ORIGINAL RESEARCH PAPER

Cardiac Surgery

FATE OF AORTA AND PULMONARY ARTERY IN PATIENTS WITH DEXTRO-TRANSPOSITION OF GREAT ARTERIES UNDERGOING ARTERIAL SWITCH OPERATION: A PROSPECTIVE STUDY

KEY WORDS: ASO -arterial switch operation, dTGA-dextro transposition of great arteries

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ABSTRACT

Background: Following the arterial switch operation, there is a risk of neoaortic root enlargement and aortic regurgitation in follow-up. This study is intended to study whether abnormalities in the histopathological finding of the neo-aorta at the time of the arterial switch operation could lead to these complications.

Patients and methods: Between January 2015 to November 2015, 50 consecutive patients undergoing the arterial switch operation were included in this prospective cohort study. A sufficient representative sample of tissue obtained from the native pulmonary artery and the native aortic root, was fixed in 10% neutral buffer formalin and sent to the department of pathology, these tissues were conservatively processed and paraffin blocks were made, sections were cut and stained by H & E, Vanhoeff elastic, Van Giessen, Masson's trichrome, elastic tissue and smooth muscle was systematically accessed, in the native aorta and native pulmonary artery. Simultaneously a note was made of all the patients pre-operative characteristics, aetiology, associated cardiac anomalies, echocardiogram findings, cardiac catheterization data(if performed), intra operative details, Histo-pathological examination of native aorta and native pulmonary artery, comparison with controls with literature, post operative course, follow up, and follow-up echocardiographic data.

Results: Fifty patients had an ASO for TGA between January 2015- November 2015, with We examined elastic lamellar count of native aorta and native pulmonary artery and compared it with the finding described in the literature. It was found that elastic lamellar counts were similar in both the neo-aorta and the neo-pulmonary artery. Hence histo-pathologically they are similar at birth, gradually as the age advances lamellar count decreases in the neo-pulmonary artery. Hence early surgery in patients with d-TGA may prevent against neoaortic root dilatation and aortic regurgitation.

Conclusions: There were no gross differences between native pulmonary artery and native aorta histopathology but an inverse relation was found between advancing age and elastic lamellar counts in both structures signifying the need for an early arterial switch to prevent long-term complications.

INTRODUCTION

Since the arterial switch operation (ASO) was first described by Jatene and colleagues in 1975 [1]. It has become the surgical procedure of choice for repair of transposition of great arteries (TGA).However long term studies have also revealed important late complications that contribute to late morbidity and need for reoperation. These late complications include coronary artery insufficiency, right ventricular outflow tract obstruction, and problems with native pulmonary root and pulmonary valve in the systemic position functioning as the neo-aortic root and the neo-aortic valve respectively [2-4].

Dilatation of the neo-aortic root has been reported in more than two third of patients following ASO [5-6]. The natural history of neo-aortic root dilatation in this setting is unclear. Previous studies have documented indexed neo-aortic root dimensions progressively increasing over time [7-8].

Neo-aortic valve regurgitation may also be an important late complication, and although uncommon, the need for aortic valve repair or replacement has now been reported in several series late after ASO [1, 8].

Larger vessels especially aorta and pulmonary arteries have a common structural plan in that they are composed of three concentric coats or tunics:Tunica intima: consists of the endothelial lining and its basement membrane and a delicate layer of loose sub-endothelial connective tissue.

Tunica media: composed predominantly of elastic lamella with intervening smooth muscle fibres and there may be a variable amount of reticular and elastic fibres. Tunica adventitia: consists predominantly of fibrous connective tissue.

The internal elastic lamella is a layer of elastic tissue that forms the outermost part of tunica intima. It separates tunica intima from tunica media. Aorta and pulmonary artery being elastic arteries have a prominent component of elastic tissue, which can be objectively assessed by counting the number of elastic lamella. Each lamellar count was evaluated by two observers simultaneously using VVG stain under light microscope. A single sample was examined and analyzed by using electron microscope to highlight the structural components of native aorta and native pulmonary artery for collagen and elastic tissue. Internal elastic lamellar count was done by two different observers simultaneously under light microscope. For ultra-structural analysis and review one sample was examined and analyzed by electron microscope.

