

Peri-operative quantification of systolic Global Longitudinal Strain by Trans-oesophageal echocardiography in functionally single ventricle patients undergoing Total Cavo-Pulmonary Connection (TCPC): A pilot study



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JANUARY 2023- DECEMBER 2023

Clinical study submitted to the Faculty of Cardiovascular and
Thoracic Anaesthesiology, SCTIMST, Thiruvananthapuram
towards the partial fulfillment of the degree of Post-doctoral
Fellow

Pediatric Cardiac Anaesthesiology

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ANAESTHESIOLOGY, DEPARTMENT OF ANAESTHESIOLOGY,
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND
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By

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Post- doctoral fellow

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DECLARATION

I hereby declare that the work embodied in the clinical study entitled “*Peri-operative quantification of systolic Global longitudinal strain by trans-esophageal echocardiography in functionally single ventricle patients undergoing Total Cavo-pulmonary Connection (TCPC): A pilot study*” is an original work carried out by me under the able guidance of my guide Dr. Thomas Koshy and co-guides Dr. Prasantha Kumar Dash, Dr. Saravana Babu MS, Dr. Baiju S Dharan and Dr. Sowmya Ramanan, faculty of the Division of Cardiothoracic and Vascular Anesthesiology and Surgery, Department of Anesthesiology and CTVS, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

30-12-2023

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CERTIFICATE

This is to certify that the clinical study entitled “*Peri-operative quantification of systolic Global longitudinal strain by trans-esophageal echocardiography in functionally single ventricle patients undergoing Total Cavo-pulmonary Connection (TCPC): A pilot study*” is a bonafide work of Dr. NANDISH.KORI.M conducted in the Department of Anaesthesiology, SCTIMST, Thiruvananthapuram, Kerala under the direct supervision and guidance.

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Thanks

Yours sincerely

Dr. Nandish.Kori.M



Glossary of Abbreviations

1. SV- Single ventricle
2. RV- Right Ventricle
3. LV- Left ventricle
4. STE- Speckle Tracking Echocardiography
5. 2D- Two dimension
6. RA- Right atrium
7. IVC- Inferior vena cava
8. EF- Ejection fraction
9. CPB- Cardio-pulmonary Bypass
10. BT shunt- Blalock Taussig
11. PDA- Patent ductus arteriosus
12. BDG- Bidirectional Glenn
13. PA band- Pulmonary artery
14. GCS- Glasgow Coma Scale
15. NYHA- New York Heart Association
16. TTE- transthoracic
17. TEE- transesophageal
18. TCPC- Total Cavo-pulmonary connection
19. LOS- Length of stay
20. STE- Speckle tracking echocardiography

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INTRODUCTION

Single ventricle cardiac anomaly constitutes 7.7% of congenital heart disease diagnosed in childhood. Here, a functionally single ventricle pumps blood to both systemic and pulmonary circulation in a parallel fashion. The incidence at birth is 0.08-0.4 per 1000 live births. Completion Fontan, also called Total Cavo-Pulmonary Connection (TCPC) is the final step in the palliation of these patients after (BT) Blalock Taussig shunt placement in the first stage and (BDG) Bi-directional Glenn in second stage palliation. The surgery is usually done at around 18 months to 4 years. This surgery was first performed in 1968. This establishes a circulation in series wherein the pulmonary blood flow is driven by the passive systemic venous pressures without a sub-pulmonary ventricle. As a result, these patients have chronically elevated systemic venous pressure leading to chronically underfilled single ventricles, reducing the cardiac output and exercise capacity. Also, the myocardial fiber disarray can contribute to systolic and diastolic ventricular dysfunction. Therefore, serial echocardiographic monitoring and follow-up of ventricular function is very crucial. The trend obtained is valuable in clinical decision-making and in optimizing medical therapy. A baseline peri-operative quantification of ventricular function serves as a valuable aid for future comparison and analysis of the trend in follow-up. Also, it helps in peri-operative management of the patients in terms of analyzing and optimizing pre-load and contractility.

Single ventricular volumes and ejection fraction quantification by cardiac magnetic resonance (CMR) is considered the gold standard for assessing ventricular filling status and function. However, myocardial deformation imaging techniques like Speckle tracking echocardiography show a comparable quantification of ventricular systolic and diastolic functions by measuring longitudinal and circumferential strain and strain rates. GLS (Global Longitudinal Strain) measured by MRI can predict major adverse cardiac events in Fontan patients and helps in risk stratification. Pre-operative circumferential strain rate (CSR) predicted the post-operative prolonged length of stay (LOS). GLS can predict sub-clinical ventricular dysfunction in Fontan patients. End-diastolic volume index, GCS and NYHA class predicted transplant-free survival or death in Fontan patients. There are studies involving speckle-tracking echocardiography that study the correlation between GLS and atrioventricular valve (AVVR) regurgitation. GLS being devoid of any geometric assumptions of the shape of the ventricle and having overcome the influence of acute preload

can thus quantify ventricular function fairly and detect sub-clinical dysfunction early.

Despite its immense benefits, there is a paucity of studies evaluating single ventricular function by speckle-tracking echocardiography. Also, there are no studies quantifying single ventricular systolic function by transesophageal speckle tracking echocardiography in the perioperative period. Therefore, we attempt to study the functionally single ventricle, intraoperatively by two-dimensional speckle tracking echocardiography using a Transesophageal echocardiography probe, before and after TCPC surgery.

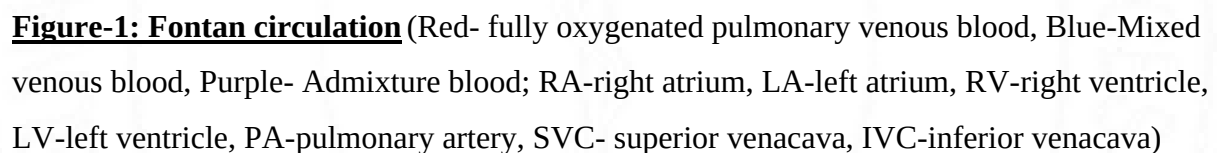
Literature review:

Single ventricle and speckle tracking echocardiography.

The disease burden of single ventricle physiology amounts to 7.7% of congenital heart disease diagnosed in childhood. ⁽¹⁾The incidence at birth is 0.08-0.4 per 1000 live births. ⁽²⁾TCPC is the final step in the surgical palliation of these patients thereby establishing a circulation in series wherein the pulmonary blood flow is driven by the passive systemic venous pressures without a sub-pulmonary ventricle (Figure-3). This surgery was first performed in 1968. ⁽³⁾Persistently elevated systemic venous pressure, ventricular dysfunction, and atrioventricular valve regurgitation are the main causes of morbidity. ⁽⁴⁾The chronically underfilled single ventricle results in reduced cardiac output and exercise capacity. ⁽⁵⁾These patients will be on a chronic echocardiographic follow-up to quantify ventricular function. The trend of single ventricular function obtained by echocardiography is valuable in clinical decision-making and in optimizing medical therapy. The quantification of ventricular function during TCPC aids in the peri-operative management of the patients. More importantly, the quantified data serves as a baseline to compare with the follow-up values.

Single ventricular volumes and ejection fraction quantification by Cardiac Magnetic Resonance (CMR) are considered the gold standard. However, myocardial deformation imaging techniques like speckle tracking echocardiography show a comparable quantification of ventricular systolic and diastolic functions by measuring longitudinal and circumferential strain and strain rates. ⁽⁶⁾GLS measured by MRI can predict major adverse cardiac events in Fontan patients and helps in risk stratification. ⁽⁷⁾Pre-operative Circumferential strain rate(CSR) predicted the post-operative prolonged length -of-stay(LOS). ⁽⁸⁾GLS can predict sub-clinical ventricular dysfunction in Fontan patients. ⁽⁹⁾End-diastolic volume index, GCS and NYHA class predicted transplant-free survival or death in Fontan patients. ⁽¹⁰⁾There are studies involving speckle-tracking echocardiography that study the correlation between GLS

There is a paucity of studies evaluating single ventricular function by speckle-tracking echocardiography. Also, there are no studies quantifying single ventricular function by transesophageal speckle tracking echocardiography in the immediate peri-operative period.



Myocardial strain and strain rate analysis in congenital heart disease is a valuable imaging modality in the early detection of myocardial systolic and diastolic dysfunction, quantification of myocardial function, and dyssynchrony. (12) This imaging modality is being used increasingly in congenital heart diseases like Transposition of Great Arteries, Tetralogy of Fallot's, Atrial septal defects, and Single ventricle patients. (13) This technique has good intra-observer and interobserver reproducibility in children. (14) Strain-measured ventricular function is better than global systolic function in congenital heart disease. (15)

The Fontan procedure has improved the longevity of this subset of patients with single ventricle physiology. However, complications do occur despite Fontan's completion. It

is imperative to follow up on these patients longitudinally to detect the occurrence of the complications like failure, early and intervene early. Echocardiography is a non-invasive imaging modality that can be used for repeated and serial follow-up. 2D speckle tracking echocardiography-guided strain analysis combined with volume quantification of the single ventricle can give a fairly accurate function of the ventricle, comparable to MRI-derived parameters.

