Assessment of Right Ventricular Diastolic Function in Pediatric Tetralogy of Fallot patients: An Intra-operative Transesophageal Echocardiography Study

Thesis submitted for the partial fulfilment for the requirement of the Degree of DM (Cardiothoracic and Vascular Anesthesia)

BY

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2019 – 2021

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Declaration

I hereby declare that this thesis entitled, "***Assessment of right ventricular diastolic function in pediatric Tetralogy of Fallot patients – an intra-operative transesophageal echocardiography study***" has been prepared by me under the supervision and guidance of Prof. (Senior Grade) Thomas Koshy and Dr. Saravana Babu, Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram and Dr. Baiju S Dharan, Professor and Head, Division of Cardiothoracic and Vascular Surgery, Sree Chitra Tirunal Institute for Medical Sciences and technology, Thiruvanthapuram.

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CERTIFICATE

This is to certify that this thesis entitled, "**Assessment of right ventricular diastolic function in paediatric Tetralogy of Fallot patients – an intra-operative transesophageal echocardiography study**" is the bonafide work of Dr. Panidapu Nagarjuna., Senior resident, conducted in the Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram under our supervision and guidance. He has shown keen interest in preparing this project.

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Acknowledgments

I feel I have learnt a lot from writing this thesis. This is the greatest treasure I will cherish not only in my academic career but in my whole life.

First and foremost, I would like to express sincere gratitude to my guide **Dr. Thomas Koshy**, Senior Professor and Head, Division of Cardiac Anaesthesiology, for his continuous support of my thesis and research, for his patience, leadership, motivation and immense knowledge. I could not have imagined having a better mentor and advisor for my thesis.

Besides my advisor, I am hugely indebted to my co-guide **Dr. Saravana Babu**, Assistant professor, for his encouragement, insightful comments and constant feedback about the progress of my thesis. His guidance helped me at all the times of research and writing of this thesis

I would like to take this opportunity to extend my immeasurable gratitude to **Prof. Shrinivas Vittal Gadhinglajkar** and **Prof. Unnikrishnan Konniparambil** who has always been the fountain of inspiration and an unfailing source of guidance.

I have much pleasure in expressing my grateful thanks to the faculty members of the Division of Cardiothoracic and Vascular Anaesthesiology of SCTIMST, **Senior Prof. Rupa Sreedhar**, **Prof. Prasanta Kumar Dash, Prof. Suneel Puthuvassery Raman, Dr. Subin Sukesan**, Associate Professor, for their constant support and guidance.

I sincerely thank my colleagues **Dr. Azeez Aspari Mahammed, Dr. Diana Thomas, Dr. Pradeep AP** and my **seniors** who helped me in data collection, and for making learning joyous.

I would like to thank Anaesthesiology support staff for sharing my perioperative responsibilities

Last but not the least, I am greatly indebted to my patients, who allowed me to learn on them, without whose support this thesis would not have been possible.

- Dr. Nagarjuna

List of Abbreviations

ASE – American Society of Echocardiography

BSA – Body surface area

CCHD – Cyanotic congenital heart disease

COVID – Corona virus disease

CPB – Cardio-pulmonary bypass

CVP – Central venous pressure

DD – Diastolic dysfunction

FAC – Fractional Area Change

ICD – Intercostal drain

ICU – Intensive care unit

IVC – Inferior vena cava

LCOS – Low cardiac output syndrome

mPAP – Mean pulmonary artery pressure

mRAP – mean right atrial pressure

MAP – Mean arterial pressure

MPA – Main pulmonary artery

ME – Mid-esophageal

MRI – Magnetic resonance imaging

NPV – Negative predictive value

PASP – Peak pulmonary artery systolic pressure

PPV – Positive predictive value

PR – Pulmonary regurgitation

RA – Right atrium

ROC – Receiver Operator Curve

RV – Right ventricle

RVEDA – Right Ventricle End-diastolic Area

RVEDP – Right ventricular end diastolic pressure

RVEDV – Right ventricle end diastolic volume

$RVEDV_i$ – Indexed right ventricular end diastolic volume

RVEF – Right ventricular ejection fraction

RVESA – Right Ventricle End-systolic Area

RVESV – Right ventricle end systolic volume

RVOT – Right ventricular outflow tract

TAPSE – Tricuspid Annular Plane Systolic Excursion

TDI – Tissue doppler imaging

TEE – Transesophageal echocardiography

TOF – Tetralogy of Fallot

TR – Tricuspid regurgitation

TV – Tricuspid valve

UE – Upper-esophageal

VIS – Vasoactive inotropic score

VSD – Ventricular septal defect

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INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CCHD) with an incidence of 1 in 3500 live births and it accounts for up-to 7% to 10% of all congenital heart defect[1]. Due to advances in diagnosis and management of CCHD there is marked improvement in survival of the patients born with TOF. Nearly, more than 98% of the infants survive due to surgical repair of the cardiac anomaly, with repair usually performed during the first year of life. Studies on long term outcomes show a 30-year survival rate of nearly 90%[2].

Postoperative course is uncomplicated in most of the patients with TOF. However, there may be features of low cardiac output syndrome (LCOS), raised filling pressures, prolonged ventilation, need for high inotropic support, development of pleural effusions and ascites in some of the patients. Biventricular systolic function is usually normal in TOF patients; but, data regarding the diastolic function in this subset of population is sparse[3]. In TOF, right ventricle (RV) becomes a stiff conduit due to RV outflow tract obstruction, leading to poor diastolic function and the presence of diastolic dysfunction is a marker of poor short-term surgical outcome[4].

There are guidelines regarding the assessment of right ventricular diastolic function in adult patients[5], but there is limited data regarding the right ventricular diastolic function in pediatric population[5]. American society of Echocardiography (ASE) recommended the following parameters to assess diastolic dysfunction in pediatric population after surgical repair of TOF[6]:

1. Late diastolic flow reversal in MPA
2. Right atrium (RA) dilatation
3. Hepatic vein flow reversal

ASE guidelines states that a trans-tricuspid E/A ratio of <0.8 suggests impaired relaxation, and a trans-tricuspid E/A ratio >2.1 with deceleration time <120 msec suggests restrictive filling[6] in adult population, however, similar thresholds have not been advocated in patients with repaired TOF.

Assessment of RV diastolic function using Doppler parameters is very difficult in pediatric population due to varying loading conditions and age. Although there were studies regarding the assessment of long-term functional outcome of the RV after the repair of TOF, data on the immediate and early post-operative RV function is sparse[7,8]. Consequently, RV diastolic dysfunction have not been well characterized in TOF patients beyond the phenomenon of restrictive RV physiology[9,10].

Therefore, the primary aim of this study is to assess the diastolic dysfunction in pediatric TOF patients using the ASE recommended Doppler parameters of adults (E/A, E/E') and compare them with ASE recommended Doppler echocardiographic parameters in pediatric TOF patients (MPA flow reversal, RA dilatation, hepatic vein flow reversal) in the post cardiopulmonary bypass (CPB) period. The secondary aims of the study are to assess the systolic function in patients with diastolic dysfunction, etiological factors associated with diastolic dysfunction and early postoperative outcomes like duration of mechanical ventilation, vasoactive inotropic scores, duration of chest tube drainage and length of ICU stay.

ANATOMY OF RIGTH VENTRICLE

Right ventricle is a hollow, muscular chamber, which receives blood from the right atrium and pumps it through the outflow tract to the pulmonary trunk. It extends from the inferior border of the right atrium to the cardiac apex, running nearly horizontal to make up the inferior border of the heart, also referred to as the acute margin of the heart[11]. The RV's interior

is heavily trabeculated, except for the regions directly underneath the septal leaflets of the tricuspid and pulmonary valves[12]. The thickness of RV wall is around 2–5 mm, weighing about 25 ± 5 g/m^2, and mainly composed of superficial and deep muscle layers. The deep subendocardial fibres are arranged longitudinally from base to apex, while the superficial subepicardial fibres are generally arranged circumferentially, parallel to the AV groove[13,14]. These epicardial fibres turn obliquely as they extend toward the apex of the heart, and then they continue onto the LV. This continuity of fibres from RV to LV contributes to ventricular interdependence[14].

Traditionally, the RV was described in two parts – the sinus and the conus[15,16]; however, this bipartite division was inadequate for descriptions of congenital malformations[17]. Thus, a three-part description proposed by Goor and Lilleihi (1977) was adopted.

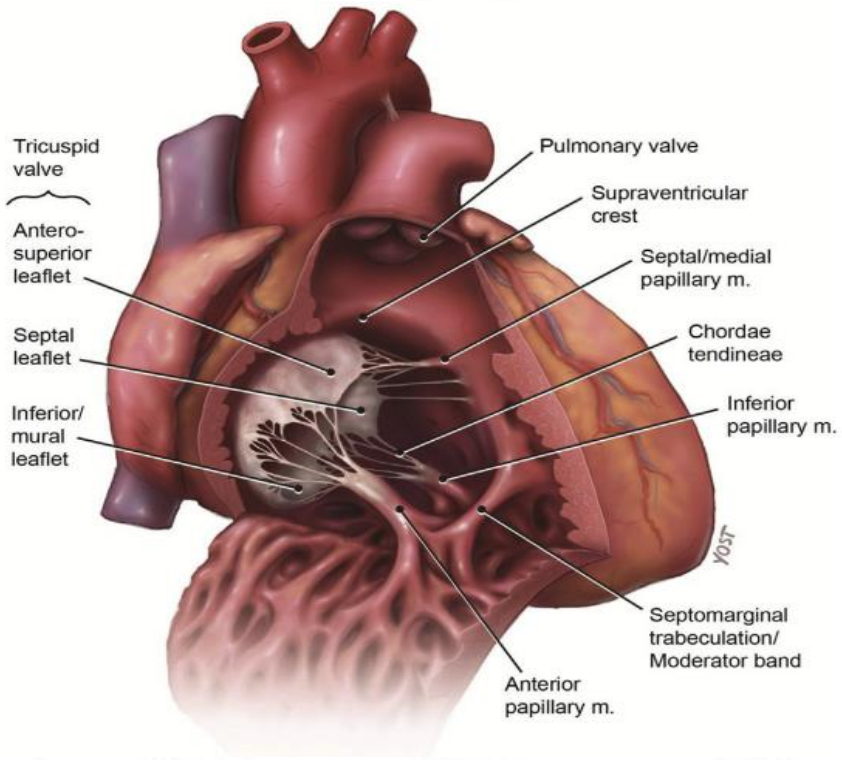
They described the RV as being composed of:

1) The inlet - including the tricuspid valve, chordae tendineae, and papillary muscles;

2) The trabeculated apical myocardium;

3) The outlet - including the infundibulum or conus and the pulmonary valve[17]. (Figure 1)

Figure 1: Anatomical features of right ventricle demonstrating the internal structures (adapted from J M H Wang et al., 2019[11])



ECHOCARDIOGRAPHY OF RIGHT VENTRICLE

Quantification of RV systolic and diastolic function by echocardiography is of paramount importance, given the prevalence of children with CHD, particularly those with involvement of right heart, such as TOF, pulmonary arterial hypertension. Identification of poor right ventricular function provides an opportunity for early intervention. For proper assessment of RV function, it is important to highlight some of the important features that differentiate it from left ventricle. Its complex geometry, precludes the easy assessment of function by traditional echocardiography[18]. Also, the muscle fibres of RV are arranged mainly longitudinally, as opposed to longitudinal, circular and oblique fibres of LV[19]. In disease states like TOF, RV shows a change in ventricular fibres with presence of a circular middle layer that resembles that of the LV[20].

Systolic function of the RV can be assessed both qualitatively and quantitatively. Tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), pulsed doppler S' wave (S') have by far, the most abundantly used parameters for systolic function assessment[21]. RV diastolic function is obtained by doppler interrogation of the tricuspid inflow (E, A), tissue doppler interrogation of the lateral tricuspid annulus (E'), doppler interrogation of hepatic veins, assessment of right atrial size, measurements of inferior vena cava and its collapsibility[8].

AIMS & OBJECTIVES

Primary objective:

To assess the diagnostic predictive ability of spectral doppler (E, A, E/A) and tissue doppler parameters (E', E/E') in pediatric TOF patients, who are already diagnosed by using ASE recommended parameters (MPA antegrade flow in late diastole, hepatic vein flow reversal and RA dilatation) in the post cardiopulmonary bypass period

Secondary objectives:

1) To assess the right ventricular systolic function in patients with diastolic function
2) To determine the etiological factors responsible for early diastolic function in postoperative TOF patients
3) To study the early postoperative outcomes and complications in patients with diastolic dysfunction

i. Duration of mechanical ventilation
ii. Highest mean inotropic score in the first 48hrs after surgery
iii. Duration of intercostal drainage
iv. Length of stay in ICU
v. Requirement of peritoneal dialysis

REVIEW OF LITERATURE

There are guidelines for assessment of RV systolic and diastolic function in adult population[5], but only limited information exists on the accuracy, prognostic value of the doppler echocardiographic data in patients with repaired TOF. ASE guidelines have clearly stated that doppler parameters of TV inflow are not reliable in children, due to variable loading conditions and age[6]. Therefore, a combination of hepatic vein flow reversal, MPA antegrade flow in diastole, RA dilatation and changes in calibre of IVC with respiratory cycle were used to label the patient as having Restrictive diastolic dysfunction (ReDD)[6]. Restrictive RV diastolic dysfunction, on the contrary is an advanced stage, and depends on the age of the patient. The prevalence of RV dysfunction ranges from 28% to 63%[7,23,24,35,41] in the literature. Also, there is limited data on the etiological factors and regarding early postoperative outcomes in this subset of population.

In a study by Sachdev and colleagues[23], RV diastolic dysfunction was present in 24 out of 50 (48%) TOF patients. According to them, presence of late diastolic antegrade pulmonary artery flow concomitant with atrial systole is a marker of restrictive physiology. Also, restrictive RV physiology correlated with prolonged intensive care unit (ICU) stay (5.1 ± 3.7 vs 2.8 ± 2 days, $p < 0.015$), longer duration of inotropic support (108.3 ± 56.2 vs 55.5 ± 28.3 hours, $p < 0.02$), and higher dosage of diuretics.

