AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA

DR. USNISH ADHIKARI

DM THESIS

Year: 2021-2023

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TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

DR. USNISH ADHIKARI

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF

DM Cardiology

YEAR: 2021-2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Usnish Adhikari, hereby certify that I had personally carried out the work depicted in the thesis titled, "**AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA"**

No part of this thesis has been submitted for the award of any other degree or diploma before this date.

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Date
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The thesis entitled, "**AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA**" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

Clearance was obtained from the Institutional Ethics Committee / Institutional Animal Ethics / Institutional Committee for Stem Cell Research / Other appropriate committees (if any, specify) for carrying out the study.

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APPROVAL OF THE THESIS

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Dr. Usnish Adhikari

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1.	AR	Aortic Regurgitation
2.	ASE	American Society of Echocardiography
3.	BDG	Bi-directional Glenn
4	BSA	Body Surface Area
.5.	BT	Blalock Taussig
6.	CPB	Cardio-pulmonary Bypass
7.	DBP	Diastolic Blood Pressure
8.	EF	Ejection Fraction
9.	FAC	Fractional Area Change
10.	HR	Heart Rate
11.	IQR	Inter Quartile Range
12.	LAD	Left Anterior Descending
13.	LV	Left Ventricle
14.	LVH	LV Hypertrophy
15.	NYHA FC	New York Heart Association Functional Class
16.	PA	Pulmonary Artery

17.	PHT	Pressure Half Time
18.	PLAX	Parasternal Long Axis
19.	PR	Pulmonary Regurgitation
20.	PV	Pulmonary Valve
21.	RBBB	Right Bundle Branch Block
22.	RVH	Right Ventricular Hypertrophy
23.	RVOTO	Right Ventricular Outflow Tract Obstruction
24.	SBP	Systolic Blood Pressure
25.	SD	Standard Deviation
26.	SOV	Sinus of Valsalva
27.	SpO2	Oxygen Saturation
28.	SPSS	Statistical Package for Social Sciences
29.	STJ	Sino Tubular Junction
30.	TAP	Trans Annular Patch
31.	TOF	Tetralogy of Fallot
32.	TR	Tricuspid Regurgitation
33.	VSD	Ventricular Septal Defect

SYNOPSIS

AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA

USNISH ADHIKARI

DM Cardiology

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

SYNOPSIS

- **Background & Objjectives**: Tetralogy of Fallot (TOF) is the commonest form of cyanotic congenital heart disease. Refinements in surgical repair techniques have led to steadily increasing population of TOF survivors. Dilation of the root of aorta & of ascending aorta has been frequently encountered in TOF in several studies. Studies are lacking in the Indian TOF population. This study provides information which may fill the knowledge gap & guide further re-intervention. The primary objective of this study is to assess the presence of aortic disease or aortopathy in survivors of TOF on follow-up (with or without surgical intervention). Secondary objective is to determine and identify the various factors associated with aortopathy in such a cohort.

- **Methods:** Single-centre cross-sectional follow-up study of a historical cohort of TOF patients, who consecutively visited our institute during the study period of August 2021 to June 2023. Patients with age greater than 10 years age, who had established diagnosis of TOF, TOF with pulmonary atresia or TOF with absent pulmonary valve and had undergone corrective surgical repair at least 5 years prior or those who were unrepaired, were included. Baseline data at initial presentation & surgical details were collected from EMR. At enrollment, 2D echo along with clinical data were taken. Primary outcome (Aortopathy) was defined as SOV/root diameter of ≥ 40 mm (for age ≥ 18 years), SOV/root Z score (as per ASE) ≥ + 2 (for age <18 years), aortic aneurysm (SOV/root ≥ 50 mm) or ≥ moderate aortic regurgitation.

- **Results:** The study enrolled 193 patients. Their mean present age was 25.05 ± 11.87 years, with male predominance (125, 64 %). Mean duration of follow-up after surgery was 17.42 ± 7.9 years. Mean aortic annulus, sinus of Valsalva (SOV) or root, sino-tubular junction (STJ) & ascending aortic dimension were 22.8 ± 4.26 mm, 33 ± 5.8 mm, 26.96 ± 5.08 mm & 29.41 ± 5.46 mm respectively. Primary outcome (Aortopathy) was noted in 69 (35.8 %) out of total 193 subjects. Features associated with aortopathy were TOF with pulmonary atresia, unrepaired TOF, those who had univentricular palliation & non-confluent pulmonary arteries. Mean increase in the ascending aortic dimension was 0.68 ± 0.6 mm/ year for the entire cohort.

- **Conclusion:** The most important finding in this study was the occurrence of significant aortopathy (35.8%) among TOF patients on follow-up. Further prospective studies with more homogeneous data sets are needed for better characterization of growth of aorta and for defining aortic outcomes in TOF survivors.

1 INTRODUCTION

Tetralogy of Fallot (TOF) is the commonest form of cyanotic congenital heart disease. Improvement in early diagnosis and surgical management has led to increase in the number of survivors among such cohort of patients. A steady rise in the number of people with TOF over the past forty years has also been attributed to improvements in surgical repair methods. Natural history of the disease is becoming more evident as more patients are surviving till adulthood. The development of severe pulmonary regurgitation (PR), tricuspid regurgitation (TR) due to right ventricular (RV) dilation, RV outflow tract obstruction, atrial or ventricular tachyarrhythmia, residual ventricular septal defect, and the silent progression of dilation of aortic root, which often leads to aortic regurgitation (AR), and with progression of time, to left ventricular (LV) dysfunction, are some of the causes of late morbidity in TOF survivors, that necessitate the need for further re-interventions. Dilation of aortic root & ascending aorta has been frequently encountered in TOF patients either during initial presentation or on follow-up. In the last decade, several studies have documented progressive dilation of aortic root in patients with repaired as well as unrepaired TOF. Various theories have been hypothesised regarding the etiopathogenesis, including genetic pre-disposition to intrinsic aortopathy, as well as altered hemodynamics, to explain aortopathy in TOF survivors. However, its exact underlying pathophysiological mechanism, incidence & natural history, remains elusive. An improvement in understanding regarding the development of aortopathy in TOF will equip us to implement effective interventions to prevent progressive aortic disease as more survivors of TOF live onto adulthood. The primary objective of this study is to assess the presence of aortic disease or aortopathy in survivors of TOF on follow-up (with or without surgical intervention). Secondary objective is to determine and identify the various factors associated with aortopathy in such a cohort.

2 LITERATURE REVIEW

It has been commonly reported that the aortic root undergoes progressive dilation over a long-term period following repair of TOF, with incidence that ranges between 6.6 % - 88 % depending on the definition used for aortic root dilation in various studies. The first case report of progressive dilation of ascending aorta in patients with TOF was published as early as 1970s (Matsuzawa et al., 1979), where a repaired TOF patient, who required replacement of aortic valve with mechanical prosthesis was reported. In 1997, Dodds et al. from Mayo clinic, were the first to publish a series of cases with dilation of aortic root and AR after the complete surgical repair of TOF, in a series of 16 patients. Aortic valve replacement was performed on all 16 patients; 11 received mechanical prostheses and 5 received bio-prostheses. Five of the 16 patients additionally underwent lateral aneurysmoplasties to reduce aortic dilation, and one patient required an ascending aorta replacement with graft. Despite complete and uncomplicated repair, there was increasing AR in eleven patients (Dodds et al., 1997). Niwa et al. (2002) published a series of 32 patients, out of which approximately 15% of adult patients with repaired TOF had been noted to have dilated aortic root, with 12% requiring surgical intervention (Niwa, 2005). Bhat et al (2004) found dilated aortic root in a cohort of 160 uncorrected TOF patients, which worsened in the first 36 months following palliative shunt and persisted into adulthood in those who had their condition surgically corrected. In children who had their aortic roots dilated as infants, the diameters had stabilized with age by middle childhood, approximately by the age of seven (Bhat et al., 2004). Chowdhury et al. in two different case series, reported that the diameter of aortic root, as measured by echocardiography, showed progressive dilation in 66.3% and 68.9% patients with unrepaired TOF patients respectively (Chowdhury, Mishra, Ray, et al., 2008). On histological examination, it was discovered that 78.4%, 96.1%, and 50.9% of the aortic samples had elastic

fragmentation, increase in ground substance, medio-necrosis, disarray and fibrosis of smooth muscle respectively. Patients with histologically aberrant aortas and those with fibrillin-1 exonic DNA variations had a risk of aortic dilation that was 8.83 times higher and 8.11 times higher, respectively (Chowdhury, Mishra, Balakrishnan, et al., 2008). Francois et al (2009) found aortic root that was initially dilated in TOF patients, normalised in size at the within 7 years post early repair. BSA-indexed sinus dimensions showed a substantial decrease from a mean of 51.4±13.4 mm/m2 to 28.9±7.2 mm/m2. The mean indexed sinus diameter even declined to 21.5±3.5 mm/m2 among patients who had more than 10 years of follow-up; this equated to a reduction rate of -4.8±5.4 mm/m2/year. The regression was more pronounced at the annulus and STJ level (François et al., 2010). Nagy et al (2013) observed the prevalence of root or SOV dilation to be 51 % in repaired TOF patients, with 1.8 % requiring aortic valve and 2.8 % requiring root or ascending aorta replacement surgery. Presence of AR, TOF with pulmonary atresia and presence of residual ventricular septal defect (VSD) were associated with increased odds of dilation (Nagy *et al.*, 2013). Egbe et al (2018) found that in repaired TOF, 12% patients had significant aortic valve or ascending aortic disease & 29% of them underwent aortic surgery (Egbe et al., 2018). Most recently Kim et al (2021) found that in repaired TOF, size of annulus of aorta was stable and steady, whereas SOV and STJ dimension showed progressive increase with growing age. Male gender and TOF having pulmonary atresia were noted to be associated with increased dimensions of aortic root (Kim *et al.*, 2005). Surgeries for repair of TOF increasingly include interventions on ascending aorta. In operated TOF patients, the cause of dilation of root of aorta is postulated to be mainly secondary to the long-term hemodynamic stress brought on by aortic volume overflow (Tan et al., 2005). Significant histological abnormalities in the aortic root and wall of ascending aorta is another contributing factor to progressive aortic root dilation (Tan et al., 2005).

Several studies have proposed hypotheses regarding the etiopathogenesis.

Prior to surgical repair, it is believed that augmented flow of blood from both the ventricles to the overriding aorta puts more strain on the aortic wall as compared to normal individuals. Another possible mechanism involves the aortic media undergoing histological changes similar to those seen in Marfan syndrome and those with bicuspid aortic valve. The pathophysiology includes non-inflammatory reduction in smooth-muscle cells, mucoid degeneration, and disintegration of the elastic fibres within the media (Chowdhury, Mishra, Balakrishnan, et al., 2008). Chronic hypoxia, which is an inevitable consequence in TOF patients until surgical repair, has also been demonstrated to produce growth factors as well as matrix-proteins that can cause irreversible remodelling of vascular wall, proliferation of smooth-muscles, and fibrosis within the wall of ascending aorta (Meguid et al., 2015). Marelli AJ et al. in 1994, proposed that unrepaired TOF with progressive RVOT obstruction, the most severe form of which is TOF with pulmonary atresia, leads to increase in the right to left shunt across the VSD, which may, in turn cause volume overload and dilation of aortic root (Marelli et al., 1994). The disproportionate and unequal distribution of cono-truncal tissue between the pulmonary artery and aorta, is an additional factor that accounts for aortic dilation in TOF patients, especially those having pulmonary atresia. Chowdhury et al. found considerable loss of lamellar tissue and aberrant histopathology in 78% and 96% of TOF patients respectively, while studying aortic histopathology in them (Chowdhury *et al.*, 2008). AR has also been postulated to be caused due to the prolapse of cusps of the aortic valve into the subaortic VSD, that lack support in TOF patients, who do not undergo surgery. Senzaki et al. demonstrated that alteration in hemodynamics, in the form of increased aortic strain, is strongly linked to dilation of aortic root, in repaired TOF (Senzaki et al., 2008). However similar studies have not been done in the Indian population. With increase in the number of TOF survivors, living till adulthood, the current study provides important information, that may guide further re-intervention for late morbidities in this cohort.

3 MATERIALS AND METHODS

This is a single-centre cross-sectional follow up study of a historical cohort of TOF patients. In the study, patients of Tetralogy of Fallot, who visited our institute, SCTIMST Trivandrum, consecutively, for routine follow-up, during the study period of August 2021 to June 2023 were enrolled.

3.1 Inclusion Criteria: Patients with age greater than 10 years age having a diagnosis of TOF, TOF with pulmonary atresia or TOF with absent pulmonary valve and had undergone corrective surgical repair at least 5 years prior to the date of enrolment or those who were unrepaired, were included. This was done, to allow for sufficient age & significant time-lapse post-surgery, for the aortic root pathology to have evolved.

3.2 Exclusion Criteria: Patients, who were lost to follow-up, not willing for consent, died on follow-up, who had at initial presentation, diseases involving aorta, history of infective endocarditis induced aortic valve disease, other complex congenital heart disease, apart from those mentioned in the inclusion list, were excluded from the study.

3.3 Sample Size: Based on pre-existing studies, proportion of proportion of similar outcome (TOF with aortic disease/ aortopathy) was estimated to be 12% (p). Keeping the margin of error (e) 5% & confidence Level (z) 95%, the calculated required sample-size comes to 162; using the formula $N= Z^2 \times p \times (1-p)/e^2$.