Aims and objectives: -

Primary objectives: -Quantification of single ventricular systolic Global Longitudinal Strain (GLS) by TEE in patients with functionally single ventricles undergoing TCPC.

Secondary objectives: - 1. Quantification of single ventricular end-diastolic, end-systolic volumes, and ejection fraction.

2. To analyze the GLS between subgroups left ventricle (LV)type and right ventricle (RV) type single ventricle)

4. To analyze the GLS between fenestrated and non-fenestrated TCPC.

5. To analyze the vasoactive inotropic score, length of ICU stay & hospital stay, incidence of arrhythmias, duration of mechanical ventilation, incidence of end-organ dysfunction, and in-hospital mortality between patients with good GLS & reduced GLS.

Material and Methods: -

Study design: - Prospective Observational study

Study setting: The study was carried out on patients undergoing Total Cavo-pulmonary Connection surgery in pediatric cardiac surgery operation theatres and intensive unit care at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.(IEC Regn No. ECRI189/Inst/KL/2013/RR-21), REF/2023/11/075970.

Study duration: The study was carried out for six months.

Ethical aspects: The study was started after getting Institutional Ethics Committee clearance. Written and informed consent was taken from one of the parents of the patient. A patient information sheet in the local language and English was used to educate the parents about the study.

Participants: -

Inclusion criteria- Patients undergoing TCPC surgery in pediatric cardiac surgery operation theatres. TEE probes were used to quantify GLS by speckle tracking method. (16)

- No arrhythmia (only sinus rhythm present)
- Normal drainage of the vena cava
- Normal right atrial (RA) volume
- Low pulmonary artery pressure (PAP), less than 15 mm Hg
- Low pulmonary resistance (less than 4 Woods Units /m2)
- Adequate pulmonary artery (PA) size (PA to aorta ratio greater than 0.75)
- Normal ventricular function, greater than 55%

Exclusion criteria-

Inadequate images with unclear borders.

Associated valve repair

Arrhythmias

Moderate to severe AV valve regurgitation

Pulmonary hypertension

Valve stenosis

Liver, kidney lung dysfunction

Procedure: -**RECRUITMENT**

Patients planned for TCPC surgeries were recruited for the study. Informed written consent was obtained from one of the parents of all the recruits.

DATA COLLECTION PROCEDURES

All the patients were monitored with ASA standard monitoring. Peri-operative transesophageal echocardiography evaluation, quantification, and monitoring of cardiac function is a routine for all patients undergoing congenital heart surgery in our institute which helps in verification of diagnosis and evaluation of surgical repair. The following echocardiographic data were obtained on two occasions using a Philips IE33 ultrasound system (Bothell, USA).

- A) Before CPB: - Transesophageal echocardiography(TEE) after induction of general anesthesia and endotracheal intubation.

B) After CPB: - Transesophageal echocardiography after coming off cardiopulmonary bypass.

Post-CPB readings were taken after optimizing loading conditions (CVP-10 to 12 mm Hg, Hb>10 mg/dl, Cardiac index) and after sternal closure.

Echocardiographic IMAGE ACQUISITION PROTOCOL: -

1. Mid-esophageal four chamber, two chamber, and long axis views were obtained by TEE probe.
2. 2D end-diastolic and end-systolic volumes and ejection fraction of the single ventricle.

Echocardiographic quantification of single ventricular global longitudinal strain by 2D trans-esophageal speckle tracking echocardiography, during breath holding and stable electrocardiographic trace with a frame rate of 60-110 frames/second.(17)The endocardial border was manually traced and tracking was automatically performed by the software as shown in figure-2. The base to apex directed myocardial deformation was noted as GLS in percentage along the entire myocardial line length as per the consensus document published by EACVI and ASE. (18–20) A more negative systolic strain indicated better ventricular function. The strain curve: Peak systolic strain corresponds to the aortic valve closure or peak of the T-wave. A small negative deflection after that was termed postsystolic strain. (21). Peak-systolic strain was noted in our study.

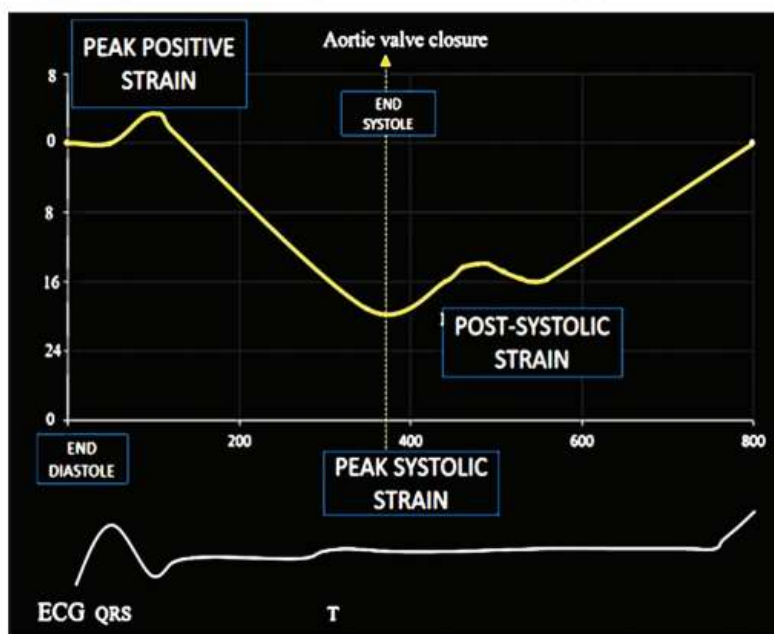


Figure-2:Strain curve showing the peak systolic strain²¹

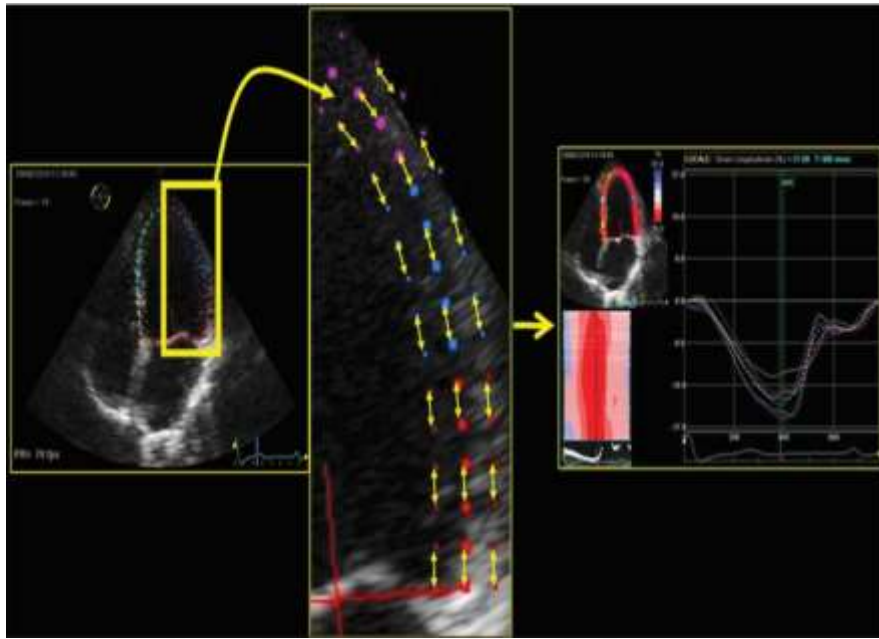


Figure-3: Global longitudinal strain

The parameters studied were the following: - before and after Total Cavo-pulmonary connection(TCPC)

- 1) GLS, Global Longitudinal Strain of the single ventricle(percentage)
- 2) EDV, indexed End diastolic volume(ml)
- 3) ESV, indexed End systolic volume(ml)
- 4) EF, Ejection fraction(percentage)
- 5) LOS, Length of ICU stay
- 6) VIS, Vaso-active inotropic score
- 7) Duration of mechanical ventilation
- 8) In hospital mortality
- 9) Incidence of arrhythmia
- 10) Fenestrated vs Non fenestrated

Outcome measure- Single ventricular GLS strain analysis by 2D trans-esophageal speckle tracking echocardiography, ventricular end-diastolic and systolic volumes, and ejection fraction (pre- and post-repair).

Statistical analysis

Quantitative Variables were expressed as mean and standard deviation. Qualitative variable was expressed as frequency and percentage. Association between categorical variables was analyzed by chi-square test. Comparison of continuous variables between two group was analyzed by independent sample t test. Association between continuous variables were analyzed by Pearson correlation. Paired comparison of continuous variables was analyzed by paired t test. A p- value less than 0.05 was considered as statistically significant. Data was entered in Microsoft excel and Data analysis was performed using SPSS version 24.