Rathore et al.[24], in a prospective study involving TOF patients, found that RV restrictive physiology is seen in 45 out of 64 patients (70%), and those with restrictive physiology had significantly longer mean inotrope support duration, longer ventilation days and chest drainage times. Correspondingly, the mean intensive care unit stay (56.7+/-9.3 v. 34.7+/-5.38 hours, $p<0.01$) and mean hospital discharge time (9.3+/-2.3 v. 6.2+/-0.5 days, $p <0.001$) was also significantly longer in patients with restrictive physiology.

Gatzoulis et al.[25], in a follow up study including 41 TOF patients, found restrictive physiology in 20 patients. In their analysis, all those 20 patients had doppler evidence of pulmonary regurgitation, but its duration was shorter in the restrictive group (P<.01) during inspiration. Cardiothoracic ratio was significantly lower in the restrictive group (P<.01), suggesting less severe pulmonary regurgitation. Both restrictive and non-restrictive groups had reduced exercise $M\dot{V}O_2$ (oxygen consumption) compared with healthy age- and sex-matched control subjects, but those with restrictive physiology had significantly better maximum oxygen uptake than the non-restrictive group (P<.001). Consequently, they concluded that patients with restrictive physiology have better exercise performance as compared to patients without restrictive physiology, owing to lesser incidence of pulmonary regurgitation.

RS Singh et al.[7], in a prospective study involving TOF patients, found RV dysfunction (systolic and diastolic) by echocardiography among 54% (13/24) of the study population in the immediate post-operative period. In the follow-up period it was reduced to 38% by 4 weeks and further to 15% by 12 weeks. Also, patients developing RV dysfunction has more ventilation hours, prolonged inotropic support requirement and prolonged stay in the hospital. However, the duration of cross clamp and cardiopulmonary bypass times were not significantly different in patients with RV dysfunction as compared to patients without any RV dysfunction.

Ahmad et al.[26], in their retrospective study including 112 TOF patients, found RV diastolic dysfunction in 52% of the population. Assessment of RV diastolic parameters was done using tricuspid doppler parameters. They found that RA length, RA area and indexed RA area were significantly higher in the restrictive group as compared to non-restrictive group. Also, there was no significant difference in trans-tricuspid E, A, E', A' velocities and E/E' ratios between the two groups. They concluded that restrictive physiology was associated with more pronounced changes in pulmonary venous flow patterns.

Sandeep et al.[27], through their study tried to focus on the etiological factors responsible for restrictive diastolic physiology after TOF repair surgeries. In their study including 50 TOF patients, RV restrictive physiology was observed in 58% of the (28/50) patients. Patients with restrictive physiology was found to have longer cardiopulmonary bypass (CPB) time (mean: 117.6 ± 23 min) with p-value< 0.001, longer aortic cross clamping time (mean: 91.4 ± 20.26 min) with p-value< 0.001 as compared to patients without restrictive physiology. Systolic function was also lowered in patients with restrictive physiology as evidenced by lower TAPSE values (13.41 ± 1.35 vs 16.70 ± 1.51, p<0.05) in restrictive group. They concluded that etiological factors responsible for restrictive physiology were lower SpO_2 values, transannular patch, longer CPB, longer cross clamp times, RV hypertrophy, lower TAPSE, lower PASP and lower TAPSE/PASP ratios.

Hui et al.[28], tried to emphasis the role of right atrium in patients after TOF surgery. They compared RA size and function between 50 patients with repaired TOF and 30 normal controls. They showed that RA size was increased (16.86 +/- 5.5 vs 13.7 +/- 5.1 cm^2; P = .013) and emptying function was decreased (mean active emptying area fraction, 19 +/- 9.8% vs 26.3 +/- 10.3%, P = .005) after TOF repair. In the 20 patients who underwent MRI examination, their study revealed a relatively higher right atrial peak diastolic strains in patients with a right ventricular ejection fraction < 50%. Similarly, RA systolic and diastolic strain values were lower in patients with TOF compared with controls. They concluded that right atrial performance is reduced after surgical repair of TOF, However, when facing right ventricular systolic function, the right atrial function was relatively enhanced.

Hayabuchi and colleagues[29], in their study comprising 25 children with repaired TOF, tried to assess the relationship between tricuspid E/E' and RV diastolic function in the long term follow-up. Right ventricular end-diastolic pressure, volume (RVEDP, RVEDV), systolic pressure, ejection fraction, mean pulmonary arterial pressure (mPAP), mean right atrial

pressure (mRAP), severity of pulmonary regurgitation (PR) and tricuspid regurgitation (TR) were all assessed using cardiac catheterization and their correlation to tricuspid E/E' ratios were assessed. They concluded that trans tricuspid E/E' does not provide a reliable estimation of RV filling pressures and also these parameters were related to the severity of pulmonary regurgitation but not to the severity of RV diastolic function.

Di Lorenzo et al.[30], in their follow up study including 94 TOF patients compared diastolic parameters derived by echocardiography with cardiac catheterization variables. Through this study they tried to assess the correlation between echocardiographic diastolic parameters with RVEDP derived from catheterization and also to identify clinical characteristics associated with RV diastolic dysfunction. 65% of the study population was found to have echocardiographic evidence of diastolic dysfunction as evidenced by deranged E/A, E/E' and deceleration time. However, RVEDP, measured by catheterization did not have any correlation with E/E' or E/A. There was poor agreement between an elevated RVEDP by catheterization and the presence of diastolic dysfunction by echocardiography. On the other side, there was significant association between the RVEDP and right atrial area, fractional area changes of RV, RV end diastolic area. Even though higher RVEDP was associated with larger right atrial areas, interestingly, there was also no significant association between indexed right atrial area or end diastolic areas and RVEDP

Covadonga and colleagues[31], did the functional assessment of left and right ventricles before and after surgical repair of TOF in 36 patients. They concluded that RV systolic function was reduced during the time of discharge in TOF patients. Also, RV systolic and diastolic parameters measured by S', E', A', and E/E' were lower at the time of discharge as compared to the preoperative values. However, there was no correlation between the development of right bundle branch block and the pleural drainage among the patients with deranged RV diastolic

function. They concluded their study by saying that TDI and strain imaging were better than conventional echocardiography in determining the right ventricular function after TOF surgery.

Maskatia and colleagues[32] in their study tried to evaluate the association between the cardiac MRI findings and echocardiographic parameters of diastolic dysfunction. They found out that RV obstruction was associated with lower E/A ratio, E/A reversal and forward pulmonary diastolic flow. RV systolic function as evaluated by MRI with RVEF <45% has lower septal S' velocity and elevated tricuspid E/E' was associated with higher RV end-diastolic volume. They concluded that echocardiographic variables of diastolic dysfunction have a reasonable PPV but poor NPV for predicting clinical risk factors as evaluated by MRI

Egbe et al.[33], in their study tried to determine the echocardiographic predictors of severe RV diastolic dysfunction and the impact of RV diastolic dysfunction on transplant free survival period in postoperative TOF patients. They classified the RV diastolic dysfunction into three classes based on arbitrary cut-off points of mean of RVEDP and RAP. Out of 173 patients, 68 patients had normal diastolic function and 69 had severe diastolic dysfunction. Additionally, among patients with severe diastolic dysfunction, dilated IVC had best sensitivity. Also, they showed that severe RV diastolic dysfunction was an independent risk factor for transplant or death. They concluded that echocardiographic indices can identify high risk patients and thus can improve the risk stratification in clinical practice.

Chaturvedi and colleagues[34] tried to analyse the RV diastolic function in the first 24hrs after TOF repair surgery using cardiac troponin levels and serum iron levels. In their study, patients with restrictive RV physiology had higher rise in troponin concentration levels and serum iron levels peaked more in restrictive group than non-restrictive group. They concluded that acute restrictive physiology was associated with greater intraoperative myocardial injury and longer stay in ICU.

Koestenberger and colleagues[35], tried to analyse the systolic function in TOF patients using TAPSE values and RV ejection fraction and compared with indexed RVEDV measured by MRI. Among 149 TOF patients in their study, there was a positive correlation between TAPSE and RVEF ($r = -0.67$; $P<0.001$) and a negative correlation between TAPSE with $RVEDV_i$ ($r = -0.42$; $P<0.001$). They concluded that volume loading in TOF patients can lead to RV systolic dysfunction, determined by TAPSE and MRI and to increased $RVEDV_i$ values, determined by MRI, with time.

Krishna et al.[36], tried to evaluate the role of right ventricular echocardiographic parameters in predicting vasoactive inotrope requirement after TOF surgery. In their study, TAPSE values had significant negative correlation values with mean VIS. They concluded that TAPSE, RV global longitudinal and radial strains could predict postoperative VIS scores with a reasonable sensitivity and specificity.

Ravi raj and colleagues[52], in a prospective study involving 50 TOF patients tried to find the correlation between the RV functional parameters and post-operative outcomes. They evaluated TAPSE, FAC and S' velocities in the postoperative period. Among these parameters, RV FAC predicted the early outcomes better after TOF repair, followed by TAPSE and lateral annular S' velocity was the least predictive parameter for post-operative outcome.

MATERIALS & METHODS

Study design:

The study was a prospective, observational study.

Study setting:

This study was conducted in the Department of Anaesthesiology, Cardiothoracic and Vascular Anaesthesiology Division, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India – A tertiary referral centre, University level teaching hospital, operating about 1000 pediatric cardiac surgeries per year

Ethical considerations:

The study was started after obtaining clearance from the Institutional Ethical Committee, (IEC Regn. No. ECR/189/Inst/KL/2013/RR-16), Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India. (IEC certificate No. SCT/IEC/1391/ 17th August 2019) (IEC approval letter, Annexure 3). The study was registered prospectively with the Clinical Trials Registry of India (CTRI/2020/04/032917).

The background, purpose, procedures involved in the study, measures which were taken to ensure confidentiality of the study participants, the voluntary nature of the study and applicability of findings were explained. The study complied with the revised Helsinki Declaration (2013) and Good Clinical Practice Guidelines. Informed and written consent (Consent form, Annexure 2) was sought from the parents/legal guardians of the participants. They were informed of the purpose and importance of the study in English and Malayalam and their wards were enrolled in the study after obtaining consent.

Study population:

Children aged between 6 months and 10 years, undergoing elective surgical repair of TOF were prospectively included in the study.

Inclusion criteria:

a) Children aged between 6 months and 10 years, with a pre-operative echocardiographic diagnosis of TOF with good PA anatomy, and no additional VSD.

Exclusion criteria:

a) Children above 10yrs of age.
b) Presence of other associated congenital cardiac defects.
c) Children who have undergone modified Blalock Taussig shunt surgery.
d) Valvular regurgitation of a grade higher than 'mild'.
e) Children posted for redo or emergency surgery.
f) Presence of any contraindications for TEE probe placement.
g) Post-operative echocardiography showing residual RVOT gradient >30mm Hg

Informed consent:

Informed written consent was obtained from all patient's parents/guardians regarding the conduct of the study.

All patients were thoroughly examined during pre-anaesthetic evaluation and parents/guardians were explained regarding study protocol

Approval from Technical Advisory Committee (TAC)

TAC approval was taken before commencing the study with Registration number – SCT/S/2019/923

Approval from Institutional Ethics Committee (IEC)

IEC approval was taken before commencing the study. IEC number – SCT/IEC/1391/August-2019

Duration of study:

The duration of study was 1 year

Funding:

No extramural or intramural funding was required for the study

Interventions:

The study was a prospective observational study and no interventions were done

Outcome parameters:

Evaluation of study objectives were the outcome parameters

Sample size calculation:

According to our hospital records, 46 and 49 TOF cases were done respectively in the past two years. Based on the previous study[31], if the sample size is ≥ 40, the sample can be assumed as representative of the population. A total of 40 children were initially planned to be included in the study. However, due to current COVID situation and missing data in some patients, we were unable to complete the sample size of 40. Hence, sample analysis was done for 30 TOF patients.

Statistical analysis:

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Non-normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate bar diagrams, pie diagrams, table and box plots.

All quantitative variables were checked for normal distribution within each category of explanatory variable by using virtual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess the normal distribution. Shapiro-wilk test p value >0.05 was considered as normal distribution.

Categorical outcomes:

Categorical outcomes were compared between study groups using Chi square test/ Fischer's Exact test (if the overall sample size was <20 or if the expected number in any of the cells is <5, Fischer's exact test was used).

For normally distributed quantitative parameters the mean values were compared between study groups using independent sample t-test (2 groups).

The change in the quantitative parameters, before and after the intervention was assessed by paired t-test (In case of two time periods)

For non-normally distributed Quantitative parameters, medians and interquartile range (IQR) were compared between the study groups using Mann Whitney U test (2 groups)

ROC Analysis:

E/A and E/E' ratios in the post CPB period were assessed by Receiver Operative curve (ROC) analysis for predicting diastolic dysfunction. Area under the ROC curve along with its

95% confidence interval and p value were presented. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test with decided cut-off values along with their 95% CI were presented.

Diagnostic tests:

Diastolic dysfunction diagnosed by using ASE recommended parameters (MPA antegrade flow in late diastole, RA dilatation and hepatic vein flow reversal)[6] were considered as gold-standard. E/A and E/E' were considered as screening tests. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test along with their 95% CI were presented. Reliability of screening tests was assessed by using Kappa statistics along with 95% CI and P value.

IBM SPSS version 22 (IBP corp. Released 2017. IBM SPSS statistics for windows, version 25.0, Armonk, NY: IBM corp.) was used for statistical analysis. p value <0.05 was considered statistically significant.

Anaesthesia protocol:

After obtaining consent from the parents, children were recruited into the study after providing thorough information. Children were well hydrated following adequate nil per mouth orders in the pre-operative period. Oral clear fluids were allowed till two hours before the scheduled time for anaesthesia induction. Syrup Triclofos 50 mg/kg were given for children less than 10 kg.

After connecting basic monitoring devices (ECG, Pulse Oximetry, NIBP), inhalational induction using Sevoflurane was used to obtain intravenous access following which intravenous induction using Ketamine 2mg/kg, Fentanyl 2-5 mcg/kg, Midazolam 100 mcg/kg and a non-depolarizing muscle relaxant, vecuronium 0.1mg/kg were used to achieve ideal

conditions for endotracheal intubation. Arterial and central venous catheterizations were performed after induction of anaesthesia. Fentanyl was given in doses up-to 20 mcg/Kg before going on cardio-pulmonary bypass (CPB).

