SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

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SERIAL CHANGES IN LEFT VENTRICULAR REMODELING AFTER BALLOON ATRIAL SEPTOSTOMY IN D-TRANSPOSITION OF GREAT ARTERIES

PROJECT REPORT

Submitted during the course of DM Cardiology

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DECLARATION

I, **Dr. Arun Gopalakrishnan,** hereby declare that the project in this book, titled **“SERIAL CHANGES IN LEFT VENTRICULAR REMODELING AFTER BALLOON ATRIAL SEPTOSTOMY IN D-TRANSPOSITION OF GREAT ARTERIES”** was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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Forwarded

The candidate, **Arun Gopalakrishnan,** has carried out the minimum required project.

Thiruvananthapuram **Prof. Dr Jagan Mohan Tharakan**
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Arun Gopalakrishnan

Serial Changes in Left Ventricular Remodeling After

Balloon Atrial Septostomy in

d - Transposition of Great Arteries

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ABBREVIATIONS

- 2D – Two dimensional
- 3D – Three dimensional
- ASD – Atrial septal defect
- ASE – American Society of Echocardiography
- ASO – Arterial switch operation
- BAS – Balloon atrial septostomy
- BSA – Body surface area
- CPB – Cardiopulmonary bypass
- DORV – Double outlet right ventricle
- d-TGA – d Transposition of great arteries
- EF – Ejection fraction
- FS – Fractional shortening
- ICU – Intensive care unit
- IVS – Intact interventricular septum
- IVSd – Interventricular septal thickness in diastole
- IVSs – Interventricular septal thickness in systole
- LA – Left atrium
- LV – Left ventricle
- LVID – Left ventricular internal diameter in diastole

- LVIS – Left ventricular internal diameter in systole
- LVOTO – Left ventricular outflow tract obstruction
- MPA – Main pulmonary artery
- PAPVC – Partial anomalous pulmonary venous connection
- PDA – Patent ductus arteriosus
- PGE1– Prostaglandin E1
- PS – Pulmonary stenosis
- PWd – Posterior wall thickness in diastole
- PWs – Posterior wall thickness in systole
- RA – Right atrium
- ROC – Receiver operating characteristic
- RT3DE – Real time three dimensional echocardiography
- RV – Right ventricle
- RVID – Right ventricular internal diameter in diastole
- RVOT – Right ventricular outflow tract
- SCTIMST – Sree Chitra Tirunal Institute for Medical Sciences and Technology
- SD – Standard deviation
- SpO2 – Oxygen saturation by pulse oximetry
- TGA – Transposition of great arteries

- TGA/IVS – Transposition of great arteries with intact interventricular septum
- VSD – Ventricular septal defect

ABSTRACT

Background: Arterial switch operation is the definitive surgical option for infants with d - transposition of great arteries (d-TGA). However this is not always feasible in the hemodynamically unstable child with desaturation. Balloon atrial septostomy (BAS) is as an effective palliative procedure in children with TGA and poor intercirculatory mixing. While the subpulmonary left ventricle (LV) is known to regress with time in these newborns due to declining afterload, it has not been studied how it behaves following BAS and consequent decrease in preload.

Aims and Objectives: The study was designed to examine the effect of BAS on the left ventricle in infants with simple d-TGA by serial 2D echocardiographic monitoring.

Materials and Methods: This was a prospective follow up observational study of all consecutive children with simple TGA with restrictive interatrial communication and a resting oxygen saturation less than 75% who underwent BAS as per institutional protocol between January 2014 and June 2015. Babies who were offered primary arterial switch operation by the cardiac surgery team and those with non-restrictive ventricular septal defects or other significant cardiac or vascular abnormalities were excluded. Serial 2D echocardiographic monitoring was done till corrective surgery. Left ventricular mass was estimated by M mode LV measurements by American Society of Echocardiography conventions as an average of three repeated measurements.

Results: The median age of the 25 children studied was 4 days (1 – 95 days) when they underwent BAS. Twenty patients underwent ASO at a mean of 9 days from BAS. The mean baseline LV mass was 47.85 g/m^2 which decreased to 38.51, 36.21, 32.07, 32.44, 25.68, 25.17 g/m^2 on days 1, 3, 6, 9, 12, 15 respectively. The indexed LV mass decreased by 1.515 g/m^2 every day following BAS adjusted for the age of the child in days. Children who underwent BAS beyond three weeks of life had faster LV regression than those who underwent BAS earlier ($t = 5.385$, $p < 0.001$).

Conclusions: Balloon atrial septostomy is associated with accelerated regression of the left ventricle in infants with simple transposition of great arteries in the first two weeks after BAS. Regression of the left ventricle is faster in children who undergo BAS beyond three weeks of life.

INTRODUCTION

Balloon atrial septostomy (BAS) has been established as an effective palliative procedure in infants with d - transposition of great arteries (d-TGA) with poor intercirculatory mixing. It reduces hypoxia by permitting adequate intercirculatory mixing and also reduces heart failure by obviating left atrial hypertension and pulmonary venous congestion. The non-restrictive atrial communication thus created is associated with improved systemic oxygen saturations and augmented cardiac output. Thus it serves as an effective procedure in preoperative stabilization prior to definitive arterial switch operation (ASO).

BAS was introduced by Rashkind and Miller in 1966 and the technique has evolved with time[1]. When introduced, it was the single most important factor affecting survival in patients with TGA. Initially several neurological complications were reported with BAS, primarily related to balloon rupture, atrial septal fragmentation and consequent embolization. Over time, the procedure has undergone several advancements and complications have minimized over time. BAS has also simplified the technical aspects of the arterial switch procedure, allowing for efficient left- and right-sided drainage on cardiopulmonary bypass with a single atrial cannula.

With recent surgical advancements, several centers have resorted to ASO in the early neonatal period. In a study by Anderson et al, the median age at ASO was five days (range: 1 to 12 days; 97% at ≤10 days)[2]. 25% were operated on or before day three of life. Seventy-one percent of these babies underwent BAS at a median age of zero days. For every day later that surgery was performed, beyond day of life 3, the odds of major morbidity increased by 47% and costs increased by 8%. Of late an increasing number of centers are opting for primary ASO in the newborn period without BAS palliation with improved survival even in the first hours of life.

The earlier presumed cutoff limit for primary ASO for TGA with intact ventricular septum (TGA/IVS) of three weeks has been revoked in the light of results from several studies. Centers have reported comparable outcome for ASO beyond three weeks in TGA/IVS and well-conditioned left ventricle[3,4]. The primary explanation for continuing trials to extend the age limit for this group of patients is that ASO results have been proved and accepted worldwide as superior to the other proposed surgical options such as Senning and Mustard procedures.

The two - stage arterial switch, which had been proposed a decade earlier, and later modified by reducing the interval between stages to one week, was put forward as a solution to infants presenting for surgery beyond the neonatal period, particularly with late referrals. However several centers have reported variable success. Of late, it is less favored because of suboptimal outcome, with higher mortality and morbidity rates, prolonged ICU stay with increased risk of nosocomial infection, and increasing hospital costs.

In India, where majority of deliveries are conducted at non tertiary health care facilities, most cases of TGA are diagnosed in the early neonatal period. In this setting of relatively late referrals compared to the West, early palliative BAS followed by ASO often in the second week of life or beyond play a significant role in the care of TGA/IVS.

While the subpulmonary left ventricle (LV) is known to regress with time in these newborns due to declining afterload, it is not been studied how it behaves following BAS and consequent decrease in preload. Thus far, the definition of LV regression has been based on an abnormal configuration of the left ventricle and the interventricular septum besides declining LV mass and posterior wall thickness. An arbitrary cut off value of 35 g/m^2 is considered the threshold for LV retraining in children with regressed LV[5]. The size of the interatrial communication and duct are known to influence LV preload and afterload. There are concerns that the institution of BAS in preoperative stabilization in d - TGA with intact atrial septum and poor intercirculatory mixing might lead to faster regression of the left ventricle posing further challenges to the surgeon during definitive repair.

In this setting, we set to examine the effect of emergency BAS on the left ventricle in newborns with d-TGA and poor intercirculatory mixing. The hypothesis was our study was that BAS would be associated with accelerated LV regression in simple TGA.

REVIEW OF LITERATURE:

D-Transposition of great arteries (TGA) accounts for 5 – 7% of all congenital heart diseases with a reported prevalence of 0.2 per 1000 live births and male preponderance[6]. Sibling recurrence rates of 0.27 and 2%, respectively, have been noted in simple and complex forms associated with a functional single ventricle or heterotaxy[6]. Among parents and siblings of infants with TGA, the mean recurrence risk for congenital heart disease is approximately 1.4%[7,8]. Some of the reported mutations associated with TGA include those in the Nodal signaling pathway, ZIC3, PROSIT240, CFC1, FoxH1, GDF1 and NPHP4[9].

The evolution of arterial switch operation for the treatment of d-transposition of great arteries has revolutionized the outcomes of these children with the vast majority surviving well into adulthood with limited morbidity. In the current era, more and more cases are being diagnosed in utero facilitating early intervention and improving outcomes. However, in developing countries like India, not every center is currently able to offer primary ASO to the hemodynamically unstable child in the first week of life and many children undergo the definitive surgery after a balloon atrial septostomy.

Accurate prenatal diagnosis minimizes maternal and neonatal risk and improves outcomes. Hypermobility of the interatrial septum and reverse flow in the patent ductus arteriosus on fetal echocardiography have been associated with presentation with hypoxemia and need for urgent BAS[10]. In late gestation, the transposed fetal circulation results in lower substrate delivery to the rapidly developing brain, which may account for the higher than expected incidence of microcephaly, white matter injury and cortical immaturity seen on neonatal MRI scans. However the most important implication of fetal diagnosis is in its role in facilitation of “intrauterine transfer” and delivery at a tertiary center performing BAS.

Most hypoxemic neonates with TGA will benefit solely from early institution of prostaglandin E1 (PGE1) therapy. However, neonates with inadequate interatrial mixing due to a restrictive foramen ovale will generally not improve on PGE1 alone. In this setting, the markedly increased pulmonary blood flow from the PDA may lead to deleterious left atrial hypertension, pulmonary congestion, and low systemic cardiac output with hypoxemia necessitating urgent BAS.

BAS offers a lifeline for infants with complete transposition of great arteries with poor intercirculatory mixing. The percutaneous procedure is an advancement over the Blalock and Hanlon technique of surgical creation of an atrial septal defect to improve saturations in these children[11]. BAS usually results in a significant increase in the interatrial communication to 5 – 11 mm (mean 8.8 mm) and significant improvement in arterial saturations in d-TGA[12]. It also results in a fall in transatrial gradient which results in reduction of pulmonary venous pressures in these children also contributing to symptomatic improvement[12].

With medical management, most neonates with an early diagnosis of TGA can be stabilized and can undergo electively timed ASO. However the preoperative management and the timing of surgery vary by institution. Clinicians are thus confronted with the decision making of the best option for a given child wherein they must weigh the risks and benefits of BAS, prostaglandin administration and a resultant PDA, and the timing of definitive neonatal surgery.