Formula

$$N_{pairs} = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\Delta^2} + \frac{z_{1-\alpha/2}^2}{2}$$

$$\Delta = \frac{(\mu_2 - \mu_1)}{\sigma} \quad \sigma = \frac{\sigma_1 + \sigma_2}{2}$$

Where,

μ_1 : Pre-test mean

μ_2 : Post-test mean

σ_1 : Standard deviation in the pre-test

σ_2 : Standard deviation in the post-test

Δ : Effect size

α : Significance level

$1-\beta$: Power

According to similar study " Insights into the Evolution of Myocardial Dysfunction in

the Functionally Single Right Ventricle between Staged Palliations Using Speckle-Tracking Echocardiography” by Edythe et al,

GLS %	mean	sd
Pre Fontan	-17.5	3.1
Post Fontan	-16.0	4.2

α : 5%

β : 20%

Sample size N= 12

Results

The study was done at the Department of Anesthesiology, cardiothoracic and Vascular Division, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala from May 2023 to October 2023.

The median age of patients who underwent TCPC surgery was 14 years (range 10-23 years).

Of the 12 (n=12) patients recruited for the study, 50% (n=6) were males.

Sex	Frequency	Percent
Male	6	50
Female	6	50
Total	12	100

Table-1: - Sex distribution of cases

58%(n=7) were of LV morphology and 42%(n=5) were of RV morphology.

Ventricle morphology	Frequency	Percent
LV	7	58.3
RV	5	41.7
Total	12	100

Table-2: -Ventricular morphology (LV and RV type)

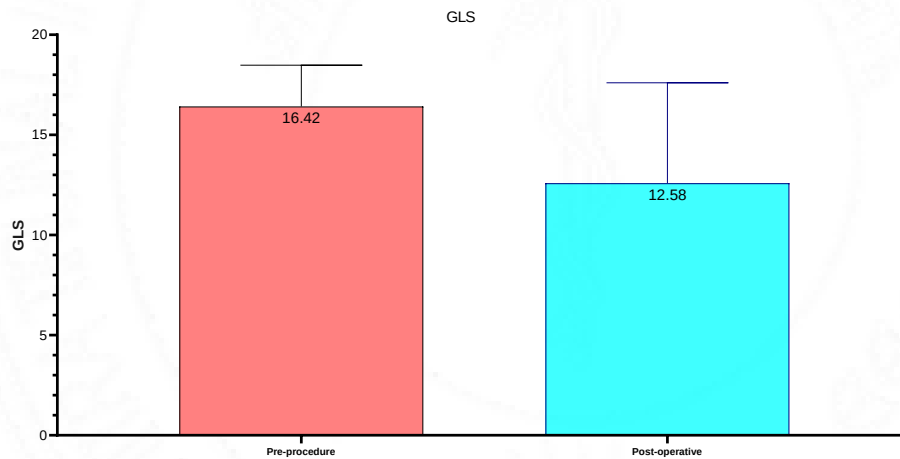
None of them(n=0) underwent fenestrated TCPC.

GLS:

	Pre-operative		Postoperative		Mean difference		Paired t-test	
	mean	sd	mean	sd	mean	sd	t	p
GLS-TEE	16.42	2.07	12.58	5.02	3.833	4.707	2.821	0.017
EDV-TEE (ml)	37.17	4.88	30.83	1.34	6.333	5.087	4.313	0.001
ESV-TEE(ml)	16.33	2.39	16.58	3.40	-0.25	2.598	0.333	0.745
EF-TEE (%)	56.83	6.21	46.75	11.70	10.083	8.084	4.321	0.001
CI	3.00	0.36	2.33	0.51	0.675	0.3621	6.457	<0.001

Table-3: -Global longitudinal strain (pre- and post-operative)

There was a significant decrease in GLS from pre-TCPC (-16.42 ± 2.07 %) to immediate post-TCPC (-12.58 ± 5.02 , $p=0.017$).

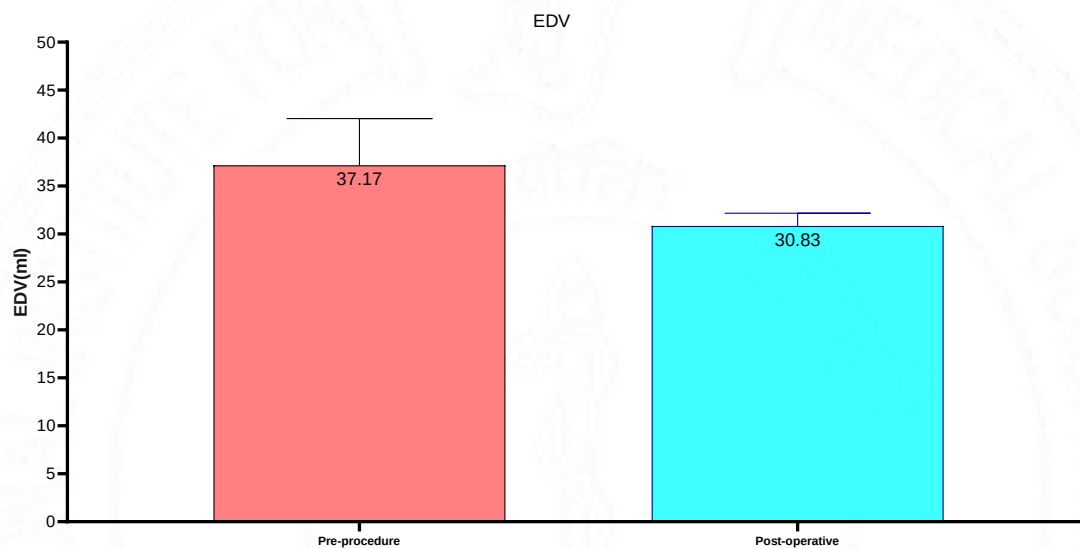
**Figure-4: -Global longitudinal strain((pre- and post-operative)**

Ventricular volumes:

	N	mean $\pm$ sd	Range	Median	IQR
Change in EDV	12	6.3 $\pm$ 5.1	2 - 21	5.5	4 - 6
Change in ESV	12	-0.3 $\pm$ 2.6	-5 - 5	0	-2 - 1.5
Change in EF	12	10.1 $\pm$ 8.1	-7 - 20	10	4 - 18

Table-4: -Change in ventricular end-systolic and end-diastolic volumes

There was a significant decrease in EDV from pre-TCPC (37.17 ± 4.88 ml/m²) to immediate post-TCPC (30.83 ± 1.34 ml/m², $p=0.001$).

**Figure-5: - Change in ventricular end-diastolic volumes (EDV-end-diastolic volume)**

There was no significant change in ESV from pre-TCPC (16.33 ± 2.39 ml/m²) to immediate post-TCPC (16.58 ± 3.40 ml/m², $p=0.745$).

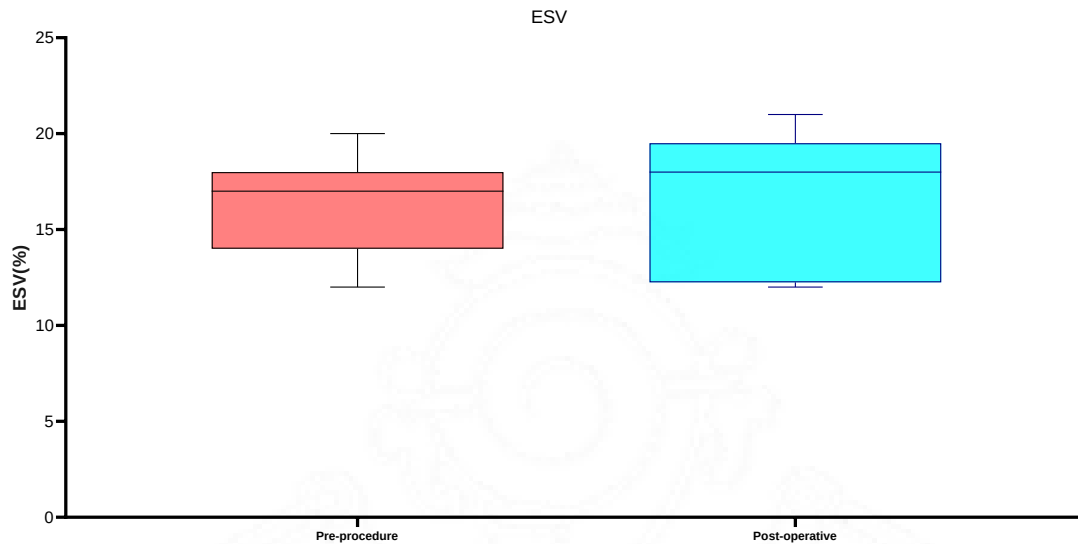


Figure-6: - Change in ventricular end-systolic volumes (ESV- end-systolic volume)

Ejection fraction:

There was a significant decrease in EF from pre-TCPC ($56.83 \pm 6.21\%$) to immediate post-TCPC ($46.75 \pm 11.70\%$, $p=0.001$).