All children were ventilated with tidal volumes of 8 ml/Kg, 5 cm H_2O PEEP and suitable respiratory rate to maintain $PaCO_2$ / $EtCO_2$ in acceptable ranges. A well lubricated pediatric TEE probe was inserted in the oesophagus after endo-tracheal intubation and securing of invasive lines. All echocardiographic data were acquired using Philips iE33 machine (Bothell, WA, USA). For children weighing 3 kg to 5 kg, S8-3t micro-TEE probe was used, for children weighing 5 to 20 Kg, S7-3t probe was used and for children weighing >25 kg, S7-2t Omni III probe was used.

Acquisition of diastolic echocardiographic data:

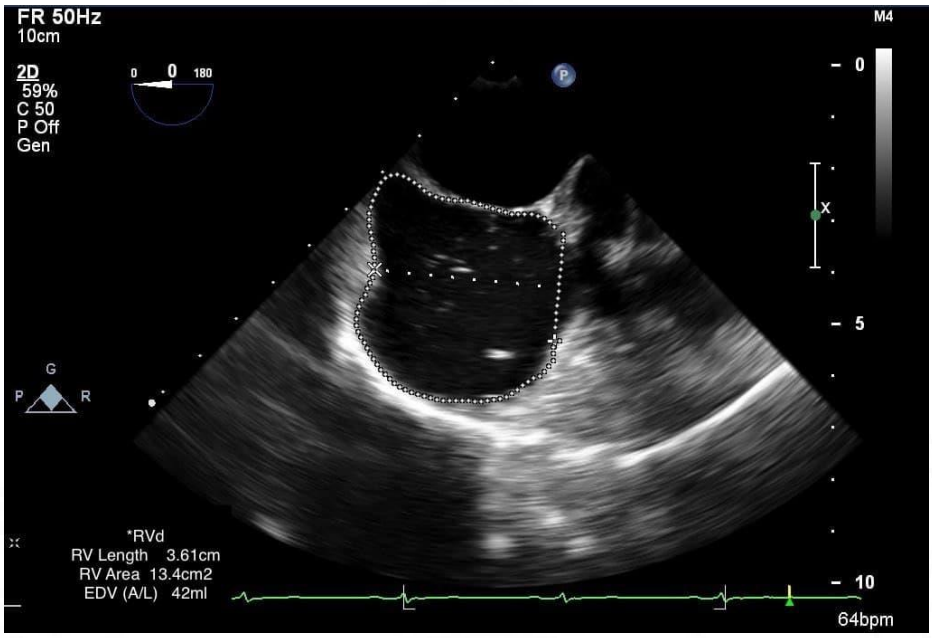
- The mid-oesophageal 4 chamber view (0^0) was acquired with the probe turned slightly to the right, so that the full RA and RV was in the image sector (Figure 2). Body surface area (BSA) was calculated using Du Bois formula as shown below:

  $BSA = 0.007184 * height^{0.725} * weight^{0.425}$

  (Height – in cm, Weight in Kg)

  Area-length method was used to calculate the RA volume and then indexed to BSA to get indexed RA volumes.

Figure 2: Mid-oesophageal 4C view focusing on Right atrium, showing calculation of RA size using area-length method



(RA – Right atrium, EDV – End-diastolic volume)

- Mid-oesophageal ascending aorta short axis view was obtained (0 – 30^0), and then continuous wave doppler was placed to diagnose the presence of antegrade flow in late diastole in main pulmonary artery (figure 3). If good alignment of doppler beam was not possible in this view, upper oesophageal aortic arch short axis view (70-90^0) was imaged to inspect the presence or absence of MPA antegrade flow (figure 4).

Figure 3: Mid-oesophageal ascending aorta short axis view showing the presence of antegrade pulmonary flow in late diastole

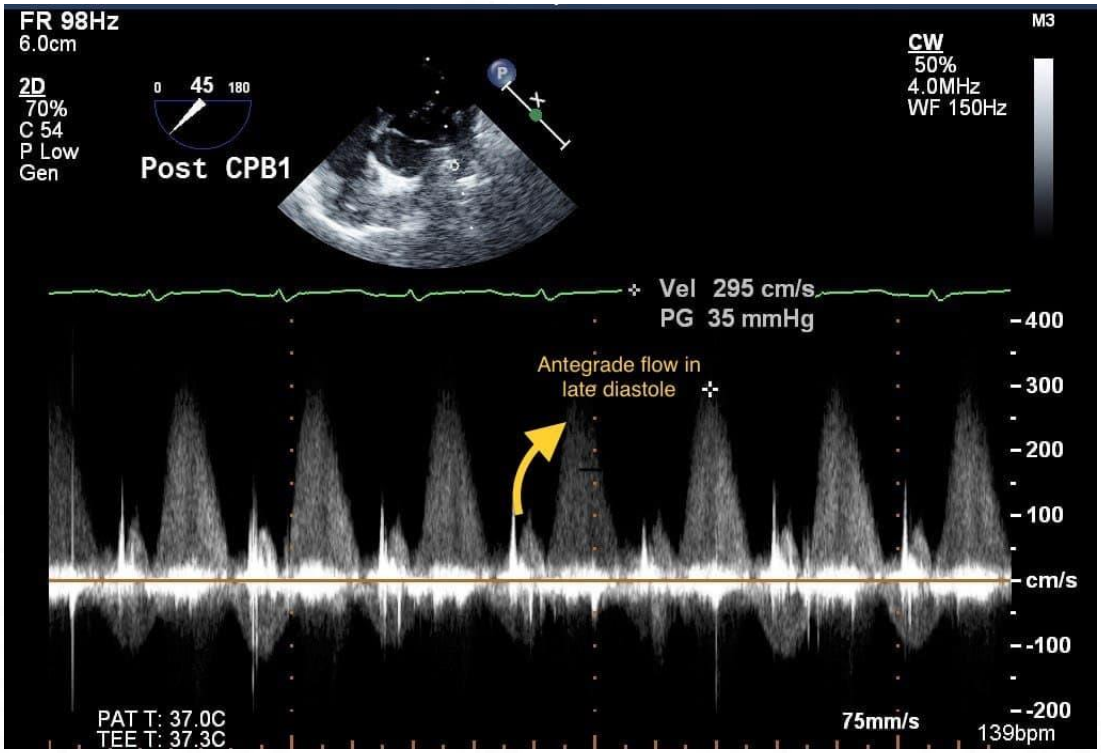
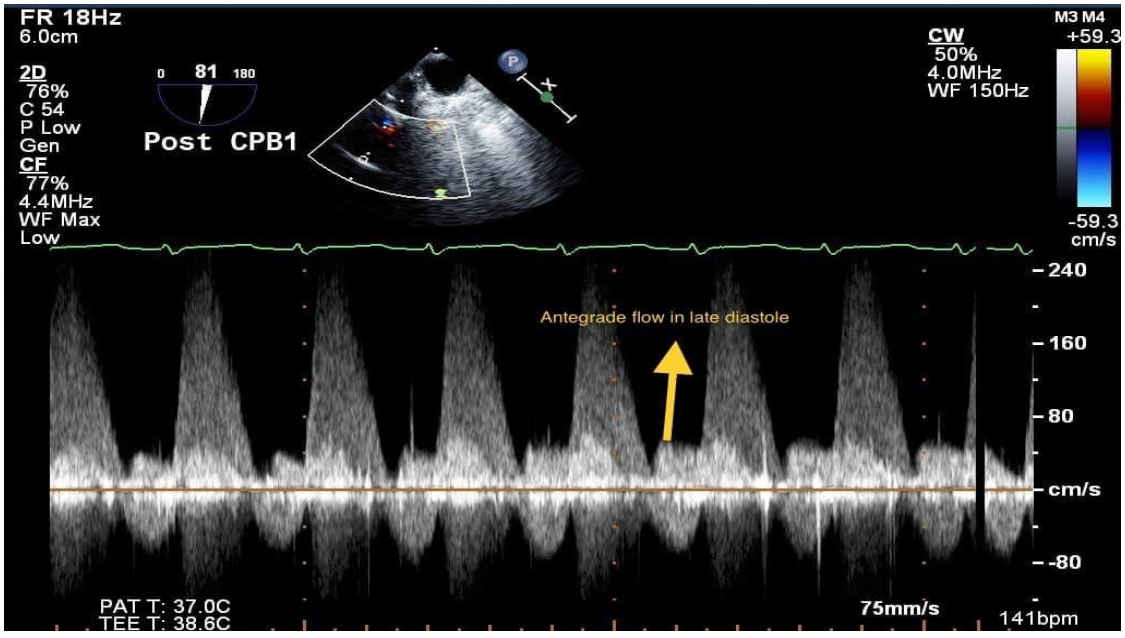
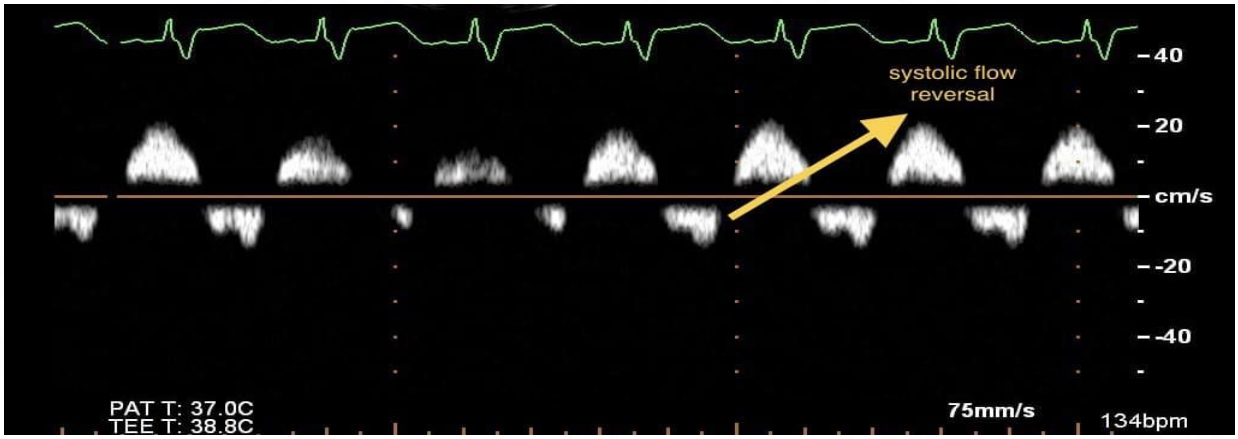


Figure 4: Upper-oesophageal aortic arch short axis view showing the presence of antegrade pulmonary blood flow in late diastole



- From mid-oesophageal bi-caval view, the probe is advanced deep till the draining of hepatic vein into inferior vena cava is seen. Doppler beam is then aligned into hepatic vein to look for any flow reversal (figure 5)

Figure 5: Pulse wave doppler imaging of hepatic vein demonstrating flow reversal in systole

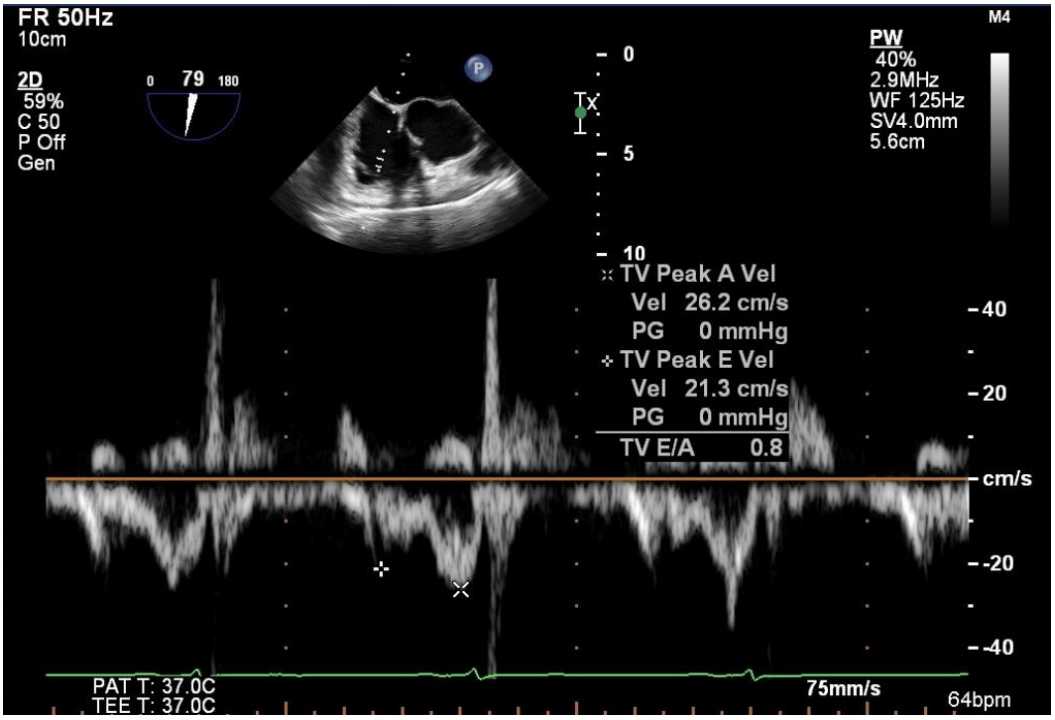


Based on the presence of these three criteria, patients were diagnosed to have diastolic dysfunction.

Once the presence or absence of diastolic dysfunction was confirmed using gold-standard parameters, the following sequence was followed to acquire doppler data.