3.4 Data Collection: Baseline demographic & echocardiographic details at initial presentation, surgical details and post-operative follow-up echocardiographic data, were collected from Electronic Medical Records (EMR). Age, sex, anthropometry data, prior palliative or surgical interventions, age at which intervention was done, duration of follow-up after surgery or intervention, post-operative 5 year & 10-year echocardiographic data for aortic measurements, were reviewed from the EMR, wherever data was available. At enrolment, clinical parameters (Heart rate, blood pressure, pulse oximetry, NYHA functional class, clinical examination), anthropometry (weight & height), electrocardiogram & other imaging (CT/ MRI if available) data were collected. Body surface area (BSA) was calculated using DuBois method (Du Bois and Du Bois, 1989). 2D Echocardiography was done for all the subjects by the primary investigator under the supervision of guides. Aortic dimensions were measured at four levels: annulus (1), sinus of Valsalva (SOV) (2), sino-tubular junction (STJ) (3) & ascending aorta (4) (Fig 1) (Roman et al., 1989) on the parasternal (PLAX) long-axis view in diastole according to the American Society of Echocardiography (ASE) guidelines (Mitchell et al., 2019). Aortic arch dimensions- proximal, transverse & isthmus, were taken in suprasternal view. Rate of increase in ascending aorta was calculated using current echocardiographic dimension & retrospectively collected echocardiographic data during time of first visit or at the time of surgery, from EMR records. Aortic-valve regurgitation (AR) if present, was further quantified as absent, trivial, mild (regurgitant jet-height/ LV outflow tract diameter < 30%, no flow reversal in the descending aorta, pressure half-time (PHT) >400 ms), moderate (regurgitant jet-height/ LV outflow tract diameter 30%-59%; early flow reversal in descending aorta or PHT 251 ms-399 ms), or severe (regurgitant jet-height/ LV outflow tract diameter >60%; holo-diastolic flow reversal in descending aorta or PHT <250 ms) as per ASE guidelines. Other associated measurements including LV ejection fraction, RVOT dimension and obstruction severity, RV Fractional area change

(FAC), pulmonary regurgitation (PR), were also evaluated and quantified.

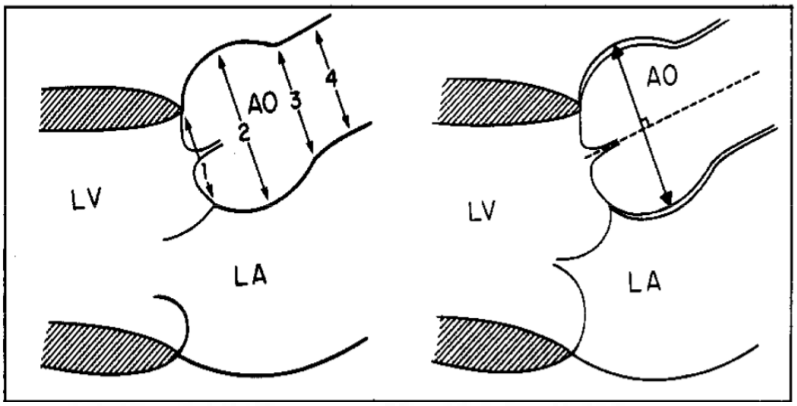


Fig 1. 2D Echo Assessment of aortic root & ascending aorta (Roman et al., 1989) Annulus (1), SOV (2), STJ (3) & ascending aorta (4); LA- Left atrium; LV- Left ventricle, AO- Aorta

3.5 Statistical analysis: Kolmogorov-Smirnov test was used for assessment of the normality of continuous variables. Continuous variables were conveyed as mean and standard deviation (SD) if they were normally distributed. Continuous variables which did not have normal distribution, were expressed as median and interquartile-range (IQR). Categorical variables were expressed in the form of frequency and percentage. Comparison of normally distributed continuous variables between two groups were analysed using independent sample t test and those which were not normally distributed was analysed using Mann-Whitney U-test. Association between the categorical variables was analysed by chi-square test. A p value <0.05 was considered as statistically significant. Data analysis was performed using SPSS version 24.

4 RESULTS

This study is an observational analysis of patients with TOF, that was conducted in SCTIMST, Trivandrum with the aim to identify aortopathy in such cohort of patients. 193 patients were enrolled in this study in accordance with the inclusion criteria. Their mean present age is 25.05 ± 11.87 years, with male predominance (124, 64.2%), their mean height & weight is 157.8 ± 11.92 cm & 52.9 ±15.21 kg respectively. Out of the 193 patients, 158 (81.8 %) had classical TOF, 30 (15.5 %) had TOF with pulmonary atresia, 5 (2.5 %) had TOF with absent pulmonary valve. 182 (94.3 %) had confluent pulmonary artery anatomy, 15 (7.8 %) had additional VSD, 27 (14 %) had right aortic arch. Majority had normal situs & levocardia. One patient had situs inversus, levocardia; one had situs solitus, dextrocardia. Coronary anomaly was seen in 8 (4.1 %) patients - 6 had LAD crossing RVOT, 1 had Common ostium & 1 had Double LAD. 2 subjects had Di-George syndrome.

Table 1: Patient present age & anthropometric parameter

Parameters (n=193)	N	Mean ± SD	Range
Present age (years)	193	25.05±11.87	10.12 - 65.17
Weight (kg)	193	52.91 ± 15.21	13 - 105
Height (cm)	193	157.85 ± 11.92	114 - 189

Table 2: Type of TOF

Type	Frequency	Percent age
TOF	158	81.8
TOF with Pulmonary Atresia	30	15.5
TOF with Absent PV	5	2.5
Total	193	100

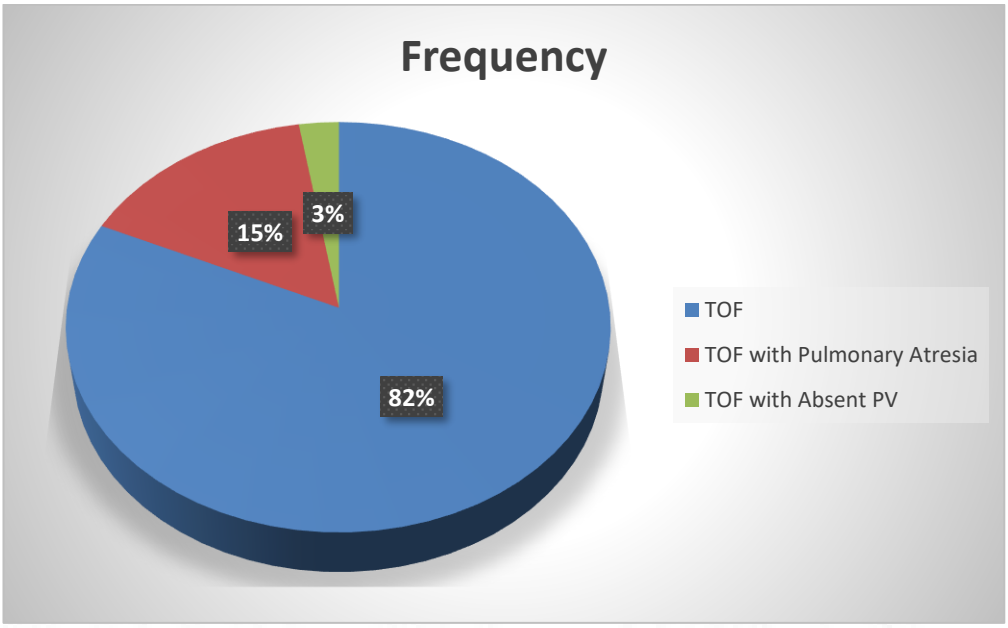


Fig 2: Type of TOF

Table 3: Patient characteristics

Patient Characteristics		**(n=193) (%)**
Sex	Male	124 (64.2)
PA Anatomy	Confluent	182 (94.3)
Additional VSD	Present	15 (7.8)
Arch	Left	166 (86)
Coronary anomaly	Present	8 (4.1)
Palliative Shunt	Yes	23 (11.9)

* 1- Situs Inversus, Levocardia; 1-Situs Solitus, Dextrocardia
* Palliative Shunts: 20 Modified BT Shunt, 1 Classical BT shunt, 1 Modified Pott shunt, 1 Modified Melbourne shunt
* Coronary anomaly- 6 LAD crossing RVOT, 1 Common ostium,1 Double LAD

Characteristics during first visit (at diagnosis):

Median age at first visit was 21 months (N=192, Range < 1 month to 600 months, IQR 8-60 months). Among patients whose data was available, median weight at first visit was 9 kg (N=143, Range 1.9 - 69, IQR 5.5 – 14 kg). Median ascending aortic size at first visit was 17 mm (N=168, Range 8-34 mm, IQR 14-21 mm); median BSA indexed ascending aortic size at first visit for those subjects whom data was available was 26.1 mm (N=38, Range 16.8 – 61.84 mm, IQR 18.28-32.58 mm/m2 BSA). Mean LV ejection fraction & RV dimension at first visit was 66.28 ± 7.73 % (N=50) & 14.74 ± 5.07 mm (N=47) respectively.

Table 4: Patient characteristics at first visit

	N	**Median**	**IQR**
Age at first visit (months)	193	21	8 - 60
Weight at first visit (kg)	143	9	5.5 - 14
Height at first visit (cm)	38	133.5	102.25 - 154
Ascending aortic size at first visit (mm)	168	17	14 - 21
BSA Indexed Aorta at first visit (mm/m2)	38	26.1	18.28 - 32.58

	N	**Mean ± SD**	**Range**
LV EF at first visit (%)	50	66.28 ± 7.73	50 - 81
RV at first visit (mm)	47	14.74 ± 5.07	6 - 34

Details of surgery:

Among the 193 subjects, 176 (91.1 %) had complete biventricular repair, 3 (1.5 %) had univentricular palliation alone (Bidirectional Glenn shunt), 16 (8.2 %) were unrepaired. Other palliative shunts were needed in 23 (11.9 %) subjects, which include modified BT Shunt in 20, classical BT shunt in 1, modified Pott shunt in 1 & modified Melbourne shunt in 1. Median age at definitive surgery, for those who were operated was 63.5 months (N=176, Range 2 – 447 months, IQR 30.2-128 months). Among patients whose data was available, median weight, height at the time of surgery was 13 kg (N=173, Range 4.3 - 70, IQR 10 – 19.8 kg), 97.5 cm (N=166, Range 55 - 189, IQR 86– 126 cm) respectively. Median ascending aortic size during surgery was 21 mm (N=174, Range 11-41 mm, IQR 17.8-25 mm); Mean BSA indexed ascending aortic size during surgery was 33.38 mm/m2 (N=166, SD ± 9.38 mm/m2 Range 15.4– 60.76 mm/m2 BSA). Mean cardio-pulmonary bypass time was 152.19 ± 50.92 minutes (N=164). Among those who underwent surgical repair, 99 required trans-annular patch, 18 underwent monocusp reconstruction of RVOT, 16 required PA plasty & 4 required RV-PA conduit/graft. Redo-ICR for residual VSD was needed for 5 patients on follow-up while 2 patients later underwent PVR.

Fig 3: Type of repair

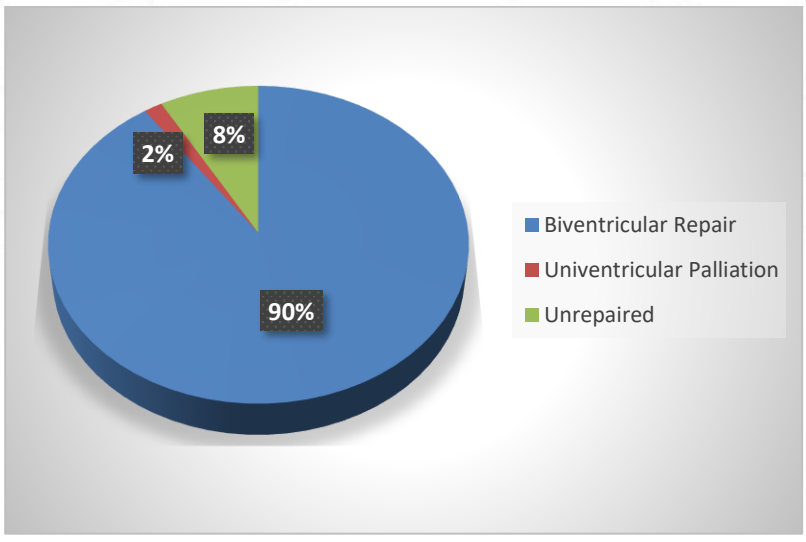


Table 5: Surgical Details

Surgical Details	Frequency (n=176)	Percentage
Trans Annular Patch	99	56.2
Monocusp Reconstruction	18	10.2
PA Plasty	16	9
RV-PA Conduit/ graft	4	2.2

Table 6: Patient details during surgery

Patient details at time of surgery	N	Range	Median	IQR
Age at surgery (months)	176	2 - 447	63.5	30.25 - 128
Aortic dimension at surgery (mm)	174	11 - 41	21	17.75 - 25
Weight at surgery (kg)	173	4.3 - 70	13	10 - 19.8
Height at surgery (cm)	166	55 - 189	97.5	86 - 126

	N	Mean ± SD	Range
BSA indexed ascending aorta size at surgery(mm/m2)	166	33.38 ± 9.38	15.4 - 60.76
CPB time (mins)	164	152.19 ± 50.92	76 - 371

Follow-up characteristics:

Mean duration of follow-up after surgery was 17.42 ± 7.9 years. Minimum follow-up after surgery being 5 years & maximum being 42.25 years. Among the 193 subjects, clinical evaluation showed mean heart rate of 85.5 ± 15.02 per minute; median blood pressure (SBP/DBP) of 116/70 mm Hg (Range: SBP- 81-194/ DBP- 43–101 mm Hg). Mean O2 saturation at room air was 97.5 ± 6.29 % (Range 70-100 %). 136 (70 %) had early diastolic murmur & 16 (8.2%) had ejection systolic murmur on auscultation. 153 (79.3%), 36 (18.6 %), 2 (1 %) & 2 (1%) were in NYHA Functional class I, II, III & IV respectively.