Prostaglandin administration may cause apnea needing mechanical ventilation, hypotension and fever (especially in low birth weight babies). PGE1 can maintain the patency of the ductus arteriosus which predominantly shunts from the aorta to the pulmonary artery in infants with TGA. This increases pulmonary blood flow in these infants. If the foramen ovale does not permit an adequate shunt from the left to the right atrium, pulmonary blood volume will increase progressively, resulting in a rise in pulmonary arterial and left atrial pressures[13]. A reasonable peripheral oxygen saturation in these infants can also be associated with paradoxically low cerebral oxygen delivery. Mean cerebral oxygen saturations in children with a PDA and normal systemic oxygen saturations are generally in the low 50s and are likely even lower in TGA[14]. This can predispose them to white matter central nervous system injury and suboptimal long term outcomes.

Delaying definitive ASO by several days after birth has potential benefits[15]. It permits transition from fetal to neonatal circulation and consequent reduction in pulmonary vascular resistance. Many infants who have renal or hepatic impairment in the early neonatal period can be stabilized and get time for function improvement before they undergo a major surgery. A delayed surgery permits initiation of enteral nutrition and can reduce the risks of necrotizing enterocolitis. It also permits evaluation for other congenital anomalies and allows time for the family to prepare for surgery. However, risks relating to BAS, prolonged exposure to PGE1 and PDA physiology, longer duration of hypoxemia, lower cerebral oxygen delivery and paradoxical emboli, may counteract the benefits of “elective” delay.

Many surgical centers are now resorting to earlier ASO due to the potential of reduced hospital morbidity, complications and cost. A recent study concluded that delayed neonatal ASO beyond three days of age is associated with increased morbidity and cost of healthcare[2]. Another study suggests that ASO can be safely performed within hours of birth using autologous umbilical cord blood to prime the bypass circuit[16]. While these recommendations require validation with larger trials, available data suggest that delay to ASO should be minimized. Many centers have shifted to early ASO within 2 to 4 days of diagnosis. However, the issues on whether to perform a BAS, and when or whether to discontinue PGE1 after BAS, remain institution-specific.

Issues are particularly challenging in the preterm and low birth-weight neonates due to the higher surgical risk and morbidity related to BAS and prostaglandin administration. Although not specifically investigated for TGA, data in congenital heart disease suggest that the relationship of risk to weight is non-linear with an inflection point at 2.0 – 2.2 kilograms[17].

Mortality in potential ASO candidates with TGA was studied by Soonswang[18]. They noted that 4.1% of infants died before potential ASO upon surgical admission. 11 out of 12 infants died of poor interatrial mixing despite prostaglandin infusions[18]. Contributing factors were prematurity, severe respiratory distress syndrome, and persistent pulmonary hypertension of the newborn.

Several teams have suggested that bedside BAS could be considered a cost – effective and safe alternative to BAS in the cardiac catheterization laboratory[19]. However the potential risk of sepsis with umbilical cannulation has dampened the enthusiasm in this direction[20].

In a large study, children with TGA undergoing BAS had lower mortality (10% versus 12%) despite associated co-morbidities and longer median length of hospital stay compared those who did not undergo BAS[21]. However BAS is fraught with issues which has led to several centers resorting to primary ASO without an intervening BAS. BAS may be associated with vascular access issues, risk of atrial arrhythmias, atrial perforation and tamponade. Some studies show that BAS is associated with an increased risk of stroke related to fragment embolization during the procedure[21,22]. The risk of brain injury was not related to the choice of access for BAS (umbilical or femoral)[22].

Preoperative brain injury is also related to the duration of hypoxemia and delay to surgical intervention[23]. Periventricular leukomalacia was found to be not associated with BAS, but with lower oxygenation and delay to surgery[23]. Systematic reviews have shown that the odds for perioperative brain injury is not significantly increased in infants undergoing BAS[23,24]. Hence BAS continues to remain a life – saving procedure for infants with TGA and significant hypoxemia and / or hemodynamic instability.

Traditionally, it has been accepted that, in d-TGA with intact interventricular septum, the left ventricle can sustain the systemic circulation up to 21 days of life[25]. Subsequently the subpulmonary left ventricle has been noted to show features of regression due to decline in pulmonary artery pressures[26]. This regression was thought to render the left ventricle incapable of maintaining systemic cardiac output after an arterial switch operation. However, subsequent studies have shown that many older infants earlier considered unfavorable for arterial switch could be offered the same[3]. Delayed arterial switch is, of course, often fraught with the need to "retrain" the left ventricle to be able to take on the higher systemic vascular resistance[27]. This could be done by pulmonary artery banding and aortopulmonary shunt, or even ductal stenting[5,28]. The institution of a Blalock – Taussig shunt without pulmonary artery banding for LV retraining has yielded inconsistent results and is not actively pursued[29].

The institution of pulmonary artery banding and an aortopulmonary shunt followed by delayed ASO was described initially in 1977[27]. However it was fraught with issues of significant dilatation of the proximal main pulmonary artery, neoaortic regurgitation and the need to interpose a prosthesis to bridge the gap in the newly constructed pulmonary artery[27,30].

The rapid 2–stage arterial switch operation was initially proposed in 1989 to recruit the less favorable left ventricles, primarily in late presenting infants, for ASO overcoming the issues associated with delayed staging. However outcomes have not been as rosy, with significant morbidity related to prolonged mechanical ventilation, extended inotropic support, extensive acidosis and prolonged hospitalization[31]. Myocardial contractility following rapid 2-stage ASO was lower than following a primary repair[32]. When ASO is delayed for a month or more after banding, the risk of postoperative death may be considerably increased[33].

Ductal stenting in TGA leads to increase in blood flow from the aorta to the pulmonary artery thereby increasing the effective pulmonary blood flow and consequent improvement in saturations. By increasing the degree of shunt, it improves the preload to the left ventricle and thereby helps in LV retraining as was described by Sivakumar et al[28]. 3.5 mm and 4 mm coronary stents are generally used to stent the patent ductus arteriosus

(PDA), instead of larger ones, to avoid pulmonary flooding and heart failure while providing the volume stimulus to the regressed LV. In cases where the ductal patency was not evident by an aortic angiogram, a 0.014 inch coated guidewire was used to probe the ductal ampulla to gain entry into the pulmonary artery followed by PDA stenting[28]. Its advantage is the avoidance of a thoracotomy prior to definitive surgical repair. ASO could be done in these infants four weeks after the PDA stenting with good outcomes[28].

The definition of a “regressed left ventricle” in d-TGA by non-invasive assessment has been a matter of consensus thus far. Two dimensional morphometric appearance of a banana shaped left ventricle, compressed chamber with interventricular septum bowing into the LV cavity have been associated with regressed LV[34,35]. Thinning of the LV free wall, reduction in LV volumes and reduction in LV mass are other measures which have been used to describe LV regression.

Lacour-Gayet in his study took an arbitrary cut-off of LV mass <35 g/m2 estimated by 2D echocardiographic evaluation as an indication for LV retraining in infants with d-TGA with intact interventricular septum[5]. Based on this criteria, among other inclusion criteria including age older than three weeks and a banana shaped septum, 19 children survived to ASO out of 22 who underwent LV retraining. 17 of them had favorable outcomes. The median age at palliation was 3.2 months (9 days to 18 months) and that between the first and second stages was 10 days. This study formed the basis of the recommendation of the cut-off of LV mass <35 g/m^2 as appropriate for LV retraining, and has subsequently been extrapolated as a definition for LV regression.

The presence of ventricular septal defect or patent ductus arteriosus are factors that lead to preservation of LV mass and prevention of its regression. Shaher showed that 92% of children with TGA and VSD had LV:RV pressure ratio more than 70% during cardiac catheterization beyond 6 months of age[36]. 45% of children with TGA/IVS with PDA had corresponding LV pressures during catheterization, while only 5% of those with TGA/IVS and without a PDA had preserved LV pressures[36]. Volumetric analysis using cineangiograms also showed similar increase in LV end diastolic volumes and LV stroke volumes in infants with TGA associated with VSD or PDA unlike in those with intact ventricular septum[37].

Graham's study included children with TGA / IVS with isolated atrial septal defect by cardiac catheterization, besides those with other associations[37]. These children were post BAS or had surgical septectomy by the Blalock-Hanlon technique. Their mean age was 0.75 years and had an average oxygen saturation of 68%. 69% of the infants in this group who did not have a patent ductus had LV volumes which were normal or less than normal. The mean LV systolic pressures in infants with TGA/IVS and ASD was 52 mm Hg (63% of RV systolic pressure) which was considerably lower than those with VSD, VSD and pulmonary artery band, and VSD with pulmonary stenosis. Cineangiography showed decline in LV end-diastolic volume and LV stroke output in three of 6 patients following BAS, while two had no change, and one showed a marginal increase. The child with the greatest increase in saturation had the maximum drop in left atrial volume post BAS.

Saito did pulse doppler evaluation of nine infants with TGA, including eight with simple TGA, and noted that the maximum flow velocity at the tricuspid valve increased significantly following BAS, while that at the mitral valve remained similar[38]. The aortic velocity time integral increased following BAS, unlike that of the pulmonary artery.

Satomi studied the blood flow pattern by pulse doppler evaluation in the interatrial communication in 24 children with TGA[39]. They demonstrated two turning points in the flows across the interatrial septum. The shunt was predominantly left-to-right in systole and right-to-left in diastole. The first turning point (T1) from right-to-left to left-to-right occurred immediately after the initiation of the QRS. The second turning point (T2) from left-to-right to right-to-left occurred just after the second heart sound (S2). The S2-T2 interval decreased on inspiration, indicating prolongation of the period of right-to-left flow. The minimum S2-T2 interval was 50 (± 18) milliseconds in TGA/IVS without PDA or VSD, 114 (± 25) milliseconds in those with associated VSD or PDA, and 75 (± 29) milliseconds in those who had pulmonary banding and a Blalock – Taussig shunt. The maximum S2-T2 interval was 88 (±21), 175 (± 36) and 111 (± 30) milliseconds in the three groups respectively. T1-T2 reflected the duration of the left-to-right shunt across the atrial septal defect. T1-T2 constituted 53% of the R-R interval in children with TGA/IVS without PDA or VSD. However, it was longer in the other groups, 74% and 65% in those with a VSD or PDA and those who had pulmonary banding and a Blalock – Taussig shunt respectively.

The atrial shunting pattern in TGA is quite different from those with normally related great arteries. In the latter, the shunt is almost exclusively left to right unless complicated by issues of severe pulmonary hypertension and / or right ventricular dysfunction. In TGA, the afterload of the subaortic right ventricle is greater than that of the left ventricle. Thus, during atrial systole and the rapid-filling phase, blood will preferentially enter the left ventricle and flow will occur from the right atrium to the left atrium. However, during the *v*-wave portion of the cycle, when pulmonary venous return is greater than systemic, blood will tend to flow into the right atrium from the left atrium, and this creates a bidirectional shunt pattern[13].