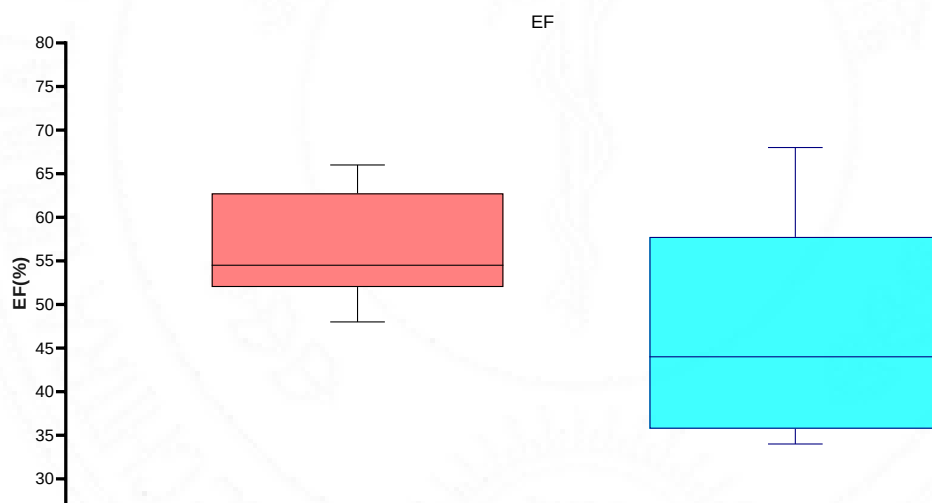


Figure-6: - Change in ejection fraction, EF (pre- and post-operative)

Cardiac Index:

There was a significant decrease in CI from pre-TCPC (3.00 ± 0.36 L/min/m²) to immediate post-TCPC (2.33 ± 0.51 L/min/m², $p<0.001$).

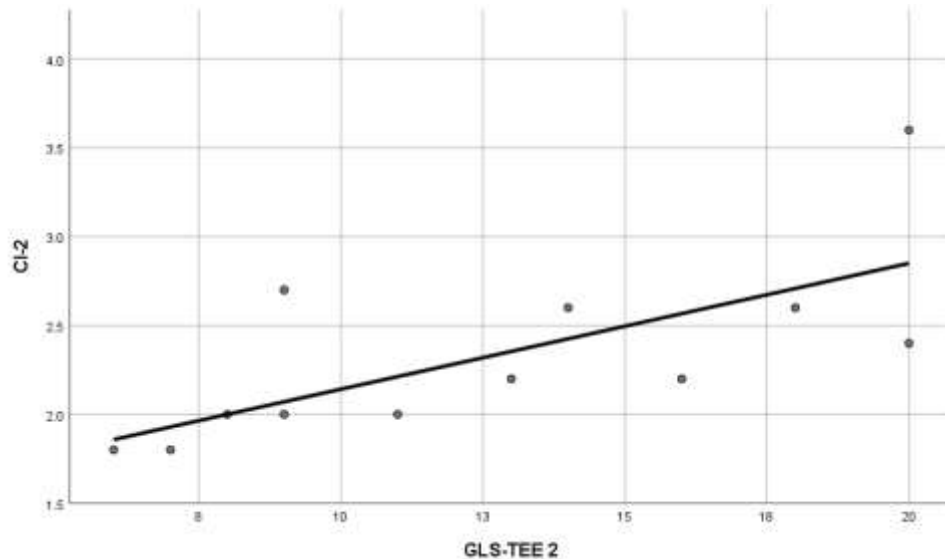


Figure-7: - Correlation between post-operative cardiac index and GLS (CI-2-post-operative cardiac index, TEE-trans-esophageal echocardiography, GLS-2- post-operative global longitudinal strain)

EF and GLS:

There was no significant correlation between pre-TCPC GLS and EF ($r=0.353$).

There was a significant correlation between post-TCPC GLS and EF ($r=0.949$).

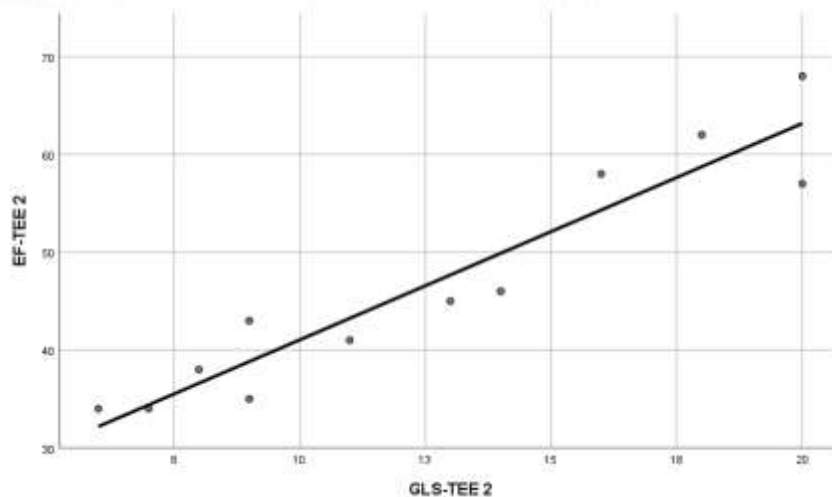


Figure-8: - Correlation between post-operative ejection fraction and GLS(EF-TEE-2-post-operative ejection fraction by trans-esophageal echocardiography; GLS-TEE-2-post-operative global longitudinal strain by trans-esophageal echocardiography)

LOS:

There was no significant correlation between Post-TCPC GLS and Length of ICU stay ($r=0.357$).

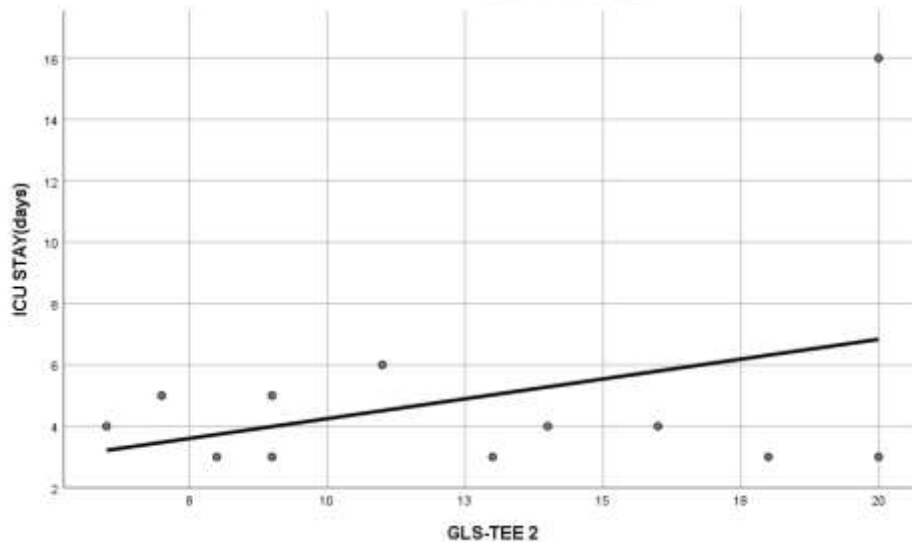


Figure-9: - Correlation between post-operative ICU stay and GLS (GLS-TEE-2- post-operative global longitudinal strain by trans-esophageal echocardiography)

There was no significant correlation between Post-TCPC GLS and Length of hospital stay ($r=0.244$).

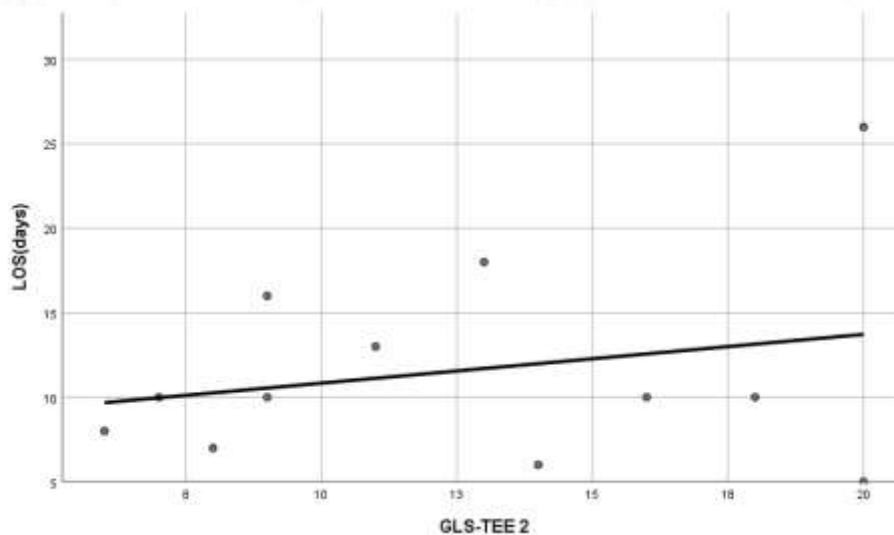


Figure-10: - Correlation between post-operative length of hospital stay and GLS (LOS-length of hospital stay; GLS-TEE-2- post-operative global longitudinal strain by trans-esophageal echocardiography)

Duration of Mechanical Ventilation and GLS:

There was no significant correlation between post-TCPC GLS and duration of mechanical ventilation ($r=0.347$).