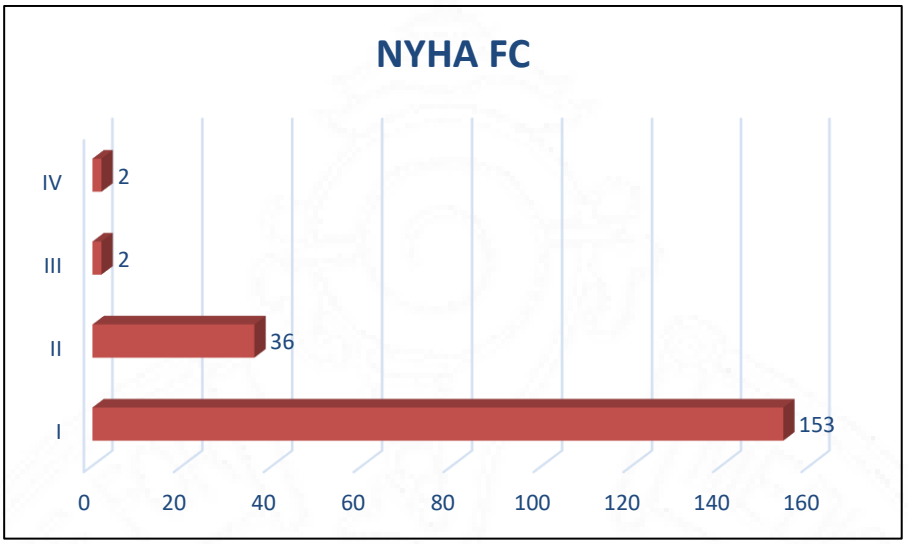
Patient clinical details at review	**N**	**Mean ± SD**	**Range**	**Median**	**IQR**
HR (/min)	193	85.54 ± 15.02	43 - 191	84.5	76 - 92.25
SBP (mm Hg)	193	117.07 ± 16.91	81 - 194	116	105 - 129.5
DBP (mm Hg)	193	72.06 ± 10.05	43 - 101	70	65 - 78
SpO2 (%)	193	97.53 ± 6.29	70 - 100	100	99 - 100

Table 6: Patient clinical details at review

Table 7: Murmurs on auscultation

Clinical Murmurs	**Frequency**	**Percentage**
Early Diastolic Murmur	136	70.1
Ejection Systolic Murmur	69	35.6

Fig 4: NYHA Functional class



ECG evaluation showed RBBB in 142 (73.5 %) with mean QRS duration 132.1±29.48 ms, LVH in 4 (1.9 %) & RVH in 157 (81.3 %) cases as per standard ECG criteria.

Table 8: ECG Characteristics

	N	Mean ± SD	Range
QRS duration (ms)	193	132.1 ± 29.48	76 - 200
	Frequency		**Percent**
RBBB	142		73.5
LVH	4		1.9
RVH	157		81.3

Echocardiographic evaluation for aortic dimensions showed mean aortic annulus, SOV (Aortic Root), STJ & ascending aortic dimension (PLAX view) of 22.8 ± 4.26 mm, 33 ± 5.8 mm, 26.96 ± 5.08 mm & 29.41 ± 5.46 mm respectively. Mean aortic arch dimensions at proximal, transverse & isthmus level (suprasternal view) were 21.7 ± 4.66 mm, 19.93 ± 4.55 mm, 16.17 ± 3.4 mm respectively. Mean indexed aortic root (SOV) size was 22.5 ± 5.71 mm/m2 BSA. 30 (15.5 %), 10 (5.1 %) & 3 (1.5%) subjects had mild, moderate & severe aortic regurgitation respectively. 1 patient had aneurysmal aortic root. Median LV ejection fraction, RVOT dimension & RV Fractional area change were 64 % (Range 23-82 %; IQR 59-69 %), 26 mm (Range 10-51 mm; IQR 22.5-30 mm), 44.5% mm (Range 20-71 %; IQR 38.5-48 %) respectively. 90 (46 %) had free pulmonary regurgitation, whereas mild & moderate pulmonary regurgitation were noted in 25 (12.9 %) & 47 (24.3 %) subjects; while 10 (5.1 %) & 5 (2.5 %) subjects had moderate & severe RV outflow tract obstruction.

Table 9: Echo parameters (A)

Echo parameters	N	Mean ± SD	Range
Aortic Annulus (mm)	193	22.8 ± 4.26	14.4 - 40.9
Sinus of Valsalva(SOV) (mm)	193	33 ± 5.8	17.0 - 50.7
Sino-Tubular Junction(STJ) (mm)	193	26.96 ± 5.08	14 - 42.5
Ascending Aorta (mm)	193	29.41 ± 5.46	16.7 - 47.5
Proximal Arch (mm)	193	21.7 ± 4.66	10.4 - 40.3
Transverse Arch (mm)	193	19.93 ± 4.55	10 .0- 37.5
Isthmus (mm)	193	16.17 ± 3.4	8.9 - 32.4
BSA indexed Aortic root size (mm/cm2)	193	22.5 ± 5.71	10.81 - 57.17

Echo parameters	N	Median	IQR
RVOT (mm)	193	26	22.5 - 30
LV Ejection Fraction (%)	193	64	59 - 69.25
RV Fractional Area Change (%)	19	44.5	38 - 48

Table 10: Echo parameters (B)

Echo Parameters on review (n=193) (%)	
Aortic Regurgitation	**Frequency (%)**
Nil	121 (62.6)
Trivial	29 (15)
Mild	30 (15.5)
Moderate	10 (5.1)
Severe	3 (1.5)
Aortic Aneurysm	1 (0.5)
Pulmonary Regurgitation	
Nil	22 (11.4)
Trivial	9 (4.6)
Mild	25 (12.9)
Moderate	47 (24.3)
Free	90 (46.6)
RVOTO	
Nil	121 (62.6)
Mild	57 (29.5)
Moderate	10 (5.1)
Severe	5 (2.5)

Primary outcome (Aortopathy) was defined as SOV/root diameter of ≥ 40 mm (for age ≥ 18 years), SOV/root Z score (as per ASE) ≥ + 2 (for age <18 years), aortic aneurysm (SOV/root ≥ 50 mm) or ≥ moderate aortic regurgitation. Primary outcome was noted in 69 (35.8 %) out of total 193 subjects. Out of 126 adult patients (age ≥ 18 years), 24 had SOV/Aortic root dimension ≥ 40 mm & out of 67 paediatric patients (age 10-18 years), 42 had SOV/Aortic root Z scores ≥ +2. 1 patient had aortic root aneurysm. 12 patients in all had more than moderate aortic regurgitation. None of the patients had aortic dissection, and none of them needed any aortic root or valve intervention. Mean increase in ascending aortic dimension in those who were operated was 0.68 ± 0.6 mm/ year (n=189) from the time of surgery or first visit (whom data was available), till follow-up (mean duration of 17.42 ± 7.9 years)

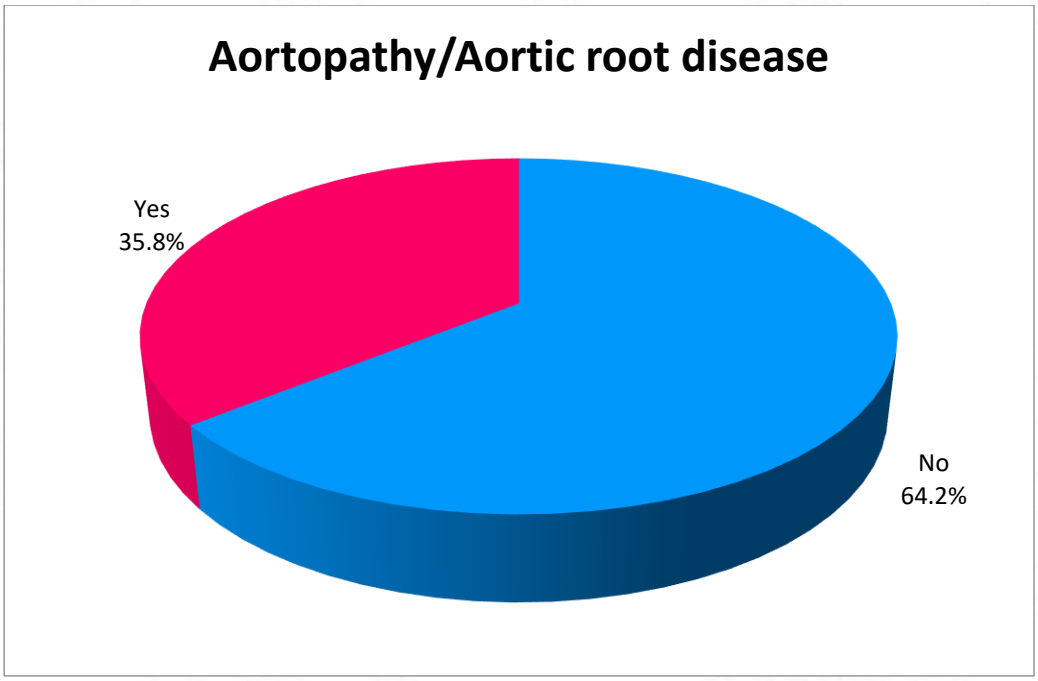


Fig 5: Primary outcome: Aortopathy

Table 11: Distribution of Aortopathy

	Frequency
Age: 10-18 years	67
SOV Z score (<+2)	25
AR 0-2	25
≥ 3	0
SOV Z score (>+2)	42
AR 0-2	39
≥ 3	3
Age ≥ 18 years	126
SOV < 40 mm	102
AR 0-2	99
≥ 3	3
SOV ≥ 40 mm	24
AR 0-2	18
≥ 3	6
Grand Total	193

Those with aortopathy

Aortopathy was significantly noted to be higher among TOF with pulmonary atresia (p <0.001), in those with non-confluent PA anatomy (p <0.001), in those who were unrepaired (p <0.001) & those who had univentricular palliation (Bidirectional Glenn Shunt). Although CPB time during surgery was higher in those with aortopathy (173 vs 151 minutes), it was not statistically significant (p=0.214). Type of arch, presence of additional VSD, aberrant coronary anatomy, palliative BT shunt were not significantly related to aortopathy. Also, use of trans-annular patch, monocusp-reconstruction of RVOT, PA plasty & those who required additional surgery, did not have significant association with aortopathy.

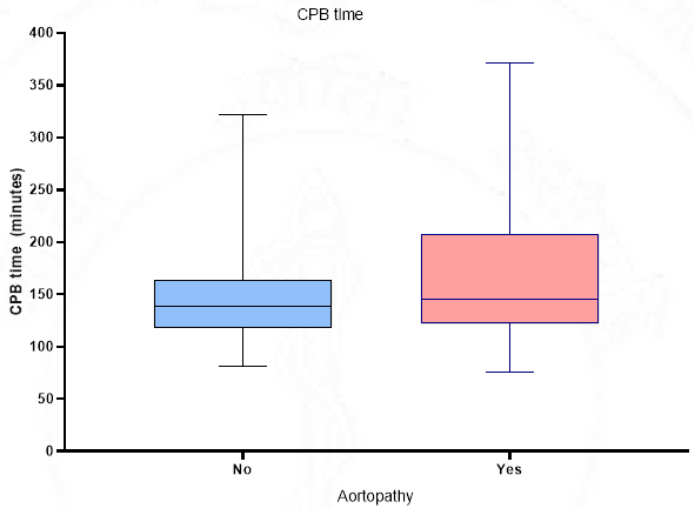


Fig 6: CPB time & aortopathy

The cohort who had aortopathy was found to be significantly younger (mean age 21.4 vs 27.1 years; p =0.001), had lower weight (46.9 vs 56.5 kg, p <0.001) & body surface area (1.4 vs 1.57 m2; p<0.001). There was significant statistical correlation between male sex and aortopathy in comparison to female sex (p= 0.016). They had a younger age at definitive surgery (73.2 vs 107.3 months; p=0.019; n= 176). Patients who persisted to have aortopathy, already had significantly increased BSA indexed ascending aortic dimension, at the time of surgery, (36.7 vs 32.1 mm/m2; n= 166; p=0.002). There was no significant correlation with

duration after surgery and development of aortic root disease.

	Without aortopathy		With Aortopathy		p Value
	Mean	SD	Mean	SD	
Present age (years)	27.1	11.4	21.4	11.9	0.001
Weight at review (kg)	56.5	13.9	46.9	15.2	<0.001
Height at review (cm)	159.2	9.9	155.3	14.7	0.028
BSA at review (m2)	1.57	0.23	1.40	0.29	<0.001
Age at surgery (months)	107.3	100.0	73.2	71.0	0.019
BSA indexed Aorta @ surgery	32.1	8.4	36.7	9.6	0.002

Table 12: Comparison between those without & with aortopathy as regard to patient characteristics

Also patients with aortopathy also had significantly higher aortic annulus (25.2 vs 21.4 mm; p<0.001), sino-tubular junction (29.3 vs 25.6 mm; p<0.001), ascending aorta (31.2 vs 28.3 mm; p < 0.001) & arch: proximal (23.5 vs 20.7 mm; p< 0.001), transverse (21.3 vs 19.1 mm; p=0.001) & distal (16.9 vs 15.7 mm; p=0.022) dimensions, as compared to those who did not have aortopathy. Clinically, those with aortic disease were significantly more symptomatic (NYHA FC II & above) (p =0.007) & had higher mean heart rate (87 vs 84 /min, p =0.037), lower mean systolic & diastolic BP (112.4/68.9 vs 119.5/73.7 mm Hg; p=0.001), and lower mean room air oxygen saturation (94.8 vs 99 %; p < 0.001), than those without aortopathy. Among 4 cases with LVH on ECG, all 4 had aortic disease.