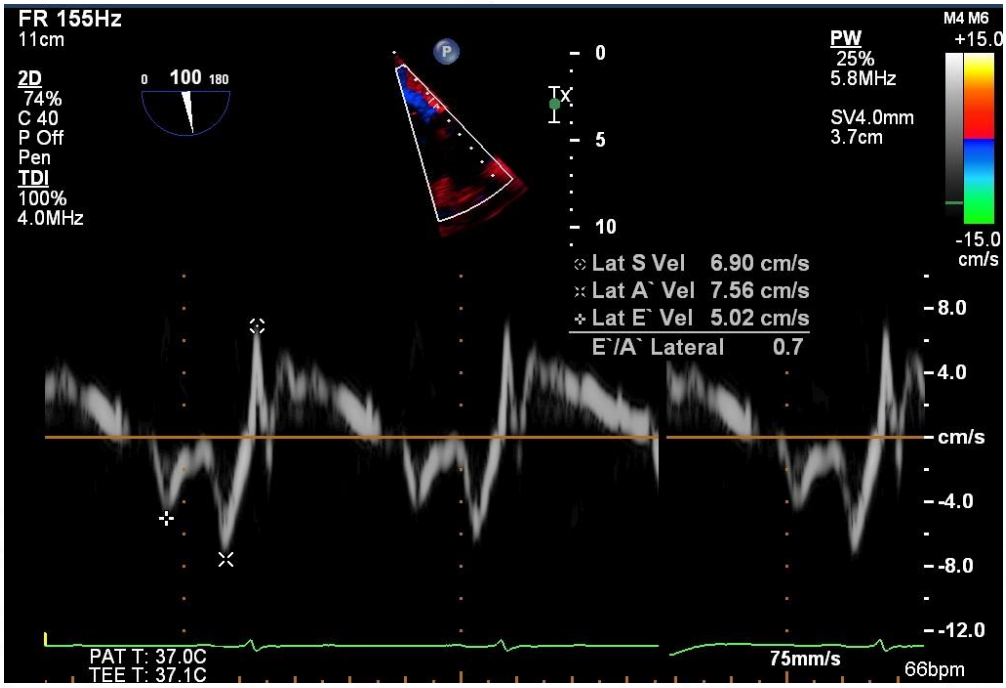
- Mid-oesophageal RV inflow-outflow view (50-70^0) was used to obtain trans-tricuspid spectral doppler parameters (E, A) (figure 6)

Figure 6: Midesophageal RV inflow-outflow view, showing calculation of tricuspid E and A values



- With the sample volume at the lateral tricuspid annulus in the trans-gastric two chamber view, and with the probe turned right (90-100^0), early diastolic velocity (E'), late diastolic velocity (A') and peak systolic velocity (S') were obtained using tissue doppler imaging. An average of three values were obtained and mean value was considered for analysis (figure 7)

Figure 7: Trans-gastric two chamber view, with probe turning right, showing calculation of E', A' and S'



Acquisition of systolic echocardiographic data:

- Mid-oesophageal 4 chamber view, focusing on right ventricle with clear endocardial borders was acquired. End-diastolic (figure 8) and end-systolic areas (figure 9) of RV were obtained and RV fractional area was calculated using the following formula –

$$\text{RV FAC} = [(RVEDA - RVESA)/RVEDA)]\ \%$$

(RVEDA: RV end-diastolic area, RVESA: RV end-systolic area)

Figure 8: Mid-oesophageal 4 chamber view, with probe focusing on RV, showing calculation of RV end-diastolic area using Simpson's method

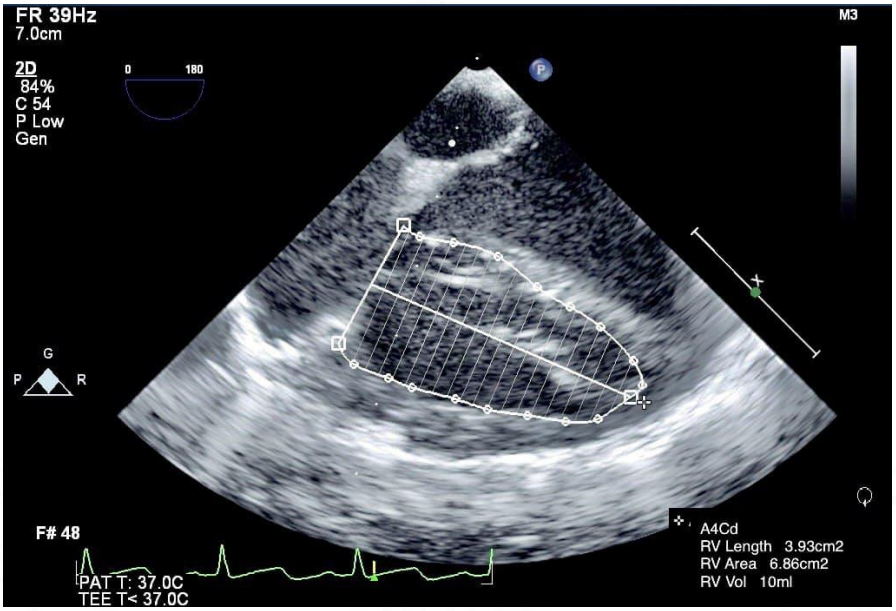
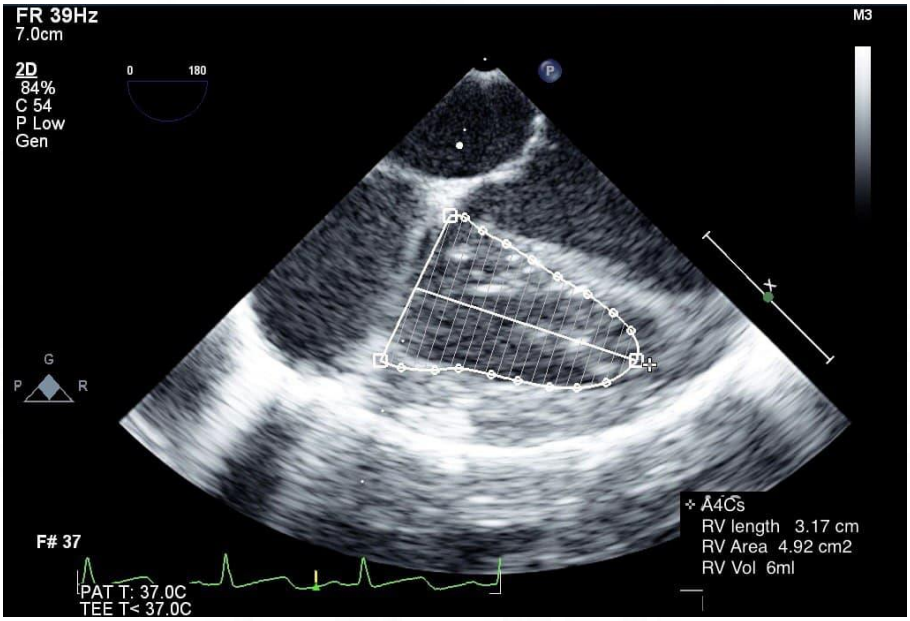


Figure 9: Mid-oesophageal 4 chamber view, with probe focusing on RV, showing calculation of RV end-systolic area using Simpson's method



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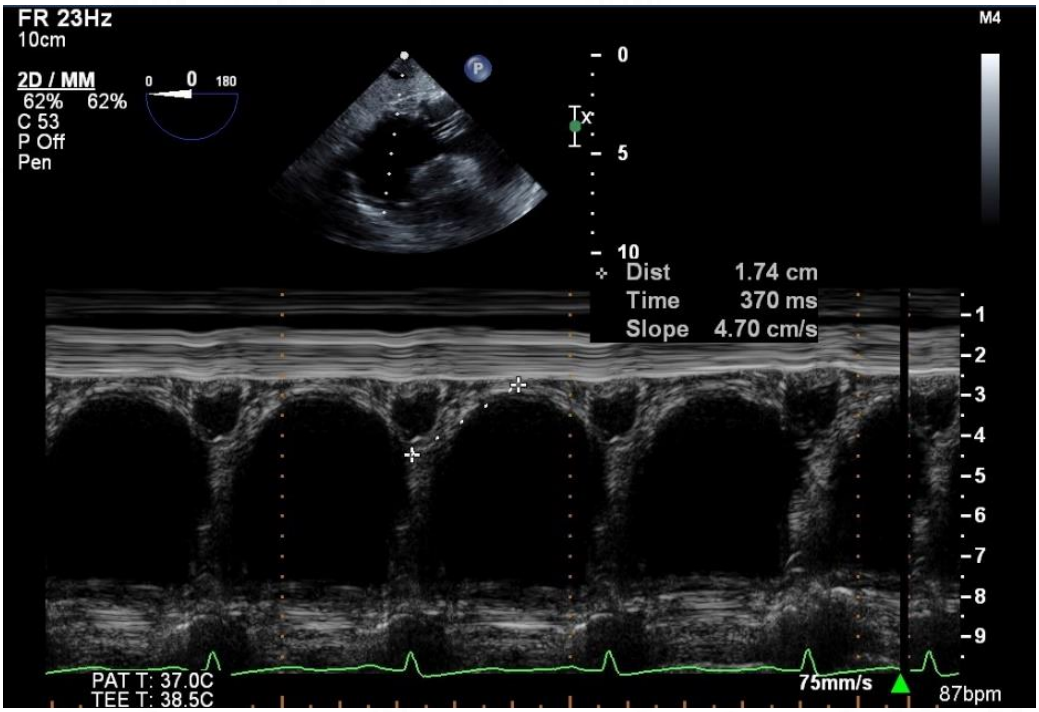
- Tricuspid annular plane systolic excursion (TAPSE) measurements were obtained using M-mode in trans-gastric RV inflow view (90-110^0) or deep trans-gastric 5 chamber view (figure 9). An average of three values were obtained as a mean value for analysis

Figure 10: Deep Trans-gastric 5 chamber view, with probe turned to right, showing tricuspid annular plane systolic motion in M-mode



Loading conditions of the heart during echocardiographic assessment will be maintained in the post CPB period similar to that of pre CPB period by maintaining the RV end diastolic area, CVP, haematocrit, heart rate and mean arterial pressure (MAP) within 20% of pre-CPB period. Inotropes will be commenced after CPB according to institution protocols.

Vasoactive inotropic score:

The drug concentration was standardized for each inotrope and vasopressors. Mean inotropic score administered in the first 48hrs was calculated using the following formula[37]:

VIS 2020:

10,000 × Vasopressin dose (U/kg/min) +
100 × Epinephrine dose (µg/kg/min) +
100 × Norepinephrine dose (µg/kg/min) +
50 × Levosimendan dose (µg/kg/min) +
25 × Olprinone dose (µg/kg/min) +
20 × Methylene blue dose (mg/kg/h) +
10 × Milrinone dose (µg/kg/min) +
10 × Phenylephrine dose (µg/kg/min) +
10 × Terlipressin dose (µg/min) +
0.25 × Angiotensin II dose (ng/kg/min) +
Dobutamine dose (µg/kg/min) +
Dopamine dose (µg/kg/min) +
Enoximone dose (µg/kg/min)

Secondary outcomes:

After surgery patients were shifted to ICU and the following parameters were recorded –

a) Duration of mechanical ventilation
b) Duration of ICD drainage
c) Length of stay in ICU
d) Incidence of post-operative complications
e) Mortality

RESULTS

In this prospective observational study, thirty-eight consecutive children posted for elective TOF surgery, without any other concomitant congenital heart disease were included. Eight children were excluded due to non-attainability of good images.

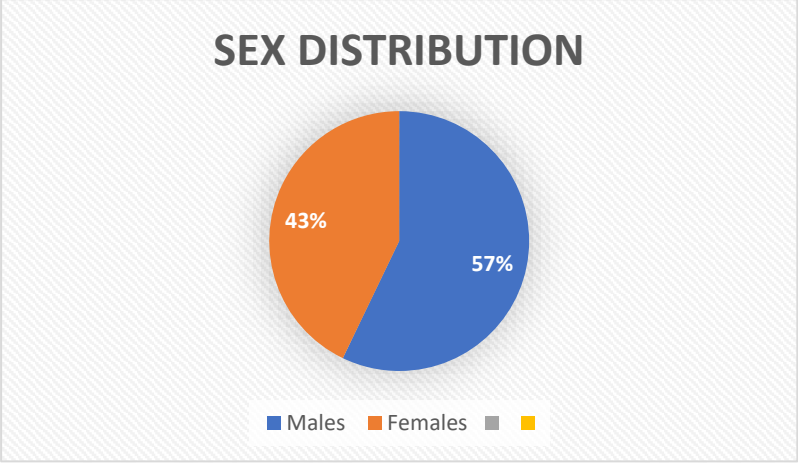
DEMOGRAPHICS OF THE STUDY POPULATION

Our study population ranged from 6 months to 10 years of age, with an average age of 4.23 ± 2.58 years. There were 16 males and 14 females in our study group (Figure 11). Average weight in the study population was 12.4 ± 4.5 kg. (Table 1)

Table 1: Demographics of study population

Parameters	Mean ± SD
Age (years)	4.23 ± 2.58
Sex ratio (Male: Female)	16: 14
Weight (Kg)	12.4 ± 4.5
BSA (m^2)	0.56 ± 0.08

Figure 11: Pie chart of sex distribution in the study population



Body surface area (BSA) was calculated using weight (in kg) and height (in cm) of the children using the Du Bois formula.

BSA = 0.007184* height$^{0.725}$ * weight$^{0.425}$

(Height: in cm, Weight: in Kg)

Mean BSA ranged from 0.32 to 0.78 with an average BMI of 0.56 ± 0.08.

DESCRIPTIVE ANALYSIS OF THE ECHOCARDIOGRAPHIC PARAMETERS IN THE PRE-CPB PERIOD

DIASTOLIC FUNCTION DATA:

The mean RA volume was 31.63 ± 12.68 ml in the study population, with minimum of 7.27 ml and maximum of 74.00 ml (95% CI is 27.09 ml to 36.16 ml). The mean indexed RA size was 10.28 ± 4.71 cm^2/m^2, with minimum of 3.87 cm^2/m^2 and maximum of 22.50 cm^2/m^2 (95% CI is 8.59 cm^2/m^2 to 11.96 $cm^2/^2$).

The mean E velocity of tricuspid valve inflow was 56.27 ±18.85 cm/s, minimum was 28.70 cm/s and maximum were 95.80 cm/s (95% CI of 49.52 cm/s to 63.01 cm/s). The mean A Velocity of tricuspid valve was 42.48 ± 9.46 cm/s, minimum was 21.80 cm/s and maximum was 65.40 cm/s (95% CI 39.10 cm//s to 45.87 cm/s). The mean tricuspid valve E/A was 1.32 ± 0.36, minimum was 0.73 and maximum was 2.50. (95%CI 1.19 to 1.44).

