between between the school age and adolescent period. Majority of the subjects were seen between 1-4 years from the time of surgery. Correlating the age of examination from the timing of surgery, it is evident that majority of the subjects were operated during the school age and adolescent period. In developing countries, TOF surgery is done at an older age compared to developed countries where total correction is done before the child reaches 2 years of age. Financial constraint plays a big factor for this phenomenon.

TOF had a prevalence of 0.26 per 1,000 live births and accounted for 5.4% of all of the lesions.¹² In the Baltimore Washington Infant Study (BWIS),¹² there is male predominance, which was also seen in this study.

Cullen et al demonstrated that isolated RV restrictive physiology, seen in 50% of subjects post-TOF correction, is characterized by pulmonary arterial antegrade flow coincidental with atrial systole and associated prominent retrograde superior vena caval flow.¹¹

It was Dr. Michael Gatzoulis who made most of the studies regarding RV restrictive physiology post-TOF correction. His findings suggested that RV restrictive physiology was seen at midterm follow up.² The presence of early post-operative restrictive right ventricular physiology is characterized by an antegrade pulmonary flow on late diastole and is highly predictive of subsequent RV restriction in midterm follow-up. Norgard et al reiterated that the determinants for midterm restrictions of RV physiology was early restriction at an odds ratio of 6 with a p-value of 0.016. In this study, from a total of 69 subjects, at least 26 had restrictive physiology, comprising 38% of the population. Restrictive physiology was already evident even 1-2 years post surgery as seen by this study.

RV restrictive physiology post-TOF correction is common in patients with transannular patch (TAP) repair compared with non-TAP repair (50% versus 21%, $P < 0.05$).³ In this study, of the 15 patients who underwent TAP, 60% versus 40% developed restrictive physiology; whereas, among the 48 subjects who underwent non-TAP surgery, 71% versus

29% had non-restrictive physiology. This data showed that TAP had an influence on the development of restrictive physiology post-op and the results were statistically significant.

The study also showed that majority of the patients with history of phlebotomy and Blalock Taussig Shunts (BTS) tend to have nonrestrictive physiology rather than a restrictive one. The chronic hypoxemia associated with cyanotic heart disease, resulting to polycythemia and the frequent phlebotomies result in "down regulation of antioxidant defenses"⁷ making cells vulnerable to oxidant damage brought about by the changes in oxygen concentration at the time of surgical repair.¹³

Table 1. Baseline Characteristics of Subjects Who Underwent TOF Correction According to the Presence of Restrictive RV

	Restrictive Physiology N = 26		Non restrictive Physiology N = 43		P Value
	n	%	n	%	
Total N = 69					
Age					
1-3	2	3	2	3	0.261
4-6	2	3	9	13	
7-12	16	23	11	16	
13-19	6	9	21	30	
Sex					
Male	13	19	23	33	0.808
Female	13	19	20	29	
History of Phlebotomy	6	9	11	16	1.000
Prior BTS	5	7	7	10	0.754

BTS- Blalock-Taussig Shung TAP Transannular Patching

Table 2. Association of Restrictive/ Nonrestrictive Physiology with RV Systolic Dysfunction in the Post-operative Period

Total N = 69	RV Dysfunction N = 40 n (%)		No RV Dysfunction N = 29 n (%)		P Value
	n	%	n	%	
Restrictive Physiology	11	42	15	58	0.042
Non-Restrictive Physiology	29	67	14	33	0.042

Restrictive RV physiology in midterm follow-up was associated with less QRS prolongation while the nonrestrictive physiology is associated with most marked QRS prolongation and at risk for chronic pulmonary regurgitation.³ In further studies, QRS prolongation predicts malignant ventricular arrhythmias. Helbing et al¹⁴ noted that among the 37 patient who underwent TOF correction, 34 had important pulmonary regurgitation. Right and left ventricular end diastolic volume and mass were increased with positive correlation with QRS duration. Chronic right ventricular volume overload after TOF repair correlates with QRS prolongation and a QRS duration on the resting ECG of >180 milliseconds is the most sensitive predictor of life threatening ventricular arrhythmia.⁴ However, in this study, the QRS duration of the restrictive group was slightly lower at 108 msec compared with the non-restrictive group at 116 msec.