Diastolic right-to-left shunting is considered to be due to the difference in distensibility of the ventricles, which is caused by low left ventricular pressure and high right ventricular pressure load[39]. Systolic left-to-right shunting is thought to result from the differences in capacitance of the pulmonary venous and systemic venous systems[39]. The phasic pressure relationships between the atria are influenced by respiration. During inspiration, the increased venous return to the right atrium and decreased pulmonary venous flow would favor shunting from the right atrium to the left atrium, whereas expiration would tend to promote increased left-to-right shunting[13]. The shunt pattern in atrial septal defects in infants post BAS or following surgical creation of an ASD in infants with TGA has been found to be similar to naturally occurring ASDs in TGA[13,39].

Thus, from available literature, it is evident that the LV regresses with time in infants with TGA, even more so in those with intact interventricular septum[36,37]. While BAS does have its role in palliation of these infants till surgery, it is speculative, from hemodynamic data that the

LV could regress faster in these infants. This hypothesis remains unproven by clinical data.

Non-invasive estimation of LV myocardial mass has been done by various methods. Both M-mode and two dimensional imaging have been employed to calculate LV mass. M-mode imaging allows better endocardial border definition due to higher frame rate with choice of appropriate plane of interrogation. The most commonly used methods involve cubed formulas to estimate volumes, with the assumption of left ventricular cavity as a prolate ellipsoid chamber. Initial M-mode standard recommended inclusion of edges as part of the interventricular septum thickness, but exclusion of the posterior wall epicardial edge. Investigators of the University of Pennsylvania developed a criteria (The Penn Convention) in which all edges are not included in parietal thickness measurements, but are considered as part of the ventricle cavity[40]. This approach underestimate LV mass when compared to the M-mode convention, proposed by the American Society of Echocardiography (ASE). This latter convention (ASE) is the most accepted border definition criteria, becoming the standard recommendation for M-mode estimations, and uses the leading edge of each layer[41].

Harmonic real-time 3D echocardiography (RT3DE) is a relatively novel technique that can be used for reliable estimation of LV mass[42]. It has the potential to be the most accurate echocardiographic measure for LV volume and mass. From a pyramidal volume data set, 3D echocardiography allows offline selection of anatomically correct apical views without foreshortening. Tracing of endocardial and epicardial boundaries of anatomically correct, non-foreshortened apical views provides more accurate quantification of LV volume and mass. Its application has only been recently explored in the pediatric population and presents an exciting development in this area[43]. Laser et al showed that RT3DE provided only a slight overestimation of LV mass when compared to cardiac magnetic resonance with no significant interobserver and intraobserver variability[43]. LV mass could be estimated by RT3DE at a mean time less than three minutes.

Radioisotopic gated myocardial perfusion imaging with 99mTc-Sestamibi has also been studied for estimation of LV mass but not commonly used in infants[44]. Some investigators have used myocardial perfusion imaging to study perfusion abnormalities in children after ASO. Perfusion abnormalities have been describes post ASO in the apical and lateral walls of the left ventricle[45]. Various postulates for this include proximal occlusion of translocated coronaries, abnormal vasomotor tone at rest or following exercise or pharmacological stimuli.

Cardiac magnetic resonance can probably be considered as the gold standard for estimation of LV mass among all other quantitative analyses of cardiac chambers. It provides the advantages of excellent reproducibility, three dimensional imaging free of geometric assumptions and acoustic window variations or ionizing radiation. The best-documented technique, however, uses a set of contiguous short-axis slices acquired from a cine sequence. Images are acquired using a combination of body matrix/torso radio frequency coils applying a 2D cardiac-gated pulse sequence. Ideally, images are acquired at resting lung volume. Myocardial volume is the area occupied between the endocardial and epicardial border multiplied by the interslice distance. By convention, LV mass is measured at end-diastole. Similar to echocardiography, LV mass is assessed as the product myocardial volume and the density of the myocardium.

Recently indexed pediatric nomograms have been developed for left ventricular volumes, mass and dimensions in systole and diastole for estimation by cardiac magnetic resonance[46]. However, they have not yet been standardized for children with TGA.

Park studied 36 patients with TGA and noted that the right ventricular end diastolic dimension was larger than normal in every patient, and tended to increase after a Mustard repair[34]. The LV end diastolic dimension reduced significantly post Mustard repair in these patients. A linear relationship was demonstrated between the ratio of LVID/RVID and the ratio of peak systolic pressures in the left and right ventricles in studies both before and after Mustard operation[34]. The ventricular septal thickness was normal and abnormal septal motion was noted in 39% of these patients.

Maroto studied 53 children aged 1 day to 10 years with simple TGA and normal pulmonary pressures and compared them with normal children of similar age[47]. The left ventricular internal dimensions in diastole and systole were noted to be normal at birth in these children. They demonstrated that there was serial decline in these dimensions with age particularly in the first month, despite an increase in age. They did not used indexed measures, but used absolute measures for analysis. The left ventricular posterior wall thickness also was normal in these children at birth, but remained relatively constant with age, unlike their results with internal LV dimensions. Interventricular septal thickness in simple TGA patients were similar to normal controls. The LV fractional shortening and mean velocity of circumferential fiber shortening were significantly greater than controls across all age groups in the study.

Data from autopsy studies show that, in infants with TGA/IVS, the left ventricular wall thickness does not increase with age and remains relatively constant throughout infancy, thus significantly below normal[48,49]. This was quite unlike the case in TGA with VSD irrespective of the presence or absence of pulmonary stenosis. The LV free wall thickness was also reduced compared to right ventricular wall thickness in TGA/IVS[49]. LV mass and volumes were lower in TGA/IVS. Pressure overload was noted to be associated with a greater increase in mass and LV free wall thickness than volume overload in TGA[49].

AIMS AND OBJECTIVES:

1. To examine the effect of balloon atrial septostomy on the left ventricle in infants with simple d - transposition of great arteries by serial 2D echocardiographic monitoring.

MATERIALS AND METHODS:

Setting: Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India - 695011

Study duration: 18 months

Study design: Prospective longitudinal follow up study.

This study was designed as a prospective longitudinal follow up study between January 2014 and June 2015. All infants referred to SCTIMST with simple TGA with no or restrictive interatrial communication and a resting oxygen saturation by pulse oximetry less than 75% taken up for emergency balloon atrial septostomy were considered for inclusion in the study after written informed consent from the parents. The term "simple TGA" referred to d - TGA with intact interventricular septum or with a tiny restrictive ventricular septal defect.

Exclusion criteria:

1. Babies with d-TGA, intact interventricular septum and restrictive interatrial communication who are offered primary arterial switch operation by the cardiac surgery team without need for palliative balloon atrial septostomy.

2. Babies with d-TGA and non-restrictive ventricular septal defect.
3. Babies with d-TGA, intact interventricular septum and an adequate interatrial communication >5 mm in the form of an atrial septal defect or a stretched open patent foramen ovale and adequate saturations who are not candidates for balloon atrial septostomy.
4. Babies with d-TGA, intact interventricular septum associated with other significant cardiac or vascular abnormalities like tricuspid atresia, coarctation of the aorta, interrupted aortic arch, total anomalous pulmonary venous connection.
5. Babies with d-TGA and fixed left ventricular outflow tract obstruction. However cases of left ventricular outflow tract obstruction clearly demonstrated as being only of dynamic nature with no fixed component by echocardiogram by consultant cardiologist and the cardiac team could be included in the study.

A basal 2D echocardiogram was done as part of diagnosis by the pediatric faculty team of the Department of Cardiology, SCTIMST. Balloon atrial septostomy was done as per institutional protocol and as part of standard care for these babies. These babies were then followed up with serial 2D transthoracic echocardiograms on the post procedure day and twice weekly thereafter till the baby was taken up for corrective surgery.

BAS was done under general anesthesia through right femoral venous access and fluoroscopy guidance in the cardiac catheterization laboratory. A 5 French septostomy balloon catheter (Rashkind, Medtronic Inc or Z-5, NuMed) was used with inflation of 1.5 – 4 ml of diluted contrast. Septostomy was done after confirmation of balloon position by 2D transthoracic echocardiography. Repeat dilatations (two to four) were done till an adequate interatrial communication was created. Post-procedure management was in the cardiac intensive care unit and done as per institutional protocol. Blade atrial septostomy was not done.

All echocardiograms were done on Philips ie33 xMATRIX Versatile X5-1 with an 8 Hertz probe. All follow up echocardiograms were done by the primary investigator on the same machine. No sedative medications other than oral dextrose analgesia were used for pacification of babies for echocardiography.

The following parameters were assessed from 2D Echocardiography:

1. Left ventricular internal dimension in end diastole and end systole from the parasternal long axis view
2. Left ventricular ejection fraction by modified Simpson's method and by area - length method from the apical 4 chamber and 2 chamber views and subcostal views.

3. Right ventricular internal dimensions in diastole from parasternal long axis view.
4. The shape of the interventricular septum, and the left ventricular cavity assessed from parasternal short axis and subcostal views
5. The size of the interatrial communication and the shunt pattern.
6. Presence and flow pattern across of patent ductus arteriosus.
7. Evaluation of pulmonary artery hypertension by continuous wave doppler evaluation of tricuspid regurgitation jet (if any), pulmonary regurgitation jet (if any).

Left ventricular mass was assessed by the American Society of Echocardiography conventions using dimensions obtained from the parasternal long axis view as an average of three repeated measurements[50].

LV mass = $0.8\ [1.04(\text{LVID} + \text{IVSd} + \text{PWd})^3 - \text{LVID}^3] + 0.6$ grams, where LVID is the left ventricular internal diameter in diastole, IVSd is the interventricular septal thickness in diastole, PWd is the posterior wall thickness in diastole, 1.04 equals the specific gravity of the myocardium, and 0.8 is the correction factor. All measurements were made at end diastole, and applied as centimeters in the formula.

The linear dimensions obtained by echocardiography and LV mass were also indexed to body surface area (BSA) using the Mosteller's formula. BSA = √(weight x length/3600), where weight is measured in kilograms and length in centimeters[51].

LV regression was defined as a combination of indexed LV mass less than 35 g/m^2, bowing of the interventricular septum to the LV in diastole, and left ventricular posterior wall diastolic thickness <3.5 mm. Cardiac catheterization data was noted when available.

Data regarding surgical outcomes were followed up by the primary investigator, including screen of surgical notes. Babies were followed up after surgery as per institutional protocol.

STATISTICAL ANALYSIS

Statistical analysis was done by the use of SPSS v21.0. Age related data are displayed as median and ranges. Other continuous data are represented by mean ± standard deviation. Continuous data was analyzed by the t-test. Categorical data was studied by Chi-square test or Fisher exact test as appropriate. The relationship between scalar dependent variable with explanatory variable(s) was studied by simple linear regression and multiple linear regression analysis as appropriate. Receiver operating characteristic (ROC) curve was used to illustrate the performance of a binary classification system for LV regression. All p-values were two tailed and a cut-off of less than 0.05 was considered for statistical significance.

RESULTS:

Forty one babies underwent BAS at SCTIMST during the study period from 1st January 2014 to 30th June 2015. 16 babies met exclusion criteria and were excluded (Table 1). 25 babies fulfilled the inclusion criteria and constituted the study cohort.

The median age of the children at the time of BAS was 4 days (range 1 – 95 days). The oldest child to undergo a BAS in the study was a 95 days old baby with TGA with a tiny restrictive muscular ventricular septal defect and no left ventricular outflow tract obstruction.