	Without aortopathy		With Aortopathy		P value
	Mean	SD	Mean	SD	
Aortic Annulus (mm)	21.4	2.7	25.2	5.3	<0.001
SOV (mm)	30.9	4.4	36.6	6.0	<0.001
STJ (mm)	25.6	4.1	29.3	5.8	<0.001
Proximal arch (mm)	20.7	3.5	23.5	5.8	<0.001
Transverse arch (mm)	19.1	3.4	21.3	5.7	0.001
Isthmus (mm)	15.7	2.8	16.9	4.0	0.022

Table 13 Comparison between those without & with aortopathy as regard to echocardiographic aortic dimensions

	Without aortopathy		With Aortopathy		P value
	Mean	SD	Mean	SD	
HR (/min)	83.4	12.2	87.4	12.8	0.037
SBP (mm Hg)	119.5	16.7	112.4	14.5	0.004
DBP (mm Hg)	73.7	10.0	68.9	9.2	0.001
SpO2 (%)	99.0	3.2	94.8	9.1	<0.001

Table 14: Comparison between those without & with aortopathy as regard to clinical parameters

Among the repaired TOF patients, whose ascending aortic dimension on echo, at first visit, at 5 years & at 10 years post-surgery was available from EMR, when mean data was plotted along with present mean ascending aorta dimension, it was noted that significant difference among those with aortopathy & those without, started arising 10 years post-surgery.

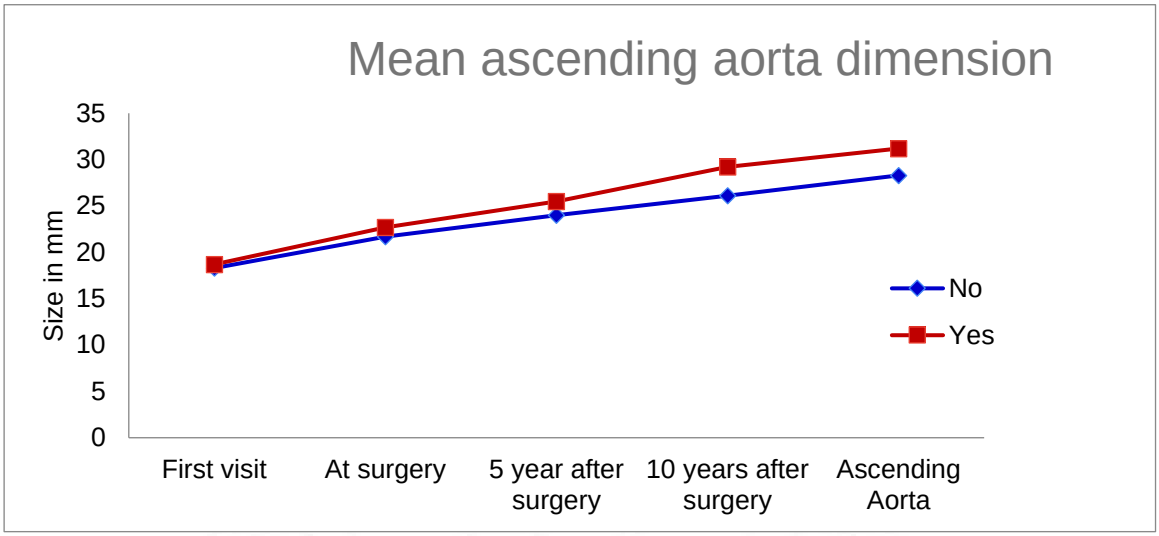


Fig 7: Increase in mean ascending aortic dimension in those without (No) & those with aortopathy (Yes)

Ascending aorta dimension (in mm)	Aortic disease				P value
	Without aortopathy		With Aortopathy		
	Mean	SD	Mean	SD	
First visit	18.3	5.6	18.7	6.5	0.685
At surgery	21.7	5.6	22.7	7.1	0.307
5 year after surgery	24.0	4.1	25.5	5.9	0.162
10 years after surgery	26.1	3.4	29.2	4.7	0.002
Present	28.3	4.4	31.2	6.6	<0.001

Table 15: Comparison between those without & with aortopathy as regard to increase in mean ascending aortic dimension

The median rate of increase in ascending aorta dimension in 189 patients, as measured from the time of surgery or first visit (for whom was available), till present day, was significantly higher for those with aortopathy in comparison to those who did not develop aortopathy (0. 65 vs 0.39 mm/year; p <0.001).

Table 16: Comparison between those without & with aortopathy as regard to rate of increase in mean ascending aorta (mm/year)

Table 16:	Aortic disease						*p value
	Without aortopathy			With Aortopathy			
	N	Median	IQR	N	Median	IQR	
Rate of increase in ascending aorta dimension (mm/year)	115	0.39	0.15 - 0.69	74	0.65	0.36 - 1.218	<0.001

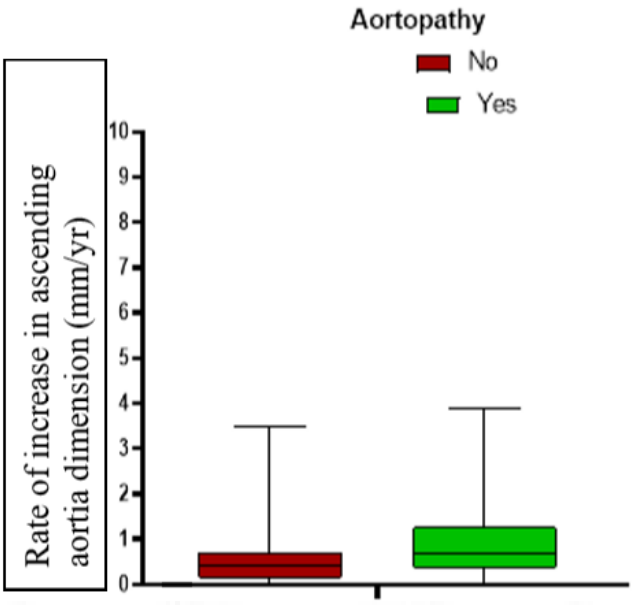


Fig 8: Increase in Ascending aortic dimension

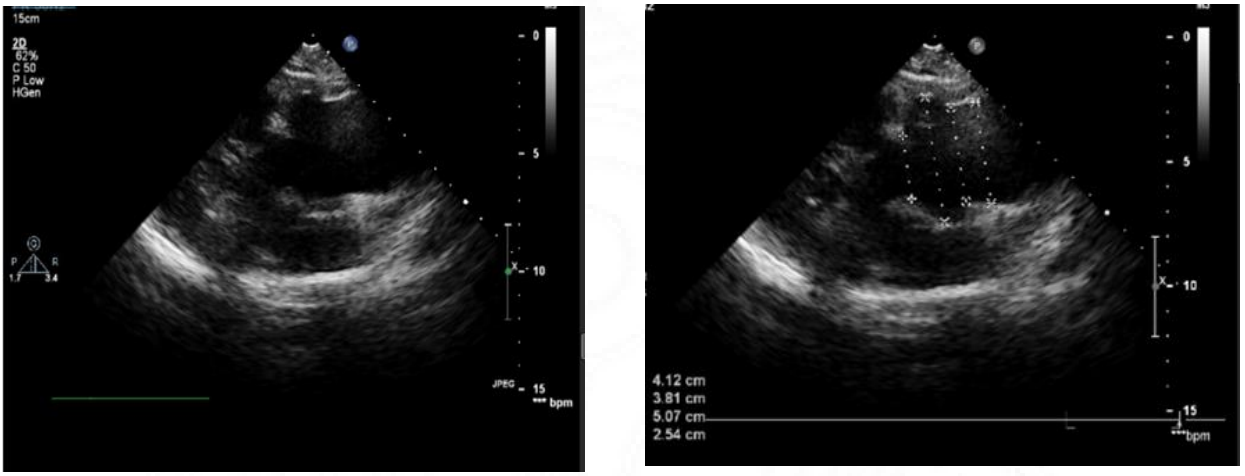


Fig 9: 40 year male, underwent ICR for TOF 32 years back, now with dilated Aortic root in echo

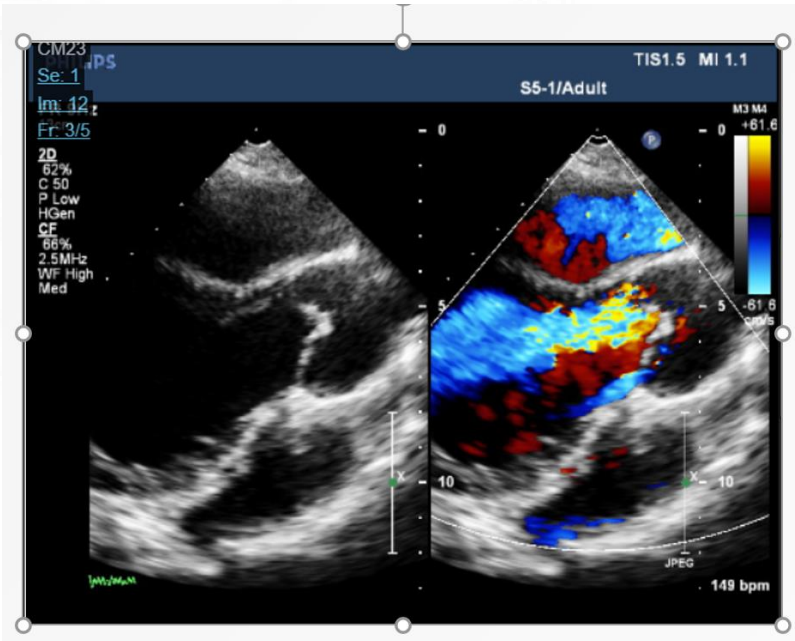


Fig 10: 27 year female, TOF repaired (ICR) 21 years back, now has severe AR on echo

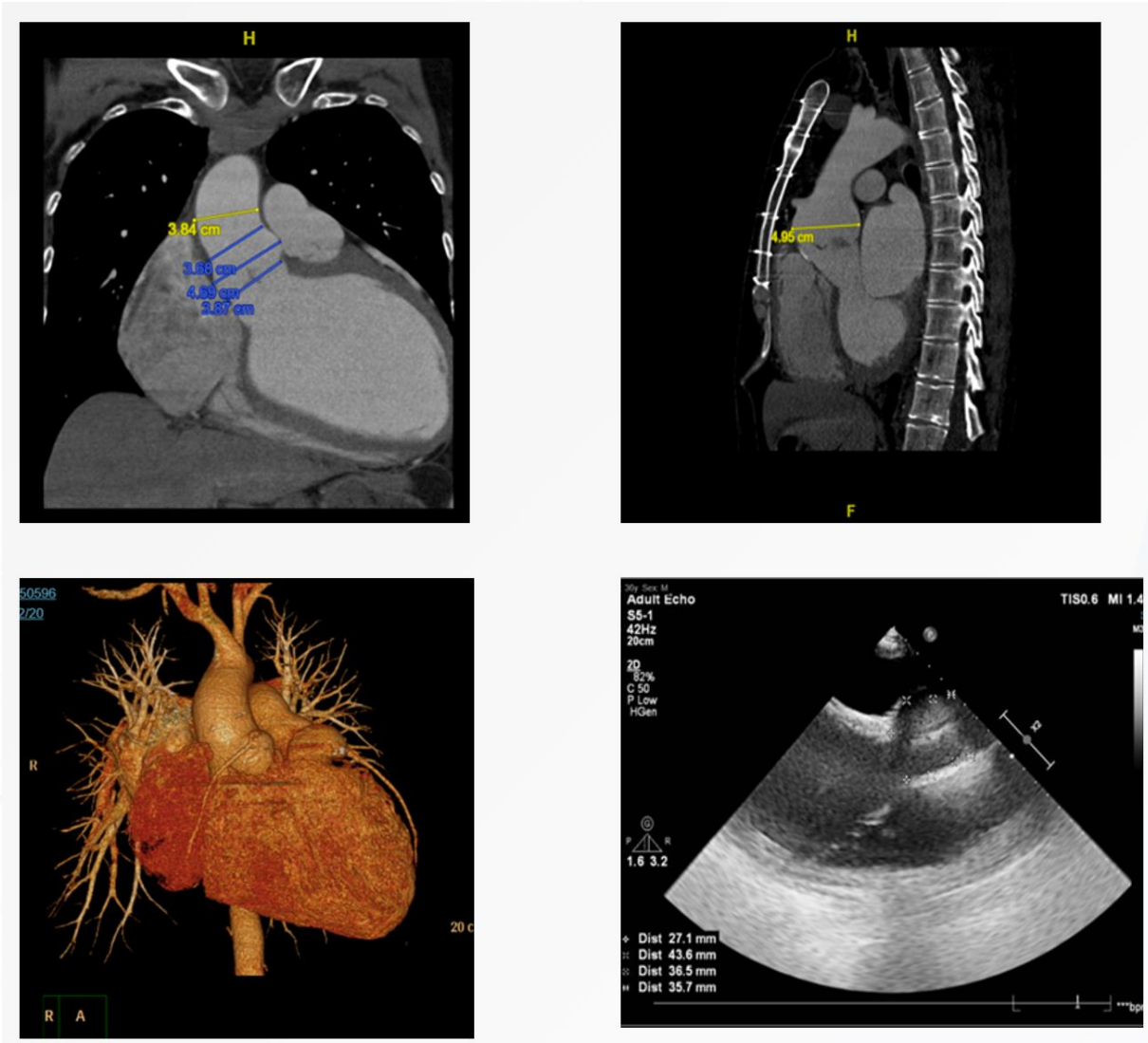
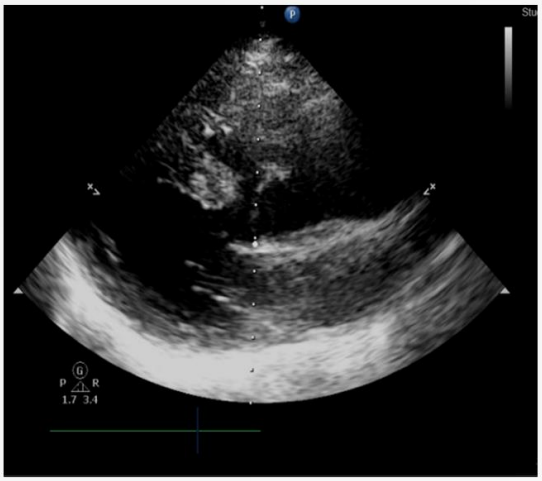