REVIEW OF LITERATURE

The atrial switch technique for TGA (Transposition of great arteries) being a physiologic correction changed the natural history of this congenital heart condition [1] and, in the current era, many of the adult survivors of simple transposition of the great arteries (d-TGA) would have undergone this physiologic correction in the form of Mustard or the Senning operation. Balloon atrial septostomy, introduced by Rashkind in Philadelphia [2] was one of the first widely applied interventional catheter techniques. The neonatal arterial switch procedure introduced by Norwood and Castaneda at Children's Hospital Boston[3] was critically important in demonstrating that corrective neonatal surgery could be performed with remarkably low mortality.Arterial switch operation has today revolutionized the surgical approach to patients of TGA. It is now looked upon as the preferred surgical option for simple transposition of great arteries (intact ventricular septum or a small ventricular septal defect [VSD]) [7-9]. Arterial switch operation, unlike Mustard and Senning operation provides a more anatomical & physiological correction. The surgical approach is a matter of debate in children, who present after first few weeks of age, particularly with IVS. Because of concern over the supposedly limited ability of the left ventricle (LV) to handle the systemic circulation, arterial switch operation has still been reserved only out for patients with transposition of the great arteries and intact ventricular septum (TGA-IVS), who present for surgery before the first few weeks of life. For patients, who present after first few weeks of life, atrial switch was the proposed surgical option, because of the concern that with advancing age, first there is a progressive fall in PVRI

(Pulmonary vascular resistance index). This leads subsequently to regression of left ventricle, consequently the left ventricle might not be able to tolerate the suddenly increased work of systemic circulation after arterial switch operation. This led to limited application of ASO and resisted surgeons from attempting ASO in older children [9]. As arterial switch had proved its worth over atrial procedures, surgeons tried the two-stage arterial switch [10] for children who had IVS and presented late. Therefore Yacoub and co-workers in 1977 advocated left ventricular preparation. This was performed by left ventricular preparation by subjecting left ventricle to pressure overload (pulmonary artery banding) and volume overload (aortopulmonary shunt). This was followed by an arterial switch operation 5 months later [10]. But problem with this approach were neoaortic valve regurgitation, dilatation of the proximal main pulmonary artery [11], and the interposition of a shunt to bridge the gap in the new pulmonary artery [10]. In 1989, Jonas et al [12] advocated rapid two-stage arterial switch operation to overcome the disadvantages of two-stage arterial switch operation, by reducing down the time interval between the two stages to 1 week. When the outcomes of primary ASO were compared with the two-stage approach, the results of late follow-up showed increased incidence of neo-aortic regurgitation [13], reduced left ventricular systolic performance [14], and right ventricular outflow tract obstruction

AIMS & OBJECTIVE

The present study has been undertaken to determine the risk factor associated with neo-aortic root dilatation and neo-aortic valve regurgitation with special reference to histopathological changes in the native pulmonary artery and native aorta while performing TGA repair with ASO technique.

This study is intended to know the relationship of histo-pathological finding of neo-aorta of TGA patients, which can lead to future complications like aortic root dilatation or aortic valve regurgitation in early or intermediate or late post operative period. As described in the literature that at birth there are about 35 elastic lamina arranged in the aortic media, which initially increases in number after birth, then becomes steady. We want to investigate through this study that is there any gross histo-pathological changes in native aorta and native pulmonary artery in patients with d-TGA. We have compared the histo-pathological finding of native aorta and native pulmonary artery with normal aorta of historical controls. (normal findings as described in literature) which will help in providing guidance about risk factors, histo-pathological abnormality, surgical technique, post operative management and follow up of the conditions associated with the procedure.