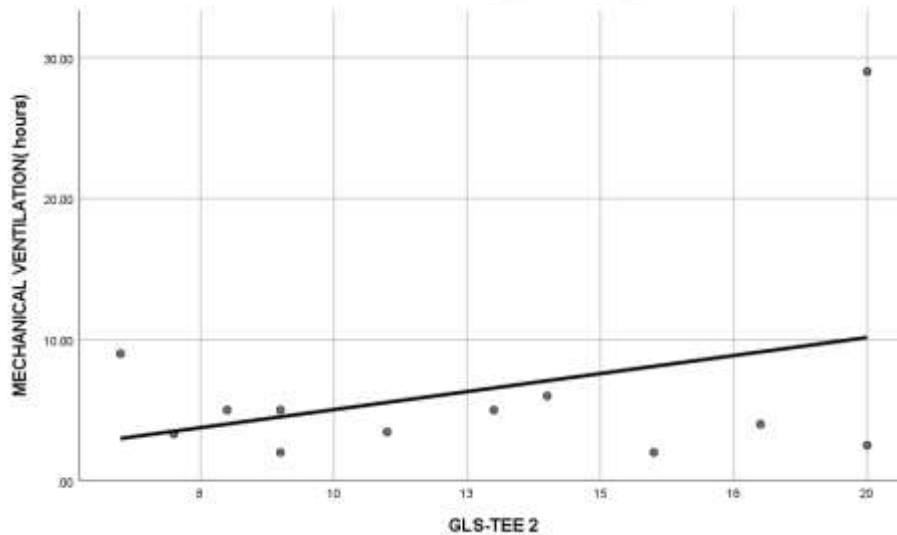


Figure-11: - Correlation between duration of mechanical ventilation and GLS (GLS-TEE-2- post-operative global longitudinal strain by trans-esophageal echocardiography)

Intercostal drain and GLS:

There was no correlation between post-TCPC GLS and the duration of the inter-costal drain ($r=0.08$).

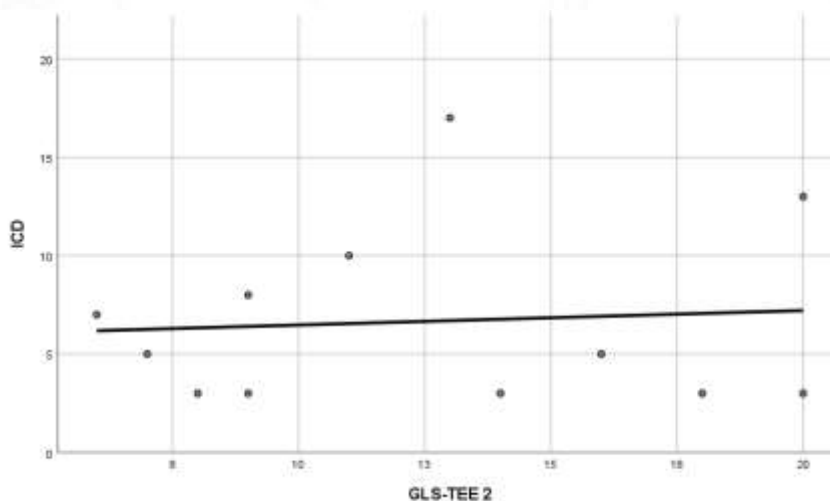


Figure-12: - Correlation between duration of intercostal drain and GLS (ICD- duration of intercostal drainage; GLS-TEE-2- post-operative global longitudinal strain by trans-esophageal echocardiography)

Vasoactive-inotropic score:

The mean VIS scores were 10.5 ± 2.6 and correlated fairly well with the GLS. ($r = -0.164$, $p = 0.61$)

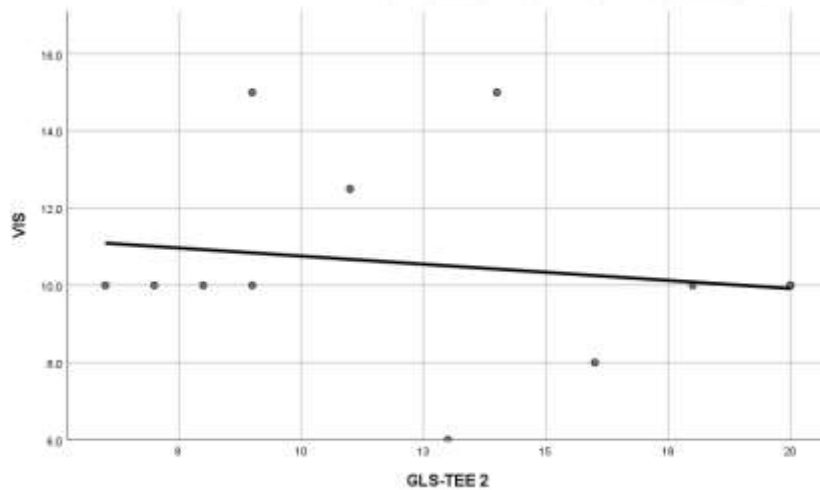


Figure-13: - Correlation between vasoactive inotropic score and GLS (VIS- vasoactive inotropic score; GLS-TEE-2- post-operative global longitudinal strain by trans-esophageal echocardiography)

Ventricular morphology:

The LV-type ventricle had a significant decrease in GLS post-bypass compared to the RV-type. ($p = 0.03$)

	N	GLS						Paired t-test	
		Pre		Post		Paired difference			
		Mean	sd	Mean	sd	Mean	sd	t	p
LV	7	15.9	2.1	11.6	4.7	4.3	4.3	2.7	0.038
RV	5	17.2	1.9	14.0	5.7	3.2	5.7	1.3	0.279

Table-5: -GLS and ventricular morphology

	N	EF(%)						Paired t-test	
		Pre		Post		Paired difference			
		Mean	sd	Mean	sd	Mean	sd	t	p
LV	7	55.3	6.4	43.4	7.3	11.9	5.6	5.6	0.001
RV	5	59.0	5.8	51.4	15.8	7.6	10.9	1.6	0.195

Table-6: -Ejection fraction and ventricular morphology

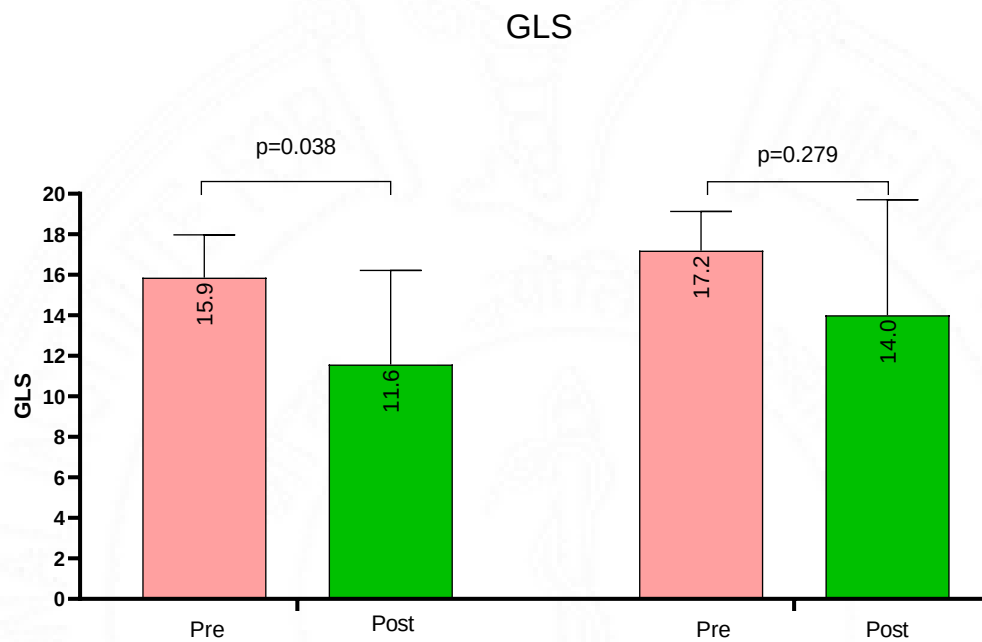


Figure-14: - Ventricular morphology and GLS (GLS-global longitudinal strain, LV-left ventricle, RV-right ventricle)

The LV-type ventricle had a significant decrease in EF in the post-bypass period when compared to the RV-type.(p=0.001)