Fig 11: 36 year male, underwent ICR for TOF 12 years back, now with dilated aortic root, severe AR & LV dysfunction with dilated LV (CT & Echo images)



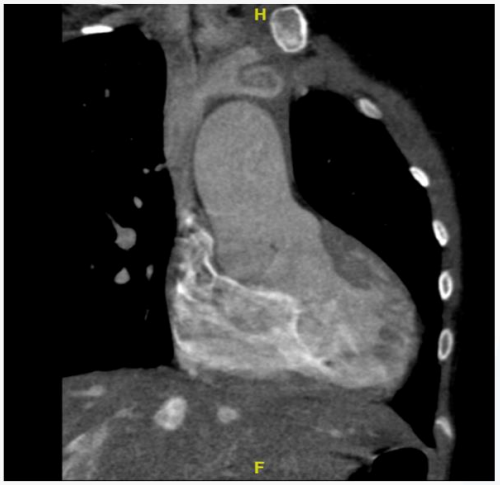
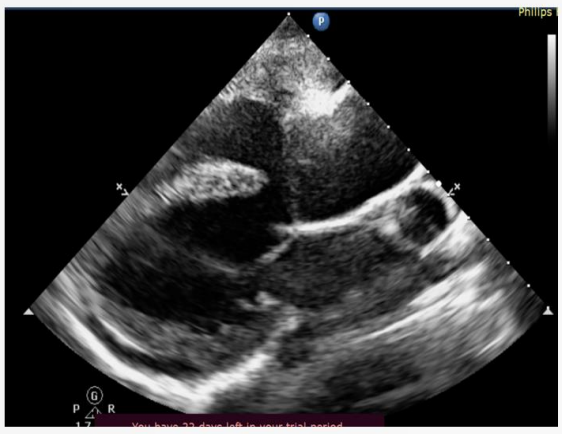


Fig 12: 22 year male with unrepaired TOF with Pulmonary Atresia; showing dilated aortic root (echo & CT)



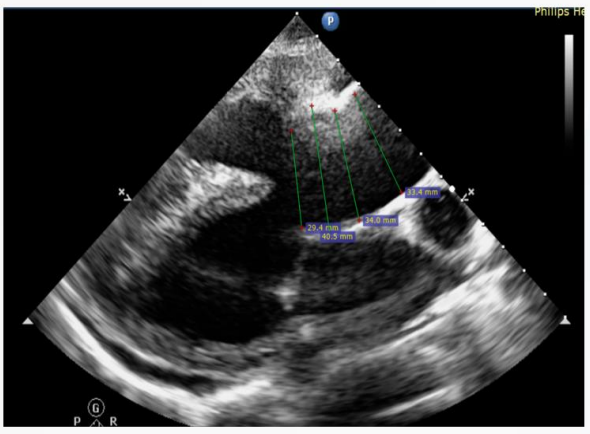


Fig 13: year old female, unrepaired TOF with Pulmonary Atresia in echo

5 DISCUSSION

TOF is the commonest cyanotic congenital heart disease, with one in 2900 live-born affected (van der Linde et al., 2011). A well-known characteristic of TOF is aortic root and ascending aorta dilation, although the natural history of progression of aortic size over time is poorly understood (Dodds et al., 1997). Though traditionally it has been considered to be a right-sided condition, depending on the population examined and the criterion utilized, dilation of aorta in this cono-truncal abnormality has been documented with a prevalence that ranges from 6.6% to 88% (Chong et al., 2006), (Mongeon et al., 2013). There is increasing evidence that supports an intrinsic aortopathy (Niwa, 2005), although long-standing volume overload of the root, that leads to progressive root dilation, is also postulated as an important cause. Aortic dilation in TOF may be detected very early during infancy & similar histological characteristics are shared with other connective tissue disorders. (Chowdhury, Mishra, Balakrishnan, et al., 2008). Risk for aortic dissection has however not been noted (Frischhertz et al., 2015). Efforts that have aimed to characterize normal aortic dimensions in TOF have been hindered by different and varying definitions used to quantify dilation. When it is defined as SOV $\geq$ +2 Z-score, 88% children (Chong et al., 2006) and 51% adults with surgically repaired TOF have been found to have dilated aortas (Nagy *et al.*, 2013) in different studies. For normal adults, the upper limit of normal for aortic root or SOV extends from 37 to 40 mm for men and 33–39 mm in women depending on age (Devereux et al., 2012); If we use this cut-off, and aortic dilation is defined as an absolute SOV dimension of $\geq$ 40 mm, it is found to be present in 23–29% adults having TOF (Mongeon et al., 2013), (Dennis et al., 2014). In other similar studies, aortic SOV dilation has been reported to be as high as 51 % in repaired TOF patients (Nagy *et al.*, 2013) with SOV mean Z score of +2.03. Another study

reported 29% of their cohort of TOF patients with significant aortic root disease (Dennis et al., 2014). Along with aortic dilation, development of aortic regurgitation is a significant complication noted in TOF survivors (Capelli et al., 1982). According to Chong WY et al. 2006, aortic regurgitation (AR) was present in 12% of TOF patients, who tended to have higher Z-scores at all the aortic levels (Chong et al., 2006). Bhat et al., in 2004, reported more than mild AR during post-infancy period in 18% of the TOF group who were surgically repaired (Bhat et al., 2004). In unrepaired TOF patients, aortic regurgitation is postulated due to the prolapse of cusps of aortic valve, that lack support, into the subaortic VSD (Bull et al., 1995). In many of the previous studies, apart from aortic root dilation, significant aortic regurgitation (more than or equal to moderate) has also been considered as a part of aortopathy in TOF.

Several cardiac MRI studies have also noted increased aortic diameters in TOF Patients, as compared with normal values. In one of such study, presence of aortic dilation in 28% has been noted in a cohort of 72 TOF patients (Ordovas et al., 2016). In another paediatric MRI study of 483 patients, Z-scores for ascending aortic areas were noted to be higher in TOF patients in comparison to normal controls (mean Z-score = 1.95, P=0.001). Some of these studies have also published MRI based aortic Z-scores for children with TOF (Grothoff et al., 2016), but these scores are not very widely used in routine clinical practice. Echocardiography can be utilised better as it is a more easily accessible method of aortic assessment during follow-up.

In this single-centre, cross-sectional follow up study of a historical cohort of 193 patients, we included patients with classical TOF, TOF with pulmonary atresia & TOF with absent pulmonary valve. The cohort was age-wise heterogeneous, 126 out of them were

adults (≥ 18 years) & 67 were of paediatric age group (10-18 years). 35.8 % (69) out of cohort were found to have aortopathy. For defining aortopathy, our study used the criteria of SOV/ root diameter of ≥ 40 mm (for age ≥ 18 years), SOV Z score ≥ + 2 (for age <18 years), presence of aortic aneurysm (SOV ≥ 50 mm) or ≥ moderate aortic regurgitation, as evaluated by 2D echocardiography. Mean (± SD) aortic SOV dimension in our study was 33 ± 5.8 mm, with mean ((± SD) indexed SOV 22.5 ± 5.71 mm. 6.7 % (13) cases had moderate or more aortic regurgitation. 1 case had aneurysmal SOV (≥ 50 mm). Our study, which is the largest such cohort of TOF patient in Indian population, shows significantly high percentage of aortopathy, which is consistent with results of previous studies.

The causes of larger sizes of aortic root in TOF have been the subject of numerous studies. Age, gender, earlier age at repair, prior history of aorto-pulmonary shunt, pulmonary atresia, and right sided aortic arch have all been noted to be associated in different earlier studies, but the data is mixed. The more severe the obstruction of RV outflow tract, larger is the size of aortic root, a relationship that is best demonstrated in TOF in its most extreme form, that is TOF with pulmonary atresia, a correlation that has been observed in several studies (Dodds et al., 1997), (Mongeon et al., 2013), (Meguid et al., 2015) , (Grotenhuis et al., 2018). Similar finding has been noted in our study, in which 70 % (21/30) of TOF with pulmonary atresia have aortopathy (p value < 0.0001). This is also consistent with the finding that AR is likewise linked to larger aortic roots, which may be explained by greater flow over the LV outflow tract. The disproportionate and unequal sharing of cono-truncal tissue between the aorta and the pulmonary artery is another explanation for dilation of aorta in TOF patients, especially those with pulmonary atresia (Anderson et al., 2010). Also, in our study, the aortopathy was significantly higher among those who were unrepaired (88.2 %; p <0.001) & those who underwent univentricular palliation (100 %; p =0.011). This finding also

corroborates with previous studies. Apart from hemodynamic factor, another contributory factor is chronic desaturation leading to tissue hypoxia in patients with unrepaired TOF (Meguid et al., 2015). This has been evidenced to produce growth-factors as well as matrix proteins that can cause irreversible remodelling of vascular wall, proliferation of smooth muscles, and fibrosis in the wall of ascending aorta (Faller, 1999). This is supported by the fact that our study also reported statistically significant lower room air oxygen saturation (SpO2) in patients who had aortopathy in comparison to those who did not (94.8 vs 99 %; $p < 0.001$). Male gender has consistently been associated with aortic dilation in repaired TOF patients along with other congenital cardiac diseases while female sex has been found to be protective against several adverse aortic outcomes in different studies (Nagy *et al.*, 2013; Dennis *et al.*, 2014; Bonello *et al.*, 2018). This has been postulated due to earlier decline in aortic distensibility & elasticity with age in males as compared to females (Sonesson et al., 1994). Our study also shows statistical correlation between male sex and aortopathy ($p= 0.016$), however since the entire cohort had male predominance, the finding may not be significant. Studies have also indicated that early repair in infancy, at less than one year age corresponded with smaller size of aortic root as compared to those who had been repaired late (Bhat et al., 2004; François et al., 2010). It implies that reducing the excessive and disproportionate flow across the aorta, can have beneficial effects on the size of aorta. Bhat et al inferred that early surgical repair eliminated the requirement for palliative shunts and all of their associated dilemmas, including distortion of pulmonary artery and dilation of aortic root (Bhat et al., 2004). Thus, in order to prevent increase in aortic root enlargement, early unloading of the volume through the aortic outflow by means of definitive repair, is recommended. However, our study did not show that those who had earlier age at surgery, were less likely to develop aortic disease. On the contrary, the cohort with aortopathy was paradoxically noted to have a younger age at definitive surgery (73.2 vs 107.3 months;

p=0.019; n= 176). Possible explanation could be that, higher proportion of aortopathy was seen in paediatric age group of patients as compared to adult group and in whom, the regression of aortic dilation post-surgical repair might not have been complete by the time of follow-up, thus giving this unexpected result. Other variables which have been found to be associated with aortic dilation in TOF patients in previous studies include palliative aorto-pulmonary shunts (like BT shunt) with increased shunt-to-repair interval, right-sided aortic arch, 22q11.2 deletion (Chong et al., 2006; Marelli et al., 1994; Meguid et al., 2015). However, our study did not find any significant association with these factors. There was no significant difference in the duration of follow-up from the time of repair in our study as well. However, when the trend of increase in the mean ascending aortic dimensions from the first visit, time of surgery, 5- & 10-years post-surgery and till present day was analysed, among the aortopathy and non aortopathy cohorts, who had undergone surgical repair, significant difference was noted after 10 years of surgery, suggesting changes in aortic dimensions might become evident even after significant duration post-surgery.