MATERIAL AND METHODS

All those children who underwent arterial switch operation (ASO) from 1st April 2015 till 31st October 2016 at All India Institute of Medical Sciences (AIIMS) New Delhi, India, were evaluated & prospectively examined. A total of 83 consecutive patients undergoing the arterial switch operation were included in this prospective cohort study. Simultaneously a note was made of all the patients' pre-operative characteristics, aetiology, associated cardiac anomalies, echocardiogram findings, cardiac catheterization data (if performed), and intra operative details. Three to four mm reprentative sample of tissue obtained from the native pulmonary artery and the native aortic root**,** were fixed in 10% neutral buffer formalin and sent to the Department of Pathology, subsequently these tissues were routinely processed and paraffin blocks were made. Four to five micron thick sections were cut and stained by Hematoxylin & Eosin, Verhoeff"s, van Gieson (VVG), Masson trichrome (MT) stains. Elastic tissue and smooth muscle components were systematically analyzed, in the native aorta and the native pulmonary artery by VVG and MT stains respectively. Histopathological examination of native aorta and native pulmonary artery was done and compared.

Subsequently post operative course, follow- up, and follow-up echocardio graphic data was noted. The study protocol was duly approved by the ethics committee of the Institute. (Ref.no.IESC/T-67;21.01.2015) Informed consent was obtained from the parents of all the patients included in the study. (Annexure 1)

STATISTICAL ANALYSIS

The study was designed and the sample size was calculated to achieve a minimum statistical power of 0.9. Statistical analysis was performed using SPSS 19 software (SPSS Inc, Chicago, Illinois). Values for normally distributed continuous variables are expressed as mean±1 SD. Nonparametric variables are expressed as the median value and range. Discrete variables are expressed as percentages. Outcomes between groups were compared using a paired and non-paired t test.

RESULT

Surgery and anesthesia

Routine anesthetic and surgical techniques which included cardiopulmonary bypass and myocardial protection strategies were used in all of the 83 patients reviewed. Intra-operative transoesophaeal echocardiography (TEE) was performed, wherever possible to confirm the diagnosis and to assess the Left ventricular function and shape, any associated abnormality, shunting of the blood etc. Surgery was performed in the standard manner through a midline sternotomy. Left sided pericardiotomy was done. Pericardial patch was harvested and treated in 0.625% glutaraldehyde for 6 minutes to be used for neo-pulmonary root reconstruction. All the patients underwent primary ASO under moderate hypothermic cardiopulmonary bypass. Intravenous phenoxybenzamine (1—2 mg/kg) is infused slowly for uniform cooling purpose just before aortic cannulation.

For children, in whom Left ventricle still had not regressed, as our routine policy, sternum was kept open, both pleural cavities were kept open, no pericardial or retrosternal tubes were placed. If hemodynamics were stable, the sternum is closed on the next day. Children who had borderline or regressed left ventricle on echocardiography, mechanical support on the form of extracorporeal membrane oxygenation (ECMO) [16] were used. Extracorporeal membrane oxygenator as described earlier by our center was used often.

The child was shifted to intensive care unit with ECMO cannulae in place, whenever needed and was started when required. Once hemodynamics remained stabilized for 24-36 h, the patient is decannulated from the ECMO.

POST OPERATIVE CARE:

All of the children were shifted to ICU after surgery and extubated only after optimizing them. We followed a standard postoperative care, which included mechanical ventilator support with paralysis and sedation for 24—36 h, avoidance of volume overloading, minimal & careful suctioning of endotracheal tube (only when signs of CO_2 retention were found in the form of increase in pCO_2 in arterial blood gas analysis, increase in airway pressure, increase in CVP etc).