The mean birth weight of the children was 2.93 (± 0.44) kg. The mean maternal age was 24 years and only one was over 35 years of age. There was a significant male predominance in the cohort (84%). Only four of them were females. Three children were born to third degree consanguineous parents. The birth order was more or less evenly distributed between first born and later born. All but one were singletons. The majority were born by uncomplicated vaginal deliveries (80%). Three mothers had gestational diabetes, while only one had pregnancy induced hypertension. While one baby had cleft lip and cleft palate, none of the other babies had clinical dysmorphism. None of the babies had a family history of congenital heart disease.

Table 1: Diagnoses of the patients who underwent BAS during the study period with inclusion and exclusion criteria:

Diagnosis	**Number of patients**	
TGA with intact interventricular septum	24	Included for study
TGA with tiny restrictive VSD and no PS	1	Excluded from study
TGA with non-restrictive VSD and PS	4	
Mitral atresia with VSD and ASD	3	
TGA with intact interventricular septum and LVOTO	2	
Pulmonary atresia, intact interventricular septum and hypoplastic RV	2	
Tricuspid atresia with TGA, VSD and PS	1	
Tricuspid atresia with truncus arteriosus	1	
DORV with subaortic VSD and mitral inflow obstruction	1	
TGA with intact interventricular septum and PAPVC (Scimitar type)	1	
TGA with non-restrictive VSD and no PS	1	

TGA was diagnosed antenatally only in one case, during a third trimester ultrasound evaluation. However, even this baby was delivered at a nearby hospital and only subsequently transferred to a tertiary pediatric facility from where the child was referred to our center with low saturations. The latest that a child was diagnosed to have TGA was at 74 days of life, and subsequently underwent BAS. This child had regressed left ventricle and subsequently underwent Senning repair at 11 months of age.

BAS was done with either Rashkind balloon or Z-5 septostomy balloon. Majority of the infants required two – three dilatations for creation of an adequate interatrial communication. Half of the babies were received in our institute with ongoing prostaglandin infusion. While the maximum dose of prostaglandin administered prior to BAS was 0.1 µg/kg/min, the majority were managed with doses between 0.02 – 0.05 µg/kg/min. The mean saturation at initial presentation was 47%. A basal blood gas was done in 22 infants, majority of which showed mixed metabolic and respiratory acidosis with a mean pH of 7.29 (± 0.13).

Table 2: Baseline characteristics of the studied children

Parameter	**Mean ± SD**
Birth weight (kg)	2.93 ± 0.44
Weight prior to BAS (kg)	2.95 ± 0.61
Maternal age (years)	24.8 ± 4.14
Paternal age (years)	28.9 ± 4.31
Consanguineous parents	3 (12%)
Birth order	
• 1	8 (32%)
• 2	9 (36%)
• 3 or higher	8 (32%)
Assisted delivery	5 (20%)
History of gestational diabetes	3 (12%)
SpO2 on room air at initial presentation	47% ± 14.10%
Prostaglandin use prior to BAS	13 (52%)
Duration of prostaglandin use (hours)	34.23 ± 47.62
Inotrope use	3 (12%)
Type of balloon used	
• Rashkind	14 (56%)
• Z – 5	11 (44%)
Balloon size	

• 4 mm	5 (20%)
• 5 mm	20 (80%)
Number of dilatations (2 / 3/ 4)	14 / 10 /1
Size of ASD post BAS (mm)	7.02 ± 1.61
SpO2 prior to BAS	56% ± 14.35%
SpO2 immediately post BAS	77% ± 9.47%

Baseline echocardiographic parameters prior to BAS are given in table 3. Only one child had a tiny restrictive ventricular septal defect. All others had intact interventricular septum. 14 infants (56%) had a Doppler detected patent ductus arteriosus at presentation. PDA could be demonstrated in one-third of babies on day 3 post BAS, but in only two children (out of 11 who were still awaiting definitive repair then) at 7 days post BAS.

Table 3: Baseline echocardiographic parameters in simple TGA prior to BAS

Parameter	**Mean ± SD**	**Indexed to BSA**
LVID (mm)	15.68 ± 2.82	78.48 ± 12.21
LVIS (mm)	8.23 ± 2.16	41.32 ± 10.80
IVSd (mm)	4.60 ± 1.17	22.93 ± 4.62
IVSs (mm)	5.70 ± 1.48	28.46 ± 6.37

PWd (mm)	3.86 ± 0.60	19.62 ± 4.15
PWs (mm)	5.06 ± 0.78	25.53 ± 4.52
FS (%)	47.73 ± 8.87	
EF (%)	80.96 ± 9.25	
LV mass (g)	9.70 ± 3.53	47.85 ± 14.43
RVID (mm)	10.73 ± 3.35	53.79 ± 15.77
LA (mm)	10.76 ± 2.47	53.29 ± 11.18
ASD maximum size (mm)	2.64 ± 0.95	
Ascending aorta (mm)	9.80 ± 1.94	
MPA (mm)	9.20 ± 1.41	
Aortic velocity (m/s)	1.08 ± 0.28	
Pulmonary velocity (m/s)	1.36 ± 0.57	

Fig 1a: Serial changes in left ventricular diastolic dimensions after BAS

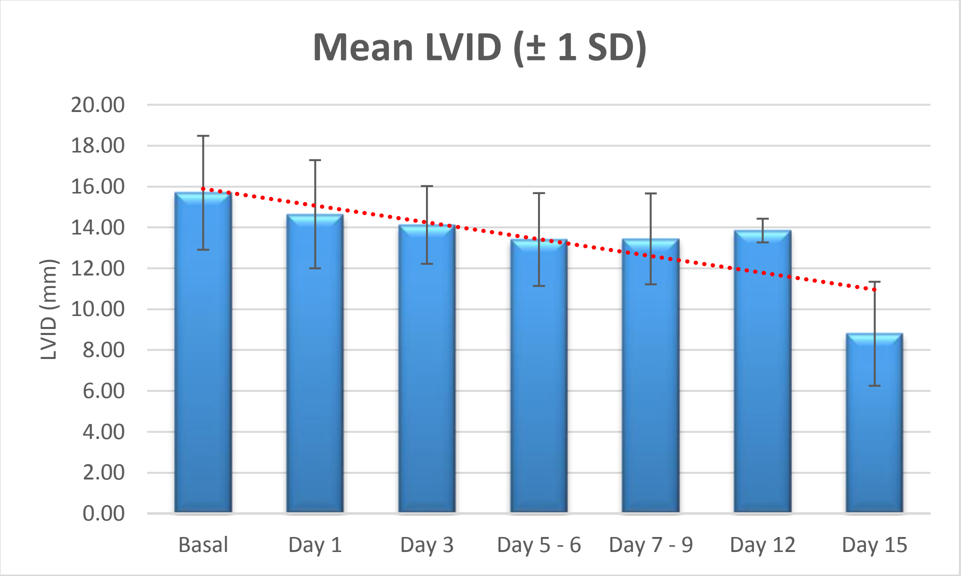
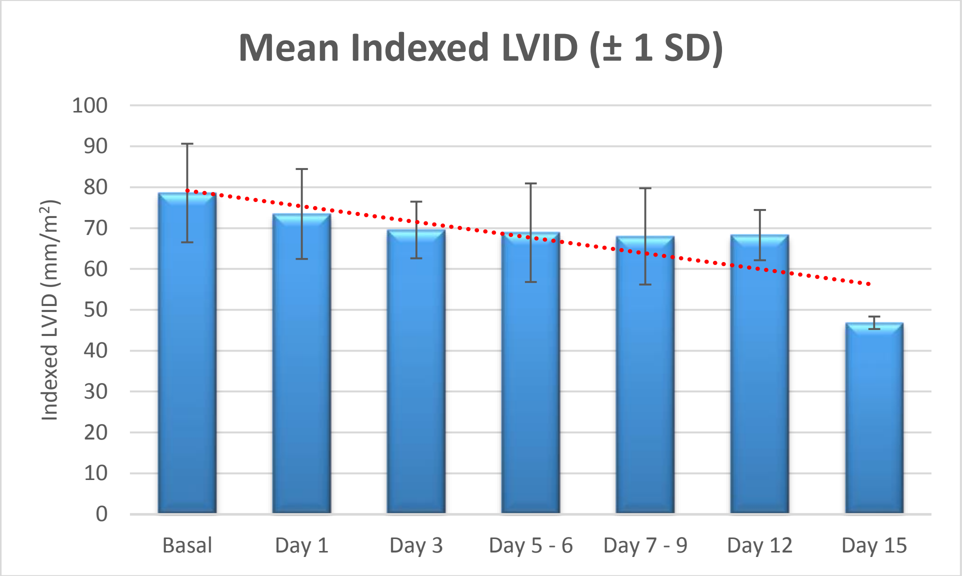


Fig 1b: Serial changes in left ventricular diastolic dimensions indexed to body surface area after BAS



A simple linear regression equation was calculated to predict the changes in indexed left ventricular internal diameter in diastole (LVID) with the number of days after BAS. A significant regression equation was found (F (1,85) = 16.468, p <0.001) with an R2 of 0.162. The child's predicted indexed LVID was 76.361 – 1.192 (number of days after BAS) mm/m^2. The child's indexed LVID decreased by 1.192 mm/ m^2 every day after BAS.

We tested for the changes in indexed LVID with the increment in actual age of the child and found that the relationship showed a non-significant decremental trend (F (1,85) = 3.788, p = 0.055 with an R2 of 0.043). A multiple linear regression analysis was done to predict the indexed LVID based on the days of life after BAS and the actual age of the child. The predicted indexed LVID was 77.947 – 1.153 (number of days after BAS) – 0.080 (age of the child) mm/ m^2. The model showed that the decline in indexed LVID was related more to the number of days after BAS rather than the actual age of the child.