Natural history of rise in the size of aorta over time in TOF patients is poorly elucidated in the paediatric and the young-adult population. One of the findings in our study was that, aortopathy was higher in paediatric age group (10-18 years) of patients - 42 out of 67 cases (62.6 %) as compared to adult age group (≥ 18 years) - 27 out of 126 cases (21.4 %). This resulted in the cohort with aortopathy, having significantly younger age (mean age 21.4 vs 27.1 years; p =0.001), with lower weight (46.9 vs 56.5 kg, p <0.001) & body surface area (1.4 vs 1.57 m2; p<0.001). Two previous studies have recorded normalization of the initial root of aorta enlargement by the time of school-going age. In one of the echocardiographic study by Bhat et al, comparison of 43 patients with TOF, who were surgically repaired in infancy (<1 year) to 342 patients, who were repaired after infancy, demonstrated that those

who underwent early repair, had normalization of their aortas by the age of 7 years, whereas those who underwent repair later in life, demonstrated to have persistent enlargement of aortic dimensions (Bhat et al., 2004). Another study by Francois et al in which, 88 TOF patients, repaired in infancy were followed up, echocardiography showed that while the annulus and STJ normalized by the 7th post-operative year (Z-score < +2), the aortic root did not normalize. Although the indexed root diameter showed notable regression over time, this process appeared to be slowed in comparison to the annulus and STJ level, where the regression was more pronounced (François et al., 2010). Both these studies, as well as findings of our study, support the theory, that an intrinsic aortopathy affects patients with TOF at an early age, however as the child grows, hemodynamic factors like volume overload of the aortic root over a long-standing period, lead to perpetuation of this aortopathy. Early surgery arrests this process to some extent, although complete regression of aortic dilation may not occur. This was also supported by our study, where increased mean BSA indexed ascending aortic size was noted at the time of surgery (33.38± 9.38 mm/m2; N=166); whereas mean BSA indexed aortic root/SOV dimension at the time of follow-up improved to 22.5 ± 5.71 mm/m2 (N=193). It was also noted that patients who persisted in having aortopathy on follow-up, already had significantly increased BSA-indexed ascending aortic dimension, at the time of surgery, (36.7 vs 32.1 mm/m2; N= 166; p=0.002). Contradictory to this finding, another echocardiographic study by Grotenhuis et al found no discernible decline in the size of aorta at the annulus or SOV in paediatric TOF patients, who had been monitored over a median period of 3.7 years, and the dimensions continued to be steadily enlarged over time. Also, the initial post-repair echocardiography revealed that ascending aorta was not dilated (Z-score < 2), but was dilated (Z-score > +2) during the final follow-up (Grotenhuis et al., 2018). In our study cohort, no patient had been found to have any evidence of aortic dissection. There are only four case reports of aortic dissection in TOF patients, reported in the literature, and almost

all of these events occurred when aortic root dimensions were 70 mm or greater (Kim et al., 2005; Konstantinov et al., 2010; Rathi et al., 2005). Aortic dissection has not been recorded in any other studies, except for these four isolated case reports, a finding which is consistent with results of our study. Incidence of aortic aneurysm is also rarely noted, our study had only 1 patient. None of those with dilated aorta or aortic regurgitation, nor the one with aortic aneurysm, undergo any aortic root/ valve surgery or intervention. Based on this study, standard recommendation guidelines for congenital heart diseases, for aortic replacement may be followed for management of patients with TOF & any intervention on the aorta may be opted for, on case-by-case basis as per the opinions of a multidisciplinary team.

6 LIMITATIONS

Firstly, the study is a cross-sectional study of a retrospective cohort. Hence availability & accuracy of retrospective data collected from the EMR review was a major limitation. Secondly, a convenient sampling method was used, in which consecutive patients coming for routine follow-up visit were enrolled. Also, this was a non-blinded study, so selection & observer bias was not eliminated. Thirdly, echocardiography was used for the measurement of outcome variable, which is subjective & user-dependent. Intra-observer variability could not be assessed. Fourthly, another limitation was wide variability in data set, especially age group & duration from the first presentation & surgery. Fifth, rate of increase in aortic dimension was calculated from retrospective data and the normal rate of growth of aorta was not accounted for during calculation. Finally, our study is not powered for detecting associations with the various individual factors, and hence the results might not apply to the entire population of TOF as a whole.

7 SUMMARY AND CONCLUSIONS

In conclusion, this study done among an Indian cohort of TOF survivors, has important clinical implications. In this study, we found that aortopathy is common in TOF patients, present in 35.8 % (69 out of 193 patients). 6.7 % (13 out of 193 patients) had moderate or more aortic regurgitation. All aortic measurements including annulus, STJ, ascending aorta & arch dimensions were higher in those with aortopathy than those without. Features associated with aortopathy were TOF with pulmonary atresia, unrepaired TOF, those who had univentricular palliation & non-confluent pulmonary arteries. Rate of increase in ascending aortic dimension was significantly higher in those with aortopathy than their counterpart. Though our study is a cross-sectional study of a retrospective cohort, it is the largest such study in India. Further prospective studies with more homogeneous data sets are needed for better characterization of the growth of aorta and for defining aortic outcomes in TOF survivors. Also the findings need to be compared with the normal population. Optimal management of aortic root dilation & aortic regurgitation in TOF patients is in an evolving phase because little evidence-based information is currently available. The need aortic root or valve surgery or intervention is low. However judicious follow-up of the aortic dimensions & monitoring the progression of AR, if present, is recommended in TOF patients even after repair.

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ANNEXURES

Curriculum Vitae

Appendices

APPENDIX A – ETHICS COMMITTEE APPROVAL

APPENDIX B – SUPPLEMENTARY TABLES/ PROFORMAS

APPENDIX C – PLAGIARISM CHECK REPORT

Curriculum Vitae

ADHIKARI	USNISH	
Last Name	First Name	Middle Name
Date of Birth (dd/mm/yy) **23/12/1991**		Sex **MALE**
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator): PI		

Professional Mailing Address (Include Institution name)	Study Site Address (Include Institution name)
Senior Resident, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011	Senior Resident, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011
Telephone (Office): **9475819303**	Mobile Number: **9779249303**
Telephone (Residence): **9779249303**	Email: **adhikari.usnish1991@gmail.com**

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MD (PEDIATRICS)	**2018**	**PGIMER, Chandigarh, India**
MBBS	**2015**	**Medical College, Kolkata, India**

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration
WEST BENGAL MEDICAL COUNCIL: **WBMC 72447 (YEAR-2015)**
THE TRAVANCORE COCHIN COUNCIL OF MODERN MEDICINE: **79613 (YEAR- 2021)**

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
01/01/2021 - date	Senior Resident (DM Cardiology)	SCTIMST
09/2018 – 12/2019	Senior Registrar (Pediatrics)	Apollo Gleneagles Hospital, Kolkata
07/2015-06/2018	Junior Resident (MD Pediatrics)	PGIMER, Chandigarh, India

Brief summary of relevant research experience:

Publications:

(i) Child with Progressive Hemiparesis: Think beyond Neoplastic Disorders. (The Indian Journal of Pediatrics, May 2018: 12098-018-2700-6)

(ii) Recurrent Cerebrospinal Fluid Pleocytosis (Indian Journal of Pediatrics 2019 Mar;86(3):308-309)

(iii) MD Thesis: Long term neurological, behavioural and functional outcome in all survivors of status epilepticus admitted to PICU of a tertiary care hospital

Current project/s at hand:

Signature: Usnish Adhikari	Date: 10/01/2022 Place: TRIVANDRUM

Format for CV of the Investigators

Krishnamoorthy	KM	
Last Name	First Name	Middle Name
Date of Birth (dd/mm/yy) 01/06/1961		Sex M
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) CI		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum		Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum
Telephone (Office): 0471-2524357		Mobile Number: 9447239424
Telephone (Residence): 0471-2542322		Email kmkmsai@gmail.com

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
DM	1994	SGPGIMS, Lucknow
DNB cardiology	1994	NBE
MD	1989	GMC, Trivandrum
MD paediatrics	1992	NBE

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration 14567, TCMC

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Apr 2016	Professor, SCTIMST	SCTIMST
Apr 2008	Additional Professor	SCTIMST
Apr 2004	Associate Professor	SCTIMST
Mar 2000	Assistant Professor	SCTIMST

Brief summary of relevant research experience: Co-PI in 1 extramural and PI in 18 non funded peer reviewed projects

Current project/s at hand: **Co-PI for 1 extramural funded project**: Development of nitinol based occlusion devices for non-surgical closure of atrial septal defects, Project 8150, entered preclinical phase, Funding TRC Rs 45 Laks

Signature:	Date: 22-2-2022 Place: Trviandrum

Last Name: Gopalakrishnan	First Name: Arun	Middle Name
Date of Birth (dd/mm/yy) 14/08/1983		Sex: Male
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) Co-investigator		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Department of Cardiology, SCTIMST		Department of Cardiology, SCTIMST
Telephone (Office): 04712524180		Mobile Number: 8547609631
Telephone (Residence): 04782594142		Email: arungk@sctimst.ac.ih
Academic Qualifications (Most recent qualification first): DM Cardiology, MD Pediatrics, MBBS		

Degree/Certificate	Year	Institution, Country
DM Cardiology	2015	SCTIMST, India
MD Pediatrics	2011	JIPMER, India
MBBS	2008	Govt. MCH, TVM, India

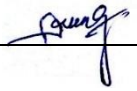
Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration: 37394, Travancore Cochin Medical Council, Dated 17th January 2008

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Sep 2019 till date	Assoc Prof Cardiology	SCTIMST
Sep 2016 to Aug 2019	Asst Prof Cardiology	SCTIMST
Jan – Aug 2016	Asst Prof (Adhoc) Cardiology	SCTIMST

Brief summary of relevant research experience:
78 journal publications. 5 completed projects

Current project/s at hand: 4 extramural funded projects, 2 intramural funded projects, 5 non funded projects
Kerala Acute Heart Failure Registry
Kerala Registry of Infective Endocarditis (KIND registry).
Evaluation of intermediate term cardiac and neurodevelopmental outcomes of children undergoing corrective arterial switch operation for complete transposition of great arteries.
Estimation study for reduction in transport of referral cases to tertiary hospitals by use of mobile enabled telemedicine system in remote hospitals.

Signature: 	Date: 05 – 01 – 2022 Place: Thiruvananthapuram

APPENDIX A
ETHICS COMMITTEE APPROVAL

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
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Grams : Chitramed, 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-21)

SCT/IEC/1880/MAY/2022 07.09.2022

Dr. Usnish Adhikari
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Usnish Adhikari,

The Institutional Ethics Committee held on 13th May, 2022, reviewed and discussed your application to conduct the study titled **"AORTOPATHY IN TETROLOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA"** (IEC/1880).

The following members of the Ethics Sub-committee were present at the meeting held on 13th May, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
4.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
5.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission
1. Checklist Form
2. Covering letter addressed to the Chairman, IEC, SCTIMST dated 05.01.2022
3. Research Proposal
4. Proforma
5. IEC Application Form
6. CV of PI and Co –PIs
7. Declaration form
8. SRC Recommendation

Revised submission
1. IEC Recommendations and reply
2. Covering letter addressed to the Chairperson, IEC, SCTIMST
3. IEC Application Form
4. Research Proposal
5. Proforma
6. Informed Consent Form in English and Malayalam
7. Assent Form in English and Malayalam
8. Patient Information Sheet
9. CV of PI and Co–PIs
10. Checklist form
11. Declaration form

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,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

APPENDIX B – SUPPLEMENTARY TABLES

PROFORMA
TOPIC: AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA

ADMISSION DETAILS

1. Patient Details:

Name: Date of first review at SCTIMST:

Hospital Number: Sex: M/F

Date of Birth

Address :

Phone No:

Age at First Contact: Years Months

Age & Date at First Diagnosis

Present Age Years Months

Repaired/ Unrepaired

2. Clinical Details at First Review:

Symptoms:

Heart Rate: /min
BP: /mm Hg
SpO2:
General Examination:

CVS Examination :

Syndromic: Yes/ No (Specify)

3. Anthropometry at First Review:

Weight: kg (Z score)
Height/Length cm (Z score)

Body surface Area: m^2

4. Investigations at first review & subsequent visits :

Investigation	Date	Result
		Situs Pulmonary anatomy Additional VSD Aortic dimension: Annulus Root (SOV) Sino-Tubular Junction Ascending Aorta Transverse Arch (Proximal, Distal, Isthmus**)** Aortic Valve Morphology LV/RV Function Arch side Coronary anomaly Impression:
ECG		
Other Radiological / Imaging: • Cardiac CT Scan • Cardiac MRI • Others:		
Genetic Study (if any)		

5. Final Diagnosis: TOF/ TOF with pulmonary atresia (TOF/PA)/ TOF with absent pulmonary valve/ Others (Specify)

6. Surgical Details

- Age & Date at definitive repair
- Type of definitive repair:
- RVOT reconstruction (transannular patch/ graft type/ conduit, monocusp reconstruction/ PA plasty/ other associated surgery)
- Palliative Procedure if any:
- Other Details:
- Complications if any:
- Redo surgery if any:
- Weight (kg) Height/ Length (cm) BSA(m2)
- Echo –
    - Ascending Aorta Dimension (mm) at surgery-
    - Ascending Aorta Dimension (mm) at 5 years post-surgery
    - Ascending Aorta Dimension (mm) at 10 years post-surgery

7. Follow-up Details

- Date of Follow up:
- Age at Follow-up
- Anthropometry at follow-up

Weight: kg (Z score)
Height/Length cm (Z score)
Body surface Area: cm^2

:

- Clinical Details**:**

Symptoms:

NYHA FC:

Heart Rate: /min
BP: /mm Hg
SpO2:
General Examination:

CVS Examination:

Medications:

8. Echocardiography at Follow Up:

Date	Results (Absolute)	BSA indexed/ Z score
	AORTIC DIMENSIONS (PLAX)- Annulus (mm) Root (SOV) (mm) Sino-Tubular Junction (mm) Ascending Aorta (mm) Transverse Arch (Proximal, Distal, Isthmus**)** AORTIC REGURGITATION (Nil/Trivial/ Mild/ Moderate/ Severe) AORTIC STENOSIS (Nil/ Mild/ Moderate/ Severe) ANEURYSM (Aortic root or ascending aorta dimension ≥50mm) OTHER PARAMETERS RVOT (mm) LV Dimension (mm) LVEF (%) RV Dimension (mm) RV FAC (%) PR RVOTO	

Aortic Root Disease/ Aortopathy: Yes / No

SOV/root diameter of ≥ 40 mm (for age ≥ 18 years),
SOV/root Z score ≥ + 2 (for age <18 years),
Aortic aneurysm (SOV/root ≥ 50 mm)
≥ Moderate aortic regurgitation