Ryle's tube feeding in the form of EBM (Expressed Breast Milk) was started after 4—6 h [17]. Vasodilators, especially intravenous phenoxybenzamine [18] at 8-hourly doses of 0.3—0.5mg/kg with the goal of maximally reducing left ventricular after load. Inotropic support was preferably dobutamine, dopamine and adrenaline, if needed. Vasodilators too in the form of nitroglycerin were added. Inotropic support was optimized as per requirement and the dose and duration of the inotropic support was recorded. Any sign which indicated that LV might not be able to cope up with workload after extubation, during weaning is handled by reparalysis and a wait of 24 h before the process is repeated.

Mechanical support in the form of ECMO was used if conventional measures fail. Postoperatively, patients were kept on oral vasodilator therapy consisting of either phenoxybenzamine or enalapril and oral diuretic therapy (furosemide) for about 6 weeks to 3 months.

Postoperative parameters that were assessed included duration of mechanical ventilation, duration of ICU and hospital stay and any

complication.
A total of 83 consecutive patients undergoing ASO were examined. Patients were divided in 2 groups, Group A (TGA with IVS) and Group B (TGA with VSD).

A total of 52 (62.6%) had associated VSD and 31 (37.3%) were having intact IVS. Other associated conditions found were Tausig-Bing anomaly (03/83, 3.6%), DORV (04/83, 4.8%), Additional vsd (4/83, 4.8%), LVOTO (2/83, 2.4%), PS (2/83, 2.4%), Anomalous coronary artery (4/83, 4.8%) and regressed LV (5/83, 6 %).

Out of the 83 cases reviewed, 68 (82%) were males. Median age was 3months (range 10days—5years). Preoperative baseline characteristics and clinical characteristics, intra-operative data and postoperative variables have been summarised in Tables 1 and 2. Many of the patient present to paediatric emergency with documented preoperative lower respiratory tract infection (LRTI). They had been diagnosed on the basis of clinical acumen, raised levels of CRP or on chest X-ray. There was no increased predilection of infection in any of the 2 groups. Balloon atrial septostomy was done in 19 (61.3%) of 31 children with IVS. These patients were operated within 2 weeks of the Balloon atrial septostomy.

Table 1. Pre-operative Baseline characteristics of the patients.

Characteristics	All Patients n=83	TGA-IVS n=31	TGA-VSD n=52
Age (months), median (range)	10days-5years	10days-9months	27days-5years
Gender			
Male	68	27	41
Female	15	4	11
Associated malformations:-			
Tausig Bing anomaly	3	0	3
DORV	4	0	4
Additional vsd	4	0	4
LVOTO	2	0	2
PS	2	0	2
Anomalous Coronary Artery	4	1	3
Regressed LV	5	4	1
Lower Respiratory Tract Infection	14	8	6

Table 2. Intra-operative and Post-operative data.

	TGA-IVS	TGA-VSD
Intra-operative Data		
Aortic Cross Clamp time (min) (±SD)	50.2±5.8	56.5±6.5
CPB time (min) (±SD)	68.7±13.8	76±18.7
ICU Stay		
Mechanical Ventilation (h) (±SD)	63.8±6.5	62.5±7.9
Inotropic support (h) (±SD)	82±29.1	84±25.1
ICU Stay (days) (±SD)	4.3±1.7	4.7±3.3
Hospital Stay (days) (±SD)	12.5±3.8	12.8±3.6
Mortality		
LV Failure	1	3
Sepsis	2	3

Histopathological evaluation:
Histopathological examination of native aorta and native pulmonary artery was done and compared. Elastic tissue and smooth muscle components were systematically analyzed. In the native aorta and the native pulmonary artery by VVG and MT stains respectively. Lamellar count was evaluated in each case (NA and NPA), simultaneously by two individuals. Figure 1a and 1b depicts the graphical distribution of the cases in six age groups (X-axis) and their corresponding lamellar counts (Y-axis) in NA and NPA respectively. Twenty eight patients who were below the age of one month, thirty two patients were between >1-3 months, ten patients were between >3-6 months of age, five patients were > 6-9 months, four patients were > 9-12 months, three patients were above 12 months of age, had lamellar counts 56-60(57), 50-55(53),45-50(48), 43-47(45), 42-47(44) and 40-45(43) respectively.