Fig 2a: Serial changes in left ventricular posterior wall diastolic thickness after BAS

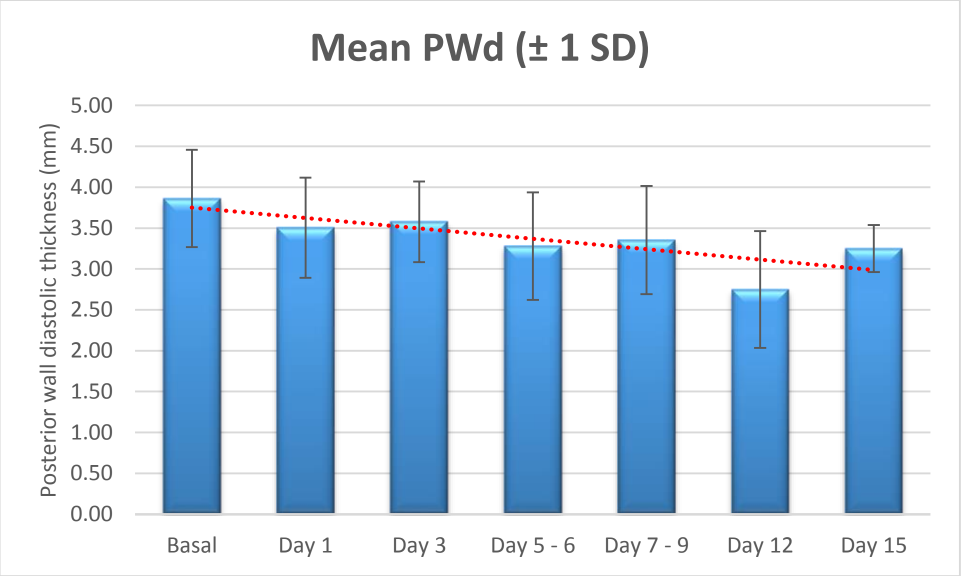
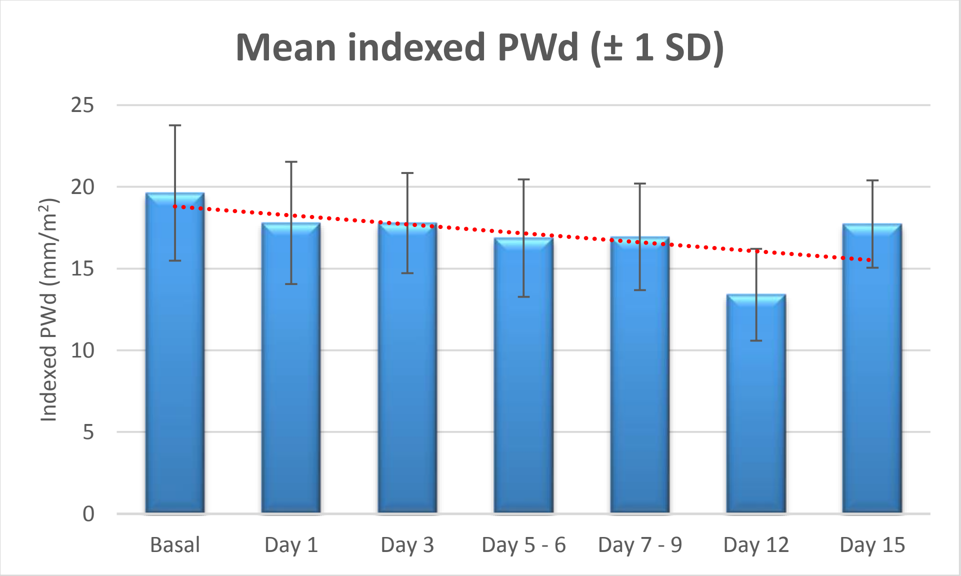


Fig 2b: Serial changes in left ventricular posterior wall diastolic thickness indexed to body surface area after BAS



A simple linear regression was calculated to predict the indexed left ventricular posterior wall thickness in diastole (PWd) based on the number of days after BAS. A significant regression equation was found (F (1,85) = 6.839, p = 0.013), with an R2 of 0.070. The predicted indexed PWd was 18.788 – 0.250 (days after BAS) mm/ m^2. The indexed PWd decreased by 0.250 mm/ m^2 every day after BAS. Though negligible in magnitude, the relationship was found to be significant.

The left ventricular posterior wall diastolic thickness showed significant decline with increasing age of the child. A significant regression equation was found (F (1,85) = 8.728, p = 0.004), with an R2 of 0.093. The predicted indexed PWd was 18.880 – 0.044 (age of the child in days). The indexed PWd was noted to decrease by 0.044 mm/m^2/day.

A multiple linear regression analysis suggested that the decline in PWd was related to the number of days after BAS over and above the progression of the actual age of the child. A significant regression equation was found (F (2,84) = 7.509, p = 0.001, with an R2 of 0.152. The predicted PWd was 19.607 – 0.229 (days after BAS) – 0.042 (days of life) where both independent variables are measured in whole numbers rounded to the nearest 24th hour.

Fig 3a: Serial changes in interventricular septum diastolic dimensions after BAS

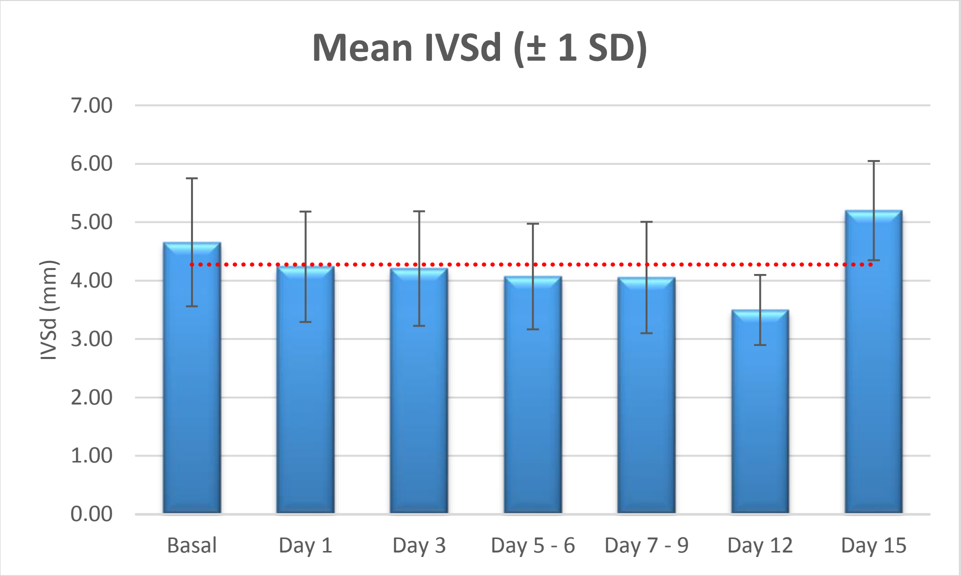
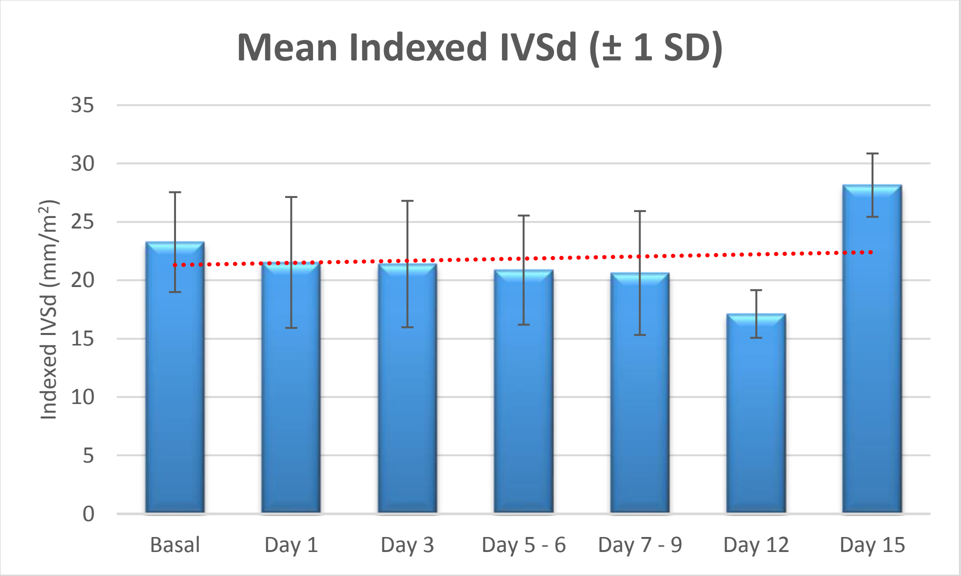


Fig 3b: Serial changes in interventricular septum diastolic thickness indexed to body surface area after BAS



Linear regression analysis showed that there was no significant change in the indexed interventricular septum diastolic thickness (IVSd) with increase in the number of days after BAS (F = 1.349, t = 31.333, p = 0.249). There was no significant change in indexed IVSd with increase in age of the child either (F = 2.591, t = 32.346, p = 0.111).

D – shaped configuration of the left ventricle was noted in five children. However only one child with marked LV regression had classical “squashed” or “banana” configuration of LV.

Fig 4a: Serial changes in left ventricular mass following BAS

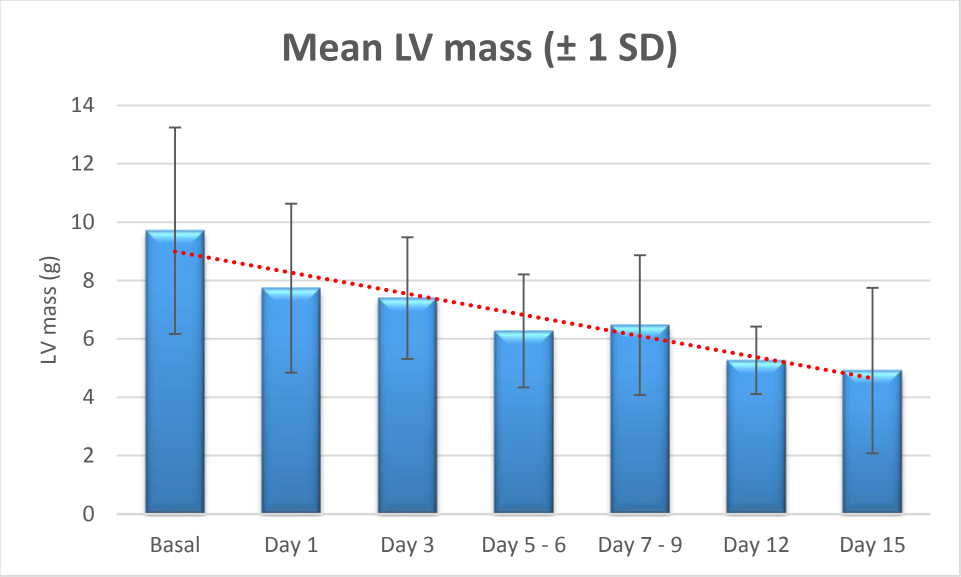
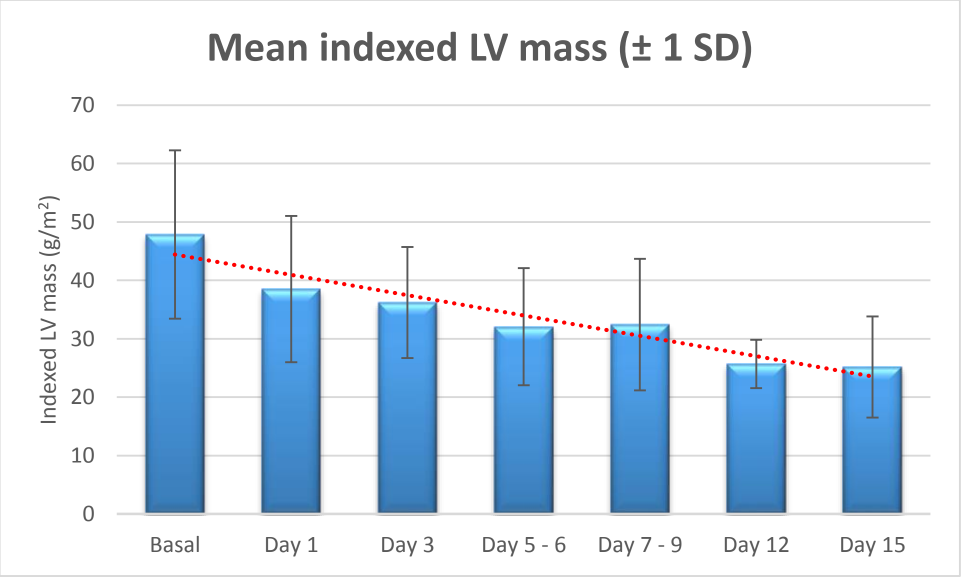


Fig 4b: Serial changes in left ventricular mass indexed to body surface area after BAS



A simple linear regression analysis showed that there was significant regression of indexed LV mass estimated by echocardiography in the first two weeks following BAS (R square 0.203, adjusted R square 0.194, F (1,85) = 21.663, ANOVA p <0.001, unstandardized coefficient Beta = - 1.500, t= - 4.654, p <0.001).