9. Other Investigations:

Investigation	Date	Result
ECG		
Other Radiological / Imaging: (if any) Cardiac CT Scan		

Cardiac MRI Others:		
Blood Investigation:		

INFORMED CONSENT FORM

Title of Study:

AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA

Principal Investigator: **DR. USNISH ADHIKARI**, DM Senior Resident
Guides **DR KRISHNAMOORTHY K.M.** HOD & Professor, Department of Cardiology,
DR ARUN GOPALAKRISHNAN, Associate Professor, Department of Cardiology
SCTIMST, Trivandrum

Please tick the following points:

(i) I agree to participate as a participant in the study described in the Participant Information Sheet attached to this form.[ ]

(ii)I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction. [ ]

(iii)Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation, and I have received satisfactory answers.[ ]

(iv)I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.[ ]

(v)I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.[ ]

(vi)I understand that if I have any questions relating to my participation in this research, I may contact my doctor, who will be happy to answer them.[ ]

(vii)I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet attached to this form [ ]

Name of Participant

_____

Signature of Participant

Date Time _____

Name of Witness

_____

Signature of Witness

Date Time _____

Name of Person conducting Informed Consent discussion

_____

Signature of Person conducting Informed Consent discussion

Date Time

- If you have any questions, concerns or complaints about the research please contact:

  Dr. Srinivas G
  Member Secretary, Institutional Ethics Committee,
  Sree Chitra Tirunal Institute for Medical Sciences and
  TechnologyTel: 0471- 2524689, Email:
  iec.mem.sec@sctimst.ac.in

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആൻഡ് ടെക്നോളജി, തിരുവനന്തപുരം, കേരളം - 695011

അറിയിച്ച സമ്മത ഫോം

പഠനത്തിന്റെ പേര്:

ഇന്ത്യയിലെ ഒരു ടെർഷ്യറി കെയർ സെന്ററിൽ ഫാലോട്ട് ഫോളോ-അപ്പിലെ ടെട്രോളജിയിൽ അയോർട്ടോപ്പതി

പ്രധാന അന്വേഷകൻ: ഡി.ആർ. യുഎസ്മിഷ് അധികാരി, ഡിഎം സീനിയർ റസിഡന്റ്
ഗൈഡുകൾ ഡോ. കൃഷ്ണമൂർത്തി കെ.എം. HOD & പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം,
DR സഞ്ജയ് ജി, പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം,
ഡോ.അരുൺ ഗോപാലകൃഷ്ണൻ, അസോസിയേറ്റ് പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം
SCTIMST, തിരുവനന്തപുരം

ഇനിപ്പറയുന്ന പോയിന്റുകൾ ടിക്ക് ചെയ്യുക:

(i)ഈ ഫോമിൽ ഘടിപ്പിച്ചിട്ടുള്ള പങ്കാളി വിവര ഷീറ്റിൽ വിവരിച്ചിരിക്കുന്ന പഠനത്തിൽ ഒരു പങ്കാളിയായി പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു.[ ]

(ii) എന്നെ തിരഞ്ഞെടുത്തത് എന്തുകൊണ്ടാണെന്നും പഠനത്തിന്റെ ലക്ഷ്യങ്ങളും സ്വഭാവവും അന്വേഷണത്തിന്റെ സാധ്യതകളും അപകടസാധ്യതകളും വിശദീകരിക്കുന്ന പങ്കാളി വിവര ഷീറ്റ് ഞാൻ വായിച്ചിട്ടുണ്ടെന്നും വിവര ഷീറ്റ് എനിക്ക് തൃപ്തികരമായി വിശദീകരിച്ചിട്ടുണ്ടെന്നും ഞാൻ സമ്മതിക്കുന്നു. . [ ]

(iii) ഈ സമ്മതപത്രത്തിൽ ഒപ്പിടുന്നതിന് മുമ്പ്, എന്റെ പങ്കാളിത്തം മൂലം എനിക്ക് ഉണ്ടായേക്കാവുന്ന ശാരീരികവും മാനസികവുമായ എന്തെങ്കിലും ഉപദ്രവങ്ങളുമായി ബന്ധപ്പെട്ട് എന്തെങ്കിലും ചോദ്യങ്ങൾ ചോദിക്കാനുള്ള അവസരം എനിക്ക് നൽകിയിട്ടുണ്ട്, കൂടാതെ എനിക്ക് തൃപ്തികരമായ ഉത്തരങ്ങളും ലഭിച്ചിട്ടുണ്ട്.[ ]

(iv)എന്റെ പങ്കാളിത്തം സ്വമേധയാ ഉള്ളതാണെന്നും ഒരു കാരണവും പറയാതെ, എന്റെ വൈദ്യസഹായമോ നിയമപരമായ അവകാശങ്ങളോ ബാധിക്കാതെ എപ്പോൾ വേണമെങ്കിലും പിൻവലിക്കാൻ എനിക്ക് സ്വാതന്ത്ര്യമുണ്ടെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.[ ]

(v)പഠനത്തിന്റെ ഫലങ്ങളിൽ നിന്ന് ശേഖരിച്ച ഗവേഷണ ഡാറ്റ പ്രസിദ്ധീകരിക്കപ്പെടുമെന്ന് ഞാൻ സമ്മതിക്കുന്നു, എന്നെ

തിരിച്ചറിയാൻ കഴിയില്ല.[ ]

(vi) ഈ ഗവേഷണത്തിലെ എന്റെ പങ്കാളിത്തവുമായി ബന്ധപ്പെട്ട് എന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ, എനിക്ക് എന്റെ ഡോക്ടറെ ബന്ധപ്പെടാം, അവർക്ക് ഉത്തരം നൽകാൻ സന്തോഷമുണ്ടെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.[ ]

(vii) ഈ സമ്മത ഫോമിന്റെ ഒരു പകർപ്പും ഈ ഫോമിൽ ഘടിപ്പിച്ചിട്ടുള്ള പങ്കാളി വിവര ഷീറ്റും ലഭിച്ചതായി ഞാൻ അംഗീകരിക്കുന്നു [ ]

പങ്കാളിയുടെ പേര്
_____

പങ്കാളിയുടെ ഒപ്പ്

തീയതി സമയം
_____

സാക്ഷിയുടെ പേര്
_____

സാക്ഷിയുടെ ഒപ്പ്

തീയതി സമയം _____

വിവരമുള്ള സമ്മത ചർച്ച നടത്തുന്ന വ്യക്തിയുടെ പേര്

_____

വിവരമുള്ള സമ്മത ചർച്ച നടത്തുന്ന വ്യക്തിയുടെ ഒപ്പ്

തീയതി സമയം

ഗവേഷണത്തെക്കുറിച്ച് നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദ്യങ്ങളോ ആശങ്കകളോ പരാതികളോ ഉണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:
ഡോ. ശ്രീനിവാസ് ജി
മെമ്പർ സെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി,
ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആൻഡ് ടെക്നോളജി ഫോൺ: 0471- 2524689, ഇമെയിൽ: iec.mem.sec@sctimst.ac.in

Assent Form (For minors < 18 years)

Study Title: **AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA**

PRINCIPAL INVESTIGATOR: Dr Usnish Adhikari

Name of Participant:

We are doing a research study. I am Dr Usnish Adhikari

We are doing this study to find out to Aortopathy in Tetralogy of fallot follow-up in a tertiary care centre in india

We are asking you to take part in this study because you are eligible for the study.

But we will only take you if you allow us. If you do not want to do so your treatment will continue as usual. If you decide to take part now but wish to discontinue later, you can tell us and we will take you out of the study.

Once you agree to take part, you will have to answer a few questions and will be examined & echocardiography will be done

It is possible that the study will help you feel better. It can also occur that you do not get any benefit but the information we get from you may help other children in future.

We have asked your parents [or guardian] their permission and it is all right with them.

Do not hesitate to ask questions. You can also ask us about anything later on if there are no questions right now.

Assent form

	Child's signature
I have been explained about the study and I agree to take part in it.	

Child’s Name: Date:

Certificate by the Investigator

	Tick one	Signature of the Investigator / representative
The child can read the assent form and was able to understand it		
The child was not capable of reading the assent form, but I verbally explained the information.		

Name of Investigator / representative: Date:

സമ്മതപത്രം (8 വയസ്സിന് മുകളിലുള്ള പ്രായപൂർത്തിയാകാത്തവർക്ക്)

പഠന ശീർഷകം: ഇന്ത്യയിലെ ഒരു ടെർഷ്യറി കെയർ സെന്ററിലെ ഫാലോട്ട് ഫോളോ-അപ്പിന്റെ ടെട്രോളജിയിലെ അയോർട്ടോപ്പതി

പ്രിൻസിപ്പൽ ഇൻവെസ്റ്റിഗേറ്റർ: ഡോ ഉസ്മിഷ് അധികാരി

പങ്കാളിയുടെ പേര്:

ഞങ്ങൾ ഒരു ഗവേഷണ പഠനം നടത്തുകയാണ്. ഞാൻ ഡോ ഉസ്മിഷ് അധികാരിയാണ്

ഇന്ത്യയിലെ ഒരു തൃതീയ പരിചരണ കേന്ദ്രത്തിൽ ഫാലോട്ട് ഫോളോ-അപ്പിന്റെ ടെട്രോളജിയിൽ അയോർട്ടോപ്പതി കണ്ടെത്തുന്നതിനാണ് ഞങ്ങൾ ഈ പഠനം നടത്തുന്നത്.

നിങ്ങൾ പഠനത്തിന് യോഗ്യരായതിനാൽ ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞങ്ങൾ നിങ്ങളോട് ആവശ്യപ്പെടുന്നു.

എന്നാൽ നിങ്ങൾ അനുവദിച്ചാൽ മാത്രമേ ഞങ്ങൾ നിങ്ങളെ കൊണ്ടുപോകൂ. നിങ്ങൾക്ക് അങ്ങനെ ചെയ്യാൻ താൽപ്പര്യമില്ലെങ്കിൽ നിങ്ങളുടെ ചികിത്സ സാധാരണപോലെ തുടരും. നിങ്ങൾ ഇപ്പോൾ പങ്കെടുക്കാൻ തീരുമാനിച്ചെങ്കിലും പിന്നീട് നിർത്താൻ ആഗ്രഹിക്കുന്നുവെങ്കിൽ, നിങ്ങൾക്ക് ഞങ്ങളോട് പറയാവുന്നതാണ്, ഞങ്ങൾ നിങ്ങളെ പഠനത്തിൽ നിന്ന് പുറത്താക്കും.

പങ്കെടുക്കാൻ നിങ്ങൾ സമ്മതിച്ചുകഴിഞ്ഞാൽ, നിങ്ങൾ കുറച്ച് ചോദ്യങ്ങൾക്ക് ഉത്തരം നൽകേണ്ടിവരും, അത് പരിശോധിച്ച് എക്കോകാർഡിയോഗ്രാഫി ചെയ്യും

പഠനം നിങ്ങളെ സുഖപ്പെടുത്താൻ സഹായിക്കും. നിങ്ങൾക്ക് പ്രയോജനമൊന്നും ലഭിക്കാത്തതും സംഭവിക്കാം, എന്നാൽ നിങ്ങളിൽ നിന്ന് ഞങ്ങൾക്ക് ലഭിക്കുന്ന വിവരങ്ങൾ ഭാവിയിൽ മറ്റ് കുട്ടികളെ സഹായിച്ചേക്കാം.

ഞങ്ങൾ നിങ്ങളുടെ മാതാപിതാക്കളോട് [അല്ലെങ്കിൽ രക്ഷിതാവിനോട്] അവരുടെ അനുവാദം ചോദിച്ചിട്ടുണ്ട്, അവർക്ക് കുഴപ്പമില്ല.

ചോദ്യങ്ങൾ ചോദിക്കാൻ മടിക്കരുത്. ഇപ്പോൾ ചോദ്യങ്ങളൊന്നും ഇല്ലെങ്കിൽ നിങ്ങൾക്ക് പിന്നീട് എന്തിനെക്കുറിച്ചും ഞങ്ങളോട് ചോദിക്കാം.

സമ്മത ഫോം

കുട്ടിയുടെ ഒപ്പ്

പഠനത്തെക്കുറിച്ച് എനിക്ക് വിശദീകരിച്ചിട്ടുണ്ട്, അതിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു.

കുട്ടിയുടെ പേര്: തീയതി:

അന്വേഷകന്റെ സർട്ടിഫിക്കറ്റ്

അന്വേഷകന്റെ / പ്രതിനിധിയുടെ ഒരു ഒപ്പ് ടിക്ക് ചെയ്യുക

കുട്ടിക്ക് സമ്മതപത്രം വായിക്കാനും അത് മനസ്സിലാക്കാനും കഴിഞ്ഞു

കുട്ടിക്ക് സമ്മതപത്രം വായിക്കാൻ കഴിവില്ലായിരുന്നു, പക്ഷേ ഞാൻ വിവരങ്ങൾ വാക്കാൽ വിശദീകരിച്ചു.

അന്വേഷകന്റെ / പ്രതിനിധിയുടെ പേര്: തീയതി:

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES ANDTECHNOLOGY, THIRUVANANTHAPURAM, KERALA - 695011

PATIENT INFORMATION SHEET

Title of the study:

AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA

Principal Investigator:
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Sir/ Madam,

We invite you to take part in our study titled *"*AORTOPATHY IN TETRALOGY OF FALLOT FOLLOW-UP IN A TERTIARY CARE CENTRE IN INDIA
Before you agree to participate in this research study, it is important that you read and understand this information sheet which will provide you with all the informationneeded for participation in this study so that you can make a well informed and considered decision about participation. In addition, should you have any questions, the investigator and his team members will be happy to answer them and explain to you more about this research study, the procedure involved and the related issues. You may ask them any questions you may have regarding the study, or ask them to explain any word or information that you don't clearly understand.