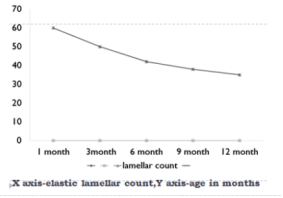


Figure 1a: graphical representation of elastic lamella count in native aorta

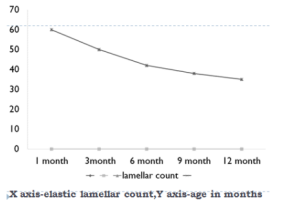


Figure1b: graphical representation of elastic lamella count in native pulmonary artery

Light microscopic evaluation did not reveal any evidence of cystic medial necrosis (mucoid extracellular matrix accumulation), smooth muscle disarray or loss of smooth muscle nuclei (H & E, fig 2a-2b; VVG, fig 3a-3b).

Ultra structural examination of native aorta and native pulmonary artery was done in a single case using electron microscope. There was no significant ultra-structural alteration. Elastic tissue component (fig 4a) in a collagenous background (fig 4b) was seen. There was minimal difference between the Group A and Group B in terms of aortic cross clamp time, CPB time, but no difference in duration of mechanical ventilation, inotropic support, ICU stay or hospital stay. ECMO was instituted in 8.4% (7/83) patients. Requirement of ECMO was slightly higher for children having VSD (4/31 i.e., 12.9%) as against children having IVS (3/45 i.e., 6.6%). Special precaution was needed while weaning the children with regressed ventricle from mechanical ventilation. In five children, the left ventricle was unable to maintain the cardiac output enough to support the work of breathing while weaning. These children required mechanical ventilation for a few more days. All of these children recovered over a period of 1 week and were slowly weaned off from mechanical ventilation. Gradual weaning from the ventilator and inotropic support depending on the hemodynamic response was the cornerstone in the management of these patients.

The improvement in the surgical outcome as seen has been due to precise expertise in intra-operative technique and postoperative intensive care management of such critically ill infants, including the use of ECMO.

Figure 2a-2b
Photo micrograph showing light microscopic features of native pulmonary artery (2a) and native aorta (1b), H&E (10X)

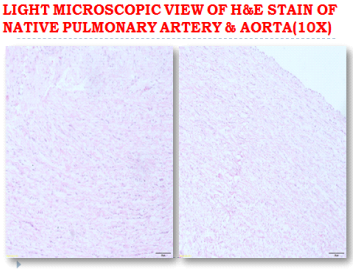


Figure 3a-3b
Light microscopic depiction of VVG stain (10X) high lighting elastic lamella of native pulmonary artery (3a) and native aorta (3b).

Figure 4a: Electron microscopic view of native aorta showing collagen©

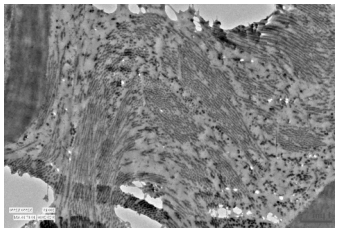
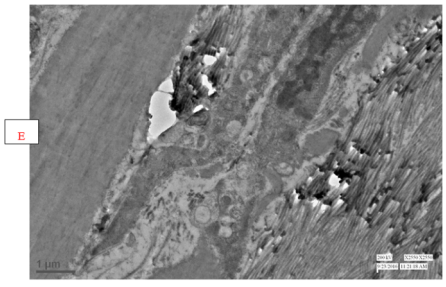


Figure 4b: Electron microscopic view of native pulmonary artery showing elastic tissue (E) in the vessel wall



DISCUSSION

Since the arterial switch operation (ASO) was first described by Jatene and colleagues in 1975 [1], it has become the surgical procedure of choice for repair of transposition of the great arteries (TGA). Peri-operative mortality has improved in the more recent eras, and several case series have described good long-term survival in patients up to 30 years after the ASO [2–5]. However, these long-term studies have also revealed important late complications that contribute to late morbidity and the need for reoperation. These late complications include coronary artery insufficiency, right ventricular outflow tract obstruction, and problems with the native pulmonary root and pulmonary valve in the systemic position functioning as the neo-aortic root and the neo-aortic valve, respectively [4 –9].(Jennifer G. Co-Vu, MD,* Salil Ginde, MD et.al, Wisconsin,US).