The mean TV E' velocity in the preoperative period was 13.90 ± 4.19 cm/s in the study population, minimum was 5.35 cm/s and maximum were 24.60 cm/s (95% CI 12.40 cm/s to 15.40 cm/s). The mean TV E/E' was 4.25 ± 1.58 in the study population, minimum was 1.56 and maximum was 8.01. (95%CI 3.69 to 4.82) (Table 2)

Table 2: Diastolic parameters in the pre-CPB period

Diastolic parameters (Pre CPB)	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
RA vol. (ml)	31.63 ± 12.68	7.27	74.00	27.09	36.16
Indexed RA size (cm^2/m^2)	10.28 ± 4.71	3.87	22.50	8.59	11.96
E Velocity (cm/s)	56.27 ± 18.85	28.70	95.80	49.52	63.01
A Velocity (cm/s)	42.48 ± 9.46	21.80	65.40	39.10	45.87
TV E/A	1.32 ± 0.36	0.73	2.50	1.19	1.44
TV E' Velocity (cm/s)	13.90 ± 4.19	5.35	24.60	12.40	15.40
TV E/E'	4.25 ± 1.58	1.56	8.01	3.69	4.82

(RA – Right atrium, TV – Tricuspid valve, CPB – Cardiopulmonary bypass, CI – Confidence interval, SD – Standard deviation)

SYSTOLIC FUNCTION DATA:

The mean RV free wall thickness in the preoperative period was 8.67 ± 2.17 mm in the study population, minimum was 5.70 mm and maximum were 14 mm (95% CI 7.90 mm to 9.45 mm) (Table 3).

The mean EDA of RV was 5.77 ± 2.33 cm^2 in the study population, minimum was 2.08 cm^2 and maximum was 11.80 cm^2 (95%CI 4.93 to 6.60). The mean ESA was 4.46 ± 5.36 cm^2, minimum was 1.72 cm^2 and maximum was 31.70 cm^2 (95%CI 2.54 to 6.38). Mean FAC was 38.29 ± 10.41 %, minimum was 17.20% and maximum was 56.80% (95%CI 34.57% to 42.02%).

Table 3: Systolic parameters in the pre-CPB period

Systolic parameters (Pre CPB)	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
RV thickness (mm)	8.67 ± 2.17	5.70	14.00	7.90	9.45
EDA (cm^2)	5.77 ± 2.33	2.08	11.80	4.93	6.60
ESA (cm^2)	4.46 ± 5.36	1.72	31.70	2.54	6.38
FAC (%)	38.29 ±10.41	17.20	56.80	34.57	42.02
TAPSE (mm)	14.08 ± 3.51	7.00	19.90	12.82	15.33
S' TDI (cm/s)	11.74 ± 4.85	6.82	29.20	10.00	13.47

(RV – Right ventricle, EDA – End-diastolic area, ESA – End-systolic area, FAC – Fractional area change, TAPSE – Tricuspid annular plane systolic excursion, TDI – Tissue doppler)

The mean TAPSE was 14.08 ± 3.51 mm, minimum was 7mm and maximum was 19.90 mm (95%CI 12.82 mm to 15.33 mm).

The mean S' TDI was 11.74 ± 4.85 cm/s in the study population, minimum was 6.82 cm/s and maximum were 29.20 cm/s (95%CI 10 cm/s to 13.47 cm/s) (Table 3)

DESCRIPTIVE ANALYSIS OF THE ECHOCARDIOGRAPHIC PARAMETERS IN THE POST-BYPASS PERIOD

RV DIASTOLIC FUNCTION

The mean RA volume was 34.45 ± 11.98 ml in the study population, minimum was 19.30 ml and maximum were 59.00 ml (95% CI 30.16 ml to 38.74 ml). The mean Indexed RA

size was 9.70 ± 3.76 cm^2/m^2 in the study population, minimum was 3.32 cm^2/m^2 and maximum was 19.18 cm^2/m^2 (95%CI 8.35 cm^2/m^2 to 11.50 cm^2/m^2).

The mean E velocity of tricuspid valve inflow was 57.26 ± 13.74 cm/s, minimum was 39.80 cm/s and maximum were 90.50 cm/s (95%CI 52.35 cm/s to 62.18 cm/s). The mean A Velocity of tricuspid valve inflow was 44.69 ± 10.70 cm/s, minimum was 17.30 cm/s and maximum was 71.20 cm/s (95%CI 40.86 cm/s to 48.52 cm/s). The mean tricuspid valve E/A was 1.34 ± 0.43 in the study population, minimum was 0.70 and maximum was 2.40. (95% CI 1.19 to 1.49).

The mean tricuspid valve E' velocity was 13.83 ± 6.69 cm/s in the study population, minimum was 4.80 cm/s and maximum were 27.30 cm/s (95%CI 11.44 cm/s to 16.23 cm/s). The mean tricuspid valve E/E' was 5.44 ± 2.87 in the study population, minimum was 2.10 and maximum was 12.80. (95% CI 4.41 to 6.46) (Table 4)

Table 4: Diastolic parameters in the post-bypass period

Diastolic parameters (Post CPB)	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
RA volume (ml)	34.45 ± 11.98	19.30	59.00	30.16	38.74
Indexed RA size (cm^2/m^2)	9.70 ± 3.76	3.32	19.18	8.35	11.05
E Velocity (cm/s)	57.26 ± 13.74	39.80	90.50	52.35	62.18
A Velocity (cm/s)	44.69 ± 10.70	17.30	71.20	40.86	48.52
TV E/A	1.34 ± 0.43	0.70	2.40	1.19	1.49
TV E' Velocity (cm/s)	13.83 ± 6.69	4.80	27.30	11.44	16.23
TV E/E'	5.44 ± 2.87	2.10	12.80	4.41	6.46

(RA – right atrium, TV – Tricuspid valve, CPB – Cardiopulmonary bypass, CI – Confidence interval, SD – Standard deviation)

SYSTOLIC FUCNTION DATA

The mean RV thickness in the post CPB period was 6.66 ± 1.50 mm in the study population, minimum was 4 mm and maximum was 10.10 mm (95%CI 6.12 mm to 7.19 mm). The mean EDA of RV was 6.68 ± 4.50 cm^2, minimum was 2.97 cm^2 and maximum was 25.70 cm^2 (95% CI 5.07 cm^2 to 8.29 cm^2). The mean ESA of RV was 5.16 ± 6.12 cm^2, minimum was 1.56 cm^2 and maximum was 35.80 cm^2. (95% CI 2.97 to 7.35). The mean FAC was 34.15 ± 10.47 % in the study population, minimum was 17.20 % and maximum was 57 %. (95% CI 30.41 % to 37.90 %). The mean TAPSE was 10.34 ± 3.84 mm, minimum was 4.50 mm and maximum were 18.50 mm (95% CI 8.96 mm to 11.72 mm). The mean S' TDI was 11.61 ± 4.60 cm/s in the study population, minimum was 5.40 cm/s and maximum were 25.40 cm/s (95% CI 9.96 cm/s to 13.26 cm/s) (Table 5).

Table 5: Systolic parameters in the post-bypass period

Systolic parameters (Post CPB)	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
RV thickness (mm)	6.66 ± 1.50	4.00	10.10	6.12	7.19
EDA (cm^2)	6.68 ± 4.50	2.97	25.70	5.07	8.29
ESA (cm^2)	5.16 ± 6.12	1.56	35.80	2.97	7.35
FAC (%)	34.15 ± 10.47	17.20	57.00	30.41	37.90
TAPSE (mm)	10.34 ± 3.84	4.50	18.50	8.96	11.72
S' TDI (cm/s)	11.61 ± 4.60	5.40	25.40	9.96	13.26

(RV – Right ventricle, EDA – End-diastolic area, ESA – End-systolic area, FAC – Fractional area change, TAPSE – Tricuspid annular plane systolic excursion, TDI – Tissue doppler)

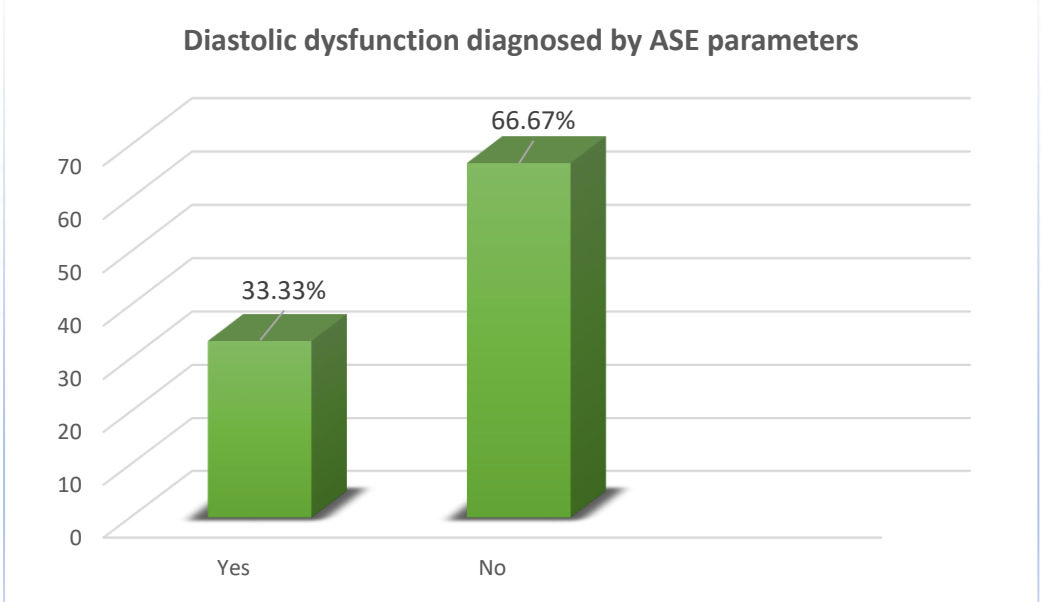
DIAGNOSING DIASTOLIC DYSFUCNTION IN THE POST-CPB PERIOD

Out of 30 patients, 10 were found to have diastolic dysfunction based on ASE recommended patients (MPA antegrade flow in diastole, hepatic vein flow reversal and RA dilatation) (Table 6, Figure 11).

Table: 6 – Diastolic dysfunction - diagnosed by ASE recommended parameters

Diastolic dysfunction (Using ASE parameters)	Frequency (N = 30)	Percentage (%)
Yes	10	33.33%
No	20	66.67%

Figure 12: Diastolic dysfunction - diagnosed by ASE recommended parameters



ROC ANALYSIS – E/A ratio

Based on the ROC analysis, it was decided to consider E/A value ≥1.34 as the cut off value for labelling the patient as having diastolic dysfunction. Among the patients with diastolic dysfunction, diagnosed by ASE recommended parameters, 7 (70%) were identified as having diastolic dysfunction based on E/A values and 3 (30%) were having normal diastolic function. Additionally, among the patients with normal diastolic function as diagnosed by ASE recommended parameters, 5 (25%) patients were identified as having diastolic dysfunction using E/A values and 15 (75%) patients were identified as having normal diastolic function using E/A values in the post CPB period (Table 7, Figure 13).

Also, there exists a statistically significant difference in E/A values between patients with and without having diastolic dysfunction. (P value: 0.018) (Table 7).

In our study, the E/A values in the post CPB period have reasonable predictive validity in predicting diastolic dysfunction, as indicated by area under the curve of 0.693 (95% CI 0.468 to 0.917, P value 0.090) (Table 8 & Figure 14)

Table 7: Comparison between ASE recommended parameters and E/A values in diagnosing diastolic dysfunction

	Diagnosing diastolic dysfunction using ASE parameters		Chi square	P value
	Yes (N=10)	No (N=20)		
DD Present (using E/A)	7 (70%)	5 (25%)	5.625	0.018
DD Absent (using E/A)	3 (30%)	15 (75%)		

Figure 13: Staked bar chart of comparison of E/A ratios in children with diastolic dysfunction

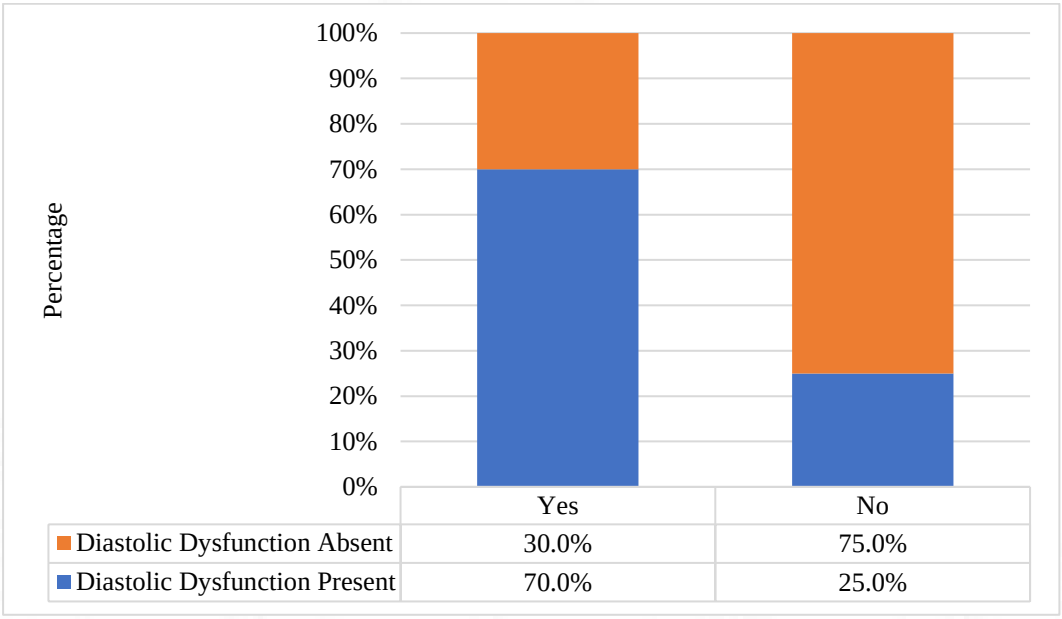
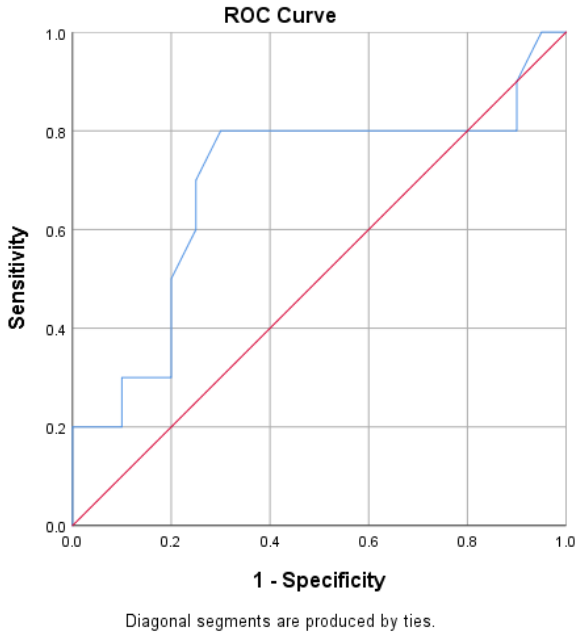


Table 8: Predictive validity of E/A ratio in post-CPB period

E/A ratio (Post CPB) in predicting diastolic dysfunction				
Area Under the Curve	**Std. Error**	**95% Confidence Interval of AUC**		**P value**
		Lower Bound	**Upper Bound**	
0.693	0.114	0.468	0.917	0.090

Figure 14: ROC analysis of E/A ratio in predicting diastolic dysfunction



The E/A ratio in the post CPB period has sensitivity of 70.00% (95% CI 34.75% to 93.33%) in predicting diastolic dysfunction, specificity was 75.00% (95% CI 50.90% to 91.34%), false positive rate was 25.00% (95% CI 8.66% to 49.10%), false negative rate was 30.00% (95% CI 6.67% to 65.25%), positive predictive value was 58.33% (95% CI 27.67% to 84.83%), negative predictive value was 83.33% (95% CI 58.58% to 96.42%), and the total diagnostic accuracy was 73.33% (95% CI 54.11% to 87.72%) (Table 9)

Table 9: E/A ratio in post CPB period in predicting diastolic dysfunction

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	70.00%	34.75%	93.33%
Specificity	75.00%	50.90%	91.34%
False positive rate	25.00%	8.66%	49.10%
False negative rate	30.00%	6.67%	65.25%
Positive predictive value	58.33%	27.67%	84.83%
Negative predictive value	83.33%	58.58%	96.42%
Diagnostic accuracy	73.33%	54.11%	87.72%

ROC ANALYSIS - E/E' ratio

Based on the ROC analysis, it was decided to consider ≥6.265 as the cut off value for labelling the patient as having diastolic dysfunction.