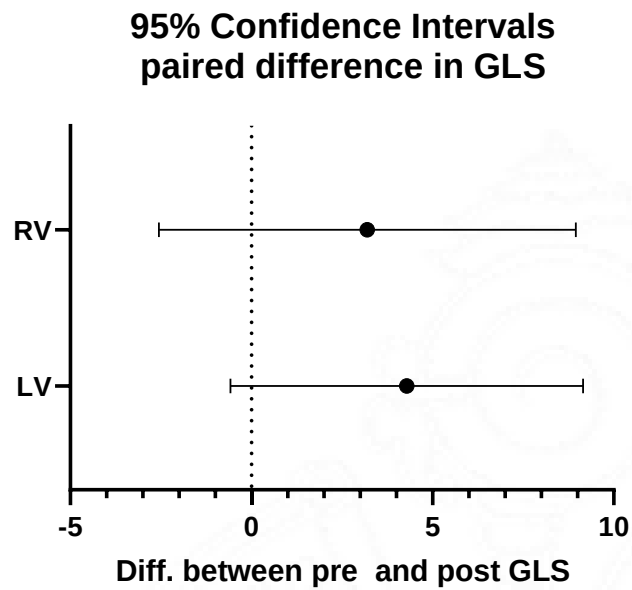


Figure-15: - Ventricular morphology and GLS(global longitudinal strain)

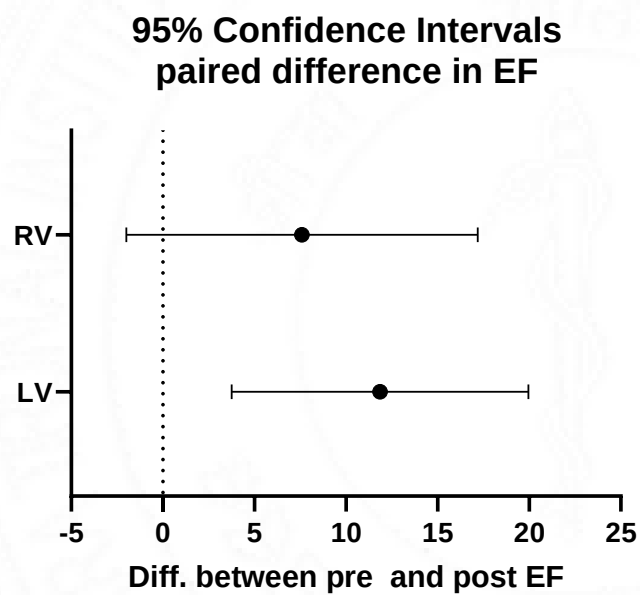


Figure-16: - Ventricular morphology and ejection fraction

Discussion:

Global longitudinal strain:

Patients after TCPC palliation have to be followed up closely by clinical and imaging methods for the onset and progression of ventricular dysfunction. This helps in early diagnosis and implementation of therapeutic measures like ventricular assist devices and transplants. Trans-thoracic echocardiography may be sub-optimal in these subsets of patients because of the deteriorating acoustic windows with age, and scars due to previous multiple surgeries. Peri-operative GLS by speckle tracking Transesophageal echocardiography serves as a baseline with which the follow-up values can be compared giving a fair trend analysis of ventricular function over some time. This mode of imaging comes with its benefits like easiness of use, less invasive and giving an anatomical and functional assessment, angle-independent and fairly independent of loading conditions, and is comparable to the CMR, though with a sub-optimal agreement. Also, subtle sub-clinical dysfunction can be detected by strain imaging early and treatment implemented.

Single ventricular systolic function quantified by Global Longitudinal Strain speckle tracking echocardiography, immediately after cardio-pulmonary bypass showed a significant decrease when compared to pre-bypass (pre-CPB=-16.42±2.07 %; immediate post-CPB=-12.58±5.02, p=0.017).

Liwei et al, in their retrospective study comparing 2D and 3D strain in Fontan patients and controls, showed that GLS is significantly lower in Fontan patients when compared to normal children. (22) Large-scale multicenter studies involving more patients are required to know the correlation between strain parameters, conventional echocardiographic parameters, and CMR.

The GLS cut-off to define ventricular dysfunction in a single ventricle is lacking. GLS cut-off of -24.5% to define ventricular dysfunction, as measured in the general pediatric population may not be applicable in single ventricles given the fact that the myofiber arrangement and molecular differences exist. (6,23,24). Umiko et al defined a GLS <-11.8% in patients after the Fontan procedure which predicted MACE, Major adverse cardiac events. (7)

The reasons could be because of further ventricular unloading after TCPC resulting in reduced pre-load to the single ventricle, though GLS is less pre-load dependent.

Myofiber architecture in single ventricles is disorderly due to genetical reasons. Sub-optimal ventricular mechanics resulting in altered bioenergetics and ventriculo-arterial coupling. The torsion component which exists in the bi-ventricle is lost in a single ventricle thereby depending solely on fiber shortening to generate cardiac output. The lack of a complete interventricular septum affects the ventricular interdependence and reduces the effective forward flows. (4) Chronic hypoxia and ventricular distention due to partially volume unloaded ventricle results in areas of myocardial fibrosis adding to ventricular dysfunction. The diastolic dysfunction leading to increased pulmonary vascular resistance ends up in reduced ventricular filling and systolic dysfunction. Increased afterload induces ventricular dysfunction as the single ventricle has to overcome resistances at three different levels, SVR, PVR, and the conduit. Myocardial perfusion is impaired in the single ventricle due to increased demand by a volume-loaded ventricle working against increased afterload and decreased supply due to inherent coronary artery anomalies and fistulas. Cardio-pulmonary bypass, aortic cross-clamp, and myocardial protection are other factors that may explain the ventricular dysfunction in the immediate post-bypass period. Aorto-pulmonary collaterals which may exist after TCPC may continue to burden the single ventricle with additional volume. Stage 3 palliation is done at the age of 18 months-4 years in most centers. (20) However, the patients in this study cohort presented lately for TCPC (Age, median-14 years), resulting in an extended period of single ventricular volume overload and chronic hypoxia leading to ventricular dysfunction.

However, studies are showing no significant correlation between strain parameters and MRI. (6) So, further studies are required comparing strain with CMR.

Ejection fraction:

Ejection fraction measured by the 2D modified-Simpsons method showed a corresponding decrease after CPB, for the reasons discussed above. Correlation with the GLS was strong ($r=0.949$). Renee Margossian has categorized the ventricular systolic dysfunction in functionally single ventricle as normal (55%), mild (41% to 55%), moderate (31% to 40%), or severe (30%) dysfunction. (25)

Going by this classification, our patients had mild systolic ventricular dysfunction after TCPC (46.8 ± 11.7) Even though studies have shown varying correlations between GLS and 2D EF, our study showed a strong correlation only in the dysfunctional ventricles. This was associated with a significant decrease in cardiac index as well ($2.33 \pm 0.51 \text{ L/min/m}^2$,

$p < 0.001$). Ventricular dyssynchrony might have contributed to lower cardiac output, however this was not evaluated in our study. (26)

Ventricular volumes:

Staged palliation in the single ventricular pathway results in a staged unloading of the single ventricular volumes. This reduces the volume overload of the single-functioning ventricle and thereby reduces the failure.

There was a significant decrease in EDV from pre-TCPC (37.17 ± 4.88 ml/m²) to immediate post-TCPC (30.83 ± 1.34 ml/m², $p = 0.001$). There was no significant change in ESV from pre-TCPC (16.33 ± 2.39 ml/m²) to immediate post-TCPC (16.58 ± 3.40 ml/m², $p = 0.745$).

Ventricular volumes are underestimated by echocardiography when compared to CMR. No reference ranges for ventricular volumes have been deducted for functionally single ventricles. (27) In this scenario, our study gives a baseline estimation of ventricular volumes for future comparison as the ventricular dilation results in failure and requirement of ventricular assist devices or transplants.

Sophie et al have shown that an EDV index > 156 ml/m² strongly predicts death or transplant listing. (10)

Length of ICU and hospital stay:

Our study did not show any significant correlation between the post-bypass GLS and the Length of ICU and Hospital stay ($r = 0.357$; $r = 0.244$, respectively). The ventricular dysfunction that existed immediately after the bypass may have improved with time, inotropic support, and adaptation to new hemodynamics like pre-load, and ventricular unloading. For the same reasons, there could not have been any correlation between GLS with duration of mechanical ventilation and ICD drainage.

Single ventricle morphology:

Patients with SV of RV morphology are at higher risk of failure because the geometry, fiber orientation, and metabolic adaptations of the RV are not suited to support the high-pressure, systemic circulation in the long term. (28) Kazuhiro et al showed that RV strains are lower than LV strains in single ventricles and correlated better with EF. (29)

However, in our study, both GLS and EF showed a significant decrease in the post-cardiopulmonary bypass period in the LV-type ventricle when compared to RV morphology. (GLS $P=0.003$ for LV, EF $p=0.001$ for LV). This is in contrast to the well-established fact that the RV morphology ventricle is more susceptible to dysfunction and failure when compared to LV morphology. This finding could be because of the small sample size.

Limitations

Our study has a limited sample size of 12 cases which is small to make a meaningful conclusion. Ventricular volumes are more accurately measured by 3D volume assessment compared to the 2D volume assessment that we have used.