A multiple linear regression analysis was done to study whether the regression of indexed LV mass was related to actual age of the child beside the number of days of life after BAS. A significant regression equation was found (F(2,84) = 10.949, p <0.001), with an R2 value of 0.455. Participants' predicted indexed LV mass is equal to 43.057 + 0.031 (day of life) – 1.515 (days after BAS) where both independent variables are measured in whole numbers rounded to the nearest 24th hour. The indexed LV mass decreased by 1.515 g/m^2 every day following BAS adjusted for the age of the child in days. Only the number of days after BAS predicted the regression of indexed LV mass by our model, and not the age of the child in days.

Fig 5a: Serial changes in right ventricular internal diameter after BAS

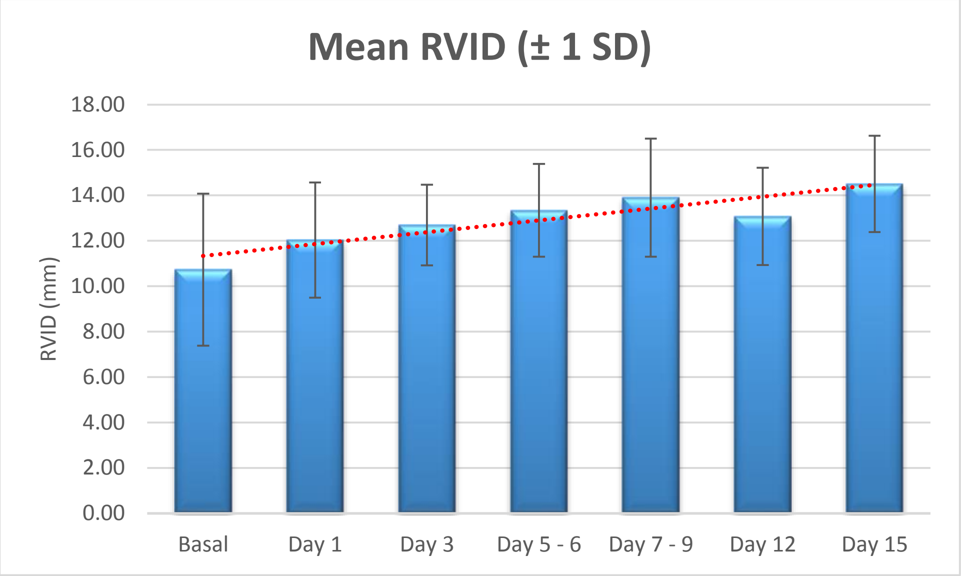
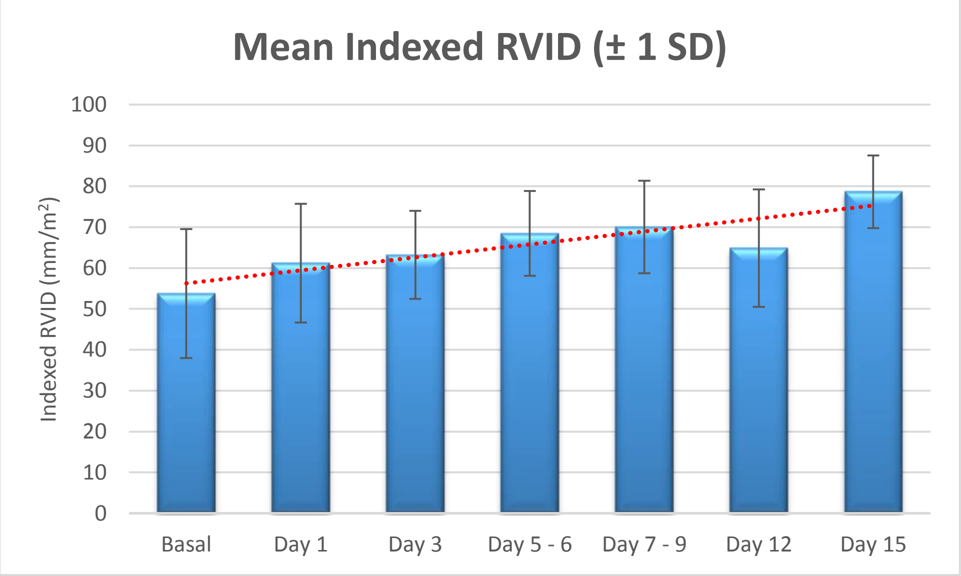


Fig 5b: Serial changes in right ventricular internal diameter indexed to body surface area after BAS



A simple linear regression was calculated to predict the indexed right ventricular internal diameter (RVID) in diastole based on the number of days after BAS. A significant regression equation was found (F (1,85) = 13.662, p<0.001), with an R2 of 0.138. The predicted indexed RVID was 57.351 + 1.340 (days after BAS). The indexed RVID increased by 1.340 mm/m^2 every day after BAS.

The relationship of indexed RVID was also evaluated for changes related to the actual age of the child. However linear regression showed no significant change in the indexed RVID with the actual age of the child in days (F = 0.187, p = 0.667).

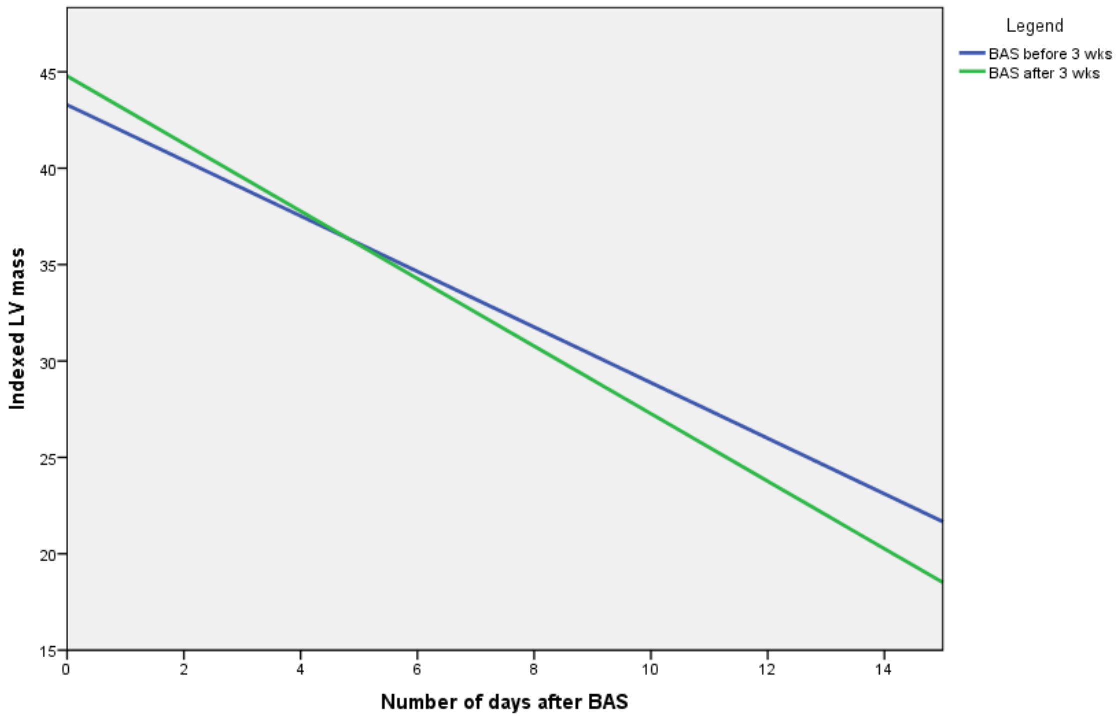
Multiple linear regression analysis showed a significant regression equation for the indexed RVID predicted by the days of life after BAS, adjusted for the actual age of the child in days (F (2,84) = 7.073, p = 0.001.

There was no significant change in the aortic velocity ascertained by pulse wave doppler in the days following BAS (F = 1.449, t = 50.892, Beta = - 0.127, p = 0.232). There was no significant change in the pulmonary artery velocity as well following BAS (F = 0.175, t = 16.192, Beta = 0.046, p = 0.677).

Table 4: Follow up echocardiographic parameters after BAS:

Parameters indexed to BSA	**Basal**	**Day 1**	**Day 3**	**Day 6**	**Day 9**	**Day 12**	**Day 15**
LVID (mm/m^2)	78.57 ± 12.07	73.47 ± 11.01	69.52 ± 6.94	68.88 ± 12.05	68.00 ± 11.77	68.27 ± 6.14	46.85 ± 1.55
LVIS (mm/m^2)	41.32 ± 10.80	39.77 ± 11.24	33.88 ± 7.37	32.39 ± 9.12	30.27 ± 8.16	28.98 ± 5.22	19.98 ± 0.53
IVSd (mm/m^2)	23.27 ± 4.28	21.52 ± 5.60	21.38 ± 5.41	20.87 ± 4.68	20.61 ± 5.30	17.11 ± 2.05	28.15 ± 2.71
IVSs (mm/m^2)	28.66 ± 6.19	27.53 ± 6.14	27.58 ± 6.22	26.86 ± 5.74	27.60 ± 6.46	23.98 ± 0.98	30.59 ± 2.96
PWd (mm/m^2)	19.62 ± 4.15	17.79 ± 3.73	17.78 ± 3.06	16.86 ± 3.59	16.94 ±3.26	13.40 ± 2.81	17.72 ± 2.67
PWs (mm/m^2)	22.53 ± 4.52	23.60 ± 4.87	22.11 ± 3.64	21.26 ± 3.17	22.24 ± 4.41	19.15 ± 2.87	26.64 ± 0.70
RVID (mm/m^2)	53.79 ± 15.77	61.21 ± 14.54	63.22 ± 10.77	68.47 ± 10.35	70.06 ± 11.31	64.85 ± 14.37	78.66 ± 8.91
LV mass (g/m^2)	47.85 ± 14.43	38.51 ± 12.51	36.21 ± 9.51	32.07 ± 10.05	32.44 ± 11.27	25.68 ± 4.15	25.17 ± 8.66

Figure 6: Regression curves of indexed LV mass in patients with simple TGA undergoing BAS before 3 weeks and after 3 weeks of age



Linear regression analysis showed that children who underwent BAS beyond three weeks of life had faster LV regression than those who underwent BAS earlier (t = 5.385, p <0.001).

A hemodynamic catheterization study was not routinely done during BAS. Pressure data was available in seven cases after BAS (table 5).