Study Overview

You are invited to take part in this study as you have Tetralogy of Fallot and might be at risk of developing aortopathy. As part of follow-up, you would be clinically & echocardiographically evaluated in this study. Patients with TOF, reviewed from 2005 to 2015 at, SCTIMST will be included in the study.

Purpose of this study

The purpose of this study is to evaluate the development of Aortopathy in TOF follow-up.

Study Procedures

If you are willing to participate, you will be interviewed and examined by investigator and the clinical findings will be noted. This shall be planned when you are followed up in OPD. You will have to 2D/3D echocardiography as per standard protocol which will be done free of cost as a part of the study. The investigators will share the details with you.

Risks and Discomfort

This study involves only history, clinical examination along with echocardiography, which will be completed in 30 to 40 minutes time. There are no specific risks associated with the study.

Benefits

Taking part in this research study may benefit you in early detection of aortopathy. We also do hope that this study will shed light on whether TOF patients are at risk of developing aortopathy on follow-up and in future for decision making based on the same.

Confidentiality

Your privacy is very important to us and the results of the tests performed on you will be treated as highly confidential, and nobody other than the investigators listed above will be knowing the test results. Your name or any other identifiable details will not be published in any researchpaper or scientific presentation arising out of the study.

Rights

Your participation in the trial is voluntary. You do not have to take part in this study if you are unwilling and you will not be losing any of your rights as a patient if you choose not toparticipate. You will also be at the liberty to withdraw from the study at any stage (even after signing this consent form) of the study in case you want to withdraw.

Contact Information

- When you read this information, your treating doctor will be available to discuss and answerany questions you may have. If you have any queries please contact:

  Dr Usnish Adhikari
  Senior Resident, Department of Cardiology,
  Sree Chitra Tirunal Institute for Medical Sciences and
  TechnologyTel: +91 9779249303, Email:
  adhikari_usnish@sctimst.ac.in

- If you have any questions, concerns or complaints about the research please contact:

  Dr. Srinivas G
  Member Secretary, Institutional Ethics Committee,
  Sree Chitra Tirunal Institute for Medical Sciences and
  TechnologyTel: 0471- 2524689, Email:
  iec.mem.sec@sctimst.ac.in

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആൻഡ് ടെക്നോളജി, തിരുവനന്തപുരം, കേരളം - 695011

രോഗിയുടെ വിവര ഷീറ്റ്

പഠനത്തിന്റെ തലക്കെട്ട്:
ഇന്ത്യയിലെ ഒരു ടെർഷ്യറി കെയർ സെന്ററിൽ ഫാലോട്ട് ഫോളോ-അപ്പിലെ ടെട്രോളജിയിൽ അയോർട്ടോപ്പതി

പ്രധാന അന്വേഷകൻ:
ഡോ. ഉസ്മിഷ് അധികാരി ജെ, സീനിയർ റസിഡന്റ്, കാർഡിയോളജി വിഭാഗം, SCTIMST

കോ-പ്രിൻസിപ്പൽ ഇൻവെസ്റ്റിഗേറ്റർ:
ഡോ. കൃഷ്ണമൂർത്തി കെ.എം, പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം, SCTIMST, തിരുവനന്തപുരം
DR സഞ്ജയ് ജി, പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം, SCTIMST, തിരുവനന്തപുരം
DR ഡോ.അരുൺ ഗോപാലകൃഷ്ണൻ, അസോസിയേറ്റ് പ്രൊഫസർ, കാർഡിയോളജി വിഭാഗം, SCTIMST, തിരുവനന്തപുരം

സർ/ മാഡം,
ഇന്ത്യയിലെ ഒരു ടെർഷ്യറി കെയർ സെന്ററിലെ ഫാലോട്ട് ഫോളോ-അപ്പിലെ അയോർട്ടോപ്പതി ഇൻ ടെട്രോളജി എന്ന തലക്കെട്ടിലുള്ള ഞങ്ങളുടെ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞങ്ങൾ നിങ്ങളെ ക്ഷണിക്കുന്നു.
ഈ ഗവേഷണ പഠനത്തിൽ പങ്കെടുക്കാൻ നിങ്ങൾ സമ്മതിക്കുന്നതിന് മുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതിന് ആവശ്യമായ എല്ലാ വിവരങ്ങളും നൽകുന്ന ഈ വിവര ഷീറ്റ് നിങ്ങൾ വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടത് പ്രധാനമാണ്, അതുവഴി നിങ്ങൾക്ക് പങ്കാളിത്തത്തെക്കുറിച്ച് നന്നായി അറിയാവുന്നതും പരിഗണിക്കുന്നതുമായ തീരുമാനമെടുക്കാൻ കഴിയും. കൂടാതെ, നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ, അന്വേഷകനും അദ്ദേഹത്തിന്റെ ടീം അംഗങ്ങളും അവർക്ക് ഉത്തരം നൽകാനും ഈ ഗവേഷണ പഠനത്തെക്കുറിച്ചും ഉൾപ്പെട്ടിരിക്കുന്ന നടപടിക്രമങ്ങളെക്കുറിച്ചും അനുബന്ധ പ്രശ്നങ്ങളെക്കുറിച്ചും നിങ്ങൾക്ക് കൂടുതൽ വിശദീകരിക്കാനും സന്തോഷമുണ്ട്. പഠനവുമായി ബന്ധപ്പെട്ട് നിങ്ങൾക്കുണ്ടായേക്കാവുന്ന ഏത് ചോദ്യങ്ങളും നിങ്ങൾക്ക് അവരോട് ചോദിക്കാം, അല്ലെങ്കിൽ നിങ്ങൾക്ക് വ്യക്തമായി മനസ്സിലാകാത്ത ഏതെങ്കിലും വാക്കോ വിവരമോ വിശദീകരിക്കാൻ അവരോട് ആവശ്യപ്പെടാം.

പഠന അവലോകനം
നിങ്ങൾക്ക് ടെട്രോളജി ഓഫ് ഫാലോട്ട് ഉള്ളതിനാലും രക്തപ്രവാഹത്തിന് സാധ്യതയുള്ളതിനാലും ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ നിങ്ങളെ ക്ഷണിക്കുന്നു. ഫോളോ-അപ്പിന്റെ ഭാഗമായി, ഈ ടൂഡിയിൽ നിങ്ങളെ ക്ലിനിക്കലിയും എക്കോകാർഡിയോഗ്രാഫിക്കലിയും വിലയിരുത്തും. SCTIMST എന്നതിൽ 2005 മുതൽ 2015 വരെ അവലോകനം ചെയ്ത TOF ഉള്ള

രോഗികളെ പഠനത്തിൽ ഉൾപ്പെടുത്തും.

ഈ പഠനത്തിന്റെ ഉദ്ദേശ്യം
TOF ഫോളോ-അപ്പിൽ അയോട്ടോപ്പതിയുടെ വികസനം വിലയിരുത്തുക എന്നതാണ് ഈ പഠനത്തിന്റെ ലക്ഷ്യം.

പഠന നടപടിക്രമങ്ങൾ
നിങ്ങൾ പങ്കെടുക്കാൻ തയ്യാറാണെങ്കിൽ, നിങ്ങളെ അന്വേഷകൻ അഭിമുഖം നടത്തുകയും പരിശോധിക്കുകയും ക്ലിനിക്കൽ കണ്ടെത്തലുകൾ രേഖപ്പെടുത്തുകയും ചെയ്യും. നിങ്ങളെ ഒപിഡിയിൽ പിന്തുടരുമ്പോൾ ഇത് ആസൂത്രണം ചെയ്യും. പഠനത്തിന്റെ ഭാഗമായി സൗജന്യമായി ചെയ്യുന്ന സ്റ്റാൻഡേർഡ് പ്രോട്ടോക്കോൾ അനുസരിച്ച് നിങ്ങൾ 2D/3D എക്കോകാർഡിയോഗ്രാഫി ചെയ്യേണ്ടതുണ്ട്. അന്വേഷണ ഉദ്യോഗസ്ഥർ നിങ്ങളുമായി വിശദാംശങ്ങൾ പങ്കിടും.

അപകടസാധ്യതകളും അസ്വസ്ഥതയും

ഈ പഠനത്തിൽ ചരിത്രവും ക്ലിനിക്കൽ പരിശോധനയും എക്കോകാർഡിയോഗ്രാഫിയും ഉൾപ്പെടുന്നു, ഇത് 30 മുതൽ 40 മിനിറ്റ് സമയത്തിനുള്ളിൽ പൂർത്തിയാകും. പഠനവുമായി ബന്ധപ്പെട്ട പ്രത്യേക അപകടസാധ്യതകളൊന്നുമില്ല.

ആനുകൂല്യങ്ങൾ
ഈ ഗവേഷണ പഠനത്തിൽ പങ്കെടുക്കുന്നത് അയോട്ടോപ്പതി നേരത്തെ കണ്ടെത്തുന്നതിന് നിങ്ങൾക്ക് പ്രയോജനം ചെയ്തേക്കാം. തുടർനടപടികളിലൂടെയും ഭാവിയിൽ അതിനെ അടിസ്ഥാനമാക്കിയുള്ള തീരുമാനങ്ങൾ എടുക്കുന്നതിലും TOF രോഗികൾക്ക് അയോട്ടോപ്പതി ഉണ്ടാകാനുള്ള സാധ്യതയുണ്ടോ എന്നതിലേക്ക് ഈ പഠനം വെളിച്ചം വീശുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു.

രഹസ്യാത്മകത
നിങ്ങളുടെ സ്വകാര്യത ഞങ്ങൾക്ക് വളരെ പ്രധാനമാണ്, നിങ്ങൾക്കായി നടത്തിയ പരിശോധനകളുടെ ഫലങ്ങൾ അതീവ രഹസ്യാത്മകമായി കണക്കാക്കും, കൂടാതെ മുകളിൽ ലിസ്റ്റുചെയ്തിരിക്കുന്ന അന്വേഷകർക്ക് പുറമെ മറ്റാർക്കും പരിശോധനാ ഫലങ്ങൾ അറിയാൻ കഴിയില്ല. നിങ്ങളുടെ പേരോ തിരിച്ചറിയാനാകുന്ന മറ്റേതെങ്കിലും വിശദാംശങ്ങളോ പഠനത്തിൽ നിന്ന് ഉയർന്നുവരുന്ന ഒരു ഗവേഷണ പ്രബന്ധത്തിലോ ശാസ്ത്രീയ അവതരണത്തിലോ പ്രസിദ്ധീകരിക്കില്ല.

അവകാശങ്ങൾ
ട്രയലിലെ നിങ്ങളുടെ പങ്കാളിത്തം സ്വമേധയാ ഉള്ളതാണ്. നിങ്ങൾക്ക് താൽപ്പര്യമില്ലെങ്കിൽ ഈ പഠനത്തിൽ നിങ്ങൾ പങ്കെടുക്കേണ്ടതില്ല, പങ്കെടുക്കേണ്ടെന്ന് തീരുമാനിച്ചാൽ ഒരു രോഗിയെന്ന നിലയിലുള്ള നിങ്ങളുടെ അവകാശങ്ങളൊന്നും നഷ്ടപ്പെടുകയുമില്ല. നിങ്ങൾക്ക് പിൻവലിക്കാൻ താൽപ്പര്യമുണ്ടെങ്കിൽ പഠനത്തിന്റെ ഏത് ഘട്ടത്തിലും (ഈ സമ്മതപത്രം ഒപ്പിട്ടതിന് ശേഷവും) പഠനത്തിൽ നിന്ന് പിന്മാറാനുള്ള

സ്വാതന്ത്ര്യവും നിങ്ങൾക്കുണ്ടാകും.

ബന്ധപ്പെടാനുള്ള വിവരങ്ങൾ

• നിങ്ങൾ ഈ വിവരങ്ങൾ വായിക്കുമ്പോൾ, നിങ്ങൾക്ക് ഉണ്ടാകാവുന്ന ഏത് ചോദ്യങ്ങളും ചർച്ച ചെയ്യാനും ഉത്തരം നൽകാനും നിങ്ങളുടെ ചികിത്സിക്കുന്ന ഡോക്ടർ ലഭ്യമാകും. നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദ്യങ്ങൾ ഉണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:
ഡോ ഉസ്നിഷ് അധികാരി
സീനിയർ റസിഡന്റ്, കാർഡിയോളജി വിഭാഗം,
ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആൻഡ് ടെക്നോളജി ഫോൺ: +91 9779249303, ഇമെയിൽ: adhikari_usnishj@sctimst.ac.in

• ഗവേഷണത്തെക്കുറിച്ച് നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദ്യങ്ങളോ ആശങ്കകളോ പരാതികളോ ഉണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:
ഡോ. ശ്രീനിവാസ് ജി
മെമ്പർ സെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി,
ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആൻഡ് ടെക്നോളജി ഫോൺ: 0471- 2524689, ഇമെയിൽ: iec.mem.sec@sctimst.ac.in

APPENDIX -C
PLAGIARISM REPORT

grammarly

Report: Aortopathy in Tetralogy of Fallot follow-up in a tertiary care centre in India

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General metrics

46,221	7,359	680	29 min 26 sec	56 min 36 sec
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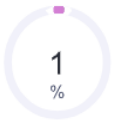
Plagiarism



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