To prove the reproducibility of a diagnostic test, Inter-observer agreement is important, which we haven't done. A comprehensive strain imaging of a functionally single ventricle involves evaluation of strain in other dimensions like circumferential strain, radial strain, torsion, strain rate, and dyssynchrony which have not been evaluated. Post-operative follow-up strain imaging was not done to follow up the course of ventricular dysfunction. This being done on a south Indian population; results can't be generalized to all ethnic groups. Inter and intra observer variability were not studied in this study.

A comprehensive evaluation of the functional ability of the single ventricle involves CMR, TTE, and Cath data like LVEDP, cardiac biomarkers like pro-BNP, Cardiopulmonary exercise testing like peak O_2 consumption, and clinical grading of symptoms like NYHA class. Further studies are required to incorporate all the above parameters along with strain imaging.

3D data sets like 3D volume and 3D speckle tracking quantification can correlate more accurately with CMR when compared to 2D volumes. Quantification of dyssynchrony can help in targeted therapies like resynchronization therapy. A large-scale study in functionally single ventricular hearts can help in forming reference values for strain parameters, ventricular volumes, and ejection fraction in these subsets of patients. This also helps in grading the severity of ventricular dysfunction, volumes and ejection fraction and to observe the peri-operative course.

Conclusions

We conclude that GLS by 2D speckle tracking echocardiography can quantify systolic ventricular dysfunction in the immediate post-cardiopulmonary bypass period in patients undergoing TCPC. It correlates well with the Ejection fraction quantified by the modified Simpsons method. There was a significant reduction in end-diastolic volumes and cardiac index in the immediate post-bypass period. There was no correlation between the GLS and the clinical outcomes like duration of mechanical ventilation, length of ICU and hospital stay, and duration of intercostal drainage.

Tables: -

Table-1: - Sex distribution of cases

Table-2: -Ventricular morphology (LV and RV type)

Table-3: -Global longitudinal strain (pre- and post-operative)

Table-4: -Change in ventricular end-systolic and end-diastolic volumes

Table-5: -GLS and ventricular morphology

Table-6: -Ejection fraction and ventricular morphology

Figures: -

Figure-1: Fontan circulation

Figure-2: Strain curve showing the peak systolic strain²¹

Figure-3: Global longitudinal strain

Figure-4: -Global longitudinal strain((pre- and post-operative)

Figure-5: - Change in ventricular end-diastolic volumes (EDV-end-diastolic volume)

Figure-6: - Change in ventricular end-systolic volumes (ESV- end-systolic volume)

Figure-7: - Correlation between post-operative cardiac index and GLS

Figure-8: - Correlation between post-operative ejection fraction and GLS

Figure-9: - Correlation between post-operative ICU stay and GLS

Figure-10: - Correlation between post-operative length of hospital stay and GLS

Figure-11: - Correlation between duration of mechanical ventilation and GLS

Figure-12: - Correlation between duration of intercostal drain and GLS

Figure-13: - Correlation between vasoactive inotropic score and GLS

Figure-14: - Ventricular morphology and GLS

Figure-15: - Ventricular morphology and GLS (global longitudinal strain)

Figure-16: - Ventricular morphology and ejection fraction

Parameter		Units
GLS	Global Longitudinal Strain	Percentage
EF	Ejection Fraction	Percentage
EDV	End-Diastolic volume	ml
ESV	End-systolic volume	ml
TEE	Transesophageal echocardiography	
LOS	Length of hospital stay	Days
ICU stay	Intensive Care Unit stay	Days
BSA	Body Surface Area	Square meters
LV	Left ventricle	
RV	Right ventricle	
AVVR	Atrio-ventricular valve regurgitation	
HR	Heart rate	Beats/minute
SBP	Systolic Blood Pressure	mm of Hg
DBP	Diastolic Blood Pressure	mm of Hg
MBP	Mean Blood Pressure	mm of Hg
1	Before TCPC	
2	After TCPC	
SPO2	Oxygen saturation	Percentage
CVP	Central Venous Pressure	mm of Hg
Glenn	Pulmonary artery Pressure	mm of Hg
CI	Cardiac index	Litres /min/square metre
VIS	Vaso-active Inotropic Score	
Mechanical ventilation	Duration of Mechanical ventilation	Hours
ICD	Duration of Intercostal drain	Days
CPB	Duration of Cardio-pulmonary bypass	Hours

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Appendix-1 (Proforma)

STUDY PROFORMA

Title- Peri-operative quantification of systolic Global longitudinal strain by trans-oesophageal in functionally single ventricle patients undergoing Total Cavo-pulmonary connection-A Pilot study

Serial no. Age/sex: Hospital No:

Date of surgery:

Height: Weight: BSA:

Diagnosis:

Type of Single ventricle: -LV/RV/Indeterminate

Perioperative parameters:

Fenestrated/Non-fenestrated

		Pre-TCPC	Post-TCPC
1	HR (per minute)		
2	Rhythm		
3	BP systolic/diastolic/mean (mm of Hg)	/ /	/ /
4	CVP (mm of Hg)		
5	Glenn Pressure (mm Hg)		
6	SPO2(percentage)		
7	EDV (ml), indexed		
8	ESV (ml), indexed		
9	EF (percentage)		
10	AVVR (mild/moderate/severe)		
11	GLS (percentage)		
12	Haemoglobin(g%)		
13	Cardiac Index (litres/minute/m2 BSA)		

The above-mentioned echocardiographic data will be obtained on two occasions Philips IE33 ultrasound system (Andover, MA) with 30-40. The endocardial border was manually traced and tracking was automatically performed by the software. A more negative systolic strain indicates better ventricular function.

A) **Before Fontan completion:** - Transoesophageal echocardiography after induction of general anaesthesia and endotracheal intubation.

B) **After Fontan completion:** - Transoesophageal echocardiography after coming off cardiopulmonary bypass.

Echocardiographic data: -

1) Mid-esophageal four chamber, two chamber and long axis views will be obtained by 3D Trans-esophageal echocardiography probe.

2) 2D end-diastolic and end-systolic volumes(indexed) and ejection fraction of the single ventricle.

Post-operative data: -

Length of ICU stay(days)	
Length of Hospital stay (LOS) in days	
Incidence of arrhythmia (type and number of episodes)	
Duration of mechanical ventilation (hours)	
Organ dysfunction (Liver/Renal/stroke)	
In-hospital Mortality	
CPB time(minutes)	
Intercostal tube drainage(days)	

Vasoactive-inotropic Score (VIS)

<u>Medication</u>	<u>Dose</u>
Dopamine(micrograms/kg/min)	
Dobutamine(micrograms/kg/min)	
Epinephrine(micrograms/kg/min)	
Norepinephrine(micrograms/kg/min)	
Milrinone(micrograms/kg/min)	
Vasopressin(U/kg/min)	
<u>Vaso-active inotropic score</u>	

APPENDIX-2(Patient Information Sheet)

PATIENT INFORMATION SHEET

**Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram, Kerala-695011**

TITLE OF THE STUDY:

Peri-operative quantification of systolic Global longitudinal strain by trans-oesophageal echocardiography in functionally single ventricle patients undergoing total Cavo-pulmonary connection (TCPC)-A Pilot study

Principal Investigator:

Dr Nandish Kori M, PDF, Paediatric Cardiothoracic and Vascular Anaesthesia, SCTIMST

Co-Principal Investigator:

Prof. Dr Thomas Koshy, Professor (senior grade), Cardiothoracic and Vascular Anaesthesia

Co Investigators:

Prof Prasantha Kumar Dash, Professor in Cardiothoracic and Vascular Anaesthesia, SCTIMST

Dr Saravana Babu, Associate Professor in Cardiothoracic and Vascular Anaesthesia, SCTIMST

Prof Baiju S Dharan, Professor in CVTS, SCTIMST

Dr Soumya Ramanan, Additional Professor in CVTS, SCTIMST

Sir/ madam,

We invite your child to take part in our study titled 'Peri-operative quantification of systolic Global longitudinal strain by trans-oesophageal echocardiography in functionally single ventricle patients undergoing total Cavo-pulmonary connection (TCPC)'. 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 information needed for participation in this study so that you can make a well informed and considered decision about your child's participation. In addition, if 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. In this study we aim to find out the Global longitudinal strain of the single ventricle by trans oesophageal echocardiography probe. We will also attempt to describe if the strain evaluation can predict the post-operative icu course.

Why is this study being done?

Transoesophageal echocardiography is an invaluable tool in the perioperative monitoring and management of all the patients undergoing cardiac surgeries. Quantification of single ventricular function by Global longitudinal strain can predict the post-operative course like number of ICU stay days apart from fairly evaluating ventricular systolic function. In this study, the authors attempt to quantify the Global longitudinal strain by Trans-oesophageal echocardiography. An attempt is also made to describe the correlation between the strain values and parameters like inotropic score, number of ICU stay days, ventricular volumes and ejection fraction. This would help us in establishing a baseline ventricular systolic function for a further serial evaluation and immediate peri-operative hemodynamic management.

What is the purpose of this study?

There are no studies quantifying the global longitudinal strain by trans-oesophageal echocardiography in single ventricle patients undergoing Total Cavo-pulmonary connection.