Table 5: Hemodynamic data from cardiac catheterization in simple TGA

Sl No	**Age at catheterization**	**Basal SPO2 (%)**	**SpO2 after BAS (%)**	**RA**	**LA**	**RV**	**LV**	**Basal indexed LV mass**	**Surgery done**	**LV status on echo**	**Surgical findings**	**Outcome**
1	15 days / M	55	72	A5 v5 m4	A5 v5 m4	56 Ed 6	32 Ed 4	38.23	Open pericardial drainage and suturing of RAA perforation	Preserved	RAA perforation	Died
2	45 days / M	55	80	A6 v5 m4	A5 v5 m4	60 Ed 5	30 Ed 4	66.80	ASO	Regressed	Small PDA, large ASD	Survived
3	46 days / M	58	78	A6 v8 m6	A6 v8 m6	60 Ed 12	53 Ed 12	57.12	-	Preserved		Died of fungal sepsis
4	95 days / F	36	80	A6 v6 m5	A6 v6 m5	70 Ed 8	43 Ed 5	60.66	ASO + VSD closure	Preserved	10 mm PDA, 0.5 mm SPVSD	Survived
5	75 days / M	63	77	A6 v4 m3	A5 v5 m4	68 Ed 5	25 Ed 5	34.57	Senning	Regressed	3 mm ASD, tiny PDA	Survived
6	30 days / M	60	82	A12 v12 m11	A13 v12 m11	94 Ed 10	61 Ed 10	47.64	ASO	Regressed	8 mm ASD, tiny PDA	Survived
7	62 days / M	62	89	A12 v11 m11	A12 v12 m11	100 Ed 12	52 Ed 10	31.91	ASO	Preserved	10 mm ASD, 2 mm PDA	Survived

Twenty children underwent arterial switch operation (ASO) at a mean 9 days following BAS. The median age at ASO was 17.5 days (range 2 – 106 days). One child underwent Senning repair at 11 months of age, and another underwent modified Blalock – Taussig shunt with pulmonary artery banding. Three babies did not survive till surgery. One child developed cardiac perforation and tamponade during BAS, and succumbed to refractory acidosis despite emergent open pericardial drainage and closure of perforation.

One child underwent a repeat BAS on day 46 of life after a BAS elsewhere on day 2 of life and could not undergo definitive surgery due to late onset neonatal fungal sepsis with a protracted course. Subsequently on recovery of his comorbid illness, he presented to us with very low saturations, inadequate intercirculatory mixing and was subjected to a repeat BAS prior to definitive surgery. However the baby continued to have refractory sepsis and succumbed to the same. Another baby with an abnormal right coronary artery course had sudden hemodynamic collapse 15 hours after BAS and died before he could be taken up for ASO. One child who presented with shock had persistent desaturation after BAS. The baby continued to remain in cardiogenic shock after ASO and succumbed within 24 hours of ASO.

The mean LV mass of the twenty children who underwent ASO was 6.20 (± 1.77) g on the day prior to surgery. The corresponding mean indexed LV mass was 31.20 (± 9.35) g/m^2 at a mean age of 27 days. The median age at ASO was 17.5 days. 15 children had indexed LV mass less than 35 g/m^2 in the last echo prior to ASO. Their corresponding mean indexed posterior wall diastolic thickness was 16.55 (± 3.59) mm/m^2.

The left ventricle was considered regressed on 2D echocardiography based on a combination of LV mass <35 g/m^2, bowing of the interventricular septum to the LV in diastole, thinning of the posterior wall <3.5 mm.

Five children out of the cohort had regressed left ventricle prior to ASO. Three of them underwent ASO. The mean indexed LV mass of these three children was 25.12 (± 7.57) g/m^2 and the indexed posterior wall diastolic thickness was 14.88 (± 3.02) mm/m^2. There was no significant difference in the cardiopulmonary bypass time or in the mean aortic cross clamp time during ASO ($p = 0.349$, 0.911 respectively). However those with regressed LV required longer duration of mechanical ventilation in the postoperative period (174.67 hours vs 88.35 hours, $p = 0.023$). There was no significant difference in the long term survival after ASO between those who had regressed or preserved LV. However one child with regressed LV developed a large intracranial infarct with hemorrhagic transformation one month after ASO. The baby presented with shock and seizures, and was stabilized with medical measures. Baby has residual hemiparesis and remains on follow up.

Table 6: Surgical data of the children of those who underwent ASO

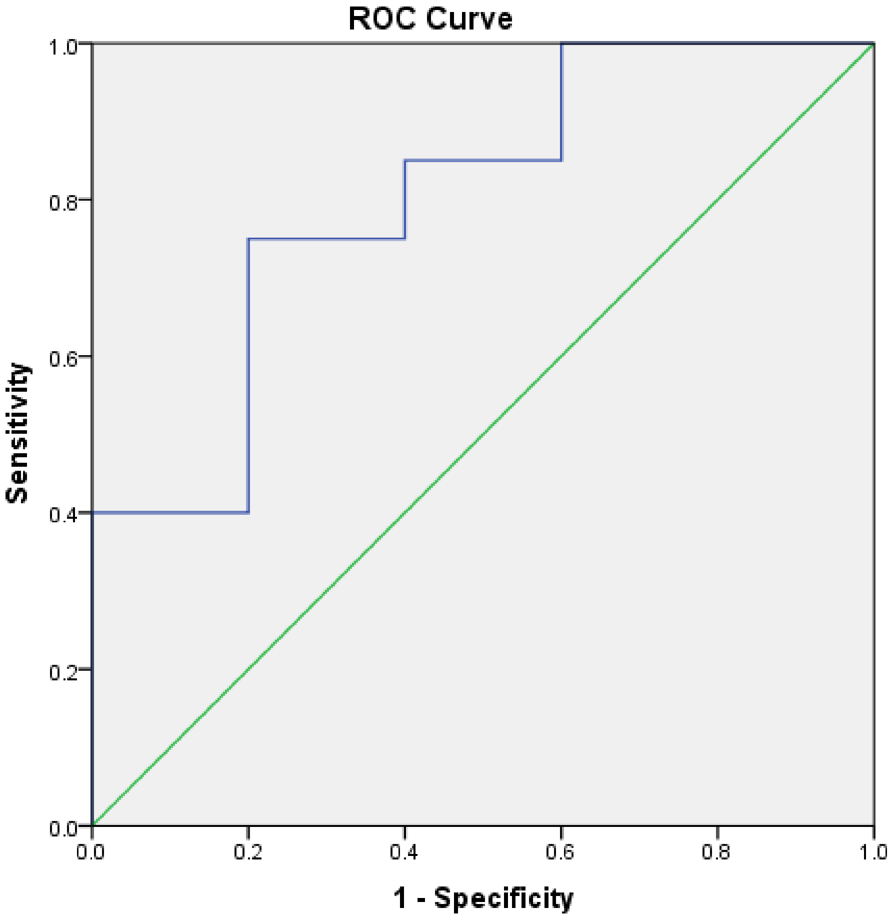
Parameter	**Details**
Indexed LV mass (mm/m^2)	30.01 ± 10.03
Regressed LV	3 / 20 (15%)
Cardiopulmonary bypass time (minutes)	217.5 ± 51.98
Aortic cross clamp time (minutes)	127.7 ± 26.37
Mechanical ventilation (hours)	101.3 ± 62.59
Post-operative in-hospital complications • Sepsis • Diaphragmatic palsy • Arrhythmia	3 1

• Hypotension	1
• Ventilation related complications	2
	1
Survival to discharge	19 / 20 (95%)
Survival to last follow up	19 / 20 (95%)

Table 7: Comparison of findings in simple TGA with regressed and preserved left ventricle among those who underwent surgical repair

	Preserved LV **N = 17**	**Regressed LV** **N = 5**	**P value**
Age at surgery (days)	24.41 ± 26.51	160.60 ± 162.45	0.002
ASO done	17 (100%)	3 (60%)	0.043
Last echo details			
- **LV mass (g)**	6.42 ± 1.85	5.22 ± 1.59	0.203
- **Indexed LV mass (g/m^2)**	32.31 ± 9.32	23.38 ± 6.10	0.059
- **PWd**	3.35 ± 0.70	3.10 ± 0.22	0.443
- **Indexed PWd**	16.86 ± 3.67	14.85 ± 4.02	0.303
- **Indexed RVID**	67.08 ± 13.13	71.19 ± 29.67	0.653
CPB time (minutes)	212.94 ± 45.87	217.50 ± 89.05	0.883
Aortic cross – clamp time (minutes)	127.41 ± 28.41	122.75 ± 16.38	0.758
Duration of mechanical ventilation (hours)	88.35 ± 40.79	109.60 ± 123.08	0.534
Survival to discharge	16 (94.1%)	4 (80%)	0.411
Survival to last follow up	16 (94.1%)	4 (80%)	0.411

Figure 7: Receiver operating characteristic (ROC) curve for indexed LV mass in simple TGA.



The area under the ROC curve was 0.800, p = 0.042. An indexed LV mass of less than **26.32 g/m²** was suggestive of regressed LV with a sensitivity of 75% and a specificity of 80%.

Table 8: Coronary artery anatomy pattern in simple TGA

Coronary artery pattern	**Number of patients**
1LCx 2R	13
1L 2RCx	4
1LCx 1R	1
1LR 2Cx	1
1L 2R 2Cx	1
1LCxR 2Sinus nodal artery	1
1Conal A 2RLCx	1
Conal branch from LAD	1
Conal branch crossing RVOT	1

Figure legend: Coronary patterns are described by Leiden convention as coronary origin from sinus 1 followed by sinus 2[52]. Cx – Left circumflex, L – LAD, R – right coronary artery

The coronary origins were normal in 13 patients (52%). The most common coronary abnormality was origin of the circumflex artery from the right coronary artery (16%). Separate coronary origins of all three coronaries was seen in one patient.

DISCUSSION:

This study involving serial prospective echocardiographic follow up of children with TGA after BAS for interrogation of ventricular remodeling is the first of its kind. While BAS has its role in palliation of hemodynamically unstable children with TGA and poor intercirculatory mixing and desaturation, our study brings to light other aspects that need to be followed up in the interim period prior to definitive surgery.

BAS resulted in improvement in systemic saturations with hemodynamic stabilization. Interatrial gradients were abolished with establishment of good intercirculatory mixing which allowed the surgeon to take these patients electively for definitive surgery. No patient with TGA with intact interventricular septum underwent primary ASO without BAS during the study period. While two infants were taken up for ASO within one day of BAS due to inadequate improvement in saturations, the remainder underwent ASO as elective procedures. The results of ASO for these children was excellent.

Simple TGA had a significant male preponderance in our study which is in tune with results from other studies[6,53]. Syndromic association was uncommon. While the average birth weight was normal as expected with TGA, the association with gestational diabetes was only 12%.

Our study showed that there is significant LV remodeling that occurs after BAS in infants with TGA. Serial decline in LV internal diameter and posterior wall thickness resulted in significant decrease in LV mass in the days after BAS. These changes occurred irrespective of the actual age of the child. Autopsy studies show that in TGA with intact IVS, the LV posterior wall thickness was normal at birth with no significant change in the absolute values in first six months of life. Beyond the age of three months, they were noted to be below the 95th centile as expected for age[48].