There are many limitations in the use of echocardiographic parameter due to the complexity of the RV geometry. Tei Chuwa in 1995 devised an index of myocardial performance (TEI Index) that evaluates LV and RV systolic and diastolic in combination.¹⁰ This index proved to be a reliable method for evaluation of systolic performance and had a prognostic value in many kinds of heart diseases in the study of right ventricular dysfunction. The index appears to be a useful quantitative measure of RV and LV function. A progressive pathologic increase in its value is associated with an increase in RV dysfunction. However, in this study, there was technical difficulty for the echocardiographer in obtaining the parameters used to calculate the TEI index due to the complexity of the RV geometry compared to the LV.

Another method of measurement of RV function is through TAPSE. It measures the distance of systolic excursion of the RV annular segment along its longitudinal plane. The published lower reference value for impaired RV systolic function is 16mm.⁷ However, this value is based on European values and there is no local data for normal values of TAPSE with respect to patients' weight. Using these criteria, a lot of the subjects have values below the lower reference value and were labeled with RV systolic dysfunction.

The presence of restrictive RV physiology was considered beneficial in children and adolescents with repaired TOF in the long run. It is considered protective against RV dilatation usually seen after TOF repair. The presence of this physiology was associated with morbidities in the early post-op period, such as low cardiac output, effusions and prolonged post-op course. However, late after repair, there were superior exercise performance, less ventricular dilatation and fewer arrhythmias among those with restrictive RV physiology.³ An explanation for this is that in a restrictive physiology, the stiff RV acts as a passive conduit with little or no true RV filling during the period of diastole which prevents RV dilatation and pulmonary regurgitation.¹³

In this study, the presence of an RV restrictive physiology favors the absence of RV systolic dysfunction. Among the 26 subjects who had restrictive physiology, there were more who had no RV systolic dysfunction. In addition, for the 43 subjects who had non-restrictive physiology, majority developed RV dysfunction.

Other journals used late diastolic antegrade pulmonic flow as the sole criteria for RV restrictive physiology while this study used several parameters. The use of a single best parameter could limit variability. The lower reference value of < 16mm used for TAPSE was based on European data since there are no local data. A lot of the subjects were labelled with RV systolic dysfunction based on this parameter. Using two or more parameters before labelling the subjects with systolic dysfunction could offer greater sensitivity in detecting those with true RV dysfunction.

The following are the limitations of the study. First, the subjects were selected as they follow up in the OPD. The subjects included were those with history of operation for a minimum of 1 year and above. This variable follow up might affect the status of restrictive physiology. Some subjects had incomplete data in the medical chart wherein the type of TOF correction was not specified. Second, there was also technical difficulty for the operator in getting the Tei index in the RV. Thirdly, there is no local data for the lower reference value for TAPSE. The value used in this study was taken

from the European journals. The use of this value may result to an overestimation of the number of subjects with RV dysfunction. Lastly, the ideal study design for this study is a prospective cohort study. However, due to the long period of time to observe the development of RV dysfunction, this was not feasible.

Based on the results of the study, the following are recommended: a prospective study can be done to monitor the evolution of restrictive versus non-restrictive physiology in TOF patients with special emphasis on the type of repair used; a single best parameter in labeling a subject with restrictive physiology can be used; developed criteria for labeling a patient with RV systolic dysfunction based on 2 or more parameter instead of only 1 and using a local reference value for TAPSE in pediatric patients.

CONCLUSION

RV restrictive physiology occurs postoperatively in TOF patients who underwent total correction. It is present as early as 1-2 years post-op. The history of phlebotomy and BTS favors more a non-restrictive physiology post-op. Transannular patching favors more the development of RV restrictive physiology post-op versus non-restrictive physiology.

The study also shows that RV systolic dysfunction is more evident in patients with non-restrictive physiology. The presence of RV restrictive physiology could offer a protective effect against RV systolic dysfunction.

Parameters like pulmonary regurgitation, low TAPSE and prolonged QRS duration are, when used combined, are better predictors of RV systolic dysfunction than when used alone.

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