Among the patients with diastolic dysfunction, diagnosed by gold standard ASE recommended parameters, 8 (80%) patients were identified to have diastolic dysfunction using E/E' and 2 (20%) patients were identified to have normal diastolic function. Similarly, among the patients with normal diastolic function as diagnosed by ASE recommended parameters, 3 (15%) patients were identified to have diastolic dysfunction based on E/E' ratio and 17 (85%) patients were identified to have normal diastolic function in the post CPB period (Table 10, figure 15).

Also, there exists a statistically significant difference in E/E' ratios between patients with and without diastolic dysfunction. (P value <0.001) (Table 10).

In our study, E/E' ratio had good predictive validity in predicting diastolic dysfunction, as indicated by area under the curve of 0.825 (95% CI 0.647 to 1.000, P value 0.004) (Table 11 & Figure 16).

Table 10: Comparison between ASE recommended parameters and E/E' ratios in diagnosing diastolic dysfunction

	Diagnosing diastolic dysfunction using ASE recommended parameters		Chi square	P value
	Yes (N=10)	No (N=20)		
Diastolic Dysfunction Present (using E/E')	8 (80%)	3 (15%)	12.129	<0.001
Diastolic Dysfunction Absent (using E/E')	2 (20%)	17 (85%)		

Figure 15: Staked bar chart of comparison of E/E' ratios in children with diastolic dysfunction

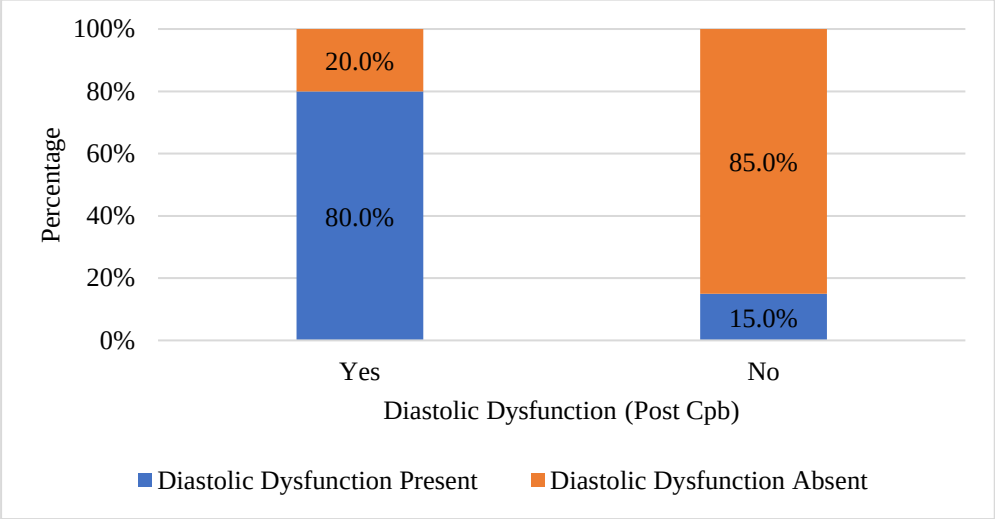
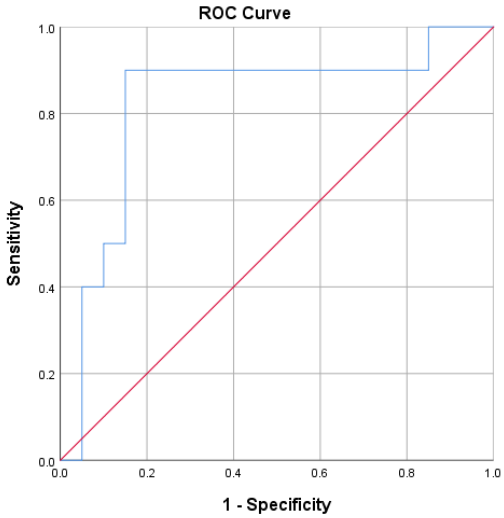


Table 11: Predictive validity of E/E' ratio in predicting diastolic dysfunction

E/E' ratio post-CPB in predicting diastolic dysfunction				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.825	0.091	0.647	1.000	0.004

Figure 16: ROC analysis of E/E' in predicting diastolic dysfunction



The E/E' ratio in the post CPB period has sensitivity of 80.00% (95% CI 44.39% to 97.48%) in predicting Diastolic Dysfunction, specificity was 85.00% (95% CI 62.11% to 96.79%), false positive rate was 15.00% (95% CI 3.21% to 37.89%), false negative rate was 20.00% (95% CI 2.52% to 55.61%), positive predictive value was 72.73% (95% CI 39.03% to 93.98%), negative predictive value was 89.47% (95% CI 66.86% to 98.70%), and the total diagnostic accuracy was 83.33% (95% CI 65.28% to 94.36%) (Table 12).

Table 12: E/E' ratio in post-CPB period in predicting Diastolic Dysfunction

Parameter	Value	95% C. I	
		Lower	Upper
Sensitivity	80.00%	44.39%	97.48%
Specificity	85.00%	62.11%	96.79%
False positive rate	15.00%	3.21%	37.89%
False negative rate	20.00%	2.52%	55.61%
Positive predictive value	72.73%	39.03%	93.98%
Negative predictive value	89.47%	66.86%	98.70%
Diagnostic accuracy	83.33%	65.28%	94.36%

Comparison of Systolic function among patients with diastolic dysfunction:

The mean RV free wall thickness and TAPSE values were 6.84 ± 1.71 and 9.63 ± 3.75 respectively in patients with diastolic dysfunction, while it was 6.57 ± 1.42 and 10.7 ± 3.93 respectively in patients without diastolic dysfunction, and the difference was not significant (P = 0.651, 0.484 respectively).

The mean FAC was 34 ± 9.81% in children with diastolic dysfunction, and it was 44.23 ± 11.03%. This difference in FAC between the two groups was statistically significant (P = 0.019).

Similarly, the mean S' velocities were 8.90 ± 2.34 in children with diastolic dysfunction, while it was 12.23 ± 3.81 among children with normal diastolic function and the difference was statistically significant (P= 0.017) (Table: 13)

Table 13: Systolic data comparison in the study population

Systolic parameters (Post CPB)	Diagnosing diastolic dysfunction using ASE recommended parameters		P value
	Yes (n=10)	No (n=20)	
RV wall thickness (mm)	6.84 ± 1.71	6.57 ± 1.42	0.651
TAPSE (mm)	9.63 ± 3.75	10.7 ± 3.93	0.484
FAC (%)	34 ± 9.81	44.23 ± 11.03	0.019
S' TDI (cm/s)	8.9 ± 2.34	12.23 ± 3.81	0.017

(RV – Right ventricle, FAC – Fractional area change, TAPSE – Tricuspid annular plane systolic excursion, TDI – Tissue doppler imaging)

DESCRIPTIVE ANALYSIS OF HAEMODYNAMIC DATA

Pre CPB parameters

The mean HR was 116.03 ± 14.45 beats/min in the study population, minimum was 85 beats/min and maximum was 141 beats/min (95CI% 110.86 beats/min to 121.20 beats/min). The mean MAP was 62.20 ± 6.23 mm Hg in the study population, minimum was 47 mm Hg and maximum was 75 mm Hg (95CI% 59.97 mm Hg to 64.43 mm Hg). The mean CVP in the pre CPB period was 8.27 ± 1.60 mm Hg, minimum was 4 mm Hg and maximum was 11 mm Hg (95CI% 7.70 mm Hg to 8.84 mm Hg). The mean HCT was 44.00 ± 6.06 gm%, minimum was 33 gm% and maximum of 57 gm% (95CI% 41.84 gm% to 46.17 gm%). (Table 14)

Table 14: Hemodynamic parameters in the pre-CPB period

Hemodynamic parameters	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
HR (bpm)	116.03±14.45	85.00	141.00	110.86	121.20
MAP (mm Hg)	62.20 ± 6.23	47.00	75.00	59.97	64.43
CVP (mm Hg)	8.27 ± 1.60	4.00	11.00	7.70	8.84
HCT (gm%)	44.00 ± 6.06	33.00	57.00	41.84	46.17

Post CPB parameters

The mean HR in the post CPB period was 122.83 ± 12.47 beats/min, minimum was 92 beats/min and maximum was 142 beats/min (95CI% 118.37 beats/min to 127.29 beats/min). The mean MAP was 59.23 ± 7.96 mm Hg, minimum was 45 mm Hg and maximum was 79 mm Hg (95CI% 56.39 mm Hg to 62.08 mm Hg). The mean CVP was 8.93 ± 2.50 mm Hg, minimum was 4 mm Hg and maximum was 14 mm Hg (95CI% 8.04 mm Hg to 9.83 mm Hg). The mean HCT was 40.28 ± 5.46 gm% in the study population, minimum was 31 gm% and maximum of 56.30 gm% (95CI% 38.33 gm% to 42.24 gm%) (Table 15).

Table 15: Hemodynamic parameters in the post CPB period

Hemodynamic Parameters	Mean ± SD	Minimum	Maximum	95% C. I	
				Lower	Upper
HR (bpm)	122.83±12.47	92.00	142.00	118.37	127.29
MAP (mm Hg)	59.23 ± 7.96	45.00	79.00	56.39	62.08
CVP (mm Hg)	8.93 ± 2.50	4.00	14.00	8.04	9.83
HCT (gm%)	40.28 ± 5.46	31.00	56.30	38.33	42.24

Comparison of hemodynamic data before and after CPB

The mean HR before CPB was 116.03±14.45 beats/min and after CPB was 122.83±12.47 beats/min, and the difference was statistically insignificant (P value 0.082).

The mean MAP before CPB was 62.2 ± 6.23 mm Hg and after CPB was 59.23 ± 7.96 mm Hg, and the difference was statistically insignificant (P value 0.370).

The mean CVP before CPB was 8.27 ± 1.6 mm Hg and after CPB was 8.93 ± 2.5 mm Hg, the difference between them before and after CPB was not statistically significant (P value 0.192).

The mean HCT before CPB was 44 ± 6.06 gm% and after CPB was 40.28 ± 5.46 gm%, and the difference between was statistically insignificant (P value 0.160) (Table 16).

Table 16: Comparison of hemodynamic parameters in pre CPB and post CPB period

Hemodynamic parameter	Mean± STD	Mean Difference	95% CI of mean difference		P-value
			Lower	Upper	
HR (beats/min)					
Pre CPB	116.03 ± 14.45	6.80	1.96	11.64	0.082
Post CPB	122.83 ± 12.47				
MAP (mm Hg)					
Pre CPB	62.2 ± 6.23	2.97	0.19	5.74	0.370
Post CPB	59.23 ± 7.96				
CVP (mm Hg)					
Pre CPB	8.27 ± 1.6	0.67	0.35	1.69	0.192
Post CPB	8.93 ± 2.5				
HCT (gm%)					
Pre CPB	44 ± 6.06	3.72	0.40	7.04	0.160
Post CPB	40.28 ± 5.46				

(HR – Heart rate, MAP – Mean arterial pressure, CVP – Central venous pressure, HCT – Haematocrit, STD – Standard deviation, CI – Confidence interval)

Duration of cross clamp and CPB

The median cross clamp time and CPB Time was 125.00min (IQR 99.75min to 140.0min) and 155.50min (IQR 149.25min to 169.5min) respectively in patients with diastolic dysfunction. In patients with normal diastolic function, cross clamp time and CPB time was 90.50min (IQR 73.25min to 109.5min) and 132.00min (IQR 114.75min to 150.75min) respectively and the difference was statistically significant. (P value 0.034 & 0.013 respectively) (Table 17).