Dilation of the neo-aortic root has been reported in more than two-thirds of patients after ASO [6, 7]. The natural history of neo-aortic root dilation in this setting is unclear. Previous studies have demonstrated conflicting data, with reports of the indexed neo-aortic root dimensions progressively increasing [8, 9], decreasing [10], or remaining fixed [11] over time. Neo-aortic valve regurgitation may also be an important late complication, and although uncommon, the need for aortic valve repair or replacement has now been reported in several series late after ASO [12–14].

The function of the aortic root, including the pulmonary valve, that has become the new aortic valve, plays a crucial role in the long-term follow-up after the arterial switch operation for transposition of the great arteries. Disproportionate dilatation of the neo-aortic root and insufficiency has been reported [1]. The technique of the arterial switch however introduces possible growth interference at different levels, such as the pulmonary-aortic anastomosis and the introduction of aortic tissue due to coronary implantation in neo-aorta... Growth interference may have detrimental effect on the aortic valve, the neo-aortic (pulmonary) sinuses and the aortic root. (Paul A. Huttera,*, Bastiaan J.M. Thomeera et al, Netherlands)

In the present study, we sought to identify the possible aetiology of neo-aortic root dilation and neo-aortic valve regurgitation in patients with TGA repaired with ASO at our institution. We also intended to determine the risk factors for the development of the late complications.

The idea behind analysing the tissue of native pulmonary artery and native aorta is to look for any histopathological changes in them. We compared them with each other and also seen the changes in it, which occur with advancing age. We compared them with histological finding of aorta and pulmonary artery.

There is paucity of report regarding the histopathological changes of NA and NPA in the available literature. To the best of our knowledge, there is not a single report on such changes published in the English literature. Our study does not show any significant histological changes like cystic medial necrosis (MEMA), smooth muscle disarray, loss of smooth muscle cell nuclei, in any of the specimen of NA and NPA. The elastic lamellar count in NA and NPA did not show any significant difference; however there was a trend of decrease in elastic lamellar count, as compared to advancing age of the patient, during primary surgical intervention. The normal elastic lamellar count of NA is around 35 at birth (ref-book), contrary to these observation we found an increase in elastic lamellar count of NA and NPA in patients of d TGA. We do not have normal control from neonate as such controls are difficult to obtain.

Particularly in children with IVS, many of the centers have reported mortality of 1—10% for primary ASO in children. In our study the overall early hospital mortality in children was found to be 10.8%. In children with IVS particularly, early hospital mortality was 9.7%, in children with vsd it is 11.5%. But on analysis of cause of death, we found that 6.25% (5/83) of mortality was associated with preoperative sepsis or infection and which is possibly preventable. There remains a scope to further tune down this mortality figure.

CONCLUSION

Eighty three patients underwent an ASO for TGA between 1st April 2015 and 31st October 2016. We examined elastic lamellar count of native aorta and native pulmonary artery for comparison. It was found that elastic lamellar counts were almost similar in both the neo-aorta and the neo-pulmonary artery. Hence histo-pathologically they are similar at birth, gradually as the age advances lamellar count decreases in the neo aorta and neo-pulmonary artery. Whether the increment in elastic lamella count in d TGA in neonates is a remodelling process due to underlying congenital disorder or not, remains unanswered.

However an inverse relation was found between advancing age and elastic lamella count in both the structures might imply the need for an early arterial switch to prevent long-term complications like neo-aortic root dilatation and aortic regurgitation.

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