This study is an attempt in this direction. Once completed the study would prove to be useful in peri-operative management and serve as a baseline for a serial follow-up.

The aims and objectives of this study include:

- 1) The primary objective is to quantify the Global longitudinal strain of the single ventricle.
- 2) The secondary objectives are to quantify ventricular volumes and ejection fraction, inotropic score, number of ICU stay days.

How many people will take part in the study?

It is planned to recruit 10 patients from our hospital as a pilot study, as there are no prior studies evaluating ventricular strain using trans-oesophageal echocardiography in these subset of patients. Sample size will be calculated based on the evaluation of these 10 cases.

How is the study done?

SUBJECT/PARTICIPANT SELECTION

- All the paediatric patients who undergo Total Cavo-pulmonary connection in the Paediatric Cardiac Surgery Operation Theatres (PSOT) at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

Will any biological sample(s) be stored and used in the future?

This study involves quantification of global longitudinal strain by trans-oesophageal echocardiography. It doesn't require any biological samples to be collected or stored.

What are the risks of the study?

This study doesn't involve any additional risk other than the ones routinely involved with TEE probe placement (in almost all cardiac surgeries).

Will the information pertaining to my child's illness be shared with others?

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 child's name or any other identifiable detail will not be published in any research paper or scientific presentation arising out of the study.

Will the study results be shared with me?

The investigators will share the details with you if any correctable abnormality is found and advice on remedial measures if present. The scientific information resulting from the study also will be shared with you after completion if you wish to know it.

How will my child benefit from the study?

Taking part in this research study is unlikely to benefit your child immediately in any manner. However, we do hope that this study will help in the peri-operative hemodynamic management and serves as a baseline for serial follow up of ventricular function. This will immensely benefit the single ventricle patients who undergo Total Cavo-pulmonary connection.

What other choices do I have if my child doesn't take part in this study?

The study is only being done to gather scientific information. You may choose not to take part in this study without any consequences and without it affecting your child's treatment in SCTIMST in any manner.

What are the costs of the tests and the procedures?

There is no additional cost involved whatsoever.

Will my child lose his/her rights if I do not consent to take part in this study?

You do not give up any of your child's rights by taking part in this study. Taking part in this research study is your decision. Your child does not have to take part in this study if you are unwilling and your child will not be losing any of his/her rights if you choose not to participate. Your child's further treatment in the institute will in no way be affected. 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.

Will my child's personal details be kept confidential?

The results of this study will be published in a medical journal, but your child will not be identified by name in any publication or presentation of results. Your clinical details and results of the tests may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Whom should I contact for any doubts pertaining to the study?

If you have any further questions, please ask

Dr Nandish Kori M

Fellow, Division of Paediatric Cardiothoracic and Vascular Anaesthesia

Sree Chitra Tirunal Institute for Medical Sciences and Technology, Medical College PO,
Trivandrum -11

Phone:8589861515

Email: nandishkm84@gmail.com

Name of the PI: Dr Nandish Kori M

Signature of the PI:

For any clarifications regarding the study's ethics clearance, you may contact:

Dr Srinivas G

Member Secretary of the SCTIMST- IEC.

Phone number: 04712524689

Email id: iec.mem.sec@sctimst.ac.in

DEFINITIONS

1. Transesophageal echocardiography: The technique by which the images of the heart and various functional parameters regarding the integrity of the heart can be monitored from a location near the heart. This is done placing an imaging device (the probe) at the end of a long flexible rod (gastroscope) and the rod is inserted through the patient's oesophagus (food pipe).

2. Echo probe: A long, flexible, smooth rod which bears the imaging device at its end and is inserted through the patient's food pipe (the oesophagus)

3. Global longitudinal strain: An echocardiographic method to quantify ventricular systolic function

APPENDIX-3(CONSENT FORM)

TITLE OF STUDY: “Peri-operative quantification of systolic Global longitudinal strain by trans-oesophageal echocardiography in functionally single ventricle patients undergoing total Cavo-pulmonary connection (TCPC)-A pilot study”

- (i) I confirm that I have read and understood the information sheet attached to this informed consent form for the above study and have had the opportunity to ask questions. []
- (ii) I understand that my child’s participation in the study 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. []
- (iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my child’s health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my child’s identity will not be revealed in any information released to third parties or published. []
- (iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) []
- (v) I agree to participate my child in the above study. []

Name of Participant:

Signature:

Date:

Relation to participant:

Name of witness:

Signature:

Date:

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 care givers and explained to him / her in non-technical terms all the information contained in this informed consent form. I further certify that I encouraged the participant’s caregivers to ask questions and that all questions asked were answered. A copy of the informed consent form has been given to the study participant’s caregiver.

Place: Trivandrum

Date:

Principal Investigator: Dr Nandish Kori M

Name of the PI: Nandish Kori M

Address and Contact Details: Fellow, Paediatric cardiac anaesthesia, Department of Cardiothoracic and Vascular Anaesthesiology, SCTIMST, Medical College PO, Trivandrum
Phone: 8589861515

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Signature of the PI:

For any clarifications regarding the study’s ethics clearance, you may contact:

Dr Srinivas G

Member Secretary of the SCTIMST-IEC.

Phone no: 0471-2524689

Email id: iec.mem.sec@sctimst.ac.in

APPENDIX-4(IEC 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
(An Institute of National Importance under Govt. of India)

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/2086/AUGUST/2023

13.10.2023

Dr. Nandish Kori M
Post Doctoral Fellow
Department of Anaesthesia
SCTIMST, Thiruvananthapuram

Dear Dr. Nandish Kori,

The Institutional Ethics Committee held on 24th August, 2023, reviewed and discussed your application to conduct the study titled "PERI-OPERATIVE QUANTIFICATION OF SYSTOLIC GLOBAL LONGITUDINAL STRAIN BY TRANS-OESOPHAGEAL ECHOCARDIOGRAPHY IN FUNCTIONALLY SINGLE VENTRICLE PATIENTS UNDERGOING TOTAL CAVO-PULMONARY CONNECTION (TCPC): A PILOT STUDY" (IEC/2086).

Principal Investigator	Dr Nandish Kori M, Fellow in Pediatric Cardiothoracic Vascular Anesthesia, SCTIMST
Co-Principal Investigator(s)	Prof Thomas Koshy, Professor- Senior Grade in Cardiothoracic Vascular Anesthesia, SCTIMST
Co- Investigator(s)	Prof Prasanta Kumar Dash, Professor- Senior Grade in Cardiothoracic Vascular Anesthesia, SCTIMST Dr Saravana Babu MS, Associate Professor in Cardiothoracic and Vascular Anesthesia, SCTIMST Dr Baiju S Dharan, Professor & HOD in Cardiovascular Thoracic Surgery, SCTIMST Dr Sowmya V Ramanan, Additional Professor, in Cardiovascular Thoracic Surgery, SCTIMST
Duration of the study	6 months

The following members of the Ethics Committee were present at the meeting held on 24th August, 2023

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
4.	Dr. P. Manickam	BSMS, MSc (Epid), PhD	Male	Health Science Expert/ Social Scientist	No
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
8.	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 18.05.2023
3. IEC Application Form
4. Declaration Form
5. Study Proposal
6. Patient Information Sheet and Consent Form in English and Malayalam
7. Child Assent Form in English and Malayalam
8. CV of PI and Co-PIs
9. SRC Recommendation Letter

Revised submission

1. Checklist Form
2. Covering letter addressed to the Chairman, IEC, SCTIMST dated 18.05.2023
3. IEC Application Form
4. Declaration Form
5. Study Proposal
6. Proforma
7. Patient Information Sheet and Consent Form in English and Malayalam
8. Child Assent Form in English and Malayalam
9. CV of PI and Co-PIs

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



APPENDIX-5(MASTER CHART)

<u>Parameter</u>		<u>Units</u>
GLS	Global Longitudinal Strain	Percentage
EF	Ejection Fraction	Percentage
EDV	End-Diastolic volume	ml
ESV	End-systolic volume	ml
TEE	Transesophageal echocardiography	
LOS	Length of hospital stay	Days
ICU stay	Intensive Care Unit stay	Days
BSA	Body Surface Area	Square meters
LV	Left ventricle	
RV	Right ventricle	
AVVR	Atrio-ventricular valve regurgitation	
HR	Heart rate	Beats/minute
SBP	Systolic Blood Pressure	mm of Hg
DBP	Diastolic Blood Pressure	mm of Hg
MBP	Mean Blood Pressure	mm of Hg
1	Before TCPC	
2	After TCPC	
SPO2	Oxygen saturation	Percentage
CVP	Central Venous Pressure	mm of Hg
Glenn	Pulmonary artery Pressure	mm of Hg
CI	Cardiac index	Litres /min/square metre
VIS	Vaso-active Inotropic Score	
Mechanical ventilation	Duration of Mechanical ventilation	Hours
ICD	Duration of Intercostal drain	Days
CPB	Duration of Cardio-pulmonary bypass	Hours