Maroto's results showed that the LVID was normal in simple TGA in the initial days of life with rapid fall in the subsequent weeks till the end of first month of age[47]. Thereafter LV dimensions appeared to increase with age of the child. In their study, posterior wall diastolic thickness showed no significant change in the first six months of life in simple TGA. Their mean PWd was 2.3 mm. Interventricular septal thickness also remained unchanged in the first month of life, beyond which there was progressive thickening.

We also noted that there was associated serial increase in the right ventricular internal diameter. This could be explained by the decompression of the left atrium during BAS. The creation of an adequate interatrial communication relieves the child of pulmonary venous hypertension and also causes reduction of preload to the subpulmonary left ventricle. Pulmonary vascular resistance is known to decrease with age. This can result in afterload reduction as well, albeit slower, beside the reduction in preload.

It was noted that flow in the PDA decreased in the days following BAS. This was mostly observed in babies who underwent BAS in the first two weeks of life. Decrease in PDA flow was associated with significant fall in systemic saturation in the majority of our patients. Waldman noted that 48% of children with TGA and intact IVS had PDA detected by angiography, 18 of whom had significant aorta to pulmonary artery shunt noted in PDA[54]. Acute narrowing of the ductus in the first month after BAS was associated with marked decrease in oxygen saturation and clinical deterioration. At the same time, persistence of a large PDA for several months was associated with a higher incidence of pulmonary vascular disease.

There was no significant change in the thickness of the interventricular septum in these children. This could be explained by the fact that regression of LV occurs at the expense of increase in RV preload due to better intermixing, which reflected in our data as increase in RV internal diameter.

Accelerated LV regression following BAS was more pronounced in older infants in our study. It is known that the fall in pulmonary artery pressures and consequent regression of the left ventricle with age in simple TGA occurs maximally in the first month of age beyond which the curve tends to flatten out[47]. LV regression occurring beyond the third week of life in these infants suggests that the creation of a wide interatrial communication acts as a factor independent of the expected age related LV regression in TGA with intact IVS in the absence of a large ASD. Our data suggests that these babies could benefit by avoiding undue delay in definitive ASO.

Echocardiographic evaluation of ventricular dimensions and masses are generally assessed based on the use of z scores of cardiac structures. We did not use z scores for assessment of LV dimensions as there are no validated scores in TGA patients. The conventional z scores have been validated based on a study of 782 healthy patients[55]. The subpulmonary LV in TGA behaves differently from normally related hearts early in infancy due to variations in pulmonary vascular resistance.

The definition of regressed LV in TGA has been based on a combination of several factors including reduced LV mass, abnormal shape of the interventricular septum and decrease in posterior wall thickness by

2D echocardiography. The absolute cut-off value of indexed LV mass to define LV regression in TGA has been based on an arbitrary value of <35 g/m^2 which was considered for LV retraining in a study of 22 patients with TGA and intact IVS[5]. The mean age of LV retraining in their study was 3.2 months (9 days – 18 months). These patients underwent a loose pulmonary artery band targeting an LV/RV pressure of 65% after the band, and a systemic-pulmonary shunt. However LV dysfunction after banding was a significant issue and needed discontinuation of retraining in two cases. 19 out of 22 patients underwent ASO as a second stage surgery at a median delay of 10 days after the first stage when the LV mass reached 50 g/m^2. 17 patients remained asymptomatic at a mean follow up of 25 months.

However, the enthusiasm for "LV retraining" waned off due to increased morbidity and mortality associated with the procedure[32]. This has been associated with the application of ASO even beyond three weeks of life which was considered high risk in the past[3]. Only one child in our study underwent pulmonary artery banding and aorto-pulmonary shunt for LV retraining. However the child could not be weaned off cardiopulmonary bypass and expired within 18 hours of the surgery. This case could reopen the debate on whether a large decompressing atrial septal defect could actually necessitate the need for a larger aorto-pulmonary shunt or a tighter pulmonary artery band[56].

Earlier studies had suggested that LV posterior wall thickness more than 4.0 mm, LV end-diastolic volume greater than 90% of normal, LV ejection fraction more than 50%, LV to RV pressure ratio more than 85% and a predictive wall stress of 120 x 103 dynes/cm^2 could be considered as safe for a two-stage ASO[57]. However, subsequent studies showed that LV geometry, indexed LV mass or posterior wall thickness, indexed LV volumes and LV mass/volume ratio did not predict death, duration of postoperative mechanical ventilation or the need for hemodynamic support in infants who underwent ASO beyond 3 weeks of age[4].

Our results also show that there was no difference in survival outcomes in patients who underwent ASO with preserved LV mass or selected patients with regressed LV. However, ASO in regressed LV was associated with longer duration of mechanical ventilation in the postoperative period. Foran did not find any difference in the duration of mechanical ventilation or inotropic support between those who underwent ASO after 21 days or life or earlier[4]. Late presentation of TGA with intact IVS beyond three weeks of life may be associated with delayed involution of the patent ductus arteriosus or slower than usual regression of pulmonary vascular resistance which contributed to survival of these babies. The long term effects of perioperative stress in these infants with regressed LV need to be followed up.

Our results demonstrate that the threshold of 35 g/m^2 as an indication for LV retraining may not hold true in the current era for consideration of ASO. The mean indexed LV mass in those who underwent ASO in our study was 30 g/m^2 and 14 children had LV mass less than 35 g/m^2. The lowest LV mass for a child considered for ASO was 17 g/m^2 with good surgical result.

An ROC curve was generated which showed that an indexed LV mass less than 26.32 g/m^2 was associated with LV regression in simple TGA. However, this had no validation by hemodynamic catheterization or pathological assessment. The status of the LV was not assessed preoperatively by the surgeon as routine LV entry was not required in ASO. Six children who underwent ASO had indexed LV mass less than 26.32 g/m^2. This mass was reached on an average of 12 days post BAS including in infants less than three weeks of age at BAS, and at 7 – 9 days post BAS in older infants.

Early primary ASO in the current era is associated with good long term outcomes[58]. Anderson’s data suggested that ASO should be delayed no longer than the first week of life, with surgery on day 3 of life having the lowest probability of major morbidity[2]. While BAS improves intercirculatory mixing, our data suggests that these children could benefit from earlier “elective” ASO in another aspect by avoiding accelerated regression of the left ventricle.

The coronary artery anatomy pattern obtained in our results is similar to most other series of TGA[2,3]. While the origin of the left anterior descending and circumflex arteries from the left sinus (sinus 1) and right coronary artery from the right sinus (sinus 2) was the most common pattern, abnormal origin of the circumflex from sinus 2 was the next most common.

The prospective design of the trial and serial monitoring of these children from BAS till surgery and beyond is one of the merits of our study. All echocardiographic observations were done by a single observer with each observation taken as an average of three measurements to minimize intra-observer variability.

LIMITATIONS:

Our study was limited by the absence of a true control arm in our study. Ideal controls was not feasible, as would have been age matched infants with TGA and intact IVS followed up without BAS till definitive surgery. No patient with TGA and intact IVS underwent primary ASO without BAS during the study period.

Assessment of stroke volumes of the individual ventricles were not done in our study. Delineation of the velocity time integrals of the outflow tracts and calculation of stroke volumes, would have provided a more objective measure of the changes in pulmonary to systemic blood flow before and after BAS in infants with simple TGA.

Hemodynamic assessment by cardiac catheterization was not routinely done for all infants in the study. The interpretation of echocardiographic data in the absence of hemodynamic data in all patients or pathological corroboration of LV regression would have limitations.

The investigators were part of the treating team and were not blinded from the results of the study.

CONCLUSIONS:

Balloon atrial septostomy is associated with accelerated regression of the left ventricle in infants with simple transposition of great arteries in the first two weeks after BAS. Regression of the left ventricle is faster in children who undergo BAS beyond three weeks of life. These children should be considered for arterial switch operation within one week after BAS. Indexed LV mass of **26.32 g/m^2** may be more reliable threshold for the definition of LV regression in TGA.

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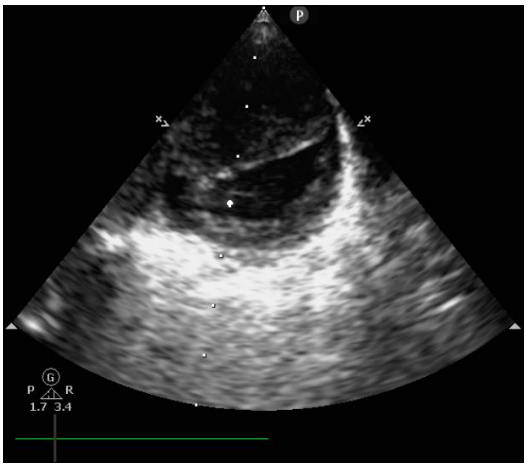
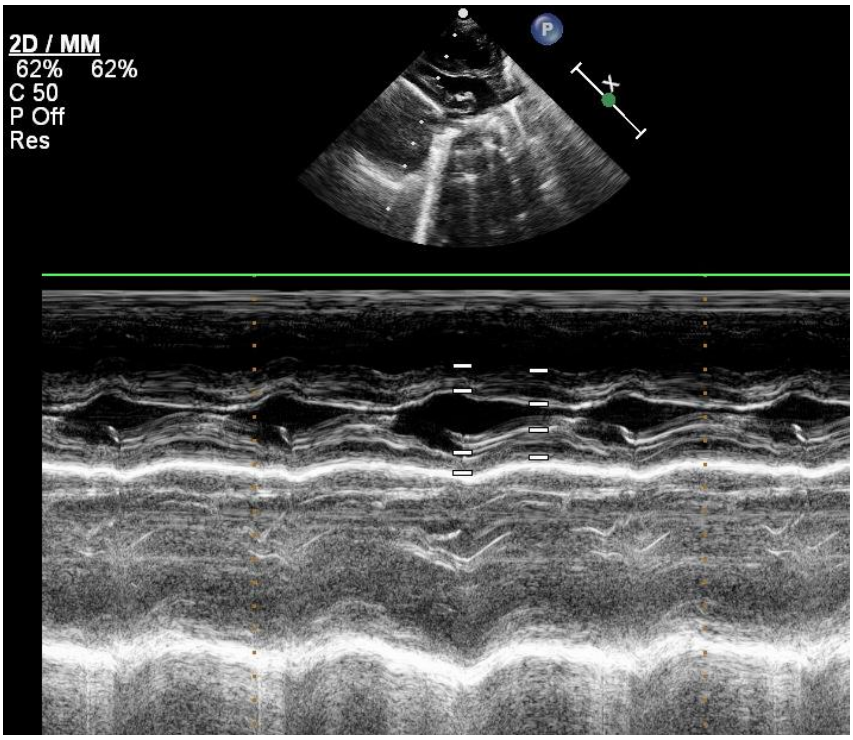


Subcostal view depicting preserved LV with normal septal configuration.

Subcostal view showing flattened IVS with RV dilation and partial LV regression.



Acquisition of LV wall dimensions from parasternal long axis view.