Table 17: Comparison of duration of cross clamp and CPB times

Parameter	Diastolic Dysfunction (Median (IQR))		P value
	Yes (N=10)	No (N=20)	
CPB Time (min)	155.50(149.25 to 169.5)	132.00(114.75 to 150.75)	0.013
CC Time (min)	125.00(99.75 to 140.0)	90.50(73.25 to 109.5)	0.034

(CPB – Cardiopulmonary bypass, CC – Cross-clamp, IQR – Inter-quartile range)

SECONDARY OUTCOMES

Inotropic score

The median inotropic score in the post-CPB period was 12.50 (IQR 10.0 to 15.0) in patients with diastolic dysfunction and 10.00 (IQR 6.88 to 10.0) in patients without diastolic dysfunction and the difference in inotropic score was statistically significant. (P value 0.0367). (Table 18)

Table 18: Comparison of median of Inotropic scores

Parameter	Diastolic Dysfunction (Median (IQR))		P Value
	Yes (N=10)	No (N=20)	
Inotropic score	12.50 (10.0 to 15.0)	10.00 (6.88 to 10.0)	0.0367

Duration of mechanical ventilation

The mean duration of ventilation was 30.35 ± 25.19 for diastolic dysfunction patients and 18.85 ± 14.71 for non-diastolic dysfunction patients. The difference in duration of ventilation between diastolic dysfunction was not statistically significant. (P value 0.124) (Table 19)

Table 19: Comparison of duration of mechanical ventilation

Parameter	Diastolic Dysfunction (Post CPB) (Mean± SD)		P value
	Yes (N=10)	No (N=20)	
Duration of mechanical ventilation (hrs.)	30.35 ± 25.19	18.85 ± 14.71	0.124

Other outcomes

The duration of requirement of chest tubes was significantly higher (P value 0.040) in patients with diastolic dysfunction as compared to patients with normal diastolic function (64.50hrs vs 48.50hrs)

The length of stay in ICU and hospital were 73.50hrs and 6days respectively in patients with diastolic dysfunction. While, the length of stay in ICU and hospital were 72.50hrs and 5.50 days respectively in patients with normal diastolic function and there was no statistically significant difference (Table 20)

Table 20: Comparison of secondary outcomes in the study population

Parameters	Diastolic Dysfunction (Median (IQR))		P Value
	Yes (N=10)	No (N=20)	
Duration of chest tube (hrs.)	64.50(52.0 to 67.75)	48.50(35.5 to 62.0)	0.040
ICU LOS (hrs.)	73.50(69.0 to 98.25)	72.50(67.5 to 83.25)	0.4214
Hospital LOS (days)	6.00(5.0 to 9.25)	5.50(5.0 to 7.0)	0.3701

Post-operative complications

Mortality

There was no incidence of mortality in the study population

Acute kidney injury

Among children with diastolic dysfunction, two patients (20%) developed acute kidney injury, requiring the need for peritoneal dialysis, while there was no requirement of peritoneal dialysis, among children with normal diastolic function. (Table 21)

Delayed sternal closure

Among ten children, who developed diastolic dysfunction, three (30%) were shifted to ICU with open sternum and was subsequently closed after 24hrs. There was no requirement for keeping the sternum open, in children with normal diastolic function. (Table 21

Table 21: Incidence of postoperative complications in the study population

Post-operative complications	Diastolic dysfunction	
	Yes (n=10)	No (n=20)
AKI requiring dialysis	2	0
Delayed sternal closure	3	0

DISCUSSION

In this prospective observational study, thirty-eight consecutive children aged between 6 months to 12 years, who were electively posted for TOF surgery were recruited. ASE recommended parameters for only restrictive diastolic dysfunction in TOF patients and also difficult to obtain in every patient, therefore, through our study we investigated the predictive ability of simpler echocardiographic parameters like E/A and E/E' in diagnosing diastolic dysfunction in the immediate postoperative period. The secondary aim was to see existence of any RV systolic dysfunction in children with diastolic dysfunction and the impact of diastolic dysfunction on the postoperative outcomes.

In our study, the mean age of the children was 4.23 ± 2.58 years. The mean age was higher in patients with diastolic dysfunction as compared to normal diastolic function. There were 16 males and 14 females and the average weight in the study population was 12.4 ± 4.5 kg.

Incidence of RV Diastolic dysfunction

We labelled the children as having diastolic dysfunction if all the three ASE recommended criteria (MPA antegrade flow in late diastole, hepatic vein flow reversal and RA dilatation) in TOF patients were fulfilled. Based on this, the incidence of diastolic dysfunction in our study population was 33.33% which was similar to the study by Chaturvedi and colleagues[34]. Some other studies[38-40] have shown incidence between 28% to 63%, which was very high. The mean age of our study population was very less as compared to the previous studies[38-40], which explains the lower incidence of diastolic dysfunction. Echocardiographic evaluation of the patients at discharge also showed diastolic dysfunction in 33% of study population.

Rationale in using doppler parameters

It is a well-known fact that assessment of RV diastolic function using doppler echocardiographic parameters is influenced by changing loading conditions in pediatric population. In fact, Valente and colleagues[6] suggested against the use of doppler parameters for assessing diastolic function citing the same reason. In our study, we tried to maintain the loading conditions same, before and after CPB, in patients with and without diastolic dysfunction, thereby reducing the errors caused during assessment of doppler parameters. Also, tissue doppler variables like E' and A' are less preload dependant. Very few studies have evaluated the role of tissue doppler indices in patients with TOF[29,41]. Although studies in adult population showed an association between the severity of diastolic dysfunction and exercise intolerance after TOF repair in long term follow up[40,42], little is known about the effects of the diastolic dysfunction in the immediate postoperative period. Through our study, we intended to diagnose the diastolic dysfunction using doppler parameters and how presence of diastolic dysfunction is going to affect the immediate postoperative outcome.

E/A Ratio in diastolic dysfunction

Sachdev and colleagues[23] in their study on TOF patients, showed that restrictive physiology was associated with lower values of peak E velocity and E/A ratios. Similarly, Maskatia and colleagues[32] observed that severe RV diastolic dysfunction was associated with lower E/A and higher E/E' ratios. Greenberg and colleagues[43] studied E and A values using MRI flow quantification method and found that children with E/A < 1.4 was associated with RV diastolic dysfunction. R S Singh et al.[7], in their study found that the mean E/A values was 1.24 ± 0.77 in patients with RV diastolic dysfunction, 24hrs after surgical repair of TOF.

The E/A ratios obtained in our study were in agreement to the previous studies[7,32,43]. Based on ROC analysis, E/A ratio cut-off value of ≥1.34 (AUC 0.693, sensitivity of 70% and

specificity of 75%, P value 0.090) was taken to label the patient as having diastolic dysfunction in our study. After confirming the diagnosis of diastolic dysfunction using ASE recommended parameters, 70% (7/10) of these patients were shown to have E/A ≥1.34 and 30% (3/10) have E/A ≤ 1.34 and the difference was statistically significant (P value 0.018).

E/E' Ratio in diastolic dysfunction

The trans-tricuspid E/E' has been shown to have good correlation with hemodynamic parameters. In a study by Sade et al[44], a tricuspid E/E' ratio of ≥4 has been shown to have good sensitivity and specificity for predicting rise in RA pressures in patients undergoing non-cardiac surgery. Sundareswaran et al.[45] in their study on cardiac transplantation patients, showed an E/E' ≥6 has good sensitivity and specificity in predicting rise in RA pressures. In another study by Utsunomiya and colleagues[46], an RV E/E' >7.3 correlated better with mean RAP >10mm Hg with sensitivity of 87% and specificity of 97% and AUC of 0.92, suggesting good diagnostic utility of E/E' in chronic pulmonary arterial hypertension patients. These findings were in consistent to our findings, with E/E' ≥ 6.25 as the cut off value (AUC 0.825, sensitivity of 80%, specificity of 85%, P value of 0.004) for diastolic dysfunction. After confirming the diagnosis of diastolic dysfunction using gold standard parameters, 80% (8/10) of these patients were shown to have E/E' ≥ 6.25 and 20% (2/10) have E/A ≤ 6.25 and the difference was statistically significant (P value <0.001). In contrast to these findings, Hayabuchi et al.[29] found no significant association between RV E/E' and mean RAP in pediatric TOF patients after surgery (r = 0.263, P = 0.11). However, there was no ROC analysis was done in their study

Systolic function in patients with diastolic dysfunction

Systolic function in our study was assessed by using FAC, TAPSE, thickness of RV and S' velocity. There were significantly lower FAC values and S' velocities in patients with

diastolic dysfunction as compared to normal diastolic function in our study (P value 0.019 & 0.017 respectively). However, there was no statistically significant difference in TAPSE and RV wall thickness in the study population. Measurement of TAPSE values after pericardiectomy is not a reliable measure of RV systolic function, due to loss of suspension effect of free RV wall by the pericardium. Ravi Raj and colleagues[48], showed that RV FAC is the best predictor of RV systolic function in the postoperative period with AUC of 0.944, while TAPSE and S' velocity has reasonable predictive ability (AUC of 0.875 & 0.655 respectively). Laura Mercer-Rosa and colleagues[49] in turn proved that TAPSE cannot be used for global RV functional assessment in TOF patients due to the fact that longitudinal shortening is not the dominant factor contributing to RV systolic function. On the contrary, Sandeep et al.[27], in their study showed that RV restrictive physiology was associated with lower TAPSE values.

Etiology of RV diastolic dysfunction

Most of the previous studies[27], demonstrated the mechanism of development of RV restrictive physiology in TOF patients in the adolescent and adult patients. However, to the author's knowledge very few looked into etiological factors responsible for RV diastolic dysfunction development. Clark and colleagues[50] suggested that transannular patch repair is the main risk factor for developing RV restrictive physiology, owing to gradual dilatation of RV secondary to pulmonary regurgitation. In our study, among patients with diastolic dysfunction, seven out of ten (70%) patients underwent transannular patch repair, while in patients without diastolic dysfunction it was done in only five patients (25%) (P = <0.01). Also, patients with diastolic dysfunction have prolonged CPB run time (155.5min vs 132min, P =0.01) as compared to patients with normal diastolic function. We found that when the CPB time was less than 135 min there was no diastolic dysfunction, but in patients who developed diastolic dysfunction, CPB time was definitely more than 145min. Sandeep et al.[27], in their

study showed that CPB time >110min is an independent risk factor for developing restrictive dysfunction in TOF patients.

Inotropic score comparison

The mean inotropic score in the first 48hrs was 12.5 in patients with diastolic dysfunction, while it was 10 in normal diastolic function patients and the difference was statistically significant in our study (P = 0.036). Krishna et al.[36], in their study showed that children with RV systolic dysfunction when assessed by echocardiography, has higher inotropic score as compared to children with normal systolic function. This higher requirement of inotropes could be due to development of systolic dysfunction in children with diastolic dysfunction

To the best of our knowledge, the present study is the first to investigate the relationship between RV diastolic function and mean VIS scores in the first 48hrs after TOF surgery.

Association between clinical parameters

***ICU stay*:**

It has been previously demonstrated by Sachdev and colleagues[23], that restrictive physiology in TOF patients was associated with prolonged length of stay in ICU and requirements of higher inotropes. Sandeep et al.[27], also, through their study demonstrated that RV restrictive physiology was associated with longer stay in ICU and hospital. Our study had similar findings as previous studies in terms of length of stay in ICU and hospital, however, the difference was not statistically significant.

Intercostal drainage:

In our study the mean duration of intercostal drain was 48.5hrs in children with normal diastolic function, while it was 64.5hrs in children with diastolic dysfunction. C M Liang and

colleagues[51], in their study showed that patients with prolonged CPB run time have significantly higher pleural drains in postoperative TOF patients. Development of diastolic dysfunction can lead to rise in filling pressures in right sided cardiac chambers, leading to elevated hydrostatic pressures, which explains the higher intercostal drains.

Days of mechanical ventilation:

Sandeep and colleagues[27], showed that children with diastolic dysfunction have significantly higher requirements of days of mechanical ventilation, as compared to children with normal diastolic function. In our study, the duration of mechanical ventilation was higher in children with diastolic function, however, it was statistically insignificant.

Postoperative complications:

- There was no mortality in our study population.

- Acute kidney injury, requiring dialysis, was observed in 20% of the children with diastolic dysfunction. Griksaitis et al[51], reported the incidence of requirement of PD in the post-operative TOF patients was 17% in their study. Zulieka et al.[52], in their retrospective analysis of 173 TOF patients, showed that overall incidence of PD catheter insertion was 6%, however, they didn't mention about the requirement of PD in children with diastolic dysfunction.
- Delayed sternal closure was frequently done in children with complex congenital heart diseases. In a retrospective study by Daniel Hurtado-Sierra and colleagues[53], the incidence of delayed sternal closure was 11% and 74% of these patients fall into higher RACHS group of 3 and 4. In our study, the incidence of DSC was 30%, among the children who developed diastolic dysfunction, while it was similar to previous study[53], if the whole study population was considered (10%).

LIMITATIONS

- Age is one of the important factors which influences the diastolic doppler parameters, the age group in our study population was very wide, ranging from 6months to 12years.
- Indexing the echocardiographic parameters to the body surface area could have standardized the results further
- Anaesthetic effects on preload parameters and size of the right atrium couldn't be ruled out, although we tried to maintain adequate hydration
- We also didn't evaluate the respiratory effects on preload and thereby doppler echocardiographic variables
- There are no gold standard reference values for RA volumes in children. Hence, the possibility of systematic bias couldn't be ruled out
- It is a well-known fact that doppler parameters are angle dependant. Even though we tried to minimize the errors due to angulation, there is still a possibility of minor errors
- Given the small size of our cohort, further larger studies are required to validate the predictive ability of E/A and E/E' ratios
- We excluded patients with TOF with additional VSD or PDA, and by doing so, our study population may not be a representative of a larger population of patients with repaired TOF
- Also, it can't be ruled out that recent advances in surgical practice may have affected our study result

CONCLUSIONS

- The tricuspid E/E' ratio is a good indicator to predict the occurrence of diastolic dysfunction in the immediate postoperative period in TOF patients
- Tricuspid E/A ratio can be a reasonable indicator to predict diastolic dysfunction in the immediate postoperative period in TOF patients
- In TOF's patients etiology for RV restrictive physiology are associated with longer cross clamp and CPB times
- Children with diastolic dysfunction are associated with higher inotropic score, longer stay in ICU, higher drains in ICU and higher incidence of AKI requiring peritoneal dialysis

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ANNEXURES

ANNEXURE 1: Observation chart

PROFORMA

NAME: **DATE:**

AGE: **BSA:** **SEX:** **IP NO:**

PREOP TTE DIAGNOSIS:

SURGERY PROPOSED:

INTRAOPERATIVE TEE FINDINGS:

RV DIASTOLIC FUNCTION EVALUATION	PRE CPB	POST CPB
RA size(mm)		
Indexed RA size (mm/m^2)		
RA dilatation(y/n)		
MPA ante grade flow(y/n)		
Hepatic venous flow reversal(y/n)		
Diastolic dysfunction(y/n)		
TV E wave velocity(cm/s)		
TV A wave velocity(cm/s)		
TV E/A ratio		
TV E' velocity (cm/s)		
TV E/E' ratio		

RV SYSTOLIC FUNCTION EVALUATION	PRE CPB	POST CPB
RV EDA(m^2)		
RV ESA(m^2)		
RV FAC(%)		
TAPSE(mm)		
RV TDI S'(cm/s)		

	PRECPB	POST CPB
HR		
MAP		
CVP		
HCT		

CPB TIME:

CROSS CLAMP TIME:

INOTROPES:

NAME OF THE INOTROPE	POST CPB DOSE
MILRINONE	
NORADRENALINE	
ADRENALINE	
LEVOSIMENDAN	

POST OPERATIVE DATA:

REINTUBATION:

DURATION OF INOTROPIC SUPPORT:

DURATION OF CHEST TUBE DRAINAGE:

DURATION OF MECHANICAL VENTILATION:

ICU LENGTH OF STAY:

HOSPITAL LENGTH OF STAY:

IN HOSPITAL MORTALITY

ANNEXURE 2: Consent form

CONSENT FORM

I give consent for my child _____ (Participant's name _____Date of Birth / Age _____(in months/years), son/daughter/of)

_____ (Father/Mother's name) to participate in

this study titled "Assessment of right ventricular diastolic function in pediatric tetralogy of fallot patients – an intra-operative transesophageal echocardiography study "

Please tick the relevant boxes

- And have clarified any doubts that I had. [ ]
- I also understand that my child's participation in this study is entirely voluntary and that I am free to withdraw permission for my child to continue to participate at any time without affecting his/her usual treatment or legal rights [ ]
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my child's health records even if I withdraw permission for my child to participate in this trial. I agree to this access [ ]
- I understand that my child's identity will not be revealed in any information released to third parties or published in future [ ]
- I voluntarily agree for my child to take part in this study [ ]
- I have received a copy of this signed consent form [ ]

Name:
Signature:
Date:

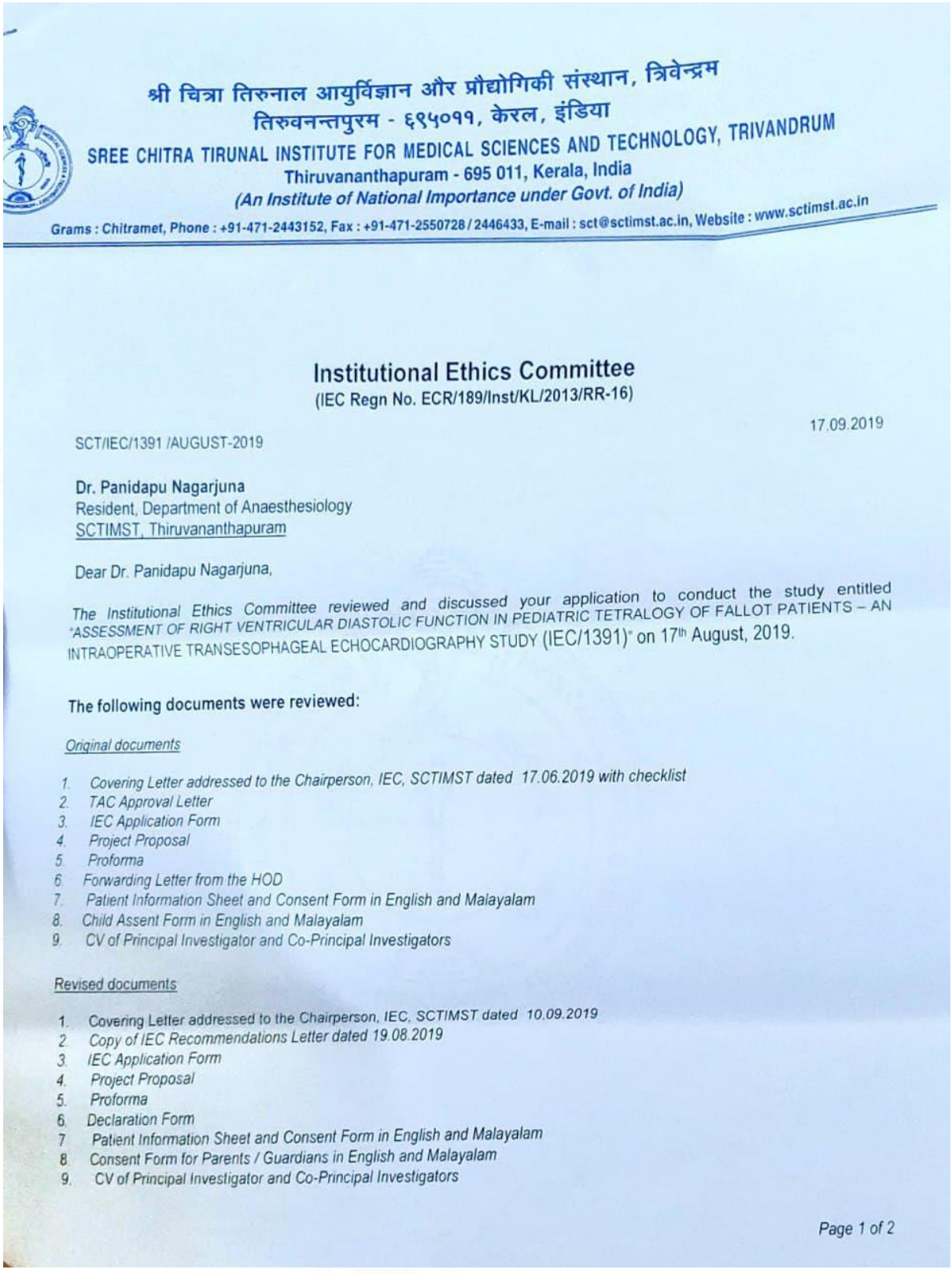
Name of witness:
Relation to participant:
Date:

(Person Obtaining Consent)

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant's guardian and explained to him/her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant's guardian to ask questions and that all questions asked were answered by me.

Name and Signature of Person Obtaining Consent

ANNEXURE 3: IEC Approval form



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

17.09.2019

SCT/IEC/1391 /AUGUST-2019

Dr. Panidapu Nagarjuna
Resident, Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Panidapu Nagarjuna,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "ASSESSMENT OF RIGHT VENTRICULAR DIASTOLIC FUNCTION IN PEDIATRIC TETRALOGY OF FALLOT PATIENTS – AN INTRAOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHY STUDY (IEC/1391)" on 17th August, 2019.

The following documents were reviewed:

Original documents

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 17.06.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Forwarding Letter from the HOD*
7. *Patient Information Sheet and Consent Form in English and Malayalam*
8. *Child Assent Form in English and Malayalam*
9. *CV of Principal Investigator and Co-Principal Investigators*

Revised documents

1. Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 10.09.2019
2. Copy of IEC Recommendations Letter dated 19.08.2019
3. IEC Application Form
4. Project Proposal
5. Proforma
6. Declaration Form
7. Patient Information Sheet and Consent Form in English and Malayalam
8. Consent Form for Parents / Guardians in English and Malayalam
9. CV of Principal Investigator and Co-Principal Investigators

Page 1 of 2

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
8.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
9.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
10.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
11.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
12.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
13.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
14.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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ANNEXURE 4: Plagiarism chart

Curiginal

Document Information

Analyzed document	New Microsoft Word Document.docx (D110761874)
Submitted	7/26/2021 12:17:00 PM
Submitted by	Dr P K Dash
Submitter email	dash@sctimst.ac.in
Similarity	6%
Analysis address	sadh.sctims@analysis.urkund.com

Sources included in the report

SA	**opponent ex pia.pdf** Document opponent ex pia.pdf (D50938776)	1
J	**Right Ventricular Diastolic Function After Repair of Tetralogy of Fallot** URL: a16879f8-d44e-4aa1-9b6a-9d3b600b33d9 Fetched: 2/27/2020 12:50:59 AM	2
W	URL: https://www.intechopen.com/books/echocardiography-in-heart-failure-and-cardiac-electrophysiology/assessment-of-right-ventricle-by-echocardiogram Fetched: 1/17/2020 9:00:46 AM	1
W	URL: https://www.researchgate.net/publication/317446862_Insuficiencia_valvular_pulmonar_en_el_posoperatorio_alejado_de_tetralogia_de_Fallot_Aporte_del_ecocardiograma_transtoracico_convencional_para_la_toma_de_decisiones Fetched: 12/29/2020 11:56:24 AM	2
W	URL: https://www.researchgate.net/figure/Clinical-Information_tbl1_12790532 Fetched: 5/21/2021 12:19:05 PM	1
W	URL: https://cardiothoracicsurgery.biomedcentral.com/articles/10.1186/s13019-019-0909-8 Fetched: 3/12/2020 2:21:58 PM	2
J	**Ratio of Early Diastolic Tricuspid Inflow to Tricuspid Lateral Annulus Velocity Reflects Pulmonary Regurgitation Severity but Not Right Ventricular Diastolic Function in Children With Repaired Tetralogy of Fallot**	2

ANNEXURE 5: Master chart

						DIASTOLIC FUNCTION DATA				
RA SIZE	INDEXED RA	RA DILATAION	MPA ANETGRADE FLOW	HEPATIC VEIN FR	IASTOLIC DYSFUNCTIO	E VELOCITY	A VELOCITY	TV E/A	TV E' VELOCITY	TV E/E'
24.9	108.26	Y	NO	NO	NO	40.1	61	0.7	11.1	3.6
25.4	133.68	Y	no	NO	NO	76	42.4	1.79	26.4	2.8
24.1	77.7	Y	Yes	yes	yes	65.4	41.6	1.57	9.79	6.6
26.4	97.7	Y	no	no	no	58.4	52.4	1.11	10.4	5.6
28.8	120.3	Y	yes	yes	yes	51.6	58.6	0.88	6.1	8.45
35.2	146.6	Y	no	no	no	69.2	34.3	2	17.2	4.02
51.8	191.8	Y	no	no	no	49.7	52.3	0.95	15.4	3.2
49.7	150.3	Y	no	no	no	54.8	56.7	0.96	18.1	3.02
56.2	129.2	Y	yes	yes	yes	67.2	31.8	2.1	5.7	11.7
42	113	Y	no	no	no	74.7	38.9	1.9	9.8	7.62
47	123	Y	no	no	no	90.5	52.6	1.78	7.03	12.8
47.5	125	Y	no	no	no	59.6	51.8	1.1	15.5	3.9
56.1	140	Y	yes	yes	yes	59.9	32.6	1.8	10.1	5.93
43.4	127.6	Y	yes	yes	yes	54.2	39.2	1.38	7.7	7.03
29.4	101.3	Y	no	no	no	48.3	40.1	1.2	9.6	5.03
31	68.8	Y	yes	yes	yes	45.2	29	1.5	4.8	9.41
22	41.5	Y	no	no	no	68.6	49.5	1.3	9.6	7.1
59	120	Y	no	no	no	85.3	71.2	1.2	18.3	4.6
25.7	59.2	Y	yes	yes	yes	60.6	44.3	1.3	9.03	6.71
20	44.4	Y	no	no	no	68.5	43.3	1.5	19.3	4.06
20.2	67.3	Y	yes	yes	yes	49.2	56.3	0.8	5.08	9.6
35.9	78	Y	no	no	no	39.8	38.1	1.1	13.2	3.01
24	82.7	Y	no	no	no	48.2	45.6	1.1	21.1	2.29
34.1	89.7	Y	no	no	no	46.8	45.1	1	12.8	3.6
29.9	76.2	Y	no	no	no	39.8	46.9	0.8	10.2	3.9

38.5	55	Y	yes	yes	yes	68.7	42.6	1.6	27	2.5
19.3	33.27	Y	no	no	no	48.2	45.6	1.1	21.1	2.28
35.9	78	Y	no	no	no	39.8	38.1	1.1	13.2	3.01
24.5	56.9	Y	no	no	no	48.2	41.4	1.2	23.1	2.1
25.6	75.2	Y	yes	yes	yes	41.4	17.3	2.4	27.3	7.6

RV thickness	EDA	ESA	FAC	TAPSE	S' TDI
9.4	15.2	6.53	57	13.8	11.8
5.6	7.61	5.36	29.5	12.4	8.9
6.1	7.9	5.17	35.4	16.8	9.1
4.6	4.61	3.02	45.3	15.6	9.8
4	4.28	35.8	17.2	13.5	8.3
5.9	12	8.1	32	18.5	9.46
8.1	5.6	4.1	26.7	17.1	10.8
4.1	7.1	5.3	25.3	9.5	14.8
8.9	8.2	4.9	40.2	11.2	11.7
7.2	5.94	3.41	53.1	5	18.9
6.8	2.99	1.56	47.8	6.5	8.8
7	3.69	2.43	36.2	7.5	16.5
10.1	25.7	9.9	25.3	10.8	25.4
6.3	5.97	4.2	30	7.2	6.5
5.7	3.34	1.71	28.2	9.2	8.1
5.9	4.23	1.83	37.9	8.2	8.7
5	4.69	2.19	41.4	6.7	5.4
4.9	4.98	3.06	49.1	7.8	19.4
6.2	4.75	3.61	40	8.5	6.6
6.9	7.56	5.36	27.4	13.6	11.2
6.1	2.97	2	22.7	4.7	5.9
8.7	8.4	6.1	27.3	10	8.7
6.28	3.91	2.9	25.8	12	16.9
6.8	6.8	4.4	35.2	13.9	12.7
7.1	5.7	3.9	31.5	8.3	10.7

7.18	7.18	3.85	46.3	10.5	9.5
6.3	3.39	2.33	25	4.5	13.8
8.7	8.4	6.9	17.8	10	8.7
6.3	3.78	2.91	23	12	16.9
7.6	3.6	1.9	45	4.9	14.4

SECONDARY OUTCOMES

Duration of inotropes	Duration of chest tube	Duration of ventilaton	ICU LOS	Hosp LOS	MORTALITY
54	28	18	76	5	no
50	19	7	61	5	no
50	67	15.5	72	5	no
43	34	19	68	5	no
74	55	28	106	7	no
48	51	3	73	5	no
76	47	21	97	7	no
73	49	9	83	8	no
49	51	18	73	7	no
89	78	36	148	12	no
70	56	12	62	7	no
48	30	6	74	5	no
108	96	98	240	16	no
89	68	36	74	5	no
56	48	16	62	5	no
18	42	24	68	5	no
19	48	19	72	7	no
56	68	24	84	7	no
48	36	12	48	5	no
65	36	19	58	5	no
84	62	32	124	10	no
72	71	9	69	5	no
69	68	12	79	5	no
78	60	14	66	6	no
90	81	39	98	9	no

48			67			12			75		5		n
56			59			10			68		5		n
36			29			68			145		19		n
39			46			16			72		7		n
120			90			28			7		12		n